AN INVESTIGATION OF INDIVIDUAL VARIABILITY IN BRAIN ACTIVITY
DURING EPISODIC ENCODING AND RETRIEVAL

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ABSTRACT

The purpose of this study was to test the reliability of self-reported strategy measures for predicting differences in brain activity patterns during a learning and memory task and to compare their predictive value to other measures of cognitive processing and of anatomy. Fifty participants were scanned with functional MRI (fMRI) while they intentionally encoded lists of lowly imageable words and completed subsequent recognition memory tests. After scanning, subjects were asked to report their strategy for each study/test session and to complete a Visualizer-Verbalizer test battery. Our results replicated our previous work showing extensive variability in individual brain activity patterns during episodic memory. Further, we show that self-report measures are not reliable for predicting differences in learning and memory. Instead, other measures of cognitive processing, performance and connectivity properties of the brain were strong predictors.

1. INTRODUCTION

The broad objective of this research program is to understand the sources of individual variability in brain activity so that we might be able to better assess the unique characteristics of individual minds that cannot be evaluated using standard behavioral measures or self-reports. The purpose of this study is to systematically investigate the structural and cognitive factors that may account for the extensive individual variability that has been observed in brain activity across normal subjects using fMRI. This research program seeks to answer these three basic questions: 1) what makes one individual’s pattern of brain activity so deviant from another? 2) Can individual differences in brain activity be accounted for by differences in cognitive strategy, and, in turn, can information about individual brain activity be used to assess the thought processes of individuals engaged in a variety of cognitive tasks? 3) Can individual differences in brain activity be accounted for by differences in anatomy or physiology, and, in turn, can information about individual brain activity be indicative of limitations and constraints in the kinds of cognitive strategies that a particular individual is capable of or tends to engage in?

There is a large degree of between-individual variability in functional activation patterns in subjects performing episodic memory tasks. In a seminal study, Miller and colleagues (2002) found that the patterns of brain activity observed in individual subjects performing an episodic retrieval task were highly distinct from the patterns of brain activity noted at the group level and that those intersubject differences went well beyond the expected local variations due to individual differences in cytoarchitecture and to warping related to spatial normalization. They also demonstrated that individual patterns of activation were reliable over time by showing that even 5-11 months later an individual’s activity pattern was highly correlated with the activity measured during the earlier study, which lends strong support to the idea that the activation differences were not just due to noise and instead likely reflect processes that are employed by the individual to complete the task.

Of interest is what are the sources of this observed variability? While it is likely that this variability can be related to multiple factors, the degree to which variability in episodic retrieval relates to individual differences in mnemonic strategy use has been relatively unexplored. It has long been recognized that individuals spontaneously employ varied and sophisticated elaboration and retrieval processes when intentionally learning. There is substantial evidence that mature learners can and do employ a multitude of strategies, even when approaching a single task. Individuals deliberately employ processing and encoding strategies in order to enhance their encoding, storage and/or retrieval of information (Battig, 1975; Pressley, Heisel, McCormick & Nakamura, 1982; Weinstein, Underwood, Wicker, & Cubberly, 1979). A number of mnemonic strategies have been identified from reports of people performing unconstrained intentional encoding and retrieval. There is a wealth of evidence that people differ on their “preferred” strategy for a given task and that strategy preferences differ as a function of material to be learned. Furthermore, individuals routinely vary their strategy over the course of a single task/context and again, the extent to which individuals adapt their strategy varies greatly from
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individual to individual. Different mnemonic strategies have been shown to rely on different neural substrates (Kirchoff & Buckner, 2007), therefore it is conceivable that the large variability in mnemonic strategy use is, at least in part, related to the extensive variability observed in brain activity patterns.

While a number of encoding and retrieval strategies have been identified, the most extensively studied has been elaboration, including both imaginal elaboration (mental imagery) and verbal elaboration (Paivio, 1971). For example, some people (who could be called verbalizers) are better at processing words and may rely on semantic associations and verbal content when remembering a past event, while other people (who could be called visualizers) are better at processing pictures and may rely on visual imagery and visual recollections when remembering a past event. However, the value of self-reported introspections has been repeatedly called into question. To test the predictive value of self-reported strategy versus other measures of a person’s tendency or preference to think visually or verbally, subjects were scanned using functional magnetic resonance imaging (fMRI) while they studied lists of lowly imageable words, which have been shown to discourage the use of visual strategies (Paivio, 1971), and subsequently completed a recognition memory test. Participants were simply instructed to learn the words for a later memory test and hence were free to adopt whatever strategy came most naturally. During the episodic retrieval task, subjects simply made an “old/new” recognition judgment to the words, half of which were previously studied. After the scanning session, participants were asked to report whatever strategies they used to learn the words during the study phase and to complete a visualizer/verbalizer test battery so that we could measure their tendencies to visualize and verbalize written material. Differences in brain activity were measured by cross correlating individual t-maps, which are computed from a contrast of task activity (i.e., activity in response to encoding or retrieval) versus fixation. The t-maps are thus whole brain volumes of statistics reflecting activity in each voxel in response to the task. The correlation of two volumes tells us how similar are the activity patterns in those two volumes. Then we can test whether similarity in strategy predicts similarity in brain activity by computing the difference in strategy scores and regressing those differences onto the cross-correlations of the t-maps. A significant relationship would mean that the more similar two strategies (i.e., the smaller the difference score), the more similar the activity patterns.

It is also conceivable that there are a number of factors that can give rise to differences in activity patterns, strategy differences being just one. These other factors may include differences in gross-anatomy, neural connectivity, and in other cognitive factors, such as memory performance. By entering these variables hierarchically, we can measure which variables are significantly related to differences in brain activity patterns and see the relative importance of each of the variables by comparing the percentage of variability accounted for by each factor. With this method we can measure not only whether strategy difference are related to differences in brain activity patterns but also how much of that difference is attributable to strategy versus other factors.

2. METHODS

2.1 Behavioral Paradigm

A group of 50 participants (age 18-55, M=25.8) were recruited from the undergraduate and graduate student population at UCSB and were paid for their participation in the scanning sessions. Data from 3 subjects was excluded (1 for excessive motion, 1 due to scanner malfunction and 1 chose to discontinue the experiment prior to completion). The remaining 47 comprised of 24 men and 23 women.

In each session, participants learned lists of lowly imageable, abstract nouns. Words were chosen to be 4-12 letters in length. Lowly imageable words were chosen to be greater than 1 SD below the mean on the MRC Psycholinguistic Database Imageability rating. Within each study-test session, word order was randomized, and whether the word was old or new was counterbalanced across subjects.

This experiment employed an event-related design. Each study session consisted of 239 events (each lasting 2 seconds), randomly intermixed: 106 study words, 53 right/left control trials and 80 fixation (“+”). Participants were simply instructed to learn the words for a later memory test. Structural scans (first high-resolution MPRAGE and then DTI) were run between the study and test sessions to increase the time between study and test and hence increase forgetting. The test sessions consisted of 318 events: 212 test words (50% studied and 50% new) and 106 fixation, again randomly intermixed. Participants were instructed to respond with index finger if item was old and with middle finger if item was new. Once the initial experiment was complete, participants filled out a Visualizer-Verbalizer test battery and responded to questionnaires assessing strategy.

2.2 Functional MRI data acquisition

Functional images were acquired with gradient-recalled echoplanar imaging (TR = 2000 ms, TE = 30 ms, RF flip angle = 90, gradient-echo pulse sequence, 33
contiguous axial slices at 3.0 mm thick with a 0.5 mm slice gap, and an in-plane resolution of 64 x 64 pixels in a FOV of 192 cm, producing voxels of 3 mm x 3 mm x 3 mm) on a 3T SIEMENS Trio MRI scanner equipped with high-performance gradients. Echoplanar images were used for detecting susceptibility-based BOLD contrast. Each BOLD run is preceded by 4 scans to allow steady-state magnetization to be approached. Raw image data was reconstructed on-line and saved directly to a disk. In addition to the functional scans, 25-slice, T1-weighted structural images were obtained for each subject in the same slice prescription as the functional scans (TR = 650 ms, TE = 6.6 ms, fast spin-echo pulse sequence, with an in-plane resolution of 192 x 192 pixels in a FOV of 24 cm, producing voxels of 1.25 mm x 1.25 mm x 6.5 mm). A high-resolution, T1-weighted structural images was acquired using a 3-D SPGR pulse sequence (TR = 25 ms, TE = 6 ms, RF flip angle = 25°, bandwidth = 15.6 kHz, voxel size = .9375 mm x 1.25 mm x 1.2 mm). Diffusion-weighted MRI data were acquired using a diffusion weighted, single-shot spin-echo, echo-planar sequence with the following parameters: TR=9022 msec; TE=91 msec; flip angle=90 degrees; slice thickness=2.0 mm; number of slices=70 (axial); FOV=240mm; matrix size=128 x 128; acquisition time= 5:24 min. Diffusion weighting (b-value=1000 sec/mm2) was applied along 32 directions with one additional reference image acquired having no diffusion weighting (b-value=0 sec/mm2). Foam padding was used to minimize head motion.

2.3 Functional Data Analysis

Initial data processing was carried out on a MacIntosh G4 workstation. First, a custom Matlab (v. 6.5; Mathworks) script is used to convert the Siemens image data into nifti format. SPM5 (SPM5; Wellcome Department of Cognitive Neurology, London, UK) was then used for slice acquisition correction, motion correction, coregistration, spatial normalization, and smoothing. The timing of the slice acquisitions was corrected to the first acquisition. Then motion correction to the first functional scan is performed within each subject using a B-spline interpolation. The functional images were then directly co-registered to the high-resolution structural image. Then spatial normalization to the Montreal Neurological Institute template (Talairach and Tournoux, 1988) was performed by applying a B-spline interpolation. Functional images were written with 3 mm x 3mm x 3 mm voxels. The spatially normalized scans were then smoothed with an 8 mm isotropic Gaussian kernel to accommodate anatomical differences across subjects.

For each participant, analysis was conducted using custom software written in MATLAB (The MathWorks, Natick, MA). The general linear model was used to analyze the fMRI time-series. Each stimulus onset and post-stimulus time point (up to 20 sec) was modeled by a separate parameter. There are ten post-stimulus time bins covering a total window length of 20 seconds. This approach is very similar to selective averaging and is also known as a finite impulse response model (Henson, Rugg, & Friston, 2001). The benefit of this model is that it makes minimal assumptions about the shape of the hemodynamic response, thus accommodating variations in the timing of the response that have been observed across brain regions and avoiding the amplitude bias that these variations can introduce. In addition to the parameters already discussed, parameters were included to model linear drift within each session and the session-specific means. Statistical maps were then created for each subject by specifying specific t-contrasts, assessing retrieval. Once the individual analysis was completed, a group analysis was conducted in order to assess common areas of activations. A random-effects model was used to identify all voxels above a statistical threshold of p < .01 uncorrected with a minimum extent of 10 voxels. These group maps are used to assess the validity of our manipulations and for illustrative purposes only.

The DTI analysis was carried out using the diffusion toolbox as implemented in SPM5. For preprocessing, diffusion-weighted images were motion-corrected and coregistered to the high-resolution T1-weighted image, which we spatially normalized to the MNI template brain. The resulting normalization parameters were subsequently applied to the diffusion-weighted images, reorienting the gradient directions accordingly. Following preprocessing, second-order diffusion tensors and fractional anisotropy (FA) values were established using the standard multiple regression approach. Individual FA images reflect the coherence of the orientation of fibers on a voxel-by-voxel basis.

2.4 Behavioral Data Analysis

Memory accuracy and response criterion/bias was computed from the proportion of words correctly identified as studied (hits) and words falsely identified as old (false alarms). Visualizer-Verbalizer test battery data was submitted to a factor analysis to yield 4 orthogonal (uncorrelated) factors, which are related to visualizing and verbalizing tendencies. The extraction method used is principal components analysis (PCA) and VARIMAX rotation is conducted to yield orthogonal factors. Factors scores are then computed for each subject from the linear combinations of scale scores. Individual self-reported strategy questionnaire responses are classified as either visual or verbal by two blind raters.

2.5 Individual Variability Analysis.
To assess variability in the patterns of brain activations we first cross correlated each individuals’ t-map, independent of any statistical thresholding, for each task (see Miller et al., submitted). These maps are whole brain volumes of statistics reflecting activity in each voxel in response to the task (in this case, either encoding or recognition). The correlation of two volumes results in a single correlation value that tells us how similar are the activity patterns in those two volumes. Each t-map was first converted to contain rank ordered t-statistics and Spearman rank correlations were used to account for non-linearities in the distribution of t-statistics and were computed using a custom Matlab script. The resulting correlation values were then submitted to a Fisher’s Z transformation to normalize the distribution (Cohen, Cohen, West & Aiken, 2003) before being submitted to a multivariate, hierarchical regression analysis (SPSS v. 11.0.1). This type of analysis allows us to assess whether similarity/difference in other factors is related to the degree in similarity in the t-maps. By entering all our variables hierarchically, we can measure which variables are significantly related to differences in brain activity patterns and see the relative importance of each of the variables by comparing the percentage of variability accounted for by each factor.

The following factors were included to assess their relative contribution to the observed variability:

1. Anatomical differences – this is measured by cross-correlating each individual’s normalized high-resolution anatomical (mprage) image. The more similar the distribution of grey/white matter, the higher the correlation.

2. Connectivity differences – this is measured by cross-correlating each individual’s fractional anisotropy image (computed from the DTIs). The more similar the distribution of anisotropy values, the more similar the connectivity profile of the volumes and the higher the correlation.

3. Strategy differences – strategies are assessed in two ways:
   a. Self-reported strategies (subjects are asked to report what they did to try to learn the words during the study phase and how they decided if the words were ones they studied during the test). The self-reports are categorized into visual or verbal strategies. Differences are then coded as 0 if the two people reported the same strategy (either visual or verbal) or 1 is the two people reported different strategies
   b. Recognition decision criteria are computed from the responses to the recognition test (C = z(hit) + z(FA)). Differences in criteria values are then a measure of differences in retrieval strategy.

4. Differences in visual/verbal cognitive style – visual/verbal cognitive style is measured by a Visualizer-Verbalizer test battery. Responses to the items in the battery are submitted to a factor analysis to yield independent factors. Component scores are then computed for each individual, for each factor and differences in cognitive style traits are measured by computing the difference between two people’s components scores for each factor. (i.e. for each pair of individuals, there is one difference score for each cognitive style factor). The more similar the individuals, the smaller the difference.

5. Performance differences - memory performance is computed for each individual by computing d’ (d’ = z(FA)-z(hits)). Performance differences are then assessed by differences in d’. The more similar the individuals, the smaller the difference.

These variables were entered in 2 steps. The anatomical and physiological factors were entered in the first step so that any shared variance with the cognitive factors would be attributed to the earlier factor. This is a more stringent measure of the relationship between differences in brain activity patterns and differences in the cognitive factors as any spurious variance is accounted for by the earlier step, which strengthens the inferences that can be made about the role of the cognitive factors, and more specifically of the strategy measures of interest (Cohen et al., 2003).

3. RESULTS

Performance on the recognition test was uniformly high (mean d’ = 1.16, st. dev = 0.62). The functional data analysis replicates previous work showing extensive differences in activation patterns across the participants making up this group. Visual inspection of the individual t-maps for the retrieval task (figure 1) shows qualitatively distinct patterns across individuals. The similarity/difference between each pair of t-maps was measured by cross-correlating the two volumes. The average correlation for the individual activity patterns during retrieval was r = 0.29 (p<.001). This average correlation was modest at best, which indicates that there are substantial differences between individuals in this sample. It is also evident, however, that a significant source of this variance is not simply noise but instead can be attributed to specific anatomical and cognitive factors related to the individuals making up the sample. A hierarchical regression analysis was conducted to test
the relationship between differences in brain activity patterns (as measured by correlation values) and differences in a number of cognitive and anatomical factors as discussed above. Differences in activity patterns during retrieval were strongly predicted by differences between individuals (the results of this analysis are presented in Table 1). These factors together accounted for 15% of the variance in activity patterns during retrieval ($R^2 = .225$ F(9, 1080) = 15.24, $p < .001$).

The differences in activity patterns during the recognition test could be explained by both cognitive and anatomical factors. Of the anatomical factors, similarity in both hires anatomy and white matter connectivity (FA) predicted similarity in brain activity (FA partial $r^2 = .027$ $p < .001$; hires anatomy partial $r^2 = .002$ p < .01). This means that the higher correlation between two anatomy maps, the higher the correlation between

### Table 1. Hierarchical regression analysis predicts similarity in brain activity patterns during retrieval

<table>
<thead>
<tr>
<th>Variable</th>
<th>$R^2$</th>
<th>$\Delta R^2$</th>
<th>$sr^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>.198***</td>
<td>.198***</td>
<td></td>
</tr>
<tr>
<td>Anatomy</td>
<td>.076***</td>
<td>.012***</td>
<td></td>
</tr>
<tr>
<td><strong>Step 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported strategy</td>
<td>.225***</td>
<td>0.027***</td>
<td>.001</td>
</tr>
<tr>
<td>Verbal trait</td>
<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual trait</td>
<td>.015***</td>
<td>.006***</td>
<td></td>
</tr>
<tr>
<td>Criterion</td>
<td>.010***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance (d’)</td>
<td>.010***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: ** $p < .01$ ***$p < .001$. 

Figure 1. Brain activity maps (t-maps) for each individual for the contrast retrieval vs. fixation. Maps are thresholded for visualization only ($p < .001$ uncorrected for multiple comparisons; voxel extent > 10). The same horizontal slice locations are shown for each individual for comparison. Results of group analysis shown in top left corner. Group map was thresholded $p < .01$, uncorrected; voxel extent > 10.
activity maps. Differences in cognitive factors were also a significant predictor of variability in activity maps, accounting for 3% of the remaining variance (R^2 change = .027, p < .001). However, of the cognitive factors, only behavioral differences (as measured by performance and criterion) and visual/verbal trait factors were significant predictors of difference in activation patterns whereas reported strategy differences were not reliable measures of brain activity differences. This is particularly interesting given that 42 of the 47 participants reported using a verbal strategy yet brain activity differences are extensive. This replicates results from earlier studies (Miller et al., 2002; Miller, et al., submitted; Donovan, et al., submitted).

Finally, a large portion of variance related to difference in activity patterns during retrieval is still unexplained. To measure the residual variance that can be attributed to the individuals, variables coding for each individual were entered on the last step of the hierarchical regression analysis as described above. For retrieval, the individuals account for 48.0% of the remaining variance (R^2 change = .480, F Change(54, 1080) = 37.064, p <.001). Therefore, a significant portion of the variance in differences between activation patterns is related to individual factors other than those considered here. This regression model, including the physiological and cognitive factors, as well as the individual factors as just described, can explain 70.5% of the variance observed in this study (R^2 = .705, F (54, 1080) = 45.402, p<.001).

CONCLUSION

Most neuroimaging studies localize cognitive functions in the brain by conducting a statistical analysis across a group of subjects that identifies common areas of activation within that group. While this can be a useful approach to understanding the modular organization of the brain, it disregards the uncommon areas of activation that can be observed at the individual level that may also be critical for the individual to complete the task. In previous studies, we have shown that the individual patterns of brain activity during an episodic memory task are enormously variable, sometimes with non-overlapping regions of activation between any two subjects. Yet, little is known about the sources of this variability.

This study replicates our previous works and shows that there is a large degree of variability in brain activity patterns in people performing episodic memory tasks. Differences in activity were quantified by cross-correlating individual t-maps, which represent the whole-brain pattern of response to performing an encoding or retrieval task. The average correlation that was observed was modest at best, which indicates that there are substantial differences between individuals. It is evident, however, that a significant source of this variance is not simply noise but instead can be attributed to specific anatomical and cognitive factors related to the individuals making up the sample.

These results show that individuals can recruit widely dispersed brain regions during an episodic memory task. They show that self-reports of learning strategy are unreliable at distinguishing the differences between individuals. Despite reporting the use of similar strategies, brain activity was very different subject to subject. This is evidence that one can’t rely on self-report measures to predict differences in learning and memory. However, these results also show that differences between individuals can be predicted by differences in the subject’s cognitive style, and the subjects’ neuroanatomy. It suggests that individuals’ physiology contains predictive insight into their learning and memory processes, which has not been appreciated before.

Reported strategy differences were not a significant predictor in this sample. This may be due to the coarse categorization of strategies as either visual or verbal as these are only two of a possible number of strategies that are generally reported. Other types of strategy differences do predict differences in brain activity during encoding and retrieval however; large criterion differences and visualizing differences were significantly related to larger differences in brain activity patterns. The results expand on our previous work by showing that differences in cognitive style are strong predictors of differences in brain activity patterns during both encoding and retrieval. The more two people are similar in their ability/likelihood to visualize, the more similar their activity patterns when they are recognizing previously studied words. That reported strategy was unrelated to visual/verbal traits might imply that despite attempting to use the same strategy, information processing may still be different between two individuals depending on differences in cognitive style. This supports other work by Kozhevnikov, Hegarty, and Mayer (2002) and Kozhevnikov, Kosslyn, and Shephard (2005).

As we know, human capability and expertise can vary greatly from individual to individual. Understanding the neural substrates of individual differences in cognition is essential for predicting how an individual will approach a task and handle any given situation. This knowledge is pertinent to soldier and candidate selection, developing directed training methods and for improving training regimens leading to expertise. This work could also lead to methods for tailoring training based on cognitive strategy and for identifying contexts where
cognitive style is particularly variable. Understanding the extent to which structural differences account for individual variability in brain activations will greatly enhance our knowledge and understanding of individual minds, allowing human-system interfaces to be better tailored to the individual. Human capability and expertise, of course, can vary greatly from individual to individual. This is one potential solution to the increasing technology- and threat-driven dynamic complexity on the battlefield.

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