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Unique and Persistent Individual Patterns of Brain Activity Across Different Memory Retrieval Tasks

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Abstract

Fourteen subjects were scanned in two fMRI sessions separated by several months. During each session, subjects performed an episodic retrieval task, a semantic retrieval task, and a working memory task. We found that 1) despite extensive intersubject variability in the pattern of activity across the whole brain, individual activity patterns were stable over time, 2) activity patterns of the same individual performing different tasks were more similar than activity patterns of different individuals performing the same task, and 3) that individual differences in decision criterion on a recognition test predicted the degree of similarity between any two individuals' patterns of brain activity, but individual differences in memory accuracy or similarity in structural anatomy did not. These results imply that the exclusive use of group maps may be ineffective in profiling the pattern of activations for a given task. This may be particularly true for a task like episodic retrieval, which is relatively strategic and can involve widely-distributed specialized processes that are peripheral to the actual retrieval of stored information. Further, these processes may be differentially engaged depending on individual differences in cognitive processing and/or physiology.

Introduction

The field of neuroscience is focusing more and more on the individual. Psychopharmacology researchers are searching for ways to customize psychotropic drug treatments to account for individual differences in metabolism and other physiological properties (Ng et al., 2004). Cognitive neuroscience researchers are increasingly considering the variable genetic expression of brain processes and function (Posner & Rothbart, 2005; Bishop, in press). Meanwhile, many areas of endeavors (including the medical field, the military, education, and courts of law) that attempt to incorporate neuroscientific evidence to assess and train people

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have to consider the ways in which individuals vary from each other. This need presents a particular challenge to field of neuroimaging.

We have previously shown that the pattern of activations represented by the group map looked very different from the patterns of activations for the individuals making up that group (Miller et al., 2002). The individual differences went well beyond any differences in anatomy not corrected by spatial normalization. Further, despite large variations from subject to subject, we found that the individual patterns of activations were stable over an extended period of time, suggesting that the variations in active brain regions between individuals were systematic and not due to random noise. These findings imply that the group map is not necessarily a meaningful representation of the brain activity observed at the individual level.

Because there is a lot of noise in fMRI data, most neuroimaging studies not only collect repeated measurements over time from individuals but they also rely on a second level of analysis that combines data across a group of subjects in order to increase power and reliability (Friston et al., 1999a). As these methods have become more sophisticated and more population-based (Friston et al., 1999b; McNamee & Lazar, 2004), group maps have become very effective at isolating common areas of activations and many of these studies have been replicated numerous times. However, for some higher-order cognitive tasks, the group map may be an incomplete way to profile the pattern of expected BOLD responses across the whole brain because it does not reflect the extensive yet unique activations that occur at the individual level that may be critical for understanding that particular individual's performance on the task. Depending on the extent of these unique individual activations, much potential information about the neural basis of cognition may be lost by relying on a group map alone.

Episodic memory is a useful framework for studying individual variability because of the nature of the task and the nature of the brain activity underlying it. Performance in an episodic retrieval task, such as an "old/new" recognition decision, is strategic (Tulving, 1983; Roediger, 1996; Schacter, 1999) and is known to involve an extensive hippocampo-cortical network for the consolidation, storage, and utilization of episodic and non-episodic information (Squire, Stark, & Clark, 2004; Eichenbaum et al., 2007). As we will discuss further in this report, episodic retrieval may also involve a number of specialized processes that are widely distributed throughout the brain that can be differentially engaged depending on a person's strategy, cognitive style, and/or physiological constraints.

Given that unique patterns of brain activity tend to persist over time, we sought to determine whether or not unique patterns of individual brain activity also persist across different memory tasks. In other words, will an individual's pattern of brain activity be more similar to the brain activity of the same individual performing a different task than it is to a different individual performing the same task? In order to test this, subjects performed an episodic retrieval task, a semantic retrieval task, and a working memory task in each session. Two different scanning sessions were collected for each subject separated by several months.

Method

Participants

Fourteen subjects (age 18–31, 8 women) were recruited from the undergraduate population at Dartmouth College and were paid for their participation. The institutional review boards at Dartmouth College and the University of California, Santa Barbara granted human subjects approval and informed consent was obtained from each subject prior to participating.

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Apparatus

Visual stimuli were back-projected onto a screen at the head of the scanner bore. A reverse mirror was mounted on the head coil so that the participants could view the screen. A Macintosh PowerPC drove the experimental paradigm and stimuli were presented using Psyscope (v. 1.2.3). Participants responded via a fiber-optic button placed in each hand.

Behavioral Procedure

Participants completed two sessions over the course of 5 months (average time difference between sessions was 2.64 months). In each session, participants completed an episodic retrieval, a semantic retrieval and a working memory task. Session 2 followed identical procedures as Session 1 except that new stimuli were used. The stimuli for the semantic and episodic retrieval paradigms consisted of words presented centrally in the visual field in black typeset. Two different word sets, matched for word frequency and imagery, were used in Session 1 and Session 2. For each session, word sets were divided into 3 subsets - one was used for the study session prior to scanning, one for the semantic retrieval paradigm, and one used for the episodic retrieval paradigm. These subsets were counterbalanced across subjects within a session to ensure that the semantic and episodic paradigms used identical stimuli. For the working memory paradigm, single letters were presented instead of words.

Stimulus presentation—The episodic retrieval paradigm utilized an event-related design while the semantic retrieval and working memory paradigms utilized a mixed block/event-related design. Stimulus presentation parameters were identical for all three paradigms. One third of the trials were fixation trials and these were randomly intermixed with task trials. Each trial lasted 2.5 seconds (the length of the TR). During a task trial, the word or letter was presented during the first 2 seconds, followed by a fixation crosshair for 0.5 seconds. The participant was instructed to respond before the presentation of the next word or letter. Fixation trials consisted of a simple crosshair presented centrally and lasted 2.5 seconds. In each paradigm, long trials of rest were randomly intermixed as well. These rest trials consisted of a row of Xs that appeared on the screen in the same manner as the words or letters in the other trials, which signaled to the participant to rest and not push any buttons for 25 s (10 TRs).

Episodic Retrieval Paradigm—Before entering the scanner, participants studied a group of 64 words presented sequentially on a computer screen. The participants were told that the words would be used later for a recognition test. The words were presented one at a time for one second each with one second between the trials. No responses were required. Once the study session was complete, participants were scanned while they completed the recognition test. This paradigm consisted of 128 retrieval trials, 64 control trials, and 8 resting trials. During a retrieval trial, a word (in black color) appeared on the screen. Participants were instructed to decide whether they remembered the word occurring in the study session prior to scanning. If the participant recognized the word, he or she was to press the right button or press the left button if he or she did not recognize the word. This type of manipulation has been used often in neuroimaging studies to probe episodic retrieval. Half of the words were “old” (i.e., they appeared in the study session) and half of the words were “new” (i.e., they did not appear in the study session). During a control trial, the word (in red color) “right” or “left” was presented on the screen. Participants were instructed to respond to “right” by pressing the right button, and to respond to “left” by pressing the left button. Half of the trials were “right” words and half were “left” words. Retrieval trials and control trials were randomly intermixed with fixation trials.

Semantic Retrieval Paradigm—This paradigm consisted of 64 retrieval trials, 32 control trials, and 4 resting trials. As in the episodic retrieval paradigm, a word (in black color) appeared on the screen during the retrieval trials. This time participants were instructed to respond to

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the word by pressing the left button if the word represented an abstract thought or idea (e.g., future), and the right button if the word represented a concrete object or image (e.g., tree) during the "deep" condition and by pressing the left button if the word contained the letter "a" and the right button if the word did not contain the letter "a" during the "shallow" condition. There were equal numbers of abstract and concrete words, and there were equal numbers of words with and without the letter "a". This task is commonly referred to as an incidental encoding task or a semantic encoding task, but in this study none of the words from this paradigm were used as studied items in the subsequent episodic retrieval task. The task required subjects to retrieve semantic knowledge regarding the words presented (Tulving et al., 1994), so we have chosen to refer to it as a semantic retrieval task. The presentation parameters of the control trials and rest trials were identical to the episodic retrieval paradigm. In addition, the task trials were blocked (8 blocks of 8 retrieval trials and 4 blocks of control trials) so that all retrieval trials of the same condition (deep or shallow) were grouped together (this was necessary in order to cue subjects on the task response requirements). Prior to the block, a cue appeared for 2.5 seconds to indicate the task that the subject was to perform during the block.

Working Memory Paradigm—This paradigm also consisted of 64 retrieval trials, 32 control trials, and 4 resting trials. The task was an n-back test of working memory, a manipulation that is commonly used in neuroimaging. Single letters were presented in black in succession at the center of the screen. During the retrieval trials, participants were instructed to respond to each letter and indicate by button press if it matched the letter presented two trials before (i.e. a 2-back task) or they were instructed to match to three trials back (i.e. a 3-back task). The control trials had participants respond whether or not a letter matched the one that immediately preceded it (a 1-back task). As in the semantic retrieval paradigm, the task trials were grouped (4 blocks of 16 retrieval trials and 2 blocks of 16 control trials) so that all retrieval trials of the same condition (3-back or 2-back) were grouped together. 16 letters were presented randomly in each block, 3 of which were repeats. In two cases, the letter matched with the instructed n-back position and one did not. Prior to each block, a cue appeared for 2.5 seconds to indicate the task that the subject was to perform during the block. The rest trials were identical to the two previous paradigms.

FMRI Procedures and Analysis

Neuroimaging data acquisition—Functional images were acquired with gradient-recalled echoplanar imaging (TR = 2500 ms, TE = 35 ms, RF flip angle = 90°, gradient-echo pulse sequence, 25 contiguous axial slices at 5.5 mm thick with a 1 mm slice gap, and an in-plane resolution of 64 × 64 pixels in a FOV of 24 cm, producing voxels of 3.75 mm × 3.75 mm × 6.5 mm) on a 1.5T GE SIGNA Echospeed MRI scanner (General Electric, Milwaukee, WI) equipped with high-performance gradients (revision LX 8.3; maximum amplitude 4.0mT/m; slew rate 150 mT/m/s). Echoplanar images were used for detecting susceptibility-based BOLD contrast. Each BOLD run was preceded by 4 scans to allow steady-state magnetization to be approached. In addition to the functional scans, a T1-weighted structural image 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 × 1.25 mm × 1.2 mm). Foam padding was used to minimize head motion.

Preprocessing of fMRI Data—SPM2 (SPM2; Wellcome Department of Cognitive Neurology, London, UK) was used to conduct standard preprocessing. The timing of the slice acquisitions was corrected to the first acquisition. Then motion correction to the first functional scan was performed within each subject. The functional images were then directly co-registered to the high-resolution structural image. Then spatial normalization to the Montreal Neurological Institute template was performed. Functional images were resampled to 3 mm

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isotropic voxels. The spatially normalized scans were then smoothed with an isotropic Gaussian kernel (FWHM = 8mm) to accommodate anatomical differences across subjects.

Analysis of functional data—Subsequent analysis was conducted using custom software written in MATLAB (The MathWorks, Natick, MA). Our methods for event-related fMRI analysis have been described elsewhere (Keehner et al., 2006). The general linear model was used to analyze the fMRI time-series (Friston, Holmes, Worsely, Poline, Frith, & Frackowiak, 1995). Our methods for event-related analysis follow those of Ollinger, Shulman, and Corbetta (2001). Each stimulus onset and post-stimulus time point (up to a specified limit, in this case 20 s) was modeled by a separate parameter. There were eight post-stimulus time bins covering a total window length of 20 seconds. Parameters were also included to model linear drift within each session and the session-specific means. Fixation baseline was implicitly modeled as the intercept. Parameter estimates were obtained using standard least-squares estimation. Statistical maps were constructed by summing the 2^{nd}, 3^{rd}, and 4^{th} post-stimulus time-points and testing them against the baseline. In each case we compared all retrieval trials to baseline. A separate analysis also compared retrieval trials to control trials. 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 groups maps were used to assess the validity of our manipulations and for illustrative purposes within this manuscript only.

Individual variability analysis: correlations of statistical maps—In order to quantify the variability in individual patterns of activity across the whole brain, we cross-correlated the unthresholded image volumes across subjects and sessions, both within each task and also across the tasks (some of these methods were first described in Miller et al., 2002). If one takes a 3-dimensional volume of continuous values in each voxel and correlates that volume with another 3-dimensional volume of continuous values in the same voxel matrix and atlas space, then the result will be a single correlation value that represents how similar the two volumes are. A similar correlational approach has been used with smaller patches of cortex in pattern classification studies of object recognition (Haxby, 2004; Norman et al., 2006). We used the volumes containing unthresholded t-values[1] (t-maps) derived from the contrast between the retrieval trials and baseline for each subject, task, and session. For the episodic retrieval task, the retrieval trials included all “old” and “new” trials. For the working memory task, the retrieval trials included all 2-back and 3-back trials. For the semantic retrieval task, the retrieval trials included all shallow (“a”/”no a”) and deep (“abstract”/”concrete”) trials. For all tasks, baseline included all the randomly intermixed fixation trials as well as the trials during the “rest” blocks. Prior to the correlation analysis, all volumes were masked with masks derived from the group analysis to exclude extra-brain voxels and voxels with no signal in any one subject. The use of masked, unthresholded t-maps ensured a continuous value in each cell of the correlation. In our previous study (Miller et al., 2002), we correlated volumes of raw signal intensity values, but those correlations may have been sensitive to individual differences in basic physiology, such as individual differences in vasculature and individual differences in the timing of the BOLD response. Using a t-map contrast between two conditions within an individual should greatly attenuate those particular differences in physiology. The t values were first converted to ranks and then their Spearman rank order correlation was computed. This correlational method was chosen due to likely violations of normality in the t values. All correlation values were then normalized using a Fisher transformation. Throughout this report we will refer to these correlations as the degree of similarity between brain volumes. The resulting correlation values were then submitted for further analyses.

[1]The use of unthresholded t-maps is critical to our analysis because thresholded t-maps will include only areas of the brain that are active for one condition versus another condition and possibly exclude voxels that may be active for both. Furthermore, the degree of similarity between thresholded t-maps will vary greatly depending on the arbitrary setting of the threshold.

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Results and Discussion

Behavioral Results

We calculated d´ (memory accuracy) and C (decision criterion) to measure recognition performance for the episodic retrieval task using signal detection analysis. The mean d´ for session 1 was 1.48 (SD = 0.31) and the mean C for session 1 was 0.09 (SD = 0.18), while the mean d´ and C for session 2 was 1.62 (SD = 0.38) and 0.15 (SD = 0.23). For d´, performance ranged across subjects from a minimum of 0.87 to a maximum of 2.26, while the range in C was less, from a minimum of −0.23 to a maximum of 0.52. Working memory performance was calculated by simply determining the proportion of trials that the subject responded correctly when a letter was repeated across the 2-back and 3-back conditions (hits minus false alarms). The mean proportion correct for session 1 was 83% (SD = 14%) while the mean proportion correct for session 2 was 70% (SD = 22%). Performance in the semantic retrieval task could not be measured since accuracy was irrelevant in the abstract/concrete judgment. We also measured reaction times across the three tasks. Reaction time was slightly longer for the episodic retrieval task (mean = 1041 ms; SD = 160 ms) than for the working memory task (mean = 978 ms; SD = 148 ms) and for the semantic retrieval task (mean = 900 ms; SD = 159 ms).

FMRI Results

Figure 1 shows fMRI activations and deactivations for 14 subjects performing an episodic retrieval, working memory, and semantic retrieval task during each of two sessions separated by several months. This study reports on three key results. (1) We found that individual brain activity was unique and persistent in that there was extensive variability in the patterns of brain activations and deactivations across individuals in all three retrieval tasks, yet the individual patterns of activity within an individual were relatively stable over time. (2) Not only were these unique patterns of brain activity persistent over time, they were persistent across different memory tasks. The whole brain activity from the same subject performing different memory tasks across different sessions was more similar than the brain activity from different subjects performing the same memory task. This implies that there are unique aspects of individual brain activity that may transcend the task being performed. (3) Furthermore, we found that some of the variance in the similarity between individual patterns of brain activity could be accounted for by individual differences in decision criterion for the episodic retrieval task, suggesting that individual differences in cognitive processing may account for some of the variance between individuals in the patterns of brain activity across the whole brain.

The Persistence of Unique Individual Patterns of Brain Activity Over Time—A visual inspection of the thresholded maps in Figure 1 reveals an extremely variable pattern of activity from individual to individual. For example, Subject RM in Session 1 during the episodic retrieval task has an extensive pattern of activation along the middle frontal gyrus from Brodmann Area (BA) 4 down to the inferior frontal gryus in BA 44. Some of this activation is also evident in the group map, but not in Subject JK. Subject RM also has some activations in the middle temporal gyrus BA 21 and in the superior parietal lobule BA 7 that are not evident in the group map or in Subject JK. Subject JK has some unique activations in the anterior prefrontal cortex BA 45 that are not evident in the group map or Subject RM as well as extensive deactivations in the posterior occipital and parietal cortex BA 19, 39, and 40. Subject MM in Session 1 has extensive deactivations in posterior regions similar to Subject JK but also extensive activations throughout the motor cortex that are not evident in Subject JK. Subject MM also has strong activations in the extrastriate cortex that can be found in the group map but not in Subject RM or Subject JK. Also, Subject MM has some unique deactivations in the superior frontal gyrus BA 9 and in the inferior temporal gyrus BA 20. Yet, despite the extensive variability between these three individuals, their individual patterns of

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activity are relatively stable from session 1 to session 2. The consistency between sessions in episodic retrieval, which is apparent for most of the subjects, is far greater than the consistency between subjects, even within the same session and the same task.

The results of the correlation analysis replicated our previous findings and confirmed our observation noted above: patterns of brain activity between subjects were extremely variable, yet the individual patterns of brain activity were relatively stable over time (see Figure 2). The correlations submitted to an ANOVA from the same subject performing the same task in different sessions (mean r = .482) were significantly higher than the correlations from different subjects performing the same task (mean r = .224) ($F(1,1132) = 215.00$, MSE = .013, $p < .001$). In addition, we found that there was a significant difference in the correlations between the three memory tasks ($F(2,1128) = 11.76$, MSE = .012, $p < .001$), with the brain activity from the episodic retrieval task being more variable and less correlated between pairs of individuals (mean r = .188) than the working memory task (mean r = .255) and the semantic retrieval task (mean r = .228). Yet, there was no interaction between same or different subjects and task ($F(2,1128) = 1.94$, MSE = .010, n.s.). The relative strength of the persistence of activations within the same subject over time was evident in the fact that the correlations were consistently twice as high when they were between two sessions separated by months for the same subject than when they were between different subjects. This persistence suggests that unique individual activations are not necessarily noise but instead are likely to reflect cognitive processing that is unique to the individual and is related to how the individual performs the task and/or other unique physiological properties relating to that individual.

The Persistence of Unique Individual Patterns of Brain Activity Across Tasks— We not only tested to see whether the brain activity of individuals would persist over time, but we also tested to see whether unique aspects of the brain activity of individuals would persist across different memory tasks. We tested this by cross correlating the t-map volumes across subjects, sessions, and tasks. The main question was whether or not the t-map volumes from the same subject performing different tasks would be more similar to each other than the t-map volumes from different subjects performing the same task.

Figure 3 represents the findings from this analysis. Since the t-map volumes from the same subject in the same session performing the same task could only be correlated with itself, we only compared same subjects in different sessions to different subjects in the same and different sessions (there was no difference in the correlations between same and different sessions for different subjects). An ANOVA found a significant main effect for same or different subjects ($F(1,3482) = 542.01$, MSE = .013, $p < .001$) and a significant main effect for same or different tasks ($F(1,3482) = 36.12$, MSE = .013, $p < .001$). As expected, there was also a significant interaction between subjects and task ($F(1,3482) = 4.88$, MSE = .013, $p = .027$), with the difference between same and different task being greater when the correlations are from the same subject than when the correlations are from different subjects. The most informative comparison, though, was between same subjects in different sessions performing different tasks to different subjects in the same session performing the same task. The similarity between the former volumes (mean r = .350) was significantly greater than the similarity between the later volumes (mean r = .225) ($t(628) = 9.35$, $p < .001$).

Figure 4 presents a graphic example of this relationship from one of the subjects. Subject RM's pattern of activations during the episodic retrieval task in Session 1 was quite similar to both his pattern of activations during the working memory task (r = .583) and his pattern during the semantic retrieval task (r = .690), while Subject RM's pattern of activations for the episodic retrieval task did not approach the same level of similarity with any other subject performing the same episodic retrieval task (ranging from r = .105 to r = .353).

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Note that the variability observed here depends on the contrast between BOLD activity during retrieval trials and BOLD activity during a baseline fixation state. The variability that we report could reasonably be attributed to individual differences in the activity during a baseline state as well as differences in activity during retrieval trials. Indeed, previous studies have demonstrated considerable fluctuations in baseline brain activity (Fox & Raichle, 2007) and Figure 1 reveals as much variability in the deactivations as in the activations. Either alternative is compatible with the finding reported above, that unique individual patterns of brain activity were relatively persistent across memory tasks. However, the two alternatives may lead to very different sources of variability. Therefore, in order to demonstrate that all of the variability that we have observed can not be attributed to individual differences in the baseline state alone, we conducted an identical analysis to the one above, but in this analysis we used the correlations of t-maps derived from the contrast between the retrieval task trials and the control trials (either the subject press the right button in response to the word “right” or the left button in response to the word “left”). The correlations between t-maps derived from retrieval versus control trials were considerably less (mean r = .050) than the t-maps derived from the retrieval trials versus baseline (mean r = .211). This increase in variability may be the result of a contrast more constrained to activity that does not include common activations attributable to perceptual processing and motor control. Despite this difference in overall correlations, we found comparable results when we ran the same analysis as described above. For example, the correlations between the same subjects in different sessions performing different tasks (mean r = .087) was significantly higher than the correlations from different subjects in the same session performing the same task (mean r = .065) ($t(628) = 2.21$, $p = .028$).

In order to further discount the possibility that the effects we observed were simply due to individual differences in baseline activity, we conducted an additional analysis that examined the difference in variability between individuals in the mean raw signal intensity values during retrieval trials versus the mean raw signal intensity values during fixation trials (including all the trials during the rest blocks). If the effects we observed were due to differences in baseline activity, then the mean raw signal intensity values during baseline should have been more variable than during retrieval. However, we found the opposite pattern. The average correlation of whole brain activity during the retrieval trials (.799) was significantly lower (and, therefore, more variable) than during the baseline trials (.801) (paired $t(363) = -2.27$, $p = .024$, 2-tailed). We also found that all the effects reported above held up when we applied the analysis to the mean raw signal intensity values during the retrieval trials only instead of the t-map contrasts between retrieval and baseline. For instance, the average correlation of whole brain activity during the retrieval trials for the same subject performing different tasks in different sessions (.955) was significantly higher than different subjects performing the same task (.799) ($t(1174) = 33.02$, $p < .001$, 2-tailed).

The data that we present in this study clearly indicates that unique individual patterns of brain activity persist across different memory tasks. However, we do not know if this persistence across tasks would be present for tasks that are much less related to each other than the tasks in this study. It is certainly the case that there is a large degree of overlap in brain activity between episodic retrieval, working memory, and semantic retrieval (Ranganath, Johnson, & D’Esposito, 2003; Nyberg et al., 2003).

Possible Sources of Individual Variability in the Pattern of Brain Activity—The persistence over time suggests that differences in brain activity between individuals could be indicative of individual differences in cognitive and/or physiological processes and not random processes. Furthermore, the persistence across tasks suggests that some of these systematic differences could transcend the tasks themselves. Are these individual differences in brain activity epiphenomenal? For example, individual differences in vasculature could drive individual differences in brain activity that has very little to do with task-related activity.

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Although we attenuated differences in vasculature by relying on a contrast between task-related activity and baseline activity for most of our analyses, this does not completely rule out the possibility that differences in basic physiology could be contributing to the observed effects in task-related activity. We assume there are many possible factors that could be contributing to individual differences in brain activity, including individual differences in cognitive processing, psychological states or traits, physiology, anatomy, personality, and genetics. Although a full investigation of these various factors was beyond the scope of this study, we did have some factors representing individual differences in memory performance during the episodic retrieval task that we could explore post hoc[2]. Those factors included individual differences in memory accuracy (d'), response criterion (C), and reaction time. In addition, we could also examine individual differences in spatially-normalized anatomy.

In order to test whether or not any of the factors mentioned above could account for any of the variance that we observed in the degree of similarity between any two brain volumes, we conducted a hierarchical regression analysis of the values derived from the rank-order cross correlation of the t-maps across different subjects for the episodic retrieval task only. The predictor variables were entered in a predetermined order (see Table 1) as follows:

Block 1: *difference in the extent of significant activity*. This nuisance variable represented the difference in the extent of significant activations and deactivations between the two volumes being correlated. The extent for each volume of t-maps was derived by counting the number of voxels above a statistical threshold of $p < .001$ uncorrected for multiple comparisons. Although our use of unthresholded t-maps in the correlation analyses attenuates this factor to a large degree, we were still concerned that the variations in correlations between t-maps could have been driven in part by the difference in the extent of voxels that reach a significant t-value[3].

Block 2: individual difference factors - *difference in d prime values, difference in reaction time, difference in criterion values*, and *difference in anatomy*. All of these factors were entered stepwise. The three performance factors were derived by taking the absolute difference between the two subjects being correlated. That is, could the difference in performance between the two subjects account for the similarity in their two patterns of brain activity? The difference in anatomy was derived by correlating their spatially-normalized high-resolution anatomical brain volumes. The similarity between any two individuals' anatomy was measured using the same method we used to measure the similarity in functional brain activity, in this case, by cross correlating the high resolution anatomical T1 images after they have been preprocessed and spatially normalized. Could similarity in structural anatomy account for similarity in functional activity?

Block 3: *individual deviations*. This represented a set of n-1 dummy variables to represent the different individuals (i.e. a dummy variable that denoted whether or not that individual was one of the two volumes being correlated – this is a measure of to what degree any given individual contributes to the observed variability). Some individuals may be more deviant in their pattern of brain activity than others, and these variables capture the degree to which these individuals can account for the

[2]There was not enough variance in the working memory task to obtain stable measures of performance and there were no correct/incorrect responses in the semantic retrieval task, so our analyses here focuses on the episodic retrieval task only.

[3]For example, the correlation between Subject JM in session 1 of the episodic task and Subject CT in session 1 of the episodic task was only .179, while the correlation between Subject JM and Subject JW was .303. But that difference between the correlations may have been explained by the fact that Subject CT had many fewer significant voxels than Subject JM (a difference of 3541 voxels) compared to Subject JW who had a similar amount of significant voxels as Subject JM (a difference of 129 voxels). In another words, the low correlation between Subject JM and Subject CT may not have been the result of activity in different locations, but activity in Subject CT that was in the same locations as Subject JM but failed to reach the same level of significance.

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variance in the correlation values above and beyond the individual difference factors that we already identified.

The results are summarized in Table 1. The full model accounted for 50% of the variance in correlation values. The model takes into account the nuisance variable first, which was significant (R^2 change = .026, $F(1,362) = 9.85$, $p = .002$). The *individual deviations* variables that were entered last were also significant as a block (R^2 change = .446, $F(13,348) = 23.73$, $p < .001$). Within the second block of individual anatomy and performance factors that were entered stepwise, only the *difference in criterion values* accounted for a significant portion of the variance in the degree of similarity between individuals' patterns of brain activity (R^2 change = .026, $F(1,361) = 9.67$, $p = .002$). Figure 5 compares the relationship of criterion differences and performance differences to the correlation values. It should be noted that the criterion values used in this variable were specific to individuals in particular sessions since the stability of a criterion setting within an individual across sessions was relatively weak ($r(14) = .24$). Nevertheless, the bigger the difference in criterion values the less similar the patterns of brain activity.

This relationship between the difference in criterion values and the degree of similarity in brain activity indicates that some of the variance in brain activity between individuals can be accounted for by individual differences in retrieval strategy and/or general response bias. The placement of a decision criterion during a recognition test is often the result of a general strategy or bias (Murdock, 1974; Ratcliff, Sheu, & Gronlund, 1992; Miller & Wolford, 1999). For example, some subjects may have only responded "old" to a test item if they were absolutely certain they encountered the item during the study session (maybe based on some clear visual recollection). The criterion measures from those subjects would have tended to be conservative. For example, in a debriefing after the scanning session, Subject MM stated that "I only said 'recognize' when I was pretty certain," and her criterion measure reflected a conservative strategy ($C = +.46$). Other subjects may have simply responded "old" to any item that seemed familiar to them regardless of whether or not they had a clear recollection of the item in the study session. For example, Subject CT stated that "the recognition test was kind of hard, but I would just press yes if the words seemed familiar." Her criterion measure ($C = -.23$) reflected a much more liberal strategy, one based more on familiarity. A large difference in criterion values between two subjects may reflect very different strategies and/or styles that predict less similar patterns of brain activity.

Further, it should be pointed out that our other performance measure, *difference in d prime values*, was not significantly related to the degree of similarity in brain activity, despite the fact that d prime values were more variable across subjects than criterion values. Differences in memory performance did not account for a significant portion of the variance despite the fact that much previous fMRI work has consistently shown that differences in memory performance can modulate brain activity in certain common areas of activation, such as the medial temporal lobe (Nyberg et al., 1996; Tulving et al., 1999). While differences in memory strength or performance may modulate the strength of activity in certain critical regions, differences in memory strength between individuals may not produce dramatic differences in the topography of brain activity across individuals.

Episodic memory is known to rely on an extensive hippocampal-cortical network for the consolidation, storage, and utilization of information (Squire et al., 1992; Wittebenrg & Tsien, 2002; but see also Nadel & Moscovitch, 1997). A principle characteristic of this distributed network is that it affords the rapid and flexible formation of multimodal memories. Many memory researchers have suggested that prefrontal and parietal areas support episodic memory with cognitive processes peripheral to the actual retrieval process such as temporal sequencing, retrieval orientation, working memory, source monitoring, and many others (Shimamura, 1995; Fletcher et al., 1998; Moscovitch & Winocur, 2002). Therefore, we suggest that the

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emerging picture of the neural basis of episodic retrieval is a network comprised of several distinct brain regions that may be engaged differentially depending on unique individual strategies. Recent neuroimaging studies have demonstrated that specific brain regions are differentially activated depending on individual differences in strategy during an episodic memory task (Kirchhoff & Buckner, 2006). 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 individuals, and that episodic memory can recruit multiple cortical routes to accomplish the same task. The same principle may apply to working memory tasks and semantic retrieval tasks, but we did find differences in variability between the tasks that suggest that the extent of brain regions that are variably engaged during those tasks are more constrained.

It should also be noted that there are many possible individual difference factors that could account for the degree of similarity between any two patterns of brain activity. We found that the correlation between two individuals' high-resolution anatomical brain volumes (*difference in anatomy*) had no relationship to the degree of similarity between individuals' functional brain volumes, but we suspect that finer measures of individual differences in anatomy or physiology could certainly be related to correlations of BOLD responses. To that point, our results suggest that most of the variance in brain activity that can be attributed to individual differences has yet to be identified. This is evident in the finding that the variables representing *individual deviations* still accounted for 40% of the variance in the correlation values after taking into account individual differences in criterion value and reaction time (8.4% of the variance). As shown in the individual t-maps and the corresponding correlation values depicted in Figure 1, 11 out of 14 individuals' patterns of activations were extensively different from the group means (Subjects SR, JW, and CR being the exceptions). In other words, nearly all of the subjects' patterns of activity do not look like the pattern of activity represented in the group map. A critical question for future research is what makes these individuals so different?

General Discussion—Individual patterns of brain activity are extremely variable across a variety of memory tasks. These unique patterns of activity are persistent over time, and they are persistent across different tasks. And some of the variance in these individual patterns of brain activity can be accounted for by individual differences in cognitive processing.

In the early days of neuroimaging, many of the pioneers of the technique worried that averaging data across subjects may greatly diminish the signal due to inherently high individual variability in activity patterns (Raichle, 1997). Yet, those early studies, in which subjects passively viewed a rotating checkerboard, reliably demonstrated retinotopic mapping of the primary visual cortex using a group map (Fox et al., 1986). Shortly thereafter, other neuroimaging studies validated the use of group maps for higher-order cognitive tasks as well (Petersen et al., 1988). Since that time, group maps have become much more sophisticated and population-based, and more emphasis has been placed on them in attempts to overcome the inherently low overall signal-to-noise ratio of neuroimaging data. It is interesting to note, however, that many vision researchers have reverted back to relying on individual data by retinotopically mapping individuals and testing hypotheses on an individual basis with many trials (Warnking et al., 2002). In addition, many researchers are relying on functional localizers in several tasks due to individual differences in the specific location of specialized regions within the brain (Saxe, Brett, & Kanwisher, 2006). While a group map can be very effective as a tool to increase the signal-to-noise ratio in a study that is investigating an a priori hypothesis involving some particular brain region, we argue that group maps can be a problem if they are meant to characterize or profile the pattern of activity across the whole brain for a given task. That is, a group map may fail to capture the full extent of activity underlying a memory task that is evident at the individual level.

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Little attention has been paid to the underlying causes of the variability in the patterns of brain activity between individuals, though many researchers using neuroimaging techniques acknowledge that it is an issue. In general, most neuroimaging studies involving individual differences can be divided into four 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; and 4) studies that look at the degree to which group activations are reproducible. We have reviewed each of these techniques previously (Miller & Van Horn, 2007) and each of these techniques are informative in their own right. For example, a convincing way to demonstrate the function of a given brain region is to show that the activity in that region is modulated by individual differences in performance. 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 (Heun et al., 2000; Machielsen et al., 2000; McGonigle et al., 2000; Miller et al., 2002; Feredoes & Postle, 2007; Seghier et al., 2008). The results we report in this study advance our knowledge regarding the individual variability in brain activity in two ways: we have found that 1) some unique patterns of individual brain activity persist across different tasks, and 2) a significant portion of the topographical variability can be accounted for by individual differences in cognitive processing.

Future models of the brain regions underlying an episodic retrieval task (and possibly many other tasks as well) will need to consider the variable engagement of various brain regions from individual to individual. Our data suggest that there are multiple routes within the brain that can be used to accomplish an episodic retrieval task and that different individuals may instantiate different routes. Previous studies in behavioral research have demonstrated that models developed by averaging across individuals alone can be misguided and misleading (Estes, 2002; Gallistel et al., 2004). Models of brain activity face the same peril (see Feredoes & Postle, 2007). Unique and persistent individual patterns of brain activity must be considered and understood.

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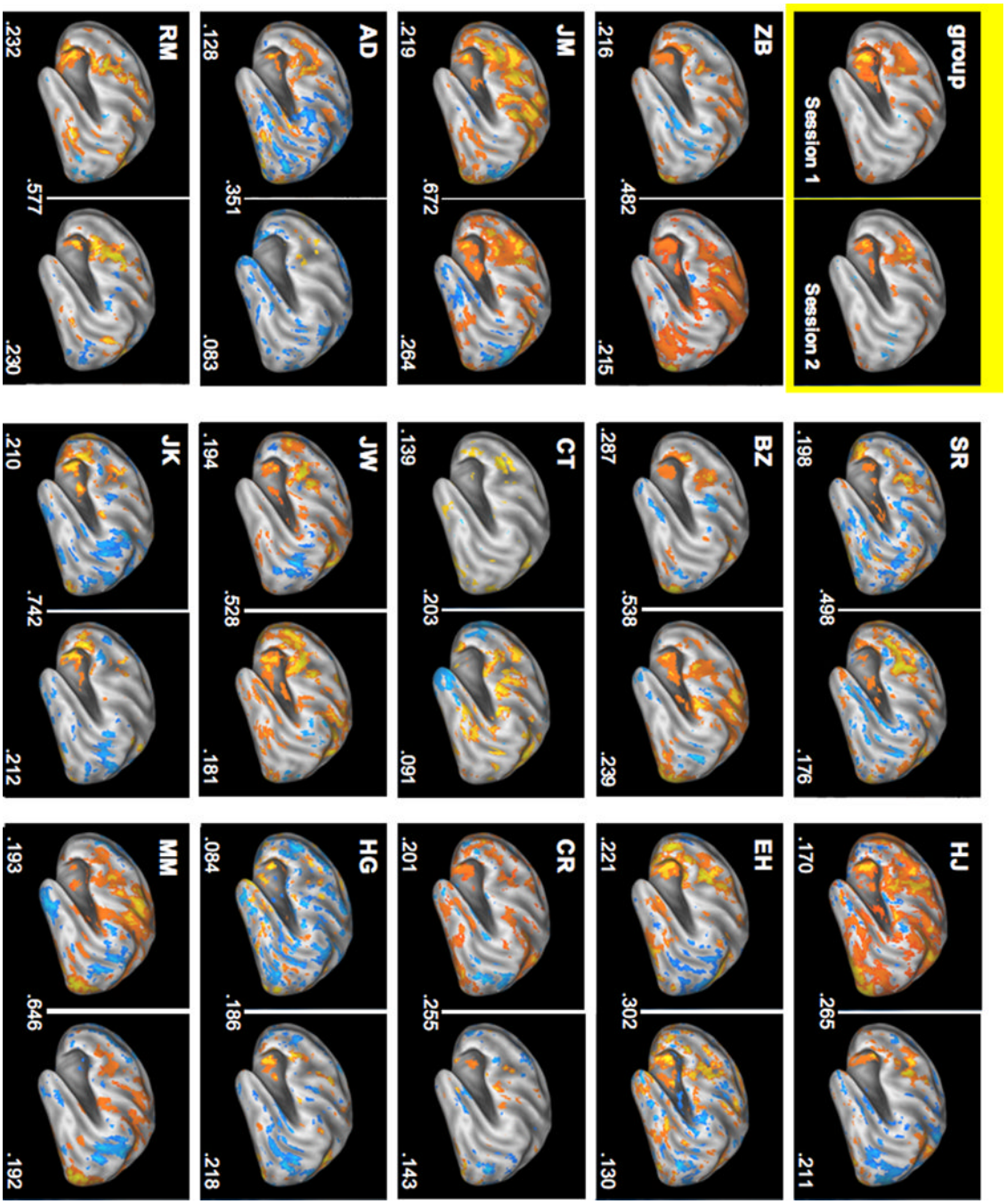

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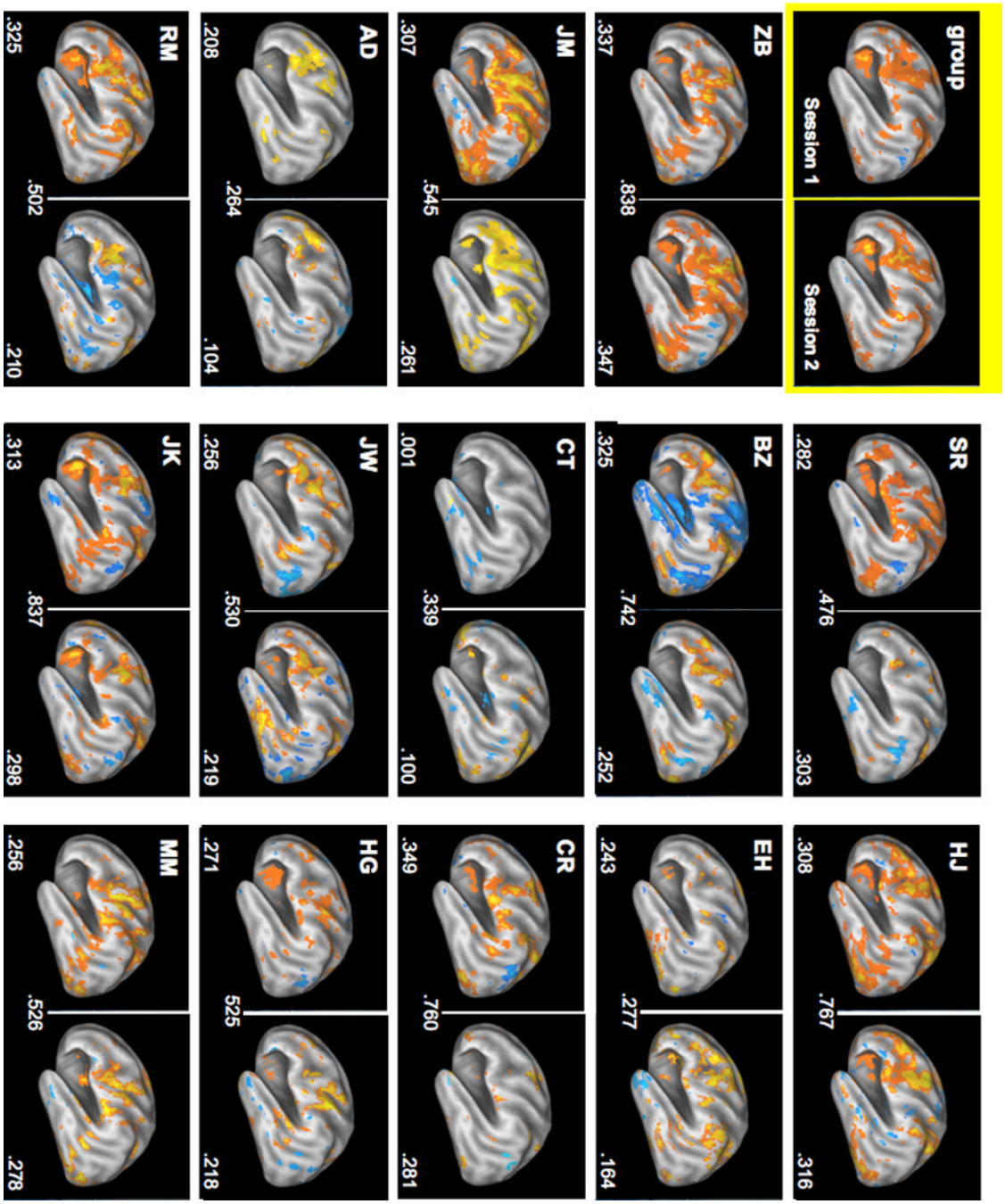

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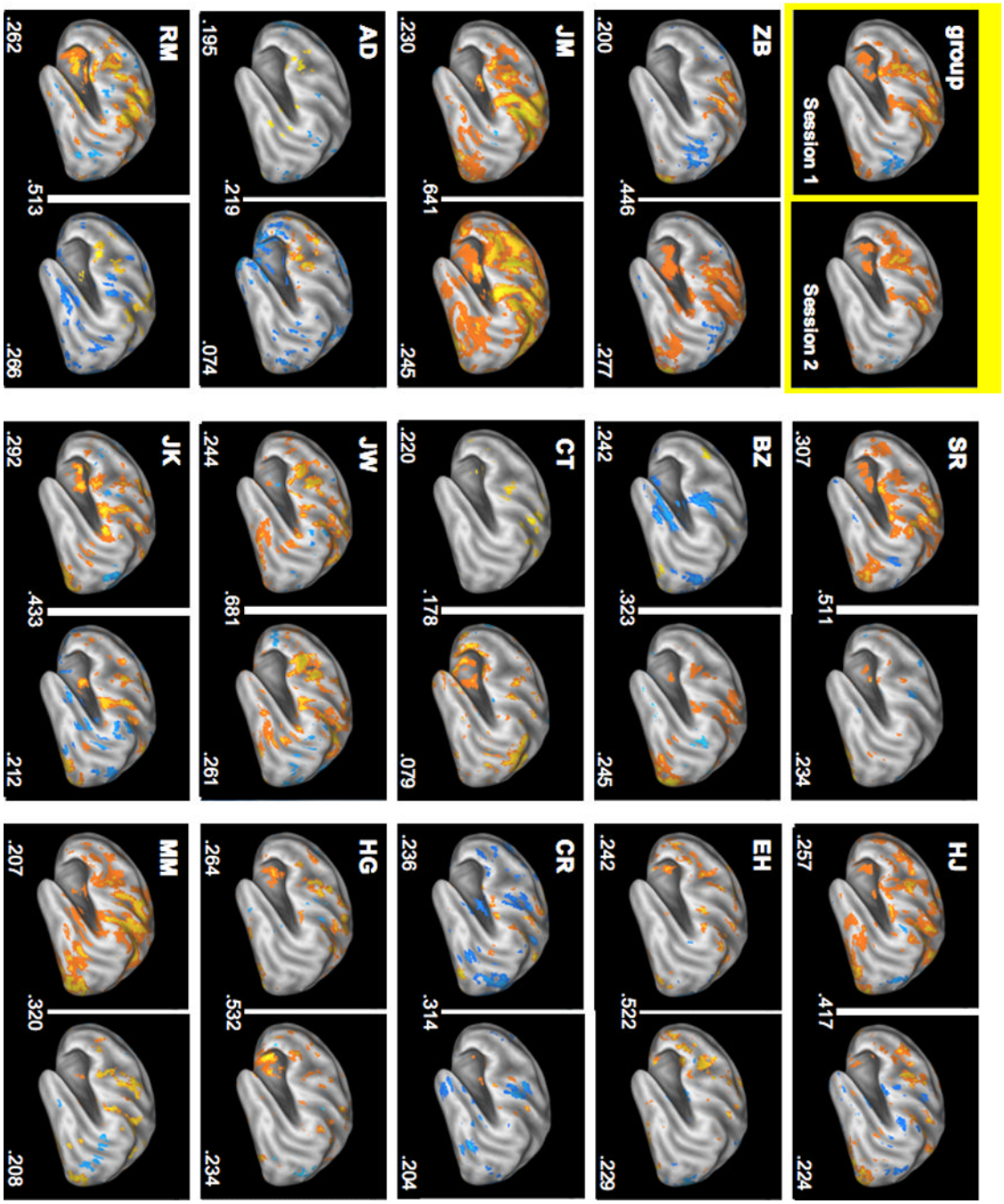

Figure 1.

The left hemisphere patterns of activations and deactivations for the group and for all 14 individuals that make up the group for the episodic retrieval task (a), the working memory task (b), and the semantic retrieval task (c). Each panel includes a random effects group analysis and 14 individual t-maps for each of the two sessions. The random effects group map (statistically thresholded at $p < .01$ uncorrected for multiple comparisons) and the individual t-maps ($p < .001$ uncorrected threshold) are a contrast between the retrieval condition and baseline. The liberal thresholding was done for visualization purposes only. Displayed for each individual is the degree of similarity (correlation) between the two sessions within that individual (the number in the middle), and the average degree of similarity (correlation)

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between that individual's t-map volume in that session with every other individuals' t-map volumes. The former correlation value provides an indication of the persistence of individuals' patterns of activity over time, and the latter correlation value provides an indication of the average degree of similarity between that individual and all the other individuals.

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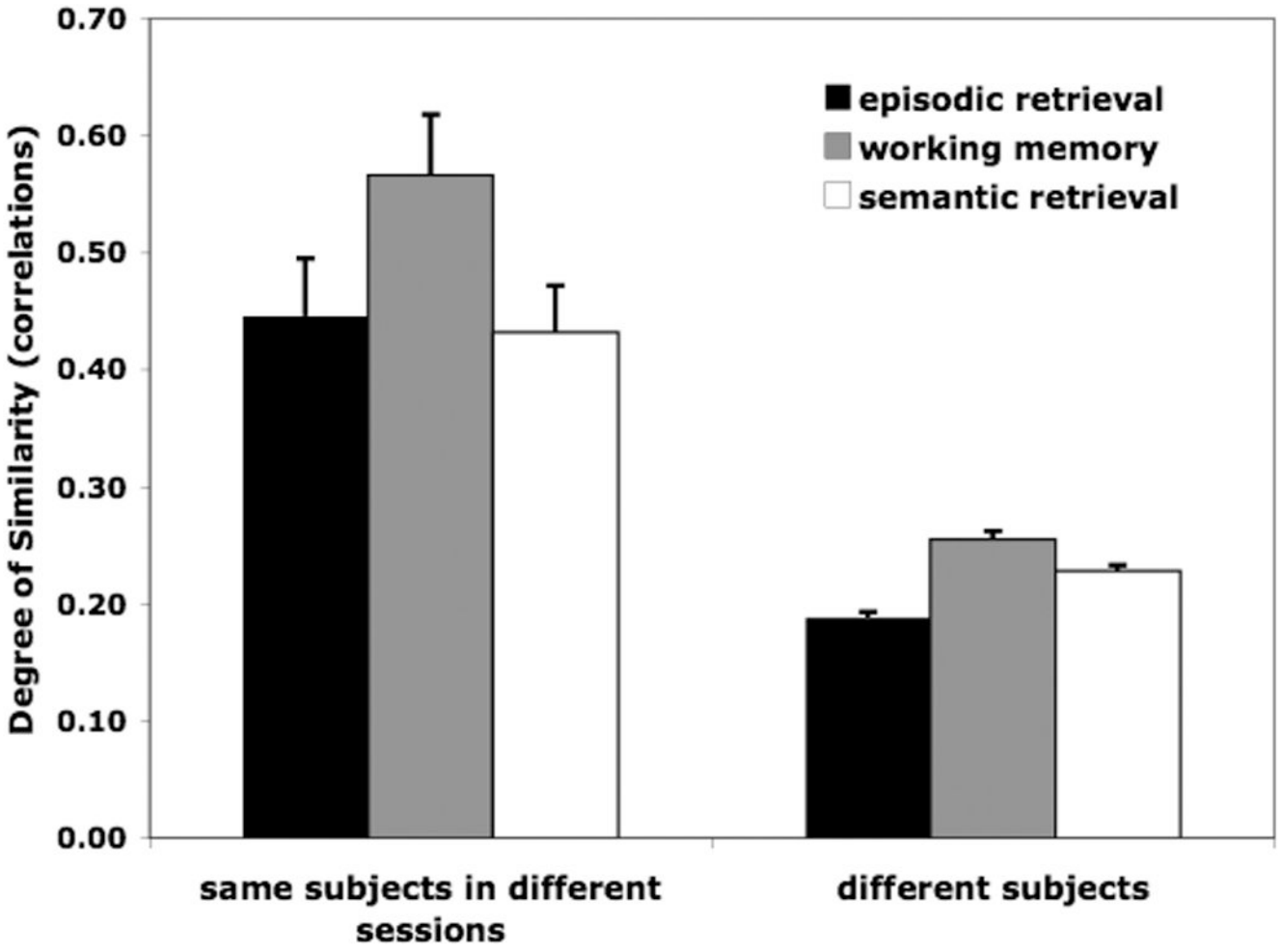

Figure 2.

The persistence of unique individual patterns of brain activity over time for all three memory tasks. Brain activity from the same individual performing the same retrieval task but from sessions separated by two to four months were significantly more similar to each other than the brain activity from two different individuals performing the same task. Further, the degree of similarity between different individuals' brain activity was lower for the episodic retrieval task than for the working memory task or the semantic retrieval task.

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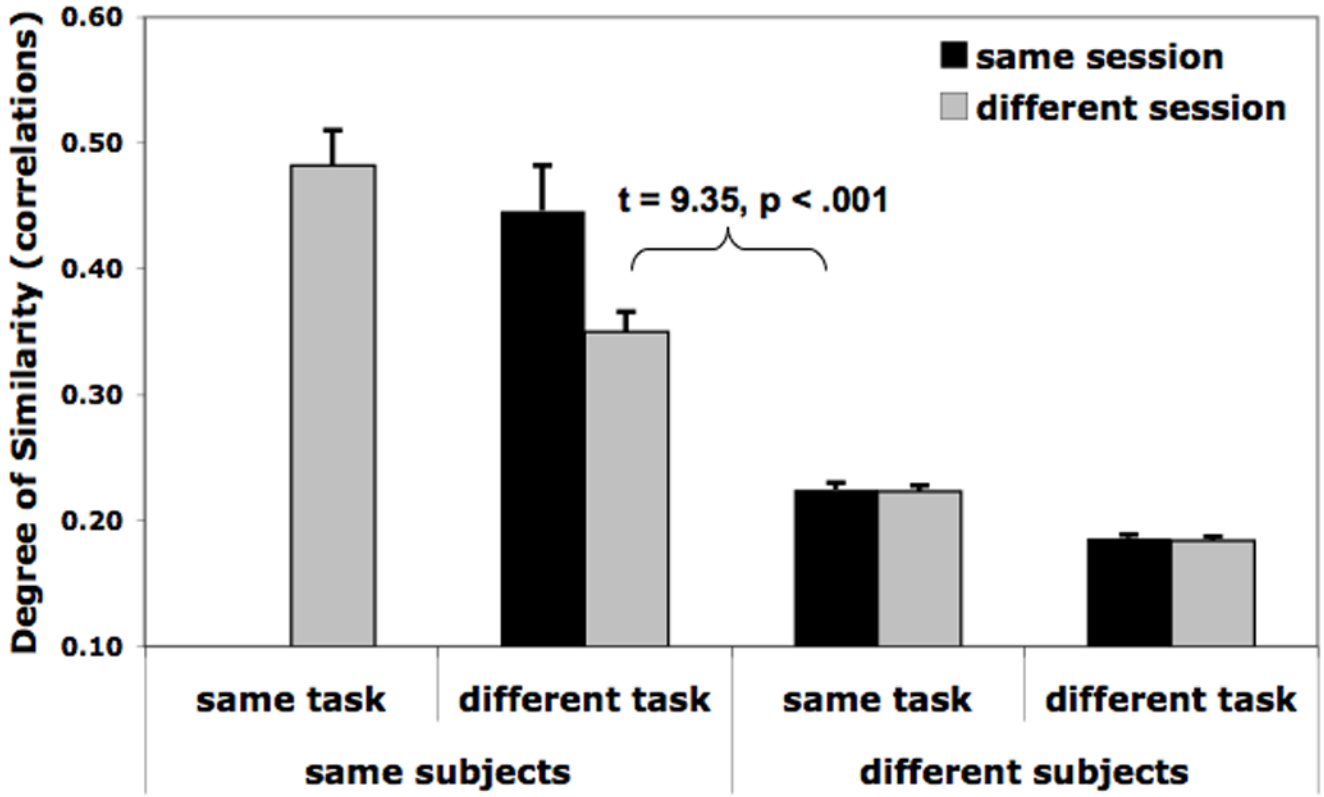

Figure 3.
The results of a cross-correlation across subjects, tasks, and sessions. Two significant predictors of the degree of similarity between two brain volumes are whether or not the two volumes are from the same subject and whether or not the two volumes are from the same task. Surprisingly, brain activity from the same subjects performing different retrieval tasks from different sessions are significantly more similar to each other than the brain activity from different subjects performing the same retrieval task in the same session.

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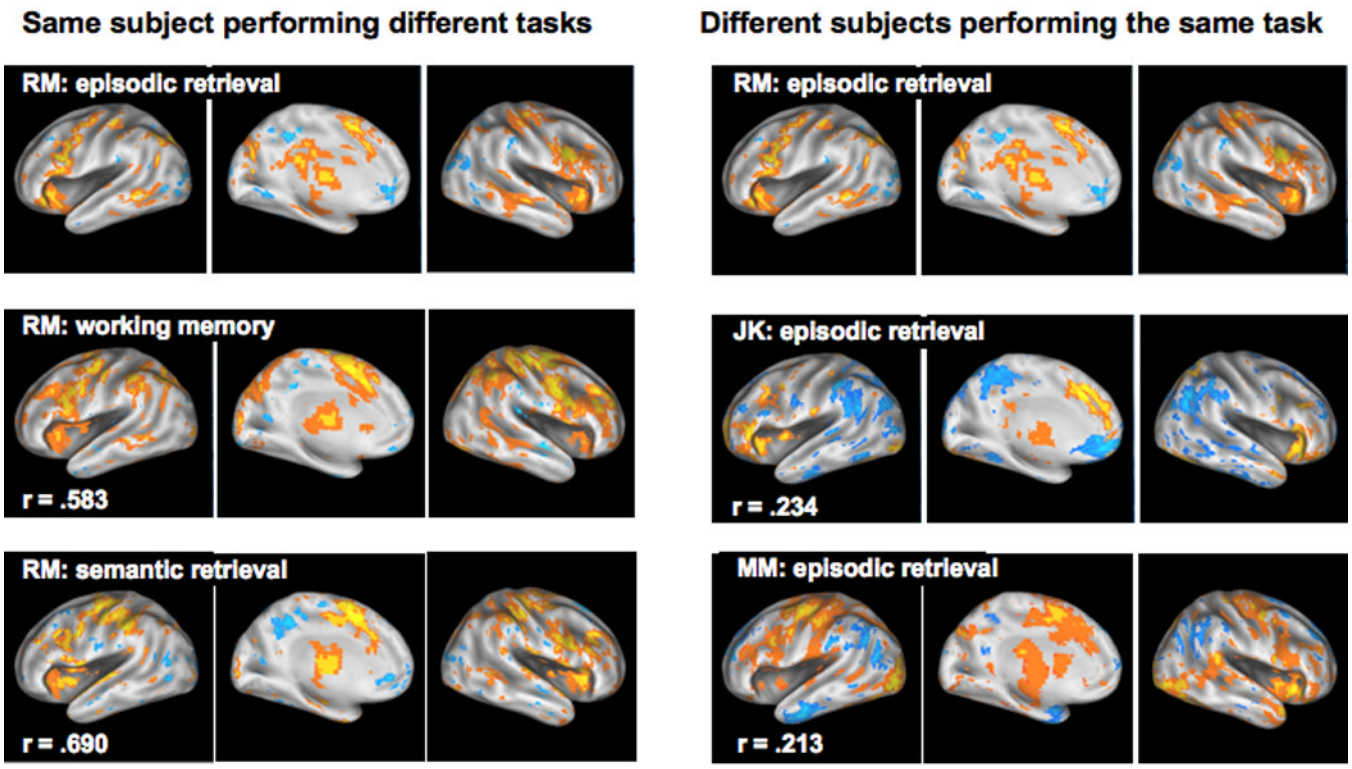

Figure 4.

A graphic example of the similarity in brain activity of the same subject performing different tasks compared to different subjects performing the same task. On the left are the thresholded t-maps (a lateral view of the left hemisphere, a medial view of the left hemisphere, and a lateral view of the right hemisphere) from Subject RM performing an episodic retrieval task, a working memory task, and a semantic retrieval task. On the right are the thresholded t-maps of Subject RM and two other subjects all performing the same episodic retrieval task. On the left of the bottom two panels on each side is the correlation (using unthresholded t-maps) between that panel and the top panel from Subject RM. These individual maps were statistically thresholded at $p < .001$ uncorrected for multiple comparisons for visualization purposes only.

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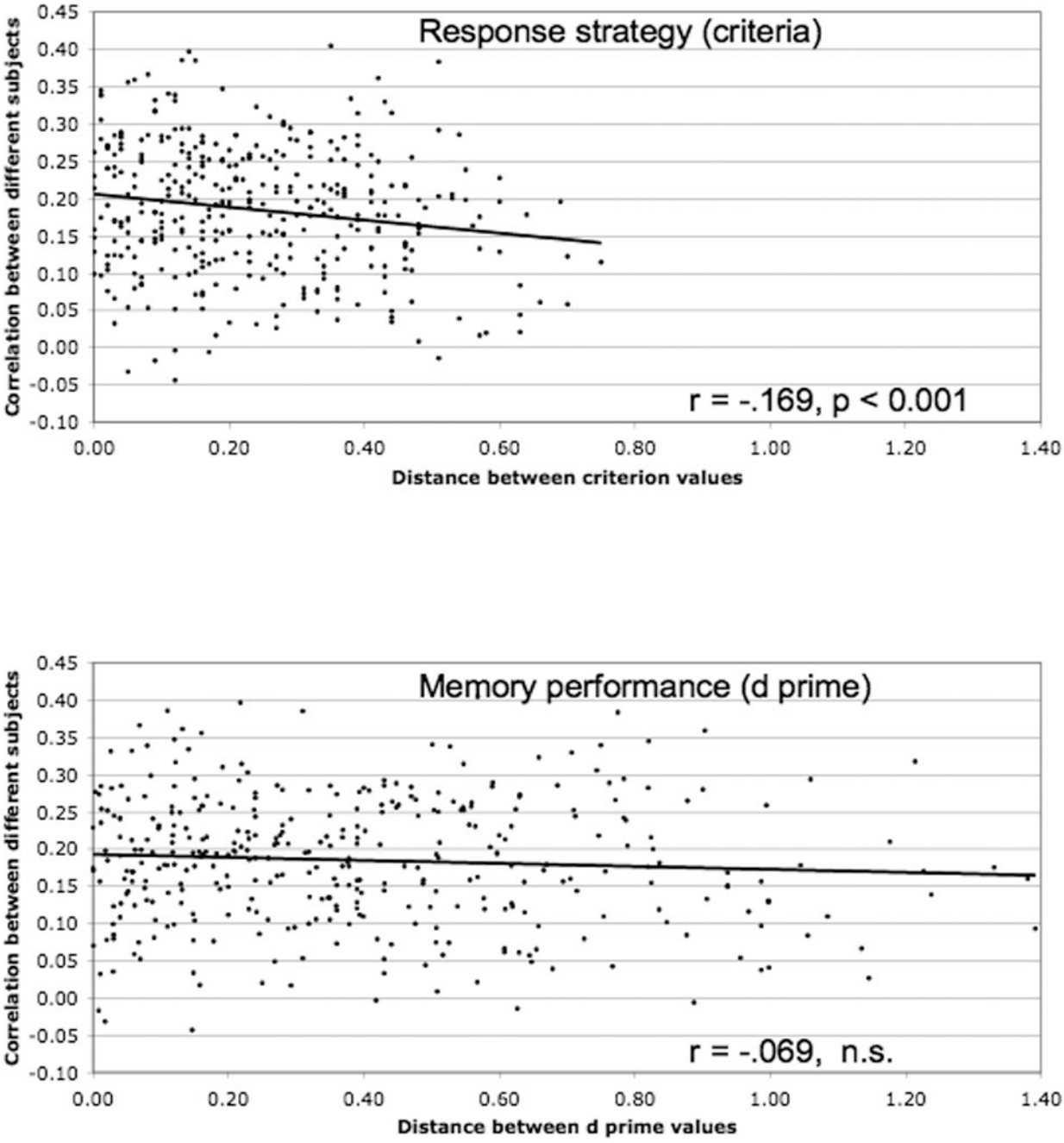

Figure 5.

A possible source of the intersubject variability during the episodic retrieval task are individual differences in retrieval strategy. The difference in the criterion values between two individuals (panel a) was a significant predictor of the degree of similarity in those two individuals' brain activity, but not the difference in the d prime values (panel b).

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Table 1

Possible Sources of Variability:Hierarchical Regression Analysis of Correlation Values Between Different Subjects During the Episodic Retrieval Task (R^2 = .50)

Steps	Factors	R^2 Change	Beta	Sign. F Change
Block 1	Difference in extent of significant activity	.026	−.163	.002
Block 2 (stepwise)	**Difference in criterion values**	**.026**	**−.160**	**.002**
	Difference in reaction time	--	--	n.s.
	Difference in d pirme values	--	--	n.s.
	Difference in anatomy	--	--	n.s.
Block 3	Individual deviances	.446	−.372*	< .001

* This beta comes from one of the thirteen dummy variables contributing to this factor, this one representing the individual with the strongest correlation.