Extensive Individual Differences in Brain Activations Associated with Episodic Retrieval are Reliable Over Time

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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 the present study, 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 go beyond the relatively small variations due to cyctoarchitectonic differences or spatial normalization. We quantify this individual variability by cross-correlating volumes of brain images. We demonstrate that individual patterns of brain activity are reliable over time despite their 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 believe that individual analysis in conjunction with group analysis may be critical to fully understanding the relationship between retrieval processes and underlying brain regions. ■

INTRODUCTION

In the 1800s, Paul Broca argued 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 the 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 & Critchley, 1998). Since that time, neuropsychologists have continued to debate issues of case studies versus group studies of patients in a variety of cognitive domains (Robertson, Knight, Rafal, & Shimamura, 1993; Sokol, McCloskey, Cohen, & Aliminosa, 1991; Caramazza, 1986). 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 (McGonigle et al., 2000; Aguirre, Zarahn, & D'Esposito, 1998; Dehaene et al., 1997; Kosslyn, Thompson, Kim, Rauch, & Alpert, 1996; Watson et al., 1993; Grafton, Woods, Mazziotta, & Phelps, 1991; Grafton, Woods, & Tyszka, 1994)? Some investigators have been particularly concerned about individual variability in task comparisons that involve higher order cognitions (e.g., McGonigle et al., 2000). Not only is it known that higher order cognitions involve variable strategic processes, it is also known that the more "associative" the cortex becomes, the more variable the location of specific gyri, sulci, and associated function (Mesulam, 1985). In the present study, we demonstrate striking individual differences in brain activity associated with episodic retrieval, differences that go beyond the expected variations due to individual differences in cytoarchitectonics and warping due to spatial normalization. In the case of episodic retrieval (a task known to be closely associated with variable individual strategies), functional localization based on group activation maps may be very different from the data based on individual activation maps. 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. Methods for coregistration have also improved, allowing for better pooling of data across subjects and emphasis has been placed on the minimization of noise associated with registration error (Friston, Holmes, & Worsley, 1999). Individual variability associated with episodic retrieval may be due to processes other than registration noise. It may be critical to understanding the true nature of this particular cognitive process. Furthermore, we will

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demonstrate that these large variations in individual activity associated with episodic retrieval are stable over time within subjects.

Some of the first investigators to use neuroimaging methods debated whether to rely on group averaging. Some of these investigators believed that averaging might show no activations in the brain because of individual differences (Raichle, 1997). Group averaging, however, was quickly validated in these first studies by showing that retinotopic mapping of the primary visual cortex occurred in response to a flashing checkerboard in the appropriate visual field (Fox et al., 1986). Even early positron emission tomography (PET) studies using group analysis to localize higher order cognitive tasks, such as the auditory processing of words using PET (Petersen, Fox, Posner, Mintun, & Raichle, 1988), showed relative consistency across subjects. These findings have been repeatedly confirmed using functional magnetic resonance imaging (fMRI). A recent study showed consistent localization in the posterior superior temporal gyrus across multiple subjects despite some individual variability within that gyrus (Burton, Noll, & Small, 2001). The question we address is not whether group averaging is a valid method for localizing functions, but whether activations that are uniquely individual are also critical to a task (particularly a higher order task like episodic retrieval). In this study, we address this issue by retesting subjects months later in the same task and see whether they produce the same individual patterns of activations.

As mentioned previously, several other neuroimaging studies have also concerned themselves with individual variability. Aguirre et al. (1998) examined the individual variability in the time course of the hemodynamic response that is critical to the modeling of event-related fMRI designs. Klein, Paradis, Poline, Kosslyn, and Le Bihan (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. So they analyzed individual subjects and found variability of activations around the calcarine sulcus. Other studies have examined the relationship between task performance and measures of blood flow for particular regions in individual subjects, including 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), and word recognition and the medial temporal lobe (Nyberg, Cabeza, & Tulving, 1996). Our study differs from these previous neuroimaging studies because of the extent of the variations (most previous studies dealt with variability within a circumscribed region) and because we will attempt to demonstrate that individual activity associated with episodic retrieval is reliable over time despite extensive individual variations.

Episodic retrieval may be particularly relevant to the study of individual differences. Despite the fact that many researchers in other areas of cognitive neuroscience have investigated individual differences in activations (e.g., mental imagery and motor sequencing), most previous neuroimaging studies involving episodic retrieval have relied on group analyses. A review of the specific sites of activation associated with episodic retrieval showed that the sites have varied greatly from study to study using similar procedures, indicating a general inconsistency in localization (see Cabeza & Nyberg, 2000, for a review of these studies). Cabeza and Nyberg (2000) list 52 studies on episodic retrieval. The general characterization of these studies is that episodic retrieval produces activations predominantly in the right anterior prefrontal cortex. Yet, if we define the right anterior prefrontal cortex as anything in Brodmann's areas 9, 10, 11, or 46, then only 23 out 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 contrasts, very little consistency is shown across studies anywhere in the brain, including the prefrontal cortex and the parietal lobe. Furthermore, despite this inconsistency in localization, only 1 of the 52 studies showed individual activations. This study focused on activations in the left and right prefrontal cortex during an episodic retrieval task in four subjects (Nolde, Johnson, & D'Esposito, 1998). Two other studies discussed individual differences but did not show the individual activations. One study correlated recognition performance with activation in the medial temporal lobe (Nyberg et al., 1996), and the other study discussed how well individual patterns of activations fit the group average (Fink et al., 1996). We believe individual differences in activation associated with episodic retrieval may reflect individual differences in strategies and approaches to the retrieval task. Extensive individual variability explains the lack of consistency in localizing episodic retrieval from study to study using only group analysis.

Many neuroimaging studies now use a random-effects model to produce group activation maps. It is generally accepted that random-effects models, in contrast to fixed-effects models, assess the variability in activation effects from subject to subject (Friston et al., 1999), allowing inferences to be made from a group of subjects to the general population. The group activation maps produced in our study also used a random-effects model (Miller, Handy, Cutler, Inati, & Wolford, 2001). 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. However, if these activations are simply noise, then they

should not appear after retesting the same individual in a different session.

In this study, some of the original subjects will be retested using the same procedures and materials used to assess activations associated with episodic retrieval. We devised a method to quantify the relationships across subjects and sessions that does not depend on particular statistical thresholds. In data analysis using Statistical Parametric Mapping (SPM99), activation thresholds may be shifted more liberally or more conservatively in a way that can greatly affect the degree to which activations overlap with each other. In order to avoid this confound, we correlate volumes of images using normalized raw signal intensity values taking into account the hemodynamic response function. This provides correlation values across conditions, sessions, and subjects. We enter these correlation values into a regression equation in order to test the statistical significance of particular variables, such as whether the image volumes were from the same or different subjects. If activations from individuals are extremely variable from subject to subject but consistent across sessions, then same subject should account for a significant amount of the variance in correlation values. Furthermore, we can compare the degree to which same subject accounts for the variance in correlational values with the degree that same condition versus different conditions accounts for the variance. We will also conduct a fixed-effects analysis of variance again using raw signal intensity values to show brain voxels with a significant subject by condition interaction. In addition, we will conduct a regression analysis using correlational values from signal intensity changes between two conditions that is less susceptible to individual variations in vascular structures.

RESULTS

Out of the nine subjects that participated in the original experiment (Miller et al., 2001), six agreed to be retested. All methods, procedures, and analysis used for the retesting were identical to the ones published in Miller et al. (2001). The original study used various retrieval conditions in order to compare activations produced by various contrasts. In this study, we will focus on the contrast between an episodic retrieval task (all retrieval conditions collapsed together) and a nonretrieval control task (manually responding to a nonword) because this contrast produced the most significant activations and because it turned out to be the least variable between subjects. The functional scans included random alternations of blocks of retrieval and nonretrieval conditions. The episodic retrieval task was word recognition. Prior to scanning, subjects studied 168 unrelated words. During retrieval blocks of the functional scan, subjects were instructed to respond either "old" or "new" using a button press to each word. During nonretrieval blocks, subjects were instructed to respond alternately with the right and left buttons to a row of Xs.

Observations of Individual Variability

The initial analysis of individual variability associated with episodic retrieval was based on data collected in Miller et al. (2001). For the present study, the contrast of

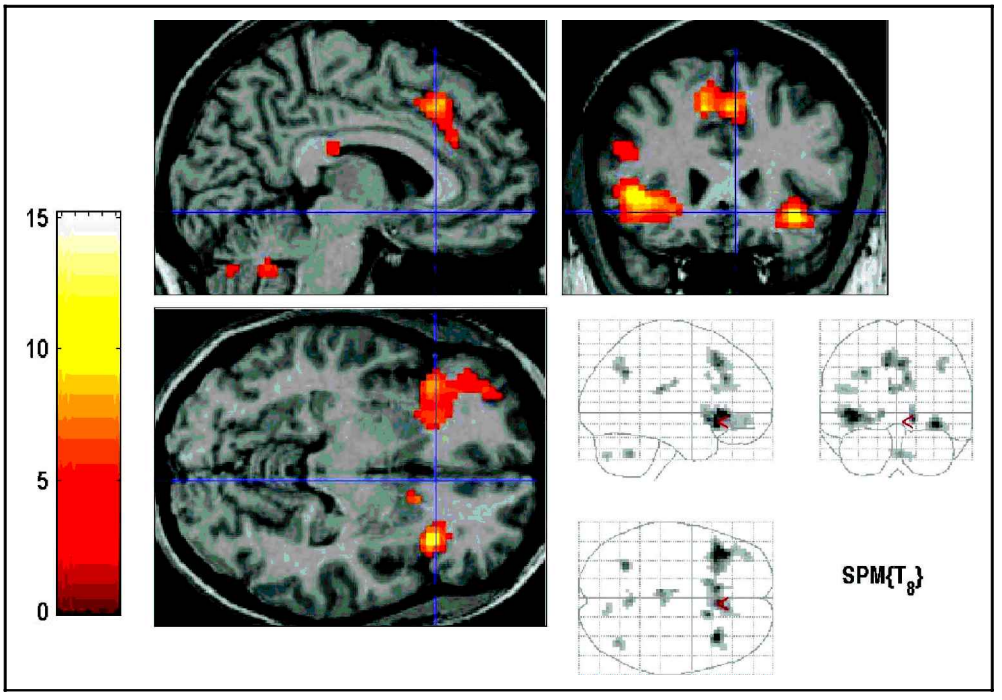

Figure 1. Group-level activations for recognition of words versus a baseline condition from Miller et al. (2001). Group activations are from 9 subjects using a random-effects model showing all voxels above the statistical threshold of $p < .001$ uncorrected for multiple corrections with a minimal voxel extent of 10. The functional data are superimposed over a spatially normalized high-resolution anatomical image in three planes revealing activations bilaterally in the inferior frontal gyrus and the anterior cingulate. Next to these images are glass-brain representations revealing all clusters of activations above the threshold throughout the whole brain.

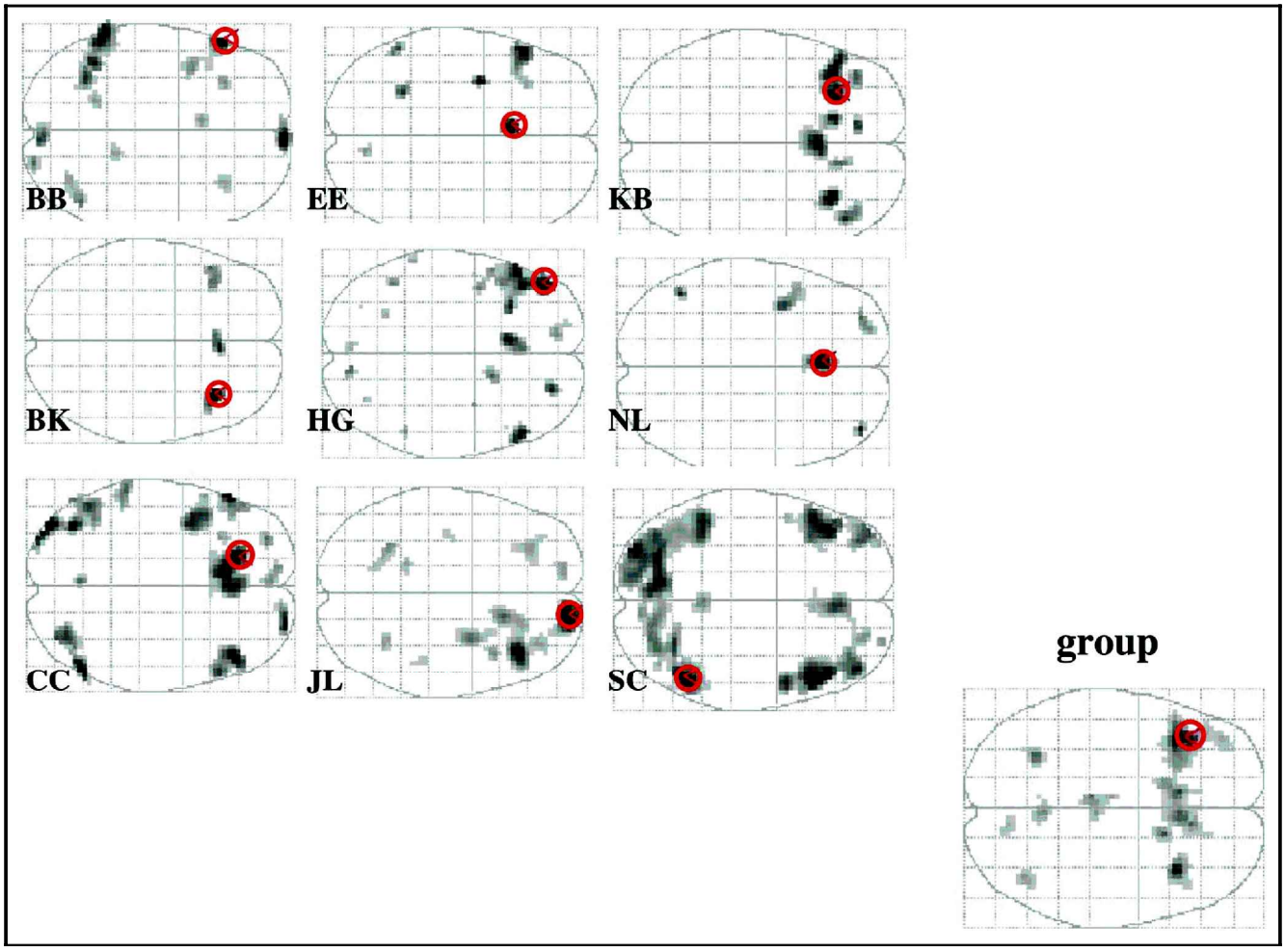

Figure 2. An axial view of glass brain representations of significant activations associated with episodic retrieval for each of the 9 subjects that contributed to the group activation map shown in Figure 1. On the bottom right is the axial view of the group activation map. Circled in red are the most significant voxels for each individual and for the group.

interest is global episodic retrieval (responding "yes" or "no" to whether a word was presented before, collapsed across all retrieval conditions) versus a nonretrieval condition (responding to a row of Xs). The group activation map shown in Figure 1 was based on nine subjects using a random-effects model (one-sample t test), statistically thresholded to reveal all voxels above $p < .001$ uncorrected for multiple comparisons with a minimum voxel extent of 10. This group analysis revealed highly significant activations (with t values greater than 15) in the left and right inferior frontal gyrus, the anterior cingulate, the left angular gyrus, the right inferior parietal lobule, and the right caudate (see Figure 1).

As shown in Figures 2 and 3, most individual patterns of activation (from which the group's statistical map is derived) are not only different from the group, but also different from each other. Individual maps were based on the general linear model (SPM99; Friston et al., 1995) to reveal all voxels above a statistical threshold of $p < .001$ corrected for multiple comparisons with a minimum voxel extent of 10. The differences observed between subjects go beyond what might be expected due to anatomical variations or to warping of the brain during spatial normalization. For example, an axial view (a glass-brain view that reveals all significant activations) of subject E.E. in Figure 2 revealed only left hemisphere activation, while an axial view of subject J.L. in Figure 2 revealed mostly right hemisphere activation. Also in Figure 2, subject H.G. revealed activations exclusively in the prefrontal cortex while subject S.C.'s strongest activations were in the parietal lobes. A sagittal view of subject S.C. in Figure 3 revealed mostly superior activations in the prefrontal cortex and in the parietal lobes, while a sagittal view of subject B.B. revealed mostly inferior activations (more in line with the group activations). In some cases, using a more liberal threshold for individual activation maps produced more overlaps between subjects, and more overlaps between a particular subject and the group map. These significant overlaps are taken into consideration in the correlational analysis discussed below. The particular threshold chosen here was used to illustrate the individual differences in the peak activations that might be reported.

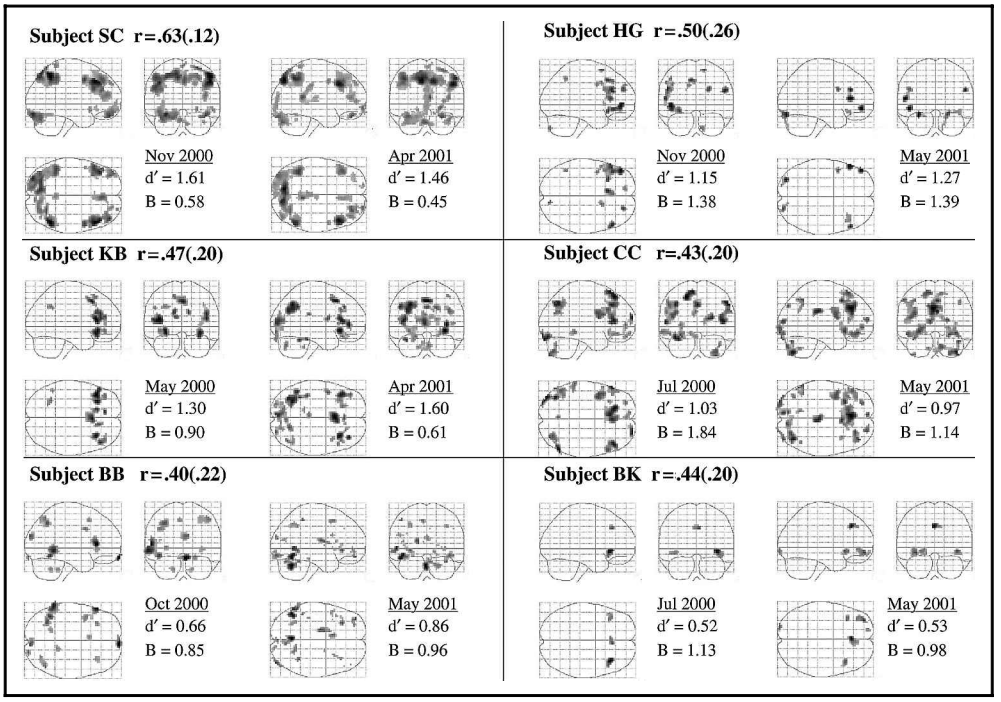

Figure 3. Significant activations associated with episodic retrieval for individual subjects during the first session compared to the significant activations for the same individuals during the second session. Next to each glass brain representation is the date when the session took place, along with a measure of memory performance (d') and response bias (B). Next to the subjects' initials are the correlation values (using difference maps as described in the Results section) between the two sessions for each subject, followed in parentheses by the average correlation values between a subject and the rest of the subjects.

Another perspective of the individual variations compared to the group is shown in Table 1. This table shows the most significant activations for each individual and for the group. These activations are broadly categorized according to location by viewing the individual activations rendered on the subject's 3-D high-resolution spatially normalized MR image. The anatomical locations were determined by sighting the individual locations of gyri and sulci and using known cyctoarchitectonic divisions (Amunts et al., 1999; Paus et al., 1996; Rajkowska & Goldman-Rakic, 1995). Included in the table are the Talairach coordinates of the peak voxel value within each cluster of activations (these coordinates were converted from the MNI coordinates provided by SPM99), the distance between the coordinates of the individual activation and the closest group activation, the t value of the peak voxel within each cluster, and the voxel extent of the cluster. This table shows that while activations may have been reported in the left inferior frontal gyrus in the group analysis, only five out of the nine subjects reported highly significant activations in that same region. Group analysis revealed significant activations in the right inferior frontal gyrus, but only two out of the nine subjects had highly significant activations within the same region. Subjects C.C. and J.L. also had activations in the inferior frontal gyrus (BA 45), but the peak of these activations were located just inferior of the inferior frontal sulcus with voxels extending beyond the sulcus into the middle frontal gyrus, whereas the group activation is located exclusively on the inferior portion of the inferior frontal gyrus (BA 47). Subjects C.C.'s and J.L.'s activations were much more similar in location to subjects H.G.'s, K.B.'s, and S.C.'s locations on the middle frontal gyrus (BA 9 and 46). Interestingly, five out of nine subjects had highly significant activations in the right anterior prefrontal cortex (an area commonly associated with episodic retrieval), yet this region does not show up on the group analysis. In addition, group activations were evident in the caudate, yet none of the nine subjects showed significant activations in that region. Again, manipulating the statistical threshold of the group or individual maps can cause the activations to be more or less overlapped with each other. For example, making the threshold of the group map much more liberal ($p < .05$ uncorrected) reveals that the activation that peaks in the right inferior frontal gyrus (BA 47; 36, 30, −9) now extends into the right anterior prefrontal cortex. Despite the overlap with some subjects obtained by the manipulation of this threshold, the anatomical peaks of these activations are still very different from each other. If we locate the coordinates from the peak activation from the right anterior prefrontal cortex of subject S.C. (the strongest of all the subjects) on the group map, we find that the voxels in that location are still not significant, even at the liberal threshold of $p < .05$ uncorrected.

As shown in Figure 3, there were also consistent behavioral differences between subjects, both in terms of memory performance (as measured by d') and bias (as measured by Beta, B). A bias to respond in a particular way on a recognition test can be viewed as a crude measure of individual strategy. The d' values ranged from a low of 0.52 to a high of 1.61, while B values ranged from a liberal bias of 0.58 to a much more conservative bias of 1.84. While no direct relationship can be determined from these results between

Table 1. Comparison of the Most Significant Group-Level Activations to the Most Significant Individual Activations by General Brain Region

Left Hemisphere	*Inferior Prefrontal*	*Middle Prefrontal*	*Superior Prefrontal*	*Anterior Prefrontal*	*Bilateral Medial Prefrontal*	*Inferior Parietal*	*Superior Parietal*	*Lateral Temporal*	*Cerebellum*
Group	−39, 26, −1				−9, 25, 37	−30, −56, −36			
	IFG 47(15.1)314				AC 32(9.7)208	AnG 39(8.9)40			
B.B.	−56, 29, 4, **18**					−33, −56, 44, **9**		−59, −47, 0	
	IFG 45(10.1)80					IPL 7(8.0)69		MTG 21(9.3)180	
B.K.	−48, 23, −9, **12**				6, 31, 32, **17**				
	IFG 47(6.5)33				MeF 9(7.0)32				
C.C.	−57, 30, 9, **21**		−18, 37, 48, **54**		0, 31, 34, **11**	−39, −65, 39, **13**			−39, −82, −11
	IFG 45(8.1)55		SFG 8(8.9)157		MeF 6(8.1)137	Prec 19(8.1)185			(8.3)77
H.G.	−45, 43, −5, **18**	−50, 30, 26, **29**			−9, 25, 40, **3**				
	IFG 45(9.8)156	MFG 9(8.5)150			MeF 8(8.7)55				
K.B.	−30, 29, −9, **12**				0, 22, 40, **10**				
	IFG 47(9.6)132				AC 32(8.8)109				
S.C.		−42, 34, 34, **36**		−36, 51, −21, **32**			−12, −67, 53, **27**		−30, −85, −11
		MFG 9(11.3)294		MFG 10(9.1)123			SPL 7(10.9)678		(11.1)409
E.E.		−53, 24, 24, **29**	−33, 0, 55, **62**		−6, 20, 40, **7**	−27, −47, 41, **11**		−53, −53, −5	
		MFG 9(7.6)130	MFG 6(7.6)18		AC 32(8.4)60	IPL 40(7.0)26		ITG 37(6.9)11	
J.L.				−12, 58, −8, **42**	15, 22, 32, **25**		−30, −49, 66, **31**		
				SFG 10(6.7)30	AC 32(7.7)80		PostCG 7(7.1)14		
N.L.		−39, 7, 25, **32**	−3, 31, 43, **57**	−30, 53, 8, **30**					−45, −59, −15
		IFG 44(6.9)55	SFG 8(8.3)77	MFG 10(6.7)27					(7.1)18

Table 1. (*continued*)

Right Hemisphere	*Inferior Prefrontal*	*Middle Prefrontal*	*Superior Prefrontal*	*Anterior Prefrontal*	*Inferior Parietal*	*Superior Parietal*	*Lateral Temporal*	*Cerebellum*	*Caudate*
Group	36, 20, −9				39, −62, 39				15, 14, −6
	IFG 47(12.4)75				IPL 39(3.9)38				(9.2)15
B.B.				6, 66, −18, **56**				21, −91, −8, **105**	
				MeF 11(10.0)80				(7.3)20	
B.K.	36, 26, −4, **8**								
	IFG 47(7.9)72								
C.C.		45, 33, 9, **24**		24, 66, 15, **53**	50, −62, 42, **12**				
		IFG 45(8.4)157		SFG 10(7.7)58	IPL 39(8.3)42				
H.G.		53, 30, 23, **39**	15, 15, 57, **70**						
		MFG 9(8.7)43	SFG 9(7.2)14						
K.B.	33, 26, −11, **7**	45, 36, 18, **32**							
	IFG 47(8.9)72	MFG 46(7.8)75							
S.C.		50, 25, 37, **49**		42, 49, −20, **31**	48, −53, 50, **17**				
		MFG 9(12.8)302		SFG 11(10.4)74	IPL 40(12.9)274				
E.E.								9, −74, −29, **92**	
								(6.3)13	
J.L.		39, 30, 12, **24**		15, 63, −11, **47**					
		IFG 45(9.6)200		SFG 10(10.6)313					
N.L.				39, 53, 11, **39**					
				MFG 10(7.4)11					

IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; AC = anterior cingulate; MeF = medial frontal gyrus; AnG = angular gyrus; IPL = inferior parietal lobule; Prec = precuneus; SPL = superior parietal lobule; PostCG = posterior cingulate gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus. **Boldface** numbers indicate the distance in millimeters from the peak of the individual activation on the peak of the nearest group-level activation.

behavioral performance and brain activations, it should be noted that the behavioral performance for individuals remained stable across the sessions as did the patterns of brain activations.

Correlational Analysis across Subjects, Sessions, and Conditions Using Raw Signal Intensity Values

Subsequent to this initial observation of individual variability, we ran another experiment examining whether these individual differences were stable over time. We retested six of the original nine subjects using the identical scanning and experimental procedures as the first session in the original experiment from Miller et al. (2001) (see Methods). The time difference between the first and second sessions ranged from 5 to 11 months. As illustrated in Figure 3, subjects showed remarkable consistency in their activations between sessions, suggesting that these activations are indeed critical to the task for that individual. For example, the voxels that were significantly active in November 2000 in subject S.C. were identical to the active voxels in April 2001. In addition, her memory performance was just as good in both sessions and her strategy was just as liberal.

We then sought a way to quantify these similarities and differences between patterns of brain activations that would not be dependent on any statistical threshold. As mentioned previously, the individual activation maps shown in Figures 2 and 3 may be more or less similar to each other depending on the statistical threshold that is used to produce those patterns of activations. Furthermore, one subject may generally produce stronger activations than another subject making them appear to be quite different from one another, but the site of those activations may be in identical regions; or one subject may be quite consistent across sessions, but if in one session the subject's activations in one region barely exceeds the threshold while in another session it barely falls below the threshold, that subject may appear to be inconsistent across sessions. Therefore, we conducted a cross correlation analysis of the complete volume of images using raw signal intensity values after spatial normalization but prior to any statistical thresholding.

Each timepoint in a functional scan contains a volume of signal intensity values at each voxel. This single volume or matrix of values from a particular subject in a particular session during a particular task can be correlated with another volume or matrix of values to produce a single correlational value representing the degree to which those two volumes are similar. We conducted a cross correlation using the volumes of signal intensities across subjects, sessions, and task conditions. We used the image volumes after they had been spatially smoothed and normalized using SPM99 (see Methods). We also used an image mask to include only voxels within each volume that contain intensity values, and we globally normalized the values across the subjects. In order to expedite analysis and further reduce signal-to-noise ratio, we also averaged across short epochs of image volumes grouped by

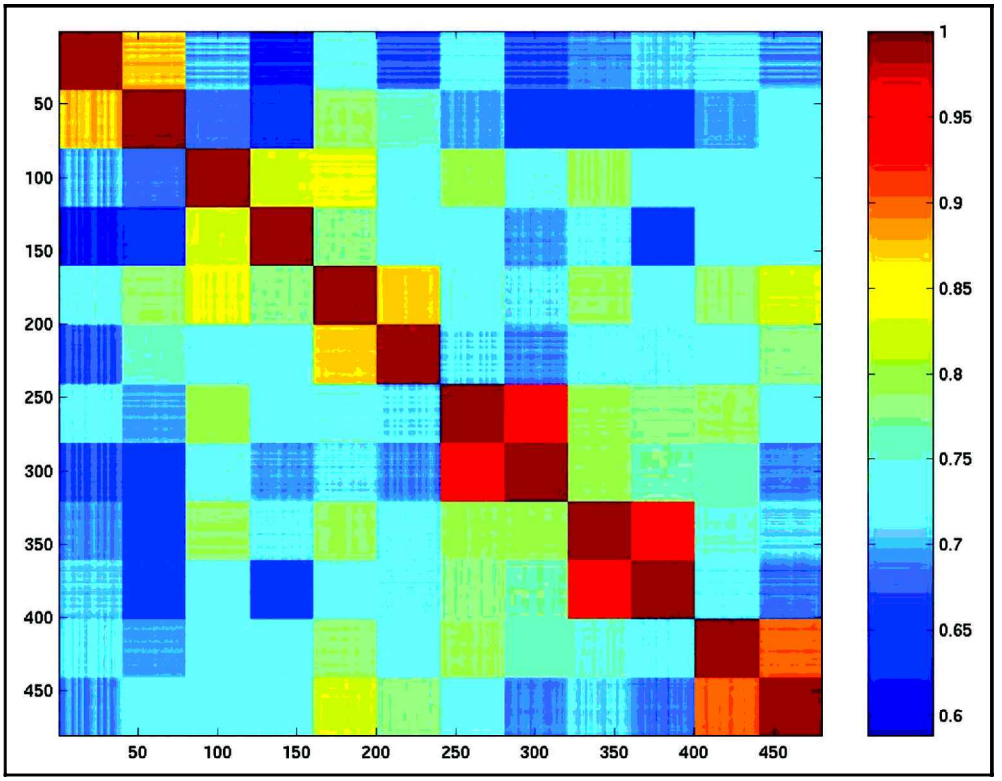

Figure 4. A graphic representation of the matrix of correlation values obtained by cross-correlating the volumes of image data. Volumes were arranged by subject first (80 volumes each), then session (40 volumes each), then condition (4–8 volumes each).

Table 2. Correlations of Voxel Intensity Values for Subjects and Conditions

	Same Subject	*Different Subjects*
Same condition	.9468	.7293
Different conditions	.9467	.7290

experimental condition (12 timepoints per epoch). The timepoints selected for each averaged epoch were offset by 6 sec to account for the hemodynamic response function (we used various time offsets but it seemed to have little effect on our correlational values). As has been utilized in Methods for principle component analysis on neuroimaging data (Friston, Frith, et al., 1993), we then constructed a 480 × 480 matrix of cross correlations between averaged epochs of image data (see Figure 4). The data contained in the upper triangle of the matrix were then coded for subject, session, and task condition, and then submitted to multivariate regression (SPSS v.10.0).

As Table 2 illustrates, the average correlation within the same subject was .947 while the average correlation between subjects was .729. Although there is a very high correlation among subjects, which may indicate a general brain state of activity that is consistent across subjects, there is a significant difference between same subjects and different subjects. Since the correlation values were clustered close to 1 for same subjects, we transformed the values using a Fisher *R*-to-*Z* transformation prior to submitting the data to a regression equation. Our model in a stepwise multivariate regression accounted for 93% of the variance in the correlation values, $F(6,114953) = 259{,}635.9$. The six dummy variables that significantly contributed to the equation were same subject versus different subjects, same session versus different sessions, same condition versus different conditions, an interaction between same subject and same session, an interaction between same subject and same condition, and an interaction between same session and same condition. Only three of these variables noticeably accounted for the variance: same subject ($t = -722.8$) accounted for 61.5% of the variance, same session ($t = -545.1$) accounted for 5.8% of the variance, and the interaction between same subject and same session ($t = 656.9$) accounted for 25.9% of the variance. The R^2 changed 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. Therefore, the most significant factor in evaluating the variations in the correlation values is whether the volumes come from the same subject, followed by whether the volume is from the same session, and with very little contribution from whether the volume is from the same condition. As shown in Table 2, the difference in correlation values between same condition and different condition was less than .001.

Fixed-Effects Analysis of Variance

The correlational analysis in the preceding section has several strengths for examining the extent of individual differences. In particular, each correlation reflects the activation pattern of the entire brain in a single number. However, those same correlations are affected by

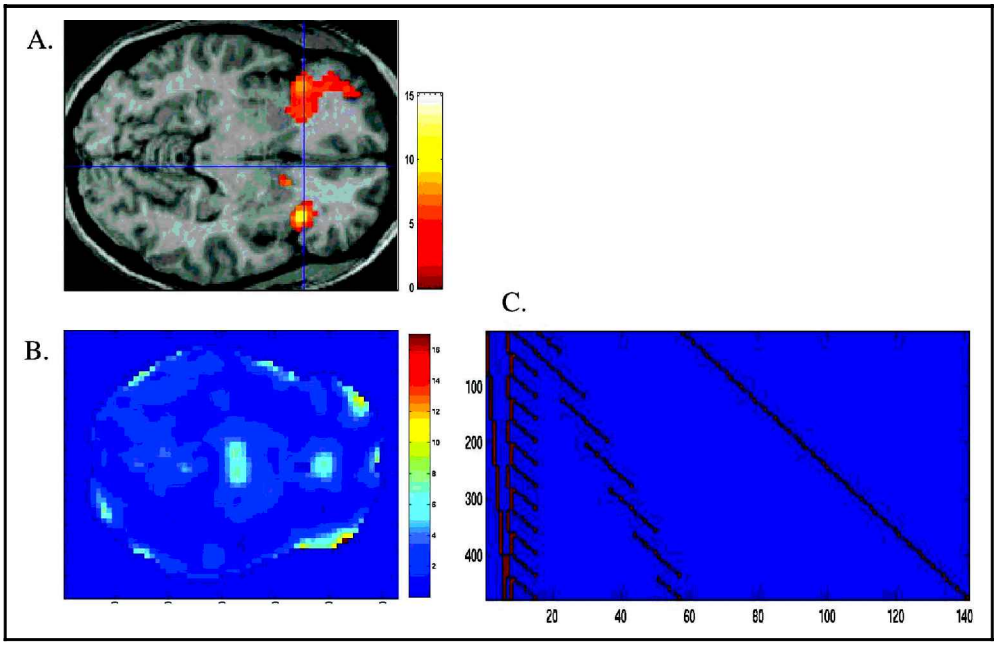

Figure 5. A comparison of a random-effects group analysis with a fixed-effects analysis of variance. (A) An axial view of the random-effects group analysis thresholded to show voxels with significant activations for the contrast of recognition versus rest, a representation of common areas of activation across subjects. (B) A fixed-effects analysis of variance thresholded to show voxels with significant interactions between subjects and conditions, a representation of areas with significant variability across subjects by retrieval condition. (C) The design matrix used to calculate sum of squares for the *F* tests at each voxel for the fixed-effects analysis of variance across subjects, sessions, conditions, Subject × Conditions interaction, and Subject × Session × Conditions interaction.

anatomical and equipment characteristics that are not related to the functional issues of primary interest. We supplemented those correlation analyses with fixed-effects analyses of variance using the same normalized raw signal intensity values. These analyses need to be carried out on a voxel-by-voxel basis but are less affected by anatomical and structural variables.

For each voxel in the brain, we did a fixed-effects analysis with condition, session, and subject as fixed effects, and replications in which subjects, conditions, and sessions were held constant as the random effect. The design matrix is shown in Figure 5. This model yields a single error term for each voxel that can be used to test each of the main effects and interactions for that voxel. We were particularly interested in the Subject × Condition interaction as this term highlights those brain regions that are differentially active for particular subjects in particular conditions. Figure 5 shows brain slices from the same location comparing the random-effects group analysis with the fixed-effects analysis. The random-effects analysis shows all voxels significantly active for the condition of episodic retrieval versus nonretrieval. The fixed-effects F test shows all voxels that were significant for the Subject × Condition interaction. As would be expected, voxel locations that were significant for the random-effects group analysis were not significant for the Subject × Condition interaction, and voxels that were significant for the Subject × Condition interaction were not significant for the random-effects group analysis. The fact that there were highly significant Fs for some voxels in the Subject × Condition interaction is another way of showing that we have stable individual differences.

Correlational Analysis across Subjects and Sessions Using Changes in Signal Intensity

We conducted a second correlation analysis because activation maps are typically based on differences between the signal intensity during one experimental condition and the signal intensity during a control condition. As mentioned with the analysis of variance, we were also concerned that our results from the correlation of the raw signal intensity values may be contaminated by possible inhomogeneities in the MR signal that are particular to certain regions and certain scanning sessions. In addition, we were concerned that the higher correlation values for same subject may be driven by unique individual configurations of vascular structures. Therefore, we performed another cross correlation analysis using volumes of images reflecting changes in signal intensity. These volumes were produced by taking the mean average of all the image volumes for a particular condition (i.e., episodic retrieval) and subtracting the mean average of all the image volumes for another condition (i.e., nonretrieval). The product of these volumes were then cross-correlated (matrix size of 24 × 24) across subjects, sessions, and functional runs (each subject participated in two functional runs per session), producing the correlation values shown in Table 3. The average correlation between a subject in Session 1 with the same subject in Session 2 is .48, while the average correlation across subjects is only .20. It is important to note that while there is a large difference in the correlation values between intersession and intersubject, a correlation value of .20 across subjects is still significantly higher than would be expected by randomly assigning timepoints instead of grouping timepoints by condition (we ran several of these random assignments and never got a correlation higher than .06). However, no subject was more correlated with another subject than with themselves between Sessions 1 and 2.

In a stepwise regression analysis, $F(1,274) = 175.2$, 39% of the variance was accounted for by a single variable, same subject versus different subjects ($t = -13.24$). Same session versus different sessions was not a factor ($p = .094$) and the interaction between the two variables was not a factor ($p = .532$).

Table 3. Correlations between Difference Maps at Sessions 1 and 2 for the Episodic Retrieval versus Nonretrieval Comparison

	S.C.	*K.B.*	*B.B.*	*H.G.*	*C.C.*	*B.K.*
S.C.	**.63**	.12	.11	.19	.08	.11
K.B.		**.47**	.19	.25	.19	.23
B.B.			**.40**	.29	.25	.25
H.G.				**.50**	.27	.30
C.C.					**.43**	.20
B.K.						**.44**

Boldface numbers indicate the average correlation between a subject in Session 1 and the same subject in Session 2.

DISCUSSION

The results reveal two important points about brain activations associated with episodic retrieval. (1) Activations produced during retrieval conditions vary significantly from individual to individual, and these activations are not adequately accounted for in group analyses. What emerges from the group pattern is a very different brain story than what emerges from the individual patterns. (2) Despite large variations from subject to subject, those individual patterns of activation are reliable over time indicating that these individual activations are more than simply noise. If an individual has brain regions that deviate greatly from the group at Time 1 (e.g., subject S.C.), it is likely that those same regions for that individual will be activated at Time 2.

There are alternative explanations for these stable individual differences that are not reflected in the group

patterns. One is that all individuals use the same strategies and cognitive processes in the retrieval task, but different brain regions serve these processes in different subjects. Alternatively, individuals may have been using very different strategies and cognitive processes during the task, and those differences were reflected by different patterns of brain activations. There is considerable evidence that individuals can use very different strategies during retrieval (Rogers, Hertzog, & Fisk, 2000; Graf & Birt, 1996; Reder & Schunn, 1996; Tulving, 1983; Mandler, 1980), lending credibility to the second alternative. Previous neuroimaging studies using a group analysis have shown that manipulations of strategy can greatly affect the pattern of activations in the prefrontal cortex and in the parietal lobes (Miller et al., 2001; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998).

Although it was not the intent of this study to show a direct relationship between individual behavior and individual patterns of activation, there are some indications from these results that a strong relationship exists. Just as the individual patterns of brain activations were quite variable between subjects but quite consistent between sessions, so to were the behavioral measures of memory performance (d') and strategic bias (B). Subject S.C. stands out in this regard. Subject S.C. clearly had the strongest correlation (.63 when correlating the volumes of images representing signal intensity changes) between her activations in Session 1 and her activations 6 months later in Session 2. A visual inspection of her activations in Figure 3 shows an almost identical pattern. She was also the subject that deviated the most from the other subjects (.12 was her average correlation between her activations and a different subject's activations). Her strongest activations tended to be much more superior than other subjects in the prefrontal cortex and in the parietal lobes. Her behavioral data were also very distinctive. Her memory performance was the strongest (average d' of 1.54) and her bias was much more liberal than any other subject (average B of 0.52). In the future, using analyses that include individual variations in patterns of activation may lead to a better understanding of the relationship among memory performance, strategy, and brain regions.

We would like to emphasize that our results concerning how well subjects are correlated with other subjects and between sessions do not depend on any arbitrary setting of a statistical threshold. Statistical maps, as shown in the figures, can be greatly influenced by a liberal or conservative setting of a statistical threshold for displaying activations. Certainly, our group map may have been influenced by using a more liberal threshold. Conversely, certain activations may have gone away if we used a more conservative threshold. This is an important debate for many studies, but our conclusions are not based on differences between statistical maps. We correlated image volumes after spatial normalization and smoothing, but prior to any statistical analysis or thresholding. We also did not depend on any visual inspection of the statistical maps in order to determine whether individual activations are reliable over time. A regression analysis demonstrated that correlation values from the same subject across sessions versus correlation values from different subjects significantly accounts for the variance in those correlation values.

We acknowledge that our initial group analysis was based on a relatively small sample of subjects ($N = 9$), and that researchers in neuroimaging are now suggesting between 12 and 16 subjects when using a random-effects model (Friston et al., 1999). However, our group analysis did produce highly significant activations (with t values greater than 15), and the number of subjects was in line with the average number of subjects in the episodic retrieval studies represented in the meta-analysis discussed in the Introduction (Cabeza & Nyberg, 2000). Further studies will need to be conducted to determine whether twice as many subjects will produce a random-effects group analysis that is more inclusive of the variable activations seen from individual to individual. We do not believe it will for episodic retrieval based on the strength of statistical values (61% of the variance in model that produced F values over 225,000) for same subject versus different subjects that we observed in this study.

As discussed in the Introduction, many previous neuroimaging studies have examined individual variability. Most of these studies were concerned with individual variability within a circumscribed brain region (Burton et al., 2001; Klein et al., 2000; Alexander et al., 1999; Aguirre et al., 1998; Dehaene et al., 1997; Cahill et al., 1996; Kosslyn et al., 1996; Nyberg et al., 1996; Watson et al., 1993; Grafton et al., 1991, 1994). Other neuroimaging studies have focused on the reproducibility of activations. McGonigle et al. (2000) examined differences in activations from single subjects across multiple sessions during a variety of simple tasks. Their results 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. Other researchers have examined the reproducibility of fMRI and PET data, including similar activation paradigms across laboratories (Casey et al., 1998), imaging modalities (Mangun, Hopfinger, & Jha, 2000; Ojemann et al., 1998), and sessions (Cohen & DuBois, 1999; Tegeler, Strother, Anderson, & Kim, 1999; Rombouts, Barkhof, Hoogenraad, Sprenger, & Scheltens, 1998; Le & Hu, 1997; Noll et al., 1997). Our study differs from these previous neuroimaging studies on variability in two ways. One is the extent of the individual variations. Most of these previous studies examined the variability within a very circumscribed region, like differences around the calcarine sulcus (Klein et al., 2000) or along the posterior superior temporal gyrus (Burton et al.,

2001). The individual variations that we observed for episodic retrieval extend well beyond cyctoarchitectonic divisions, and even beyond hemispheres. Another distinguishing characteristic of the present study is that we demonstrated that individual activity associated with episodic retrieval, despite the extensive variations, was reliable over time.

The correlational analyses that we employed in this study are useful in that they provide quantitative measures of the degree to which different variables contribute to the stability of signal intensity values over time. For example, we found that same subject versus different subjects accounted for 61.5% of the variance in correlational values whereas same condition versus different conditions accounted for less than 0.01%. This comparison between subjects and conditions provides a useful estimate of the magnitude of individual differences and a measure of the stability of those individual patterns across long periods. Same session versus different sessions also accounted for a significant portion of the variance (5.8%), as is illustrated in Figure 3. Although the individual patterns of activation are remarkably stable across time, there are some differences within subjects from session to session. It should be noted however that, in the second correlational analysis using changes in signal intensity value rather than raw signal intensity values, the same subject contributed significantly to the variance in correlational values (39%) but same session did not (*ns*). Therefore, a very small but significant amount of variance in the signal is due to the experimental condition, a larger amount of variance is due to the session, and a much larger amount of variance is due to the individual subject.

This technique can also be used to evaluate different contrasts other than episodic retrieval. For example, much has recently been made of the activations (i.e., deactivations) that are observed in rest conditions minus task conditions. Authors have proposed that these activations represent the baseline state of the brain in which certain regions are more active and in which the subject is less focused on a task and more aware of their environment as a whole (Raichle et al., 2001). We would predict that this baseline state would show the same individual variability, given that it is closely related to the inverse of volumes we created, representing changes in signal intensity. Of course, our baseline condition is better characterized as a nonretrieval control task than a rest condition. Further studies may find that different baseline conditions contribute more or less to the individual variability in episodic retrieval. We also analyzed other retrieval contrasts from the same experiment that do not include a nonretrieval control condition. These contrasts revealed even more individual variability, but also greater variability between sessions within same subject (e.g., the contrast between a mixed-criteria retrieval condition and a stable-criteria retrieval condition, or the contrast between low recognition performance and high recognition performance). Importantly, the statistics used in significance testing for group analysis ensure to some extent that the reported activations are stable across subjects. Further studies need to be conducted to determine which effects are stable across subjects and which are highly variable. Given that neuroimaging depends on a contrast between two mental states, it will be important to know these relationships in order to fully understand the nature of the comparison.

In conclusion, we are not implying that grouping activations 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). Furthermore, group analysis has revealed the critical involvement of the prefrontal cortex in episodic memory that may not have been fully appreciated by patient studies prior to neuroimaging (Shimamura, 1995; Tulving, Kapur, Craik, Moscovitch, & Houle, 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. Our study shows that brain activity associated with episodic retrieval is quite variable across the frontal and parietal lobes from subject to subject, yet these individual differences are stable over time. This pattern of individual variability would seem to be more indicative of various conscious strategies underlying the performance of this task, rather than a common memory mechanism.

METHODS

Subjects

Six subjects (one man) participated in exchange for $20. The ages ranged from 18 to 25 years old. All fMRI was conducted at the Dartmouth Brain Imaging Center. The use of human subjects and fMRI procedures followed a protocol approved by the Committee for the Protection of Human Subjects at Dartmouth College.

Behavioral Paradigm

Full details of the behavioral paradigm are provided in Miller et al. (2001), including procedures used to produce various retrieval conditions. In this study, we focused on the results obtained from a contrast between word recognition (collapsed across all retrieval

conditions) and a nonretrieval control task. Prior to scanning, subjects studied 168 unrelated words. During two functional scans, subjects performed a recognition task. The paradigm for the recognition test was designed using randomly mixed blocks of trials. Word recognition blocks (16 blocks) consisted of six trials each. Half the blocks consisted of three ''old'' words and three ''new'' words, while the other half consisted of four ''old'' words and two ''new'' words. The words within a block were randomly ordered. A trial began with a word presented for 1 sec, followed by 3 sec of a blank screen during which the subject was instructed to respond using a button press. There were four nonretrieval control blocks. Instead of words, a row of ''Xs'' was presented with the same timing parameters as in the recognition blocks. The subjects were instructed to respond to each new row of Xs by alternately pressing the left and right buttons.

fMRI Parameters

A single fMRI session consisting of two functional runs (244 scans each) was obtained for each subject. Functional images were acquired with gradient-recalled echo-planar imaging (TR = 2000 msec, TE = 35 msec, RF flip angle = 90°, gradient-echo pulse sequence, 27 contiguous axial slices at 5 mm thick, and an in-plane resolution of 64 × 64 pixels in a field of view [FOV] of 24 cm, producing voxels of 3.75 × 3.75 × 5 mm) (Kwong et al., 1992; Ogawa et al., 1992) on a 1.5-T GE SIGNA Echospeed MRI scanner (General Electric, Milwaukee, WI) equipped with high-performance gradients (revision LX 8.3; maximum amplitude 4.0 mT/m; slew rate 150 mT/m/s). Twenty-seven-slice, T1-weighted structural images were also obtained for each subject in the same slice prescription as the functional scans (TR = 650 msec, TE = 6.6 msec, fast spin-echo pulse sequence, with an in-plane resolution of 192 × 192 pixels in an FOV of 24 cm, producing voxels of 1.25 × 1.25 × 5 mm). High-resolution, T1-weighted structural images were acquired as well using a 3-D SPGR pulse sequence (TR = 25 msec, TE = 6 msec, RF flip angle = 25°, bandwidth = 15.6 kHz, voxel size = 0.9375 × 1.25 × 1.2 mm). Foam padding was used for head stabilization.

Statistical Analysis of fMRI Data Using SPM99

Data were initially analyzed using SPM99b (Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995). Motion correction to the first functional scan was performed within each subject using a six-parameter rigid-body transformation. The 27-slice structural image was then coregistered to the high-resolution structural image, and the resulting transformation parameters were applied to the mean of the motion-corrected images and all motion-corrected functional images. Using mutual information coregistration, the functional images were then directly coregistered to the high-resolution structural image. Spatial normalization to the Montreal Neurological Institute template (Talairach & Tournoux, 1988) was performed by applying a 12-parameter affine transformation followed by a nonlinear warping using basis functions (Ashburner & Friston, 1999). All transformations were computed sequentially with one reslice operation at the end, and the functional images were written with 3 × 3 × 3 mm voxels. The spatially normalized scans were smoothed with an 8-mm isotropic Gaussian kernel to accommodate anatomical differences across subjects. These smoothed and normalized images were then used for statistical analysis (see Miller et al., 2001, for more details on the initial analysis using SPM99).

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The data reported in this experiment have been deposited in The fMRI Data Center (http://www.fmridc.org). The accession number is 2-2002-1136A.

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