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Individual differences in the functional neuroanatomy of verbal discrimination learning revealed by positron emission tomography

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Abstract

Why do some people have better memory abilities than others? This issue has been of long-standing interest to scientists and lay people. However, using purely behavioral methods, psychologists have made little progress in illuminating it. Now that functional brain imaging techniques have become available to study mind/brain relations, there is a new promise of understanding individual differences in learning and memory in terms of corresponding differences in brain activity. In this paper, we will present a positron emission tomography (PET) study designed to examine individual differences in learning and memory abilities. The basic assumption is that different patterns of brain activity serve as strong predictors of memory performance. Two specific questions were addressed in this study: (i) Can PET illuminate the relations between memory processes and their neuroanatomical correlates among individual learners and rememberers? and (ii) if so, how are these relations affected by the stage of practice on a given memory task? Our PET study examined individual differences in the neuroanatomical correlates of multi-trial verbal discrimination learning in 16 young healthy subjects. The results identified patterns of brain regions in which blood flow correlated with subjects' retrieval performance. However, these regions did not correlate with performance during all learning trials. Instead, a gradual shift was observed from one pattern of brain regions to another over the course of learning. These results suggest that individual differences in memory performance are related to differences in neural activity within specific brain circuits. © 2000 Elsevier Science B.V. All rights reserved.

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Why do some people have better memory than others? This question, which has always been of great interest to thinkers and lay people alike, is amongst the first raised whenever research on memory is discussed in any forum. James (1890) in his classic *Principles of Psychology*, discussed it at some length, under the heading of ‘goodness of memory’. He proposed that goodness of memory depends on two conditions. One is the physiologically determined ‘general retentivity’ or ‘native tenacity’. It is relatively fixed in an individual and cannot be changed by practice, although it ‘differs tremendously from infancy to old age, and from one person to another’ (p. 621). The other condition, the ‘number’ of associations or ‘brain paths’, depends on past experience, and on variables such as recency, repetition, and attention (p. 630).

Despite its venerable centrality, the issue of individual differences has seen relatively little systematic research. In the new *Oxford Handbook of Memory* (Tulving & Craik, 2000), individual differences are mentioned in only 6 of the 40 chapters that cover various aspects of human memory, and most of the mentions have to do with differences between groups (e.g., young versus old, depressed versus normal). Recently some interest in individual differences has been shown in connection with the phenomenon of ‘false memory’ (Hyman & Billings, 1998; Winograd, Peluso, & Glover, 1998) but, by and large, the issue has been neglected. In addition, the results of much of the research that has been published are not informative regarding the mechanisms or processes underlying individual differences. The purely behavioral methods that have been used in the past, although suited for describing individual differences and their derivatives, such as their factor structure (e.g., Underwood, Boruch, & Malmi, 1978), are less suited for identifying the variables that determine or influence these differences. For this latter purpose, other techniques are required.

If it is accepted that individual differences in memory arise because of individual differences in the brain, then modern functional neuroimaging tools such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) can be used to probe differences in the neuroanatomical correlates of the young, healthy subjects’ performance on different learning and memory tasks. A fair amount of functional brain imaging research on memory-related processes has been done in the last half a dozen years or so (for reviews see Buckner & Tulving, 1995; Cabeza & Nyberg, 1997, 2000; Fletcher, Frith, & Rugg, 1997; Nyberg & Cabeza, 2000; Schacter, Wagner, & Buckner, 2000), but most of the findings have been framed in terms of statistical averages. The correlations between cognitive variables (processes, materials, sensory modalities, and the like) and brain activations have typically been based on the data pooled over a given sample of subjects.

There has been research, however, that is indirectly relevant to the question of the neural correlates of individual differences in learning and memory. For example, there have been comparisons between subject groups: young and elderly (Grady

et al., 1995; Cabeza et al., 1997), males and females (Buckner, Raichle, & Petersen, 1995; also see Nyberg, Habib, & Herlitz, in this issue), and various neurological patients and controls (Herbster, Nichols, Wiseman, Mintun, DeKosky, & Becker, 1996; Becker, Mintun, Aleva, Wiseman, Nichols, & DeKosky, 1996; Buckner, Corbetta, Schatz, Raichle, & Petersen, 1996). The findings have shown that neuro-anatomical correlates of various memory tasks differ for these comparison groups. A recent fMRI study by Fernández et al. (1998) has revealed individual differences within a single-‘normal’ group of subjects as well. In this study, it was observed that, during verbal encoding, brain activity in the posterior hippocampus and medial temporal lobe (MTL) regions correlated with subsequent recognition performance. Interestingly, in six subjects, left hippocampal and MTL activity was greater than right hippocampal and MTL activity, whereas in the remaining five subjects, the opposite pattern was observed. There are also some studies that have reported correlations between blood flow and measured behavior (Grasby, Frith, Friston, Frackowiak, & Dolan, 1993; Grafton, Woods, & Tyszka, 1994; Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996b; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Wagner, Schacter, Rotte, Koutstaal, Maril, Dale, Rosen, & Buckner, 1998; Tulving, Habib, Nyberg, Lepage, & McIntosh, 1999). These brain-behavior correlational studies have indicated that activity in certain brain structures is systematically related to some measure of behavior across subjects. Finally, research in domains of cognition other than long-term memory has indicated that individual differences in functional neuroanatomy may exist (Braver et al., 1997; Alexander et al., 1999; Rypma & D’Esposito, 1999).

In addition to functional imaging studies of individual and group differences in memory, an exciting new technique allows exploration of the relation between brain volume and memory capacity. For example, it has been shown in both elderly people and patients suffering from Alzheimer’s disease that the volume of the hippocampus is correlated with long-term memory performance (Foster et al., 1999; Martin et al., 1999; Petersen et al., 2000). Other brain volumes which have also been shown to correlate, across individuals, with memory performance include the amygdala (Martin et al., 1999; Mizuno, Wakai, Takeda, & Sobue, 2000), mammillary bodies (Martin et al., 1999), and frontal lobes (Baare et al., 2000). Volumetric correlations with memory performance provide a complementary technique to functional imaging, and suggest that differences in memory ability may arise from both morphological and physiological differences in the brain. To fully characterize individual memory differences both facets must be considered together.

Here we report the results of a PET experiment conducted in our laboratory to directly examine individual differences in multi-trial learning and memory. The basic assumption underlying this study was that different patterns of brain activity serve as strong predictors of memory performance. To identify such patterns we examined correlations between blood flow and memory performance. The analysis we used is different from subtraction analyses (Friston et al., 1995) which have been used in the majority of published studies. The brain regions identified by this brain-behavior correlational analysis have previously been labeled ‘how’ memory sites, to highlight the fact that activity in these regions reveals how well individuals perform on the given

memory task (Tulving et al., 1999). ‘How’ memory sites are contrasted with ‘what’ memory sites, which are revealed by standard subtraction analyses (Friston et al., 1995) and indicate what mental processes differentiate the two tasks being compared.

The present study extends previous correlational research in several ways: (1) we employed the multivariate partial least squares (PLS; (McIntosh, Bookstein, Haxby, & Grady, 1996)) statistical technique which allowed us to identify patterns of brain activity related to individual differences in learning and memory, (2) we examined how these patterns of brain activity were affected by various stages of practice on the memory task, and (3) we examined individual differences in a multi-trial learning task that has not been previously used in functional neuroimaging research, namely verbal discrimination (Ekstrand, Wallace, & Underwood, 1966). This is a human version of the well-known concurrent object discrimination task frequently used with non-human primates (Bachevalier & Mishkin, 1984; Gaffan & Murray, 1992; Buffalo, Stefanacci, Squire, & Zola, 1998). In our verbal discrimination study, subjects saw 50 pairs of words in succession and were required to learn to discriminate between the ‘correct’ (underlined) and ‘incorrect’ (not underlined) word of each pair. Following the learning phase of each trial, subjects saw the same pairs of words, without any underlinings, and had to indicate which of the two words was ‘correct’. This study-test block was repeated five times. Performance was measured in terms of discrimination accuracy during the test phase of each trial. We identified individual differences in the neuroanatomical correlates of multi-trial verbal discrimination learning by examining brain-behavior correlations between discrimination accuracy, on the one hand, and blood flow measured during the test phases of three trials (1, 2, and 5) on the other. This analysis revealed patterns of brain activity which related to subjects performance accuracy – it revealed locations of ‘how’ memory sites. The main goal of this study was to identify individual differences in the neuroanatomical correlates of verbal discrimination learning. A secondary purpose was to examine whether brain activity in these regions was affected by practice.

1. Methods

1.1. Subjects

Sixteen (7 males) young healthy right-handed subjects between the ages of 20 and 32 participated in the study. Subjects were remunerated for their participation. The study was approved by the Human Subjects Use Committee of Baycrest Centre and written informed consent was obtained from all subjects.

1.2. Experimental procedures

The experiment consisted of five study-test trials. In the study phase of a trial, subjects saw a list of 50 unrelated word pairs. Word pairs were shown beside each other on a computer screen (one to the left of centre and the other to the right) for 3 s with a 1 s inter-stimulus interval. Five hundred milliseconds after the onset of a word

pair, one word in the pair was underlined. The underlined word of each pair had been randomly pre-selected for each subject prior to the experiment and held constant throughout. Subjects were instructed to learn which word in each pair was underlined and to press the mouse button corresponding to its side (left or right) on the computer screen. Following a 10-min break at the end of the study phase, the test phase began. Subjects saw the same set of word pairs presented on the computer screen. Although the word pairs were the same as those encountered earlier, their screen position (left side or right side) was varied randomly in order to prevent subjects from learning the underlined words by associating them with their screen positions. Subjects were instructed to select, with the mouse, the word which had been underlined during study. When a mouse button was pressed, the corresponding word on the screen was underlined to indicate their selection (regardless of whether the response was correct or incorrect). Performance on this test was measured in terms of the number of underlined words correctly identified (chance performance was 50%).

Blood flow was measured with PET during both the study and test phases of the first, second, and fifth trial. The rest periods following the second, third, and fourth study-test blocks and between the study and test phases of the third and fourth study-test block were reduced to 1 min in order for the third and fourth study-test blocks to be completed during the 10 min rest period between the second and fifth study-test blocks.

1.3. PET procedures

Blood flow was measured with a Scanditronix/GEMS PC 2048-15B PET Scanner using ^{15}O -water and 60 s data acquisition scans. Head movement was minimized with a custom-fitted thermoplastic face mask. All subjects' blood flow images were aligned to their first image, spatially transformed into the standard stereotaxic atlas space of Talairach and Tournoux (Talairach & Tournoux, 1988), and smoothed using a 10 mm isotropic Gaussian filter using Statistical Parametric Mapping software (SPM96, Wellcome Department of Cognitive Neurology, London (Friston et al., 1995)).

Statistical analysis was performed using PLS (McIntosh et al., 1996). PLS is a multivariate statistical approach, similar in nature to principal components analysis (PCA) and factor analysis, that examines the relation between a set of exogenous measures such as experimental design or performance measures and blood flow. The main difference between PLS on the one hand, and PCA and factor analysis on the other, is that whereas PLS is designed to explicitly identify patterns of image activity that relate directly to the design or performance measures, these relationships are typically identified post-hoc in PCA or factor analysis. The outcome of a PLS analysis is a new set of variables consisting of functional brain images and scatter plots which optimally relate patterns of brain regions to particular aspects of the experimental design or to a measure of performance. In the present case, PLS examined the image-wide relationship between blood flow and memory performance across all trials of the experiment simultaneously, producing a series of variables which represented the optimal relationship between blood flow and performance at each point in the brain.

The reliability of the correlated regions was assessed by means of a bootstrap procedure. Bootstrapping assesses the reliability of correlations by guarding against the effects of outlier observations. In bootstrapping, subjects are randomly selected into the analysis with replacement from the entire group of subjects. For each new sample, the entire PLS analysis is recalculated. This sampling and analysis procedure was carried out 100 times, resulting in estimates of the standard error of the covariance between blood flow and memory performance at each voxel. The ratio of the covariance to its standard error is similar to a *Z*-score, and for the present results, we thresholded the bootstrap results at a ratio of 2.33, approximately equivalent to $P < 0.02$ on a two-tailed normal distribution. Because PLS assesses the relationship between blood flow and memory performance simultaneously over the entire brain volume and across all experimental conditions, it does not require correction for multiple comparisons, as is required by univariate statistical procedures. For this reason, the selected bootstrap threshold is not excessively lenient. In addition, we thresholded the spatial extent of the activations to those correlation regions greater than 20 voxels in size.

2. Results

Behavioral results on the verbal discrimination task are shown in Table 1. It can be seen that performance steadily improved from the first to the fifth trial.

The PLS analysis identified three patterns of brain structures in which blood flow correlated with individual performance on the verbal discrimination task – we have previously referred to these as ‘how’ memory sites. Therefore, these patterns identify sites of individual differences in the neuroanatomical correlates of verbal discrimination learning – activity in these regions differs as a function of how well subjects’ perform on the verbal discrimination task. Blood flow in two of these three patterns was differentially affected by practice, whereas in the third pattern it was not (the third pattern also accounted for the least amount of covariance). Here, we will focus on the two patterns in which practice did affect blood flow during the verbal discrimination task.

Indicated on each brain image (see Figs. 1(a) and 2(a)), to be discussed below, are regions of positive and negative correlations between blood flow and verbal dis-

Table 1
Performance on verbal discrimination task^a

Trials	Mean	S.D.	Minimum	Maximum
1	0.66	0.10	0.48	0.80
2	0.79	0.11	0.64	0.96
3	0.85	0.10	0.62	0.98
4	0.92	0.08	0.80	1.00
5	0.93	0.07	0.76	1.00

^a Note: Chance performance is 0.50.

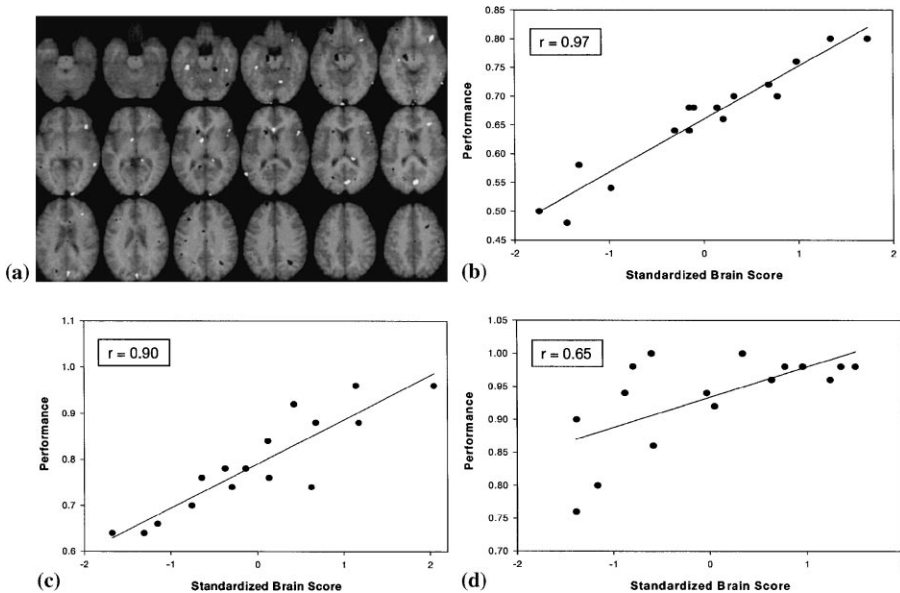


Fig. 1. (a) Shown are brain regions in which activity correlates positively, across individuals, with discrimination performance during the first (black) and second (white) trials of the verbal discrimination task. Identified brain structures are shown on horizontal slices of an averaged MRI template. Top left slice is ventral ($Z = -28$) and bottom right slice is dorsal ($Z = 40$). Slices at 4 mm increments. The Talairach & Tournoux coordinates of the identified regions are presented in Table 2. (b) The graph demonstrates the relationship between standardized brain scores (yielded by the PLS analysis) and trial 1 discrimination performance across individual subjects. A least squares regression line is fitted to the data ($r = 0.97$). (c) The graph demonstrates the relationship between standardized brain scores (yielded by the PLS analysis) and trial 2 discrimination performance across individual subjects. A least squares regression line is fitted to the data ($r = 0.90$). (d) The graph demonstrates the relationship between standardized brain scores (yielded by the PLS analysis) and trial 5 discrimination performance across individual subjects. A least squares regression line is fitted to the data ($r = 0.65$).

crimination performance. In regions with positive correlations, as blood flow increases, so does verbal discrimination performance; in regions with negative correlations, as blood flow increases, verbal discrimination performance declines. As in subtraction analysis, where deactivations can be interpreted as either reduced activity in the target condition or increased activity in the reference condition, negative brain-behavior correlations can be interpreted as negative correlations with performance in one condition or positive correlations with performance in another condition. Here, we follow the convention in subtraction analysis and focus only on positive brain-behavior correlations. The relationship between verbal discrimination performance and blood flow is shown on scatter plots where blood flow is represented in terms of standardized brain scores (see Figs.1(b)–(d) and 2(b)–(d)). Since PLS is a multivariate statistical tool which identifies patterns of brain structures related to the experimental design or behavior, we do not examine correlations between performance and rCBF in individual voxels. Rather, brain scores represent,

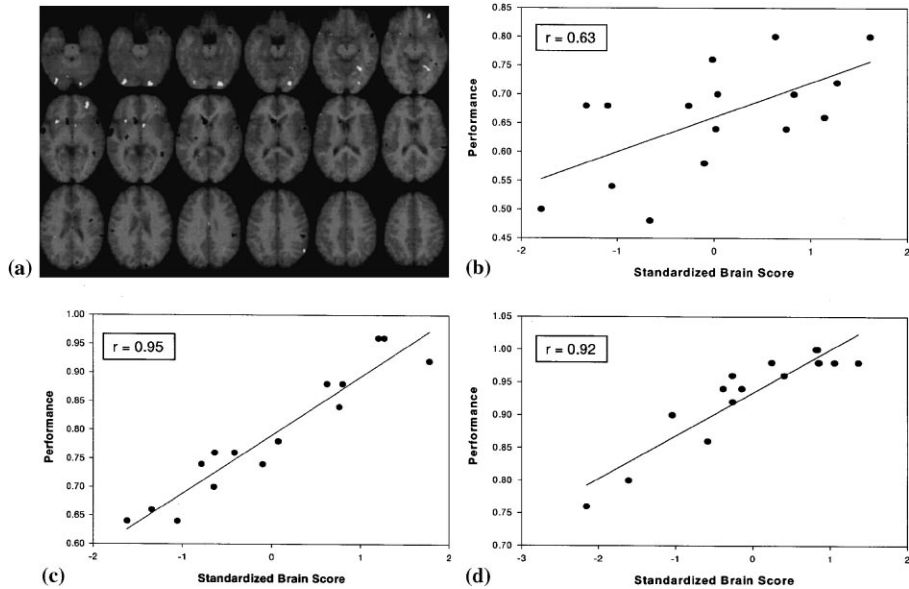


Fig. 2. (a) Shown are brain regions in which activity correlates positively, across individuals, with discrimination performance during the second (white) and fifth (black) trials of the verbal discrimination task. Identified brain structures are shown on horizontal slices of an averaged MRI template. Top left slice is ventral ($Z = -28$) and bottom right slice is dorsal ($Z = 40$). Slices at 4 mm increments. The Talairach & Tournoux coordinates of the identified regions are presented in Table 2. (b) The graph demonstrates the relationship between standardized brain scores (yielded by the PLS analysis) and trial 1 discrimination performance across individual subjects. A least squares regression line is fitted to the data ($r = 0.63$). (c) The graph demonstrates the relationship between standardized brain scores (yielded by the PLS analysis) and trial 2 discrimination performance across individual subjects. A least squares regression line is fitted to the data ($r = 0.95$). (d) The graph demonstrates the relationship between standardized brain scores (yielded by the PLS analysis) and trial 5 discrimination performance across individual subjects. A least squares regression line is fitted to the data ($r = 0.92$).

for each subject, the collective activity of all structures within a pattern – the more activation within the pattern of regions as a whole for a given subject, the greater that subject's brain score will be.

The two patterns, identifying sites of individual differences in the neuroanatomical correlates of verbal discrimination learning, were influenced differentially by practice: one pattern (Early Pattern) was affected by the early but not late stages of practice (trials 1 and 2), whereas the other pattern (Late Pattern) was affected by the late but not early stages of practice (trials 2 and 5). The Early Pattern accounted for 36% of the covariance between blood flow and verbal discrimination performance. These regions are shown in Fig. 1(a) and their coordinates, in the stereotaxic space of Talairach and Tournoux (1988), are presented in Table 2. Regions indicated in black on Fig. 1(a) correlated positively with performance during trial 1 ($r = 0.97$). These correlations occurred in left prefrontal cortex, left insula and brainstem, and right middle temporal gyrus. Regions indicated in white on Fig. 1(a) correlated

Table 2

Coordinates of peak positive and negative brain-behavior correlations in the Early and Late Patterns revealed by PLS^a

<i>X</i>	<i>Y</i>	<i>Z</i>	Region
<i>Early Pattern – positive correlation with trial 1 performance (black regions – Fig. 1(a))</i>			
–24	36	–12	Middle Frontal Gyrus (BA 47/11)
–16	–14	–8	Brainstem
–22	18	12	Insula
26	–58	28	Middle Temporal Gyrus (BA 39)
–18	60	28	Superior Frontal Gyrus (BA 9)
<i>Early Pattern – positive correlation with trial 2 performance (white regions – Fig. 1(a))</i>			
–36	–34	–20	Fusiform Gyrus (BA 36)
32	22	–8	Inferior Frontal Gyrus (BA 47)
4	–80	16	Cuneus (BA 18)
<i>Late Pattern – positive correlation with trial 2 performance (white regions – Fig. 2(a))</i>			
–32	–84	–24	Cerebellum
20	–86	–20	Cerebellum
22	–54	–12	Cerebellum
28	44	–4	Middle Frontal Gyrus (BA 10)
<i>Late Pattern – positive correlation with trial 5 performance (black regions – Fig. 2(a))</i>			
40	–48	–4	Inferior Temporal Gyrus (BA 37)
48	12	–4	Superior Temporal Gyrus (BA 22)
–28	–18	0	Putamen
–54	–4	0	Superior Temporal Gyrus (BA 22)
–10	16	0	Caudate Nucleus
58	–34	20	Superior Temporal Gyrus (BA 22 / 42)
44	–32	32	Inferior Parietal Lobule (BA 40)

^a Note: Negative *X* values refer to left hemisphere, positive *X* values refer to right hemisphere. BA = Brodmann Area.

positively with performance during trial 2 ($r = 0.90$). These correlations occurred in left fusiform gyrus, right inferior frontal gyrus, and the cuneus. Correlations between blood flow and trial 5 performance were less strong ($r = 0.65$) than in the other two trials. These correlations are plotted in Figs. 1(b) (trial 1), (c) (trial 2), and (d) (trial 5).

The Late Pattern accounted for 44% of the covariance between blood flow and verbal discrimination performance. These regions are shown in Fig. 2(a) and their coordinates, in the stereotaxic space of Talairach and Tournoux (1988), are presented in Table 2. Regions indicated in white on Fig. 2(a) collectively correlated positively with performance during trial 2 ($r = 0.95$); as blood flow in these regions increased, performance improved. These correlations occurred mainly in the cerebellum; one peak was observed in right prefrontal cortex. Regions indicated in black on Fig. 2(a) collectively correlated positively with performance during trial 5 ($r = 0.92$). These correlations occurred mainly in bilateral temporal gyri and structures of the left basal ganglia. Correlation between blood flow and trial 1

performance was less strong ($r = 0.63$) than in the other two trials. These correlations are plotted in Figs. 2(b) (trial 1), (c) (trial 2), and (d) (trial 5).

3. Discussion

We conducted a PET study to examine individual differences in the neuroanatomical correlates of verbal discrimination, a human version of the concurrent object discrimination task used in non-human primates. A second objective was to assess how the functional neuroanatomy of the verbal discrimination task changed as a function of learning. We analyzed the data using the multivariate PLS technique. PLS allowed us to examine the interindividual correlation between blood flow and discrimination performance over all voxels in the brain and all practice trials simultaneously. The analysis yielded three orthogonal patterns of brain activity related to individual differences in discrimination accuracy. We did not consider the results of the third pattern because it reflected brain-behavior correlations which did not differentiate amongst the different stages of practice; it also accounted for the least amount of covariance. On the other hand, the results of each of the first two patterns were of interest because they did identify brain structures in which activity was modulated by verbal discrimination performance across individuals and at various stages of practice. Specifically, the Early Pattern identified brain structures in which activity increased as discrimination accuracy improved during the first and second practice trials, whereas the Late Pattern identified brain structures in which activity increased as discrimination accuracy improved during the second and fifth practice trials.

3.1. Sites of individual differences in verbal discrimination

The main purpose of this experiment was to identify brain regions whose activity was related to individual differences in verbal discrimination performance. The Early and Late Patterns identified such regions. The collective activity of the regions identified in each pattern correlated positively, across individuals, with discrimination accuracy at various stages of practice. That is, as performance improved across subjects, neural activity in the identified structures increased. Brain structures sensitive to individual differences in trial 1 discrimination accuracy included left middle and superior frontal gyri, left brainstem and insula, and right middle temporal gyrus. Brain structures sensitive to individual differences in trial 2 discrimination accuracy included left fusiform gyrus, right inferior and middle frontal gyrus, the cuneus, and bilateral cerebellum. Brain structures sensitive to individual differences in trial 5 discrimination accuracy included bilateral temporal gyri, left basal ganglia structures including the putamen and caudate nucleus, and the right inferior parietal lobule.

Surprisingly, there was little overlap between these sites of brain-behavior correlations and those identified in a meta-analysis of individual differences in four PET studies of recognition memory previously conducted in our laboratory (Tulving et al., 1999). Overlaps were observed only in the right cerebellum and right middle

frontal gyrus. However, although blood flow in these two regions correlated positively with discrimination accuracy in the present study, blood flow in these regions correlated negatively with recognition performance in the meta-analysis. The lack of overlap and the discrepancy in the direction of the correlations suggests that the functional neuroanatomy of individual differences on verbal discrimination may be quite different from the functional neuroanatomy of individual differences on recognition (which the meta-analysis was based on).

This notion is supported by the finding that blood flow within the medial temporal lobes (MTL) and specifically the hippocampus did not correlate, across subjects, with discrimination accuracy in the present study. The majority of previous studies examining brain-behavior correlations, including our own individual differences meta-analysis (Tulving et al., 1999), indicate that activity within hippocampus consistently correlates, across individuals, with performance on tests of recognition memory. For example, Nyberg et al. (1996b) observed strong positive correlations between hippocampal activity and recognition performance following semantic encoding. Also, Fernández et al. (1998), Wagner et al. (1998), and Brewer et al. (1998) demonstrated that hippocampal activity during encoding correlated with individual subjects' performance on a subsequent recognition memory test. Finally, we observed hippocampal brain-behavior correlation in each of the four recognition studies we included in our meta-analysis (Tulving et al., 1999).

This discrepancy in hippocampal/MTL brain-behavior correlations between the present verbal discrimination results and others based on recognition paradigms are unlikely to be attributed to either differences in materials or differences in statistical procedures. This is because hippocampal activations have been observed in studies using paired verbal stimuli (Dolan & Fletcher, 1997) as well as many other types of stimuli (Tulving et al., 1999), thus suggesting that hippocampal/MTL correlations are not stimulus-sensitive. It is also unlikely that use of the PLS statistical procedures accounts for the lack of hippocampal/MTL brain-behavior correlations in the present study since the exact same data-analytic procedure was utilized in our previous meta-analysis (Tulving et al., 1999) which did identify hippocampal/MTL brain-behavior correlations in each of the four recognition memory PET studies. For the time being then, the most likely explanation for the absence of brain-behavior correlations within the hippocampus and MTL regions is probably that the verbal discrimination task does not engage these structures. Lesion studies in monkeys employing the concurrent object discrimination task, the non-human primate version of our task, support the hypothesis that verbal discrimination does not engage the hippocampus. These studies have noted that the integrity of the hippocampus and other MTL structures is not required for successful discrimination performance (Deacon & Rawlins, 1996; Bachevalier, Beauregard, & Alvarado, 1999; Teng, Stefanacci, Squire, & Zola, 2000). Therefore, the absence of brain-behavior correlations within the hippocampus and MTL regions of the present study, together with the lack of overlap between other sites of brain-behavior correlations in the present study and those observed in functional imaging studies of recognition memory, in conjunction with evidence gathered from primate studies, suggest that the functional neuroanatomy of individual differences on verbal discrimination may be quite different from that of recognition.

3.2. *Interaction between sites of individual differences and stages of practice*

A second purpose of this study was to examine the effect of practice on brain structures related to individual differences in verbal discrimination. We did so by having subjects perform the verbal discrimination task on five successive trials. Blood flow was measured on the first, second, and fifth of these trials. The first two brain patterns revealed by PLS identified brain structures in which activity not only correlated with individual differences in discrimination accuracy, but also distinguished between stages of practice. Therefore, practice modulated the activity of brain circuits underlying individual differences in verbal discrimination.

These results suggest that the brain circuits underlying individual differences in discrimination performance gradually change from the first to the fifth trial. The Early Pattern revealed brain structures whose activity correlated, across individuals, with performance on trials 1 and 2 of the verbal discrimination task, whereas the Late Pattern revealed brain structures whose activity correlated, across individuals, with performance on trials 2 and 5 of the verbal discrimination task. The fact that brain circuits underlying trial 2 performance appear in two independent patterns suggests that two separate neural systems may underlie these individual differences in performance: one system which is more similar to trial 1 brain circuits and another system which is more similar to trial 5 brain circuits. This overlap between brain circuits underlying trial 2 performance and those underlying trial 1 and 5 performance suggests that there may be a gradual progression, from trial 1 to 2, and then from trial 2 to 5, in the brain circuits related to individual differences in discrimination performance. This idea will be tested in the future using statistical analysis of functional (McIntosh, Nyberg, Bookstein, & Tulving, 1997) and effective connectivity (McIntosh & Gonzalez-Lima, 1994).

This finding is reminiscent of the original multi-trial verb generation study reported by Raichle et al. (1994). The study showed that the brain regions underlying naive verb generation (left prefrontal cortex, anterior cingulate, right cerebellum) were different from those underlying verb generation after eight practice trials (bilateral sylvian-insular). Our results suggest that the shift between sets of brain regions may occur even earlier in the course of practice than eight trials.

Of even greater interest is the finding that on the first trial of the task, frontal (executive) regions were more engaged than on subsequent trials, with activations slowly shifting, on later trials, to learning-related non-frontal structures such as the basal ganglia and cerebellum. For example, during the first trial of the verbal discrimination task, activity in two left prefrontal sites and a right middle temporal site correlated with discrimination performance. During the second trial of the verbal discrimination task, activity in two right prefrontal sites correlated with discrimination performance, however, the cerebellum was also recruited in support of performance. By the fifth trial of the verbal discrimination task, no correlations between activity in prefrontal sites and discrimination performance were observed. Instead, structures in the left basal ganglia and bilateral temporal regions were recruited to support performance. These shifts may reflect the automatization of the processes underlying verbal discrimination (Raichle et al., 1994).

3.3. *'How' and 'what' memory sites*

The majority of functional neuroimaging research has been concerned with identifying what brain regions underlie specific cognitive processes or tasks (Cabeza & Nyberg, 1997, 2000). The most common way to address such research questions is to 'subtract' activity between two tasks, a target task 'containing' the process of interest and a reference task not 'containing' the process of interest. In a previous report, we labeled activations revealed by the subtraction technique as 'what' sites: brain regions whose activity reveals what individuals are doing. In contrast to subtraction analysis, brain-behavior correlational analyses such as the multivariate variety performed here with PLS or its univariate counterpart identify brain regions in which activity is correlated with the 'goodness' of the subjects' cognitive/behavioral performance. We have labeled brain regions revealed by brain-behavior correlation analyses as 'how' sites: brain regions whose activity reveals how well individuals are performing on a given task. For studying individual differences in functional neuroanatomy, researchers need to focus on 'how' sites instead of 'what' sites.

3.4. *Reliability and interpretation of the findings*

A concern in the present study, and generally in any functional neuroimaging study, has to do with the 'reality' of the observed 'brain-behavior' correlations. As previously discussed (Andreasen et al., 1996; Tulving et al., 1999), within any large dataset there is a non-negligible probability that some correlations arise simply due to chance. Unfortunately, there is no foolproof way to distinguish true brain-behavior correlations from spurious ones within a single-study. The only way to guard against false positives is through replication and meta-analysis. In our meta-analysis examining individual differences in recognition memory (Tulving et al., 1999), we were careful to discriminate between sites of brain-behavior correlations which occurred in only a single-study and those which were common to at least two or more studies. The use of meta-analysis in functional neuroimaging has already paid dividends and promises to continue to do so in the future. Patterns of activations described by meta-analytic models such as HERA (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; Nyberg, Cabeza, & Tulving, 1996a) and HIPER (Lepage, Habib, & Tulving, 1998) have already identified consistencies in prefrontal and hippocampal involvement in encoding and retrieval processes across many different PET studies. The continued use of meta-analyses and multi-study analyses (Lepage, Ghaffar, Nyberg, & Tulving, 2000), in conjunction with replication studies, promises to help separate spurious activations and brain-behavior correlations from 'real' ones.

In the present case, because of the novelty of the verbal discrimination task in functional neuroimaging, we have little previous evidence to rely on in identifying its functional neuroanatomy. Although we have taken measures to ensure that the present findings are robust (larger than normal sample size, bootstrapping), the findings must be considered preliminary until verified and replicated in future studies.

It is also important to note that activity in the brain regions identified here correlate, across individuals, with discrimination accuracy. The causal direction, if there be one, is unknown: do differences in neural activity produce differences in discrimination accuracy, or differences in discrimination accuracy produce the differences in neural activity? One way that this ambiguity has been addressed is by examining the relationship between blood flow measured during encoding and memory performance measured at a later time. Since encoding occurs first, differences in memory performance during retrieval, if all else is held constant, must be due to how well the information was initially encoded. Therefore, blood flow measured during encoding can predict subsequent retrieval performance. Such studies have been carried out (Cahill et al., 1996; Fernández et al., 1998; Brewer et al., 1998; Wagner et al., 1998) and indicate that individual differences in blood flow during encoding, especially within the hippocampus and MTL regions, can indeed predict how well subjects will later remember the studied items. These studies indicate that differences in physiology lead to differences in memory performance across individuals.

4. Conclusion

In sum, we carried out a PET study to examine individual differences in the neuroanatomical correlates of multi-trial verbal discrimination learning. The results identified patterns of brain regions in which blood flow correlated with differences in discrimination performance across trials: ‘how’ memory sites. It was observed that these patterns of brain activity gradually shifted, with learning, from frontal regions (Early Pattern) to posterior regions (Late Pattern). We hypothesized that these shifts may reflect automatization of the processes underlying verbal discrimination. These results suggest that the study of individual differences can be a successful endeavour. Such endeavours may provide a full answer to the question: why do some people have better memory than others? We have taken a small initial step in that direction.

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