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Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect

(cognition/activation/frontal cortex/positron emission tomography/human)

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ABSTRACT **Cognitive studies of memory processes demonstrate that memory for stimuli is a function of how they are encoded; stimuli processed semantically are better remembered than those processed in a perceptual or shallow fashion. This study investigates the neural correlates of this cognitive phenomenon. Twelve subjects performed two different cognitive tasks on a series of visually presented nouns. In one task, subjects detected the presence or absence of the letter a; in the other, subjects categorized each noun as living or nonliving. Positron emission tomography (PET) scans using ^{15}O-labeled water were obtained during both tasks. Subjects showed substantially better recognition memory for nouns seen in the living/nonliving task, compared to nouns seen in the a-checking task. Comparison of the PET images between the two cognitive tasks revealed a significant activation in the left inferior prefrontal cortex (Brodmann's areas 45, 46, 47, and 10) in the semantic task as compared to the perceptual task. We propose that memory processes are subserved by a wide neurocognitive network and that encoding processes involve preferential activation of the structures in the left inferior prefrontal cortex.**

Cognitive studies of episodic memory have shown that performance in long-term memory tests is determined by two major principles, one relating to the conditions of acquisition or encoding (1, 2) and the second dealing with the relation between encoding and retrieval operations (3, 4). The first principle reflects the observation that more meaningful analyses of stimuli are associated with higher levels of subsequent retention. Craik and Lockhart (1) suggested that incoming stimuli can be analyzed to different levels, ranging from shallow sensory analyses (form, pitch, color, etc.) to deeper semantic analyses involving meaning and implications. The level at which a stimulus is analyzed depends on factors such as the meaningfulness of the stimulus to the subject, the amount of attention devoted to its analysis, and the subject's purpose and intentions with respect to the stimulus. It was emphasized by Craik and Lockhart that intention to memorize is not an important determinant of subsequent retrieval; rather, it is the type of encoding operation, carried out for whatever purpose, that substantially controls episodic memory performance. In a series of experiments designed to explore this notion, Craik and Tulving (2) demonstrated that correct recognition of verbal stimuli ranged from 15% to over 80%, depending only on the type of encoding that the subject was induced to perform. This dependence of memory performance on different types of encoding operations is termed the "levels of processing effect." It is an extremely robust effect, can be obtained reliably in a single subject, and has been shown by several other investigators (5, 6). Despite the obvious relevance of this finding to an understanding of memory processes, essentially nothing is known about its neural basis.

Positron emission tomography (PET) using ^{15}O-labeled water as a tracer to measure regional cerebral blood flow has provided an important means of investigating the neural correlates of mental processes (7, 8). By undertaking repeated scans in a subject while the subject is engaged in specified cognitive tasks, it is possible to detect the neuronal regions involved in the component cognitive processes. This method has been used extensively for the study of language, perception, and attention (9, 10), but relatively few studies have investigated memory processes, and those that have were focused largely on retrieval processes (11, 12).

This study was explicitly designed to explore the neuroanatomical basis of encoding processes in episodic memory. We asked subjects to engage in shallow and deeper levels of processing of verbal stimuli during different PET scans. By comparing the scans of these two encoding processes we hoped to delineate areas of the brain especially involved in deeper levels of processing.

METHODS

Task Design. Subjects performed a baseline task and two active tasks during the scans; each task was performed twice, making six scans in all. Scan 1 and scan 6 were baseline scans involving responses to nonverbal stimuli. These scans are not pertinent to the memory experiment and hence are not analyzed as a part of this study. In scans 2–5, the subject carried out one of two tasks on single words (two scans each, in an ABBA design counterbalanced over subjects). The words used were common concrete nouns, three to seven letters in length, presented visually at the center of a computer screen 60 cm in front of the subject. The words were presented at a 1.5-sec rate (0.5-sec presentation of the word, white letters on black screen, followed by 1.0 sec of a white fixation point on black screen). Eighty words were presented in each task. PET scans were recorded for 60 sec between words 30 and 70. In one task, representing shallow processing, the subject studied each word and decided whether it contained the letter a; the subject conveyed his decision by pressing one of two buttons on a hand-held computer mouse. In the second, deeper processing condition, the subject studied each word and decided whether its referent was living or nonliving; again, the decision was conveyed by means of computer mouse. The 320 words presented were selected such that half contained the letter a, half referred to living things, half of the words with the letter a were "living," and

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Abbreviations: PET, positron emission tomography; SPM, statistical parametric mapping.

half of the words with the letter a were "nonliving." The two tasks were identical in sensory input and motor output—only the cognitive demands differed: shallow processing (requiring orthographic analysis) versus deep processing (requiring semantic analysis). Half of the subjects carried out the shallow task and half carried out the deep task on each block of 80 words. Subjects were not forewarned of the subsequent memory test, and no subject expected such a test. Twenty minutes after the last scan, subjects were given a yes/no recognition memory task in which the 80 shallowly processed words (40 during each of two scan intervals) were mixed randomly with the 80 deeply processed words and 80 nonpresented but otherwise similar distractor words. The 240 words were presented serially on the computer screen at a 1.5-sec rate, and the subject decided whether or not each word had been presented previously by pressing the appropriate mouse button.

Subjects. Twelve right-handed (13) men, aged 21–35 years (mean, 25.3 years), participated in the study. Subjects were screened to ensure that none suffered from a current or past medical, neurological, or psychiatric disorder (14). Subjects were also screened for any prior history of serious head injury, prolonged loss of consciousness, or active use of medications or recreational drugs. There were no exclusions. Data for all subjects are presented here.

PET Scanning. PET scanning was done with a GEMS Scanditronix PC-2048 head scanner (15). Subjects were scanned lying down, with a thermoplastic custom-fitted facemask for head stabilization. Each scan was done using a 40-mCi (1 mCi = 37 MBq) bolus injection of ^{15}O-labeled water into a left forearm vein through an indwelling catheter (16, 17). The cognitive task was started 45 sec prior to the 60-sec data acquisition for each scan. The scans were 10 min apart. The images were corrected for attenuation by using a transmission scan acquired prior to the first PET scan, using a ^{68}Ge rotating pin source. The scans were reconstructed using a Hanning filter with a cutoff frequency of 0.5 Hz.

To obtain absolute measures of regional cerebral blood flow, arterial sampling is required, which adds an element of invasiveness and risk for the subject. To avoid this, most recent PET studies for delineating neural correlates of mental phenomena have used normalized integrated regional counts as an index of regional cerebral blood flow (18, 19), since it has been shown that integrated regional counts are linearly correlated with actual blood flow (20, 21). In keeping with this practice, we have measured and report integrated regional counts as an index of regional cerebral blood flow.

PET scans were analyzed by using statistical parametric mapping (SPM) developed and made available to us by K. J. Friston and colleagues at the Hammersmith Hospital, London, England. The SPM method of PET image analysis has four major steps. The first step involves the stereotactic reorientation of the images along the bi-commissural line, using normalized PET templates (22). The next step involves a plastic transformation of these images by a nonlinear resampling technique to correct for anatomical variance across subjects (23). Differences in the whole-brain global counts are accounted for across scans by using the global mean as a covariant (24). The data are analyzed statistically on a voxel-by-voxel basis, where each voxel corresponds to the Talairach and Tournoux atlas (25, 26). For this analysis a given voxel was considered to be significantly activated if, on comparison with a reference task, there was an increase in regional cerebral blood flow which was statistically significant at $P < 0.05$ (Bonferroni correction). These values correspond to Z scores of 3.4 and above in this study. A region was considered to be activated if a spatially contiguous set of voxels were all independently significant at a level of $P < 0.001$. Such a method of analysis has been shown to guard against excessive false positives (27). Software for the SPM was provided by the Medical Research Council Cyclotron Unit, Hammersmith Hospital (London), and was run on a Sun-Sparc 10 workstation (Sun Microsystems, Mountain View, CA) using MATLAB version IV (Mathworks, Natick, MA) and ANALYZE (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN).

RESULTS AND DISCUSSION

Cognitive Performance. Subjects performed the tasks with a high level of accuracy. Mean accuracy levels for the shallow processing task and deep processing task were 97% and 94%, respectively. In line with previous work (2), subjects' responses were faster in the shallow, "a - checking" task than in the deeper, "living/nonliving" task (mean response time, 989 msec vs. 1034 msec, $t_{\mathrm{df}11} = 2.36$; $P < 0.05$). In the recognition memory task, the mean hit rates for words originally processed in the shallow and deeper tasks were 0.57 and 0.75, respectively. The mean false-alarm rate was 0.25. The hits-minus-false-alarms scores were therefore 0.32 and 0.50 for shallow and deeper tasks. The corresponding d' values were 0.81 and 1.30, respectively. The difference was statistically reliable: $t_{\mathrm{df}11} = 6.4$; $P < 0.001$.

Image Analysis. The relevant data for the present study were provided by subtraction of the image obtained during shallow processing from that obtained during deeper processing. This comparison revealed an increase in regional cerebral blood flow, in a single contiguous region in the left inferior prefrontal cortex. The region of activation extended from Brodmann's areas 45 and 46 in the left inferior frontal gyrus posterosuperiorly [representative pixel in Talairach coordinates (27): $x = 38$ mm, $y = 28$ mm, $z = 16$ mm] to Brodmann's areas 47 and 10 in the left middle frontal gyrus anteroinferiorly (representative pixel: $x = 28$ mm, $y = 34$ mm, $z = -4$ mm). The region is graphically represented in Fig. 1. No other regions demonstrated activations at our specified level of significance.

Discussion. When subjects carry out deeper as compared to shallow processing operations on the same verbal stimuli, the deeper encoding operations are accompanied by increased neural activity in the left inferior prefrontal cortex in Brodmann's areas 45, 46, 47, and 10. Additionally, and in line with previous cognitive studies (2), the deeper processing condition was associated with enhanced episodic recognition of the processed words.

Although no previous PET studies have explicitly examined encoding operations, Petersen and Fiez (9) have carried out a series of experiments to study the neural correlates of single-word processing. Their purpose was not to investigate processes of episodic memory and thus they did not take any measures of recall or recognition. However, their "verb generation" condition required more elaborate semantic processing of each presented word (generate an appropriate verb for each presented word: e.g., food—*eat*) whereas their "noun repetition" condition involved less elaborate processing (repeat presented nouns: e.g., food—*food*). These two tasks may be conceptualized as "deep" and "shallow", respectively, and can be expected to have cognitive results similar to those reported in our study. Indeed, a recent cognitive study conducted in our laboratory, using the same stimuli as Petersen and Fiez, showed that verb generation was associated with substantially higher recognition memory performance 5 days later than was noun repetition (hit rate minus false-alarm rate, 0.39 vs. 0.15, respectively) (28). Consistent with our PET observations, Petersen and Fiez (9) also reported an activation of the left inferior prefrontal cortex with the deeper processing task.

In addition, several other investigators have observed left inferior prefrontal activation when comparing deeper, semantic processing with relatively shallow processing of ver-

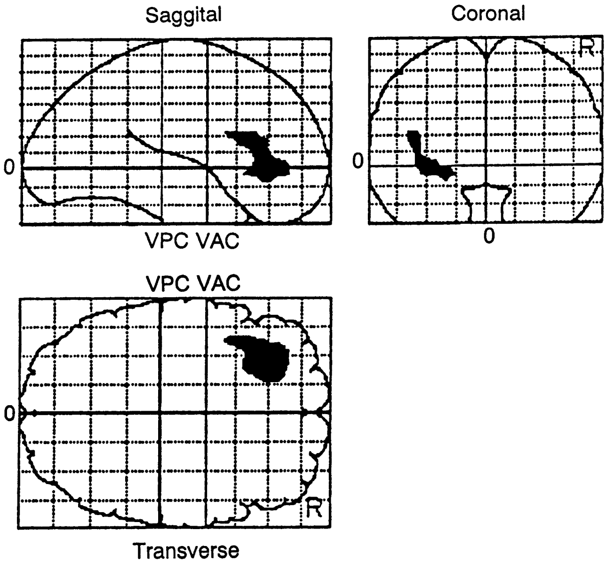

FIG. 1. Regions of the brain which show an increased regional cerebral blood flow in the deep processing condition as compared to the shallow processing condition. The results are projected in three two-dimensional planes. Clockwise from below these are as follows: transverse projection, as seen from above (R, signifies right side; VAC, vertical line through the anterior commissure; VPC, vertical line through the posterior commissure); sagittal projection, as seen from the side (frontal regions to the right, occipital regions to the left); and coronal projection, as seen from behind (R, right side). The superimposed grid and the numbers in the margin represent Talairach and Tournoux (27) coordinate space, a vertical line through the anterior commissure (VAC), and a vertical line through the posterior commissure (VPC).

bal stimuli (29–31). While those studies were not designed to explore memory processes as such, similar tasks have yielded reliable differences in episodic memory in many previous cognitive experiments (6).

Consistent with these previous studies, our results demonstrate an association between semantic processing (as required by the semantic task and confirmed by the high accuracy level of task performance), higher subsequent memory performance (as confirmed by the recognition test), and increased activity in the left inferior prefrontal cortex. Given our present state of knowledge of the relations between cognitive processes and their neuroanatomical substrates, the interpretation of these findings must be speculative. Although left prefrontal activation was associated with enhanced memory performance in our study, it seems quite unlikely that this region constitutes the locus of memory storage. It is more plausible that the left inferior prefrontal structures identified are part of a more complex network of cortical and subcortical structures that subserve memory functions. In keeping with similar previous suggestions (32–34), we propose that when subjects process verbal stimuli in a semantic manner, either under experimental or real life conditions, this involves increased neuronal activity in the left inferior prefrontal cortex. Increased activity in this region, irrespective of the individual's intention to remember, leads to a more readily retrievable memory trace.

How the activation in the left inferior prefrontal cortex leads to a more retrievable memory trace, the manner in which these memory traces are stored, and how these traces become accessible at retrieval are still unclear. We address the relation between encoding and retrieval in an accompanying article (35). Finally, we emphasize that for a fuller understanding of human memory processes, it is imperative that cognitive processes, neural activity, and memory performance be integrated into a single framework. By relating a well-known cognitive phenomenon (the levels of processing effect) to its neural correlates (left inferior prefrontal cortex) and its behavioral consequences (enhanced episodic memory retrieval), we believe we have identified some of the essential components of such a framework.

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