

Research report

The neural correlates of intentional learning of verbal materials: a PET study in humans

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Abstract

The purpose of this study was to identify the brain regions invoked when subjects attempt to learn verbal materials for a subsequent memory test. Twelve healthy subjects undertook two different tasks: *reading* and *encoding* of word pairs, while they were being scanned using [¹⁵O]H₂O positron emission tomography (PET). As expected, the *encoding* pairs were remembered much better (recall 39% vs. 8%; $P < 0.001$) than *reading* pairs in a subsequent memory test. The *encoding* scans, as compared to *reading* scans, showed activation of the left prefrontal cortex, the anterior cingulate cortex and the left medial temporal cortex. The left prefrontal activations were in two discrete regions: (i) a left anterior and inferior left prefrontal (Brodmann's areas 45, 46) which we attribute to semantic processing; and (ii) a left posterior mid-frontal region (BA 6, 44) which may reflect rote rehearsal. We interpret the data to suggest that when subjects use cognitive strategies of semantic processing and rote-rehearsal to learn words, they invoke discrete regions of the left prefrontal cortex. And this activation of the left prefrontal cortex along with the medial temporal region leads to a neurophysiological memory trace which can be used to guide subsequent memory retrieval.

Keywords: Positron emission tomography; Encoding; Memory; Episodic; Human; Prefrontal cortex

1. Introduction

Episodic memory is the distinctively human ability to remember personal happenings with reference to one's own past. An act of remembering begins with the encoding of a stimulus-event and ends with the retrieval of it. Encoding refers to the processes that convert a perceived event into an enduring neurophysiological trace [31]. The information stored in an engram (or memory trace) can be used to guide subsequent retrieval. Retrieval refers to the process that transforms the neurophysiological engram into the mental experience which we usually call a 'memory' of a previous event.

Encoding and retrieval are independent, yet closely linked memory processes [7,31]. The neuronal underpinnings of these processes are still largely unknown, primarily because lesion data cannot readily be used to separate encoding from retrieval. The problem is that the confirmation of successful encoding of a given stimulus requires successful retrieval. Therefore, if a patient with a certain lesion fails to retrieve information it is not known to what extent the lesion has affected encoding, storage, retrieval, or some combination of these processes and mechanisms. While innovative experimental designs and analyses have been used in neuropsychological studies to distinguish brain regions crucial in encoding versus retrieval; inferences from these approaches remain indirect at best [32,1].

Functional neuroimaging of cognitive processes provides a unique opportunity to observe the brain during encoding, independently of retrieval processes [32]. The

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use of the standard subtraction technique allows one to identify the brain regions that show differential activation, as indexed by differences in regional cerebral blood flow (rCBF), when the rememberer engages in an activity that leads to encoding. In a previous study we have delineated the neural correlates of efficient encoding as achieved by subjects while they process stimuli semantically [1]. In that study, participants were asked to make judgments about concrete nouns either in terms of the perceptual properties of the word (“Does the letter A occur in the word?”) or in terms of its meaning (“Does the word denote a living thing?”). No explicit instructions to learn the words were given nor were the participants advised of a subsequent memory test. It is well known that meaning-based encoding of verbal items is more effective than perceptual encoding — the Levels of Processing Effect [4,5,17]. The results showed that meaning-based processing, in comparison with perceptual processing, led to: (i) a significantly higher performance on a subsequent recognition test; and (ii) an enhanced rCBF, reflecting increased neuronal involvement, of the left dorsolateral prefrontal cortex. We interpreted these observations as suggesting that meaning-based processing at a cognitive level engages the left prefrontal cortex at a neural level and that this results in efficient encoding of stimuli in the absence of any intent on the subject’s part to learn the material [15].

While unintentional learning characterizes most real-life learning situations, most laboratory or neuropsychological tests rely on explicit instructions to ‘learn’, ‘remember’ or ‘commit to memory’ a list of materials. It is of obvious interest how the neuroanatomical correlates of intentional learning of verbal materials compare with those associated with incidental learning. Prior research in cognitive psychology provides guidance in terms of what to expect. Most subjects tend to use a mix of two basic cognitive strategies: (i) rote rehearsal involving subvocal repetition of individual items; and (ii) elaboration or organizational strategies in which items are related to one another through various kinds of semantic associations [25,27,13]. Interestingly enough, Shaughnessy found that while semantic associations are clearly more effective in encoding, most subjects do not think so and tend to engage in rote rehearsal when given a choice [27].

Results from recent PET studies permit us to hypothesize what brain activations would accompany the above cognitive strategies. Subvocal rehearsal entails the use of verbal working memory and recent studies point the involvement of the posterior mid-dorsolateral frontal cortex in this task [23,21,28], whereas elaborative rehearsal requires manipulation of the semantic content of the stimulus and has been shown to activate the anterior inferior frontal gyrus [22,15,16]. Therefore we hypothesised that encoding under intentional learning conditions would engage the left prefrontal cortex; antero-inferiorly through the semantic processing required for elaborative rehearsal, and postero-

inferiorly through the subvocal rehearsal and verbal working memory requirements.

2. Materials and methods

Twelve healthy right-handed volunteers (six men, six women), age range 19–31 years, participated in this study approved by the Human Subject Use Committee of the University of Toronto and the Baycrest Centre. Prior to the day on which the PET scan was done subjects visited the laboratory and were given a test-run of the experiment with dummy stimuli. On the day of scanning each subject undertook a total of eight PET scans, two scans in each of four task conditions. The conditions are named: *reading*, *encoding*, *recognition* and *recall*. Each subject did the *reading* task first, the *encoding* task third, while *recognition* and *recall* were systematically balanced in positions two and four across subjects. Scans five through eight were a mirror-image of the first four scans (ABCD-DCBA), thus counterbalancing any linear order-effects. The results of the recognition and recall aspects of this experiment have been described elsewhere [2].

In both the *reading* and the *encoding* task subjects saw two words on the screen, e.g., ‘motorcycle tattoo’. The members of each pair were moderately related such that a meaningful association between the two was possible. The words were presented white on black background on a computer screen suspended 60–75 cm in front of the subjects. The words were in lowercase, and appeared for four seconds followed by a one second inter-stimulus interval. The task started 35–45 s prior to the start of the PET scan and continued for a total of 24 stimuli over two minutes. The list-materials presented for encoding and reading were counterbalanced across subjects. In the *reading* task the subjects were asked to read aloud the second word of the pair and were told not to make an intentional effort to memorise the material. In the *encoding* task the subjects were told to read aloud the second word and to memorise the word-pairs for a subsequent memory test. The subjects were informed that the purpose of the *encoding* task was to investigate brain regions involved in learning. They were told that they should try and make meaningful associations between the words, as an example they were told that one could meaningfully associate ‘motorcycle’ to ‘tattoo’ with reference to a biker’s gang where these two things are commonly observed.

Ten minutes after the last PET scan subjects’ memory for the stimuli encountered during both the *reading* and *encoding* tasks was tested. Memory for the word-pairs was tested using separate recognition and cued-recall tests with blocks of six targets from each of the *reading* and *encoding* conditions.

PET scans were obtained with a GEMS-Scanditronix PC2048-15B head scanner using a bolus injection of 40 mCi (1.48 GBq) of [¹⁵O]H₂O and 60-s data acquisition.

The PET data were analysed using the new version of the Statistical Parametric Mapping (SPM) technique using software from the Wellcome Department of Cognitive Neurology, London, UK [11] and implemented in Matlab (Mathworks, Sherborn, MA, USA). The analysis involved the following steps: the four images from each subject were realigned to the first image, using a rigid body transformation [9]. These realigned images from each subject were then transformed into a standard space by matching to a reference image that already conforms to the standard Talairach and Tournoux space [30]. These images were then smoothed using an isotropic Gaussian kernel of FWHM of 15 mm. The effects of the conditions (cognitive tasks) on the regional cerebral blood flow at each voxel were then estimated using a general linear model, wherein the changes in global counts were considered as a covariate [10]. The effects of each condition were estimated using linear contrasts, which yield a t -statistic for a given comparison at each voxel. The t -statistic was expressed as a standardised Z -score to assist comparisons [11]. Since SPM involves multiple comparisons, a few voxels may reach the threshold of significance by chance. To obviate this, the significance of each region was estimated using distributional approximations from the theory of Gaussian Fields [11]. The regions were considered significant only if: (i) the probability of observing the peak difference in a given region was < 0.05 after correction for multiple comparisons; and (ii) the probability of observing a contiguous volume of activated voxels of the observed size was < 0.05 [11].

3. Results

All twelve subjects were recruited for this study all subjects completed the study and their results are reported. During the PET scans the subjects were to read aloud the second word in both the *reading* as well as the *encoding* task — all subjects did this without error. The fact that subjects did encode as required is confirmed by the results

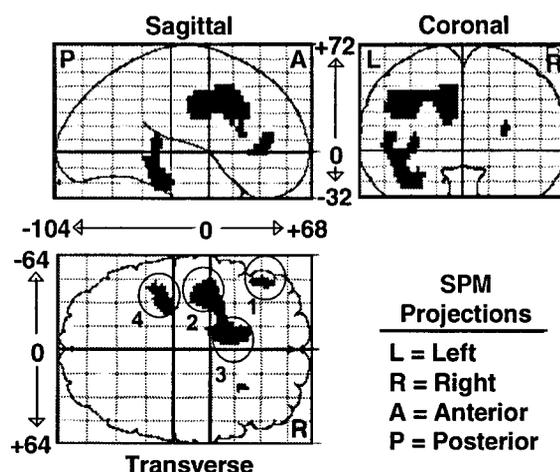


Fig. 1. Regions of the brain which showed a significant change in regional cerebral blood flow in the *encoding* task as compared to the *reading* task. The regions are numbered corresponding to Table 1; and the precise coordinates of the peaks with their Z -scores are listed in Table 1. The SPM is displayed in a standard format as a maximum intensity projection viewed from the back, the right hand side and the top of the brain. The anatomical space corresponds to the atlas of Talairach and Tournoux [30].

of the cued-recall and recognition tests subsequent to the PET scan. Words seen in the *encoding* task were significantly better remembered than words seen in the *reading* task in both recognition (Hit-rates were 0.89 vs. 0.59 respectively, paired t -test $t_{df=11} = 3.02$; $P < 0.05$; Hit-rates minus False Alarm rates were 0.82 vs. 0.50 respectively; paired t -test $t_{df=11} = 2.73$, $P < 0.05$) and cued-recall (39% vs. 8% respectively, paired t -test $t_{df=11} = 5.60$; $P < 0.001$).

The brain regions more activated in encoding were ascertained by subtracting the *reading* rCBF scans from the *encoding* rCBF scans in SPM — the results are tabulated in Table 1 and presented in Fig. 1. As the tables show the encoding task differentially involves the left dorsolateral prefrontal cortex (BA 45 and 46); the left posterior mid-dorsolateral frontal cortex (BA 6 and 44);

Table 1
Brain regions activated by intentional learning

Region (Brodmann's areas)	Talairach coordinates(in mm)			Z	Probability P
	X	Y	Z		
1. Left inferior frontal gyrus — anterior (BA 45, 46)	-48	36	0	4.29	0.024
2. Left inferior frontal gyrus — posterior (Broca's area, BA 6, 44)	-32	-4	32	6.15	< 0.001
3. Left anterior cingulate (BA 24, 32)	-10	12	32	5.88	< 0.001
4. Parahippocampal/fusiform gyrus	-38	-34	-4	4.53	0.009
5. Right superior longitudinal fasciculus	26	22	16	4.32	0.021

Regions of the brain which showed a significant change in regional cerebral blood flow in the *encoding* task as compared to the *reading* task. Only those regions which were significant at a $P < 0.05$ after correction for multiple comparisons were considered to be significantly activated. This corresponded to a Z -score of 4.0. The pixel within each region which shows the highest statistical significance for a given comparison is reported as its X , Y and Z coordinates in mm, using the Talairach and Tournoux reference system. On the X -axis right is positive; on the Y -axis regions anterior to the anterior commissure are positive; on the Z -axis regions above the bicommissural line are positive. The highest pixel does not give an indication of the spatial extent of the activations which can be better appreciated with reference to the accompanying Fig. 1.

the left anterior cingulate (BA 24, 32) and the left medial temporal region. In addition there was a small region localized to the superior longitudinal fasciculus in the right prefrontal cortex which also met statistical threshold.

4. Discussion

The study reveals the network of brain regions which subjects engage in an intentional effort to memorize verbal material. In particular it shows an almost completely unilateral activation involving four relatively discrete regions: two distinct regions within the left prefrontal cortex; the anterior cingulate and the left medial temporal region. The results provide the first direct comparison of brain regions involved in intentional encoding of verbal material to those involved in just reading; and in doing so complement previous efforts [26,11] to identify the brain regions involved in encoding of verbal materials. We discuss these results in light of previous studies, and then discuss the plausible roles of different brain regions in encoding.

To our knowledge three previous studies have explicitly addressed the issue of encoding. In the first such report [15], we studied the brain regions involved in encoding information using the Levels of Processing paradigm. In that study the subjects were not given any explicit instructions to remember the words, therefore, encoding was incidental and unintentional as occurs in many everyday situations. We had observed an activation in the left anterior inferior frontal gyrus (BA 45, 46, 47 and 10) when the perceptual condition was subtracted from the semantic condition. The same region of the left prefrontal cortex was activated in our present study (region 1, Table 1). However, the present study activated several regions in addition to those observed previously, namely: Broca's and adjacent regions of the left prefrontal cortex, the left anterior cingulate, and the left medial temporal cortex regions.

A second study of verbal encoding used a different approach — Shallice and colleagues asked subjects to remember pairs of words [26,8], but their subjects performed a distractor task simultaneously. Shallice found that an activation of the anterior left inferior frontal gyrus was associated with encoding. The region they report is consistent with that observed in our study (region 1) and lends support to the putative role of this region in encoding verbal material. Shallice also found an activation in the retrosplenial region, which we did not find in our study.

Finally, in a recently published report, Grady and colleagues [14] studied subjects as they learned a series of faces for a later memory test. While their study involved encoding of a non-verbal stimuli, they also found an activation in the left prefrontal region and in the anterior cingulate, similar to the regions activated in the present study.

It seems then that the left anterior inferior frontal gyrus

is reliably linked to encoding [15,26]. It is observed both when the encoding is intentional [26,14], and when it is incidental [15]. Notably it is seen with both verbal [15,26], and non-verbal material such as faces [14]. This raises the question: what exactly does the left prefrontal cortex contribute to the encoding process?

Activation of this region is seen when subjects generate verbs in response to nouns [18,22], generate category exemplars, [12] make category decisions about presented words [15], regardless of perceptual or output modality [16]. Since all these studies include accessing and manipulating semantic representations, we have suggested this region is involved in 'working with meaning' [16]. There is a rich literature in cognitive psychology linking working-with-meaning to encoding — the Levels of Processing effect [4,17]. It has been known for over two decades that stimuli processed with reference to their semantic attributes are remembered much better than those learned with reference to perceptual attributes. In fact, it has been shown that as long as the stimuli are processed semantically, explicit instructions to 'try and remember' are superfluous [5].

In light of these previous findings it appears that whenever subjects process stimuli semantically, whether under instruction or by their own choice, with either verbal or non-verbal stimuli, it requires the participation of the left prefrontal cortex. Exactly why information processed by the left prefrontal cortex leads to a better trace, is a project for future study. We do not think of the left prefrontal cortex as the site of a stored engram, if indeed there could be such a single site. However it seems plausible that the neuronal connectivity of the left prefrontal cortex to the posterior regions, including the medial temporal regions, may put it in a vantage position such that information processed with the involvement of the left prefrontal cortex, either under instruction or by default, leads to a better and more retrievable engram.

In addition to the anterior prefrontal region, we also found an activation in the posterior mid-dorsolateral frontal regions, BA 6 and 44, superior to Broca's area. This region is distinct from the anterior prefrontal activation discussed previously, and was not observed in our previous studies [15,16]. We had expected that such a posterior prefrontal region would be activated since it is known that normal subjects engage subvocal rehearsal and verbal working memory in an effort to memorise [25,27,13] and three previous PET studies have localised these functions to posterior mid-dorsolateral frontal regions [23,21,28]. Our finding (Region 2, Table 1) is consistent with this expectation and it is a reasonable speculation that when subjects are asked to encode, they engage in subvocal rehearsal even though it is not necessarily the most effective strategy for learning [5,27]. Our results provide preliminary support for a dissociation between the involvement of the two frontal regions one related to semantic processing the other to rote-rehearsal. However, our experimental approach did

not explicitly manipulate the level of rote-rehearsal. Therefore, a future experiment explicitly manipulating the two components of encoding — semantic processing and rote-rehearsal — would help confirm the dissociation suggested by our findings.

The anterior cingulate (BA 24, 32) (Region 3, Fig. 1) was activated on the left of midline, in the *encoding* condition. This is consistent with the previous findings in studies of encoding by Shallice [26] and Grady [14]. Fletcher [8] has suggested that left anterior cingulate reflects the greater 'selective attention' required during successful encoding, an interpretation consistent with previous experiments investigating the role of the anterior cingulate using the Stroop or other visual attention tasks. The only discordant note, perhaps, is our previous study of encoding wherein subjects undertook unintentional learning; and while they showed activation of the dorsolateral prefrontal cortex they exhibited no activation of the anterior cingulate [15]. Even with a further extension of that sample we did not observe an anterior cingulate activation [16], suggesting that the absence of the finding in our previous study was not just an issue of lack of sufficient statistical power. The observation of robust encoding in the previous study suggests that whatever the role of the anterior cingulate, its differential activation is not a prerequisite for successful encoding.

The fourth major activation observed during encoding was the in the left medial temporal region (Region 4, Fig. 1) extending inferiorly from the fusiform gyrus to include the lateral aspect of the hippocampus. In many ways the medial temporal region, especially the hippocampus, is the brain region which most firmly associated with encoding in neuropsychological studies [29]. It has been suggested that the hippocampus is crucial to memory formation; and has an important role in binding together neuronally distributed events that happen at the time of perception and encoding [6,29,20]. However two issues complicate a simple interpretation of the hippocampal activation that we have observed in this study.

First, the process of data analysis of PET rCBF images applies a smoothing filter to the raw data, in an effort to improve the signal to noise characteristics of the images and to compensate for anatomical heterogeneity across subjects. It has been shown that boundaries and well as the peak of activation are sensitive to the exact filter width used for analysis [24]. In our experience, we have found that altering the filter from 10 to 15 mm FWHM often causes a shift in the exact location of the peak or the boundary of the activation. When the activation lies in a large cortical region, a slight shift of the exact peak location does not change the interpretation in a significant fashion. However, if the activation is localized to small subcortical structures a small shift in location may lead to an exclusion of the structure and change the interpretation greatly.

In the present data we have presented the results using

the filter width of 15 mm FWHM. This is in keeping with the present standards for such data. When we analyse this data using a smaller filter, 10 mm FWHM, the peak activation shifts from the parahippocampal region ($x = -38$ mm, $y = -34$ mm, $z = -4$ mm) to the inferior fusiform gyrus ($x = -42$, $y = -32$, $z = -16$). All the other reported activations remain within 8 mm of localization with the 15 mm FWHM and since they are located in large cortical regions this shift does not in anyway change the regional interpretation. None of the previous cognitive activation studies have provided an analysis of their findings at different filter widths, though we are quite certain that changes in filter width must lead to shifts in the peak activity even in the previously presented data. This shift of the peak with a smaller filter casts some doubt on whether the medial temporal activation extended to involve the hippocampal region. We do not think that filter-width discrepancies are the cause for absence of the hippocampus from most studies of memory, but we do feel that our present localization of the medial temporal activation to the hippocampus should be considered tentative and needs replication.

A second issue that complicates the interpretation of the hippocampal finding is that previous studies of verbal encoding did not find this region activated despite unequivocal evidence that encoding occurred [26,15]. In our previous study of encoding we also found no comparable activation [15]. One could argue that our previous study differed in that encoding was unintentional. However, that does not seem sufficient cause since neuropsychological studies show a role of hippocampus in intentional as well as incidental learning. Furthermore, intention alone could not explain the difference since previous studies [26,8], which required intentional encoding did not find a hippocampal activation. Various reasons — spatial resolution, temporal scale, physiological, etc. — have been forwarded by Fletcher [8] for the absence of hippocampal activations in the previous studies. But, it would be fair to say that a satisfactory answer to this discrepancy between neuropsychological and functional imaging data is not as yet available.

Regardless of whether the hippocampus proper and its adjoining cortex is activated, there is a robust activation of the anterior fusiform gyrus. The activation of this region in a visual verbal-stimuli experiment is understandable as this region, especially on the left, has been implicated in the processing of complex visual form [3]. However, the processing of visual forms, words in this experiment, was required both in the reading and the encoding condition. Now, one could argue that when attempting to learn subjects engage in greater and more attentive lexical processing; this may explain the greater activation of this region in encoding since it has been shown that directing attention to a particular attribute of a stimulus leads to a greater activation in the region usually involved in the processing of that attribute [19,3]. However, such an expla-

nation is essentially post-hoc and would require more direct demonstrations.

Finally, there was an activation in the superior longitudinal fasciculus in the right hemisphere. The activation was spatially limited, but it met the criterion for statistical threshold. Increases in regional cerebral blood flow reflect change in synaptic firing; therefore the increase localised to a long-association fiber may well reflect a false-positive. We await a replication before offering an interpretation regarding its possible role.

In summary then, our study outlines a network of regions involved in encoding of verbal material. When subjects try to remember words with the anticipation of a subsequent test, they tend to semantically process the material and rehearse it in a subvocal fashion. This study suggests that these mental processes engage the left prefrontal cortex in the anterior inferior gyrus and in the posterior mid-frontal cortex. We suggest that these regions may be accorded to semantic processing and rote-rehearsal respectively, though an experiment which experimentally manipulates these two processes would be required to confirm this hypothesis. It is hoped that future studies will elucidate the functional interactions between the left prefrontal cortex, the anterior cingulate and the medial temporal cortex, and will explain why the involvement of the prefrontal cortex leads to more retrievable memory traces.

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