Priming of new associations: a PET study

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Cognitive properties of associative priming are different from those of the non-associative priming. We examined areas associated with associative priming to understand its cortical processing. After subjects had studied pairs of unrelated words, they were shown one of the studied words and a 3-letter word-stem that could be completed using either the word that was paired with the presented studied word (same context), or with a different word (different context). As compared to the fixation, both conditions elicited increased activations in the left prefrontal and decreased activation in the extrastriate cortex. Medial temporal lobe was activated only in the same-context condition. This finding helps to understand why associative priming is impaired in some amnesic patients. *NeuroReport* 14:2475–2479 © 2003 Lippincott Williams & Wilkins.

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INTRODUCTION

A number of cognitive studies have demonstrated that priming effects on implicit memory tests are influenced by new associations between previously unrelated items. Thus, in a word-stem completion task administered after subjects had studied pairs of unrelated words, subjects are more likely to complete stems with previously studied words when the stem of a target word is presented along with the previously paired word, rather than with a different studied word [1,2]. Subjects make faster responses in a lexical decision task when the target word is preceded by its original partner than when it is not [3]. These observations suggest that priming is influenced by the relational characteristics of studied items.

This associative priming phenomenon has a number of characteristics that are not shared by non-associative priming. For example, while associative priming is increased significantly by deep compared to shallow encoding [1], or when subjects become aware of the relation between the priming task and prior study [4]; non-associative priming is largely unaffected by these manipulations (for review see [5]). In addition, associative priming on the stem completion task is typically compromised in amnesic patients [1], who generally exhibit intact non-associative stem completion priming (for review see [5]).

These differences suggest that associative and non-associative priming depend, at least in part, on separate neural networks. It has been suggested that processing of relational information between studied items is a characteristic of declarative (explicit) memory and that non-declarative (implicit) memory does not involve relational processing [6]. It implies that associative priming depends on explicit memory mechanisms. This assumption is supported by the observation that densely amnesic patients, with grossly impaired explicit memory, do not consistently show a priming advantage for a newly formed association [1,7]. Nonetheless, associative priming does not share all the attributes of explicit memory. For instance, while associative priming is sensitive to changes in sensory modalities between study and test [2], and is attenuated by temporal separation of the associated item [8], explicit memory remains largely unaffected by these manipulations (for review see [5]).

In the present experiment, we used PET to examine brain mechanisms involved in associative priming. Previous imaging studies have reported priming-related activation reductions in various cortical regions, including extrastriate [9–12], and left prefrontal areas [10]. On the other hand, explicit, relational processing has been linked with increased activations in the left prefrontal and medial temporal lobe (MTL) areas [13,14]. We studied the pattern of cortical activation elicited during an associative priming task that employed a word-stem completion test in a paired associate paradigm. After subjects had studied pairs of unrelated words, they were shown one of the studied words and a 3-letter word stem, which could be completed using either the word that was paired with the presented studied word (same context condition), or with a different studied word (different context condition). Subjects were scanned during stem completion, and also during a control and a fixation condition.

MATERIALS AND METHODS

Experiments were conducted on eight, right-handed, native English-speaking, young healthy volunteers (mean age 22 years; range 21–25 years; male three, female five). Before recruitment, informed consents were obtained and volunteers were screened to rule out a history of neurological or psychiatric condition and prolonged use of recreational or prescription drugs. A handedness test was also administered [15].

During the study phase, volunteers were shown a list of 100 pairs of words that were not semantically related (e.g. window–faculty). Each pair was presented for 3 s (white on black background) and subjects were asked to indicate, by pressing a key, whether the two words were related to each other by their use in a similar context or by rhyme. Approximately 5 min after the study task, a word-stem completion test was administered under the same- and different-context conditions. In the same-context condition, the first 3 letters (word stem) of a studied target word were shown, along with the word with which it was paired at the study (e.g. window–fac). Subjects were asked to complete the word stems using the first word that came to mind. In the different-context condition, studied words were re-paired such that the word presented with the stem had not been paired with the target word during the study task (e.g. moon–fac). No new words were used in this condition. Subjects were scanned during stem completion tasks and also under a control condition in which non-studied words were used. We made sure that none of the word stems could be completed using a studied word. Each test block had 40 pairs, and each pair was shown for 3 s. Half of these pairs were presented in a pre-scan window. To avoid anticipatory and automatic responses, expected in a blocked design paradigm, pairs from both same- and different-context conditions were mixed randomly in each block. In the pre-scan window, the number of pairs belonging to the two conditions was the same, but during the scan period the majority of pairs (75%) belonged either to the same- or to the different-context condition. There were two study blocks, each of which was followed by three test blocks (same context, different context, and control). Words in each list were matched for frequency of occurrence and the lists were counterbalanced across subjects and test conditions. Each stem made at least six legal words and each word had a unique stem.

Subjects were also scanned under a fixation, look-only condition in which they looked at a cross-mark presented at the center of the monitor. There were two fixation blocks. One of them was presented before, and the other after, the stem completion blocks. The sequence of stem completion blocks was counterbalanced across subjects. Verbal responses were recorded using a magnetic tape recorder and response time was recorded using a PsyScope button box.

PET data acquisition and analysis: Procedures used for data acquisition were similar to those used in the earlier experiments [10,13,16,17]. The task was started at time zero. The PET camera was started at 30 s and continued for 90 s. At 60 s, radioactive tracer inhalation (^{15}O-labeled CO_2) and emission data acquisition began. Tracer inhalation and data

acquisition lasted for 60 s. The camera recorded data in 5-s epochs for a total of 90 s. For analysis and image formation, the data collected between 60 and 120 s were used. A washout period of ~10 min was allowed between successive scans.

After image reconstruction, PET data were analyzed using SPM99. The data at each voxel, normalized by the global mean, were considered to be the independent variable and analyzed using univariate linear statistical model. We set thresholds for significance according to the theory of Gaussian fields [18]. When no localizing hypothesis or prior experimental data were available, a threshold of $z = 4.2$ was considered significant. We settled for this value because a threshold of 4.2 is considered significant (corrected $p < 0.05$) for unplanned comparisons according to the theory of Gaussian fields (for calculation and discussion see [18]). When we had *a priori* hypotheses that localized the putative activation to a specific anatomic region, we considered a threshold of $z = 3.09$ to be significant. This threshold ($z = 3.09$) constitutes a compromise between a low threshold, uncorrected for multiple comparisons ($z = 1.96$), and a higher threshold ($z = 4.2$) suggested for unplanned comparisons [19].

RESULTS

In the same-context condition, subjects completed $52.5 \pm 2.6\%$ of stems with a studied word (Table 1); the percentage of stems completed using studied words in the different-context and the control conditions were 32.0 ± 1.3 and $22.4 \pm 0.9\%$ respectively. Compared with the control condition, more stems were completed using target words in both the same- ($p = 0.0001$) and different- ($p = 0.0005$) context conditions. Further, more stems were completed with studied words in the same-context than the different-context condition ($p = 0.0005$). The response times were shorter in the same- (1198 ± 55 ms) and different- (1227 ± 60 ms) context conditions than in the control condition (1273 ± 60 ms).

Imaging data: Regions showing changes in regional cerebral blood flow (rCBF) in the three test conditions are shown in Table 2. Compared with the fixation, increased rCBF was observed in the same-context condition in the left inferior frontal gyrus (Brodmann's area, BA 44 and 45), and in the right superior temporal sulcus in close proximity to the MTL (Fig. 1). In the different context condition, there was increased rCBF in the left inferior frontal (BA 45), and left middle temporal gyri (BA 21).

Significantly increased rCBF was observed in the right MTL in the same context condition compared with that in the different context condition. In the control condition,

Table I. Percentage of stem completed using the target word and response time in the same-context, different-context and control conditions.

Condition	Correct response (%)	Response time (ms)
Same context	52.5 ± 2.6	1198 ± 55
Different context	32.0 ± 1.3	1227 ± 60
Control	22.4 ± 0.9	1273 ± 60

Table 2. Regions showing rCBF changes under different contrast conditions.

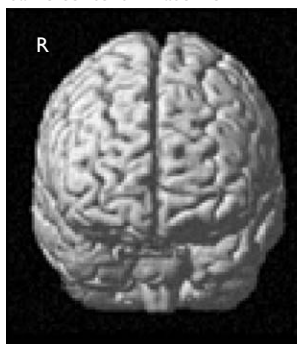| Condition and cortical area	MNI coordinate (x,y,z)	Z-score
Same context > fixation		
Inferior frontal gyrus (BA 44)	−46,10,24	6.15
Motor cortex (BA 4)	−56,−2,42	5.70
Inferior frontal gyrus (BA 45)	−54,30,16	5.34
Superior temporal sulcus	42,−28,2	3.85
Same context < fixation		
Superior frontal gyrus (BA 10)	16,60,6	5.75
Superior frontal gyrus (BA 10)	−12,62,4	4.81
Post cingulate (BA 31)	2,−52,38	5.72
Angular gyrus (BA 39)	54,−66,18	4.74
Extrastriate cortex (BA 19)	−46,−72,26	4.38
Different context > fixation		
Inferior frontal gyrus (BA 45)	−56,32,14	5.42
Motor cortex (BA 4)	−54,−2,44	5.28
Mid temporal gyrus (BA 21)	−68,−28,4	4.54
Motor cortex (BA 4)	58,−6,42	4.25
Different context < fixation		
Post cingulate (BA 31)	−4,−54,30	6.62
Extrastriate cortex (BA 19)	−44,−72,28	5.62
Inferior parietal (BA 40)	62,−30,30	5.03
Anterior cingulate	0,50,−4	6.23
Mid frontal gyrus (BA 9)	30,32,36	5.63
Superior frontal gyrus (BA 9)	14,62,6	5.43
Same context > different context		
Medial temporal lobe	42,−34,−4	3.59
Control > fixation		
Motor cortex (BA 4)	−54,−4,44	5.74
Mid temporal gyrus (BA 21/22)	−52,−30,2	4.50
Control < fixation		
Post cingulate (BA 23)	−6,54,30	6.27
Mid frontal gyrus (BA 9)	30,34,34	4.91
Superior frontal gyrus (BA 6)	48,−10,−38	4.78
Mid frontal gyrus (BA 9)	−28,34,44	4.59

When no localizing hypothesis or prior experimental data were available, a threshold of z = 4.2 was considered significant. When we had *a priori* hypotheses that localized the putative activation to a specific anatomic region, we considered a threshold of z = 3.09 to be significant. The coordinates provided are in the Talairach proportional stereotaxic space based on the data of the Montreal Neurological Institute (MNI), and were generated by SPM99. The x,y,z coordinates refer to left–right, posterior–anterior, and ventral–dorsal dimensions respectively.

Fig. 1. Statistical parametric maps showing increased rCBF in the left prefrontal cortex in the same and different context conditions compared with fixation. Also shown is the increased rCBF in the right MTL region in the same-context condition. The changes were localized in the MTL in contrast with the different-context condition while it was located in the superior temporal sulcus, in close proximity to the MTL in contrast with the baseline. The maps are superimposed over MRI templates.

there was increased rCBF in the right middle temporal gyrus. All three test conditions showed increased rCBF in the left motor cortex (BA 4), possibly because subjects used their right hands to make responses in these conditions. In the control condition, significantly increased rCBF over that in fixation was observed only in the left motor area and the middle temporal gyrus. The changes were not significant in contrast with the same or different context condition.
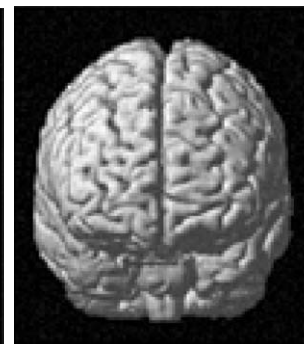
Significantly reduced rCBF, compared with fixation, was observed in both same and different context conditions in the extrastriate area (BA 19). In addition to this, reductions were significant in the same context condition in the superior frontal gyrus, right posterior cingulate (BA 31), and in the right angular gyrus (BA 39). In the different context condition, decreases were observed in the cingulate, the right parietal (BA 40), and prefrontal regions (BA 9), besides the extrastriate cortex. The reductions in the control condition were significant only in the cingulate and the middle (BA 9) and dorsal frontal gyri (BA 6, 10).

DISCUSSION

As expected from previous research [1,7], reliable priming effects were observed in both the same and different context conditions when a studied word was presented along with a word stem, and subjects were asked to complete the stem using the first word that came to mind. The priming effect was significantly larger in the same-context condition, in which stems could be completed using the word that was previously paired with the studied word, than in the different-context condition. The same-context advantage confirms that priming effects were influenced by new associations formed during the paired presentation of unrelated words.

We observed increased rCBF in the left inferior frontal gyrus in both the same- and different-context conditions, compared with fixation. This finding is interesting in view of our earlier observation of similar increases during conscious relational processing [13]. In this experiment, the left frontal activation was observed both during presentation of the intact (studied-pair condition) and rearranged (rearranged-pair condition) pairs of studied words. We have argued that relational processing occurred in both conditions [13]. Interestingly, in the present experiment we observed increased rCBF in both the same- and

different-context conditions, which were similar to the studied- and rearranged-pair conditions, respectively, of the earlier study.

Increased activation of the left prefrontal cortex is generally associated with explicit memory, and has been reported in a variety of explicit retrieval tasks [13,20]. In priming experiments this region usually shows reduced activation [10]. Increased activation observed in the present experiment therefore indicates possible involvement of the aspects of explicit memory in associative priming. In addition to the left prefrontal cortex, increased rCBF was observed in right temporal lobe, in close proximity to the MTL in the same-context, but not in the different-context, condition. Because the MTL is the only area where rCBF differed significantly in the direct contrast between the same- and different-context conditions, it is likely related to the same-context advantage observed in the present experiment and other studies [1,2]. Since, MTL activation is also generally associated with explicit memory [12,21], the observation reinforces the suggestion that aspects of explicit memory are involved in associative priming. Further, it may help to understand why amnesic patients with damage in the MTL often fail to show the same-context advantage in associative priming tasks [1,7].

It is important to note that we did not observe increased activation in the MTL region in the same-context condition in comparison with the control condition. However, because the most appropriate control for the same-context condition was the different-context condition, and we observed significantly increased right MTL activation in a direct contrast with different-context, the activation appears to be specifically associated with the same-context condition. The MTL activation in the same-context condition was no different from that in the control condition, possibly because of the use of novel stimuli in the control condition. Since novel stimuli are known to elicit increased activation in the MTL [14], novelty-related activation in the control condition might have prevented observation of activation in this area in the same-context condition.

While increased rCBF in the prefrontal and MTL indicates a role for explicit memory in associative priming, reduced rCBF observed in the extrastriate area in both same- and different-context conditions suggests involvement of implicit memory. Reductions in this area have been consistently reported in priming tasks [9,10,12,21], and are considered a characteristic feature of repetition priming (for reviews see [22]). The association of reduced extrastriate rCBF with priming in the present experiment is supported by the fact that the reduction was observed only in conditions in which primed words were presented, and not in the control condition, in which novel items were used. The overall pattern of cortical activation therefore indicates that associative priming involves the neural substrates of both explicit and implicit memory mechanisms.

Involvement of aspects of explicit memory in a priming task is not a unique feature of associative priming. We have earlier reported evidence for such an involvement in cross-modality priming [10,23]. As in the present experiment, we observed increased rCBF in the prefrontal area, both in the auditory to visual [10] and visual to auditory [23] cross-modality priming conditions. We suggested in these papers that prefrontal activations were evoked as a result of the involvement of explicit memory. Unlike within-modality priming, cross-modality priming is not driven by perceptual features of the primed items because there are no perceptual similarities between the prime and the cue in the cross-modality condition. It is possible that in the priming conditions for which perceptual representations are unavailable, aspects of explicit memory are activated [9]. It appears that associative priming may be processed in two steps. The first step is driven by perceptual representation and identifies the primed items. This step is characterized by reduced rCBF in the extrastriate cortex. The second step involves recognition of the relational properties of paired unrelated studied words, and probably facilitates identification of a target word in the same context condition. The relational information is probably not encoded perceptually and is retrieved using the component of explicit memory that is responsible for relational processing. This step is characterized by increased rCBF in the left prefrontal cortex and right hippocampal area. Both of these regions have been implicated in explicit relational processing [6,13,14]. Recruitment of both regions, as in the same-context condition, may enhance associative priming effect, probably by establishing stronger relational identity between studied items [6]. This enhancement explains the same-context advantage observed in the present and earlier experiments of associative priming [1,2].

The results support the view that implicit and explicit memory systems share common neural elements, and complement each other for efficient task execution [9].

CONCLUSION

The results indicate that the associative priming is processed by the cortical networks that mediate implicit memory as well as the network that supports aspects of explicit memory. Involvement of the explicit memory network explains why associative priming is impaired in some amnesic patients.

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