



## REMEMBERING FAMILIAR PEOPLE: THE POSTERIOR CINGULATE CORTEX AND AUTOBIOGRAPHICAL MEMORY RETRIEVAL

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**Abstract**—Most functional imaging studies of memory retrieval investigate memory for standardized laboratory stimuli. However, naturally acquired autobiographical memories differ from memories of standardized stimuli in important ways. Neuroimaging studies of natural memories may reveal distinctive patterns of brain activation and may have particular value in assessing clinical disorders of memory. This study used functional magnetic resonance imaging to investigate brain activation during successful retrieval of autobiographical memories elicited by name-cued recall of family members and friends. The caudal part of the left posterior cingulate cortex was the most strongly activated region and was significantly activated in all eight subjects studied. Most subjects also showed significant activation of the left anterior orbitomedial, anterior middle frontal, precuneus, cuneus, and posterior inferior parietal cortices, and the right posterior cingulate and motor cortices.

Our findings are consistent with prior studies showing posterior cingulate cortex activation during autobiographical memory retrieval. This region is also consistently activated during retrieval of standardized memory stimuli when experimental designs emphasizing successful retrieval are employed. Our results support the hypothesis that the posterior cingulate cortex plays an important role in successful memory retrieval. The posterior cingulate cortex has strong reciprocal connections with entorhinal and parahippocampal cortices. Studies of early Alzheimer's disease, temporal lobectomy, and hypoxic amnesia show that hypometabolism of the posterior cingulate cortex is an early and prominent indicator of pathology in these patients. Our findings suggest that autobiographical memory retrieval tasks could be used to probe the functional status of the posterior cingulate cortex in patients with early Alzheimer's disease or at risk for that condition. © 2001 IBRO. Published by Elsevier Science Ltd. All rights reserved.

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Neuroimaging studies of memory retrieval typically require subjects to learn standardized stimuli, such as lists of words or sets of pictures, and later study the subjects during retrieval of these stimuli. However, memories for standardized stimuli learned in a laboratory setting are dissimilar in important ways from naturally acquired, autobiographical memories. The latter are more likely to involve complex, multimodal and emotionally salient memories embedded in a rich context of personal, social and environmental information (Rubin, 1998). Neuroimaging studies of the retrieval of naturalistic, autobiographical memories may reveal distinctive patterns of regional brain activation, and may have particular relevance to clinical disorders characterized by deficits or distortions in naturalistic memories, such as

Alzheimer's disease (AD), post-traumatic stress disorder, dissociative disorders, and other conditions.

To our knowledge, there have been no prior functional magnetic resonance imaging (fMRI) studies investigating autobiographical memory. Four recent positron emission tomography studies have attempted to identify the distributed networks involved in the retrieval of naturalistic, autobiographical memories (Andreasen et al., 1995; Fink et al., 1996; Maguire and Mummery, 1999; Conway et al., 1999). The findings from these studies have been very inconsistent. However, one cortical region, the posterior cingulate cortex, was observed to be significantly activated in three of the studies. In each of these studies, the caudal part of the posterior cingulate cortex, posterior to the splenium of the corpus callosum, was activated during successful retrieval of autobiographical memories. Activation of this region has also been observed during some studies of episodic retrieval of standardized stimuli, but not in others (Cabeza and Nyberg, 2000). The posterior cingulate cortex is well positioned to play a key role in memory, as it has particularly strong reciprocal connections with medial temporal lobe memory structures, including the entorhinal and parahippocampal cortices (Suzuki and Amaral, 1994; Morris et al., 1999b).

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Abbreviations: AD, Alzheimer's disease; BA, Brodmann's area; BOLD, blood oxygenation level-dependent; fMRI, functional magnetic resonance imaging;  $T2^*$ , total transverse relaxation time.

In functional imaging studies, the most consistently replicated clinical finding associated with the posterior cingulate cortex has been decreased metabolic activity of this region in AD (Nyback et al., 1991; Minoshima et al., 1994; Vander Borght et al., 1997; Ishi et al., 1997). Most striking is the observation that the posterior cingulate cortex is the region with the greatest reduction in metabolic activity in patients with very early AD (Minoshima et al., 1997). This region is also hypometabolic in individuals who are at risk for AD (homozygous for the apolipoprotein E e4 allele and having a positive family history for AD) but currently have no clinical evidence of the disease (Reiman et al., 1996). Hypometabolism of the posterior cingulate cortex is also a prominent finding in patients following temporal lobectomy and in patients with hypoxic amnesia and associated medial temporal atrophy (Minoshima et al., 1999; Reed et al., 1999). In contrast, *increased* metabolic activity in the posterior cingulate cortex has been observed in other neuropsychiatric disorders, including schizophrenic, mood and anxiety disorders (Bench et al., 1992; McGuire et al., 1994; Perani et al., 1995; Ho et al., 1996; Andreasen et al., 1997; Haznedar et al., 1997).

The translation from fMRI studies of normal memory function to clinically useful assessment tools will require the development of memory tasks that consistently elicit significant activation of specific brain regions in individual subjects. Activations that require group analyses to be clearly detected cannot be used to evaluate individual patients. An autobiographical memory retrieval task that consistently activates the posterior cingulate cortex in individual subjects may have clinical value as a probe of the functional state of this region in patients with early AD or at risk for that condition. The current study uses fMRI to examine the individual patterns of brain activation associated with successful autobiographical memory retrieval in eight normal subjects.

## EXPERIMENTAL PROCEDURES

### *Subjects*

Eight right-handed subjects (five women and three men, aged 22–45) were recruited from the faculty, staff and students at the University of California at Davis and gave informed consent to participate in this study. Subjects were free of any known psychiatric or neurological illness or any condition known to affect cerebrovascular function.

### *Stimuli and task procedures*

Prior to entering the scanner, subjects were interviewed to obtain the names of the eight people with whom they currently had the closest relationships. In every case this yielded the names of their immediate family members (spouse, parents, children and siblings) and closest friends. The first names of these individuals were designated 'familiar names'. Additional first names were screened until eight names were identified that did not readily evoke memories of specific individuals known to the subject. These names were designated 'unfamiliar names'. In most cases 'unfamiliar names' were selected from the 'familiar names' of previous subjects. The unfamiliar names were matched for gender and number of syllables with the familiar names for each subject. Immediately prior to scanning, subjects

were instructed to listen carefully to all names, and to recall each person named as fully and rapidly as possible. They were instructed to attempt to recall a person for each name even though they might not be successful with some of the names (unfamiliar). Thus, subjects sustained the mental set associated with autobiographical memory retrieval during both conditions but only the familiar names condition was consistently associated with successful retrieval.

The fMRI scan began with a 32-s period during which no stimuli were presented. Then alternating blocks of familiar and unfamiliar names were presented. Each block included eight names of the same type, presented at a rate of one name every 2 s for a total block duration of 16 s. A total of 16 blocks (eight familiar and eight unfamiliar) were presented. The same eight names of each type were repeated in a different pseudo-random order within each block. This relatively rapid rate of presentation of name cues was intended to maximize the number of individuals recalled during each familiar name block. For half of the subjects the first block consisted of familiar names and for half the first block was unfamiliar names. The spoken names were presented to the subject through headphones via a pneumatic audio system.

### *Imaging protocol*

All images were obtained with a General Electric Signa Advantage 1.5 Tesla Magnetic Resonance Imaging System running OS Version 5.7, with a local gradient coil insert (Medical Advances, Milwaukee, WI, USA) to provide higher gradient performance (2 g/cm peak strength, 34 g/cm/ms maximum slew rate). For each subject, a coronal high resolution fast spin echo sequence was first used for anatomic localization. Scan parameters for this sequence were: repetition time: 3100, effective echo time: 17 and 136, echo train: 8, matrix: 256 × 256, field of view: 22 cm, slice thickness: 6 mm, gap: 2 mm, slice range: posterior 96 mm to anterior 88 mm, 24 slices. Subsequently, a total transverse relaxation time ( $T2^*$ ) weighted, gradient recalled, echo planar imaging sequence was tuned, including linear shimming, and used for the functional scan. Parameters were: repetition time: 2000 ms, effective echo time: 40 ms, flip angle: 90°, matrix: 64 × 64, field of view: 22 cm, slice thickness: 6 mm, slice gap: 2 mm, voxel size: 3.4375 × 3.4375 × 6 mm, slice range: posterior 72 mm to anterior 56 mm, 18 slices. Activation was detected by the blood oxygenation level-dependent (BOLD) contrast mechanism (Ogawa and Lee, 1990). The local gradient coil insert fit closely around the subject's head and provided improved signal to noise ratio and left little room for head motion. Head motion was further constrained by foam padding.

### *Data analysis*

A Fourier transform-based algorithm was used for reconstruction of the functional images and simultaneous removal of  $n/2$  ghost artifacts (Buonocore and Gao, 1997). All functional scans were then checked for motion by a weighted and thresholded center of intensity algorithm using Medx (Sensor Systems, Sterling, VA, USA). Motion correction was performed with sinc interpolation using statistical parametric mapping (SPM96, Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995) for scans in which total displacement was 20–30% of a pixel width (0.69–1.03 mm) in any direction at any time during the scan. Subjects would be rejected altogether if any displacement exceeded 30% of a pixel width. A linear detrending correction was then applied to remove linear drift.

An individual subject's analysis was used as the primary statistical analysis for this study. For this analysis, correlation coefficients were calculated between each pixel time series and a temporally offset, Poisson-convolved, boxcar vector reflecting the experimental design and adjusted for the acquisition time of each slice. The optimal temporal offset for each subject was determined empirically from the distribution of  $r$  values at each time lag from 1 to 8 s (tested at 1-s intervals). The temporal

offset resulting in the largest number of significantly activated pixels was used in subsequent analyses. Effective degrees of freedom ( $df_e$ ) were calculated for each subject as

$$df_e = (1/s^2) - 1$$

where  $s^2$  is the variance of the distribution of  $r$  values at the optimal temporal offset, as described by Buonocore and Maddock (1997). Significant activation was defined as a minimum of two contiguous suprathreshold pixels with a cluster-wise  $P \leq 0.001$  (assuming spatial autocorrelation equivalent to a Gaussian filter of width  $\leq 0.6$  pixels) (Forman et al., 1995). Clusters of significantly activated, positively and negatively correlated pixels were superimposed on the functional images and registered to the corresponding high resolution anatomical images for each subject, as described by Mangun et al. (1998). Each positive and negative activation cluster was manually localized to one of 84 specific cortical or subcortical regions for each subject by two independent raters (RJM and ASG) using the high resolution images and the atlas of Talairach and Tournoux (1988), as previously described (Maddock and Buonocore, 1997). A brain region was considered significantly activated across subjects if the majority of subjects ( $\geq 5$  of 8) individually showed activation within that region. For each subject with a significantly activated cluster within such a region, the Talairach coordinates of the most significantly activated pixel within the cluster were manually estimated from the high resolution images and the atlas of Talairach and Tournoux (1988).

To facilitate comparison with other functional imaging studies, a secondary group analysis was performed by combining spatially normalized statistical maps from each individual subject, using Medx and SPM software. First,  $z$ -score maps were calculated from the correlation maps obtained for each subject. Then a mean functional image was created for each subject by averaging the 128 realigned functional images. Each subject's mean functional image was then spatially transformed onto a  $T2^*$  echo planar imaging template conforming to the Talairach brain atlas (Evans et al., 1993) using sinc interpolation (Friston et al., 1995), and resliced to a final pixel size of  $3.4375 \times 3.4375 \times 3.4375$  mm. The same transformation parameters were then used to spatially normalize each subject's  $z$ -score map. Finally, normalized  $z$ -score maps for the eight subjects were combined into a single group  $z$ -score map by dividing the sum of the eight  $z$ -scores by  $\sqrt{8}$ , at each pixel location. Significant clusters of activated pixels were identified by using a pixel threshold of  $z \geq 3.09$  ( $P \leq 0.001$ ) and a cluster size threshold of 20 contiguous pixels (corresponding to a cluster threshold of  $P \leq 0.0001$ ) (Friston et al., 1994).

## RESULTS

All subjects reported they were able to clearly hear all stimuli and consistently recall all of the familiar individuals. Subjects reported attempting but only rarely succeeding in recalling individuals associated with the unfamiliar names. No subject had motion greater than 30% of a pixel width. Thus, according to our criteria, none were excluded for excessive motion. Two subjects had motion greater than 20% of a pixel width (maximum = 25%, 0.85 mm) and were corrected. The other six subjects had motion  $< 20\%$  of a pixel width and were not corrected (mean = 9.6%, 0.33 mm). The optimal temporal offset ranged from 2 to 8 s (mean = 4.6 s). The  $df_e$  ranged from 47 to 95 (mean = 72).

For significant activations associated with greater response to the familiar than unfamiliar names, the two raters agreed on the classification of 81 of the 84 regions as either activated in the majority of subjects or not ( $\kappa = 0.82$ ). A consensus was reached that eight regions were significantly activated in the majority of subjects. The extent, significance and location of the peak activations within each of these regions are described in Table 1.

Only the left posterior cingulate cortex was significantly activated in all eight subjects. In seven subjects the posterior cingulate activation was bilateral. In all cases the peak activation in the posterior cingulate cortex was posterior to the splenium of the corpus callosum (Fig. 1). Three other midline cortical regions were activated in the majority of subjects. Six subjects had significant activation in the left precuneus. In all cases, this activation was contiguous with activation in the posterior cingulate cortex. Six subjects had significant activation in the left cuneus. In four of these subjects, this activation was contiguous with activation in the precuneus and posterior cingulate cortex. Six subjects had significant activation in the left orbital frontal cortex. In all cases, this activation was localized to the anterior medial part of the orbital frontal cortex. To exclude the possi-

Table 1. Significant activations during cued recall of familiar people: individual subjects analysis

Cortical region (BA <sup>a</sup> )	Mean Talairach coordinates of peak activation X, Y, Z	S.D. of Talairach coordinates of peak activation X, Y, Z (in mm)	Proportion of subjects with significant activation	Mean number of activated pixels	Mean $z$ of peak pixel <sup>b</sup>
<b>Midline regions</b>					
L. posterior cingulate <sup>c</sup> (23, 31, 30)	-2, -52, 18	1.8, 4.5, 5.7	8/8	13	5.1
L. precuneus (31, 7)	-1, -65, 20	0.8, 2.6, 4.3	6/8	10	4.8
L. cuneus (18, 19)	-2, -77, 20	2.7, 8.5, 9.7	6/8	5	4.4
L. orbital frontal (11, 10)	-6, 48, -16	5.0, 7.0, 2.0	6/8	3	4.0
<b>Left hemisphere</b>					
Posterior inferior parietal (40, 39)	-44, -59, 34	6.7, 7.2, 9.7	6/8	4	4.0
Anterior middle prefrontal (9/46, 9)	-43, 36, 28	7.0, 7.0, 4.5	6/8	3	3.9
<b>Right hemisphere</b>					
Motor cortex (4)	53, -5, 45	1.7, 1.9, 3.7	6/8	4	4.0

<sup>a</sup>BA = Brodmann's area in the region of observed activation.

<sup>b</sup> $z$  approximated from  $t$  score.

<sup>c</sup>Area of contiguous activation included right posterior cingulate in seven subjects.

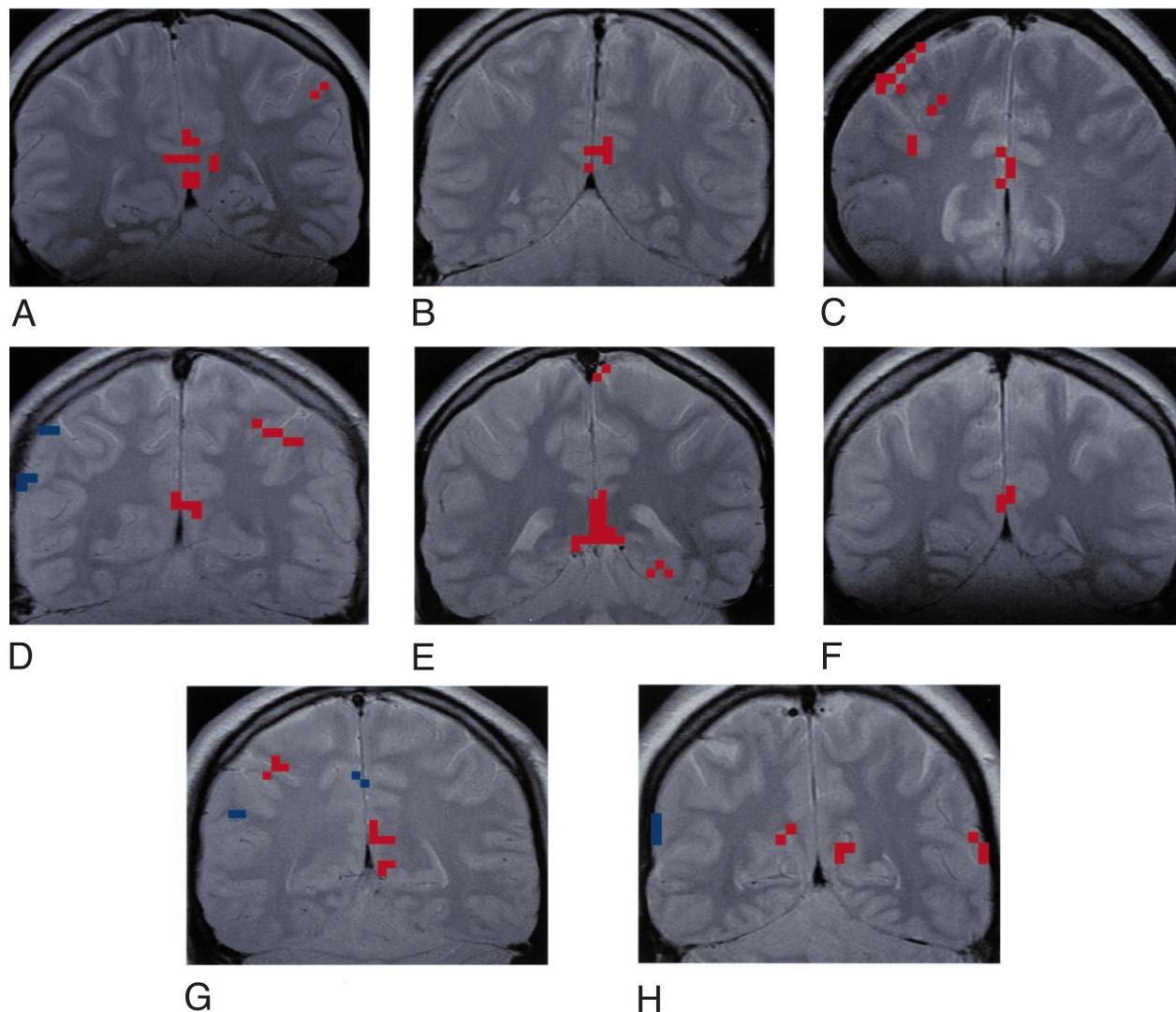


Fig. 1. Activation of posterior cingulate cortex during autobiographical memory retrieval. Clusters of cortical pixels showing significant activation during name-cued recall of familiar people are shown for subjects A–H. The coronal slice containing the most strongly activated posterior cingulate cortex pixel is shown for each subject. Red pixels have greater BOLD signal during familiar names, blue pixels have greater BOLD signal during unfamiliar names. Note the consistent activation of the posterior cingulate cortex posterior to the splenium.

bility that activations in the orbital frontal cortex could be attributed to susceptibility artifact in this region, we examined the  $T2^*$  signal intensity at the significantly activated pixels in the orbital frontal cortex. These signal intensity values ranged from 58 to 119% of the whole brain average  $T2^*$  signal intensity value for each subject (mean = 93%). This suggests that the significantly activated pixels in the orbital frontal cortex were not in regions of appreciable signal loss due to susceptibility artifact. Fig. 2 displays the location of all significantly activated clusters in medial cortices for each subject, superimposed on a mid-sagittal Talairach template.

Three dorsolateral cortical regions were activated in the majority of subjects. Six subjects activated the left posterior inferior parietal lobule. Six subjects activated the left anterior middle frontal gyrus. Six subjects activated the right precentral gyrus.

Significant activations associated with greater response

to the unfamiliar than familiar names were infrequently observed in individual subjects. Both raters agreed that none of the 84 regions were significantly more activated during the unfamiliar names in the majority of subjects.

Results of the group analysis are shown in Table 2. All of the cortical regions identified as activated in the individual subjects analysis were also identified as activated in the group analysis. The group analysis also identified additional medial and left lateral frontal regions, left temporal polar and lateral temporal regions, right parietal regions, bilateral thalamic and cerebellar regions, and left caudate as activated. No pixel clusters were significantly more activated during the unfamiliar than the familiar names, using the same statistical thresholds. Using a slightly lower pixel threshold ( $z \geq 2.58$ ;  $P \leq 0.005$ ) and cluster size threshold (16;  $P \leq 0.001$ ), small clusters of pixels in the right temporo-parietal junction [+58, -48, +24; Brodmann's area (BA) 40, 22] and

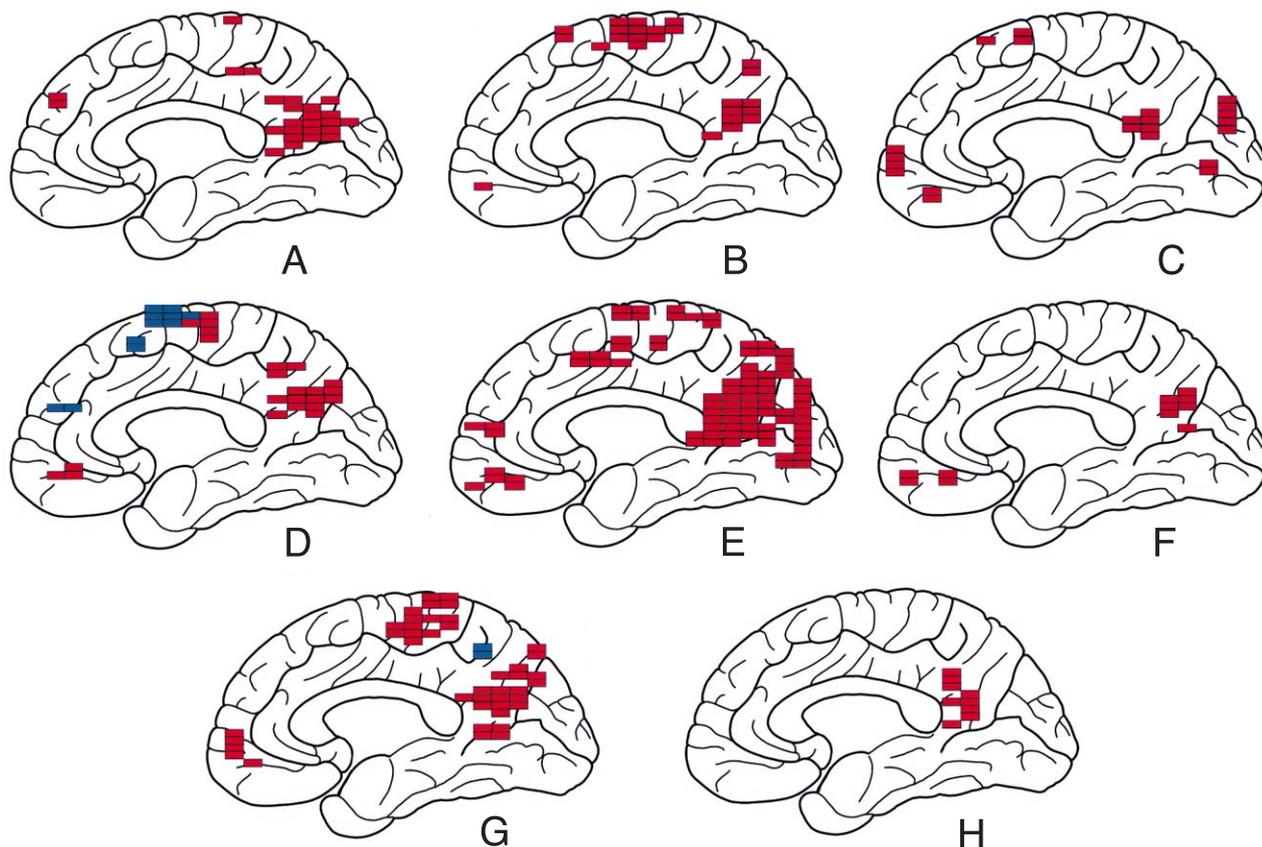


Fig. 2. Activations in medial cortices during autobiographical memory retrieval. Clusters of pixels showing significant activation in medial cortices during name-cued recall of familiar people are shown superimposed on a mid-sagittal Talairach template for subjects A–H. Red pixels indicate regions with greater BOLD signal during familiar names, blue pixels indicate regions with greater BOLD signal during unfamiliar names. All significantly activated clusters of cortical pixels within 1.0 cm of the mid-sagittal line (left or right) are shown. Pixel dimensions are  $3.4 \times 8$  mm. Note the consistent activation of the caudal posterior cingulate, precuneus, cuneus and anterior orbitomedial cortices. Pixel locations were estimated from each subject's high resolution images and the atlas of Talairach and Tournoux (1988).

the right middle frontal cortex (+45, +24, +38; BA 9) were identified as having higher BOLD signal during the unfamiliar than the familiar names.

#### DISCUSSION

##### *Posterior cingulate cortex and memory*

Activation of the caudal part of the left posterior cingulate cortex was the strongest and most consistent brain response associated with the successful retrieval of autobiographical memories. The caudal left posterior cingulate cortex was the only region which showed significant activation in all eight subjects (Figs. 1 and 2). Converging evidence from neuroanatomical, lesion, clinical, and neuroimaging studies suggests that this region plays an important role in memory retrieval. It has strong reciprocal connections with the parahippocampal and entorhinal cortices, and is among the most important sources of cortical afferents to those regions (Goldman-Rakic et al., 1984; Suzuki and Amaral, 1994; Morris et al., 1999b). The caudal posterior cingulate cortex is also strongly linked by reciprocal pathways to dorsolateral

prefrontal and anterior cingulate cortices and the anterior and lateral thalamic nuclei, and may serve to connect the dorsolateral prefrontal cortex with the hippocampal formation (Goldman-Rakic et al., 1984; Musil and Olsen, 1993; Bentovoglio et al., 1993).

This pattern of connectivity is consistent with functional evidence that the posterior cingulate cortex is involved in memory-related processes. Lesion studies in animals show that the posterior cingulate has an essential role, in concert with hippocampal structures, in spatial memory and other types of configural learning (Sutherland and Hoesing, 1993), and that it has a distinctive role in the maintenance of discriminative avoidance learning (Gabriel, 1993). Beginning with Valenstein et al.'s (1987) initial report of 'retrosplenic amnesia', a number of clinical cases have been reported of amnesic syndromes associated with lesions of the posterior cingulate cortex posterior to the splenium of the corpus callosum. Loss of verbal episodic memory has been associated with left retrosplenic damage (Valenstein et al., 1987; Katai, 1992; Kasahata, 1994), and loss of memory for spatial relationships has been associated with right retrosplenic damage (Takahashi et al., 1997). Gainotti et al. (1998) recently described a patient

Table 2. Significant activations during cued recall of familiar people: group analysis

Cortical region <sup>a</sup> (BA <sup>b</sup> )	Number of pixels in cluster	Talairach coordinates of local maximum <sup>c</sup> X, Y, Z	z score of local maximum
<i>Bilateral midline activations</i>			
Posterior midline	581		
Posterior cingulate (23, 31, 30)		0, -42, 10	7.92
Precuneus (31, 7)		0, -65, 17	8.00
Cuneus (17, 18, 19)		0, -65, 7	8.12
Midline cerebellum		3, -48, -7	5.77
Orbital frontal (11, 10)	25	0, 58, -14	4.34
Medial frontal	163		
Descending frontal (6)		0, 10, 58	6.17
Superior frontal (6)		-24, 3, 48	5.63
Thalamus	72	10, -14, 10	3.99
<i>Left hemisphere activations</i>			
Lateral frontal	94		
Middle frontal (46)		-34, 38, 24	5.07
Inferior frontal (45, 47)		-45, 34, -3	6.3
Precentral (6)		-55, 3, 34	4.12
Dorsolateral frontal	59		
Middle frontal (9, 10)		-41, 48, 14	4.03
Middle frontal (8)		-24, 28, 55	4.95
Dorsolateral frontal	244		
Middle frontal (6)		-50, 3, 44	8.85
Precentral (4)		-48, -7, 55	5.78
Inferior frontal-temporal pole (47, 38)	45	-58, 21, -7	4.44
Caudate/lenticular	25	-14, 3, 14	5.28
Lateral temporal (21, 20)	69	-62, -14, -3	4.49
Inferior parietal (40)	40	-48, -38, 55	5.06
Lateral cerebellum	82	-24, -48, -21	6.02
<i>Right hemisphere activations</i>			
Fronto-parietal	24		
Precentral (4)		52, -10, 52	5.14
Postcentral (1)		55, -24, 55	4.21
Inferior parietal (40)		45, -52, 45	4.01
Lateral cerebellum	73	28, -58, -34	5.71

<sup>a</sup>Main headings indicate clusters of  $\geq 20$  contiguous activated pixels (cluster size threshold =  $P \leq 0.0001$ ; pixel threshold =  $z \geq 3.09$  ( $P \leq 0.001$ )). Subheadings indicate specific brain regions within a cluster that include a local maximum of  $z \geq 3.73$  ( $P \leq 0.0001$ ).

<sup>b</sup>BA = Brodmann's area in the region of observed activation.

<sup>c</sup>Highest local maximum in each region.

with a retrosplenial tumor who demonstrated a dense retrograde amnesia for personal events, suggesting this region has an important role in memory retrieval.

Four prior neuroimaging studies have investigated the retrieval of autobiographical memories (Andreasen et al., 1995; Fink et al., 1996; Maguire and Mummery, 1999; Conway et al., 1999). Their most consistent finding has been activation of the caudal part of the posterior cingulate cortex, which was noted in three of the four studies (Andreasen et al., 1995; Fink et al., 1996; Maguire and Mummery, 1999). The reported location of this activation is in close proximity to that observed in our study, with the mean location (in Talairach coordinates) across the three studies situated within 5 mm of the mean location observed in the current study (Table 1). Unlike these three studies, the fourth study used a design emphasizing retrieval effort but not retrieval success (Conway et al., 1999) and did not observe posterior cingulate activation. Some functional neuroimaging studies of memory retrieval using standardized stimuli have also observed activation of the caudal part of the posterior cingulate cortex (Grasby et al., 1993; Nyberg et al., 1995; Owen et al., 1996; Rugg et al., 1997; Henson et al., 1999). A recent review of functional imaging studies of memory

using standardized stimuli shows that posterior cingulate cortex activation is most likely to be observed with experimental designs emphasizing successful retrieval (Cabeza and Nyberg, 2000). Our results add further support to this body of evidence that the caudal posterior cingulate cortex plays an important role in successful memory retrieval.

The posterior cingulate cortex is reciprocally connected to regions involved in emotional processing, including the anterior cingulate and orbital frontal cortices (Baleydier and Mauguier, 1980; Van Hoesen et al., 1993). In a recent review, Maddock (1999) concluded that the caudal posterior cingulate cortex was the cortical region most consistently activated by emotionally salient stimuli, and that this region may have a role in the interactions between emotion and memory. The emotional salience of many autobiographical memories (Rubin, 1998), including those retrieved in this study, may contribute to the strong and consistent activation of the posterior cingulate cortex.

#### *Posterior cingulate cortex in Alzheimer's disease*

Signs of posterior cingulate cortex hypofunction may

aid the early diagnosis of AD. Reduced metabolic activity in this region has been consistently observed in AD (Nyback et al., 1991; Minoshima et al., 1994; Vander Borgh et al., 1997; Ishi et al., 1997) and is the most prominent functional imaging finding in the earliest stages of AD. Minoshima et al. (1997) showed that the posterior cingulate cortex is the region with the greatest reduction in metabolic activity in patients with very early AD. Reiman et al. (1996) studied clinically normal subjects at risk for later development of AD (subjects homozygous for the apolipoprotein E  $\epsilon$ 4 allele and with a positive family history for AD) and found the posterior cingulate cortex to be the most abnormally hypometabolic brain region. Although the earliest neurodegenerative changes in AD are observed in medial temporal structures, hypometabolism of these regions is not consistently detected by functional imaging studies in early AD (Braak and Braak, 1998; Minoshima et al., 1999). The level of metabolic activity in the posterior cingulate cortex appears to depend, in part, on the integrity of these medial temporal structures, and may be a useful proxy for their functional activity. The recent finding of prominent posterior cingulate but not medial temporal hypometabolism in a group of patients with hypoxic amnesia and medial temporal atrophy is also consistent with this proposal (Reed et al., 1999). An fMRI method for assessing the functional state of the posterior cingulate cortex in individual patients could have value in the clinical evaluation of memory disorders resulting from dysfunction of medial temporal structures. This may be especially useful in patients at risk for or in the earliest stages of AD. Our study demonstrates that an easily performed autobiographical memory retrieval task consistently activates this region in individual normal subjects. Further study will be necessary to evaluate whether this activation is abnormal in early AD.

#### *Activations in frontal regions*

In addition to the posterior cingulate cortex, most subjects also activated six other cortical regions (Table 1). Many of these regions, including the anterior orbitomedial, anterior middle frontal, precuneus, and posterior inferior parietal cortices, have substantial monosynaptic connections with the caudal posterior cingulate cortex (Price, 1999; Goldman-Rakic et al., 1984; Morris et al., 1999a,b; Petrides and Pandya, 1999; Baleyrier and Mauguier, 1980; Van Hoesen et al., 1993). The left anterior orbitomedial prefrontal cortex (BA 11 and/or 10) was activated in six of eight subjects (Fig. 2). Five of these subjects showed significant activation in a circumscribed region appearing to correspond to the medial part of BA 11 (11m). Two additional subjects had a single suprathreshold pixel (rather than the required cluster of two contiguous pixels) in this region. Area 11m is strongly connected to the caudal posterior cingulate cortex, as well as to the entorhinal and posterior parahippocampal cortices, the amygdala, and area 9/46 of the dorsolateral prefrontal cortex (Price, 1999). Clinically, lesions of the orbitomedial prefrontal cortex are associated with impairments in social and emotional

functioning (Damasio, 1994; Eslinger, 1999), including recognition of facial and vocal expressions of emotion (Hornak et al., 1996) and empathy (Grattan et al., 1994; Eslinger, 1998). Previous imaging studies have found the anterior orbitomedial cortex and the posterior cingulate cortex to be activated during autobiographical memory retrieval (Andreasen et al., 1995) and during implicit (Gorno-Tempini et al., 1998) and explicit (Leveroni et al., 2000) recognition of the faces of familiar individuals. Activation of area 11m in the current study may reflect social and emotional processes associated with the mental representation of intimately familiar people.

Six of the eight subjects activated the left anterior middle frontal gyrus in BA 9/46 and/or BA 9. Activation of this region has previously been associated with working memory and the retrieval of semantic information (Cabeza and Nyberg, 2000). This region has strong, reciprocal connections with the caudal posterior cingulate cortex (Goldman-Rakic et al., 1984; Morris et al., 1999a,b; Petrides and Pandya, 1999). It is also connected with area 11m of the orbital cortex, the entorhinal and parahippocampal cortices, and the amygdala (Goldman-Rakic et al., 1984; Amaral et al. 1992; Petrides and Pandya, 1999; Price, 1999). This region may contribute to semantic or working memory processes associated with successful retrieval of autobiographical memories.

The right precentral cortex was activated in six of eight subjects. This activation was localized to the anterolateral portion of the primary motor cortex (BA 4), a region associated with movements of the left side of the face (Lotze et al., 2000). We interpret this finding as a consequence of either overt or covert facial expressions of emotion, such as smiling, elicited during the cued recall of family members and friends.

#### *Activations in posterior regions*

In six of eight subjects, the cluster of posterior cingulate cortex activation extended into the left precuneus cortex (BA 31 and 7) (Fig. 2). BA 31 includes both posterior cingulate and precuneate cortices, and the two regions are reciprocally connected (Baleyrier and Mauguier, 1980; Van Hoesen et al., 1993; Morris et al., 1999b). Activation of the precuneus cortex has often been observed during episodic memory retrieval (Cabeza and Nyberg, 2000) and Nyberg (1999) has proposed that this region may have a specific role in successful retrieval. Fletcher et al. (1995) have shown increased activity in this region during retrieval of verbal stimuli associated with visual imagery and hypothesized that the precuneus is part of the neural substrate for visual imagery in conscious memory recall. However, it remains uncertain whether this association is specific to the visual modality, as precuneus activation has also been associated with memory involving auditory and motor imagery (Zatorre et al., 1994; Ogiso et al., 2000). This region may have a role in the representation of polymodal imagery associated with successful memory retrieval. Activation of the left cuneate cortex (BA 18 and 19) in six of eight subjects

may reflect the involvement of this region in visual imagery components of the memory retrieval task.

The left posterior inferior parietal lobule was significantly activated in six of eight subjects in BA 40 and/or 39. This activation was more variably localized across subjects than most of the other activations (Table 1). Activation in this region has been most consistently associated with tasks involving working memory, attention, spatial/motion imagery, and spatial memory encoding (Cabeza and Nyberg, 2000), but was also noted in a prior study of autobiographical memory retrieval (Maguire and Mummery, 1999). It is unclear if this activation reflects attentional or working memory components of our task or processes specific to autobiographical retrieval.

#### Group analysis

Group analyses of spatially normalized data have greater statistical power than individual subject analyses, but the latter are more applicable to the diagnostic assessment of individual patients. Our group analysis identified as activated all of the regions noted in the individual subjects analysis, as well as additional regions (Table 2). Findings from the group analysis of medial frontal, left temporal polar and left lateral temporal activations agree with prior studies of autobiographical memory retrieval (Andreasen et al., 1995; Fink et al., 1996; Maguire and Mummery, 1999). The bilateral thalamic activation included the anterior and lateral thalamic regions reciprocally connected to the posterior cingulate cortex. The group analysis also showed activation extending into the left posterior parahippocampal cortex from the left posterior cingulate cortex. However, the local maximum in the parahippocampal cortex did not reach our criterion of  $z=3.73$  for inclusion in Table 2.

#### Limitations

Name-cued recall of familiar individuals is expected to involve both semantic (general knowledge) and episodic memories (event-specific knowledge). Thus, no conclusions can be drawn about the specific role of either type of memory in the brain activations observed. Furthermore, the emotional and interpersonal elements integral to the mental representation of intimately familiar individuals do not allow us to separate mnemonic from social and emotional processes in this study. It is possible that the process or content of memory retrieval may have changed over the eight blocks of repeated familiar name

cues in this study. However, the magnitude of posterior cingulate cortex activation (mean peak to trough change in BOLD signal) was uncorrelated with block number ( $r=+0.18$ ,  $df=6$ ,  $P=0.66$ ). Thus, any changes in memory retrieval over the course of the eight blocks did not alter the magnitude of posterior cingulate cortex activation. Activation of medial temporal lobe structures was only observed in two of the eight subjects individually, and was comparatively small in the group analysis. While neuroimaging studies of memory retrieval frequently fail to observe activation of medial temporal structures, this may reflect the ongoing metabolic activity of these structures during control conditions, rather than a lack of involvement in memory retrieval (Fletcher et al., 1997). Susceptibility effects in the anterior medial temporal regions may also have made detection of activation more difficult.

#### SUMMARY

In this study, successful autobiographical memory retrieval elicited by name-cued recall of family members and close friends was associated with extensive, predominantly left-sided, activation of the caudal posterior cingulate cortex. Activation of the left precuneate, cuneate, anterior orbitomedial, dorsolateral frontal, and inferior parietal cortices and the right precentral cortex was also observed. The caudal left posterior cingulate cortex was the most strongly activated region, and the only region which showed statistically significant activation in all subjects tested. Anatomical and clinical studies suggest an important role for the posterior cingulate cortex in memory. Consistent with the findings of prior functional imaging studies, our study supports the hypothesis that the memory function of the posterior cingulate cortex is related to the successful retrieval of memories. The interconnections between posterior cingulate, anteromedial orbital, middle frontal, inferior parietal and precuneate cortices suggest that these regions may be part of a network involved in the retrieval and representation of naturally acquired memories of highly familiar people. Abnormally low metabolic activity in the posterior cingulate cortex has been consistently observed in AD, and may be the earliest metabolic abnormality detectable by functional imaging in that disorder. Future studies should assess the possible clinical value of autobiographical memory retrieval tasks as fMRI probes of the functional status of this region in individual patients being evaluated for early AD.

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