

Characterizing spatial and temporal features of autobiographical memory retrieval networks: a partial least squares approach

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Conway (Conway, M.A., 1992. A structural model of autobiographical memory. In: Conway, M.A., Spinnler, H., Wagenaar, W.A. (Eds.), *Theoretical Perspectives on Autobiographical Memory*. Kluwer Academic Publishers, Dordrecht, The Netherlands, pp. 167–194) proposed that two types of autobiographical memories (AMs) exist within a hierarchical AM system: unique, specific events and repeated, general memories. There is little research on whether retrieval of these AMs relies on different neural substrates. To investigate this issue, we used a multivariate image analysis technique, spatiotemporal partial least squares (PLS), to identify distributed patterns of activity most related to AM tasks that we have found to be associated with a medial and left-lateralized network. Using PLS, specific and general memories were more strongly associated with different parts of this retrieval network. Specific AM retrieval was associated more with activation of regions involved in imagery in episodic memory, including the left precuneus, left superior parietal lobule and right cuneus, whereas general AM retrieval was associated with activation of the right inferior temporal gyrus, right medial frontal cortex, and left thalamus. These two patterns emerged at different lags after stimulus onset, with the general AM pattern peaking between 2 and 6 s, and the specific AM pattern between 6 and 8 s. These lag differences are consistent with Conway's theory which posits that general AMs are the preferred level of entry to the AM system. A seed PLS analysis revealed that the regions functionally connected to the hippocampus during retrieval did not differentiate specific from general AM retrieval, which confirms our earlier univariate

analysis indicating that some aspects of the memory retrieval network are shared by these memories.

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What constitutes autobiographical memory (AM) has been debated for at least the past two decades. Traditionally, AM has been defined only as episodic memory for personally experienced events that occurred at a specific place and time. Conway (Conway, 1992, 1996; Conway and Pleydell-Pearce, 2000), however, distinguishes between two types of AMs: AMs for unique, specific events and for repeated, general events. Both neuroimaging (Fink et al., 1996; Gilboa et al., 2004; Maguire and Mummery, 1999; Maguire et al., 2000, 2001; Piefke et al., 2003; Ryan et al., 2001) and lesion studies (e.g., Kopelman et al., 1990; Viskontas et al., 2000; for a review, see Conway and Fthenaki, 2000) have focused on the retrieval of specific AMs, with the virtual exclusion of research exploring the neural correlates of general AMs and whether they differ from those of specific AMs (but see Graham et al., 2003). In this paper, we aim to help rectify this imbalance.

Conway (1992, 1996) and Conway and Pleydell-Pearce (2000) conceptualize AM as a personal knowledge base that is organized hierarchically, according to three levels of specificity. 'Lifetime periods' are an abstract level of autobiographical knowledge organized by theme and time periods. 'General events' are composed of events memories which are either repeated or temporally extended, and thus lack temporal specificity. In contrast, specific events, or what Conway terms 'event specific knowledge', refer to AMs for events that occurred at one specific point in time, and represent what is typically called episodic memory. Conceptually, a repeated, general AM can be thought of

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as many instances of a particular episode being superimposed to create a generic version of that event. Thus, even though these AMs lack temporal specificity, they likely contain fragments of event-specific information, such as contextual details (e.g., Conway and Pleydell-Pearce, 2000; Haque and Conway, 2001). On the whole, general AMs consist of more abstract information than specific AMs, which contain more visual imagery (Greenberg and Rubin, 2003). Thus, their retrieval may be supported by different neural structures according to differential content; for example, specific AM retrieval may be supported by brain regions involved in episodic imagery (Conway et al., 2001, 2003; Graham et al., 2003; Haque and Conway, 2001), whereas general events may be supported by structures associated with complex object and scene recognition, and possibly, semantic memory.

Specific and general events are thought to differ not only in terms of content, but also in the time taken to access these memories (Conway et al., 2001; Haque and Conway, 2001; Graham et al., 2003). It is argued that general events represent the preferred level of access into this system (Conway and Pleydell-Pearce, 2000; Burt et al., 2003), primarily because the AMs comprising this level are neither too abstract nor too specific, and thus can facilitate retrieval of specific events. Indeed, individuals tend to structure their personal memories as extended or repeated general events (Barsalou, 1988), particularly according to content associations (i.e., repeated events) rather than temporal sequences (i.e., extended events; Burt et al., 2003). Additionally, sampling the contents of consciousness at different times across the AM retrieval process confirmed that general events tend to be accessed before specific AMs (Haque and Conway, 2001). Taken together, these findings suggest that general AMs, particularly repeated general events, do represent a form of AM psychologically distinct from specific memories, and accessed earlier than them. Whether retrieval of these types of autobiographical events is associated with activation of distinct neural networks, and if so, whether the general AM network is activated earlier, remains to be determined.

In a recent functional magnetic resonance imaging (fMRI) study, we compared the neural correlates of specific and general AM retrieval using univariate analysis techniques (Addis et al., 2004). No differences between the regions activated during specific and general AM retrieval were found: both tasks activated the previously documented medial and left-lateralized memory network (Fink et al., 1996; Gilboa et al., 2004; Maguire and Mummery, 1999; Maguire et al., 2000, 2001; Piefke et al., 2003). Nonetheless, specific and general memories did differ from one another in other ways, such as the laterality of hippocampal modulation by the recollective qualities of the memories. Briefly, during specific AM retrieval, it was primarily the left hippocampus, which exhibited these modulatory effects, while during general AM retrieval, this was limited to the right hippocampus. Further, at a sub-threshold level, direct contrasts revealed that specific and general AMs were associated with different regions, including the right and left parahippocampal gyrus, respectively. These results suggest that different neural substrates may mediate retrieval of specific and general AMs, though such differences may not be captured readily by direct univariate contrasts. This is particularly true if time to activate the substrates is a crucial variable, as univariate analyses specify the same time parameters for all experimental conditions. Moreover, whereas retrieving specific or general AMs recruits the same neural regions, it is possible that each task is associated more strongly with a subset of these common regions.

Multivariate techniques, such as spatiotemporal partial least squares (PLS), can be used to address such questions (McIntosh, 1999; McIntosh et al., 1996; Lobaugh et al., 2001). This multivariate technique provides an omnibus exploratory analysis of data, identifying distributed patterns of activity most related to the experimental tasks or conditions (task PLS), providing information regarding which effects are strongest within the data and assessing whether the functional connectivity of regions of interest varies over tasks (seed PLS). In general, multivariate analyses are more sensitive than univariate techniques, particularly so for imaging data where the dependent measures are correlated (Harris, 1975; Mardia, Kent and Bibby, 1979). Furthermore, it provides a more sensitive statistical assessment at the image level (i.e., activity at all voxels is analyzed in one single analytic step) through permutation testing and bootstrapping, eliminating the need to correct for multiple comparisons. Unique to *spatiotemporal* PLS is its application to event-related imaging data to determine how the activation of functional networks changes over the duration of the event.

The primary aim of the present study, therefore, was to examine further the imaging data presented in Addis et al. (2004) by using PLS to identify spatiotemporal patterns of brain activity related to specific and general AM retrieval. Although we know from our univariate results that specific and general AMs activate a very similar network of regions, PLS enables us to investigate whether these memories are associated more strongly with particular brain regions of this shared network. An additional aim was to use seed PLS to investigate whether functional connections with critical components of this network, such as the hippocampus, differ between these two retrieval tasks. Finally, we sought to explore the utility of using spatiotemporal PLS with event-related imaging data to obtain information about the temporal characteristics of these networks. In particular, we were interested in testing the prediction that activation of the network associated with retrieval of general AMs would precede that of specific AMs.

Materials and methods

Participants

Fourteen healthy right-handed adults (seven females; mean age, 28 years; range, 20 to 40 years), with no prior history of neurological or psychiatric impairment, participated in this study. All participants gave written informed consent for the study, approved by the University Health Network Research Ethics Board.

Pre-scan interview

At least 48 h before scanning, participants completed a 2-h pre-scan interview, in which they produced 20 specific and 20 general AMs. Specific AMs were defined as events that happened only once, while general AMs were repeated events that had occurred at least 10 times. Only AMs that had not occurred within the past year were permitted to decrease the likelihood of general AMs cuing a specific exemplar (Conway, 1992, 1996) which may have additional salience as the most recent repetition of that event. A list of cues was provided to facilitate retrieval, but event memories were not limited to those elicited by these cues. For each AM, participants provided a brief “title” to be used later as a cue during scanning. Additionally, participants rated each AM on

a five-point scale for the level of detail, emotionality and personal significance, though these data were not used in the present analyses.

Scanning

Immediately before scanning, the AM and control tasks were explained to participants. They were shown the five-point rating scales that they would use in the scanner, and were presented with the AM titles they produced in their pre-scan interview to ensure there was no confusion during scanning.

During scanning, all stimuli were presented in black text on a white background, and were back-projected onto a white screen viewed by the participants through a mirror incorporated into the head coil. SuperLab Pro 2.0 (Cedrus Corporation, San Pedro, CA) was used for the presentation and timing of stimuli. Each trial was 16 s, and consisted of the task presentation, rating, and rest. Participants completed two functional scans (each 10 min, 50 s) in a single session.

Autobiographical memory tasks

During each scan, the titles for 10 general and 10 specific AMs produced in the pre-scan interview were presented as retrieval cues. Each AM title was presented visually for 6 s, and participants retrieved the relevant memory. This short-time window was used to decrease the likelihood of a general event cuing specific instances of that general event (Conway, 1992, 1996). As the average time taken to retrieve specific AMs is 5 s (Conway et al., 2003), this time-window was considered sufficient. A five-point rating scale (either detail, emotionality or personal significance) was then presented visually for 4 s, during which participants rated the AM by lifting the finger of the right hand corresponding to their rating (thumb = one, etc.) A researcher present in the scanning room recorded each rating. To reduce the load on the participant and shorten the duration of the scan, only one dimension was rated for each AM. Further, the dimension rated remained the same over the duration of a scan, but differed between the two scans. The rating tasks were included during scanning to enable later correlations with the ratings on the same dimension obtained within more extensive post-scan ratings. Such correlations were conducted to ensure post-scan ratings were indeed based on the AM retrieved in the scanner. A rest period of 6 s followed the rating task, during which a blank screen was presented and participants were instructed to focus on resting.

Control tasks

Twenty control task trials were randomly interspersed between the 20 AM task trials in each scan. Ten of these were sentence completion tasks (Ryan et al., 2001). Participants were presented visually with a sentence missing the last word (e.g., 'The dog ate a _____'), and were instructed to complete the sentence silently with a word. This task served as a control task for retrieval of information, but from semantic memory rather than AM. Ten size discrimination tasks were also included in each scan to provide a similar control for visuospatial processing. The names of two objects were presented (e.g., "CD or coin") along with the word "Biggest" to cue participants to judge the larger of the two items. Each control task was presented for 4 s followed by the presentation of a five-point rating scale for difficulty of task completion for 4 s to control for the rating decision in the AM retrieval tasks. A rest period of 8 s followed.

Post-scan interview

Immediately following the scanning session, participants completed a post-scan interview, in which they reported whether they were able to retrieve the memory. One event (a general AM) from one participant was dropped from all analyses due to a failure to retrieve the AM in the scanner.

Data acquisition

Functional data were acquired on a 1.5-T Signa MR System (GE Medical Systems, Milwaukee WI), using single-shot spiral acquisition (TE = 40 ms, TR = 2000 ms, FOV = 220 mm). Slices were 5 mm thick, with a 1-mm gap, covering the entire brain. These were acquired in a coronal-oblique orientation, with each slice being perpendicular to the long axis of the hippocampus to avoid partial volumes of this structure. The first three frames were dropped to allow for signal equilibrium. To acquire anatomical images, a standard three-dimensional T₁-weighted sequence (FOV = 200) was used to generate 60 axial slices (2.2 mm thick).

Data processing

All pre-processing and analyses of imaging data were performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK; Friston et al., 1995). All functional images were co-registered to a structural image, realigned for motion correction, corrected for within-frame time of acquisition, spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed using a Gaussian kernel of 8 mm full-width half maximum.

PLS analysis

Spatiotemporal task PLS is a multivariate technique that analyses the covariance of brain voxels and the experimental design (i.e., the conditions or "tasks") across the length of an event (Lin et al., 2003; Lobaugh et al., 2001). Note that unlike univariate event-related analyses, spatiotemporal PLS is not dependent upon assumptions about the shape and time course of the hemodynamic response function (hrf), and thus enables investigation of changes in task-related activity at different lags along the whole course of the event. For all analyses, a 16-s temporal window was specified for each event (i.e., 8 TRs). Firstly, the cross-covariance between a matrix of vectors coding for the tasks (i.e., design matrix) and a matrix containing all of the voxels across each event, in each image, across all subjects and tasks (i.e., data matrix) was computed. The resulting matrix was then decomposed using singular value decomposition. In doing so, a new set of orthogonal variables (latent variables; LVs) that provide the optimal relation between these data sets is identified. Contributing to each latent variable was a linear contrast, or set of contrasts, between the experimental tasks. The accompanying image displays the brain regions exhibiting the greatest covariance with these contrasts in each lag (i.e., each TR or 2 s). The amount of covariance for which the latent variable accounts is known as the singular value. Further, each brain voxel has a weight or salience that is proportional to these covariances. Multiplying the raw images by the singular image enables derivation of subject scores for each subject in each task condition. Each extracted latent variable successively accounts for a smaller portion of the covariance pattern until all is accounted for.

The statistical significance of each latent variable was determined using permutation tests, that is, randomly re-ordering the data matrix rows and calculating a new set of latent variables (using singular value decomposition) for each re-ordering. At each permutation, the singular value of each latent variable is compared to the singular value of the original latent variable. The initial value is assigned a probability based on the number of times a statistic from the permuted data exceeds this original value (McIntosh et al., 1996). In the present study, 500 permutations were computed. The reliability of the saliences for the brain voxels within a latent variable was determined using bootstrap estimation of the standard errors. This involves randomly resampling subjects with replacement, and computing the standard error of the saliences after several bootstrap samples (McIntosh et al., 1996). In the present study, this sampling and analysis procedure was carried out 300 times. Note that unlike univariate analyses, saliences are identified in one single analytic step and thus correcting for multiple comparisons is *not* necessary.

In the present study, two analyses using spatiotemporal task PLS were conducted. Firstly, to investigate the regions associated with all four tasks, a task PLS analysis involving the two AM tasks and two control tasks was conducted. Clusters of 10 or more voxels, in which the salience to standard error ratio was greater than 3.0 (roughly equal to a z-score), were considered to represent reliable voxels. Note that this effect was so robust, most of these saliences survived a more conservative threshold of 4.0, and for brevity only these saliences are reported here. To investigate further the brain regions associated with specific and general AM retrieval, a second task PLS analysis involving the two AM tasks was carried out. Clusters of 10 or more voxels, in which the salience to standard error ratio was greater than 3.0, were considered to represent reliable voxels. In both analyses, local maxima for the brain areas with reliable saliences on each latent variable were considered to be the voxel with a salience to standard error ratio higher than any other voxel in a 10-mm cube centered on that voxel. MNI coordinates were converted to Talairach space and regions of activations were localized in reference to a standard stereotaxic atlas (Talairach and Tournoux, 1988).

Additionally, based on the finding that the hippocampus was activated bilaterally during both specific and general AM retrieval (Addis et al., 2004), we were interested in investigating which regions demonstrated activity that correlated with the left and right hippocampus. To do this, a spatiotemporal seed PLS analysis was conducted. The left ($x = -24, y = -20, z = -16$) and right hippocampus ($x = 24, y = -20, z = -16$) seeds correspond to the peak maxima in the univariate fixed effects contrast of all AMs with the control tasks (Addis et al., 2004). We extracted the BOLD values for these two regions (averaged across the time interval) during specific and general retrieval. These were then entered as “seeds” into the PLS analysis. The correlation between seed activity and activity in all brain voxels within each task was calculated and then PLS was used to contrast these correlations across tasks. Results from the seed PLS were submitted to permutation testing and bootstrap estimation of the standard errors, as described above.

Results

Spatiotemporal task PLS of AM and control tasks

This task PLS analysis identified one significant pattern of brain activity across tasks (*LV1.1*, $P < 0.001$). This latent variable

differentiated between AM tasks and control tasks (Fig. 1a). The positive and negative saliences are listed in Table 1 and are illustrated in Fig. 1c. Note that all lags are documented in Fig. 1c and Table 1, but only those lags corresponding to the peak of standard hrf approximately 4 to 6 s after stimulus onset (Aguirre et al., 1998) will be discussed in detail.

The positive saliences in *LV1.1* correspond to greater activity in the AM tasks (specific and general AMs), which peaks at lag three (6 to 8 s after stimulus onset; see Fig. 1b). This is consistent with the hrf and provides evidence to support the temporal aspect of this PLS analysis. The pattern of brain activity found to characterize AM retrieval was predominantly medial and left-lateralized, and included left superior, middle and orbital frontal gyri, left posterior cingulate (extending into the left parahippocampal gyrus and hippocampus), left inferior temporal gyrus, in addition to activity in the right parahippocampus (extending into the right hippocampus), and bilateral angular gyrus and cerebellum. The positive saliences at lags five to seven likely correspond to the AM rating task, occurring 4 to 10 s after the onset of this secondary task. Rating AMs was associated with extensive activation of the bilateral prefrontal cortex, left posterior cingulate, left precuneus, and left inferior parietal lobule.

The negative saliences correspond to greater activity during the control tasks (sentence completion and size discrimination), and are evident in lag four (8 to 10 s after stimulus onset) when activity in these regions is maximally differentiated from AM tasks (see Fig. 1b). In addition to bilateral inferior frontal regions, negatively salient voxels were evident predominantly in posterior regions: right superior temporal gyrus, bilateral postcentral gyri, left inferior parietal lobule, right supramarginal gyrus, middle occipital gyrus bilaterally, and right cuneus and superior occipital gyrus. The negative saliences at lags five to seven likely correspond to the control task ‘completion difficulty’ rating, being 6 to 8 s after the onset of this task. This rating task was associated with activity in similar posterior regions, and additional activation in the right medial frontal gyrus, bilateral precentral gyrus, left insula, and hippocampus bilaterally.

Spatiotemporal task PLS of AM tasks

As we were interested particularly in the similarities and differences between specific and general AM retrieval, we conducted a spatiotemporal task PLS analysis of these two AM tasks. This analysis identified one significant latent variable, *LV2.1* ($P < 0.001$) that differentiated between specific and general AM retrieval (Fig. 2a). The positive saliences correspond to greater activity during specific AM retrieval, while negative saliences correspond to greater activity during general AM retrieval. For this analysis, only results from the lags where the two conditions were maximally differentiated (lags one to three, 2 to 8 s after stimulus onset) are considered here (see Table 2 and Fig. 2).

The weighted average of activity in all voxels across all participants is presented in Fig. 2b, and illustrates two major differences between specific and general AMs. Firstly, the overall level of activity across the brain associated with specific AM retrieval is greater than that associated with general AM retrieval (as indicated by the absolute value of the brain scores associated with each task). Secondly, overall brain activity associated with general AM retrieval peaked in lag one (2 to 4 s after stimulus onset), and that associated with specific AM retrieval peaked in lag three (6 to 8 s after stimulus onset).

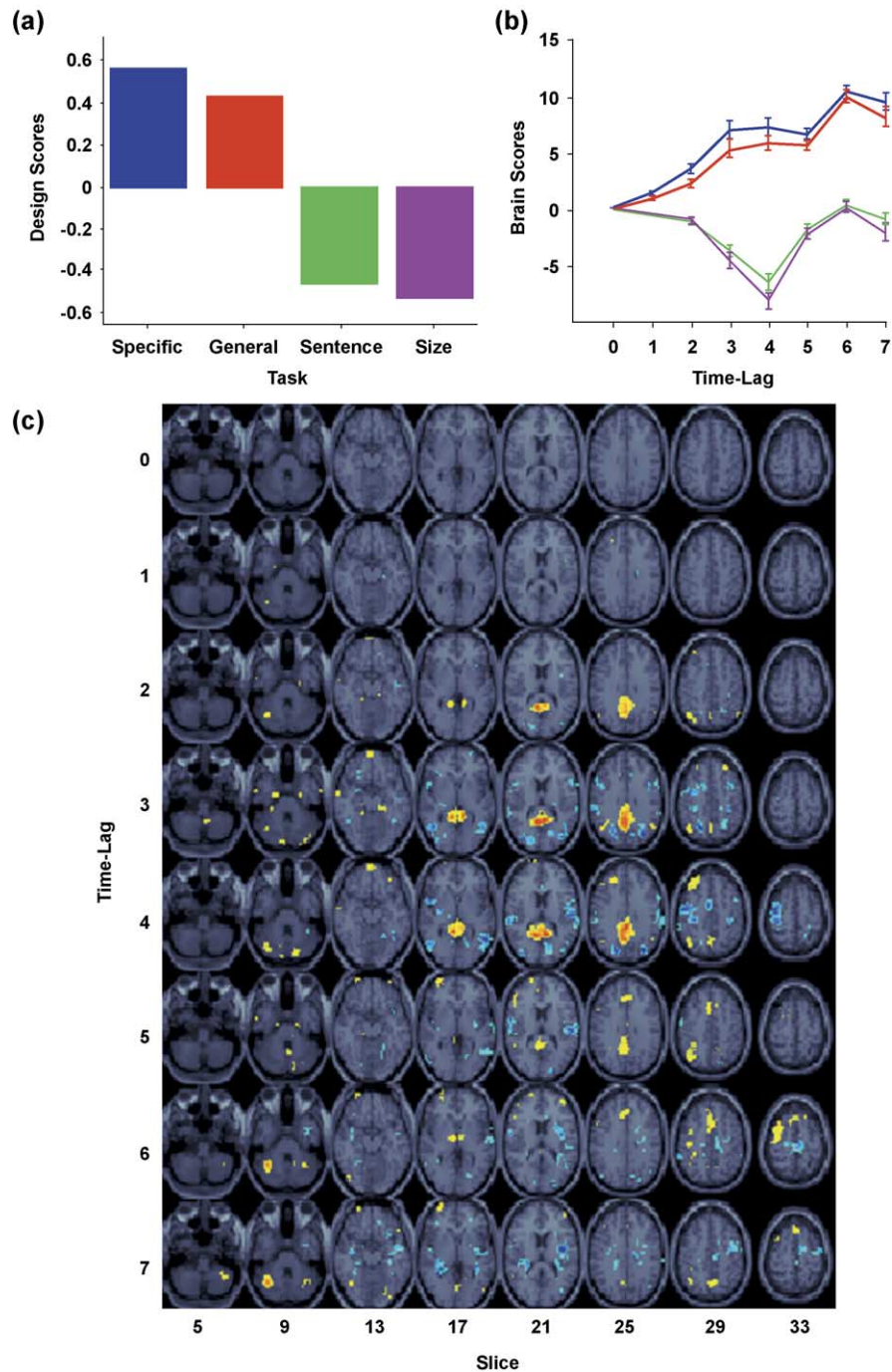


Fig. 1. (a) This graph corresponds to scores for the significant latent variable (*LVI.1*; AM/control tasks differences) from the spatiotemporal task PLS analysis of AM and control tasks. (b) This graph illustrates the weighted average of activation across all voxels in all subjects across the length of the experimental tasks. The AM tasks (blue, red) peak during Lag 3, while the control tasks (green, purple) peak during Lag 4. A later peak relating to the rating tasks is evident in Lag 6. (c) The brain regions in which activation was positively (yellow-red; AM tasks) and negatively (blue; control tasks) associated to *LVI.1* shown in (a) are superimposed over a standard MRI template (1–33 slices) and divided into 2-s lags. Note that this does not represent an hrf.

Negative saliences associated with general AM retrieval were evident in lag two, in the right medial frontal gyrus, left thalamus, and right inferior temporal gyrus. The independent contribution of these voxels to the distributed pattern of activity associated with these AMs is illustrated in Fig. 2c. Activity in the right inferior temporal gyrus during general AM retrieval showed the predicted temporal pattern, with an increase of activity peaking during lag two. However, examination of the hrf in the

left thalamus and right medial prefrontal gyrus revealed that although activity in these regions was maximally differentiated from specific AMs in lag two (contributing to the significance of these negative saliences), the general AM curve was essentially flat. In other words, in contrast to the pattern exhibited by the right inferior temporal gyrus, the maximal differentiation between general and specific AMs in the left thalamus and right medial prefrontal gyrus did not reflect increased activity during general

Table 1

Coordinates of positive and negative saliences of Latent Variable 1.1 from the spatiotemporal task PLS analysis of AM and control tasks

Brain region	Coordinates			Bootstrap ratio ^a
	x	y	z	
<i>Lag 2-positive saliences</i>				
L. middle frontal gyrus (BA 9)	-32	41	35	6.01
L. posterior cingulate (BA 30)	-8	-50	14	9.75
L. inferior parietal lobule (BA 7)	-40	-68	44	6.63
<i>Lag 2-negative saliences</i>				
L. middle occipital gyrus (BA 18)	-16	-85	15	4.93
<i>Lag 3-positive saliences</i>				
L. superior frontal/orbitofrontal gyrus (BA 11)	-4	61	-20	6.97
R. parahippocampal gyrus (BA 36)	24	-17	-23	9.15
L. posterior cingulate (BA 30)	-16	-53	21	13.67
L. angular gyrus (BA 39)	-44	-64	33	6.48
R. angular gyrus (BA 39)	48	-60	36	5.37
R. cerebellum	20	-87	-23	5.37
<i>Lag 3-negative saliences</i>				
L. inferior frontal gyrus (BA 44)	-48	9	18	5.75
R. inferior frontal gyrus (BA 44)	51	12	14	6.37
L. cingulate gyrus (BA 24)	-8	6	44	5.92
L. precentral gyrus (BA 6)	-40	-2	41	6.69
R. postcentral gyrus (BA 2)	32	-29	42	5.76
L. midbrain	-20	-24	-6	6.06
L. inferior parietal lobule (BA 40)	-59	-26	27	5.53
R. supramarginal gyrus (BA 40)	59	-41	35	6.64
R. cuneus (BA 18)	12	-73	22	6.65
L. middle occipital gyrus (BA 19)	-48	-62	-4	8.16
R. middle occipital gyrus (BA 19)	32	-73	26	8.42
<i>Lag 4-positive saliences</i>				
L. middle frontal gyrus (BA 46)	-48	32	17	6.08
R. parahippocampal gyrus (BA 35)	20	-9	-23	5.24
L. posterior cingulate (BA 23)	-8	-45	24	12.62
L. inferior parietal lobule (BA 7)	-40	-68	44	5.83
L. cerebellum	-36	-75	-27	5.57
R. cerebellum	12	-83	-19	6.08
<i>Lag 4-negative saliences</i>				
R. inferior frontal gyrus (BA 44)	59	13	29	4.55
L. cingulate gyrus (BA 24)	-8	-2	41	7.22
L. postcentral gyrus (BA 3)	-55	-9	45	8.99
L. postcentral gyrus (BA 40)	-51	-26	20	8.26
R. postcentral gyrus (BA 2)	40	-25	45	6.01
R. superior temporal gyrus (BA 22)	63	-34	16	8.46
R. superior occipital gyrus (BA 19)	32	-76	30	8.99
R. cuneus (BA 18)	12	-69	15	5.32
R. cerebellum	16	-51	-18	8.97
<i>Lag 5-positive saliences</i>				
L. superior frontal gyrus (BA 10)	-32	62	-6	6.45
L. middle frontal gyrus (BA 46)	-51	32	17	9.18
L. posterior cingulate (BA 29)	-8	-46	6	9.13
L. inferior parietal lobule (BA 40)	-44	-64	44	6.12
R. cerebellum	8	-79	-23	5.22
<i>Lag 5-negative saliences</i>				
L. precentral gyrus (BA 6)	-59	-3	11	6.59
R. transverse temporal gyrus (BA 41)	55	-23	12	7.01

Table 1 (continued)

Brain region	Coordinates			Bootstrap ratio ^a
	x	y	z	
<i>Lag 5-negative saliences</i>				
R. middle temporal gyrus (BA 37)	48	-54	-1	5.96
R. supramarginal gyrus (BA 40)	59	-41	35	5.95
L. fusiform gyrus (BA 37)	-24	-51	-8	5.54
R. lingual gyrus (BA 19)	16	-66	-3	5.18
R. precuneus (BA 31)	8	-73	26	7.01
L. middle occipital gyrus (BA 19/37)	-51	-74	4	6.55
<i>Lag 6-positive saliences</i>				
L. medial frontal gyrus (BA 6)	0	10	44	9.02
L. middle frontal gyrus (BA 6/46)	-40	14	51	7.67
R. middle frontal gyrus (BA 46)	40	47	9	6.13
L. Subthalamic nucleus	-8	-12	-3	6.42
L. cerebellum	-36	-63	-24	8.40
R. cerebellum	32	-60	-31	5.65
<i>Lag 6-negative saliences</i>				
L. precentral gyrus (BA 6)	-59	-3	11	7.19
R. precentral gyrus (BA 6)	16	-16	63	5.98
L. insula	-44	-12	-6	5.58
L. hippocampus	-36	-24	-9	6.37
R. superior temporal gyrus (BA 22)	44	-50	14	6.36
L. lingual gyrus (BA 18)	-12	-74	-6	6.09
L. cerebellum (BA 6)	-32	-51	-14	6.00
<i>Lag 7-positive saliences</i>				
L. precuneus (BA 7)	-4	-68	44	6.74
L. inferior parietal lobule (BA 40)	-40	-56	43	5.72
L. cerebellum	-36	-67	-24	9.11
R. cerebellum	40	-56	-41	6.48
<i>Lag 7-negative saliences</i>				
R. medial frontal gyrus (BA 6)	8	-1	52	6.86
L. insula	40	-7	11	7.55
L. hippocampus	-32	-27	-5	7.92
R. hippocampus	24	-28	-9	6.10

Note. All coordinates are reported in Talairach space.

^a The bootstrap ratio is the parameter estimate for that voxel over its standard error and is proportional to a z score.

AM retrieval but rather deactivations during specific AM retrieval.

Positive saliences associated with specific AMs were evident during lag three, in the left superior parietal lobule, left precuneus and right cuneus. The time-courses illustrating the independent contribution of these voxels to the distributed pattern of activity associated with specific AMs (Fig. 2d) indicate that these regions all show an increase in activity during the retrieval of specific rather than general AMs. The left superior parietal lobule voxel exhibits a peak in activity during lag three, which is not evident for general AMs. Additionally, activity in the precuneus voxel also peaks during lag three, while for general AMs the peak evident at this time lag is remarkably smaller.

Spatiotemporal seed PLS of AM tasks

To assess the distributed functional connectivity patterns of the left and right hippocampus, we conducted a spatiotemporal seed

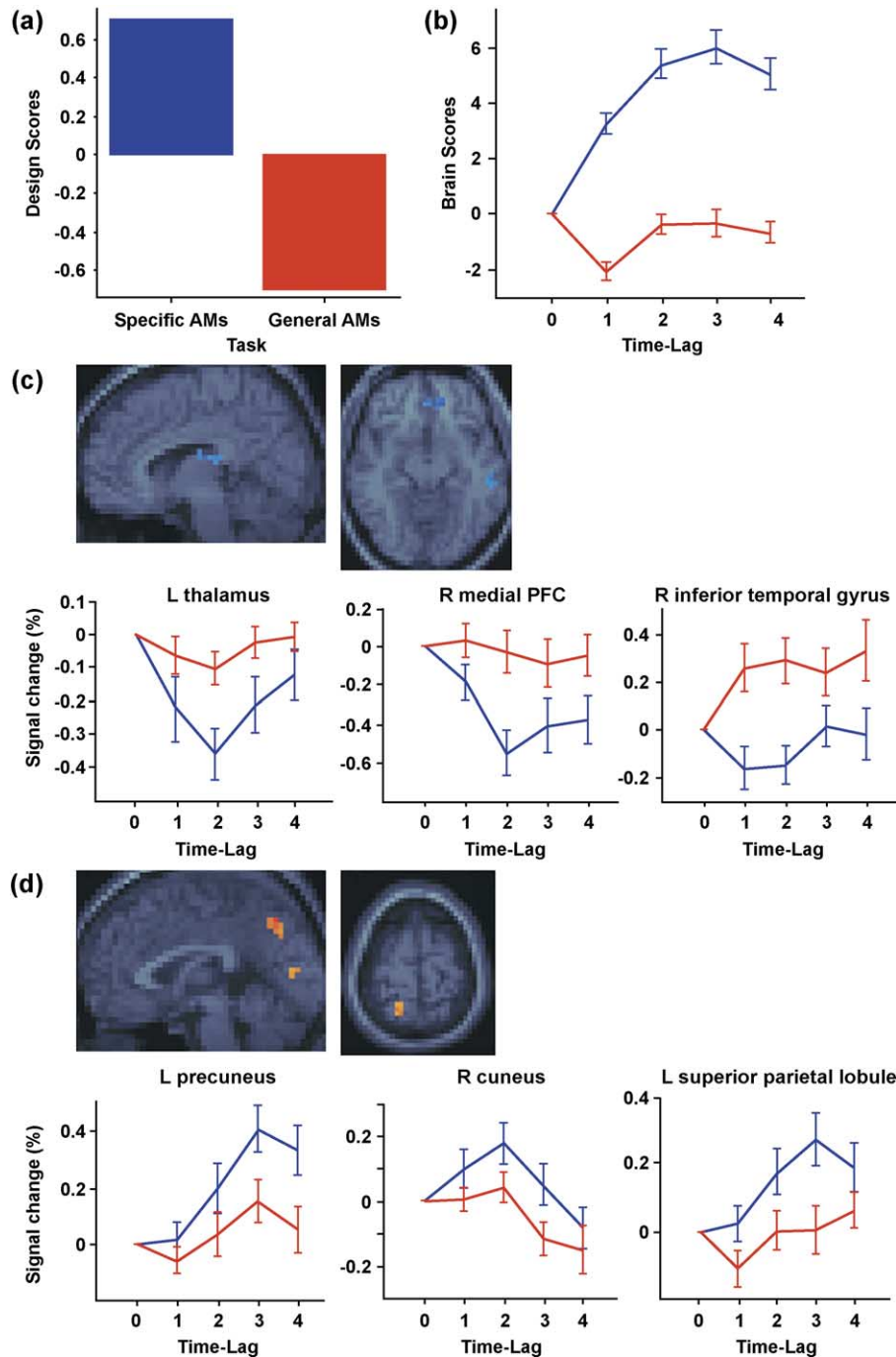


Fig. 2. (a) This graph corresponds to scores for the significant latent variable (*LV2.1*; specific/general AM retrieval differences) from the spatiotemporal task PLS analysis of AM tasks, and the graph in (b) shows the weighted average of activation across all voxels in all subjects across the length of the AM tasks. General AMs (red) peak during Lag 1, while specific AMs (blue) peak during Lag 3. Note that this does not represent an hrf. (c) The brain regions in which activity characterized general AM retrieval and were negatively associated to *LV2.1* (peaking in Lag 2) are superimposed (in blue) over a standard MRI template. The hemodynamic responses of salient voxels are also displayed. (d) Brain regions in which activity characterized specific AM retrieval and were positively associated to *LV2.1* (peaking in Lag 3) are superimposed (in yellow-red) over a standard MRI template, and the hemodynamic responses of salient voxels are displayed. Note: PFC = prefrontal cortex.

PLS analysis on the AM tasks. This revealed one significant latent variable, *LV3.1* ($P < 0.008$), that demonstrated commonalities between specific and general AMs (Fig. 3a). Therefore, positive saliences correspond to regions which correlate positively with the left and right hippocampus, while negative saliences indicate negatively correlated regions. As in the task PLS analysis of the

AM tasks, only results from lags two and three (4 to 8 s after stimulus onset) are discussed here. The positive and negative saliences evident during these lags are listed in Table 3 and are illustrated in Fig. 3b.

Specifically, a network of regions associated with the left and right hippocampus was activated during the retrieval of both

Table 2
Coordinates of positive and negative saliences of Latent Variable 2.1 from the spatiotemporal task PLS analysis of AM tasks

Brain region	Coordinates			Bootstrap ratio ^a
	x	y	z	
<i>Lag 2-positive saliences</i>				
R. cuneus	4	-77	8	3.96
<i>Lag 2-negative saliences</i>				
R. medial frontal gyrus (BA 11)	4	38	-15	4.12
L. thalamus	-8	-19	12	3.85
R. inferior temporal gyrus (BA 20)	55	-36	-15	4.59
<i>Lag 3-positive saliences</i>				
L. superior parietal lobule (BA 7)	-20	-55	62	3.67
L. precuneus (BA 7)	0	-64	44	4.85
R. cuneus (BA 17)	8	-81	11	4.06

Note. All coordinates are reported in Talairach space.

^a The bootstrap ratio is the parameter estimate for that voxel over its standard error and is proportional to a z score.

specific and general AMs. The network included the left medial frontal and postcentral gyri, right middle temporal gyrus, right parahippocampal gyrus, bilateral hippocampus and the right cerebellum. In contrast, the right inferior and middle frontal gyri, left precentral gyrus, right thalamus, left superior temporal and parahippocampal gyri, and bilateral fusiform gyrus were negatively correlated to the hippocampal seeds during AM retrieval.

To assess whether this functional network revealed by *LV3.1* was more strongly associated with the left and right hippocampus during specific or general AM retrieval, separate seed PLS analyses were conducted for specific and general AMs. The same left and right hippocampal seeds were entered into these seed PLS analyses, and the resulting brain latent variables were correlated with the brain latent variable from the full seed PLS analysis. The results indicated that general AMs were more strongly associated with *LV3.1* from the full seed PLS analysis ($r = 0.83$) than were specific AMs ($r = 0.64$).

Discussion

The purpose of this study was to use PLS, a multivariate imaging analysis technique, to examine data from an event-related fMRI study on AM retrieval. By doing so, we hoped to determine whether specific and general AM retrieval recruit distinct neural networks, as would be expected if they are psychologically distinct forms of memory. Furthermore, with aid of *spatiotemporal* PLS in the analysis of these event-related fMRI data, we hoped to specify the time course of distributed patterns of activity associated with general and specific AM retrieval. PLS analyses also presented an opportunity to consider the advantages of using multivariate techniques for examining neural networks and to see whether and how the results of these analyses correspond with and complement the findings of previous univariate analyses on these data. We expected results to be complementary, with PLS providing information about the contribution of patterns of activity across the entire brain to distinctions between tasks, and univariate analyses imparting information about the importance of a given

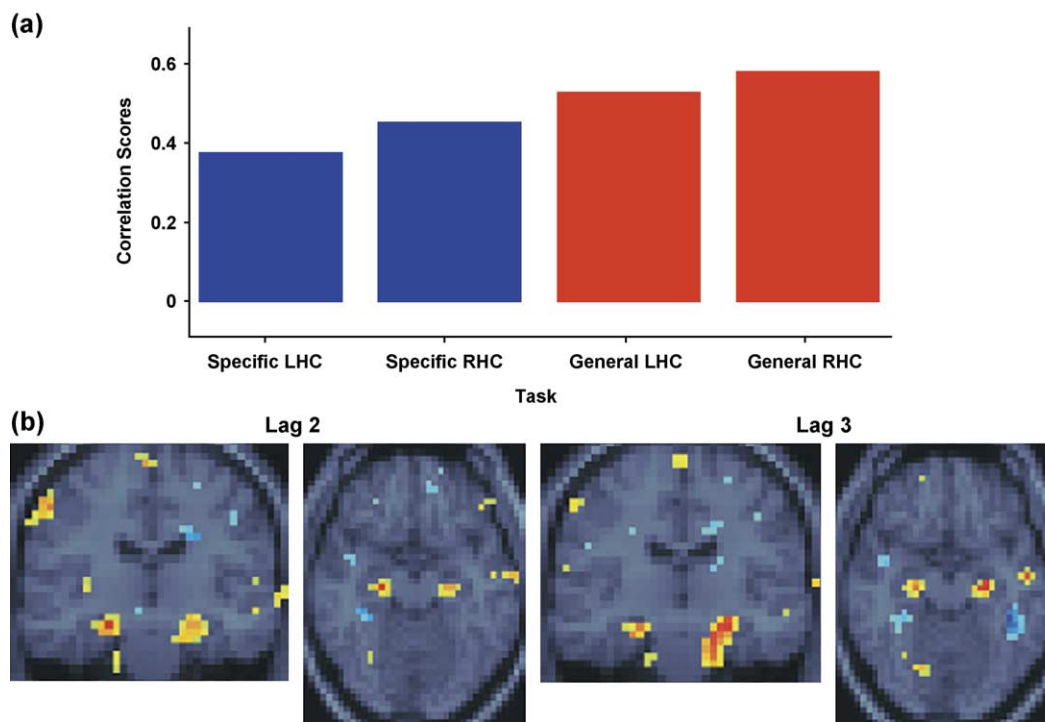


Fig. 3. (a) This graph corresponds to correlation scores for the significant latent variable (*LV3.1*; similarities in hippocampal functional connectivity during specific/general AM retrieval) from the spatiotemporal seed PLS analysis of AM tasks. (b) The brain regions in which activation was positively (yellow-red) and negatively (blue) correlated to hippocampal seeds during Lags 2 and 3 are superimposed over a standard MRI template. Note: LHC = left hippocampal seed; RHC = right hippocampal seed.

Table 3

Coordinates of positive and negative saliences of Latent Variable 3.1 from the spatiotemporal seed PLS analysis of AM tasks

Brain region	Coordinates			Bootstrap ratio ^a
	x	y	z	
<i>Lag 2-positive saliences</i>				
L. postcentral gyrus (BA 4)	-55	-17	41	5.64
R. middle temporal gyrus (BA 21)	63	-12	-9	5.56
L. hippocampus	-24	-20	-16 ^b	8.05
R. parahippocampal gyrus (BA 28)	20	-20	-16	5.04
<i>Lag 2-negative saliences</i>				
R. middle frontal gyrus (BA 46)	48	36	17	5.38
L. fusiform gyrus (BA 20)	-36	-36	-18	4.67
<i>Lag 3-positive saliences</i>				
L. medial frontal gyrus (BA 6)	-4	-12	63	4.77
L. hippocampus	-24	-20	-16 ^b	5.54
R. hippocampus	24	-20	-16 ^b	7.87
R. cerebellum	44	-64	-37	5.17
<i>Lag 3-negative saliences</i>				
R. inferior frontal gyrus (BA 46)	48	39	13	4.99
L. precentral gyrus (BA 6)	-51	-7	22	5.06
R. thalamus	16	-31	5	6.09
L. parahippocampal gyrus (BA 36)	-32	-35	-8	4.19
L. superior temporal gyrus (BA 38)	-40	14	-31	3.77
R. fusiform gyrus (BA 37)	40	-40	-15	6.39

Note. All coordinates are reported in Talairach space.

^a The bootstrap ratio is the parameter estimate for that voxel over its standard error and is proportional to a z score.

^b Voxel used for seed PLS.

region within this distributed pattern (Vanlancker-Sidtis et al., 2003). To our knowledge, this is the first study to use spatiotemporal PLS with event-related fMRI data to investigate networks associated with higher cognitive processes (see Lin et al., 2003, for use of spatiotemporal PLS with fMRI data from a motor task).

The PLS analysis of all four tasks (AM and control tasks) revealed a latent variable, *LV1.1* that identified a pattern of brain activity which distinguished the AM and controls tasks (sentence completion and size discrimination). The network of brain regions that characterized the control tasks included posterior regions such as lateral temporal, superior parietal and occipital regions, consistent with the semantic and visuospatial processing necessary to complete these tasks. The pattern of brain activity associated with AM retrieval is strikingly similar to regions identified by univariate comparison of AM retrieval to the control tasks (Addis et al., 2004). The regions identified here as maximally distinguishing AM retrieval from lower-level control tasks included left medial frontal cortex, left posterior cingulate (extending into the left parahippocampal gyrus and hippocampus) and right parahippocampus (extending into the right hippocampus), left inferior parietal lobule, and bilateral angular gyrus and cerebellum. These regions correspond to those in the ‘memory retrieval network’ (Maguire and Mummery, 1999) reported to be engaged during AM retrieval (Addis et al., 2004; Fink et al., 1996; Gilboa et al., 2004; Maguire and Mummery, 1999; Maguire et al., 2000, 2001; Piefke et al., 2003; Ryan et al., 2001).

This spatiotemporal task PLS analysis also provided interesting information about the lag in the peak activations associated with

the different tasks, highlighting a unique advantage of using spatiotemporal PLS with event-related imaging data. We found that activations characterizing AM retrieval peaked 6 to 8 s after stimulus onset, while those associated with the control tasks did not peak until 8 to 10 s. It was also possible to distinguish networks of regions related to the rating tasks, which commenced 4 and 6 s into the control and AM events, respectively, and thus peaked during lags five to seven. Note that even though the onset of rating task was not jittered, and there was possibly some overlap in the AM and rating tasks, PLS still allows for the differentiation of activity. Specifically, by analyzing the time-series without a canonical hrf or focusing on one time-point, we can identify places where there are independent activity patterns related to the rating task. Providing ratings led to an increase in activation of the frontal cortex, which likely is related to the evaluative and decision components of this task.

The significant latent variable from the first task PLS analysis, *LV1.1*, not only distinguished AM retrieval from the control tasks but also delineated the similarities between specific and general AMs. Overall, the two types of AMs rely on similar distributed patterns of brain activity, namely, the AM medial and left-lateralized retrieval network identified in previous univariate analyses (Addis et al., 2004; Fink et al., 1996; Maguire and Mummery, 1999; Maguire et al., 2000, 2001; Piefke et al., 2003). Despite the general similarity, closer examination by subsequent PLS analyses identified patterns of distributed activity differentiating the two types of AM retrieval.

Based on research by Conway and colleagues (Burt et al., 2003; Conway, 1992; 1996; Conway and Pleydell-Pearce, 2000; Haque and Conway, 2001), we predicted that if specific and general AMs are distinct forms of memory, they should show stronger associations with different aspects of this AM retrieval network. This prediction was supported by our second task PLS of the AM tasks. Firstly, the overall level of distributed activity was greater during the retrieval of specific compared to general AMs, as indicated by the weighted average of activity across all voxels. Furthermore, *LV2.1* revealed that activity in regions such as the left superior parietal lobule, left precuneus, and right cuneus characterized specific AM retrieval, with the precuneus in particular exhibiting remarkably more activity than during general AM retrieval. These regions are known to play a role in visuospatial processing, and the precuneus and parietal regions have been associated with visual imagery in episodic memory retrieval (e.g., Andreasen et al., 1999; Burgess et al., 2001; Cabeza and Nyberg, 2000; Cabeza et al., 2003; Fletcher et al., 1995). This is consistent with the hypothesis that specific AMs are composed of visual and contextual information and so should rely on such regions during retrieval (Conway et al., 2001, 2003; Haque and Conway, 2001; Greenberg and Rubin, 2003). Further, this is reflected in the behavioral data collected during this study (Addis et al., 2004), which indicated that these specific AMs were rated by participants as more detailed than general AMs, though the effect size of this difference was modest (.32 SD units; Cohen, 1988). This finding also complements the results of our univariate contrast of specific and general AMs, which at a liberal threshold, revealed that retrieval of specific AMs was associated with left precuneus activation (Addis et al., 2004).

In contrast to the clear predictions regarding regional activations associated with specific AM retrieval, neither previous functional imaging work nor the cognitive literature provided strong predictions regarding the recall of general AMs, as defined

here. Indeed, the pattern of regions that characterized such retrieval here was quite difficult to interpret. Saliences associated with general AM retrieval were in the left thalamus, medial prefrontal gyrus, and lateral aspect of the right inferior temporal gyrus. It was only in the latter structure, however, that the maximal differentiation from specific events reflected an increase in activity during general AM retrieval, but it is unclear what retrieval processes more strongly associated with general events are supported by this region. Graham et al. (2003) suggest the right temporal lobe may be involved in the retrieval of the conceptual event and people knowledge of AMs, and thus it is possible that in this study, general AMs were associated with more conceptual knowledge than specific AMs.

Our finding of right inferior temporal activity associated with general AMs differs from that of Graham et al. (2003), who found that AMs rated high in specificity were associated with increased activation in the right temporal lobe, though at a more anterior location. It is difficult, however, to compare the findings of Graham et al. directly with those of the present study, due to major differences in the AM tasks, imaging technique and analyses used in each. Firstly, Graham et al. imaged AM retrieval across a 30-s interval (cf. 6-s in this study), and thus their findings reflect activity not only from initial retrieval period (as do our data), but also from AM elaboration and maintenance. Their data do suggest, however, that there may be even more complex relationships between specific and general AMs over a longer period of memory elaboration. The 6-s length of the AM task in the present study is sufficient, nonetheless, to examine the initial retrieval of AMs, as was our intention. To accommodate for the brevity of the task, AM cues were individually tailored through use of a pre-scan interview making ours a direct AM retrieval task, rather than a generative one used by Graham et al. Finally, the difference between the definition of “generic” (Graham et al.) and “general” AMs may account for some of the apparent disparity of findings. Graham et al.’s AMs were rated by independent raters as being generic (or specific), whereas in the present study, participants generated general AMs according to detailed instructions based on Conway’s (1996) definition of general, repeated AMs. This likely resulted in differences in the content of generic AMs (e.g., “I eat toast for breakfast everyday”; Graham et al., 2003, pp. 241) and general AMs (e.g., a memory of having Christmas at Grandma’s every year, including contextual, event and people information). Despite these differences, both these and other studies (Addis et al., 2004; Fink et al., 1996; Maguire and Frith, 2003; Viskontas et al., 2000) emphasize the important role of right medial and lateral temporal regions in AM retrieval that should not be ignored given the recent focus on the role of left hemispheric regions (e.g., Maguire and Mummery, 1999; Maguire et al., 2000, 2001; Piefke et al., 2003).

General AM retrieval also was associated with maximal differences of activity in the left thalamus and medial prefrontal gyrus. The effect in these regions, however, was attributable to a deactivation during specific AM retrieval. This pattern of results highlights the importance of investigating the contributions of salient voxels to the whole brain pattern of activity associated with a task and what the maximal differentiation between two tasks actually signifies.

Overall, these results indicate that specific and general AMs can be distinguished at a neural level, in terms of their greater associations with different regions of a common AM retrieval network. Furthermore, specific and general AM retrieval appears to be differentiable at a temporal level, with activations associated

with general AM retrieval appearing up to two lags (4 s) earlier than those associated with specific AM retrieval. This is clearly evident in the weighted average of overall brain activity during general and specific AM retrieval (Fig. 2b), which shows general AMs peaking during lag one, and specific AMs later, during lag three. Additionally, the time-courses of some of the salient voxels, such as the right inferior temporal gyrus, left superior parietal lobule and precuneus, show a consistent temporal pattern. Shorter latencies to access general AMs is consistent with the idea that they are the entry point to AM representations, and thus are accessed more quickly than specific memories (Burt et al., 2003; Conway and Pleydell-Pearce, 2000). Further, this result is in line with findings from two slow cortical potential studies of specific AM retrieval (Conway et al., 2001, 2003), which reported that specific AMs were associated with activity later in the retrieval phase. Specifically, the formation of a specific AM was associated with a shift in activity from left anterior to right posterior regions supporting episodic imagery processes. Our finding regarding the temporal aspects of specific and general AM retrieval adds another dimension to the evidence that these two forms of AM are psychologically and neurally distinct. Further work is still necessary, however, to couple reaction times for the retrieval of specific and general AMs with the lag of activation of underlying neural networks.

We also employed spatiotemporal seed PLS to investigate the functional connectivity of the hippocampus with other brain regions during the retrieval of specific and general AMs. This produced one significant latent variable, *LV3.1*, which characterized the similarities between specific and general AMs. Thus, while retrieval of these memories results in stronger activations of different regions of a common AM network identified by our other analyses, the “sub-network” functionally connected to the hippocampus is associated with both types, though general AMs are somewhat more strongly correlated. The regions comprising the pattern of activation identified by *LV3.1* included the hippocampus bilaterally, indicating that the left and right hippocampi are functionally connected during both types of AM retrieval. This could explain the failure of univariate analyses to expose any differences in hippocampal activation between specific and general AM retrieval. Further, although it has been noted that the left hippocampus is more extensively activated during AM retrieval (e.g., Maguire et al., 2001), it is clear from these results that the right hippocampus plays an important role in the functional network supporting all AM retrieval. Other regions functionally associated with the hippocampal seeds included those regions which comprise the overall AM retrieval network identified in *LV1.1* and our univariate analyses (Addis et al., 2004), such as the left medial frontal gyrus, left middle temporal gyrus, right temporal pole, right parahippocampal gyrus, and right cerebellum. This sub-network, therefore, is common to the retrieval of both forms of AM, and thus may reflect more generalizability. Graham et al. (2003) have suggested that the right anterior temporal regions may be involved in retrieval of conceptual event and people knowledge during AM and other memory retrieval, rather than an AM-unique retrieval process. Thus, one can conceive of this hippocampal network acting as a hub in a larger network of AM retrieval, with different spokes related to the different types of memories that are being retrieved.

In addition to a network of regions positively correlated with the hippocampus, *LV3.1* also produced several saliencies that exhibited negative correlations with the seed regions during AM

retrieval. Of particular interest is that the left parahippocampal gyrus was a part of this pattern, an intriguing result in light of Maguire and Mummery's (1999) finding that this region showed increased effective connectivity with the left hippocampus and left temporal pole during specific AM retrieval. This apparent discrepancy may occur because functional connections do not account for mutual or mediating influences and so may not map directly to effective connections. It may also suggest that although these regions likely work together as a functional unit, the nature of the interaction between regions may be more complex than initially thought. The hippocampus and parahippocampus are known to be closely connected anatomically (Lavanex and Amaral, 2000; Witter et al., 2000) and both have been found to be engaged during the retrieval of AMs (e.g., Addis et al., 2004), so it is most straightforward to assume that these regions work in concert so that a unit increase in one region corresponds to a unit increase in the other. In this scenario, they could be responsible for the same or different processes in AM retrieval. A second possible relationship is that these regions are responsible for complementary AM retrieval processes, and that the more the parahippocampal gyrus provides, the less the hippocampus is required to contribute, and vice versa. This is an interesting result and further research is needed to clarify the role of the parahippocampal gyrus, and its association with the hippocampus, during AM retrieval.

In summary, overall our results indicate that specific and general AMs recruit both similar and distinct aspects of the AM retrieval network. The recruitment of distinct "sub-networks" during retrieval of these types of AM supports the hypothesis that they are distinct forms of AM, as proposed by Conway and Pleydell-Pearce (2000) and Haque and Conway (2001). Both the univariate and multivariate PLS analyses suggest that the differences observed may reflect differences in content between these types of AMs, in particular, the increased imagery inherent in specific AMs, and the increased conceptual knowledge associated with general AMs. Additionally, the differences in the lag to peak activation of these networks indicate that it takes a different amount of time to gain access to general and specific AMs, with general AMs likely being the point of entry to autobiographical representations. Despite these differences, the sub-network functionally connected to the hippocampus is activated by both general and specific AM retrieval.

These findings highlight the contribution of multivariate imaging analyses, such as PLS, to understanding imaging data. This contribution is not limited to confirming and complementing the results of univariate analyses by providing information about distributed patterns of brain activity distinguishing various tasks. By also by providing spatiotemporal information, multivariate analyses help to clarify further the roles of different neural networks in memory and other cognitive processes.

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