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Neuroimaging studies of autobiographical event memory

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Commonalities and differences in findings across neuroimaging studies of autobiographical event memory are reviewed. In general terms, the overall pattern across studies is of medial and left-lateralized activations associated with retrieval of autobiographical event memories. It seems that the medial frontal cortex and left hippocampus in particular are responsive to such memories. However, there are also inconsistencies across studies, for example in the activation of the hippocampus and dorsolateral prefrontal cortex. It is likely that methodological differences between studies contribute to the disparate findings. Quantifying and assessing autobiographical event memories presents a challenge in many domains, including neuroimaging. Methodological factors that may be pertinent to the interpretation of the neuroimaging data and the design of future experiments are discussed. Consideration is also given to aspects of memory that functional neuroimaging might be uniquely disposed to examine. These include assessing the functionality of damaged tissue in patients and the estimation of inter-regional communication (effective connectivity) between relevant brain regions.

Keywords: positron emission tomography; functional magnetic resonance imaging; autobiographical events; human; hippocampus

1. INTRODUCTION

There are a number of approaches to neuroimaging episodic memory. In many studies, subjects are scanned as they learn and/or remember stimuli such as words or word-pairs. Using paradigms such as this we continue to learn much about, for example, frontal lobe contributions to memory operations (for a review, see Fletcher & Henson 2001). The focus here, however, is the retrieval of autobiographical event memories, those personally relevant episodes with a specific spatio-temporal context, the storehouse of our life's experiences ranging from the recent to the very remote. Although neuroimaging embraces techniques such as electroencephalography (EEG) and event related potentials (ERPs), only positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) will be considered in this instance, and the relevant literature briefly reviewed. While one might consider the data to raise more questions about the nature of autobiographical event memory than they answer, my aim here is to highlight issues pertinent to the interpretation of the neuroimaging findings. I will then focus on further questions about autobiographical event memory that functional neuroimaging might be uniquely disposed to address.

The background to any discussion of real world autobiographical event memory is the widely acknowledged difficulty of quantifying personal memories and assessing their retrieval (Hodges 1995; Warrington 1996). When asking someone to recall past events, they re-orientate to the past, they recall abstract semantic (people, general knowledge) as well as specific information, in revisiting an event they may re-encode it, and events will naturally differ in their salience and significance to the subject. Kapur (1999) summarizes many of the variables that are likely to affect autobiographical event memory: 'encoding variables'—novelty of an event, its distinctiveness, its predictability, the number and type of sensory modalities involved, cognitive and emotional significance of events, the exposure duration and repetition profile; 'retention testing variables'—time from event to test, sensitivity of the testing measure, response modality, strategies used by the subject; in the case of patients, 'lesion variables'—site, pathology, severity, acuteness of onset, other pathology, plasticity.

It is unsurprising, given the many influencing factors, that no current method of assessment is completely satisfactory, although a wide variety of tests have been employed. One commonly used method involves variations on the Crovitz & Schiffman (1974) technique, where subjects remember specific, personally experienced events in response to cue words. However, there are problems with this technique (Hodges 1995), e.g. subjects are typically not constrained to produce memories from specific time periods. There may also be considerable variation between subjects in the time taken to produce a memory and also in factors such as emotional valence of memories. The Autobiographical Memory Interview (AMI) (Kopelman *et al.* 1990) is a test designed for use in the clinical context where subjects are questioned about memories from specific time periods, as well as personally relevant factual or semantic memories. However, there are problems here also (Oxbury *et al.* 1997), e.g. in younger subjects there is more overlap between time

Table 1. Functional neuroimaging studies (PET/fMRI) involving retrieval of real-world autobiographical event memories.

study[a]	modality	pre-scan context	scanning context	examples of relevant contrasts[b]	areas active[c]
Andreasen *et al*. (1995)	PET	15 min prior to scan, recalled one specific event from their past; no information on whether recent/remote; no rating of the memories.	One scan per task; 3 conditions: 1, recalling aloud the personal event; 2, verbal fluency (letter C) aloud; 3, rest—but here interpreted as random free associations—no verbal output	1–2	Med frontal; retrosplen; L DLPFC.
Fink *et al*. (1996)	PET	1 h prior to scan, presented with autobiographical information on a previously unknown person. Weeks prior to scan, semi-structured interview to obtain information on personal events from childhood to early adulthood—emphasis on affect-laden events; subjects unaware of purpose of the interview.	Auditory presentation of stimuli as sentences; no overt response; 3 conditions: 1, hear sentences from unknown person's autobiography, imagining what happened to them in the situation; 2, hear sentences about own past, imagining what happened to themselves; 3, rest—eyes closed no auditory input.	2–1	R: sup temp gyrus/insula; post cing; HC; PHG; amygdala; TPJ; prefrontal.
Markowitsch *et al*. (1997)	PET	Patient 59 RH female; history of child abuse; produced drawings depicting scenes from childhood; some of vivid consciously remembered events, others where she did not know specific meaning of the scene.	15 s prior to scan, shown: one of the drawings. During scan, eyes closed, had to imagine what kind of past event the scene represented. 3 conditions: 1, rest; 2, 'conscious' memories; 3,where specific meaning not known.	only 2 reported: 2–1 3–1	R temp pole R temp pole; R PHG; L HC.
Maguire & Mummery (1999)	PET	Several weeks prior to scan, subjects interviewed and questionnaire completed but not aware of specific purpose of either; memories sampled from across 20 or more years, up to very recent memories. Rated across parameters such as: amount of details recalled, emotional salience, vividness, how often rehearsed. All consciously recollected, not merely told to them by a third party.	Heard sentences during scan and responded by keypress if what they heard was true/false; ratio = 3:1; if sentences were obviously altered actual memories (pilot data showed subjects recalled original event in this context—no. of false matched across scans/tasks). For episodic events, sampled across lifetime during each scan. 6 conditions: 1, autobiographical events; 2, public events; 3, autobiographical facts; 4, general facts; 5, control—sets of function words/prepositions, decide if last word had one or more syllables; 6, as in 5, but included self-reference words such as 'you'. 8 s per stimulus (3–4 s per sentence,the remainder to respond).	1–2/3 or 4–5 1–2/3 or 4	Network of medial and L areas: temp pole, med frontal; lat temp; HC; PHG; retrosplen; TPJ and R TPJ L HC; med frontal; temp pole.
Conway *et al*. (1999)	PET	Subjects trained prior to scan on recalling an event from their past in response to a cue word so could report the specific memory in detail. Taught a set of 15 verbal paired associates for later recall during scanning. For cues, common emotion words were excluded; frequency, imagability of words not controlled.	Stimuli presented visually (for 200 ms; ISI[d] 4800 ms); respond aloud. 3 conditions: 1, visual baseline—look at box of random intensity pixels; 2, saw first word of pairs and had to speak aloud the second word; 3, retrieved memory in response to cue word, had to respond with a word of their own. For some cues, had to respond with a recent memory (last 12 months), for others remote memories (when aged 15 years old or younger).	3–2 remote-recent recent-remote	L prefrontal; L post parietal; L occipital; L lat temp. no diffs occipital lobe brain stem

continued

Table 1. *continued*

study[a]	modality	pre-scan context	scanning context	examples of relevant contrasts[b]	areas active[c]
Andreasen *et al*. (1999)	PET	Nothing specific mentioned.	2 tasks: 1, told to lie quietly with eyes closed and think about a specific event experienced in the past; 2, think about anything that occurred to them.	1–2	R cerebellum; L lat cerebellum; L med dors thal; L orbito-frontal cortex; ant cing; L parietal; med frontal.
Maguire *et al*. (2000)	fMRI	Same as Maguire & Mummery (1999) above.	Similar to Maguire & Mummery (1999) above except control conditions 5 and 6 amalgamated (here called 5); 6 was a rest condition.	1–2/3 or 4–5	Network of L and medial areas: temp pole; and R temp pole; med frontal; lat temp; HC; PHG; retrosplen, TPJ; R post cerebellum
				1–2/3 or 4	L HC; med frontal
				effective connectivity	PHG-HC increased for 1 as was PHG-temp pole; lat temp-temp pole increased for 2 and 4.
Maguire *et al*. (2001*a*)	e-fMRI	Same as Maguire & Mummery (1999) above.	Similar to Maguire *et al*. (2000) above but used an event-related analysis to model the parametric effect of memory age for autobiographical events and public events over 20 or more years.	Parametric effect	R VLPFC decrease the more remote the autobiographical event memory.
				Recent autobiographical events — autobiographical facts	L HC; med frontal.
				Remote autobiographical events— autobiographical facts.	L HC; med frontal.
Ryan *et al*. (2001)	fMRI	Immediately prior to scan, shown a list of general life event categories, noting if had happened to them, when, if positive/negative. 10 recent (less than 4 years ago) and 10 remote (over 20 years ago) events gathered, equal numbers of positive and negative events. In 3 extra subjects, cues collected from spouses and presented to subjects for first time during scanning.	Visual cues during scanning; 3 conditions: 1, recall past event for 20 s on viewing the relevant category label from pre-scan list; 2, visual cue to relax for 16 s; 3, shown sentences with last word missing, had to covertly complete sentence with an appropriate word.	recent-remote	No diffs
				recent-remote—2/3 (similar results for the 3 extra subjects)	L,R prefrontal; L,R precentral gyrus; L sup temp sulcus; L mid temp gyrus; L,R HC; R pulvinar; post cing; L,R precuneus; L fusiform; L inf parietal; R lat cerebellum.

continued

Table 1. *continued*

study[a]	modality	pre-scan context	scanning context	examples of relevant contrasts[b]	areas active[c]
Maguire *et al*. (2001*a*)	fMRI	Patient 22 RH male; selective bilateral hippocampal damage of perinatal origin. Preserved semantic but impaired episodic memory. Same procedure as Maguire & Mummery (1999), enough events recalled for viable scanning; accuracy checked with parents. Jon made a distinction the controls did not: for some events he had conscious recollection, for others, although he knew as much about, did not remember the event occurring.	Same as in Maguire *et al*. (2000) except two extra conditions, as well as 1, and 2, also autobiographical events he knew about but not remember the context (no. 7) and similarly for public (no. 7) events (no. 8).	1/2/3/ 4/7 or 8–5 1–2/3/4/7 or 8 effective connectivity	Same as controls in Maguire *et al*. (2000) but bilateral. Also L,R prefrontal regions. L,R HC; med frontal needed extra conns; PHG-temp pole increased for 1 as was retrosplen-HC; retrosplen-HC and retrosplen med. frontal increased in Jon versus controls for autobiographical events.
Burgess *et al*. (2001)	e-fMRI	VR complex town adapted from Maguire *et al*. (1998). The town was used as the real world context where events were experienced by subjects prior to scanning—certain people giving them objects in certain places.	Subjects scanned during retrieval of aspects of the events: 1, place; 2, person; 3, object; 4, visual control task.	1–4	L HC; retrosplen; R precuneus; L,R VLPFC; L,R PHG; L,R DLPFC; L,R post parietal; mid and ant cing; L fusiform.

[a] Liotti *et al*. (2000) was not included because autobiographical events, while used to elicit emotions prior to scanning, during scanning subjects had to focus only on the emotions and not specific events.
[b] The numbers refer to the conditions as described in the adjacent left column.
[c] /, or; ant, anterior; cing, cingulate; DLPFC, dorsolateral prefrontal cortex; dors, dorsal; e-fMRI, event-related fMRI; HC, hippocampus; inf, inferior; L, left; lat, lateral; med, medial; mid, middle; PHG, parahippocampal gyrus; post, posterior; R, right; retrosplen, retrosplenial; RH, right-handed; sup, superior; temp, temporal; thal, thalamus; TPJ, temporoparietal junction; VLPFC, ventrolateral prefrontal cortex; VR, virtual reality.
[d] ISI, inter-stimulus interval.

periods than in older subjects and personal semantic questions can often be easier than those for event memory. The AMI and most similar tests assess the recall of autobiographical event memories. Autobiographical event recognition memory is generally not assessed, but may provide additional information about preserved memories in amnesia (N. Kapur, personal communication). Despite the limitations of current tests, we continue to learn much from their use and, as is apparent in the next section, they have also been adapted for use in several PET and fMRI studies.

2. NEUROIMAGING AUTOBIOGRAPHICAL EVENT MEMORY: A REVIEW

Studying memory using neuroimaging has many acknowledged advantages—healthy brains can be scanned *in vivo*, one can achieve good spatial resolution, in the case of fMRI one can study discrete cognitive events as brief as 1–2 s, and one can examine neural activity during encoding based on whether stimuli were subsequently remembered or not (Brewer *et al*. 1998; Wagner *et al*. 1998). Neuroimaging studies of autobiographical event memory, however, are subject to all of the issues outlined in § 1 and some more besides. For example, in fMRI, avoiding speech-related movement artefacts makes free recall difficult to operationalize. In PET (not a problem for fMRI), given that blood flow is averaged across approximately 90 s, one cannot examine discrete events. Because of these technical issues and the time and resource demands of examining autobiographical event memory *per se* (i.e. the requirement for subject-specific stimuli), functional neuroimaging studies involving the retrieval of autobiographical event memories are not numerous.

All known (eleven) studies are listed in table 1. For each study, the scanning modality, general pre-scan context, scanning conditions and stimulus presentations are given. Also included are examples of the main contrasts relating to autobiographical event memory, and a summary of brain areas active in these contrasts. I will briefly highlight some of the findings, considering commonalities and differences across studies.

In general terms, the overall pattern across studies is of medial and left-lateralized activations associated with retrieval of autobiographical event memories. In the one study where the emphasis was on affect-laden memories, activations are described as right-sided (Fink *et al*. 1996). Areas active in many of the studies include retrosplenial cortex, parahippocampal gyrus, temporo-parietal junction, medial frontal cortex, temporal pole, cerebellum and the hippocampus. These areas clearly form the basis of a memory retrieval network but it is not clear from many of the studies (given the control tasks and comparisons, see further on in this section) whether some areas are preferentially active for the retrieval of autobiographical events as opposed to memory retrieval *per se*. Where this was specifically investigated (Maguire & Mummery 1999; Maguire *et al*. 2000, 2001*a*,*b*) it seems that the medial frontal cortex and left hippocampus are particularly responsive to retrieval of autobiographical event memories. Given the acknowledged role of the hippocampus in episodic memory (Scoville & Milner 1957; O'Keefe & Nadel 1978; Tulving 1983), it is perhaps surprising that some of the studies do not report hippocampal activations (Conway *et al*. 1999; Andreasen *et al*. 1995, 1999). Dorsolateral prefrontal cortex (DLPFC) is another area that is present in the results of some studies but not in others. It is likely that differences in methodological factors between studies contribute to the disparate findings. Several of these factors will now be considered; the intention is not to criticize what are difficult studies to design and execute, but rather to understand better the data collected so far.

In the first instance, it is clear that interaction with subjects prior to scanning differs widely across studies. In some studies, there was very little interaction, or subjects were given general instructions about the task just prior to scanning using variations on the Crovitz & Schiffman (1974) technique (e.g. Conway *et al*. 1999; Ryan *et al*. 2001), or the memories being tested were recently encoded (Burgess *et al*. 2001). In other studies, information was elicited from subjects weeks prior to the experiment, where subjects were naive to the specific purpose of the interviewing (e.g. Fink *et al*. 1996; Maguire & Mummery 1999; Maguire *et al*. 2000, 2001*a*,*b*). The issue of how to elicit stimuli for presentation during scanning is closely related to that of testing retrograde memories in general (see § 1 above). Does questioning subjects, even briefly, before scanning, change the essential nature of the memory one wishes to examine? Is the memory now recent as opposed to what might have been a remote memory? Has the event been re-encoded and is that what one is scanning and not recall of the original event? But if one scans subjects 'cold', so to speak, with no prior interaction, then there is less control over the time-scale of memories recalled and one is less able to control for the Kapur (1999) factors. One could, as did Ryan *et al*. (2001), glean the necessary information from spouses and/or family members, although there is no guarantee that the subject will recall the specific events or in a similar manner to the spouse.

Further cross-study differences emerge during scanning itself. Although the goal in all studies was for subjects to think about the original autobiographical events, the manner in which they are cued, the time they have to think about each personal event, the degree of retrieval effort and the requirement for a response, differed across studies. In some studies (e.g. Conway *et al*. 1999) there may not have been enough time for each event to be fully retrieved and hence the lack of hippocampal activation (although see below). Perhaps the DLPFC was not apparent in some studies (e.g. Maguire & Mummery 1999) because the amount of retrieval effort *per se* was minimized, or monitoring and response selection requirements (Fletcher & Henson 2001) were similar across all tasks and so DLPFC activations were subtracted out.

One of the principal methodological differences across studies is in the conditions used for comparison with autobiographical event memory. In terms of baseline or control conditions, various tasks have been employed which include looking at a box of pixels (Conway *et al*. 1999), or making syllable judgements (the Maguire studies). In many experiments 'rest', either interpreted as relaxation or freely associating thoughts (Andreasen *et al*. 1995, 1999), was the main baseline task. While accepting

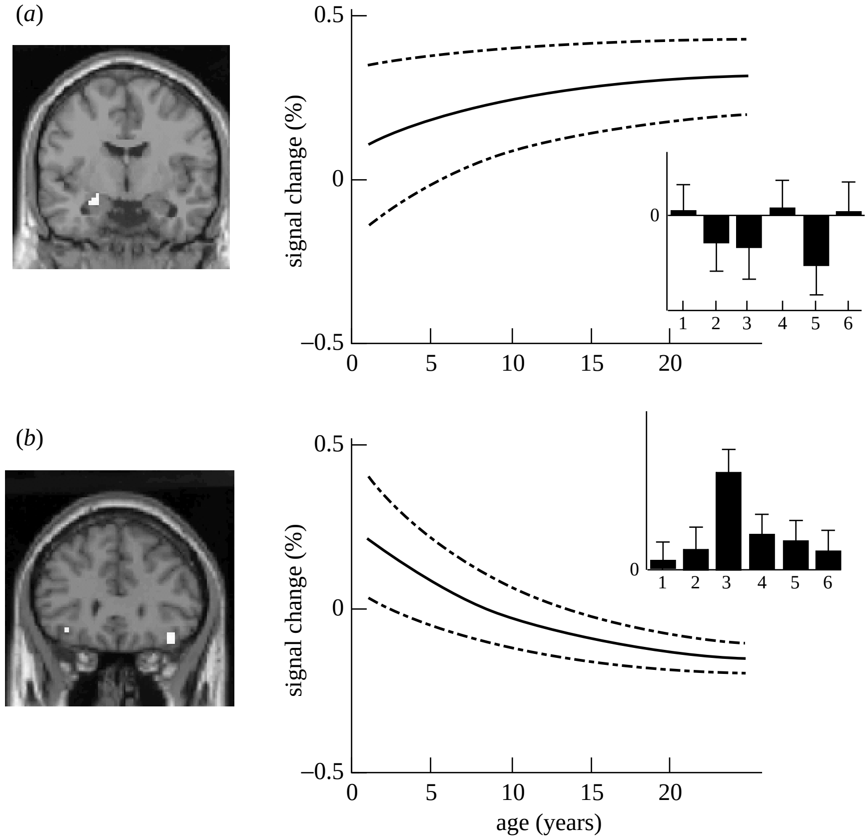

Figure 1. Data from Maguire *et al*. (2001*a*) showing the parametric modulation of brain activity by memory age (see § 2). The plots show the mean fitted response (full lines) across subjects ± one standard error (dashed lines). The bars inset into each panel depict the parameter estimate for the age effect change for each subject ± one standard error for that subject. N.B. a positive parameter estimate = a decrease with age effect. (*a*) No consistent effect in the hippocampus although there was activation associated with memory type (autobiographical event memory in particular). (*b*) Significant parametric decrease in right ventrolateral prefrontal cortex the more remote the memories; the effect is apparent in all subjects.

that the design of control tasks is a difficult issue in scanning experiments such as these where real-world memories are involved, rest is not an optimal choice for a control or comparison task. Its unconstrained nature is particularly unsuitable given the richly stimulating nature of the autobiographical memory task and key activations might be subtracted out if there is overspill from the active memory task (see McGuire *et al*. 1996). In some studies, memory tasks were included to compare with autobiographical event memory, such as the retrieval of paired associates learned just prior to scanning (Conway *et al*. 1999) or exposure to biographical information about an unfamiliar person, initially heard just prior to scanning (Fink *et al*. 1996). While interesting to compare with a low level non-memory task, one should be cautious in making direct comparisons of either of these tasks with autobiographical event memory as they differ in recency (autobiographical events maybe decades old compared with the newly learned material) and in the degree of personal relevance of the material.

The sentence completion task used by Ryan *et al*. (2001) raises another point in relation to these experiments—the need to compare encoding with retrieval of autobiographical event memory. Although not intended as an encoding task, they found that subjects did recall the information post-scanning, and activation of the hippocampus in relation to this presumed learning was less than that during the recall of autobiographical events. This may speak to the issue alluded to above of whether we are merely imaging re-encoding of information in these experiments. The Ryan *et al*. (2001) data suggest not, although clearly further studies are required, and a task involving encoding of autobiographical information would be particularly useful.

Other than in the Maguire experiments, none of the studies included memory comparison tasks to control for orientating towards the past and recalling specific events or personal information that evokes the same sorts of imagery, people, places, etc. as autobiographical event memory. If such memory control tasks are not included, then specific claims cannot be made about the neural basis of autobiographical memory retrieval—rather the results could be true for remembering any type of material. Hence the inclusion in our (Maguire & Mummery, 1999; Maguire *et al*. 2001, 2001*a*,*b*) studies of public events (also specific events but not personally relevant) and autobiographical facts (personal but not event-specific).

As is clear from table 1 and the above discussion, the tasks we have used in our various studies have given consistent results across scanning modalities and even within single subjects. The approach we have taken (summarized in table 1), however, has a number of potential disadvantages. First, it is time consuming in terms of subject-specific stimulus preparation. Second, in its current form there is no encoding condition, so potentially the activations observed may be due to re-encoding and not retrieval of memories. However, this re-encoding is true for all of the memory types and does not explain differential activations found for autobiographical event memory retrieval. Third, it may be that subjects remember the prior interview during scanning and not the actual events themselves. However, all subjects reported that the hearing of a statement evoked a sense of the original event in the case of both autobiographical event and public event memories. When directly probed about the prior interview, none of the subjects reported recalling this during scanning. Even if the interview had been recalled during scanning, again it is unlikely that this would have caused the differential effects across the memory types that were in fact found. Furthermore, in their study Ryan *et al*. (2001) scanned subjects where the memory information was elicited from spouses and not the subjects themselves and the same results pertained as when the information was gathered from subjects directly. Also, when we used our paradigm with a memory-impaired patient who was able to perform the tasks during scanning, similar activation patterns to control subjects were found, although the patient was amnesic for the prior interview (Maguire *et al*. 2001*b*).

There are several advantages to the approach we have used: as well as having a range of memory types controlling for personal and context factors, we know the precise timings of events, we have information about salience and emotional aspects associated with the events, the task is easy to operationalize in the scanner, there is a record of subjects' responses (and reaction times) and patients as well as healthy controls are able to perform the task in the scanning environment. While the tasks could be described as involving recognition memory, the memories were originally elicited via recall, and subjects report the statements to elicit the memory of the original events. In cases of real-world complex stimuli such as these, the tasks probably reflect a mixture of recognition and recall, so we refer to the task in generic terms as tapping memory 'retrieval'.

Using this approach we recently investigated the time-scale of neocortical and hippocampal involvement in memory, as well as the type of memories of particular interest to the hippocampus (Maguire *et al*. 2001*a*). Two prominent positions present divergent views on these issues. The oft-termed 'traditional' view (e.g. Squire 1992) is of a hippocampus which has a brief involvement in memory formation and consolidation before neocortical areas assume responsibility for storage and retrieval independent of the hippocampus. The principles of the traditional position are disputed, however, and an alternative view (Nadel & Moscovitch 1997; Nadel *et al*. 2000) holds that the hippocampus is involved during retrieval of both recent and remote memories. In functional neuroimaging terms, the traditional view would predict decreasing hippocampal activity and increasing possibly posterior neocortical activity the more remote the memories. The contrasting view would predict similar levels of hippocampal activation for both recent and remote memories. Rather than make arbitrary categorical decisions about what was recent or remote, we modelled the parametric modulation of responses to autobiographical events and public events by the age of the memories, ranging from the very recent to those dating back to 20 years or more ago. Each event—be it autobiographical or public—constituted an event in an event-related fMRI analysis.

While our design was sensitive enough to detect modulation of left hippocampal activity in relation to memory type (autobiographical events in particular), we failed to find any evidence for sensitivity of this region to the age of memories (figure 1*a*). Half the subjects show no effect for age of memory and half actually show a trend for the opposite effect to the classic theory—actually more hippocampal activation the more remote the memory. Similarly, no consistent pattern was found for public event memories. Categorical comparison of recent (last two years) or remote memory versus the control task both showed activation of the left hippocampus for autobiographical events (as did Ryan *et al*. (2001) bilaterally in their block design study). This result is contrary to the classic view of a time-limited role for the hippocampus but concordant with the view of hippocampal involvement in autobiographical memory retrieval throughout the lifetime, whether memories be very recent or very remote.

We did observe a brain region whose activity was responsive to the age of memories. A right ventrolateral prefrontal region (BA 47) showed increased activation during retrieval of recent autobiographical events and subsequent parametric decrease in activity the more remote the memories became over 20 years or more. From figure 1*b* one can see this effect was apparent for all subjects. Activation of this region has been reported in numerous previous neuroimaging studies of episodic memory retrieval (e.g. Lepage *et al*. 2000) and has been associated with specification of retrieval cues (Fletcher *et al*. 1998). We believe the present findings in ventrolateral prefrontal cortex reflect the degree of integration of the memory trace with relevant contextual information, such as temporal information—more active integration occurring the more recently acquired the memory.

Thus, in our event-related study, we see increased activity in the left hippocampus associated with the retrieval of autobiographical events but not public events. In an fMRI block design analysis, when any of the memory types described in table 1 (autobiographical events, autobiographical facts, public events, general knowledge) was compared with the syllable judgement control task, we observed activation of the left hippocampus as well as a network of other mostly medial and left-lateralized areas (see Maguire *et al*. 2000, and table 1). However, when autobiographical events were compared with any of the other memory types, there was increased activation of the left hippocampus and medial frontal cortex specifically for autobiographical events.

3. FUNCTIONAL NEUROIMAGING OF A PATIENT

Having outlined in control subjects the basic memory retrieval network and differential responses of certain regions therein, one might consider using functional neuroimaging to examine patients with lesions to specific parts of this network. We recently had the opportunity to study such a patient using fMRI: Jon, a 22 year old man with selective bilateral hippocampal pathology induced by hypoxic–ischaemic episodes of perinatal origin (Vargha-Khadem *et al.* 1997; Gadian *et al.* 2000). When tested, Jon had a striking episodic memory impairment in the context of excellent general knowledge. A great many of the personal events from his life Jon could not remember but he recollected just enough episodic events in detail for viable functional scanning (Maguire *et al.* 2001*b*).

Interestingly, Jon spontaneously made an extra distinction between events that control subjects did not make, namely that some of the autobiographical and public events he clearly remembered, while others he found he knew about but did not truly remember the events occurring. To the interviewer, there was no difference in the amount or sorts of information he recalled between the two memory types. 'Remember' judgements are generally associated with the evocation of a specific, previously experienced episode, while 'knowing' is typically thought to entail a sense of familiarity, but no information about the source of familiarity (Tulving 1985; Gardiner & Java 1991; Knowlton & Squire 1995). In the case of Jon, he makes a kind of remember–know distinction, but he remembers the contexts both for the events he remembers and those that he knows, although he clearly has autonoetic conscious awareness only for the former.

Jon's behavioural performance during scanning was comparable with control subjects. Comparison of any of the individual memory tasks with the control task in Jon showed activation of the same network in each case, namely, a similar set of brain regions as in the control subjects (including the hippocampus) but active bilaterally in Jon (see table 1).

A key comparison between autobiographical events that Jon remembered, compared with autobiographical events he merely knew about, showed that the hippocampus bilaterally was more active for personal events that he remembered experiencing. The control subjects also activated the medial frontal region for autobiographical events and indeed so did Jon (see figure 2). Thus, when Jon successfully remembered something, the same set of regions active in control subjects during memory retrieval were active in Jon, albeit bilaterally. The bilateral picture might be a reflection of the early nature of Jon's damage. Of particular interest here, the hippocampi of Jon, despite being damaged, were nevertheless functional. This finding has implications for the study of patients in the clinical context, demonstrating the possibility and importance of assessing the functionality of damaged brain tissue and its contribution to partially or completely retained functions—and functional neuroimaging is well disposed to do this. Findings from Jon enable us to refine further the contribution of the hippocampus in memory retrieval beyond that discernible from control subjects. In controls, autobiographical events were always accompanied by conscious recollection of the episodes. Jon's data show that it is not enough for a memory to be an autobiographical event about which one can recall rich details—there must also be recollection of the experience in order to be of particular interest to the hippocampus. A related issue for future research concerns whether a similar functional anatomical distinction could be observed for remember–know memories in control subjects, where amount and type of details about events are matched, as, for example, in the case of real versus false memories (Dodson *et al.* 2000).

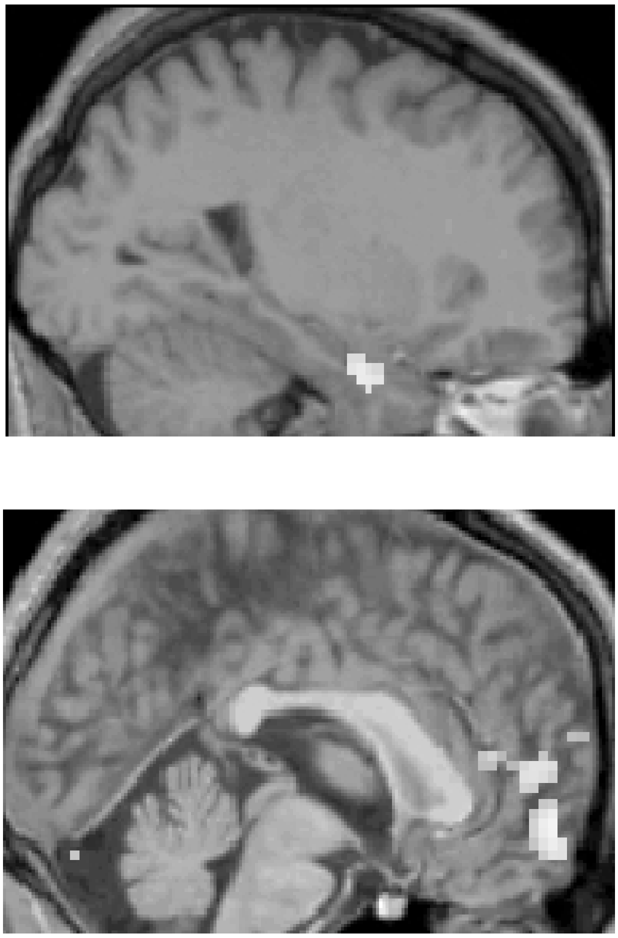

Figure 2. Data from Maguire *et al.* (2001*b*) showing increased activation of patient Jon's hippocampus and medial frontal cortex during retrieval of autobiographical events he remembers (lower scan). Activations are superimposed onto a structural MRI scan of his brain.

4. FUNCTIONAL INTEGRATION

So far, I have outlined the anatomy of memory retrieval and the response patterns of specific regions in control subjects and also in a patient with selective bilateral hippocampal damage. However, memory is not the property of brain regions operating in isolation but rather of brain networks; thus, functional integration within this network must also be considered. In this regard, structural equation modelling has now been applied to functional neuroimaging data in several studies to estimate effective connectivity (e.g. Büchel *et al.* 1999; Horwitz *et al.* 1999), i.e. the influence one neural system exerts on another (Friston *et al.* 1993). This approach looks at the coupling between the time courses of activity in the relevant brain regions, estimating their connectivity based on putative connections between them.

I will briefly describe analyses examining regional interactions between the main limbic and cortical left-sided

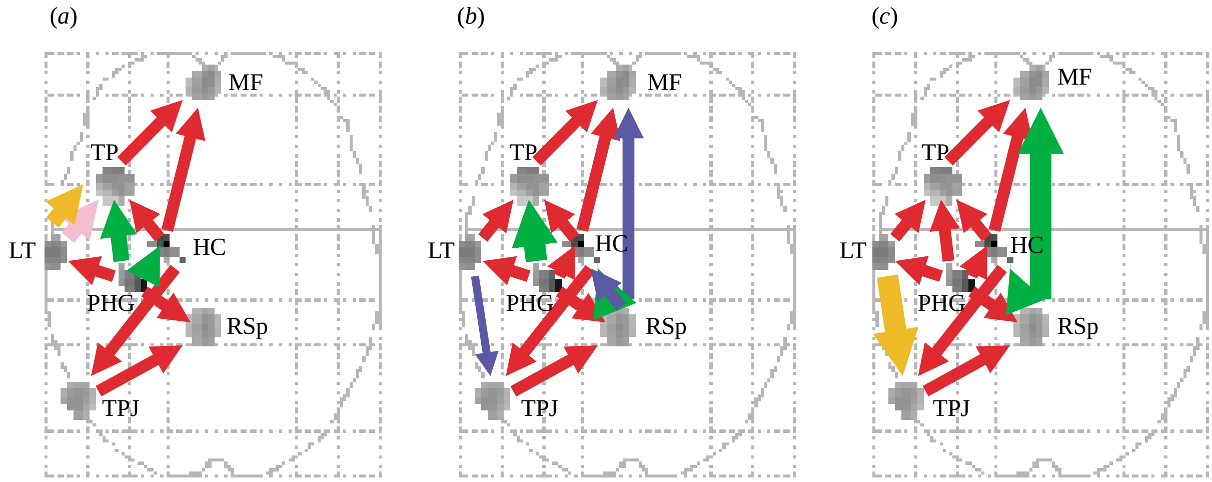

Figure 3. Data from Maguire *et al*. (2001*b*) showing the results of estimation of effective connectivity (§ 4). Transverse views of a glass brain are shown which permits viewing of all significant activations simultaneously. The memory retrieval model comprises the seven brain regions of interest and the connections between them: MF, medial frontal cortex; TP, temporal pole; HC, hippocampus; LT, left anterior middle (lateral) temporal gyrus; PHG, parahippocampal gyrus; RSp, retrosplenial cortex; TPJ, temporo-parietal junction. (*a*) Significant changes in connectivity between regions are shown in green for increased connectivity during retrieval of autobiographical events in particular, in pink for retrieval of public events and in gold for retrieval of general facts. (*b*) The memory retrieval model for the estimation of effective connectivity in patient Jon, with the extra connections required for his model shown in blue. Significant changes in connectivity between regions are shown in green for increased connectivity in particular during retrieval of autobiographical events that Jon remembered. (*c*) Direct comparison of estimates of effective connectivity for control subjects and Jon. In green, the connections where connectivity was increased in Jon compared with the control subjects during retrieval of autobiographical events that were remembered. In gold, the connection where connectivity was increased in Jon compared with the control subjects during retrieval of general facts.

areas we observed to be involved in memory retrieval (Maguire *et al*. 2000, 2001*b*). Regions were: medial frontal cortex, temporal pole, hippocampus, anterior middle temporal gyrus, parahippocampal gyrus, retrosplenial cortex, temporo-parietal junction. Although activations in the patient Jon are more bilateral than in control subjects, analysis of effective connectivity was also performed for the left hemisphere in Jon to afford direct comparison with the control subjects. Firstly, in the control subjects, increased connectivity was found in two of the connections during retrieval of autobiographical event memory compared with the other memory tasks, between parahippocampal gyrus and the hippocampus, and between parahippocampal gyrus and temporal pole (figure 3*a*). In contrast, the connection that showed increased connectivity during the retrieval of public events and facts was between lateral temporal cortex and the temporal pole (figure 3*a*).

Extra connections were required in Jon to make the model stable (shown in blue in figure 3*b*), these being between retrosplenial–medial frontal cortices, retrosplenial cortex–hippocampus, and lateral temporal cortex–temporo-parietal junction. For Jon, the only changes in the estimation of effective connectivity were in two connections during retrieval of autobiographical event memories that he remembered compared with the other memory tasks, namely increases in connectivity between retrosplenial cortex and hippocampus, and parahippocampal gyrus and temporal pole.

Finally, the estimates of effective connectivity for Jon and the control subjects were directly compared, particularly for the three extra connections that Jon required (figure 3*c*). In the case of the retrosplenial–hippocampal connection and the retrosplenial–medial frontal cortex connection, effective connectivity was significantly increased for Jon compared with the controls during retrieval of remembered autobiographical events in particular. The lateral temporal–temporo-parietal junction connection was significantly increased in Jon compared with the controls during retrieval of general facts.

Although Jon activates the same network of brain regions as the controls (albeit bilaterally), and with the same pattern of responses in the hippocampus, the communication between regions differs from controls with regard to hippocampal–cortical connectivity. The interplay between regions in response to autobiographical events in particular requires greater interaction in Jon between the hippocampus and retrosplenial cortex, and also increased extra-hippocampal interaction specifically between retrosplenial and medial frontal cortex. That these are possibly not optimal pathways (unlike the parahippocampal–hippocampal pathway as seen in control subjects), and might be capacity-limited, may explain Jon's ability to remember only a limited number of autobiographical events in the context of a general deficit for such memories.

Obviously, there are caveats associated with the estimation of effective connectivity. For example, the models are simple and it is difficult to infer whether changes reflect excitatory or inhibitory influences—and detailed knowledge of human neuroanatomical connectivity is still lacking. Nevertheless, modelling functional integration using neuroimaging may be particularly pertinent in the context of memory breakdown where some clues about impairment may be detectable only at this level.

5. LATERALITY

As mentioned earlier, the balance of findings from functional neuroimaging studies of autobiographical memory show left-sided activations, including left hippocampus. It may be that this is due to the nature of stimulus presentation, e.g. hearing (verbal) statements, although Markowitsch *et al*. (1997) used a visual stimulus prior to scanning. Recently, we examined personally experienced events but with a less obviously verbal task (Burgess *et al*. 2001). As described in table 1, in an event-related fMRI study, before scanning, subjects navigated around a virtual reality town and met people who gave them salient objects in different places, these being the autobiographical events, so to speak. During scanning, the subjects again navigated around the town but this time on their way answered forced-choice questions: a content question, namely 'Which object did you get?', then two context questions, namely 'Which object did you get from this person?', and 'Which object did you get in this place?'. Memory for aspects of the context of events resulted in activation of the left hippocampus.

In a parallel behavioural patient study involving left and right temporal lobectomy patients (Spiers *et al*. 2001), we examined the patients and matched controls using the same virtual reality paradigm. The results confirmed the lateralization. We found that right temporal lobectomy patients were more impaired on several navigation measures, while the left temporal lobectomy patients were more impaired on retrieving aspects of the autobiographical events, such as who they met, when they met them and so on. Of course, these patients had more than just hippocampal tissue removed; nevertheless, the pattern of results is in line with the neuroimaging data outlined. It may be that, in humans, the hippocampal role in spatial memory and navigation (O'Keefe & Nadel 1978) has become more right-hippocampal, while the left human hippocampus has evolved a more general role in supporting autobiographical event memory (Burgess *et al*. 2001; Maguire 2001).

6. CONCLUSIONS

I have reviewed here the known functional neuroimaging experiments that have examined episodic memory specifically in the form of autobiographical events. As mentioned at the outset, the data perhaps raise more questions than they answer but evidence does seems to suggest a role for the hippocampus in retrieving autobiographical event memories throughout the lifetime, and a preferential interest of the (possibly left) hippocampus in these memories, in particular. Results from neuroimaging of a patient with selective bilateral hippocampal pathology underline the need to assess the functionality of remnant tissue as a contributor to the pattern of deficits and preservation seen in such cases. Neuroimaging is well-placed to do this, and in addition is able to examine inter-regional communication where valuable information might also lie. Finally, Jon's data underlines the hippocampal interest in the conscious recollection of events. Whether this reflects the essence of a specifically human memory system remains an open question.

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