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Abstract

Remembering the past and envisioning the future are at the core of one's sense of identity. Neuroimaging studies investigating the neural substrates underlying past and future episodic events have been growing in number. However, the experimental paradigms used to select and elicit episodic events vary greatly, leading to disparate results, especially with respect to the laterality and antero-posterior localization of hippocampal and adjacent medial temporal activations (i.e., parahippocampal, entorhinal and perirhinal cortices, amygdala). Although a central concern in today's literature, the issue of hippocampal and medial temporal lobe laterality and antero-posterior segregation in past and future episodic events has not yet been addressed extensively.

Using the Activation Likelihood Estimation (ALE) procedure (Turkeltaub et al., 2002), we performed a meta-analysis of hippocampal and adjacent medial temporal coordinates extracted from neuroimaging studies examining past remembering and future envisioning. We questioned whether methodological choices could influence the laterality of activations, namely (1) the type of cue used (generic versus specific), (2) the type of task performed (recognition versus recall/imagine), (3) the nature of the information retrieved (episodic versus "strictly" episodic events) and (4) the age of participants. We consider "strictly" episodic events as events which are not only spatio-temporally unique and personal like episodic events, but are also associated with contextual and phenomenological details. These four factors were compared two-by-two, generating eight whole-brain statistical maps. Results indicate that (1) specific cues tend to activate more the right anterior hippocampus compared to the use of generic cues, (2) recall/imagine tasks tend to recruit more the left posterior parahippocampal gyrus compared to recognition tasks, (3) (re/pre)experiencing strictly episodic events tends to activate more the bilateral posterior hippocampus compared to episodic events and (4) older subjects tend to activate more the right anterior hippocampus compared to younger subjects. Importantly, our results stress that strictly episodic events triggered by specific cues elicits greater left posterior hippocampal activation than episodic events elicited by specific cues. These findings suggest that such basic methodological choices have an impact on the conclusions reached regarding past and future (re/pre)experiencing and their neural substrates.

Key words: autobiographical memory, episodic events, hippocampus, medial temporal lobe, neuroimaging.

Introduction

In its current definition, episodic memory is closely related to episodic autobiographical memory (Wheeler et al., 1997, 2004; Wheeler 2000; Tulving, 2002, 2005). Autobiographical memory (AM) is composed of different types of self-representations, from general knowledge about oneself (semantic AM, also referred to as “personal semantics”) to very specific personal events (episodic AM) (Tulving, 1985; Tulving et al., 1988; Conway, 2001). Episodic AM is characterized by a particular self-reflective mental state, termed autonoetic consciousness, which implies that the person recollects or imagines his/her personal events with a sense of (re/pre)experiencing, by mentally “travelling in time” whether in the past or in the future (Wheeler et al., 1997; Tulving, 2001). A further distinction can be made between episodic and strictly episodic AMs (Viard et al., 2007, 2010; for reviews, Moscovitch et al., 2005; Piolino et al., 2009). Strictly episodic events are not only spatio-temporally unique and personal like episodic events, but are also accompanied by subjective (re/pre)experiencing (autonoetic consciousness) associated with recall/imagination of phenomenological details, i.e., sensory, perceptual, cognitive, affective internal contextual details (Moscovitch, 1995, 2000; Tulving & Markowitsch, 1998; Brewer, 1996; Conway and Pleydell-Pearce, 2000; Conway, 2001; Conway et al., 2004; Tulving, 2001).

Autobiographical investigations generally concern the retrieval of the personal past. They can be subdivided between those dealing with the more general aspects of AM (semantic AM), in which participants retrieve the general facts about a personal event without re-experiencing it (e.g., recall familiar self-relevant faces or places), and those which focus on the specific aspects of AM (episodic AM) in which participants have to consciously recollect a personal past event, in its original encoding context (e.g., recall a specific event, in a unique spatio-temporal context). Concerning episodic future thinking (Atance and O’Neil, 2001), studies have required participants to either imagine future specific events which are not necessarily going to happen (Addis et al., 2007; Hassabis et al., 2007; D'Argembeau et al., 2008) or future specific events which are actually planned or are reasonably going to happen in the future (Viard et al., 2011a; Weiler et al., 2010a; Peters and Büchel, 2010; Botzung et al., 2008a; Szpunar et al., 2007; Okuda et al., 2003).

Findings from neuroimaging studies in healthy adults have brought new insights on the cerebral organization of episodic events, completing findings from neuropsychology (for autobiographical memory: Rosenbaum et al., 2001, 2009; Andelman et al., 2010; Spiers et al., 2001; Piolino et al., 2003; Eustache et al., 2004; St-Laurent et al., 2009; Noulhiane et al., 2007; for episodic future thinking: Tulving, 1985; Hassabis et al., 2007; Klein et al., 2002). Previous reviews have shown that episodic AM retrieval involves a circumscribed cerebral network comprising both anterior and posterior regions, including prefrontal and medial temporal cortices, medial parietal (posterior cingulate and retrosplenial cortices), posterior parietal (precuneus and temporo-parietal junction), occipital regions and the cerebellum (Maguire, 2001; Conway et al., 2002; Moscovitch et al., 2005, 2006; Svoboda et al., 2006; Cabeza and St Jacques, 2007). This neural pattern has striking similarities with the one recruited during episodic future thinking (for reviews, Buckner and Carroll, 2007; Schacter and Addis, 2007; Hassabis and Maguire, 2007, 2009).

Neuroimaging studies of past remembering and future thinking have shown many consistencies, but some aspects remain unclear or obscure, especially concerning hippocampal and adjacent medial temporal lobe (MTL) laterality and antero-posterior activity. Within the MTL, the hippocampus is particularly important in episodic memory. Concerning its laterality, results are discrepant: several episodic AM studies have shown preferentially left-sided hippocampal activations (Maguire and Mummery, 1999; Maguire et al., 2000; Maguire et al., 2001; Markowitsch et al., 2003; Piefke et al., 2003; Daselaar et al., 2008; Oddo et al., 2010; Svoboda and Levine, 2009; St Jacques et al., 2011a), while others have detected predominantly right hippocampal activations (Fink et al., 1996; Okuda et al., 2003; Steinvorth et al., 2006). Furthermore, an increasing number of studies have shown bilateral hippocampal recruitment during episodic AM retrieval (Ryan et al., 2001; Maguire and Frith, 2003a, b; Piolino et al., 2004, 2008; Gilboa et al., 2004; Addis et al., 2004a; Cabeza et al., 2004; Mayes et al., 2004; Greenberg et al., 2005; Rekkas and Constable, 2005; Viard et al., 2007, 2010; Nadel et al., 2007; Mendelsohn et al., 2009; Trinkler et al., 2009; Rabin et al., 2010; Hoscheidt et al., 2010). Concerning episodic future thinking, results are also inconsistent since some studies detect left hippocampal (Addis et al., 2007, 2008; Spreng and Grady, 2010), right hippocampal (Okuda et al., 2003; Weiler et al., 2010a; Addis et al., 2011a) or bilateral activation (Abraham et al., 2008; Hassabis et al., 2007; Weiler et al., 2010b; Addis et al., 2009; Viard et al., 2011a).

Hypotheses have been formulated concerning the differential contribution of each hippocampus in episodic AM retrieval. It has been suggested that the left hippocampus is more involved in context-dependent episodic memory and is triggered by retrieval details (Addis et al., 2004a) or vividness of remote AMs (Gilboa et al., 2004), whereas the right hippocampus is more linked to the emotional nature of AMs (Fink et al., 1996) or more engaged by spatial memory (for reviews, Burgess et al., 2002; Svoboda et al., 2006), sense of remembering and richness of mental visual imagery (Viard et al., 2007, 2010). Personal importance of AMs was shown to correlate with activation in the hippocampus bilaterally (Addis et al., 2004a). The age of the participants can also affect hippocampal laterality as several studies have shown greater right hippocampal activation in older compared to younger adults (Maguire and Frith, 2003b; St Jacques et al., in press). However, inconsistencies remain, for example, in several context-dependent episodic memory tasks which do not detect left-hippocampal activation, but right activation instead (Okuda et al., 2003; Steinvorth et al., 2006) or in tasks with a strong spatial component which do not recruit the right hippocampus

(Niki and Luo, 2002). A further point concerns studies reporting no hippocampal activations during personal episodic AM retrieval (see below; Andreasen et al., 1995, 1999; Conway et al., 1999; Markowitsch et al., 2000; Nyberg et al., 2002; Tsukiura et al., 2002; Graham et al., 2003; Niki and Luo, 2002; Levine et al., 2004; Gardini et al., 2006; Denkova et al., 2006a; D'Argembeau et al., 2010).

Furthermore, the antero-posterior hippocampal differentiation has been shown to depend on a variety of different processes. The anterior hippocampus has been associated with processing environmental context (Bannerman et al., 2004; Kjelstrup et al., 2008), stimulus novelty (Strange et al., 1999; Daselaar et al., 2006; Dudukovic and Wagner, 2007; Doeller et al., 2008; Poppenk et al., 2010), arousal, emotion, reward and goal proximity (Moser and Moser, 1998; Fanselow and Dong, 2010; Royer et al., 2010; Viard et al., 2011b). The posterior hippocampus is thought to support spatial navigation (O'Keefe and Nadel, 1978; Burgess et al., 2002; Maguire et al., 1998; Ekstrom et al., 2003; Hartley et al., 2003; Moser and Moser, 1998; Doeller et al., 2008; Moser et al., 2008). Various claims have been advanced regarding the locus of activation along the antero-posterior axis of the hippocampus during encoding versus retrieval. Its anterior portion would support episodic encoding (Lepage et al., 1998; Schacter and Wagner, 1999; Spaniol et al., 2009), while its posterior portion, and adjacent parahippocampal structures, would support episodic retrieval (Spaniol et al., 2009; Lepage et al., 1998; Greicius et al., 2003; Henson et al., 2005; Ludowig et al., 2008; Schacter and Wagner, 1999).

A role of the parahippocampal gyrus in episodic AM (Tsukiura et al., 2002; Okuda et al., 2003; Addis et al., 2004a; Levine et al., 2004; Greenberg et al., 2005; Steinvorth et al., 2006; Gardini et al., 2006; Denkova et al., 2006a, b; Burianova and Grady, 2007) and future thinking (Okuda et al., 2003; Szpunar et al., 2007, 2009; Addis et al., 2007, 2008, 2009, 2011a; Abraham et al., 2008; Botzung et al., 2008a; Spreng and Grady, 2010; Viard et al., 2011a) is well established, as well as its interaction with the hippocampus during autobiographical recognition (Maguire et al., 2000) or recall (Greenberg et al., 2005; Viard et al., 2010). Its role according to its laterality is not yet clear, although some studies suggest that the right parahippocampal gyrus is implicated in the retrieval of topographical or spatial episodic AMs and could be related to the recruitment of posterior visual areas (Tsukiura et al., 2002; Viard et al., 2010). Its specialization along an antero-posterior axis seems more evident, the anterior part involved in item information and the posterior part processing context information (Diana et al., 2007; Davachi, 2006; Slotnick, 2010).

Another region within the MTL is the amygdala which has a well documented role in processing of emotional AMs (Greenberg et al., 2005; Hoscheidt et al., 2010; Nadel et al., 2007; Daselaar et al., 2008; Markowitsch et al., 2000, 2003; Fink et al., 1996; Viard et al., 2010) and future events (Sharot et al., 2007; Addis et al., 2009). Episodic AMs tend to be highly emotional due to their personal involvement which, in most cases, facilitates their accessibility at retrieval (Talarico and Rubin, 2003). Emotional intensity affects the perceptual and phenomenological properties of AMs, such as its vividness, level of detail and the degree to which the memory is relived (Talarico et al., 2004; for reviews, see Phelps, 2004; LaBar and Cabeza, 2006). Functional interactions have been detected between the amygdala and the hippocampus during encoding (Hamann et al., 1999; Dolcos et al., 2004), as well as during retrieval (Dolcos et al., 2005; Viard et al., 2010), especially if recall is accompanied by a sense of recollection (Talarico et al., 2004; Ochsner, 2000; Sharot et al., 2004). Concerning amygdalar laterality, results are inconsistent, some showing preferentially left (Dolan, 2000) or right activation (Fink et al., 1996) during AM retrieval. Inconsistencies regarding the influence of emotional valence on amygdalar laterality have also emerged (Markowitsch et al., 2003; Piefke et al., 2003; Viard et al., 2007).

The contradictory findings concerning MTL laterality and antero-posterior activity could arise, at least in part, from the use of various experimental procedures which do not tap the same aspects of (re/pre)experiencing and could, hence, limit the extent of previous findings. Methodological choices vary across studies and encompass differences in time frames, trial designs (segregation of search and elaboration phases), method to elicit memory (generic cue versus personal cues from a pre-scan interview; Addis et al., 2007, 2009; Rabin et al., 2010), re-encoding, number of lifetime periods (or memory remoteness), number of memories recollected, true/false recognition versus recall tasks (St Jacques et al., in press; Oddo et al., 2010; Piefke et al., 2003), age of subjects (Maguire and Frith, 2003b; Viard et al., 2007). A previous review, centered on the prefrontal cortex, suggested that laterality effects on neural activation patterns associated to encoding and retrieval of laboratory based episodic memory depend on stimulus characteristics (type of material, modality of presentation), complexity of stimulus material, information to be retrieved and task demands, rather than on functional hemispheric specializations (Lee et al., 2000). Up to date, no meta-analysis has yet attempted to tackle this issue within the MTL to determine the impact of methodological choices on hippocampal and adjacent MTL activations for past and future episodic events. Here, we chose to focus on four factors which can be identified in all studies: the type of cue used (generic versus specific), type of task performed (recognition versus recall/imagine), nature of the information retrieved (episodic versus strictly episodic) and age of participants (younger versus older).

Indeed, studies vary immensely in terms of the *type of cue* (generic or specific) used to elicit (re/pre)experiencing. The cue-word technique is often used in which participants are required to recall/imagine a personal event related to an impersonal cue word (e.g., flower), phrase or picture (Table 1). Cues are identical for all participants and might not elicit the most personally significant events which may influence hippocampal activation. Specific (personal) cues provide more direct access to episodic information, while generic (impersonal) cues do not and need more elaborate cue-specification and further retrieval attempts. Studies also vary with respect to the *type of task* (recognition or recall/imagine) performed in the scanner. In recognition verification tasks, participants must indicate if they recognize a cued event, responding by yes or no, without full (re/pre)experiencing. This procedure seems unlikely to engage participants to recollect/imagine richly detailed events, compared to recall/imagine tasks (Table 1). Recognition tasks can be executed by accessing the general levels of autobiographical knowledge without retrieving the episodic details. The *nature of the information* retrieved (semantic, episodic or strictly episodic) may also influence (re/pre)experiencing. In some studies, participants are asked to retrieve information derived from their “personal semantics”, while in others, they must recall a spatio-temporally unique and specific event. Stimuli belonging to the subjects’ personal semantics may not incite participants to recall specific context-rich personal events (i.e., names of acquaintances, familiar faces, repeated events, topographical recall of personal routes or places visited). On the contrary, they may retrieve the general facts about an event in the absence of recollection of episodic details. In a growing number of studies, participants are incited to retrieve “strictly episodic” events by recollecting events unique in time and place, accompanied by subjective (re/pre)experiencing and phenomenological qualities, such as emotion, details, visual imagery, vividness, personal significance and autonoetic consciousness (Table 1). Similarly, for future thinking, imagining a fictitious future event which is not necessarily going to happen might not require the same personal and emotional involvement, and phenomenological experiencing, than future events which are planned and will happen in the participants’ lives. Finally, the age of participants has been previously shown to affect hippocampal activation with older adults recruiting the right hippocampus, in addition to its left counterpart generally detected in young adults (Maguire and Frith, 2003b; St Jacques et al., in press; Ryan et al., 2001; Viard et al., 2007; Nadel et al., 2007; Gilboa et al., 2004). Maguire and Frith (2003b) suggested that a hemispheric asymmetry reduction in older adults could account for the bilateral involvement of the hippocampus, as proposed in prefrontal areas (HAROLD model, Cabeza 2002).

The variety of experimental designs used to study past and future episodic events and, consequently, the disparate results obtained, make it difficult to compare studies, particularly on the question of hippocampal and extra-hippocampal MTL laterality and antero-posterior activity. Growing evidence suggests that activity in this region may be modulated by factors such as the type of cue used (Addis et al., 2007, 2009; Oddo et al., 2008; Rabin et al., 2010; St Jacques et al., in press), the type of task (St Jacques et al., in press; Piolino et al., 2004; Piefke et al., 2003), the nature of the information required (Viard et al., 2007, 2011; Piolino et al., 2004, 2008) or the age of participants (Maguire et al., 2003a; St Jacques et al., in press; Ryan et al., 2001; Viard et al., 2007; Nadel et al., 2007; Gilboa et al., 2004). The present meta-analysis is an extensive investigation of hippocampal and adjacent MTL activations reported in neuroimaging studies of past remembering and future thinking. Hence, studies on episodic AM and future thinking were included. Its originality compared to other recent meta-analyses on episodic memory (Svoboda et al., 2006; Spreng et al., 2009; McDermott et al., 2009; Kim et al., in press; Gilboa, 2004) lies in the way it aims at identifying which methodological factors are more likely to influence hippocampal and extra-hippocampal MTL laterality and antero-posterior activity, using a meta-analysis centred on MTL coordinates.

Concerning hippocampal laterality, we predicted that specific cues (versus generic cues), recall/imagine tasks (versus recognition tasks) tasks and (re/pre)experiencing strictly episodic events (versus episodic events) would elicit greater bilateral hippocampal engagement, since these factors tend to favour (re/pre)experiencing accompanied by contextual and phenomenological details. For the same reasons, we predicted that specific cues, recall/imagine tasks and (re/pre)experiencing strictly episodic events would elicit greater anterior and posterior hippocampal recruitment. Concerning the age of participants, we predicted that older adults would elicit greater right hippocampal activation compared to younger subjects, based on current hypotheses of hemispheric reduction due to age (HAROLD, Cabeza, 2002). Based on models on the functional segregation of the parahippocampal gyrus (Graham et al., 2010), we predicted that specific cues, recall/imagine tasks and (re/pre)experiencing strictly episodic events would elicit greater posterior parahippocampal activation. Given the role of the amygdala in the retrieval of rich emotional AMs, we predicted that strictly episodic events would elicit greater amygdalar activation compared to episodic events.

Methods

Study selection

We conducted multiple literature searches using Pubmed to find all PET and fMRI studies published before October 2011 whose titles, keywords, or abstracts included the terms "autobiographical memory", "episodic memory", "everyday memory", "personal events", "future thinking", "episodic simulation", "episodic future thinking", "future envisioning", "imagining", "self-projection", "mental time travel", "fMRI" or "PET". We identified additional relevant studies by searching through reference lists of these articles not identified by the online database query. These search results were filtered to include only studies that (i) performed voxel-wise contrasts (i.e., whole-brain or within a region-of-interest) (ii) used univariate or multivariate analysis approaches with uniform significance and cluster size thresholds applied throughout the brain, and (iii) reported standard-space stereotactic coordinates within the hippocampus, parahippocampal gyrus or amygdala for at least one of the contrasts of interest (see below). We selected contrasts comparing the episodic event condition (past or future) to a control condition. Twenty-four studies did not fit inclusion criteria, either because they did not provide MTL stereotactic coordinates (7 studies), did not detect MTL activation (4 studies) or did not detect MTL activation for the contrast of interest (i.e., episodic event versus control conditions; 2 studies), used electroencephalography (3 studies) or reported contrasts inappropriate to the present analyses (8 studies), e.g. comparisons of two personal event conditions (remote vs. recent, past vs. future, positive vs. negative events) or comparisons including semantic conditions compared to control (all conditions including semantic condition vs. control). A reason which may explain the failure to detect MTL activation in 4 studies may be the use of PET (Andreasen et al., 1995, 1999; Conway et al., 1999; Nyberg et al., 2002), an imaging technique which is less sensitive than fMRI to detect subtle hippocampal activations. Another reason could be that methods to analyze data have improved in recent neuroimaging studies (e.g., regions-of-interest method), enabling finer and more accurate explorations of particular regions, such as the hippocampus. We excluded data from patients and children. Coordinates were classified as belonging to the MTL based on how the authors of the original articles classified the regions. With this approach, 269 MTL foci showing a greater activation for the episodic event condition (past or future) compared to baseline were obtained from 58 studies, involving 866 participants. Table 1 lists the number of participants, contrast and number of foci for each study included and Table 2 lists the studies which did not fit the inclusion criterion and reason for exclusion.

Contrast of interest

Separate ALE analyses (Turkeltaub et al., 2002) were conducted for each contrast listed below. The ALE approach conceptualizes activation foci not as single points but as probability distributions surrounding each reported peak coordinate. Across studies, these probability distributions are summed, and the result is a whole-brain map in which each voxel represents the activation likelihood within the literature. To test our predictions described in the introduction, we examined four types of contrasts.

Generic vs. specific cues

To elicit past or future (re/pre)experiencing, participants are prompted to evoke personal past or future events upon (auditory or visual) presentation of cues (e.g., words, sentences, pictures). Different types of cues have been used, either generic (i.e., non-personal) or specific (i.e., personal). Generic cues are single words, impersonal phrases or pictures, usually derived from the cue-word technique, similar to the Crovitz technique (Crovitz and Schiffman, 1974), or from prior pilot studies. Specific cues are unique to each participant and strongly associated with the to-be-retrieved memories, individually constructed, inciting subjects to remember specific personal past events or envision specific future events. Two ALE comparisons were computed, one contrasting studies using generic cues compared with those using specific cues and the reverse.

Recognition vs. recall/imagine tasks

After presentation of a cue, participants are asked to either recognize the information by providing a yes/no response or to recall (i.e., re-experience) or imagine (i.e., pre-experience) the personal past or future event, respectively. Studies were classified as using a recognition task if participants were required to produce a veridical judgement upon cue presentation. Studies were classified as using a cued recall or imagination task if participants were asked to retrieve or imagine an event with full (re/pre)experiencing upon cue presentation. Two ALE comparisons were computed, one contrasting studies using a recognition task compared with those using a recall/imagine task and the reverse.

Episodic vs. strictly episodic events

Studies were classified as either episodic if participants were asked to recall or imagine a personal event, unique in time and place or as strictly episodic if participants were required to recall or imagine a personal event, unique in time and place, with at least one of the following phenomenological qualities: emotion, details, visual imagery, vividness, personal significance and/or autonoetic consciousness. The strictly episodic categorization takes into account not only the specificity of the personal events that are retrieved (uniqueness, spatiotemporal location, details), but also the subjective experience of (re/pre)experiencing (Moscovitch, 1995, 2000; Tulving & Markowitsch, 1998). Two ALE comparisons were computed, one contrasting studies requiring retieval/imagination of episodic compared to strictly episodic events and the reverse.

Younger vs. older participants

Studies were classified according to the age of the participants (age range: young = 15-42.4; middle-aged and aged = 50.75-77). Data from middle-aged and aged participants were grouped to obtain better statistical power. Two ALE comparisons were computed, one contrasting young compared to old subjects and the reverse.

ALE meta-analysis

Fifty-eight studies comprising a total of 866 subjects reported coordinates falling within the MTL when comparing the episodic event condition to baseline. Eight ALE analyses were computed (Turkeltaub et al., 2002) for the contrasts of interest listed above. Because a large majority of the studies included in the meta-analysis (40/58 studies) reported their results in Talairach space, results were reported in this space, as other meta-analyses in the field (Spreng et al., 2009; Spaniol et al., 2009; Kim et al., in press). Activation coordinates from studies using the standard space of the Montreal Neurological Institute (MNI) were converted to Talairach space (Talairach and Tournoux, 1988) using the Brett transform (Brett et al., 2001). Each activation peak was classified as left or right, according to the x coordinate. For the distinction between the anterior and posterior portions of the hippocampus, the division of y=–22 in Talairach space was chosen based on previous studies; Preston et al., 2004; Addis et al., 2008; Henson, 2005).

Meta-analyses were carried out using the revised version of ALE (ALE 2.1; Eickhoff et al., 2009). The algorithm aims at identifying areas showing a statistical convergence of reported activations across different experiments. The applied algorithm weights the between-subject variance by the number of examined subjects per study. It could be argued that the contribution an experiment makes to an ALE map is dependent on the number of foci it reports. Yet, Turkeltaub et al. (2012) show that these within-experiment effects only account for 2-3% of cumulative ALE values and removing them has little impact on thresholded ALE maps. Differences between conditions were tested by first performing an ALE analysis separately for each condition and computing the voxel-wise difference between the ensuing ALE maps. The resulting ALE maps were thresholded using 5000 permutations, controlling the false discovery rate (FDR) at $p<0.05$, with a minimum cluster volume of $100mm^3$. Thresholded ALE maps were overlaid onto the “colinbrain” Talairach template (Kochunov et al., 2002; see Figure 1).

Results

Generic vs. specific cues

The resulting ALE map for paradigms using generic rather than specific cues is presented on Table 3 and Figure 1. MTL regions which are significantly associated with greater activity for paradigms using generic compared to specific cues are the left (BA 30) and right (BA 36) posterior parahippocampal gyri.

The resulting ALE map for paradigms using specific compared to generic cues is presented on Table 3 and Figure 1. The right anterior hippocampus showed significantly greater activity for paradigms using specific compared to generic cues.

Recognition vs. recall/imagine tasks

The resulting ALE map for paradigms using recognition rather than recall/imagine tasks is presented on Table 4 and Figure 1. The right (BAs 34, 28) and left (BAs 28, 34) anterior parahippocampal gyri and bilateral amygdala showed significantly greater activity for recognition compared to recall/imagine tasks.

The resulting ALE map for paradigms using recall/imagine compared to recognition tasks is depicted on Table 4 and Figure 1. The left posterior parahippocamapl gyrus (BA 30) showed significantly greater activity for recall/imagine compared to recognition tasks. It is important to note however that given the small number of studies classified as "recognition", these results must be interpreted with caution.

Episodic vs. strictly episodic events

The resulting ALE map when thinking about episodic rather than strictly episodic events is depicted on Table 5 and Figure 1. MTL regions significantly associated with greater activity for episodic compared to strictly episodic events are the left anterior parahippocampal gyrus (BA 28) and left amygdala.

The resulting ALE map when thinking about strictly episodic compared to episodic events is presented on Table 5 and Figure 1. The bilateral posterior hippocampus showed significantly greater activity for strictly episodic compared to episodic events.

To determine if the specific combination of strictly episodic events and specific cues was associated with greater hippocampal activation, we performed a further ALE analysis which compared strictly episodic to episodic (re/pre)experiencing triggered exclusively by specific cues (i.e. “episodic events and specific cues” vs. “strictly episodic events and specific cues”). Results, depicted on Table 6, show that specific cues associated to strictly episodic events elicit greater activity within the left posterior hippocampus compared to specific cues associated to episodic events. The reverse contrast reveals no greater activation for specific cues associated to episodic events compared to specific cues associated to strictly episodic events.

Younger vs. older participants

Results depicted on Table 7 show significantly greater activation in older subjects in the right anterior hippocampus, right anterior (BA 35) and bilateral posterior (BAs 27, 36) parahippocampal gyri, and left amygdala compared to the younger group. The reverse contrast revealed no greater activation for younger compared to older subjects.

Discussion

The principal aim of this meta-analysis was to focus on functional neuroimaging studies of past remembering and future thinking depicting activations in the MTL (hippocampus, parahippocampal gyrus and amygdala) and determine the influence of methodological factors on MTL laterality and antero-posterior activation. The meta-analysis, including 58 studies, showed that the type of cue used (generic versus specific), type of task performed (recognition versus recall/imagine), nature of the information retrieved (episodic versus strictly episodic) and the age of participants are important factors which influence MTL laterality and antero-posterior activation when thinking about past or future episodic events.

We will first focus our discussion on the role of the hippocampus in past and future episodic events and the effect of the different methodological factors on its laterality and antero-posterior activity. Then, we will concentrate on the additional roles of extra-hippocampal MTL regions.

Contribution of the hippocampus to past and future episodic events

Substantial evidence has shown that the hippocampus is crucial for episodic memory, in particular when (re/pre)experiencing is accompanied by the autonoetic consciousness of the contextual episode (Eldridge et al., 2000; Maguire et al., 2001; Moscovitch and McAndrews, 2002). Differential roles have been attributed to the right and left hippocampi in episodic memory. Results from the meta-analysis show that the laterality of hippocampal activation may also depend on the methodology used to elicit past and future (re/pre)experiencing.

Bilateral hippocampus

Concordant with our predictions, ALE results show that (re/pre)experiencing strictly episodic events lead to greater activity in the bilateral hippocampus compared to episodic events. Strictly episodic events are not only spatio-temporally unique and personal like episodic events, but are also accompanied by the subjective experience of (re/pre)experiencing (Moscovitch, 1995, 2000; Tulving & Markowitsch, 1998), associated with recall/imagination of contextual and phenomenological details (i.e., sensory, perceptual, cognitive, affective internal contextual details). Bilateral hippocampal activation has been previously attributed to retrieval of specific AMs rich on recollective qualities (e.g., level of detail, emotionality, personal significance, (re/pre)experiencing, vividness; Ryan et al., 2001; Okuda et al., 2003; Piefke et al., 2003; Graham et al., 2003; Addis et al., 2004a; Gilboa et al., 2004; Mayes et al., 2004; Greenberg et al., 2005; Piolino et al., 2004; Steinvorth et al., 2006;

Viard et al., 2007; Piolino et al., 2008; Abraham et al., 2008; St Jacques et al., in press). Bilateral hippocampal activation has also been linked to imagination of specific future events (Viard et al., 2011a; Weiler et al., 2010b; Hassabis and Maguire, 2007) and phenomenological characteristics (e.g., richness of details, temporal distance, emotional valence) were shown to affect activation patterns of future events (Addis and Schacter, 2008; Addis et al., 2008; D'Argembeau et al., 2008). It is plausible that bilateral hippocampal activation is detected for strictly episodic events because they lead to more intense (re/pre)experiencing (Eldridge et al., 2000; Yonelinas et al., 2001; Yonelinas, 2001), binding together numerous contextual and phenomenological characteristics, compared to episodic events. This relational property may be necessary to construct coherent scenes of past and future (Hassabis et al., 2007; Addis et al., 2007; Spreng and Grady, 2010; Viard et al., 2011a).

Left hippocampus

Previous literature has attributed different roles to the left and right hippocampi. ALE results show that the strictly episodic nature of memory/imagination elicits greater activity in the left hippocampus (compared to standard episodic memory/imagination), especially when (re/pre)experiencing is triggered by specific cues. The left hippocampus seems specifically associated with the retrieval of detailed strictly episodic events (Gilboa et al., 2004; Addis et al., 2004a) and is modulated by phenomenological quality (Gilboa et al., 2004; Rabin et al., 2010; Addis et al., 2008). The left hippocampus has a role in time-specific memory and personal experience (Maguire and Mummery, 1999) and self-projection of one's self compared to others (St Jacques et al., 2011a). Its role has also been highlighted to facilitate general coherence of an episode or scene (Rabin et al., 2010; Hassabis and Maguire, 2007). There is an overlap for episodic past and future event construction in the left hippocampus (Addis et al., 2007) and it remains online during elaboration suggesting it might have a role in generating complex coherent scenes (St Jacques et al., 2011b). The greater left hippocampal involvement may be explained by the generation of more complex scenes for strictly episodic compared to episodic events. This effect appears to be exacerbated when (re/pre)experiencing is triggered by specific cues probably because they prompt recall/imagination more directly, unlike generic cues (see below).

Right hippocampus

Greater right hippocampal activation was detected with the use of specific (i.e., personal) compared to generic (i.e., impersonal nouns or words) cues, regardless of the strict nature of events. Specific cues provide more direct access to episodic information (Addis et al., 2009), while generic cues require more elaborate cue-specification and further retrieval attempts (Addis et al., 2007). During construction, generic cues do not result in hippocampal activation, while specific cues directly evoke recollection of personal events leading to MTL activation (Addis et al., 2007; Rabin et al., 2010; Conway et al., 2003). Right activation may reflect emotional properties (Fink et al., 1996), self-perspective or retrieval of spatial details (see below). Right hippocampal activation may also depend on the time allotted for retrieval (Graham et al., 2003; Piolino et al., 2004) which can be circumscribed by the use of specific cues which directly trigger a personal event.

It is now well established that the right hippocampus plays a role in spatial episodic representation (O'Keefe and Nadel, 1978; Hirshhorn et al., in press; for review, Burgess et al., 2002), notably in autobiographical recall (Maguire and Frith, 2003a, b; Gilboa et al., 2004; Piolino et al., 2004; Viard et al., 2007). The right hippocampus may be driven by initial spatial or relational processing of complex visual scenes (Hassabis et al., 2007; Binder et al., 2005; Köhler et al., 2005), the spatial context of recalled/imagined episodes being retrieved early in the construction process (Weiler et al., 2010a). It has also been shown that the right hippocampus is responsive to the sense of (re)living the contextual episode (Gilboa et al., 2004; Graham et al., 2003; Mayes et al., 2004; Piolino et al., 2004, 2008; Steinvorth et al., 2006; Viard et al., 2007, 2010, 2011a; St Jacques et al., in press) presumably by providing a spatial context to recall/imagine these events (Viard et al., 2011a; Burgess et al., 2001).

Right hippocampal activation may also depend on the age of participants. Older adults show greater activation in the right hippocampus (Ryan et al., 2001; Viard et al., 2007; Nadel et al., 2007; Gilboa et al., 2004) compared to younger subjects (Maguire and Frith, 2003b; St Jacques et al., in press) which may reflect increased use or salience of spatial context in older subjects. Results of the meta-analysis indicate that older adults show greater right hippocampal activation compared to younger adults which is concordant with the hemispheric asymmetry reduction due to age observed in prefrontal regions (HAROLD model, Cabeza, 2002).

Overall, results from the meta-analysis show that laterality of hippocampal activation may depend on the methodology used to elicit past remembering and future envisioning, with strictly episodic events and specific cues more likely to activate the bilateral and right hippocampus, respectively. Interestingly, strictly episodic (re/pre)experiencing triggered by specific cues elicits greater activation in the left hippocampus, compared to episodic events triggered by specific cues. Differential roles have been attributed to the hippocampus according to its laterality, but also along its antero-posterior axis. Results from the meta-analysis show that the methodology used to elicit past and future (re/pre)experiencing may also account for differential antero-posterior activation.

Anterior hippocampus

ALE results show that the use of specific cues lead to greater activity in the anterior hippocampus compared to generic cues. The anterior hippocampus supports relational processing (Chua et al., 2007; Davachi et al., 2003; Jackson and Schacter, 2004), including flexible recombination of details for past and future events (Preston et al., 2004). Addis and Schacter (2008) showed that future-associated activity in the anterior hippocampus was associated with higher demands on recombination of details. Specific cues, which trigger precise personal events, may require immediate binding of disparate details compared to generic cues. Hoscheidt et al. (2010) showed that the anterior hippocampus is predominantly activated by episodic memory rather than by semantic memory.

Posterior hippocampus

Results from the meta-analysis show significantly greater posterior hippocampal activation for strictly episodic compared to episodic events, in line with our predictions, and this is observed particularly when (re/pre)experiencing is triggered by specific cues. The posterior hippocampus is predominantly activated by spatial memory (Hoscheidt et al., 2010), spatial content (see Chadwick et al., 2010) or navigation (O'Keefe and Nadel, 1978; Maguire et al., 1998; Moser and Moser, 1998; Ekstrom et al., 2003; Hartley et al., 2003). Recent evidence shows that it may have a general role in recollection memory which is not limited to spatial memory (Poppenk and Moscovitch, 2011). The posterior hippocampus has been shown to respond to the amount of detail integrated into a coherent event, irrespective of past and future distinction (Addis et al., 2008). Compared to episodic events, strictly episodic events are indeed richer on phenomenological characteristics which include spatial content and level of detail. This posterior hippocampal activation is especially observed when (re/pre)experiencing is triggered by specific cues which directly trigger recall/imagination and its associated spatial context. The posterior hippocampus has a role in relational processing, as its anterior part, and is engaged by tasks requiring retrieval of relational information, for both past and future thinking (Addis et al., 2008).

Overall, results from the meta-analysis show that activity of the hippocampus along its antero-posterior axis may depend on the methodology used to elicit past and future episodic thinking, with specific cues and strictly episodic events more likely to recruit its anterior and posterior parts, respectively. Additionaly, when triggered exclusively by specific cues, (re/pre)experiencing strictly episodic events elicits greater activation in the posterior hippocampus, compared to episodic events. Yet, the hippocampus does not work alone and extra-hippocampal MTL regions also contribute to past and future episodic (re/pre)experiencing, in particular, via interactions with the hippocampus (Viard et al., 2010; Greenberg et al., 2005; Maguire et al., 2000; Söderlund et al., in press; Addis et al., 2004b, 2009).

Contribution of the extra-hippocampal MTL regions to past and future episodic events

Laterality within the parahippocampal gyrus

Like the hippocampus, the parahippocampal gyrus can be subdivided depending on its laterality and along its antero-posterior axis. Although there is evidence of a functional specialization along its antero-posterior axis (Graham et al., 2010), it is not yet clear if the left and right parahippocampal gyri have a differential role in past and future episodic thinking. Hence, the laterality of the parahippocampal peaks resulting from the ALE analyses must be interpreted with caution and be considered as exploratory statistics. Tsukiura et al. (2002) suggest that the parahippocampal gyrus, particularly on the right, may be implicated in the retrieval of topographical or spatial AMs and could be related to the recruitment of posterior visual areas during the retrieval of older episodic memories (Niki and Luo, 2002; Mayes et al., 2004; for reviews, see Burgess et al., 2002; Moscovitch et al., 2005). Indeed, the parahippocampal gyrus is involved in the retrieval of spatial compared to non-spatial contexts (Burgess et al., 2001; King et al., 2005; see also Bar et al., 2008; Epstein and Ward, 2009;

Viard et al., 2011b) and responds selectively to visual scenes depicting places (Epstein and Kanwisher, 1998). The left parahippocampal gyrus remains online during elaboration of episodic AMs and might have a role in generating a complex coherent scene (St Jacques et al., in press). It is indeed involved in memory retrieval and encoding of spatial scenes (Hoscheidt et al., 2010). The parahippocampal gyrus (along with the hippocampus, retrosplenial cortex, posterior parietal cortex and ventro-medial prefrontal cortex) is also engaged during the construction of new fictitious scenes and when remembering both previously imagined and real personal experiences. This network supports (re)construction, maintenance and visualization of complex scenes (Hassabis et al., 2007).

Anterior parahippocampal gyrus

ALE results indicate that the anterior parahippocampal gyrus (entorhinal and perirhinal cortices) is activated for recognition compared to recall/imagine tasks and for episodic compared to strictly episodic events. Several models have proposed a functional segregation of the parahippocampal gyrus along its antero-posterior axis. According to Aggleton and Brown (1999), the perirhinal cortex supports familiarity judgments and the relational memory view proposes that the perirhinal cortex supports memory for individual objects (Eichenbaum et al., 2007). A complementary view, the binding of item and context theory (BIC), posits that it processes item information (Diana et al., 2007), while the posterior parahippocampal gyrus (or parahippocampal cortex) processes context information (both spatial and non-spatial). The role of the hippocampus would be to bind together item and context (item-context associations) which are separately processed by the parahippocampal gyrus. Recognition tasks may prompt subjects to focus on the decision and familiarity rather than vivid recollection (Piefke et al., 2003), explaining the greater anterior parahippocampal activation observed for recognition compared to recall tasks. Recruitment of the anterior parahippocampal gyrus suggests that familiarity judgments, mental manipulation of individual objects or processing of item information is greater for episodic than strictly episodic events.

Posterior parahippocampal gyrus

ALE results indicate that the posterior parahippocampal gyrus (parahippocampal cortex) is significantly more activated for recall/imagine compared to recognition tasks, in line with our predictions. Activity in the (bilateral) parahippocampal cortex during elaboration (along with the retrosplenial cortex, posterior cingulate cortex and precuneus) supports contextual processing (Bar and Aminoff, 2003). The parahippocampal cortex is preferentially engaged during remembering, supporting retrieval of visuo-spatial details (Addis et al., 2009). Indeed, contextual processing and retrieval of visuo-spatial details are more engaged for recall/imagine compared to recognition tasks.

Results show greater posterior parahippocampal activation for generic compared to specific cues which was unexpected, as we predicted the opposite. We can only speculate that a generic cue, which is not as personally-oriented as specific cues, may require greater processing of contextual information to find an appropriate personal event corresponding to this generic cue.

Overall, results of the meta-analysis indicate that basic methodological choices may have an impact on activation within the parahippocampal gyrus, most notably along its antero-posterior axis, with episodic events and recognition tasks more likely to recruit its anterior part, compared to strictly episodic events and recall tasks respectively, the latter recruiting more its posterior part associated with greater contextual processing.

Amygdala

ALE results show greater activity within the bilateral amygdala for recognition compared to recall/imagine tasks. It is well known that the enhanced memory capability observed for emotional events is due, at least in part, to the amygdala's influence on encoding and storage of hippocampal-dependent memories, as suggested by many studies showing amygdala activation during the encoding of emotional stimuli predicts subsequent retention (Cahill et al., 1996; Canli et al., 2000; Kensinger and Corkin, 2004). While the left amygdala is more responsive to conscious, language-dependent processing (Markowitsch, 1998; Phelps, 2006), the right amygdala has been shown to subserve a system of automatic detection of emotional stimuli (Kensinger and Corkin, 2004; Costafreda et al., 2008), which can be triggered by recognition tasks (Clark-Foos and Marsh, 2008). The right amygdalar activation for recognition compared to recall/imagine tasks may reflect this automatic process in emotional processing.

ALE results also show greater activity within the left amygdala for episodic compared to strictly episodic events, which was unexpected, as we predicted the opposite. Although the amygdala's role in the encoding of emotional stimuli is well documented, its role during recall/imagination of episodic events is not as clear (Greenberg et al., 2005; Daselaar et al., 2008). Several studies have detected amygdalar activation during the retrieval of emotional AMs (Fink et al., 1996; Markowitsch et al., 2000, 2003; Maguire and Frith, 2003a; Greenberg et al., 2005; Daselaar et al., 2008) or when imagining positive future events (Sharot et al., 2004), although sometimes subthresholded (Addis et al., 2004a) or inconsistently even when emotions were specifically probed (Maguire and Frith, 2003a; Piefke et al., 2003).

Conclusion

The present meta-analysis explored the effect of methodological factors on MTL activity, in an attempt to explain the contradictory findings concerning MTL laterality and antero-posterior activity found in the neuroimaging literature on past and future (re/pre)experiencing. Four main results emerge: (1) specific cues tend to recruit the right anterior hippocampus more than generic cues, (2) recall/imagine tasks tend to activate the posterior parahippocampal gyrus more than recognition tasks, (3) (re/pre)experiencing strictly episodic events recruits the bilateral posterior hippocampus more than episodic events and (4) older subjects activate more the right anterior hippocampus compared to younger subjects, confirming our predictions. Importantly, our results stress that strictly episodic events triggered by specific cues elicits greater left posterior hippocampal activation than standard episodic memory/imagination elicited by specific cues. These findings suggest that basic methodological choices have an impact on MTL laterality and antero-posterior activity. Here, we investigated the effect of four factors only and focussed exclusively on the MTL. Future meta-analyses may address whether other factors (e.g., differences in time frames, number of memories recollected, trial designs, re-encoding processes…) are likely to influence MTL activity and, more broadly, their impact on other brain regions elicited by episodic (re/pre)experiencing. Multi-voxel pattern analysis and similar approaches will be important to factor in future considerations of this topic, once a sufficient number of studies have been published.

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Table 1: Studies included in the meta-analysis, specifying the contrast, number of subjects, nature of the information retrieved (episodic or strictly episodic), type of task (recognition or recall), type of cue (generic or specific) and number of foci falling within the MTL (hippocampus, parahippocampal gyrus, amygdala).

	Study	Contrast	Past /Future	N	Age	Cue	Task**	Nature	Foci
1	Abraham et al., 2008a	PE-ctl	F	20	26	generic	recog	episodic	3
2	Addis et al., 2004a	PE-ctl and PM	P	14	20-40	specific	recall	strict	13
3	Addis et al., 2004b*	PE-ctl	P	14	28	specific	recall	strict	2
4	Addis et al., 2007	PE-ctl and PM	F	14	23	generic	recall	strict	4
5	Addis et al., 2008	PE-ctl and ANOVA	F	16	23	generic	recall	strict	2
6	Addis et al., 2009*	PE-ctl	F	18	21,9	generic	recall	strict	5
7	Addis et al., 2011a	PE-ctl	F	15	18-33	generic	recall	strict	2
8	Addis et al., 2011b*	PE-ctl	F	28	gp1=19,5; gp2=72,9	generic	recall	episodic	3
9	Addis et al., 2012*	PE-ctl	P	15	22	specific	recall	strict	4
10	Botzung et al., 2008b	PE-ctl	P	10	42,4	specific	recall	episodic	1
11	Burianova et al., 2007*	PE-ctl	P	12	26,8	generic	recall	strict	1
12	Cabeza et al., 2004	PE-ctl and ANOVA	P	13	20,8	specific	recog	episodic	3
13	Daselaar et al., 2008	PM	P	17	18-35	generic	recall	strict	3
14	Denkova et al., 2006a	PE-ctl	P	10	42,4	specific	recall	episodic	2
15	Denkova et al., 2006b	PE-ctl	P	10	40,6	specific	recall	episodic	1
16	Donix et al., 2010	PE-ctl	P	15	gp1=28; gp2=60,5	specific	recall	episodic	1
17	Fink et al., 1996	PE-ctl	P	7		specific	recall	episodic	1
18	Ford et al., 2011	PE-ctl	P	16	21-37	generic	recall	strict	3
19	Gardini et al., 2006	PE-ctl	P	14	37,93	generic	recall	strict	3
20	Gilboa et al., 2004	PE-ctl	P	9	50,75	specific	recall	strict	3

21	Greenberg et al., 2005	PE-ctl	P	11	18-25	specific	recall	strict	5
22	Hassabis et al., 2007	PE-ctl and PM	F	21	24,8	specific	recall	strict	2
23	Holland et al., 2011	PE-ctl	P	25	21,8	generic	recall	strict	1
24	Hoscheidt et al., 2010	PE-ctl and PM	P	17	22,2	generic	recog	episodic	16
25	Levine et al., 2004*	PE-ctl	P	5	26-37	specific	recall	strict	1
26	Maguire & Mummery, 1999	PM	P	8	28-41	specific	recog	episodic	1
27	Maguire et al., 2003a	PE-ctl	P	12	53,58	specific	recog	episodic	2
28	Maguire et al., 2003b	PE-ctl	P	12	gp1=32,42; gp2=74,75	specific	recog	episodic	13
29	Markowitsch et al., 2000	PE-ctl	P	8	25,6	specific	recall	episodic	2
30	Markowitsch et al., 2003	PE-ctl	P	13	30	generic	recall	strict	1
31	Mayes et al., 2004	PE-ctl	P	9	22	generic	recall	episodic	19
32	Mendelsohn et al., 2009	PM	P	1	29	specific	recall	episodic	2
33	Milton et al., 2011a	PE-ctl & PM	P	15	18-25	specific	recog	episodic	7
34	Nadel et al., 2007	PE-ctl	P	12	54,6	specific	recall	strict	10
35	Oddo et al., 2008	PE-ctl	P	15	20,8	specific	recall	strict	1
36	Okuda et al., 2003	PE-ctl	P and F	12	20,7	generic	recall	episodic	15
37	Piefke et al., 2003	PE-ctl	P	20	26	specific	recall	strict	1
38	Piolino et al., 2008	PM	P	12	59	specific	recall	strict	16
39	Rabin et al., 2010	PE-ctl	P	18	57,2	specific	recall	strict	16
40	Rekkas et al., 2005	PE-ctl	P	12	21	generic	recall	episodic	7
41	Ryan et al., 2001	PE-ctl	P	6	60,3	specific	recall	strict	2
42	Sharot et al., 2007	PE-ctl	F	18		generic	recall	strict	1
43	Soderlund et al., in press*	PE-ctl	P	12	33,7	specific	recall	strict	4
44	Spreng & Grady, 2010*	PE-ctl	F	16	25,9	generic	recall	episodic	4
45	St Jacques et al., 2011a	PE-ctl and PM	P	23	23,7	specific	recall	strict	2
46	St Jacques et al., 2011b	PE-ctl	P	17	24,43	generic	recall	strict	2
47	St Jacques et al., in press	PE-ctl	P	28	gp1=24,43; gp2=64,21	generic	recall	strict	8

48	St-Laurent et al., 2011*	PE-ctl	P	30	gp1=20-33; gp2=63-77	generic	recall	strict	1
49	Svoboda et al., 2009	PE-ctl	P	11	30	specific	recall	strict	6
50	Szpunar et al., 2007	PE-ctl	F	21	22,52	generic	recall	strict	5
51	Szpunar et al., 2009	PE-ctl	F	27	23,3	generic	recall	strict	2
52	Trinkler et al., 2009	PE-ctl and PM	P	14	20-23	specific	recog	episodic	7
53	Tsukiura et al., 2002	PE-ctl	P	9	20,6	generic	recall	episodic	2
54	Vandekerckhove et al., 2005	PE-ctl	P	16	21-32	specific	recall	episodic	2
55	Viard et al., 2007	PE-ctl	P	12	67,17	specific	recall	strict	16
56	Viard et al., 2011a	PE-ctl	F	12	67,17	specific	recall	strict	4
57	Weiler et al., 2010a	interaction	F	17	19-24	generic	recall	strict	1
58	Weiler et al., 2010b	ANOVA	F	32	24	generic	recall	strict	2
	Total			**866**					**269**

Abbreviations: ANOVA = analysis of variance; ctl = control; F = future; gp = group; P = past; PE = personal event; PM = parametric modulation.

* Multi-variate analyses
** For the future, recall corresponds to the imagination task.

Table 2: Studies excluded from the meta-analyses and reasons.

	Study	Reason for exclusion
1	Andreasen et al., 1995	No MTL activation
2	Andreasen et al., 1999	No MTL activation
3	Botzung et al., 2008a	No MTL coordinates provided
4	Burianova et al., 2010	All memory conditions (including semantic) > control
5	Conway et al., 2001	Electroencephalography
6	Conway et al., 2003	Electroencephalography
7	Conway et al., 1999	No MTL activation
8	D'Argembeau et al., 2008	Positive > negative future events
9	D'Argembeau et al., 2010	No MTL activation for the contrast of interest*
10	Graham et al., 2003	No MTL coordinates provided
11	Maddock et al., 2001	No MTL coordinates provided
12	Maguire et al., 2000	All memory conditions (including semantic) > control
13	Maguire et al., 2001	All memory conditions (including semantic) > control
14	Milton et al., 2011b	No MTL activation for the contrast of interest*
15	Niki & Luo et al., 2002	Recent > remote AMs
16	Nyberg et al., 2002	No MTL activation
17	Piefke et al., 2005	Same contrasts as Piefke et al., 2003
18	Piolino et al., 2004	No MTL coordinates provided
19	St Jacques et al., 2008	Inappropriate contrast (temporal-order judgments)
20	Steinvorth et al., 2006	No MTL coordinates provided
21	Summerfield et al., 2009	Conjunction with semantic condition
22	Tulving et al., 1989	No MTL coordinates provided
23	Viard et al., 2010	No MTL coordinates provided
24	Weiler et al., 2011	Electroencephalography

Abbreviations: > = versus.

* Contrast of interest: episodic event condition (past or future) compared to control condition.

Table 3: Results from the ALE meta-analyses for Generic versus Specific cues.

Region	Lat	Axis	BA	Volume (mm^3)	Peak ALE Value	x	y	z
Generic > specific								
Parahippocampal Gyrus	L	P	30	3400	3,353	-12	-32	-6
Parahippocampal Gyrus	R	P	36	1152	2,620	22	-42	-8
Specific > generic								
Hippocampus	R	A		1552	1,967	26	-14	-18

Abbreviations: A = anterior; ALE = activation likelihood estimation; BA = approximate Brodmann area; Lat. = laterality; L = left; P = posterior; R = right; x. y. z coordinates = peak voxel in Talairach space.

Table 4: Results from the ALE meta-analyses for Recognition versus Recall tasks.

Region	Lat	Axis	BA	Volume (mm^3)	Peak ALE Value	x	y	z
Recognition > recall								
Amygdala	R	A	34	3112	3,540	23	2	-16
Parahippocampal Gyrus	R	A	28		3,353	22	6	-15
Parahippocampal Gyrus	R	A	28		2,549	20	-18	-16
Parahippocampal Gyrus	L	A	28	1120	2,400	-20	-14	-20
Parahippocampal Gyrus	L	A	34		2,304	-16	-16	-22
Amygdala	L			120	2,050	-26	0	-18
Parahippocampal Gyrus	L	A	34		2,034	-30	2	-18
Recall > recognition								
Parahippocampal Gyrus	L	P	30	544	1,855	-24	-36	4

For abbreviations, see Table 3.

Table 5: Results from the ALE meta-analyses for Episodic versus Strictly episodic events.

Region	Lat	Axis	BA	Volume (mm^3)	Peak ALE Value	x	y	z
Episodic > strictly episodic								
Parahippocampal Gyrus	L	A	28	1232	3,090	-14	-22	-22
Amygdala	L			144	2,007	-28	-8	-10
Strictly episodic > episodic								
Hippocampus	L	P		576	2,155	-26	-34	0
Hippocampus	L	P		224	1,866	-34	-26	-10
Hippocampus	R	P		176	1,710	32	-38	0

For abbreviations, see Table 3.

Table 6: Results of the ALE comparison between strictly episodic events and specific cues > episodic events and specific cues.

Region	**Lat**	**Axis**	**BA**	**Volume (mm^3)**	**Peak ALE Value**	**x**	**y**	**z**
Strictly episodic events and specific cues > episodic events and specific cues								
Hippocampus	L	P		2472	2.619	-29	-37	-1
Hippocampus	L	P			2.245	-30	-24	-10

For abbreviations, see Table 3.

Table 7: Results of the ALE comparison between data from younger and older subjects.

Region	Lat	Axis	BA	Volume (mm^3)	Peak ALE Value	x	y	z
Older > younger								
Parahippocampal Gyrus	R	A	35	5816	3.090	25	-17	-11
Hippocampus	R	A			2.878	32	-18	-16
Parahippocampal Gyrus	R	P	27		2.576	12.8	-30	1.6
Parahippocampal Gyrus	L	P	36	2896	3.719	-33	-23	-16
Parahippocampal Gyrus	L	P	36		3.540	-35	-26	-13
Amygdala	L			2352	2.214	-18	-4	-10

For abbreviations, see Table 3.

Figure 1: ALE maps thresholded at $p<0.05$ corrected for the following comparisons: (top left) Generic > Specific cues centered on the bilateral posterior parahippocampal gyrus; (top right) Specific > Generic cues centered on the right anterior hippocampus; (middle left) Recognition > Recall/imagine tasks centered on the bilateral anterior parahippocampal gyrus; (middle right) Recall/imagine > Recognition tasks centered on the left posterior parahippocampal gyrus; (bottom left) Episodic > Strictly episodic events centered on the left anterior parahippocampal gyrus; (bottom right) Strictly episodic > Episodic events centered on the bilateral posterior hippocampus.