Hippocampal Contribution to Ordinal Psychological Time in the Human Brain

Baptiste Gauthier[1], Pooja Prabhu[2], Karunakar A. Kotegar[2], and Virginie van Wassenhove[3]

Abstract

■ The chronology of events in time–space is naturally available to the senses, and the spatial and temporal dimensions of events entangle in episodic memory when navigating the real world. The mapping of time–space during navigation in both animals and humans implicates the hippocampal formation. Yet, one arguably unique human trait is the capacity to imagine mental chronologies that have not been experienced but may involve real events—the foundation of causal reasoning. Herein, we asked whether the hippocampal formation is involved in mental navigation in time (and space), which requires internal manipulations of events in time and space from an egocentric perspective. To address this question, we reanalyzed a magnetoencephalography data set collected while participants self-projected in time or in space and ordered historical events as occurring before/after or west/east of the mental self [Gauthier, B., Pestke, K., & van Wassenhove, V. Building the arrow of time… Over time: A sequence of brain activity mapping imagined events in time and space. *Cerebral Cortex*, *29*, 4398–4414, 2019]. Because of the limitations of source reconstruction algorithms in the previous study, the implication of hippocampus proper could not be explored. Here, we used a source reconstruction method accounting explicitly for the hippocampal volume to characterize the involvement of deep structures belonging to the hippocampal formation (bilateral hippocampi [hippocampi proper], entorhinal cortices, and parahippocampal cortex). We found selective involvement of the medial temporal lobes (MTLs) with a notable lateralization of the main effects: Whereas temporal ordinality engaged mostly the left MTL, spatial ordinality engaged mostly the right MTL. We discuss the possibility of a top–down control of activity in the human hippocampal formation during mental time (and space) travels. ■

INTRODUCTION

By analogy to the ways the brain represents space, the representation of memory has been hypothesized to rely on the coexistence of allocentric (landmark-based) and egocentric (self-based) coordinate systems (Buzsáki & Moser, 2013). Whereas an egocentric representation of temporal memories intimately engages the concept of self (Arzy & Schacter, 2019), the basis for an allocentric representation of time may be more difficult to conceptualize. One possibility is that, just as the mental representation of space capitalizes on allocentric maps to make sense of the recurring updating of sensory information, the enduring representations of events in time may temporally frame one's immediate, but also past and future, experiences. A core question is thus whether different coordinate systems may coexist to represent time in the human brain and whether we can investigate their existence in a prelinguistic form (Gallistel, 2002).

In Western cultures, the closest concept to an allocentric representation of time is the idea of "mental timelines"; such concept uses a spatial metaphor as a pervasive means to make sense of time (Bonato, Zorzi, & Umiltà, 2012; Boroditsky, 2000; Bergson, 1922). From a computational perspective, the metaphor of mental timeline conveniently captures the necessity for the representation of an ordinal sequence of events in time, that is, the necessity of a 1-D and oriented code for the past-to-future chronology of events (whether experienced in real-time, remembered retrospectively, or imagined prospectively). Hence, by analogy to the "geocentric" spatial cognitive maps representing space in allocentric coordinates (Wang & Spelke, 2002), the "chronocentric" representations of events in time should code for the past-to-future orientation of time.

The study of temporal order as a specific feature of (serial) memory has provided many insights on the involved neuroanatomical structures. For instance, in episodic memory, the retrieval of temporal order involves hippocampal regions that are distinct from those involved in the retrieval of the spatial associations of previously encountered items (Ekstrom, Copara, Isham, Wang, & Yonelinas, 2011). In addition to the reported implication of pFCs (Ekstrom et al., 2011), distinct connectivity patterns between hippocampus and neocortex have also

been described (Watrous, Deuker, Fell, & Axmacher, 2015; Schedlbauer, Copara, Watrous, & Ekstrom, 2014; Watrous & Ekstrom, 2014), again reporting separate hippocampal regions for temporal processing (Copara et al., 2014). The order of events and their temporal distances (i.e., the elapsed episodic time experienced between two events) in various tasks entailing path integration or remembering have systematically implicated medial temporal lobes (MTL; Clewett, DuBrow, & Davachi, 2019; Deuker, Bellmund, Schröder, & Doeller, 2016b; Jenkins & Ranganath, 2016; Nielson, Smith, Sreekumar, Dennis, & Sederberg, 2015; Jenkins & Ranganath, 2010). In the current state of research, the hippocampus thus appears a reasonable candidate for the representation of mental timelines.

The spatial and temporal dimensions of episodic events can be reconstructed a posteriori, that is, by mental manipulation during or after memory retrieval. Retrieval engages a core network of neocortical regions (Peer, Salomon, Goldberg, Blanke, & Arzy, 2015; Ekstrom & Bookheimer, 2007), which are distinct for the temporal and spatial dimensions, although they commonly engage the hippocampal formation (Schedlbauer et al., 2014; Watrous & Ekstrom, 2014). This pattern has been observed for the mapping of nonepisodic time, in a study requiring participants to overtly judge the order of events with respect to different positions on their mental timelines (Gauthier, Pestke, & van Wassenhove, 2019; Gauthier & van Wassenhove, 2016b). Hence, mental timelines may enable the flexible remapping of events on internal temporal coordinate systems, or temporal cognitive maps, thereby enabling mental time travel, an arguably unique human ability (Suddendorf, Addis, & Corballis, 2009; Suddendorf & Corballis, 2007; although see Clayton, 1998). Last, the ability to navigate mental time may rely on the integrity of the hippocampus (Buckner, 2010).

To empirically test mental time travel in humans, Arzy, Adi-Japha, and Blanke (2009) devised a task in which participants were asked to mentally project themselves away from the now, either a few years in the past or in the future. This mental operation was referred to as self-projection, which is the ability to represent oneself in an alternate situation, spatial location, or moment in time (Buckner & Carroll, 2007). From this new mental perspective or positioning on their mental timeline, participants had to judge whether autobiographical events occurred before or after their mental position. This experimental protocol described two important behavioral effects: First, an increase in RT was observed when the task was accomplished in a different temporal perspective than the now ("absolute distance effect"). This observation supported the psychological reality of self-projection in time and the possibility of representing flexible temporal coordinates. Second, the study showed a decrease in RTs with increasing distance of autobiographical events from the mental self ("relative distance effects"). These results crucially indicated that mental timelines

could be relative to the temporal locus of the projected self with a flexible use of temporal representations. Since this seminal work, we extended these findings to ordinal judgments of historical events in time as well as to their spatial dimension (Gauthier & van Wassenhove, 2016a): In this series of experiments, participants self-projected in space (west or east of their physical location) or in time (past or future) or mentally stayed in the here and now. After self-projection (or absence thereof), participants were asked to estimate whether a learned historical event occurred before or after (time), or east or west (space), of their mental location. Relative and absolute distance effects were observed in both the temporal and spatial dimensions of the task.

Navigating time with autobiographical and historical events recruited hippocampal, medial temporal, and posterior parietal regions during temporal self-projection (Gauthier et al., 2019; Gauthier & van Wassenhove, 2016b; Arzy, Collette, Ionta, Fornari, & Blanke, 2009). This was consistent with most fMRI work looking at the past-to-future distinction and showing the involvement of large networks encompassing the MTL and parietal, dorsolateral, and medial pFCs Gauthier & van Wassenhove, 2016b; Viard, Chételat, et al., 2011; Botzung, Denkova, & Manning, 2008; Okuda et al., 2003). In addition, structures of the cortical midline such as the medial prefrontal and parietal regions have been reported as core regions for the representation of self and have been tightly linked to self-projection (Northoff, 2016; Northoff et al., 2006; Northoff & Bermpohl, 2004).

In this context, we wished to investigate the role of hippocampal activity in mental time (and space) travels. For this, we capitalized on the magnetoencephalography (MEG) data set collected while participants self-projected in time or in space and ordered historical events as occurring before/after or west/east of the mental self (Gauthier et al., 2019). The MEG activity revealed the involvement of both medial temporal and neocortical regions with distinct sequential activity supporting the predicted cognitive operations implicated in this mental time and space travel task (Gauthier et al., 2019). However, as we did not include MTL in the previous source reconstruction algorithms, whether the hippocampus proper was implicated was unknown; herein, we used a source reconstruction method accounting explicitly for the hippocampal volume as a possible generative source of the activity. Hence, we could now characterize the involvement of deep structures belonging to the MTL, namely, bilateral hippocampi (hippocampi proper [HPs]), entorhinal cortices (ECs), and parahippocampal cortices (PHCs). We report the nonselective involvement of the MTL during self-projection and dimension selection but its selective implication in representing egocentric and allocentric time and space. We discuss these findings in the context of possible allocentric temporal cognitive maps in the hippocampus and neocortical top–down control on processing temporal ordinality.

METHODS

Participants

The MEG data collected in Gauthier et al. (2019) served as experimental materials to test a novel set of working hypotheses. The pool of participants consisted of 19 healthy volunteers (nine men, mean age = 24 ± 4 years), who were right-handed, with normal or corrected-to-normal vision and with no history of psychological or neurological disorders. All participants resided in the Parisian Ile-de-France region and received compensation for their participation in the study. All participants provided written informed consent in accordance with the Ethics Committee on Human Research at the Commissariat à l'Energie Atomique et aux Energies Alternatives (Direction de la Recherche Fondamentale/Institut Joliot, NeuroSpin, Gif-sur-Yvette, France) and the Declaration of Helsinki (2013).

Experimental Design and Procedure

Participants were provided with a list of historical world events at least 48 hr before they took part in the neuroimaging experiment (Gauthier & van Wassenhove, 2016a). We selected historical events so that their dates (historical time) and places (spatial longitudes) were distributed uniformly around each possible reference and for each dimension. This selection resulted in a set of 36 historical events for the "here" and "now" reference (Figure 1), among which 24 historical events were uniformly distributed for past, future, east, and west references. Participants studied the list and were then tested before the combined MEG and EEG recordings. Participants were presented with the historical events in a randomized order, and they rated their memory of each event by selecting "sure", "not sure" or "forgotten." Eleven percent of trials were disregarded because of participants not responding, replying "forgotten," or actually misreporting the date or location of a given event (Gauthier & van Wassenhove, 2016a; Experiment 2). All analyses included correctly recalled events only.

Figure 1 shows one experimental block consisting of two main phases: First, a self-positioning cue instructed participants to mentally position themselves here and now (Paris, today) or to project themselves in time (9 years ago or 9 years in the future, in Paris) or in space (now, in Cayenne or in Dubai). The presentation of one of the five possible references was followed by a series of eight experimental trials. Each trial started with a question, which indicated whether the ordinal judgment had to be made along the temporal or spatial dimension (Time: "before/after?" or Space: "west/east?", respectively). Time or Space could follow any reference. After the presentation of the question, 1 of the 36 historical events was presented on the screen. Participants' task was to order the historical event with respect to their mental position along the dimension specified by the question. In short,

the retrieval of a historical event was fully contextualized by its position and its dimension.

MEG Recordings

The experimental instructions emphasized speed and accuracy equally. Participants' responses were recorded using two amagnetic FORP button response pads (FORP Systems, Inc.). PsychToolbox-3 (psychtoolbox.org/) was used for coding the experiment, presenting the stimuli on the screen, recording the behavioral responses, and sending the triggers to the MEG acquisition system. Additional details can be found in Gauthier et al. (2019).

The experiment was conducted in a dimly lit, standard, magnetically shielded room located at Neurospin (Commissariat à l'Energie Atomique et aux Energies Alternatives/Direction de la Recherche Fondamentale). Participants sat in an upright position and read the instructions projected on a screen from a projector located outside the magnetically shielded room. The electromagnetic brain activity was recorded using the whole-head Elekta Neuromag Vector View 306 MEG system (Neuromag Elekta Ltd.) equipped with 102 triple-sensor elements (two orthogonal planar gradiometers and one magnetometer per sensor location). Participants' head position was measured before each block using four head-position coils placed over the frontal and mastoid areas. The four head-position coils and three additional fiducial points (nasion, left, and right preauricular areas) were digitized for subsequent coregistration with the individual's anatomical MRI (aMRI). MEG recordings were sampled at 1 kHz and bandpass filtered between 0.03 and 330 Hz. The EOGs (horizontal and vertical eye movements), electrocardiograms, and EMGs were recorded simultaneously with MEG. The locations of the coils were digitized with respect to three anatomical landmarks using a 3-D digitizer (Polhemus).

Data Analysis

MEG Data Preprocessing

We performed signal space separation correction (Taulu & Simola, 2006), head movement compensation, and bad channel rejection using the MaxFilter Software (Elekta Neuromag). Trials containing excessive ocular and movement artifacts, amplifier saturation, or SQUID artifacts were automatically rejected using a rejection criterion applied on magnetometers ($55e^{-12}$ T/m). Eye blinks, heartbeats, and muscle artifacts were corrected using independent component analysis (Bell & Sejnowski, 1995) with MNE-Python. Preprocessed MEG data were analyzed using MNE-Python 0.13 (Gramfort et al., 2014) and custom-made Python codes. A low-pass zero-phase lag finite impulse response filter (40 Hz) was applied to the raw data.

MEG Data Baselining

On the basis of the behavioral results published in Gauthier and van Wassenhove (2016a), the presentation
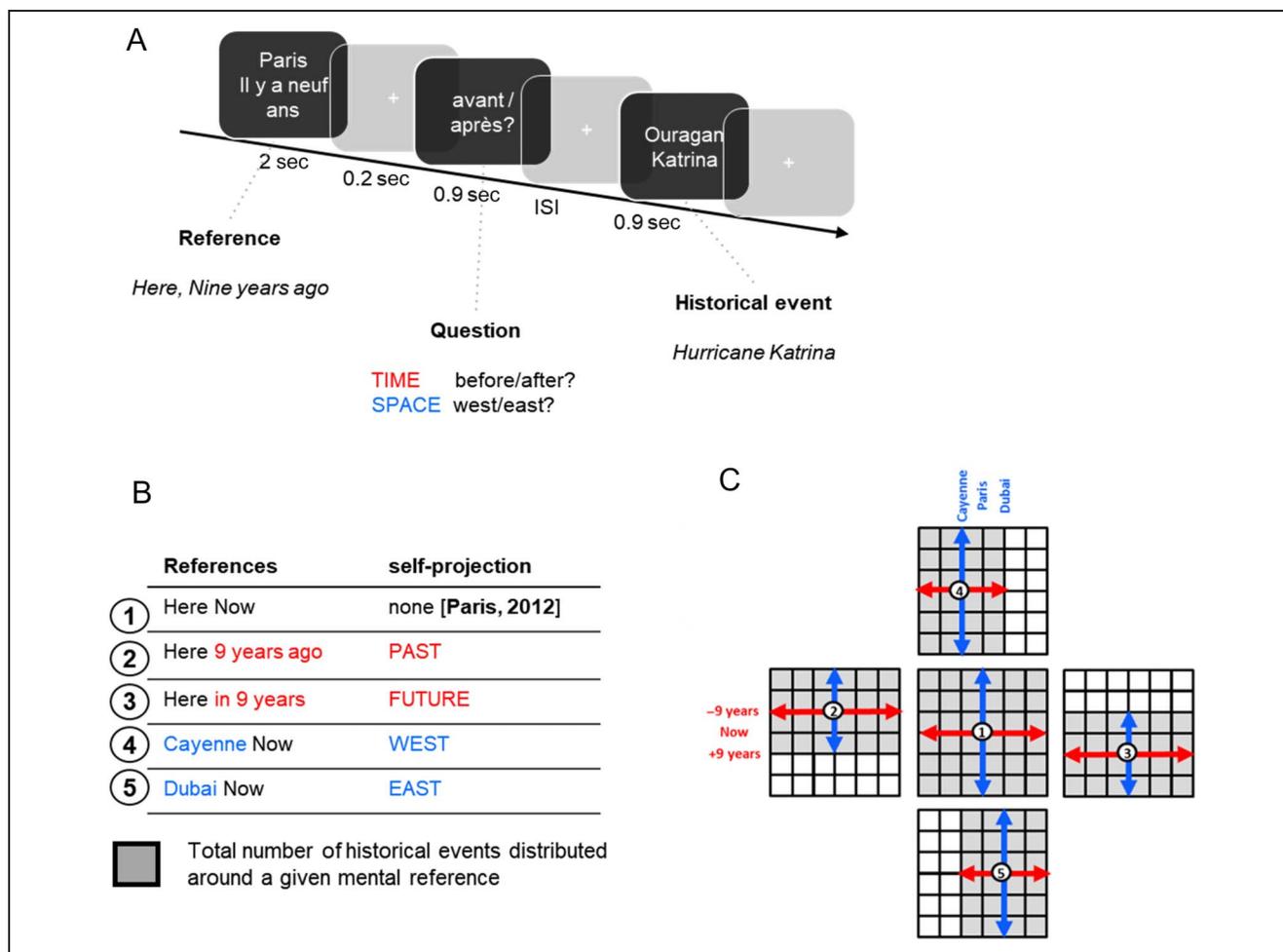
Figure 1. Experimental paradigm. (A) The main task consisted of ordering historical events (for instance, "Hurricane Katrina") as a function of one's mental position or reference (for instance, "Here, Nine years ago"). The ordering had to be made in time (red, "before/after") or in space (blue, "west/east"). The dimension of the ordering was specified by the question so that participants judged whether a historical event occurred before or after (TIME), or east or west (SPACE), of where they were mentally positioned. Each block consisted of one of the five possible references, followed by eight trials (question followed by an event). (B) Five possible references tested two self-projections in time (PAST/FUTURE; red), in space (EAST/WEST; blue) and the control "Here and NOW" (no self-projection; black). (C) Events (gray shading) were evenly distributed around their relative west/east and before/after positions with respect to each possible reference (open circles).

of the reference, question, and event was baseline-corrected to measure incremental changes in the course of the stimuli presentation as a function of the hypothesized sequential mental operations: self-projection, dimension selection, and distance mapping. For baselining the epochs corresponding to the presentation of the reference, the question, and the historical event, we used −0.2 to 0 sec with the "0" corresponding to the onset of the reference, the question, and the historical event presentation, respectively.

MEG-aMRI Coregistration

aMRI provided high-resolution structural images of each individual's brain. The aMRI was recorded using a 3-T Siemens Trio MRI scanner. The parameters of the sequence were as follows: voxel size = 1.0 × 1.0 × 1.1 mm, acquisition time = 466 sec, repetition time =

2300 msec, and echo time = 2.98 msec. The volumetric segmentation of participants' aMRI and the cortical surface reconstruction were performed using FreeSurfer (surfer.nmr.mgh.harvard.edu/). The coregistration of the MEG data with the individual's structural MRI was carried out by realigning the digitized fiducial points with the MRI slices. Using *mne_analyze* within the MNE suite, digitized fiducial points were aligned manually with the multimodal markers on the automatically extracted individual's scalp. To ensure reliable coregistration, we used an iterative refinement procedure to realign all digitized points with the individual's scalp.

MEG Source Reconstruction With Linear Constrained Minimum Variance Beamforming

We used MNE-Python (Gramfort et al., 2014) for source estimations. Here, the ROIs were hippocampal deep

structures. We thus performed source reconstruction using the beamformer technique linear constrained minimum variance (LCMV; Van Veen, Van Drongelen, Yuchtman, & Suzuki, 1997): A mixed source space was generated, which comprised two surface source spaces (left and right hemispheres) and two volume source spaces (left and right hippocampi). In volume source space, the possible neural generators (sources) were placed over the surface and inside the hippocampal volumes. The number of sources across individuals varied from 140 to 200 vertices for the hippocampus and from 10,200 to 10,800 vertices for the cortex. A spherical head model was created using cortical reconstruction generated with Freesurfer. The forward model was computed using the mixed source space and the head model. The orientation of the sources was considered in all three possible directions. The inverse solution was computed with the LCMV beamformer (Pu, Cheyne, Cornwell, & Johnson, 2018; Meyer et al., 2017), and the activity time courses for MTL (including HP, EC, and PHC) were extracted using the *aparc* labels (Destrieux, Fischl, Dale, & Halgren, 2010; Fischl et al., 2004). Note that the *aparc* labels are defined by the Destrieux cortical atlas, which is a parcellation dividing the neocortex into gyral and sulcal regions. The boundaries between these regions are defined by the curvature of the cortical surface.

We based our analysis on the assumption that the sources of neural activity are distributed across the whole cortical and hippocampal volumes. Unlike other distributed inverse methods (standardized low resolution brain electromagnetic tomography [sLORETA] and minimum norm estimate), beamforming techniques (Sekihara, Hild, & Nagarajan, 2006) scan each source independently within each volume. To estimate the source activity in each volume, beamformers minimize the contributions of all the other sources, and they are thus referred to as spatial filters. Beamformers are voxel-wise spatial filters: Each volume is uniformly divided into a number of voxels, which is equal to the number of sources distributed across the volume. Spatial filters belong to two categories, adaptive and nonadaptive. Our study uses an adaptive spatial filter whose parameters rely on the forward solution and on the data. We employed beamforming in the time domain, and the typical method is based on the LCMV approach (Van Veen et al., 1997). The LCMV beamformer estimates the activity of each source (A) at the ith voxel for a given time window by simultaneously filtering out the activities from other voxels and the noise observed in the data covariance matrix (C). The solution for LCMV beamformer can be given as $A_i = (L_i^T C_r L_i)^{-1} L_i^T C_r^{-1}$, where $C_r = C + \alpha I$, α is the regularization parameter, and L is the lead field matrix that contains the forward solution of three orthogonal unit current dipoles placed at the ith voxel. The beamformer
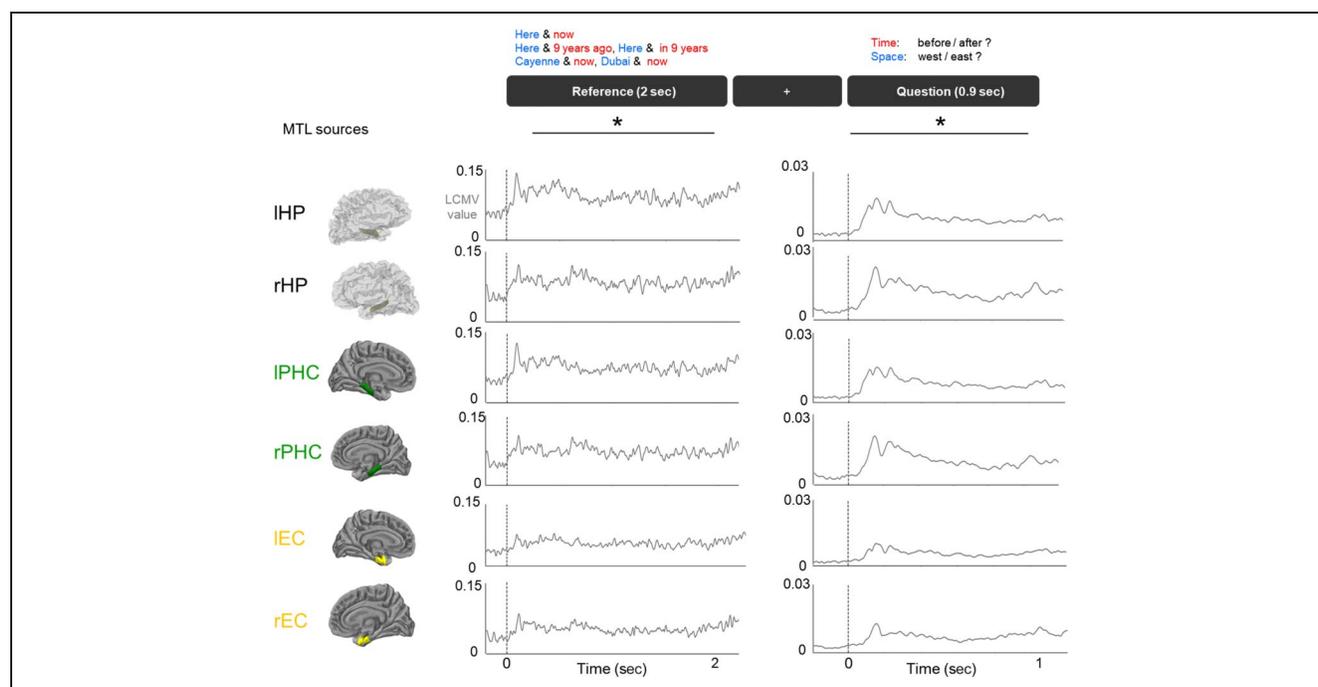
Figure 2. Self-projection in time and in space elicits an undifferentiated activity in MTL. Evoked activity in the three structures of the MTL (HP, PHC, and EC) after the presentation of the reference (left) and of the question (right). A significant increase of evoked activity as compared to baseline (FDR-corrected $p < .05$) was found bilaterally in all three structures. However, comparing hippocampal activity between the different references or between the different questions yielded no significant differences. Thus, early in the task, MTL showed no selective involvement in temporal or spatial self-projection. lHP = left hippocampal volume; rHP = right hippocampal volume; lPHC = left parahippocampal vertices; rPHC = right parahippocampal vertices; lEC = left entorhinal vertices; rEC = right entorhinal vertices.

output was computed for each dipole component of each voxel. The dipole component with maximum amplitude was reported in this study as the magnitude of the source activity.

Statistical Analysis

In all statistical tests, we used a temporal cluster analysis (Maris & Oostenveld, 2007) corrected for multiple comparisons (corrected $p < .05$) with a hat variance adjustment ($\sigma = 10^{-3}$). Most analyses were performed to test for significant activity in MTL (HP, PHC, and EC).

For the reference-locked tests, all epochs after the presentation of a reference were grand-averaged irrespective of the dimension (Time, Space), and the reference-locked evoked responses were contrasted against baseline. A second analysis contrasted all epochs in the Time condition against those in Space. A third analysis used an F test to contrast the three references in each dimension (Time: 9 years ago, now, in 9 years; Space: Cayenne, Paris, Dubai).

Similarly, all epochs after the presentation of the question were contrasted against baseline to test the implication of HP, PHC, and EC in the selection of the task dimension. The direct contrast between Time (before/after) and Space (west/east) was also tested. To directly compare our results with a previous report of medial temporal activity (Gauthier et al., 2019), we performed an ANOVA of the hippocampal source amplitude responses at the latencies of a previously reported cluster (1606–1928 msec).

To test the implication of MTL in the sequential ordering of events in time and space, we binned brain activity evoked by the presentation of a historical event as a function of the distance of the historical event from the mental reference. This was performed for all references. In this analysis, the activity evoked by the presentation of a historical event was realigned to the mental reference corresponding to the egocentric placement in time or in space of the participant and not his or her bodily self-reference ("here and now"). This resulted in eight possible distance bins (values in Time: 27.7, 12.9, 8.3, 3.5, 2.5, 7.94, 13.4, or 21.8 years; values in Space: 124°, 82°, 47°, 10°, 15°, 50°, 76°, or 120°). Figure 3 synthesizes this procedure. The eight distance bins could be defined in two different ways: By preserving the ordinal relations (i.e., past/future and east/west orientation), we could evaluate the signed distance metric between the reference and the historical event; when disregarding the ordinal relation between the reference and the historical event, an absolute distance metric could be explored. The temporal distances were used for Time; and the spatial distances, for Space. On a per-individual basis, we performed a linear regression analysis of the source estimates in each of the three MTL regions (HP, PHC, and EC) yielding time courses of the resulting regression slopes for each participant. The individuals' regression slopes (betas) were then submitted to a temporal cluster analysis combining all 19 participants with a hat variance adjustment

($\sigma = 10^{-3}$). The criteria for significance were a false discovery rate (FDR)-corrected significance threshold using an alpha = 0.05 and 10 msec of consecutive significance with this threshold. To directly compare our results with previous observations in medial temporal activity (Gauthier et al., 2019), we also performed a regression of the hippocampal source amplitude responses at the latencies of the previously reported significant cluster in sensor space (see details in Results when appropriate).

RESULTS

Activity in MTL Shows Undifferentiated Responses to Self-positioning and Dimension Selection in Time and Space

First, we assessed whether the presentation of the reference elicited activity in MTL. For this, we combined all epochs after the presentation of the reference and contrasted the evoked activity elicited by the presentation of the reference to baseline. We found a significant bilateral activity ($p < .05$) in PHC, HP, and EC from 300 to 2000 msec (Figure 2, left). Contrasting the self-projection in Time with the self-projection in Space yielded no significant differences, nor did an F test contrasting each reference within each dimension. Hence, this analysis indicated that, while MTL was activated after the presentation of the reference, we could not find robust selectivity of hippocampal responses to the dimension or to the location of the reference within each dimension.

The lack of specificity in the activity evoked by a temporal reference was surprising considering the previous observation that sources in PHC showed a late ranked evoked response as a function of self-projection in time (past, present, future: ~1606–1928 msec [Gauthier et al., 2019]). Using this a priori knowledge, we conducted a one-way ANOVA for each hippocampal source estimate (HP, PHC, EC) as a function of self-projection in time. We found no significant differences in the magnitude of response between self-projection in past, present, and future. However, the activity in right HP evoked by the presentation of the past reference "9 years ago" significantly occurred much earlier (0.3–1.1 sec; $p < .01$) than the one elicited by the presentation of the future reference "in 9 years" (1–2 sec; $p < .01$). This pattern in source estimates may have contributed to the graded pattern previously reported at the scalp level. No significant activity was otherwise observed in EC or in PHC. The reliability of the source-reconstructed data fully depends on the reconstruction algorithm and the inclusion of various cortical structures. In earlier findings (Gauthier et al., 2019), we discussed the likelihood that MTL may be one possible generator of the effects reported at the scalp level. With this new analysis, we report no robust evidence of reference selectivity in the MTL during the process of self-projection in time or in space. This suggests that the middle pFCs, bilaterally, and the left supramarginal
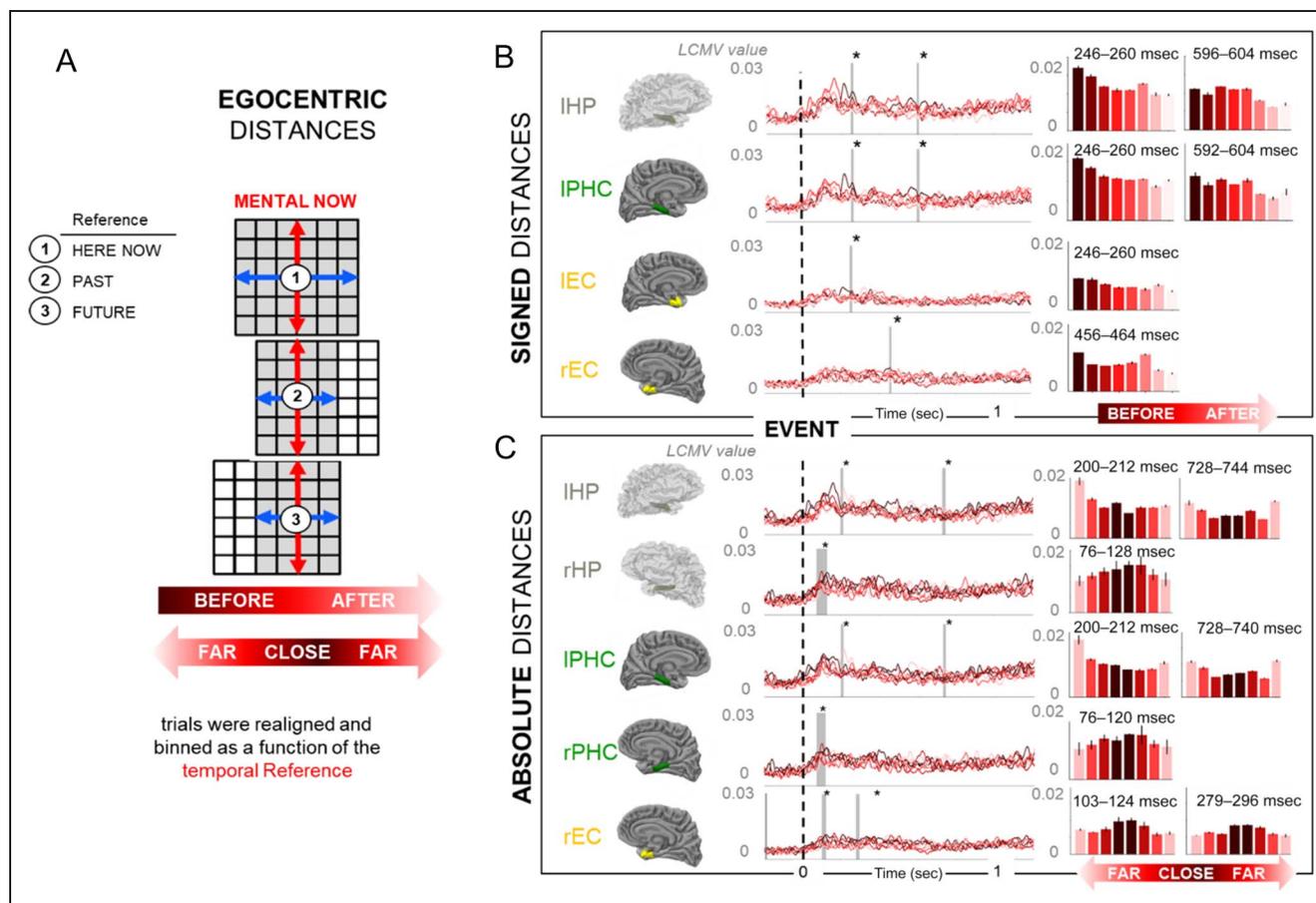
Figure 3. MTL contribution to symbolic distances in mental time travel. (A) Trials were sorted as a function of the signed (before/after) and absolute (close/far) distances of the events with respect to the required mental self-positioning in time (red). The logic for this analysis was to capture brain activity sorted as a function of the self-projection with the a priori assumption that the temporal cognitive mapping of the events was anchored on the mental representation of the self (egocentric mapping). In (B) and (C), the slope values of each participant's outcome of the linear regression over the signed (B) and absolute (C) temporal distances for each MTL structure were submitted to a population-level temporal clustering. The criteria for significance were as follows: FDR-corrected $p < .05$ and 10 msec of consecutive significance (gray highlights). (B) The amplitudes of hippocampal source estimates elicited by the presentation of a historical event were sorted as a function of signed temporal distance (ordinality). Overall, source estimates in MTL decreased monotonically with signed distances, so that the largest amplitudes were elicited by the most distant past events from self, and the smallest amplitudes were elicited by the most distant future events. The histograms illustrate the source amplitude of the effects along with their latencies. (C) The amplitudes of hippocampal source estimates elicited by the presentation of a historical event were sorted as a function of absolute temporal distances. We found significant monotonic changes of source amplitudes with distance irrespective of whether events happened in the past or in the future of the participant's mental self-position. All right hemispheric structures (HP, EC, PHC) showed a decrease with egocentric distance, whereas the left HP and PHC showed an increase with egocentric distance. Histograms illustrate the amplitude of the effects and latencies. lHP = left hippocampal volume; rHP = right hippocampal volume; lPHC = left parahippocampal vertices; rPHC = right parahippocampal vertices; lEC = left entorhinal vertices; rEC = right entorhinal vertices.

gyrus, which were part of the activated sources after the presentation of a temporal reference, remain the likeliest major contributors for self-projection in time (Figure 3D in Gauthier et al., 2019).

After the presentation of the reference, the presentation of the question "before/after?" or "west/east?" specified the mental dimension in which the participant had to perform their ordinality judgment. As previously stated, we tested whether the presentation of the question elicited activity in MTL. In all cases, bilateral PHC, HP, and EC showed significant activity compared to baseline ($p < .05$) from 0 to 1100 msec (Figure 2, right). However, the presentation of the temporal or spatial question did not evoke significantly different responses. We found no

significant differences applying an F test contrasting the response evoked by the question as a function of the previous reference (past, present, and future in Time; west, here, and east in Space).

Collectively, this analysis suggested that the MTL was activated by the presentation of the question, with no clear differential responses as a function of the dimension of the question or of the self-position within each dimension.

In previous work, we reported significant differences between the three spatial positions over the cingulate and dorsolateral pFCs from 673 to 809 msec (Figure 3B and 3D in Gauthier et al., 2019). Using this a priori knowledge, we used a one-way ANOVA on the averaged activity over this time window for each participant to explore possible

differences between the conditions (WEST, HERE, and EAST) in each MTL area: No significant effects were found with this a priori time window in HP, PHC, or EC. This is consistent with previous source estimations of the effects observed at the scalp level that were involving cortical regions far from the MTL, namely, the cingulate and pFCs.

Hippocampal Activity Contributes to the Allocentric Mapping of Ordinal Sequences in Time and in Space

We then assessed our main experimental question, namely, does MTL show a selective response during the mental ordering of events as a function of self-positioning? To address this question, we realigned the trials as a function of their temporal (Figure 3) or spatial (Figure 4) distance to the mental self-positioning across all possible references. Using this data sorting, we generated two sets of trials. One set of trials was sorted as a function of the signed distances, which preserved the before/after and east/west directions in time and space, respectively. The second set of trials was sorted as a function of the absolute distances, which neglected the direction and solely preserved the close/far relation of the events with respect to the mental positioning of the self in time or in space.

This approach followed the experimental design illustrated in Figure 3A and Figure 4A. This realignment is crucial to identify effects that are solely dependent on
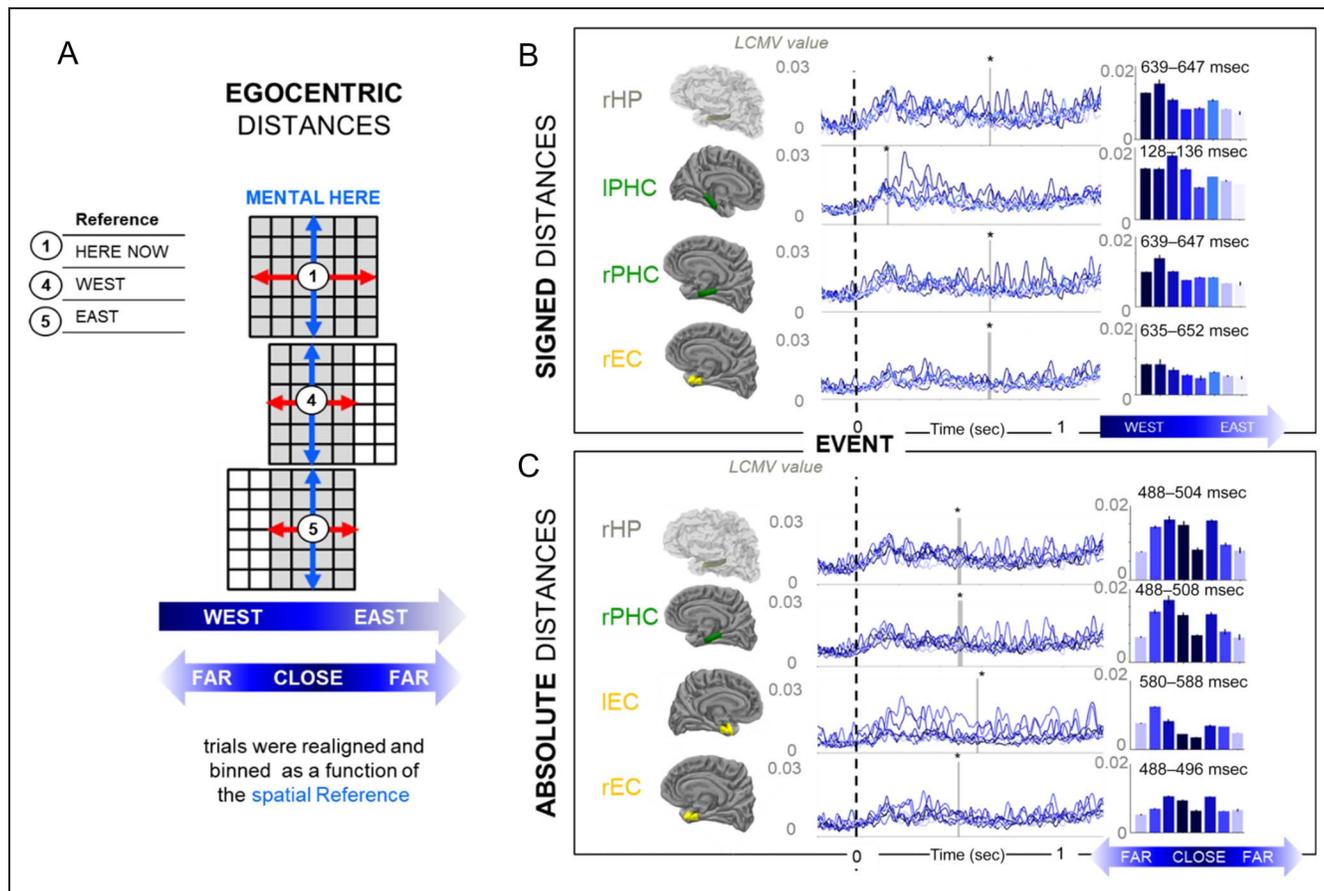
Figure 4. MTL contribution to symbolic distance effects in mental spatial navigation. (A) Trials were sorted as a function of the signed (west/east) and absolute (close/far) distances of the events with respect to the mental self-positioning in space (blue). The logic of this analysis was to capture brain activity sorted as a function of the self-projection with the a priori assumption that the spatial cognitive mapping of the events was anchored on the mental representation of the self (egocentric mapping). In (B) and (C), the slope values of each participant's outcome of the linear regression over the signed (B) or absolute (C) spatial distances for each MTL structure were submitted to a population-level temporal clustering. The criteria for significance were FDR-corrected $p < .05$ and 10 msec of consecutive significance (gray highlights). (B) The amplitudes of hippocampal source estimates elicited by the presentation of a historical event were sorted as a function of the signed spatial distances. Overall, source estimates in MTL decreased monotonically with signed distances, so that the largest amplitudes were elicited by the most distant past events, and the smallest amplitudes were elicited by the most distant future events. Histograms illustrate the amplitude of the effects and their latencies. Overall, the amplitude of source estimates in this structure decreased monotonically with distance, so that the largest amplitudes were found for the most distant events in the west, whereas the smallest amplitudes were found for the most distant events in the east. (C) Grand-averaged source estimation observed in MTL showing selective responses to absolute temporal ordinality. The amplitude of source estimates in this structure changed monotonically with distance irrespective of it being in the west or east of the participants' mental position. The right hemispheric structures (HP, EC, PHC) showed a decrease with egocentric distance, whereas the left EC tended to show an increase in amplitude with egocentric distance. Histograms illustrate the amplitude of the effects and report latencies. lHP = left hippocampal volume; rHP = right hippocampal volume; lPHC = left parahippocampal vertices; rPHC = right parahippocampal vertices; lEC = left entorhinal vertices; rEC = right entorhinal vertices.

Table 1. Summary of the Latency and Laterality of Significant Effects Reported in the Six MTL Structures of Interest

	Left			Right		
	PHC	*HP*	*EC*	*PHC*	*HP*	*EC*
Time			Latency (msec)			
Ordinality						
Early	246–260	246–260	246–260			
Late	592–604	596–604				456–464
Symbolic distance						
Early	200–212	200–212		76–120	76–128	103–124 279–296
Late	728–740	728–744				
Space						
Ordinality						
Early	128–136					
Late				639–647	639–647	635–652
Symbolic distance						
Early						
Late			580–588	488–508	488–504	488–496

The latencies of the effects observed for temporal ordinality and symbolic temporal distances are reported under the "Time" label. The latencies of the effects observed for spatial ordinality and symbolic spatial distances are reported under the "Space" label. We separated the early (< 300 msec) and late (> 300 msec) latencies for clarity. This dichotomy is based on hippocampal single-neuron response latencies (Quian Quiroga, 2019). This highlights the right lateralization and late latencies observed for all spatial effects as compared to the left lateralization and early latencies observed for temporal effects. The left lateralization of temporal ordinality effects is particularly salient.

the "now" specified by the reference and not on the actual date of the reference: For instance, events that happened in the future when the reference was "9 years ago" could also be past events when the reference was "in 9 years." In short, we estimated brain activity with reference to the "imagined mental now." On a per-individual basis, we separately performed a linear regression of the MTL activity, binned as a function of signed or absolute distances (eight bins for each set), with the corresponding distance values. The resulting regression provided beta time courses for each participant's hippocampal structures, which we submitted to a group-level temporal cluster permutation test corrected for multiple comparisons.

The regression over the signed temporal distances showed a significant decrease of the source estimate amplitudes from the distant past to the distant future ($p <$ .05; Figure 3B and Table 1) in the left HC (246–260 msec), in the left PHC (596–604 msec), and bilaterally in the EC (left EC: 246–260 msec; right EC: 456–464 msec). The same regression analysis for absolute distances (Figure 3C and Table 1) showed hemispheric differences of the evoked source amplitudes: A significant increase of the source amplitude estimates with absolute distance was found in the left HP (200–212 and 728–744 msec), whereas a significant decrease with absolute distance

was observed in the right HP (76–128 msec) and bilaterally in the PHC (left: 728–744 msec; right: 76–120 msec). The right EC showed a decreased source amplitude with increasing distance from mental self (103–124 and 279–296 msec).

We then carried out the same analysis on event-locked data for the spatial dimension and for the signed and absolute distances, separately (Figure 4 and Table 1). We found a significant decrease in the estimated source amplitudes with signed distance in the right HP (639–647 msec), bilaterally in the PHC (left: 128–136 msec; right: 639–647 msec), and in the right EC (635–652 msec). For the absolute distances, the overall pattern was consistent across structures with a decrease of the response amplitude with distance from the mental self position in the right HC and the right PHC (488–504 msec) and bilaterally in the EC (left: 580–588 msec; right: 488–496 msec): The most absolute distance effects in space were thus right lateralized.

DISCUSSION

In this study, we tested the contributions of MTL to the different mental operations required in a mental time (and space) travel task by integrating their volumetric

reconstitutions in the MEG source model of previously acquired data (Gauthier et al., 2019). We found a significant involvement of hippocampal, entorhinal, and parahippocampal structures for each mental operation entailed in the task. Self-projection in time and space and the dimension selection of the task elicited significant but nonselective activity in MTL, suggesting that these structures may contribute to a larger distributed network. Conversely, the order (signed distances) and absolute distances of events, with respect to the mental self, elicited distinct graded cortical responses in both time and space. We discuss the possible role of the MTL in the egocentric and allocentric cognitive mapping of time in the human brain.

MTL Activity May Contribute to the Representation of Mental Timelines

Hippocampus plays a fundamental role in the online temporal structuration of memories (Clewett et al., 2019; Clewett & Davachi, 2017; Ranganath & Hsieh, 2016; Davachi & DuBrow, 2015) including episodic time seen as the memory of experienced serial order (Buhusi, 2019; Tsao et al., 2018; Heusser, Poeppel, Ezzyat, & Davachi, 2016) and, more generally, the recall of temporal sequences (Lehn et al., 2009). In a recent set of studies (Gauthier et al., 2019; Gauthier & van Wassenhove, 2016a, 2016b) and in previous work (Arzy, Adi-Japha, et al., 2009; Arzy, Collette, et al., 2009), participants were asked to establish, endogenously, the order of events from a different mental anchor (i.e., the required reference). In other words, the generation of the chronology of events was a task requirement, not an episodic component in memory. Under such constraints, much less is known regarding the structuration of temporal representations of events, which were not contiguous or had not been associated to a common temporal context. In this new analysis, we found that the retrieval of nonepisodic events, contextualized by the mental position on a timeline, evoked systematic responses of the MTL. Our results provide further support for the involvement of the MTL in the mental representation of time for nonepisodic events.

The primary expected signature of mental timelines is ordinality, that is, the ranking of brain activity according to a specific endogenous temporal order. Here, we found evidence for a neural representation of temporal ordinality (signed distances) in the hippocampus using a source reconstruction approach dedicated to model deep neural structures of the MTL (HC, PHC, EC). Specifically, the signature of ordinality in these structures was a mainly left-lateralized and transient ranked decrease of source amplitudes from past to future. This pattern was observed irrespective of the mental reference and was thus independent of the contextualization induced by self-projection (Gauthier et al., 2019). Relatedly, functional hippocampal gradients have been discovered in humans based on rodents' studies. These anteroposterior

gradients manifest larger to finer spatial scaling with increasing coding complexity as well as preferred spatial scales that possibly underlie more conceptual coding (Brunec et al., 2018). The anatomical resolution of MEG recordings in this study could not dissociate a spatial gradient from a graded activity, and it is thus an open question whether the graded amplitude directly relates to spatial gradients observed in fMRI studies. Future studies specifically calibrated to this question may be able to entertain this possibility.

Our novel findings fuel evidence to the notion of an allocentric representation of time in the hippocampus, that is, a "chronocentric" timeline that would provide the cognitive scaffold for the ordering of events. Because of our experience of time being entrenched in the present, we take as granted that cognitive representations of time may be anchored in a present viewpoint or relived through vivid memories so that only egocentric representations of time may make sense. As such, very few references to the possibility of coexistent egocentric and allocentric representations of time have been expressed in the literature. Yet, we are able to attribute ordinal relations between fictitious or imaginary events as well as generate a chronology of events we may not have actually experienced in the past. This capacity, whether phenomenological through imagination or articulated in more intelligible forms (storytelling, novels, movies, etc.), is a critical feature of being human (Suddendorf et al., 2009; Suddendorf & Corballis, 2007).

The role of the MTL structures remains to be specified. One possibility is that timelines are related to the hippocampal preplay of temporal sequences corresponding to potential future event sequence encounters (Eichenbaum, 2015; Silva, Feng, & Foster, 2015; Dragoi & Tonegawa, 2011). This computational affordance could be, when under top–down control, used to endogenously map imagined sequence of events, whether past or future. Consistent with this, recent evidence shows that EC is supporting the representation of the succession of events (Bellmund, Deuker, & Doeller, 2019) for episodic memory. Our results suggests that the hippocampus and other medial temporal structures like EC may be involved in a system dedicated to the generation of temporal sequences (Buzsáki & Tingley, 2018) contributing to the explicit oriented representation to the future—the colloquial "arrow of time" metaphor—which may be under top–down control in humans.

MTL and Spatial Ordinality

In support of this working hypothesis, we found activity in the same structures when participants were involved in the spatial ordering of events along an arbitrary cardinal west–east axis. The finding that hippocampal activity is implicated in the mental ordering of spatial events is largely consistent with human neuroimaging literature: Cardinal directional coding has been reported not only

in EC and PHC with grid cell-like representations in humans (Bellmund, Deuker, Schröder, & Doeller, 2016; Doeller, Barry, & Burgess, 2010) but also in the hippocampus presubiculum (Chadwick, Jolly, Amos, Hassabis, & Spiers, 2015; Vass & Epstein, 2013). This finding is also consistent with prominent models of spatial memory processing attributing the representation of allocentric space to MTL (Burgess, 2006; Burgess, Becker, King, & O'Keefe, 2001). Although seminal models of allocentric representation of space were developed in the context of spatial navigation, here, we found hippocampal activity indexing allocentric spatial representations for cognitive, high-level representations of events in mental space without any acquisition through active navigation. This is consistent with the idea of truly "geocentric" maps (Tolman, 1948), which were used here for purely mental navigation rather than real spatial exploration.

When comparing the results related to the temporal and spatial ordinality tasks, we found that the evoked responses to cardinal directions mostly occurred in the right MTL, whereas temporal order mostly implicated the left MTL. This finding appears consistent with previous studies of MTL lesions associating spatial processing to the right side (Abrahams, Pickering, Polkey, & Morris, 1997) and semantic and verbal processing to the left side (Ojemann & Dodrill, 1985). Recent direct functional evidence using a large intracranial data set (Miller et al., 2018) suggested that low theta activity is associated to the right hippocampus for spatial navigation but to the left hippocampus for associative memory. Such functional lateralization has also been found in EC: Whereas spatial memory in humans is associated to the right EC (Bellgowan, Buffalo, Bodurka, & Martin, 2009), nonspatial memory is reported for the left EC (Tsao, Moser, & Moser, 2013). A dichotomy between sequential (egocentric) and allocentric spatial representations in the left and right hippocampi, respectively, has also been suggested (Iglói, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010).

Overall, our finding of distinct lateralization profiles for cardinal direction (i.e., allocentric spatial representations) and temporal ordinality (i.e., allocentric temporal representations) appears consistent with previous reports in the domains of spatial navigation and episodic memory, respectively. This further suggests that the functional specialization of MTL structures for these processes may be recycled for the manipulation of allocentric representations involved in our experiment.

MTL and Symbolic Distances

The MTL has been systematically associated with the representation of spatial (Gauthier et al., 2019; Deuker, Bellmund, Schröder, & Doeller, 2016a; Nielson et al., 2015) and temporal (Deuker et al., 2016a; Nielson et al., 2015; Addis & Schacter, 2008) distances. As temporal and spatial distances were calculated with respect to the mental reference, the absolute distances can be

considered egocentric distances. Here, we found that the effects of absolute temporal and spatial egocentric distances occurred at similar latencies with no strong lateralization pattern. The specific involvement of hippocampus for egocentric distances has been sparsely reported in the literature. In virtual navigation, both Euclidean egocentric distance and path distances to a goal are found in the hippocampus, whereas Euclidean distance alone is associated with EC (Howard et al., 2014; Viard, Doeller, Hartley, Bird, & Burgess, 2011). Yet, in the available literature on the representation of nonepisodic or imagined events, there is little evidence favoring hippocampal coding of egocentric distances defined as self-referenced.

One interesting avenue for understanding the coding of egocentric distance resides in the study of the spatial scaling and its neural substrates. EC contains many different types of neurons, among which are the grid cells that tessellate space into regular hexagonal grids and display interesting properties like spatial scaling or realignment. Those cells are the main inputs to hippocampal place cells after a similar spatial gradient (Brun et al., 2008). This complex may support the representation of distance for distinct spatial scales of abstract representations. A recent study demonstrates a specific hippocampal tuning for the spatial scales of cities as compared to smaller scales (rooms) and larger scales (continents; Peer, Ron, Monsa, & Arzy, 2019). This study suggests that our spatial task may be impacted by such preexisting spatial tuning and that other cortical regions may be preferentially tuned for the spatial scale of the world map used in this study and previous ones. Future human studies could be conducted to decipher the role of hippocampus for coding egocentric distances in abstract representations of space and time.

The study of egocentric distance has also a long story in experimental psychology. Seminal behavioral investigations of the "distance effects" on map-like spatial representations (Tversky, 1992; Holyoak & Mah, 1982) showed that familiarity somehow distorts the endogenous representations of spatial distances: Using a familiar reference point reduces the perceived distance to other points in space. As familiarity may bias hippocampal activity during memory retrieval, we selected inhabitants of the Parisian region who did not live anywhere else so as to avoid as much as possible the biases because of a priori spatial referencing. It is thus unlikely that the present results would not relate to specific effects of active self-projection and mental referencing.

MTL and Self-projection

Although there is a consensus on the role of MTL for the mental mapping of time and space, less is known regarding its possible role in the representation of self. The activation of the hippocampus has been linked to the recollection and subjective experience of episodic memory, thus to self-consciousness (Schacter, Alpert, Savage, Rauch, & Albert, 1996; Tulving, 1985). Some hippocampal cells

can dissociate self from others in rats (Danjo, Toyoizumi, & Fujisawa, 2018) and in bats (Omer, Maimon, Las, & Ulanovsky, 2018), suggesting the implication of hippocampus for the processing of self-related information. Here, we found involvement of the MTL in self-projection; however, it was not specific for the reference or the dimension of self-projection, as previously observed (Gauthier et al., 2019). The involvement of the MTL during self-projection is nevertheless consistent with human lesion studies showing a specific impairment for self-projection (Kurczek et al., 2015) as well as with a previous intracranial study (Schurr et al., 2018).

The precise function of MTL in self-projection remains to be understood. Recent investigations have shown that the parahippocampus is a defining region of a default-mode subnetwork or network, raising the possibility that MTL could be a hub of the core network of self-projection (Braga, Van Dijk, Polimeni, Eldaief, & Buckner, 2019; Buckner & DiNicola, 2019), consistent with previous reports employing memory tasks (Schedlbauer et al., 2014; Watrous, Tandon, Conner, Pieters, & Ekstrom, 2013). One possibility, which we entertain here, is that the hippocampus is under top–down cortical influence to provide allocentric representations of time and space as a scaffold for the explicit representation of mental events. The medial pFC is strongly connected to MTL at rest, is activated during self-projection, and could thus be a good candidate region to influence the hippocampus during self-projection (Gauthier et al., 2019; Nyberg, Kim, Habib, Levine, & Tulving, 2010; Botzung et al., 2008; Okuda et al., 2003).

In short, although hippocampal activity may be required for self-projection, the representation of alternative locations in time or space may likely depend on neocortical processing. In line with the hypothesis of allocentric timelines in the hippocampus, the elicitation of alternative timelines during self-projection may require the maintenance of the succession of events in time in the hippocampus, whereas neocortical regions may represent alternative self-locations in time. Previous fMRI investigations have emphasized the importance of a widespread parieto-frontal network for self-projection in time, generally involved in the representation of self and involving the medial pFC (Gauthier & van Wassenhove, 2016b; Nyberg et al., 2010; Botzung et al., 2008; Okuda et al., 2003) and regions surrounding the TPJ (Gauthier & van Wassenhove, 2016b; Viard, Chételat, et al., 2011; Arzy, Collette, et al., 2009). Consistent with this, some of these regions have recently been hypothesized to be pivotal for the emergence of a narrative self from cognitive maps (Arzy & Schacter, 2019).

Limitations of Our Approach

Although MEG provides a tremendous gain in temporal resolution as compared to fMRI, the fine-grained source reconstruction remains limited. One cautionary note for the findings reported herein is the use of several neighboring regions to show the possible anatomical segregation of the effects. On the other hand, we contend that the lack of hippocampal activity previously reported with fMRI studies may stem from the coarse BOLD dynamics, preventing to see transient dynamics that seem to govern the chronology of events. Future work using intracranial recordings or combining different neuroimaging techniques will be needed to better understand the dynamics of well-specified brain regions in such complex tasks.

A second limitation, discussed earlier, concerns the origin of graded source amplitudes we report here. Graded activity can arise from cytoarchitectonic spatial gradients (Strange, Witter, Lein, & Moser, 2014), which support functional gradients along the anteroposterior axis of hippocampus (Peer et al., 2019; Brunec et al., 2018). As preferred spatiotemporal scales have been reported, our reconstruction may merge spatially close but disparate signals after such gradient. Recent work has shown that such gradients are relevant for self-related processing of abstract representations in spatial navigation and in episodic memory (Plachti et al., 2019), which may well be involved in our task as well. Critically, this possibility remains compatible with our claim of MTL involvement while changing the physiological interpretation of graded activity as spatial gradients. Biophysical modeling work would be needed to properly solve this potential functional ambiguity.

Conclusions

Using a volumetric reconstruction of the hippocampus with MEG, we confirmed the likely involvement of the MTL in the representation and maintenance of allocentric mental timelines. The MTL showed selective patterns of activity as a function of the cardinal direction and temporal ordering as well as egocentric distances in mental time and space. Crucially, these patterns were found for nonepisodic events, that is, never experienced but learned and imagined events. Overall, these results are compatible with the idea that the temporal and spatial relations of events to the self can be found in MTL activity.

Acknowledgments

Reprint requests should be sent to Virginie van Wassenhove, CEA/DRF NeuroSpin - INSERM Cognitive Neuroimaging Unit, Bât 145 PC 156, Gif s/Yvette F-91191, France, or via e-mail: virginie.van.wassenhove@gmail.com.

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