Neuropsychologia 64 (2014) 1–12

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

The human hippocampus is sensitive to the durations of events and intervals within a sequence

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ARTICLE INFO

Article history:
Received 14 July 2014
Received in revised form
15 August 2014
Accepted 4 September 2014
Available online 16 September 2014

Keywords:
Episodic memory
Hippocampus
Temporal memory
Functional magnetic resonance imaging
Medial temporal lobe

ABSTRACT

Temporal details are an important facet of our memories for events. Consistent with this, it has been demonstrated that the hippocampus, a key structure in learning and memory, is sensitive to the temporal aspects of event sequences, including temporal order, context, recency and distance. One unexplored issue is whether the hippocampus also responds to the temporal duration characteristics of an event sequence, for example, how long each event lasted for or how much time elapsed between events. To address this, we used a temporal match–mismatch detection paradigm across two functional neuroimaging studies to explore whether the human hippocampus is sensitive to the durations of events and intervals that comprise a sequence lasting on the order of seconds. On each trial participants were shown a series of four scenes during an encoding and a test phase, and had to determine whether the durations of the intervals or events were altered. We observed hippocampal sensitivity to temporal durations within event sequences. Activity was significantly greater when participants detected repeating, in comparison to novel, durations. Moreover, greater functional connectivity was observed between hippocampus and brain regions previously implicated in second and millisecond timing when durations were novel, suggesting that the hippocampus may receive duration information from these areas for use within a mnemonic context rather than generate an independent timing signal. Our novel findings suggest that the hippocampus may integrate temporal duration information when binding event sequences.

1. Introduction

The hippocampus is believed to process sequences of events in support of episodic memory (Eichenbaum, 2000). Since event sequences play out over time and are, therefore, rich with temporal information, one important question is whether the hippocampus integrates this information, for example, when binding events to form episodes. To support this possibility, increasing evidence indicates that the hippocampus is sensitive to the temporal order, context, recency and distance of events within a sequence (Charles, Gaffan, & Buckley, 2004; Ezzyat & Davachi, 2014; Fortin, Agster, & Eichenbaum, 2002; Hsieh, Gruber, Jenkins, & Ranganath, 2014; Mankin et al., 2012; Naya & Suzuki, 2011). Notably, one form of temporal information that has not, to our knowledge, been explored in the context of event sequences is temporal duration. It is conceivable that the hippocampus incorporates temporal duration when binding a sequence of events and that this information can help us remember how much time elapsed during an event or an interval between two successive events.

Recent suggestions that the hippocampus may be sensitive to duration information within event sequences come from observations that rodent CA1 neurons fire in a temporally ordered manner, on the order of seconds, throughout an interval between two events (MacDonald, Lepage, Eden, & Eichenbaum, 2011; Pastalkova, Itskov, Amarasingham, & Buzsaki, 2008). This activity can distinguish separate mnemonic sequences (Gill, Mizumori, & Smith, 2011) and is distinct from hippocampal contributions to spatial cognition (Kraus, Robinson, White, Eichenbaum, & Hasselmo, 2013; MacDonald, Carrow, Place, & Eichenbaum, 2013). Critically, it is unknown how these findings apply to humans. Human studies examining duration have focused primarily on the discrimination or estimation of a single time period in association with rudimentary auditory/visual stimuli that are not typically associated with hippocampal involvement (Wittmann, 2013). This work is inconclusive as to whether the human hippocampus is sensitive to durations of a few seconds. Many studies have not implicated the hippocampus in processing very short durations (Bueti, Lasaponara, Cercignani, & Macaluso, 2012; Coull, Nazarian, & Vidal, 2008; Noulhiane, Pouthas, Hasboun, Baulac, & Samson, 2007; Richards, 1973; Shaw & Aggleton, 1994)

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http://dx.doi.org/10.1016/j.neuropsychologia.2014.09.011
0028-3932/

(see, however, Harrington et al., 2004). Rather, other areas are believed to underpin second and millisecond timing, including the caudate, supramarginal gyrus, insula, supplementary motor area, and cerebellum (Lewis & Miall, 2003; Merchant, Harrington, & Meck, 2013). Even where human hippocampal damage has been associated with impaired sub-minute interval judgment (Perbal, Ehrle, Samson, Baulac, & Pouthas, 2001), the diffuse nature of the lesion has precluded the assessment of the specific contributions of this structure. Importantly, if the hippocampus is indeed sensitive to duration information within event sequences, a key question is whether this structure is functionally connected to other brain regions that support duration timing. These regions may provide timing information to the hippocampus for use within a mnemonic context or alternatively, hippocampal neurons may generate a separate timing signal.

To address these questions, we used functional magnetic resonance imaging (fMRI) in Experiment 1 to examine whether the human hippocampus is sensitive to interval durations within an event sequence lasting seconds. Experiment 2 then compared hippocampal sensitivity to interval durations with that to event durations, replicating and extending Experiment 1. Further, functional connectivity between the hippocampus and timing regions at the whole brain level was investigated.

2. Materials and methods

2.1. Participants

Twenty-two young adults (mean=23.55 years old, SD=4.73; 11 female) participated in Experiment 1, whereas 25 individuals were recruited to participate in Experiment 2. Data from 5 subjects were not used in Experiment 2 due to poor performance (2 subjects performed at chance on at least one condition) or scanner malfunction (functional data failed to acquire for 3 subjects), leading to a final group of 20 participants (mean=22.25 years old, SD=2.55; 8 female). All participants were right-handed and English speaking with normal or corrected vision. There was no history of neurological or psychiatric disorders, and all participants received monetary compensation for their time. Written informed consent was obtained from all subjects prior to participation, in line with the research ethics boards of the University of Toronto (approval #27455), and the Centre for Addiction and Mental Health (CAMH) (approval #096/2012).

2.2. Behavioural procedure

In both Experiments 1 and 2 (Fig. 1), participants were instructed to complete a match–mismatch detection task in which they were asked on each trial to determine whether a change had occurred between an initial sequence of 4 scene images (encoding phase) and an immediately ensuing sequence of 4 scenes (test phase). Spatial scenes were chosen as the stimulus category due to the well established involvement of the hippocampus in spatial cognition (O'Keefe & Nadel, 1978). All images were grayscale, 350×350 pixels in dimension, and presented serially in the centre of a screen of 1280×768 resolution. To ensure that participants understood the task, in each experiment a short practice task was administered prior to scanning, which used different stimuli. During scanning, the subjects performed three runs of the task, each 48 trials in length, divided into four blocks of 12 trials. The run order was counterbalanced across all participants within each experiment. The experimental tasks were programmed in E-Prime (Psychology Software Tools Inc., Sharpsburg, PA) and stimuli were presented to participants using a projector via a mirror placed in front of the subject. Responses were collected using two pre-specified buttons on a button box held in the right hand.

2.2.1. Experiment 1 details

On each trial, participants were instructed to monitor the initial (study) and subsequent (test) presentation of an image sequence to determine if a change had occurred. To determine match status, participants were instructed to remember either the durations of the inter-stimulus intervals (ISIs) (interval duration) or the order of the scene images (event sequence). The latter is suggested to recruit the hippocampus (Fortin et al., 2002; Kesner, Gilbert, & Barua, 2002; Tubridy & Davachi, 2011) and was primarily included as a sanity check due to limited existing evidence for hippocampal sensitivity to duration information within sequences. This led to four different trial types: (1) Event Sequence Match (ESM); (2) Event Sequence Mismatch (ESM-M); (3) Interval Duration Match (IDM); and (4) Interval Duration Mismatch (IDM-M). As an initial pilot study in 16 subjects revealed that detecting sequence order changes was substantially easier than detecting interval duration changes within an event-related design due to the saliency of order information (ESM-M mean accuracy=83.6%, SD=13.8%; IDM-M mean accuracy=50.35%, SD=21.2%; $t(15)=7.00$, $p<0.0001$), ES and ID trials were presented in blocks of 12, with a total of 36 trials per condition. Participants were alerted to what type of information they were to monitor by a cue slide (500 ms) prior to the start of each block and there was a reminder at the top of the screen throughout. Each trial consisted of a study phase, a test phase, and a response screen. The study phase consisted of four scene images presented sequentially for 700 ms each. These scenes were separated by 3 blank ISIs that were jittered around mean durations of 500 ms, 1000 ms, and 2000 ms (all SD 80 ms), with the order of these ISIs pseudo-randomized across trials. Following presentation of a 3500 ms fixation cross, the same four scene images were presented during the test phase of each trial. In ES blocks, ISI durations were kept constant, whereas the order of the pictures was either preserved (ESM) or manipulated completely (ESM-M). In ID blocks image order was unchanged, whereas ISIs were kept constant (IDM) or rearranged completely (IDM-M). Participants were not made aware that the event sequence and interval durations were changed completely in ESM-M and IDM-M trials and were instructed to base their match/mismatch decision on the entire sequence. To encourage this, the participants were asked to indicate their response after the test phase during a 2500 ms response screen with the question "Change (1) or No change (2)?". Moreover, due to the saliency of event order and to increase the difficulty of monitoring this information type, 3 ESM-M trials were included per run in which the first image was constant across study and test, and the remainder of the images were reordered.

There was a jittered inter-trial interval of 3500 ms (SD 500 ms) and the average trial duration was 18.6 s (block length=4.27 min; run length=17.1 min). All scene images and ISI values were trial unique. It is important to note that spatial information was controlled for across all trials, allowing us to isolate the contribution of the hippocampus to temporal order or duration memory.

2.2.2. Experiment 2 details

Prior to each block of trials, the participants were instructed to monitor either the durations of the scene images (event duration) or the durations of the ISIs (interval duration) resulting in four different trial types: (1) Event Duration Match (EDM); (2) Event Duration Mismatch (EDM-M); (3) Interval Duration Match (IDM); and (4) Interval Duration Mismatch (IDM-M). The number of trials per trial type and the structure of each trial were identical to Experiment 1 with a few exceptions. The study phase of each trial consisted of four scene images presented sequentially for 100 ms (SD 40 ms), 500 ms (SD 80 ms), 1000 ms (SD 80 ms) and 2000 ms (SD 80 ms). Each scene was followed by a blank interstimulus interval (ISI) of 100 ms (SD 40 ms), 500 ms (SD 80 ms), 1000 ms (SD 80 ms) or 2000 ms (SD 80 ms) and the order of all duration lengths was pseudo-randomized across trials. In the test phase of ED trials, the order of the picture durations was either preserved (EDM) or manipulated completely (EDM-M) with the ISIs as well as the sequence of the scenes kept constant. For ID trials the ISI order was either preserved (IDM) or manipulated (IDM-M) with the stimulus durations and the order of scenes unchanged. Similar to Experiment 1 there was a jittered inter-trial interval of 3500 ms (SD 500 ms) after the response screen, although the average trial duration was longer at 20.4 s (block length=4.70 min; run length=18.87 min). All scene images and duration values were trial unique.

It is important to note that while participants were instructed to make their match/mismatch decisions based on the full sequence in each trial and were not made aware that mismatch test sequences were a complete re-ordering of those presented at encoding (as in Experiment 1), it cannot be ruled out entirely that the first event/interval was more informative than the subsequent events/intervals in each sequence. Critically, however, as this possibility is applicable to all conditions, there is no reason to suggest that it would differentially impact the various information (ES/ED/ID) or trial types (M/M-M) and thus, cannot account for the observed hippocampal findings. Moreover, the drop in behavioural accuracy in the IDM and IDM-M conditions in Experiment 2 (where participants monitored 4 intervals) compared to Experiment 1 (where participants monitored 3 intervals) undermines the likelihood that participants solved these trials solely on the basis of the first interval (see Section 3). Finally, the aim of using short jittered durations was to discourage counting, or other verbal strategies. Informal post-scan debriefing indicated that this was successful. Participants reported that they relied primarily on non-verbal strategies to detect match/mismatch status (i.e. violations in temporal expectation), suggesting that verbal strategies such as labelling of the interval durations, were unlikely to contribute to the pattern of findings reported here.

2.2.3. Behavioural data analyses

Three out of four behavioural variables (percent correct) from Experiment 1 and all four variables from Experiment 2 did not meet the criterion of normality as indicated by the Shapiro–Wilk test (all $W \leq 0.88$, $p \leq 0.02$). Since Experiments 1 and 2 incorporated factorial designs; however, and for ease of examination of interactions, performance data for both experiments were submitted to two separate repeated measures analyses of variance (ANOVA), with factors of memory type (Experiment 1: interval duration vs. event order; Experiment 2: interval

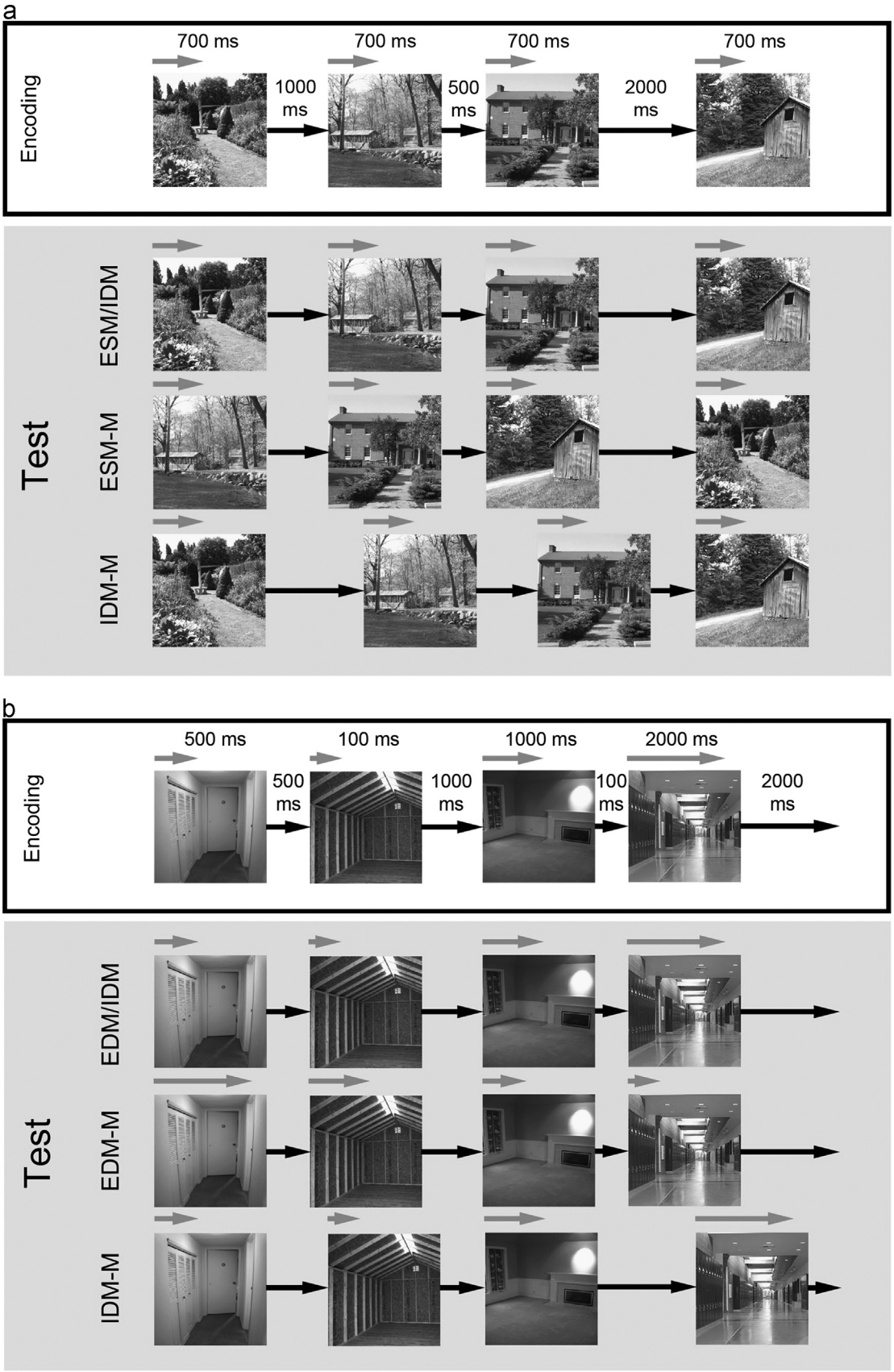

Fig. 1. (a) In Experiment 1, participants were presented with blocks of trials in which they were instructed to monitor event sequences (ES) or interval durations (ID), and make a match (M) vs. mismatch (M-M) decision. In the encoding phase of each trial, participants saw four scenes separated by three intervals (mean 500/1000/2000 ms). In a subsequent test phase, the event sequence and interval durations could stay constant (ESM/IDM), the event sequence could change with the interval durations staying the same (ESM-M), or the interval durations could change with the event sequence unchanged (IDM-M). The encoding and test phases were separated by a 3500 ms fixation cross, and participants were asked to indicate their response during a 2500 ms response screen showing the words "Change (1) or No change (2)?" at the end of each test phase. Trial unique scenes and durations were used. (b) The structure of Experiment 2 was identical to Experiment 1 except that participants were instructed to monitor four event durations (ED) (mean 100, 500, 1000, and 2000 ms) or four IDs (mean 100, 500, 1000, and 2000 ms), with ES being held constant. In the test phase of each trial, these EDs and IDs stayed constant (EDM/IDM), the EDs changed with the IDs unaltered (EDM-M), or the IDs changed with the EDs remaining the same (IDM-M). Trial unique scenes and durations were used in both experiments.

duration vs. event duration) and trial type (match vs. mismatch). Notably, use of non-parametric tests revealed highly similar findings.

2.3. Imaging procedure

2.3.1. Data acquisition

For Experiments 1 and 2, neuroimaging data were collected on a 3T Signa MR system (GE Medical Systems, Milwaukee WI) at the MRI Unit, Research Imaging Centre, CAMH, Toronto, Canada. Functional images were acquired using a Blood Oxygen Level Dependent (BOLD) Spiral In/Out sequence (Glover, 2012) (inter-slice distance=0 mm; number of slices=47; voxel size=3.5 × 3.5 × 3.5 mm, TR=3000 ms; TE=30 ms; FA=60°; matrix size=64 × 64; Experiment 1=348 volumes; Experiment 2=383 volumes). High-resolution 3D anatomical scans were acquired using a T1 BRAVO sequence (number of slices=200; voxel size 0.9 × 0.9 × 0.9 mm, TR=6.7 ms; TE=3 ms; FA=8°; matrix size=256 × 256) for individual subject hippocampal delineation and to facilitate normalization of BOLD images to a standard template.

2.3.2. Image pre-processing

For both Experiments 1 and 2, imaging data were preprocessed and analyzed using FEAT (FMRI Expert Analysis Tool) Version 5.98 and other tools from FSL (FMRIB software library; http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). Each run of functional data was first visually assessed to identify any significant distortion or movement. Images were then subjected to motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), brain extraction with BET (Smith, 2002), grand mean scaling, a high-pass temporal filter cut-off of 50 s, and spatial smoothing using a 6 mm Full-Width Half-Maximum Gaussian kernel. An independent component analysis (ICA) was also conducted using MELODIC (Beckmann & Smith, 2004) on each run to isolate any noise components, as identified by their spatial profile, time-course, and power spectrum. These noise components were subsequently removed. Finally, each participant's functional data were coregistered to their respective high resolution 3D anatomical scan and subsequently normalized to Montreal Neurological Institute space (MNI-152) using a combination of linear and non-linear transformations as implemented by FLIRT and FNIRT (Andersson, Jenkinson, & Smith, 2007; Jenkinson et al., 2002).

2.3.3. Univariate statistical analysis

Each run of preprocessed data from each participant was submitted to a general linear model (GLM) (one for Experiment 1 and one for Experiment 2), with the different event types in each task specified as predictors (or explanatory variables, EVs) and convolved with a double-gamma model of the human hemodynamic response function (HRF). In Experiment 1, there were 12 EVs in total, with each modelled event encompassing all images and intervals within a sequence: accurate trials were modelled separately for each of the 4 conditions (ESM; ESM-M; IDM; IDM-M) by phase (Study; Test). Additional predictors consisted of the study phase correct ESM-M with first image constant; test phase correct ESM-M with first image constant; study and test phases of all error trials; and response phase of all trials. For Experiment 2, there were 10 EVs: accurate trials were modelled separately for each of the 4 conditions (EDM; EDM-M; IDM; IDM-M) by phase (Study; Test). Additional predictors consisted of study and test phases of all error trials, and response phase of all trials. For each GLM, one parameter estimate image was created for each EV for each run and each participant. In addition to this, since we were interested in exploring match vs. mismatch signals, parameter estimate images were also created for contrasts between the test phases in each experiment. These included a main effect of memory type (Experiment 1: ES vs. ID; Experiment 2: ED vs. ID), a main effect of trial type (M vs. M-M), and an interaction between these two factors (Experiment 1: ([ESM vs. ESM-M] vs. [IDM vs. IDM-M]); Experiment 2: ([EDM vs. EDM-M] vs. [IDM vs. IDM-M]). Individual contrasts were also carried out between match and mismatch trials within memory type.

For each experiment, the individual runs for each participant were then combined in a fixed effects analysis and the resulting parameter estimate images were subsequently combined in a higher-level group analysis. The latter was achieved using a non-parametric permutation-based approach as implemented by threshold-free cluster-enhancement (TFCE) (Smith & Nichols, 2009) in the Randomise tool (http://www.fmrib.ox.ac.uk/fsl/randomise). TFCE identifies clusters of activity without the need for pre-determining a cluster-defining threshold in an arbitrary manner, and, in conjunction with permutation testing, uses a multi-threshold meta-analysis of random field theory cluster-p values to determine statistical significance. We used 10,000 permutations for statistical inference and since we were specifically interested in the hippocampus, we adopted a corrected family-wise threshold of $p<0.05$ within a region of interest (ROI) encompassing the hippocampus bilaterally (i.e. small volume correction, s.v.c.). Separate hippocampal ROIs were created for Experiments 1 and 2 by manually delineating the hippocampus for every participant using their T1 scan based on published criteria (Watson, Jack, & Cendes, 1997). Individual subject hippocampal masks in each experiment were then transformed into standard MNI space, added together, and then thresholded at 50% overlap. This probabilistic approach produced a bilateral hippocampal group ROI of 648 voxels for Experiment 1 (left=326; right=322), and a ROI of 816 voxels for Experiment 2 (left=395; right=421). The hippocampal masks were also used to extract mean percent signal change for the left and right hippocampi of each participant for each experimental condition. Since all variables ($W\geq 0.91$ $p\geq 0.07$) bar three ($W\leq 0.89$ $p\leq 0.03$) passed the Shapiro–Wilk test for normality, four repeated measures ANOVAs (one for each hemisphere for Experiments 1 and 2) were employed, incorporating three factors of phase (encoding vs. retrieval), memory type (Experiment 1: ES vs. ID; Experiment 2: ED vs. ID) and trial type (M vs. M-M). Any interactions were explored further with 2-way repeated measures ANOVAs and pairwise comparisons.

Although our main focus was on the hippocampus, we also conducted whole-brain univariate analyses on the data from Experiments 1 and 2. These results were examined with a voxel-wise threshold of $p<0.001$ uncorrected combined with a minimum cluster size of 20 voxels, and are reported in the accompanying Supplementary Material Tables. Regions of activity were identified using the Oxford–Harvard Cortical and Subcortical Atlases.

2.3.4. Multivariate statistical analysis

In order to probe possible distinctions in the pattern of functional connectivity between the hippocampus and the rest of the brain, we turned to a multivariate statistical approach, PLS analysis, which assesses the cross-block correlation between two matrices. In the fMRI application of the PLS approach, one of these matrices is a matrix of voxel intensities for each trial and subject. As no *a priori* HRF is modelled, a response window is defined that captures the HRF associated with each trial (in this case, 5 TRs from the onset of the test phase). The second matrix contains behavioural data, a set of design variables, or data from a seed region of the brain. While the PLS approach is similar to principle components analysis, solutions are constrained in that they must relate to the experimental manipulation or behavioural/physiological measure included in the analysis.

Seed-based PLS is used to assess the functional connectivity between a seed region and the rest of the brain in either a data-driven (mean-centred analysis) or hypothesis-driven (non-rotated analysis) manner. A correlation matrix of brain and seed data is computed across subjects within each task, yielding a within-task brain-seed correlation matrix. The non-rotated approach provides a direct assessment of a hypothesized distinction in functional connectivity, using a pre-specified contrast to restrict the patterns derived from the seed PLS analysis. Here, we examined possible distinctions in functional connectivity relating to the contrast of [EDM+IDM] vs. [EDM-M+IDM-M]. To assess functional connectivity of the hippocampal region sensitive to the effect of duration manipulation, we selected the peak voxel sensitive to the main effect of duration match as a seed (identified from the univariate analysis of Experiment 2 [−20, −20, −18]) and extracted signal from TR 3 (associated with the peak of the HR). The functional connectivity between this seed region and rest of the brain was assessed by taking the product of the task contrast matrix and the mean-centred brain-seed correlation matrix. This produces a singular image, which reflects the spatial-temporal pattern of voxels that embody the relationship specified in the contrast. The strength of this relationship is indicated by the singular value, which is the sum of squared voxel values from the singular image. Permutation tests randomize the condition labels to determine if the task distinction specified is associated with differences in functional connectivity that differ reliably from chance (i.e., the likelihood that the singular value associated with the contrast is significantly greater than that associated with the permuted analyses). Following established criteria for non-parametric tests in PLS analyses, results from the permutation tests were considered significant if they survived $p<0.05$ (as no correction for multiple comparisons is required with this approach) (Krishnan, Williams, McIntosh, & Abdi, 2011; McIntosh, Chau, & Protzner, 2004). Similarly, a bootstrapping procedure allowed assessment of the reliability of the voxel saliences that reflected this effect. Saliences were considered significant if they met a bootstrap ratio threshold of 2.81, corresponding to approximately $p<0.005$, at a cluster threshold of 15 voxels. All PLS results were assessed for statistical significance using 500 permutations and 100 bootstraps and significant regions were identified using the Oxford–Harvard Cortical and Subcortical Atlases.

3. Results

3.1. Experiment 1

3.1.1. Behavioural performance

Performance as reflected in match–mismatch detection accuracy was very high across all conditions (above 90% accuracy), although participants were still significantly better at monitoring event sequences compared to interval durations ($F(1, 21)=20.49$, $p<0.0001$). There was, however, no significant difference in accuracy between match or mismatch trials ($F(1, 21)=0.13$, $p=0.72$), nor was there a significant interaction effect ($F(1, 21)=0.60$, $p=0.45$) (Fig. 2A). Since the behavioural data from Experiment 1 were not normally distributed (see Section 2), we also used

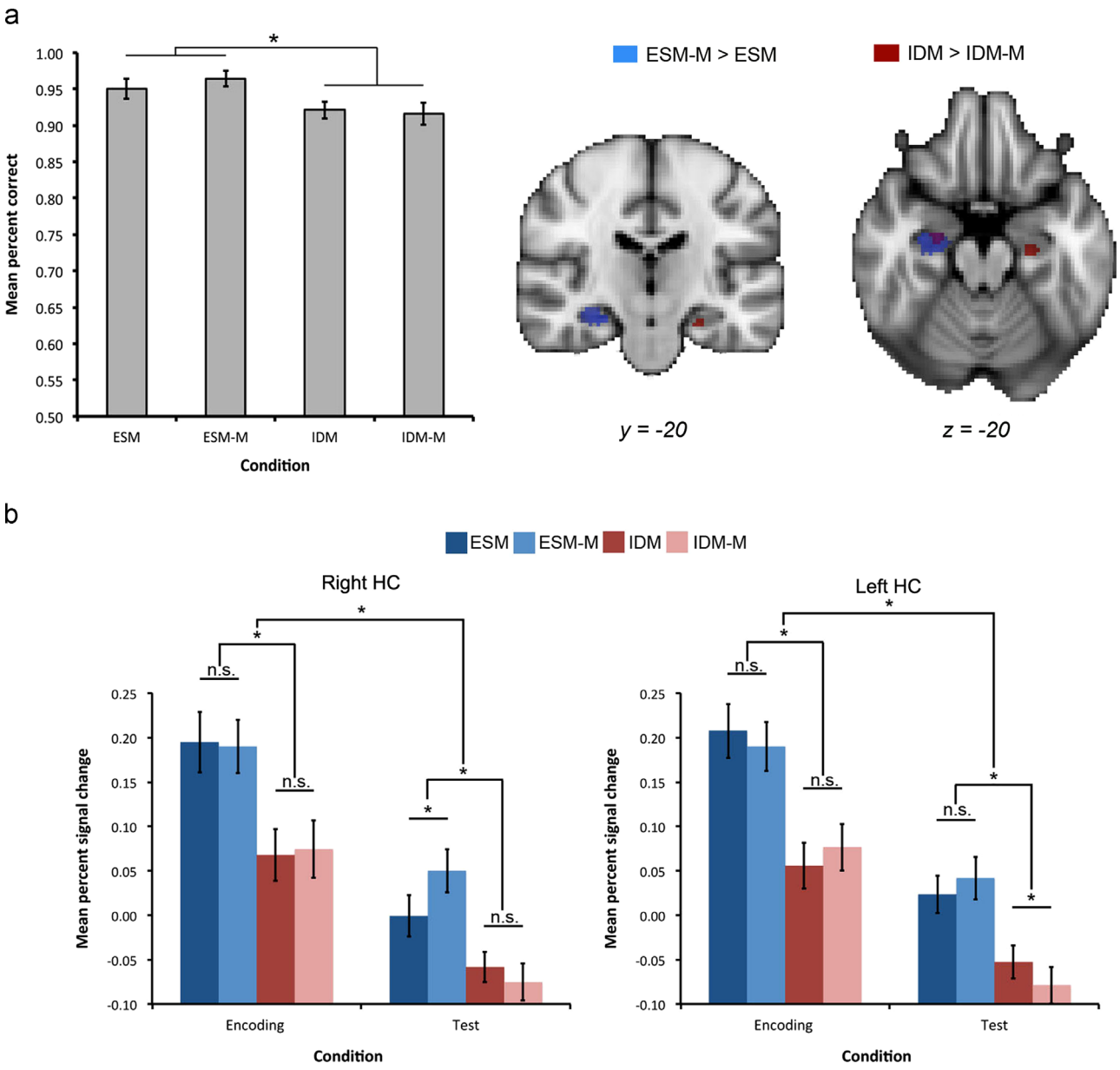

Fig. 2. (a) Mean behavioural performance (± S.E.) on Experiment 1. A significant hippocampal mismatch signal (blue) was observed for event sequences at the test phase (Event Sequence Mismatch > Event Sequence Match), whereas a significant hippocampal match signal (red) was found for interval durations (Interval Duration Match > Interval Duration Mismatch). Activity was thresholded at $p < 0.05$ corrected (s.v.c.) and rendered on coronal and transverse slices of the MNI152 template (right hemisphere = left side of image). (b) Mean percent signal change during the encoding and test phases (calculated with respect to mean activity across the whole data set) (± S.E.) for the entire right and left hippocampi. This pattern of activity at test was significantly different to that at encoding. *$p < 0.05$; n.s. not significant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

non-parametric tests to analyze these data, which revealed similar findings. A Friedman test revealed that participant performance varied significantly across conditions (χ^2 (3, $N=22$) = 10.41, $p=0.015$), with 2-tailed Wilcoxon Signed Rank tests to compare across memory and trial type revealing a significant difference between IDM-M and ESM-M trials ($W=2.22$, $p=0.026$, 2-tailed), but not between IDM and IDM-M ($W=0.13$, $p=0.90$, 2-tailed), IDM and ESM ($W=1.90$, $p=0.089$, 2-tailed), or ESM and ESM-M ($W=0.86$, $p=0.39$, 2-tailed).

3.1.2. *Imaging data: univariate contrasts on test phase data within the hippocampus*

Univariate analysis of the fMRI data at the test phase of each trial yielded clear evidence that the hippocampus not only responded differentially based on match/mismatch status during recognition of event sequences, but also during recognition of interval durations. Unlike event sequence memory, however, in which greater hippocampal activity was observed for mismatch trials compared to match trials (i.e. a mismatch signal) we observed a match signal for interval duration. There was a significant interaction between memory and trial type (i.e. contrast ([ESM-M–ESM] – [IDM-M–IDM]) in the right hippocampus (240 voxels: local maxima coordinates [x, y, z] = [28, −8, −24], $p=0.001$ corrected; [34, −24, 16], $p=0.001$ corrected; [26, −38, −2], $p=0.007$ corrected) and left hippocampus (123 voxels: maxima = [−26, −18, −18], $p=0.01$ corrected). There was also a significant main effect of mismatch detection (i.e. contrast ([ESM-M + IDM-M] – [ESM + IDM])) in the right hippocampus (5 voxels: maxima [34, −14, −18], $p=0.04$ corrected). Comparisons between individual conditions (Fig. 2A) revealed a significant cluster of activity associated with a mismatch signal for event sequences (i.e. contrast [ESM-M–ESM]) in the right

hippocampus (239 voxels: maxima=[34, −12, −18], $p=0.006$ corrected; [26, −22, −16], $p=0.003$ corrected; [28, −36, −4], $p=0.02$ corrected). Conversely, there was a significant cluster of activity associated with a match signal for interval duration (i.e. contrast [IDM–IDM-M]) in the right hippocampus (47 voxels: maxima=[28, −8, −24], $p=0.01$ corrected) and left hippocampus (17 voxels: maxima=[−24, −20, −20], $p=0.04$ corrected). An exploration of complementary contrasts revealed no hippocampal activity in association with a match signal for event sequence or a mismatch signal for interval duration, even when a liberal statistical threshold was applied ($p<0.01$ uncorrected).

3.1.3. Imaging data: mean hippocampus percent signal change during encoding and test phases

Importantly, convergent findings were observed when mean signal change was extracted across the entire hippocampus in each hemisphere of each participant (Fig. 2B) and submitted to statistical analyses. Moreover, these analyses revealed that the match/mismatch signals reported above emerged during the test phase of each trial and cannot be explained by existing differences during encoding. A repeated measures ANOVA for each hemisphere incorporating one factor of trial type (M vs. M-M), one factor of memory type (ES vs. ID), and one factor of trial phase (encoding vs. test) revealed a significant effect of memory type (left hemisphere: $F(1, 21)=38.00$, $p<0.0001$; right hemisphere: $F(1, 21)=24.38$, $p<0.0001$), phase (left: $F(1, 21)=51.15$, $p<0.0001$; right: $F(1, 21)=42.21$, $p<0.0001$) and an interaction between all three factors (left: $F(1, 21)=10.01$, $p<0.0001$; right: $F(1, 21)=9.31$, $p=0.006$). Greater activity during encoding as compared to test is likely due to the greater novelty of the stimuli at encoding, while increased activity for sequence order trials as compared to interval duration trials may reflect the greater saliency of order information or increased scene processing during the monitoring of scene order (see Section 4). Notably, comparing activity across encoding and test in each trial revealed that the pattern of activity was significantly different between these two phases. Two repeated measures ANOVAs with factors of trial and memory type were conducted for the encoding and test phases for each hemisphere to explore the aforementioned three-way interaction further. At encoding, there was only a significant effect of memory type in the left and right hemispheres (left: $F(1, 21)=32.16$, $p<0.0001$; right: $F(1, 21)=22.11$, $p<0.0001$), with no effect of trial type (left: $F(1, 21)=0.02$, $p=0.90$; right: $F(1, 21)=0.01$, $p=0.93$) or an interaction between memory and trial type (left: $F(1, 21)=1.83$, $p=0.19$; right: $F(1, 21)=1.18$, $p=0.68$). The absence of a significant difference between trial type at encoding is not surprising since participants were unaware during the encoding phase whether a match or mismatch sequence would be presented at test. In contrast, at test there was a significant effect of memory type in both hemispheres (left: $F(1, 21)=31.35$, $p<0.0001$; right: $F(1, 21)=17.65$, $p<0.0001$) as well as a significant interaction between trial type and memory type (left: $F(1, 21)=7.64$, $p=0.012$; right: $F(1, 21)=14.91$, $p=0.001$). There was no significant effect of trial type in the left hippocampus ($F(2, 21)=0.19$, $p=0.67$), with a trend towards a significant effect in the right hemisphere ($F(2, 21)=3.86$, $p=0.063$). In the right hippocampus, pairwise comparisons to investigate the observed interaction effect at test indicated significantly greater activity during event sequence mismatch trials compared to event sequence match trials ($p=0.001$), with no significant difference between interval duration match trials and interval duration mismatch trials ($p=0.14$). There was, however, significantly greater signal change for event sequence vs. interval duration for both match ($p=0.015$) and mismatch trials ($p<0.0001$). In contrast, in the left hippocampus, there was significantly greater activity during interval duration match trials in comparison to interval duration mismatch trials ($p=0.03$), and no significant difference between event sequence mismatch and match trials ($p=0.18$). Similar to the right hemisphere, event sequence was associated with significantly greater signal change compared to interval duration for match and mismatch trials (both $p<0.0001$)

3.2. Experiment 2

3.2.1. Behavioural performance

Performance was matched across all trial types (Fig. 3A). Participants performed equally well across event duration and interval duration memory ($F(1, 21)=1.82$, $p=0.19$) for match and mismatch trials ($F(1, 21)=0.49$, $p=0.49$), and there was no significant interaction between these factors ($F(1, 19)=0.19$, $p=0.67$). Similar to Experiment 1, we also used non-parametric tests to analyze the behavioural data from Experiment 2 (see Section 2), which revealed consistent findings. A Friedman test revealed that participants performed equally well across all trial types ($\chi^2(3, N=20)=2.72$, $p=0.44$).

3.2.2. Imaging data: univariate contrasts on test phase data within the hippocampus

The fMRI test phase data not only replicated the interval duration finding from Experiment 1 but more critically, also demonstrated a hippocampal match signal for event durations (Fig. 3A). This convergence of findings across Experiments 1 and 2 highlights the fact that the hippocampus is sensitive to durations within a sequence irrespective of whether attention is directed primarily at the events or the intervals between them. A significant main effect of duration match detection (i.e. contrast ([EDM+IDM] – [EDM-M+IDM-M]) was observed in the right hippocampus (59 voxels; maxima=[24, −18, −16], $p=0.002$ corrected) and left hippocampus (cluster 1, 58 voxels: maxima=[−20, −20, −18], $p=0.001$ corrected; cluster 2, 46 voxels: maxima=[−30, −38, −6], $p=0.004$ corrected), with no interaction between memory and trial type, even at a liberal uncorrected threshold ($p<0.01$). Comparing individual conditions, significant bilateral hippocampal activity was observed during match detection for both event duration (i.e. contrast [EDM–EDM-M]) (right cluster, 8 voxels: maxima=[24, −18, −16], $p=0.01$ corrected; left cluster 1, 46 voxels: maxima=[−24, −16, −18], $p=0.002$ corrected; left cluster 2, 13 voxels: maxima=[−30, −38, −4], $p=0.02$ corrected) and interval duration (i.e. contrast [IDM – IDM-M]) (right cluster 20 voxels: maxima=[24, −18, −16], $p=0.007$ corrected; left cluster 5 voxels: maxima=[−20, −20, −18], $p=0.02$ corrected). No hippocampal activity was observed in association with a mismatch signal for event duration or interval duration, even when a liberal statistical threshold was applied ($p<0.01$ uncorrected).

3.2.3. Imaging data: mean hippocampus percent signal change during encoding and test phases

As in Experiment 1, this pattern of findings was also present when analyses were conducted on mean percent signal change for the hippocampus, as anatomically defined, in each hemisphere (Fig. 3B) and the profile of activity at test was significantly different to that at encoding both in terms of overall magnitude, and with respect to differences between match and mismatch trials.

A repeated measures ANOVA for each hemisphere incorporating one factor of trial type (M vs. M-M), one factor of memory type (ED vs. ID), and one factor of trial phase (encoding vs. test) revealed a significant effect of phase (left hemisphere: $F(1, 19)=26.79$, $p<0.0001$; right hemisphere: $F(1, 19)=22.35$, $p<0.0001$)

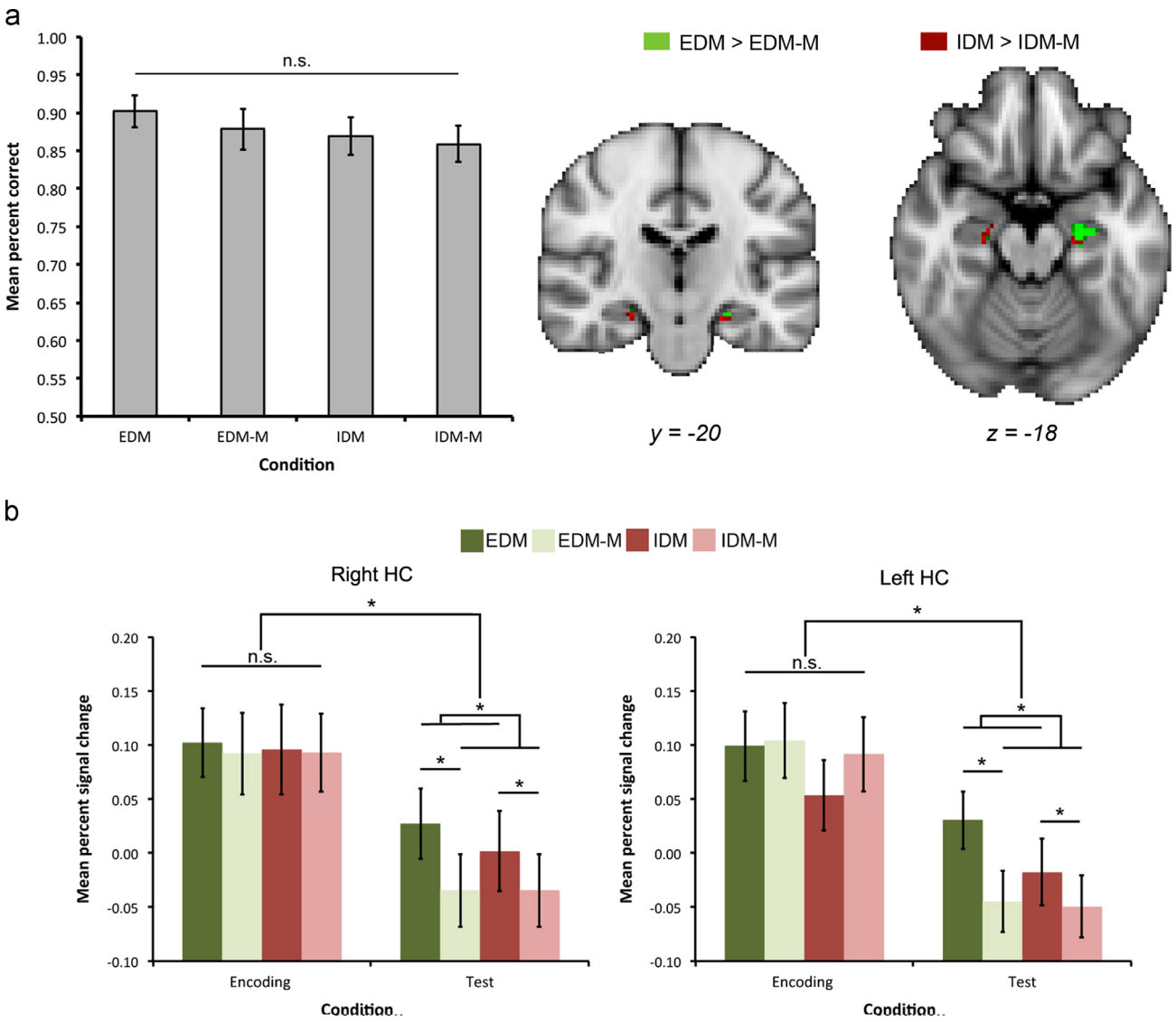

Fig. 3. (a) Mean behavioural performance (± S.E.) on Experiment 2. A significant hippocampal match signal was observed for both event durations (green) (Event Duration Match > Event Duration Mismatch) and interval durations (red) (Interval Duration Match > Interval Duration Mismatch). Activity was thresholded at $p < 0.05$ corrected (s.v.c.) and rendered on coronal and transverse slices of the MNI152 template (right hemisphere = left side of image). (b) Mean percent signal change during the encoding and test phases (calculated with respect to mean activity across the whole data set) (± S.E.) for the entire right and left hippocampi. As in Experiment 1, the pattern of activity at the test phase was significantly different to that at encoding. $^{*}p < 0.05$; n.s. not significant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

but not memory type (left: $F(1, 19) = 3.53$, $p = 0.076$; right: $F(1, 19) = 0.19$, $p = 0.67$). Importantly, there was a significant interaction between trial type and phase in both hemispheres (left: $F(1, 19) = 17.07$, $p = 0.001$; right: $F(1, 21) = 8.32$, $p = 0.01$) as well as a trial by memory type interaction in the left hemisphere ($F(1, 19) = 5.26$, $p = 0.033$). To explore these two-way interactions further, two repeated measures ANOVAs with factors of trial and memory type were conducted for the encoding and test phases in each hemisphere. At encoding there were no significant effects, in either hemisphere, of memory type (left: $F(1, 19) = 3.58$, $p = 0.074$; right: $F(1, 19) = 0.02$, $p = 0.90$), trial type (left: $F(1, 19) = 2.09$, $p = 0.16$; right: $F(1, 19) = 2.10$, $p = 0.65$) or an interaction between memory and trial type (left: $F(1, 19) = 1.19$, $p = 0.29$; right: $F(1, 19) = 0.05$, $p = 0.82$), reflecting similar levels of activity across all conditions. In contrast, at test, there was a significant effect of trial type in both hemispheres (left: $F(1, 19) = 14.53$, $p = 0.001$; right: $F(1, 19) = 9.81$, $p = 0.005$), reflecting greater signal during match trials vs. mismatch trials, irrespective of memory type. There was no significant effect of memory type in either hemisphere (left: $F(1, 19) = 2.40$, $p = 0.14$; right: $F(1, 19) = 0.45$, $p = 0.51$), nor was there a significant interaction between trial type and memory type in the right hemisphere ($F(1, 19) = 1.58$, $p = 0.22$), with a trend towards a significant interaction effect in the left hemisphere ($F(1, 19) = 4.06$, $p = 0.058$). Pairwise comparisons to investigate this interaction at test revealed a significant difference in signal between event duration and interval duration for match trials ($p = 0.017$) but not mismatch trials ($p = 0.70$), with a significant difference in signal between match and mismatch trials for both event duration ($p = 0.002$) and interval duration ($p = 0.04$). In the right hemisphere, signal at test during event duration match trials was significantly greater than that during event duration mismatch trials ($p = 0.009$), and similarly, signal at test during interval duration match trials was significantly greater than that during interval duration mismatch trials ($p = 0.022$). Thus, a significant match signal was observed at test in both hemispheres for both ED and ID conditions, and this was not present at encoding.

3.2.4. Imaging data: multivariate functional connectivity analysis

Finally, we explored the possibility that the observed differential hippocampal response to match and mismatch duration trials might also be reflected in the functional connectivity between the hippocampus and the rest of the brain, in particular regions known to support second and millisecond timing. To this end, we turned to a seed-based multivariate statistical approach (partial least squares analysis, PLS) (McIntosh, Bookstein, Haxby, & Grady, 1996). The hippocampal voxel maximally sensitive to the main effect of duration match detection, as identified from the univariate analysis of the fMRI data of Experiment 2 [−20, −20, −18], was selected for functional connectivity analysis. Using a non-rotated (contrast-based) approach, we tested the hypothesis that the connectivity between this hippocampal seed and the rest of the brain at the test phase of each trial would differ reliably during the viewing of sequences with matching and mismatching temporal structure. This contrast ([EDM+IDM] – [EDM-M+IDM-M]) revealed a pattern of distinct connectivity between the seed and the rest of the brain for duration match and mismatch conditions ($p < 0.05$) (Fig. 4; Table 1). Examination of brain regions that reliably contributed to this distinct pattern of hippocampal connectivity revealed greater coupling in a limited number of regions during the match conditions, including the left cerebellum [−2, −74, −32] and right anterior cingulate cortex [8, 38, −4]. In contrast, a larger number of regions demonstrated increased coupling during the mismatch conditions, including the caudate nucleus [−10, 8, 8] and supramarginal gyrus [−48, −38, 38] in the left hemisphere, and the pre-supplementary motor area [2, 42, 44], insula [28, 26 12], and cerebellum [22, −50, −46] in the right hemisphere (Fig. 5). These data indicate that fluctuations of lower magnitude hippocampal activity during duration mismatch were correlated significantly with activity in a large number of regions at the whole brain level including many associated with timing, whereas variations in higher magnitude hippocampal activity during duration match were correlated significantly with activity in a relatively small number of areas at the whole brain level (see Supplementary Material Table 2d for results from a standard whole brain univariate analysis for the [EDM+IDM] vs. [EDM-M+IDM-M] comparison).

4. Discussion

Although previous work has implicated the hippocampus in temporal context, recency, distance and event order memory (Charles et al., 2004; Ezzyat & Davachi, 2014; Fortin et al., 2002; Hsieh et al., 2014; Jenkins & Ranganath, 2010; Mankin et al., 2012; Naya & Suzuki, 2011; Tubridy & Davachi, 2011), the present work is, to our knowledge, the first demonstration that the hippocampus is sensitive to the event and interval duration information contained within a sequence lasting on the order of seconds. Greater hippocampal activity was observed during match trials in comparison to mismatch trials (a match signal) for interval (Experiments 1 and 2) as well as event duration (Experiment 2) and importantly, these findings cannot be explained by any differences in spatial or temporal order characteristics, which were controlled for across task conditions. Our data go beyond existing human work on the processing of single temporal intervals in association with rudimentary visual/verbal stimuli, which have focused largely on the role of regions beyond the hippocampus in second and millisecond timing, including the caudate, supramarginal gyrus, insula, supplementary motor area, and cerebellum (Lewis & Miall, 2003; Merchant et al., 2013).

The observed hippocampal activity changes during the monitoring of temporal durations converges with rodent 'episode' (Pastalkova et al., 2008) or 'time' (MacDonald et al., 2011) hippocampal cells that signal a filled or empty temporal interval between two discrete, behaviourally relevant events, respectively. These cells may contribute to the binding of discontiguous events into event sequence episodes. Notably, however, the current study adds to these findings in three ways. First, we demonstrate that the human hippocampus is involved in the active retrieval of explicit duration memory associated with a sequence of events, a process that cannot be inferred from existing rodent work. Second, we observe functional integration during duration memory between hippocampus and brain regions beyond the medial temporal lobe implicated in sub-minute timing. Finally, our results suggest that the hippocampus not only bridges the temporal gap between events (MacDonald et al., 2011; Staresina & Davachi, 2009) but is also sensitive to event duration information contained within event sequences.

The present hippocampal findings point towards the possibility that this structure plays a role in our ability to remember temporal duration associated with a sequence of events, for instance, recalling the relative difference in duration between events and/or intervals within a sequence or even those across distinct sequences. An additional possibility is that event and interval duration may be critical to the temporal segmentation and organization of our memories. The perceived length of time between events has been suggested to be a significant factor in determining whether successive events are considered as a single episode or distinct episodes, with a greater length of time increasing the likelihood that events are grouped as separate episodes (Ezzyat & Davachi, 2011). The involvement of the hippocampus in memory for event and interval temporal duration, as demonstrated here, may help underpin this process.

Notably, our data are in line with the recent demonstration that patterns of human hippocampal activity reflect judgments of temporal distance between two events (Ezzyat & Davachi, 2014). There are, however, key differences between this work on temporal distance and the current study. The former examined hippocampal activity in association with variations in participants' retrospective *subjective judgments* of a fixed temporal distance between two events separated by intervening events. In contrast, we investigated hippocampal activity when participants monitored the *durations* of intervals between successive events as well as the events themselves. Although it is conceivable that temporal duration information contributes to our ability to judge how far apart in time two events occurred, further work will be necessary to understand how differences arise between subjective and objective temporal distance, perhaps due to the influence of other types of information such as the number of intervening events and spatial context.

Although the primary finding of interest here is the observation of changes in hippocampal activity during the retrieval of event and interval duration memory, the direction of these changes is intriguing. Given the established role of the hippocampus in temporal order memory (Fortin et al., 2002; Kesner et al., 2002; Tubridy & Davachi, 2011), we included a sequence order condition in Experiment 1 as a sanity check and, consistent with previous work (Kumaran & Maguire, 2007), observed a mismatch signal (i.e. increased hippocampal involvement for altered vs. constant sequences). In contrast, a hippocampal match, and not a mismatch signal, was observed for event and interval duration when temporal order was kept constant, with greater hippocampal activity when sequences of temporal durations were unchanged. Interestingly, overlapping regions within the hippocampus were associated with both mismatch and match effects across conditions, supporting the idea that hippocampal neurons underlying these signals are not anatomically segregated (Duncan, Curtis, & Davachi, 2009). Hippocampal mismatch activity has been suggested to reflect perceptual changes or violations in expectancy during retrieval (Duncan et al., 2009; Kumaran & Maguire, 2009). For

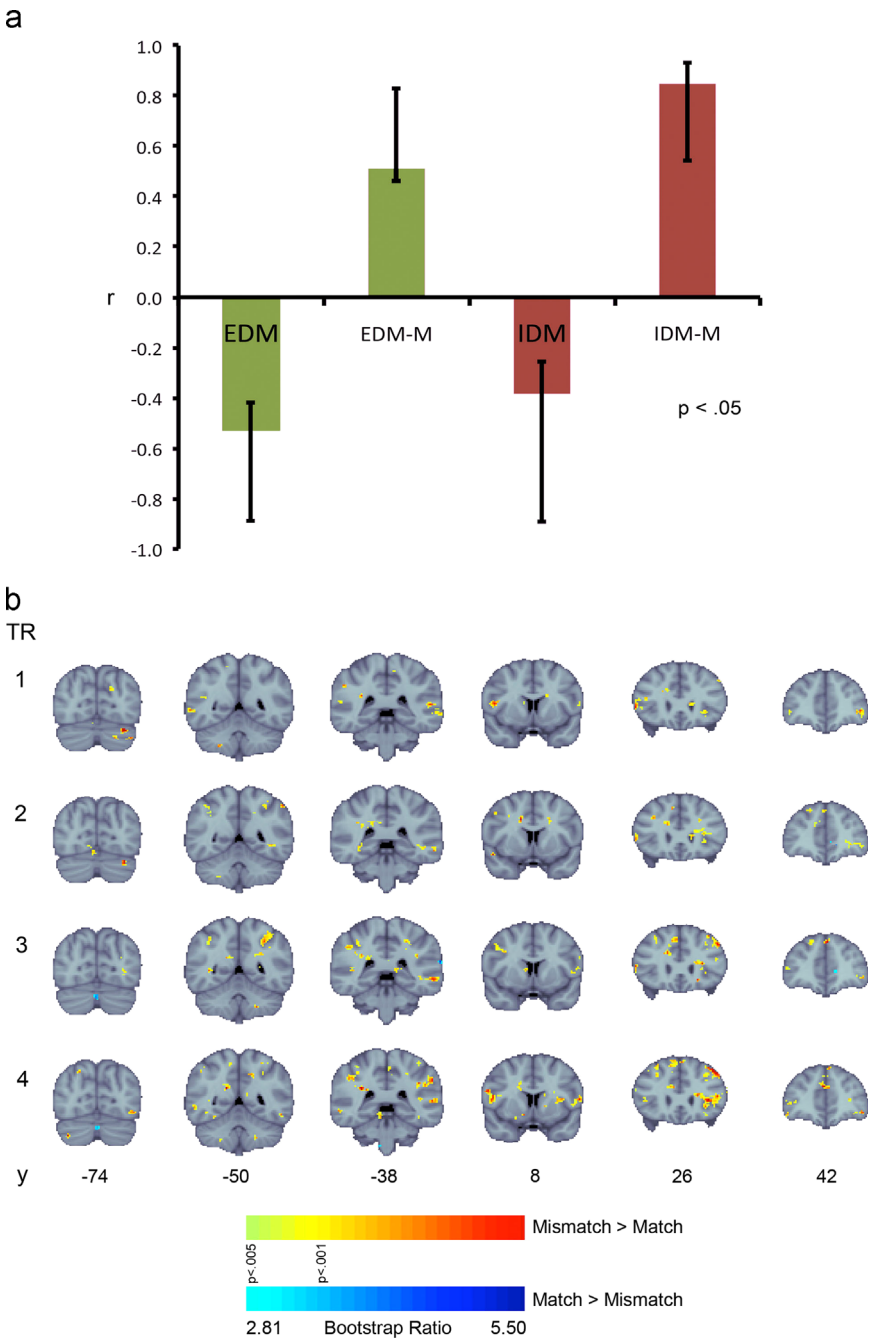

Fig. 4. (a) This plot indicates how the contrast-derived distinctions in seed connectivity, as reflected in the whole-brain spatiotemporal pattern of voxel saliences (Table 1), map onto the experimental conditions. The *y*-axis reflects the strength of the relationship between the seed voxel and the brain scores (the dot product of the voxel saliences and the fMRI data). Error bars represent 95% confidence intervals as determined using permutation tests. (b) Whole brain spatial-temporal pattern of hippocampal functional connectivity associated with (a). Cool colours display regions exhibiting stronger hippocampal connectivity during duration match conditions whereas hot colours display regions exhibiting stronger hippocampal connectivity during duration mismatch conditions. Rows reflect subsequent TRs from the onset of the test period capturing the HRF. Map thresholded at $p < 0.005$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

instance, the hippocampus may operate as a match–mismatch detector in its function as a comparator (Vinogradova, 2001) and subsequently, signal and encode novelty when a comparison between current and previous sensory experience yields a mismatch (Kumaran & Maguire, 2009). Although this explanation may account for the event order mismatch signal reported here, with greater hippocampal activity during event sequence mismatch reflecting the encoding of the novel ordering of events presented in these trials at the test phase, it is not immediately clear why a similar signal was not observed for temporal duration mismatch trials, where novel information was also presented. Similarly, while hippocampal match signals have been suggested to reflect a match in internally generated goals (Miller & Desimone, 1994), irrespective of whether a perceptual match or mismatch occurs (Duncan et al., 2009), this explanation is also unlikely to account entirely for the current findings. Participants were instructed to maintain a similar goal across event sequence and duration trials (i.e. detecting whether a change occurs), with the only difference being the type of information that they were monitoring. Although further work will be necessary to understand fully the current mismatch and match signals associated with sequence order and temporal duration, respectively, we speculate that these divergent

Table 1
Regions exhibiting distinct patterns of connectivity with the hippocampal seed during match and mismatch temporal duration conditions as identified with a multivariate partial least squares analysis. MNI coordinates indicate peak voxel at 3rd TR. Bootstrap ratios all reflect a significance of $p < 0.005$, min cluster size of 15 voxels.

Region	Hemisphere	MNI coordinates			Ratio	Cluster size
		x	*y*	*z*		
Match > Mismatch						
Superior Temporal Gyrus	R	66	−38	18	−4.91	27
Anterior cingulate	R	8	38	−4	−4.75	50
Cerebellum	Bilateral	−2	−74	−32	−3.93	15
Cuneus	R	10	−80	28	−3.88	56
Match < Mismatch						
Cingulate Gyrus	R	20	−2	38	7.74	30
Insula	L	−26	−28	34	7.36	364
Hippocampus	R	18	−42	2	7.29	112
Lingual Gyrus	L	−34	−56	6	7.14	93
Frontal Orbital Cortex	R	24	22	−8	6.78	192
Precuneus	L	−14	−58	32	6.11	146
Cingulate Gyrus	L	−20	−2	34	6.06	54
Superior Parietal Lobule	R	34	−54	44	6.00	378
Inferior Frontal Gyrus	R	46	16	8	5.97	203
Middle Temporal Gyrus	R	56	−40	−6	5.63	172
Insula/Frontal Operculum	R	28	26	12	5.55	30
Cingulate Gyrus	L	−12	30	24	5.53	67
Superior Frontal Gyrus/Pre-SMA	R	2	42	44	5.48	261
Precentral Gyrus	R	58	4	24	5.46	65
Middle Frontal Gyrus	R	48	24	38	5.43	254
Inferior Frontal Gyrus	L	−56	24	4	5.26	125
Middle Frontal Gyrus	L	−46	20	42	5.14	154
Cingulate Gyrus	R	22	−26	38	4.99	49
Frontal Pole	L	−48	48	−10	4.69	15
Precentral Gyrus	L	−12	−16	64	4.68	51
Cerebellum	R	22	−50	−46	4.55	18
Central Operculum	L	−46	4	10	4.47	31
Hippocampus	R	28	−18	−8	4.35	16
Parietal Operculum	R	38	−38	26	4.30	24
Temporal Pole	L	−52	14	−24	4.21	34
Supplementary Motor Cortex	R	4	−4	66	4.00	18
Caudate	L	−10	8	8	4.00	23
Supramarginal Gyrus	L	−48	−38	38	3.98	100
Lateral Occipital Cortex	R	30	−72	24	3.93	31
Frontal Pole	L	−20	42	42	3.84	21
Lateral Occipital cortex	R	32	−76	4	3.79	17
Insula	L	−40	−22	−6	3.64	19
Posterior Cingulate	Bilateral	0	−40	20	3.54	23

changes in hippocampal activity may be driven, at least in part, by differences in the demands that these two types of information place on hippocampal-dependent processes.

Besides a difference in match vs. mismatch signal at the test phase, overall activity for the sequence order trials was also significantly greater than that for the interval duration trials in Experiment 1. One possible explanation for this is that sequence order information was more salient than temporal duration information, given that behavioural accuracy for event order trials was superior to that for interval duration trials (Fig. 2A). In addition, participants may have paid greater attention to the identity of the spatial scenes during the monitoring of sequence order in comparison to interval (or scene) duration, leading to a higher demand on spatial processing and subsequently, hippocampal activity, given the role of this structure in spatial cognition (Bird & Burgess, 2008; Lee et al., 2005; Maguire & Mullally, 2013).

In the light of the demonstration of episode/time cells (MacDonald et al., 2011; Pastalkova et al., 2008) and the present findings that the hippocampus is sensitive to duration memory associated with a sequence, one open question is whether the hippocampus 'measures' temporal durations per se, or makes use of such information provided by other brain regions. Suggestive of the latter, a multivariate seed-based connectivity analysis in Experiment 2 revealed significant functional connectivity between hippocampus and regions that have been implicated in interval timing, including the supramarginal gyrus, anterior cingulate, caudate nucleus, cerebellum, supplementary motor area and insula (Lewis & Miall, 2003; Merchant et al., 2013; Pouthas et al., 2005). Crucially, this connectivity was greater during mismatch trials associated with reduced hippocampal activity as compared to match trials associated with greater hippocampal activity. This pattern suggests that the hippocampus may support existing temporal duration representations associated with event sequences, but the updating of novel duration information is supported by connectivity between hippocampus and more classically recognized timing regions. Thus, rather than a hippocampal temporal mechanism 'measuring' temporal durations per se, the hippocampus makes use of such information provided independently by other brain regions, for example, during mnemonic processing. One possibility is that the hippocampus combines individual novel durations, as delineated by timing regions, into sequences, in keeping with the idea that the hippocampus is important for binding information together (Olsen, Moses, Riggs, & Ryan, 2012; Yonelinas, 2013) and processing representations of spatial and temporal features (Lee, Yeung, & Barense, 2012; Maguire & Mullally, 2013; Mankin et al., 2012).

It is important to note that although a number of the regions demonstrating significantly greater functional connectivity with the hippocampus during duration mismatch trials have been demonstrated to support timing, it is conceivable that their involvement in the current task is not restricted solely to duration processing.

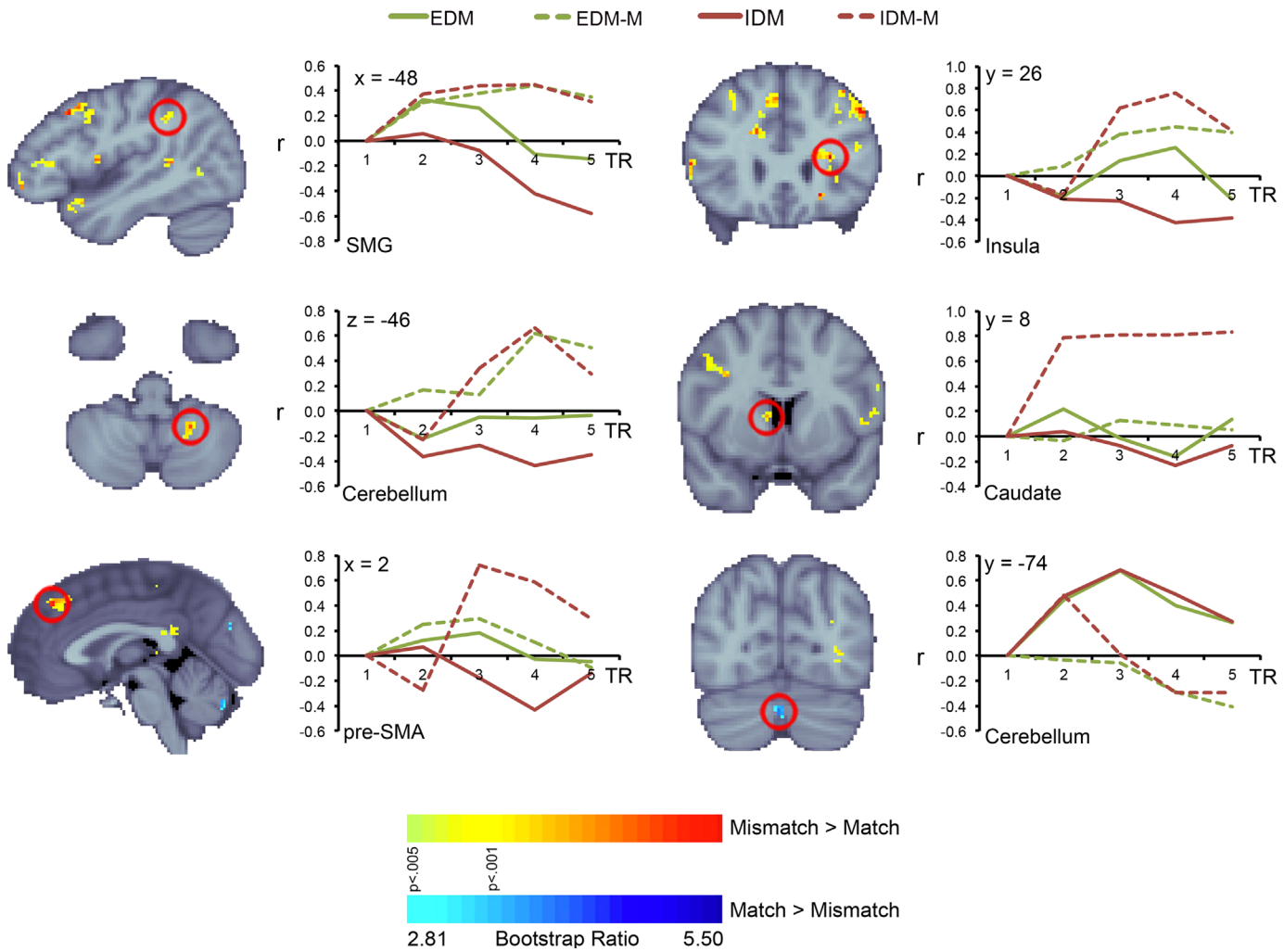

Fig. 5. Differential functional connectivity ([Event Duration Match+Interval Duration Match] – [Event Duration Mismatch+Interval Duration Mismatch]) between the hippocampal seed region and selected regions as revealed by the significant latent variable (see Fig. 4a) ($p < 0.05$). Cool colours display regions exhibiting stronger hippocampal connectivity during duration match conditions whereas hot colours display regions exhibiting stronger hippocampal connectivity during duration mismatch conditions, thresholded at a bootstrap ratio threshold of 2.81, corresponding to approximately $p < 0.005$, combined with a cluster threshold of 15 voxels. Time-courses display the correlation between hippocampal seed voxel and peak voxels of respective regions across TRs from test onset. Note that the strength of correlations is not necessarily tied to the amplitude of the hemodynamic response. Key: SMG=supramarginal gyrus; SMA=supplementary motor area. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Manipulations of temporal structure likely impact both mnemonic and attentional factors, thereby potentially contributing to the differential pattern of functional connectivity observed across the duration mismatch and match trials. For instance, increased functional connectivity between the supramarginal gyrus and the hippocampus during mismatch trials may reflect, at least in part, a role for ventral parietal cortex in bottom-up attentional processing during mnemonic tasks (Cabeza et al., 2011). Moreover, our seed-based functional connectivity analysis revealed a number of brain regions that may not play a specific role in duration processing but have been associated with the retrieval of other forms of temporal information such as the precuneus, which has been associated with mnemonic reconstruction/retrieval for temporal order and distance (Kwok, Shallice, & Macaluso, 2012; St Jacques, Rubin, LaBar, & Cabeza, 2008).

Finally, given the well-established role of the hippocampus in spatial cognition, we chose to use spatial scenes as the event stimuli in order to maximize our ability to detect changes in hippocampal activity in response to changes in temporal duration. One question, therefore, is whether the present hippocampal findings are generalizable to durations associated with other stimulus categories. Although additional work is required to address this issue definitively, it is possible that the use of other types of stimuli will lead to similar results. Hippocampal involvement in temporal memory has been observed in association with odours and objects, even when the contribution of spatial information has been controlled for (Hsieh et al., 2014; MacDonald et al., 2013).

To conclude, we have demonstrated that the human hippocampus is sensitive to temporal durations within sequences of events and intervals, on the order of seconds. Our data converge with and extend recent demonstrations of rodent hippocampal cells that fire throughout the interval between two events, and point towards functional integration between hippocampus and brain regions beyond the medial temporal lobe involved in timing during duration memory.

Acknowledgements

We would like to thank all the participants for their time, Anusha Ravichandran and Nancy Lobaugh for assistance with imaging data collection at the Centre for Addiction and Mental Health, Toronto, Canada, and Morgan Barense, Morris Moscovitch, and Rosanna Olsen for helpful discussion. This work was

supported by the Natural Sciences and Engineering Research Council of Canada (#412309-2011, #402651-2011 ACHL).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2014.09.011.

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