Neural Correlates of Temporal Context Processing

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Abstract

Temporal context memory is a type of episodic memory that refers to memory for the timing of events. Temporal context includes environmental cues that provide information about the time point at which an event happened. The purpose of the present studies is to investigate the brain mechanisms underlying temporal context processing by using both fMRI and ERP techniques. The fMRI study investigated whether hippocampal representations in CA1 and DG/CA3 subfields were sensitive to the flow of physical time, and if so, whether the number of events that occur during a time period influences the temporal representation of a target event. Results showed that both CA1 and DG/CA3 were sensitive to the flow of physical time, which was indicated by higher representational similarity between two pictures that occurred closer in time than those that occurred more distant in time. However, the variety of preceding events did not influence temporal representation, which was demonstrated by the lack of a significant representational similarity difference between two pictures that were interleaved with variable events as opposed to similar events. The ERP study compared the ERP correlates of temporal to spatial context. Results showed that temporal and spatial contexts had overlapping ERP effects except that the ERP effects of temporal context were more frontally distributed than spatial context. Both the fMRI and ERP studies indicate that temporal context is associated with similar neural correlates to other types of context in episodic memory.

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General Audience Abstract

Episodic memory is memory for where and when an event happened. The ability to memorize the timing of events relies on one type of episodic memory: temporal context memory. Temporal context includes environmental cues that provide information about the time point at which an event happened. The purpose of the present studies was to investigate the brain mechanisms underlying temporal context processing by using both functional magnetic resonance imaging (fMRI) and event and event-related potential (ERP) techniques. The fMRI study focused on hippocampus, one of the key brain regions process non-temporal contexts (i.e. spatial context, which refers to where an event happened), and investigated which subfields (CA1 and DG/CA3) in the hippocampus were sensitive to the flow of physical time. And the second purpose of the fMRI study was to examine whether the variety of events that occur during a time period influences the temporal representation. Results showed that both CA1 and DG/CA3 were sensitive to the flow of physical time. However, the variety of events did not influence temporal representation. Since CA1 and DG/CA3 are also critical for non-temporal context processing, these results indicate that temporal context has same neural mechanisms as non-temporal contexts. The ERP study investigated the brain activity as a whole and directly compared the ERP correlates of temporal to non-temporal context. Results showed that temporal and non-temporal contexts had overlapping ERP correlates except that the ERP effects of temporal context were more frontally brain region distributed than spatial context. Therefore, both the fMRI and ERP studies indicate that temporal context is associated with similar neural correlates to other types of context in episodic memory.

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Introduction

Episodic memory is memory for "where" and "when" an event happened (Tulving, 2002; Hasselmo, 2009). Episodic memory allows the mental re-experiencing of events in the place and temporal order in which the events happened. The ability to memorize the timing of events relies on one type of episodic memory: temporal context memory. The purpose of the current study is to investigate the neural correlates underlying temporal context processing. Since temporal context memory is a type of episodic memory, existing knowledge about the neural mechanisms of episodic memory will inform the understanding of temporal context memory and thus will be first summarized in the introduction. Then the evidence specifically related to temporal context memory in both animal and human studies will be reviewed.

Neural Mechanisms of Episodic Memory in General

Lesion studies have established that the medial temporal lobe (MTL) is critical for episodic memory (Eichenbaum & Cohen, 1988; Smith, 1988; Eichenbaum, Otto, & Cohen, 1992; Cohen, Poldrack, & Eichenbaum, 1997; Aggleton & Brown, 1999; Corkin, 2002; Eichenbaum, Yonelinas, & Ranganath, 2007; Squire, 2009). The MTL memory system includes the hippocampal region as well as the entorhinal (EC), perirhinal (PRc), and parahippocampal cortices (PHc). The hippocampal subregion can be further divided into the CA subfields (CA1, CA2, and CA3), the dentate gyrus, and the subicular complex (Preston & Gabrieli, 2002; Squire, Stark, & Clark, 2004). Information enters the MTL memory system from other cortical processing regions through PRc and PHc. PRc receives inputs from the ventral visual stream that processes item information (the 'what' stream). PHc receives inputs from the dorsal visual stream that processes spatial information used for visually guided movements (the 'where/how' stream) (Witter, Groenewegen, Da Silva, & Lohman, 1989; Burwell, 2000; Eichenbaum,

Yonelinas, & Ranganath, 2007). PHc and PRc project to EC separately. PRc projects to lateral EC and PHc projects to medial EC. The EC provides the vast majority of input to the hippocampus (with minor inputs coming from the fornix and the contralateral hippocampus) (Lavenex & Amaral, 2000). The hippocampus therefore receives input from both streams and presumably allows these 'what' and 'where' streams to be integrated. In addition, EC receives reciprocal projections from the hippocampus (Preston & Gabrieli, 2002; Diana, Yonelinas, & Ranganath, 2007). There are two major connectivity circuits between EC and the hippocampus. One circuit originates from the superficial layer of the EC. It projects to CA3 directly or indirectly through DG and to CA1, and then back to the deeper layer of EC. The other circuit also originates from EC's superficial layer but projects to CA1 directly and then back to the deep layers of EC (Lavenex & Amaral, 2000).

Although the interconnections among MTL regions and the circuit of information flow are relatively clear to us, there are controversies about the functions of subregions in the MTL (Squire & Zola-Morgan, 1991; Eichenbaum, Yonelinas, & Ranganath, 2007; Squire, Wixted, & Clark, 2007). Based on the circuit of information flow reviewed above, the "binding of item and context" (BIC) theory proposes that PRc and PHc drive the encoding and retrieval of item and context information respectively. The function of the hippocampus is to associate an item with its context and thus bind the information into a unique representation of an event (Diana, Yonelinas, & Ranganath, 2007). In addition, BIC theory makes predictions about episodic memory retrieval based on the information that is thought to be processed in MTL subregions (Diana, Yonelinas, & Ranganath, 2007). Familiarity-based recognition, defined as a judgment of item strength relative to expected baseline strength, only requires processing of item information and therefore BIC theory predicts that it is supported by PRc. Recollection-based recognition, defined as retrieval

of a context detail from an item cue requires retrieval of both an item-context binding and context information. Therefore, BIC theory predicts that it is supported by the hippocampus and PHc.

Within the hippocampus different subfields have different functions. DG/CA3 is sensitive to small changes in input and responds to the amount of change in a thresholded manner, which means that when the change of input exceeds a certain threshold, it is represented as an entirely new input. (Guzowski, Knierim, & Moser, 2004; Vazdarjanova & Guzowski, 2004; Leutgeb & Leutgeb, 2007; Lacy, Yassa, Stark, Muftuler, & Stark, 2011). Computational modeling, electrophysiological, and immediate early gene studies have demonstrated that DG is involved in pattern separation which refers to the process of transforming overlapping or similar neural inputs into highly dissimilar neural output (Guzowski, Knierim, & Moser, 2004). High resolution fMRI studies have shown that DG/CA3 (a combined region of interest due to the limitations of neuroimaging resolution that prevents reliable segmentation) also drives pattern separation in humans (Bakker, Kirwan, Miller, & Stark, 2008; Lacy, Yassa, Stark, Muftuler, & Stark, 2011). In contrast, CA1 linearly responds to the amount of change in input (Guzowski, Knierim, & Moser, 2004; Vazdarjanova & Guzowski, 2004; Leutgeb & Leutgeb, 2007; Lacy, Yassa, Stark, Muftuler, & Stark, 2011).

In addition to the evidence from animal studies, patient studies and fMRI studies, episodic memory has also been extensively studied using event-related potentials (ERPs), which are time-locked signals extracted from EEG recordings across various scalp locations (Paller, Voss, & Westerberg, 2009). ERPs elicited by items classified as old are more positive-going than those elicited by test items correctly classified as new. This phenomenon is known as an ERP ‘old/new effect’ (Warren, 1980). Recollection and familiarity-based recognition are associated

with distinct ERP old/new effects. Recollection elicits a positive-going, left-lateralized, parietally maximal ERP that onsets around 400-500 ms post-stimulus onset, which is termed as the 'parietal' old/new effect. The relationship of this effect to recollection is supported by evidence that the parietal old/new effect is modulated by the success of source memory retrieval, the retrieval of experimentally-manipulated details (Senkfor & Van Petten, 1998; Wilding & Rugg, 1996). Another group of evidence comes from studies using the remember/know retrieval paradigm. In this paradigm, participants are required to make a 'remember' response if recognition is accompanied by conscious recollection of details from the study episode, whereas a 'know' response should be made if recognition is not accompanied by such details. The parietal old/new effect is modulated by whether the items are endorsed as remembered or known (Curran, 2004; Smith, 1993).

In contrast to the recollection, the ERP correlate of familiarity is less clear. Rugg et al. (1998) investigated recollection and familiarity by requiring participants to do either deep or shallow encoding of words before a recognition test. In addition to the parietal old/new effect, they found an earlier (300-500ms) positive going ERP which was also maximal over the parietal scalp. This effect was elicited by studied items in general, irrespective of encoding task or recognition accuracy. Rugg et al. (1998) interpreted this old/new effect as a reflection of implicit memory because it was independent of explicit memory judgments. A second effect, occurring in the same time range but with a frontal scalp distribution, was also insensitive to depth of encoding (FN400). This mid-frontal effect was seen only for items correctly endorsed as old. On the basis of behavioral evidence that depth-of-processing manipulations influence recollection more than familiarity, Rugg et al (1998) proposed that the FN400 effect was an ERP correlate of familiarity. However, Paller and colleagues have pointed out that the FN400 may index a

combination of familiarity and a co-occurring implicit memory: conceptual priming (Paller, Voss, & Boehm, 2007; Voss & Paller, 2006; Yovel & Paller, 2004). This is supported by the evidence that the amplitude of frontal potentials from 300 to 500ms varies as a function of the meaningfulness of stimuli even when explicit memory was held constant (Voss & Paller, 2007). The reason for identifying FN400 as the index of familiarity is that conceptual priming can lead to familiarity-based recognition.

Temporal Context Memory

Time is intangible (Wittamnn & Van Wassenhove, 2009). People are not able to directly perceive time in the way they perceive the brightness of light, the pitch of sound etc. Therefore, sensing timing usually relies on environmental cues that people can directly perceive. Events that happened prior to or after the critical event, the event that is in your attention at the current moment, can be environmental temporal cues and provide timing information for the critical event (Kahana, 2002; Polyn & Kahana, 2008). These environmental cues that provide information about the time point at which an event happened are defined as temporal context. This makes temporal context different from other types of context in episodic memory, such as spatial context and associative context, because temporal context occurs at different time point from the critical event (before or after). In contrast, other types of context happen during the same time window as the critical event. Due to this difference between temporal context and other types of context, the neural mechanisms of episodic memory in general may not apply to temporal context memory specifically. In addition, temporal context has been studied less frequently than other types of context due to the difficulty in manipulating and measuring it. Therefore, the purpose of the present study is to investigate the neural correlates associated with temporal context processing by using both fMRI and ERP techniques. The fMRI study will focus

on understanding which hippocampal subfields encode the flow of time and how environmental temporal cues influence hippocampal temporal representations. The ERP study will investigate the ERP correlates of temporal context as well as compare the ERP correlates of temporal context to non-temporal context.

Literature review related to the proposed fMRI experiment.

The processing of physical time in the hippocampus. Convergent findings from human and animal studies have shown that the MTL is critical for processing temporal context (Cabeza et al., 1997; Hayes, Ryan, Schnyer, & Nadel, 2004; Fujii et al., 2004; Jacques, Rubin, LaBar, & Cabeza, 2008; Lehn et al., 2009; Ekstrom, Copara, Isham, Wang, & Yonelinas, 2011; Turk-Browne, Simon, & Sederberg, 2012; Azab, Stark, & Stark, 2014; Copara, Hassan, Kyle, Libby, Ranganath, & Ekstrom, 2014; Hsieh, Gruber, Jenkins, & Ranganath, 2014; Ezzyat & Davachi, 2014; Gilbert, Kesner, & Lee, 2001; Agster, Fortin & Eichenbaum, 2002; Kesner, Gilbert, & Barua, 2002; Suzuki, 2002; Manns, Howard, & Eichenbaum, 2007; Farovik, Dupont, & Eichenbaum, 2010; MacDonald, Lepage, & Eichenbaum, 2011; Suh, Rivest, Nakashiba, Tominaga, & Tonegawa, 2011; Mankin et al., 2012; Kraus, Robinson, White, Eichenbaum, & Hasselmo, 2013; MacDonald, Carrow, Place, & Eichenbaum, 2013; Mankin, Diehl, Sparks, Leutgeb, & Leutgeb, 2015). In particular, animal studies have consistently shown that the hippocampus is sensitive to the flow of physical time. The major approach used in animal studies (i.e. rats) is the temporally discontiguous learning paradigm (Rawlins, 1985). In this paradigm, animals are trained to associate a significant event, such as delivery of food or electric shock, with a stimulus that precedes it. The significant event does not directly follow the stimulus but rather there is a temporal gap between them. Animals have to mentally “bridge” the temporal gap between the significant event and the stimulus in order to form an association between the two.

Hippocampal neuron activity is recorded during the task. The change of neural activation patterns during the temporal gap is thought to be an indicator of temporal information processing because animals do not experience other events during the delay except the flow of time. Manns, Howard, and Eichenbaum (2007) applied this paradigm in their study and found that the firing patterns of hippocampal neurons change as a function of time, indicating that the hippocampus processes the passing of physical time.

Neuronal activity within specific hippocampal subfields has also been examined by using the temporally discontiguous learning paradigm. These studies have found that some CA1 neurons fire successively during the delay period and that the firing pattern of these CA1 neurons was modulated by the duration of the delay. This is thought to indicate that these CA1 neurons encode temporal information during the delay and they are termed as "time cells" (MacDonald, Lepage, & Eichenbaum, 2011; Kraus, Robinson, White, Eichenbaum, & Hasselmo, 2013; MacDonald, Carrow, Place, & Eichenbaum, 2013). In contrast to CA1, CA3 does not appear to process temporal information. Mankin and colleagues (2012) recorded neuronal activation patterns in CA1 and CA3 while rats experienced identical events at two time points with an intervening interval ranging from 6 to 30 hours. In CA1 cell populations, the firing pattern similarity decreased monotonically over the time between experiences, whereas CA3 neurons showed highly reproducible firing patterns that were consistent across time. This suggests that CA3 neurons are not involved in temporal coding. Mankin, Diehl, Sparks, Leutgeb, and Leutgeb (2015) studied the effects of temporal and spatial change on firing patterns in CA2 by manipulating temporal distance and spatial context. In their study rats randomly foraged in highly familiar environments in the morning and afternoon with a 6-hour interval on two consecutive days. Each morning and afternoon block consisted of four 10 min sessions, two in a

square enclosure and two in a circular enclosure. The activation pattern of CA1, CA2, and CA3 ensembles across time and different enclosures were examined for effects of time and spatial change. Results showed that the change in neuronal activity as a function of time was more pronounced in CA2 than in either the CA1 or CA3 ensembles. And CA2 was not sensitive to changes in spatial context as other CA subfields. The above studies of the function of CA1 and CA3 shed light on how temporal information flows within hippocampal subfields. Since CA1 was consistently reported to process temporal information but not CA3, temporal context information may flow directly from EC's superficial layer to CA1 and then back to EC's deeper layers. More direct evidence for this hypothesis comes from Suh, Rivest, Nakashiba, Tominaga, and Tonegawa's (2011) study. They tested the function of the projection from EC layer III (the superficial layer) to the hippocampus in associating events across time. They found that rats' ability to associate two events across a temporal gap of 15 to 30 seconds was impaired when synaptic transmission from the superficial layer of EC (layer III) to CA1/subiculum was inhibited, which indicates that EC layer III inputs to the hippocampus are critical for associating events across time. In contrast to CA1, the specific information circuit in which temporal information processing might occur in CA2 is unknown. In summary, animal studies showed that the hippocampus represents temporal information in specific subfields (CA1 and CA2).

Hsieh, Gruber, Jenkins, and Ranganath (2014) measured the sensitivity of human MTL subregions to physical time in an indirect manner. In their study, participants were instructed to memorize objects and their temporal positions in one of five sequences. Multivoxel pattern similarity analysis was used to characterize similarity of the activation patterns in MTL subregions across trials. It was found that the pattern similarity in the hippocampus and PHc across trials decreased as temporal distance between trials increased. In addition, the

hippocampal patterns were specifically sensitive to the combination of an object and its temporal position whereas PHc was sensitive to temporal position information regardless of the specific object presented in that position. The decreased pattern similarity as a function of increased temporal lag observed in Hsieh et al.'s (2014) study is very similar to what has been found in animal studies, with two important differences. First, the temporal position being measured in Hsieh et al.'s (2014) study is the *relative* position that is indicated by other objects presented in the same sequence. This manipulation is different from the passing of physical time that is recorded in animal studies, in which there is no clear cue that can be used to distinguish one time point from another. Second, the temporal position of each object was learned to criterion in Hsieh et al.'s study. Even though participants were not required to explicitly retrieve the temporal order of objects in the experimental task, it was highly likely that participants anticipated the next objects based on the current object. Since there are no existing human studies that have investigated the processing of physical time, the first aim of the current project was to test whether the hippocampal CA1 and DG/CA3 subfields are sensitive to the physical time information and, if so, how they represent the flow of time.

The processing of environmental temporal cues. The aforementioned studies investigated the brain regions that are sensitive to physical time and how these regions represent the timing of events. This representation can be modified by environmental cues such as events that precede the critical event that is in our attention currently (Kahana, 2002; Polyn and Kahana, 2008). For instance, MacDonald, Lepage, and Eichenbaum (2001) recorded the firing pattern of rats' CA1 neurons during a temporal gap between two events. They found that the firing pattern of these neurons differed depending on with which event preceded the temporal delay, which indicates that the event occurring earlier in time modifies the CA1 neuron representation of the

current event. Human studies have also shown consistent effects of preceding events serving as temporal cues. In Turk-Browne, Simon, and Sederberg's (2012) study, participants incidentally encoded a sequence of scene pictures. All the pictures were implicitly grouped into triplets, of which the first two pictures served as temporal cues for the third picture. The third item in the triplet was presented twice with either an identical repetition, the same two pictures preceding it, or a novel temporal context such that the repeated third picture was preceded by a different set of two pictures than the original presentation. Repetition suppression, or adaptation, which refers to the decreased BOLD response for repeated compared to novel stimuli, was measured as an indicator of similarity in the brain representations of these stimuli. Results showed that PHc had greater repetition suppression when the original two pictures preceded a repeated third picture than when novel pictures preceded the repeated third picture, which indicates that the events occurring before a critical event influence the representation of that event in PHc. Hsieh, Gruber, Jenkins, and Ranganath's (2014) study found similar effects of preceding events on the representation of current event. However, they also found that right posterior hippocampus, but not PHc, showed greater pattern similarity among the representations of the critical pictures when the preceding pictures were the same as compared to when they were different. Instead of studying the hippocampus as a whole, Wang and Diana (2016) investigated which hippocampal subfields were sensitive to temporal cues (i.e. preceding events) and whether they were able to distinguish similar temporal cues. They found that CA1, but not DG/CA3, was sensitive to the manipulation of preceding events. And CA1 was able to distinguish somewhat similar temporal cues from identical repeated temporal cues. When the temporal cues were extremely similar, CA1 was not able to differentiate between the cues and processed similar temporal cues as though they were repeated.

In these previous studies, the temporal cue was defined as the event(s) occurring immediately before the critical event and these studies manipulated the temporal cue available at retrieval as compared to encoding. This is different from manipulating the amout of intervening events preceding the critical event because they influence how people represent the temporal information of the critical event in different ways. The amount of intervening events probably would influence the temporal representation of the critical event by modulating people's cognitive state. A sequence of various events, compared to constant events, could make the cognitive state at one time point more different from another, which would in turn make the temporal distance between two time points seems longer. For example, if you worked on two different projects between breakfast and lunch, your cognitive state might change more from breakfast to lunch time than if you were working on only one project. The larger change in cognitive state might be a factor that would increase the perceived temporal distance between breakfast and lunch. It is not known how the number of intervening events, and the relationship among these events, influence the representation of the critical event. Therefore, the second aim of the current study is to investigate whether increased variety in preceding events influences the representation of a current event and which hippocampal subfields (CA1 and DG/CA3) are sensitive to the variety of preceding events. I propose that increased variety in preceding events would decrease the similarity in representations for two similar events when compared to constant preceding events even though the temporal delay between two events remains the same.

In order to investigate the brain regions that are sensitive to physical time and temporal cues (i.e. the variety of preceding events), I used high resolution functional magnetic resonance imaging (fMRI) techniques. I predicted that the representational similarity, measured as the pattern of BOLD signal across each voxel within an anatomical mask of a region of interest,

evoked by two instances of a picture would be greater when the temporal interval between those instances was shorter than when the temporal interval was longer in any hippocampal subfields that process physical time. I also manipulated the number of tasks intervening during the short or long temporal interval in order to examine the effect of increased event variety on representation similarity. I predicted that representational similarity between two pictures should be greater when a single task occurred between repetitions as compared when multiple tasks occurred between repetitions, even when the length of the interval is matched, in any hippocampal subfields that are sensitive to intervening events as temporal cues.

Literature review related to the proposed ERP experiment.

A relatively small number of ERP studies have been done to investigate the neural correlates of temporal context memory (Tendolkar & Rugg, 1998; Trott, Friedman, Ritter, Fabiani, &, Snodgrass, 1999; Tendolkar et al., 2004; Liverani et al., 2015). Recency judgment tasks are the most commonly used paradigm applied in these studies. In a recency judgment task, participants are presented with pairs of studied items and required to judge which item had been presented most recently. Tested items can be drawn from the same list or different lists of items which create additional temporal boundaries between items. Recency judgments have been associated with two ERP components: the parietal old/new effect, previously attributed to recollection of context information, and a frontal old/new effect. The frontally distributed old/new effect was explained as the correlate of decision making processes involved in recency judgments rather than familiarity as seen in the FN400. It should be noted that there is a potential confounding factor in the measurement of temporal context memory using recency judgment tasks. Participants may make recency judgments based on the relative familiarity of items, which means that the more familiar item can be inferred as being presented more recently. In this case

the neural correlates obtained in the recency judgment task might be contaminated by familiarity-based retrieval processes.

The current ERP experiment aims to investigate the neural correlates associated with temporal context processing without the involvement of non-temporal context, as well as to compare the neural correlates of temporal context to spatial context. The purpose of including spatial context is to provide a non-temporal, and therefore more typical, context feature which will allow comparison with previous ERP studies of recollection and context retrieval. It is predicted that temporal context will be associated with different ERP effects from spatial context.

Experiment 1

Participants

Seventeen Virginia Tech community members (12 Female, mean 24 years of age, standard deviation 2.67, range 21-30 years) participated in the experiment for monetary compensation. All participants had normal or corrected-to-normal visual acuity. Two participants were excluded from analysis due to poor resolution in the structural scans (caused by excessive motion). These participants were excluded prior to mask creation and data analysis. One participant was excluded due to excessive movement during the functional scans. This participant was excluded following inspection with the Artifact Detection Tools as described below (Mazaika, Whitfield, & Cooper, 2005). The final N for this study was 14.

Procedure

Stimuli consisted of 192 full-color images of easily recognizable objects on a black background. All pictures were selected from the Bank of Standardized stimuli (Brodeur, Dionne-Dostie, Montreuil, & Lepage, 2010). All pictures were cropped to be the same size (500×500 pixels).

The experiment included two phases. The first phase was completed outside of the scanner and the purpose of the first phase was to familiarize participants with pictures that would be presented in the scanner. There were 6 blocks in this phase. Each block included an initial study session, a test session, and a second study session. In the study session, 16 pictures were presented consecutively and each picture was presented for 2 seconds. Participants were instructed to memorize these pictures. In the test, 32 pictures were presented with half being old and half being new. The participants' task was to differentiate old pictures from new pictures. After the test, there was a second study phase in which all 16 old pictures were presented again in order to improve participants' familiarity with the pictures.

After participants completed the first phase, they were given task instructions for the second phase (Figure 1). The second phase was completed in the scanner. It included 6 blocks and each block consisted of 16 trials. Each trial started with the presentation of one of the 96 target pictures, all of which were previously viewed during the familiarization phase outside of the scanner. This target picture was repeated at the end of the trial. Participants were not told the purpose of the study but rather that each picture they saw in the scanner was very similar to one of the pictures they learned outside of the scanner. Participants' task was to rate how familiar each picture was to them on a 1-4 scale, with larger numbers indicating more familiarity. Each target picture and its repetition were separated by either a long or short interval, which was filled by unrelated tasks. In the long interval trials the interval was either 28 or 30 seconds and in the short interval trials the interval was either 8 or 10 seconds. There were four possible tasks: odd/even judgment task, letter "e" task, arrow direction task, and warm/cool color task. Each task trial was presented for 1 second. The odd/even judgment task required participants to indicate whether a presented number was odd or even. The letter "e" task required participants to

indicate whether there was a letter “e” in the presented verbs. The arrow direction task required participants to indicate the direction of a presented arrow. The warm/cool color task required participants to rate the presented color square as either warm or cool. In the “same task” condition, one of four tasks was randomly presented during the entire interval. In the “changing task” condition all four tasks were presented and each task filled a quarter of the interval. The interval between each trial was filled by a fixation cross.

The two manipulated factors were fully crossed such that there were a total of four conditions: long interval/same task, long interval/changing task, short interval/same task, short interval/changing task. The mean length of the intertrial interval was 2 seconds and varied between 0, 2, or 4 seconds according to the results of an optimization simulation using the optseq2 program (http://surfer.nmr.mgh.harvard.edu/optseq/).

MRI data were acquired at the Virginia Tech Carilion Research Institute Human Neuroimaging Lab using a 3T Siemens Tim Trio scanner equipped with a 12-channel head coil. Prescreening interviews ensured safety in the scanner. Headphones and earplugs were provided to attenuate scanner noise. Padding and adjustable head restraints minimized head movement. High resolution functional fMRI scanning took place during all six blocks in the second phase of the experiment (continuous recognition). Functional images were acquired with a T2*-weighted EPI sequence (repetition time/TR, 2000 ms; echo time/TE, 30 ms; field of view, 220 mm). Each volume included partial coverage of the head, parallel to the long axis of the hippocampus, across 28 slices with 1.77×1.77×2.25 mm voxels. Six anatomical images were collected for each participant: three using an MPRAGE T1-weighted sequence (voxel size=0.599×0.599×0.6 mm) and another three using a T2-weighted scan sequence (voxel size=0.599×0.599×0.6 mm).

Analysis of fMRI Data

All anatomical images were co-registered to the first T2-weighted image. To improve the resolution of the anatomical image, averaged T2-weighted anatomical images were obtained by averaging the three T2-weighted images and averaged T1-weighted anatomical images were obtained by averaging the three T1-weighted anatomical images. CA1 and DG/CA3 were manually segmented on the averaged high resolution structural image for each participant according to the Duvernoy (2005) hippocampus atlas and Yushkevich and colleagues' (2009) segmentation guidelines.

Minimal preprocessing of the functional data was performed using Statistical Parametric Mapping (SPM8) software. T2*-weighted EPI data were slice-time corrected with sinc interpolation to account for differences in the timing of slice acquisition. The functional images for a single participant were brought into spatial alignment by using a six-parameter, rigid-body transformation (realignment). Following realignment, the EPI images for each participant were co-registered to the averaged T2-weighted structural image for that participant. First-level general linear model (GLM) analyses of the fMRI functional data were conducted using SPM8. Outliers were identified at the individual-subject level using the Artifact Detection Tools (http://gablab.mit.edu/index.php/software) in SPM8 with thresholds for global signal intensity (z=5), translational movement (0.5 mm), and rotational movement (0.005 rad). TRs identified as outliers were modeled as covariates of no interest.

Each picture was modeled separately in the GLM as one of 192 covariates of interest that were convolved with the hemodynamic response function. Beta values associated with each picture for each voxel in the ROI were extracted and arranged into a column vector. Pattern similarity between the first and second presentation was estimated by computing the correlation coefficient between vectors of beta values across pairs of pictures. The resulting correlation

coefficient was then Fisher transformed and averaged across all of the trials in a condition.

Since the BOLD signal measurements at different time points are not independent from each other, correlation differences between the long and short interval conditions may be caused by fMRI temporal autocorrelation. The correlation between the beta values of the first or second pictures in neighboring trials that have zero second inter-trial interval was calculated separately for long and short interval trials to indicate temporal autocorrelations. These control correlation coefficients in long and short trials were then subtracted from their corresponding correlation coefficient between the first and second pictures within each trial. The subtracted coefficient should indicate the representational similarity between two pictures across time without the contamination of BOLD signal autocorrelation.

Results

Behavioral results.

The hit rate in the familiarization phase was 93.4% and the correct rejection rate was 97.3%, which indicates that the participants were familiar with all the pictures before the scanning. Therefore, any activation differences associated with the same pictures presented at different time points is unlikely to be due to differing levels of familiarity.

fMRI results.

The correlation between the beta values of first/second pictures in adjacent trials that have zero second inter-trial interval was calculated for short and long interval conditions. A 2 (short/long interval) x 2 (CA1/DG/CA3 subfields) x 2 (left/right hemisphere) repeated measure ANOVA with a Greenhouse-Geisser correction was used to examine the difference of correlation coefficients. There was a main effect for the duration of the interval; the correlation coefficient in short interval condition was significantly higher than that in long interval condition

($F(1,13)=61.60$, $p<.001$). This indicates that there was contamination from BOLD signal temporal autocorrelation. Therefore, in order to test the effect purely driven by the duration of the interval, the coefficients of BOLD signal temporal autocorrelation were subtracted from their corresponding correlation coefficients between the two identical pictures within each trial (Figure 3). A 2 (short/long interval) x 2 (same/changing task) x 2 (CA1/DG/CA3 subfields) x 2 (left/right hemisphere) repeated measures ANOVA with a Greenhouse-Geisser correction was used to examine the difference of correlation coefficients when corrected by subtracting the control trials. There was a main effect for the duration of the interval even when temporal autocorrelation was controlled ($F(1,13)=63.20$, $p<.001$). The interaction between duration, hippocampal subfield, and hemisphere was significant ($F(1,13)=6.03$, $p=.029$). The other main effects and interactions were not significant ($ps>.05$). Since the three-way interaction was significant, the corrected correlation coefficients were collapsed across same and changing tasks within each subfield. Paired sample t-tests showed that in all four subfields the correlation coefficients were significantly smaller in the long interval than the short interval condition ($t(13)_{leftCA1}=-7.68$, $p<.001$; $t(13)_{rightCA1}=-6.62$, $p<.001$; $t(13)_{leftDG/CA3}=-5.64$, $p<.001$; $t(13)_{rightDG/CA3}=-5.60$, $p<.001$), which indicates that both CA1 and DG/CA3 were sensitive to the duration of interval. The correlation coefficient was significantly larger in right DG/CA3 than in right CA1 when the interval was short ($t(13)=-2.38$, $p=.033$), suggesting that right DG/CA3 represents two events as more similar than right CA1 when the inter-event interval was short (8 or 10 seconds). This indicates that the activation pattern of right DG/CA3 changes as a function of time at a slower rate than right CA1.

The effect of intervening events was examined by testing the difference between the correlation coefficients of same and changing trials when the duration of interval was matched.

The uncorrected correlation coefficients between two identical pictures in each trial were used because the contamination caused by temporal autocorrelation should remain the same when the duration of interval was the same (Figure 4). In addition, the effect of intervening events might be lost due to subtraction process. The correlation coefficients were collapsed across long and short interval trials. A 2 (same/changing task) x 2 (CA1/DG/CA3 subfields) x 2 (left/right hemisphere) repeated measures ANOVA with a Greenhouse-Geisser correction was used to examine the difference of correlation coefficients. There was a main effect of hippocampal subfield ($F(1,13)=5.34$, $p=.038$), which indicates that the correlation coefficients were significantly smaller in both right and left CA1 than DG/CA3. The rest of the main effects and interactions were not significant ($ps>.05$), suggesting that CA1 and DG/CA3 were not sensitive to the variety of intervening task in the current study.

Discussion

The fMRI study showed that hippocampal CA1 and DG/CA3 representations of two identical pictures became less similar as the inter-picture interval increased, suggesting that both CA1 and DG/CA3 were sensitive to the flow of time. The findings that CA1 encodes physical time by changing its activation pattern are consistent with what has been found in animal studies. However, the role of DG/CA3 in processing temporal context is more controversial. While most animal studies showed that DG/CA3 did not process physical time, one study found that CA3 separated similar temporal contexts (Farovik, Dupont, & Eichenbaum, 2010). There are several human neuroimaging studies that support the involvement of DG/CA3 in temporal context processing as well (Azab, Stark, & Stark, 2014; Copara, Hassan, Kyle, Libby, Ranganath, & Ekstrom, 2014). The inconsistent findings about the function of DG/CA3 might be because DG/CA3 is involved in processing temporal context in limited circumstances. More studies are

needed to examine the boundaries within which DG/CA3 is involved in processing temporal context. Contrary to my prediction, neither CA1 nor DG/CA3 were sensitive to the variety of multiple intervening events. This indicates that the change of cognitive status induced by different intervening events did not influence temporal representation of the critical events. However, an alternative explanation is that since the intervening tasks were not related to pictures, these tasks did not work effectively to change the cognitive status at different time points.

Experiment 2

Participants

We recruited 36 volunteers (28 Female, mean 19 years of age, standard deviation 1.37, range 18-24 years) from the Virginia Tech student community using the SONA system. They were given SONA credits for participation. 12 participants were dropped from further analysis. 3 of them were excluded due to recording failure and 9 of them were excluded because of excessive ERP artifacts resulting in fewer than 15 artifact-free trials in any condition of interest. The remaining 23 participants were included in both behavioral and ERP analyses.

Procedure

Stimuli consisted of 640 full-color images of easily recognizable objects. 208 pictures were selected from the Bank of Standardized stimuli (Brodeur, Dionne-Dostie, Montreuil, & Lepage, 2010). Pictures were presented consecutively in one of eight non-centered grid-based locations on the screen (Figure 2). The duration of each picture was 1800 ms and pictures were separated by a jittered delay of 500 to 700 ms to prevent expectancy effects. Participants were instructed to perform a modified continuous recognition test with confidence ratings. For each

picture, they were asked to respond with: old/very confident, old/moderately confident, old/somewhat confident, new/somewhat confident, new/moderately confident or new/very confident responses. New responses indicated that it was the first time participants saw the picture and old responses indicated that participants had seen the picture previously in the experiment.

480 pictures were grouped into 160 triplets. Each triplet was presented twice, separated by 21 to 39 pictures. The third picture in each triplet was the target. The manipulation of spatial context was only applied to the target picture. The two pictures immediately preceding the target formed its temporal context. The temporal context pictures were either identical across the two target presentations or replaced at the second presentation by two different, but also previously studied, pictures. For the same temporal context conditions (same temporal/same spatial and same temporal/different spatial), the location of the first two context pictures remained the same across their two presentations. For the different temporal context conditions (different temporal/same spatial and different temporal/different spatial), the location of the first two context pictures in the second presentation was randomly assigned. Spatial context was defined as the position of the target picture on the screen. The spatial context of the target picture was either the same or different between its two presentations. The temporal and spatial context factors were fully crossed to create four conditions: same temporal/same spatial, same temporal/different spatial, different temporal/same spatial, different temporal/different spatial. The remaining 160 pictures served as filler items with 151 used as replacement temporal context items in the different temporal context conditions.

The experiment included 5 blocks of trials. Each block consisted of 32 trials, 8 from each of the 4 conditions. The presentation sequence of trials was pseudorandom in each block. All the

pictures were randomly assigned to condition for each participant. Pictures were only tested within a block.

Electroencephalogram (EEG) data were sampled continuously from 32 scalp locations conforming to the extended International 10-20 positioning system using a BioSemi ActiveTwo system. Four additional channels were used to monitor horizontal and vertical eye movements and two additional channels recorded from left and right mastoids. The digitization rate was 1024Hz. The recording bandpass was 0.01 to 120 Hz.

Analysis of ERP Data

EEG data were processed and analyzed by ERPLAB (Lopes-Calderon & Luck, 2014), a toolbox within MATLAB (2012a) used in conjunction with EEGLAB (Delorme & Makeig, 2004). Recordings were re-referenced off-line to averaged mastoids. ERPs were time-locked to the onset of each picture and averaged across each condition of interests in 1200 ms epochs, beginning 200ms prior to stimulus onset. Baseline correction was performed using the mean amplitude of the pre-stimulus interval. Epochs contaminated by artifacts were discarded. ERPs were averaged over latency intervals and electrode regions for statistical assessment, determined based on the visual inspection of the grand average waveforms. All electrodes were grouped into three regions including frontal (Fp1, Fp2, AF3, AF4, F7, F3, Fz, F4, F8, Fc5, FC1, FC2, FC6), central (T7, C3, Cz, T4, T8, CP5, CP1, CP2, CP6), and posterior (P7, P3, Pz, P4, P8, PO3, PO4, O1, O2, Oz). For the frontal region, latency intervals included 65-115ms, 145-195ms, 160-260ms, 230-330ms, 275-425ms, and 420-520ms. For the central region, latency intervals included 65-115ms, 165-215ms, 230-280ms, 255-305ms, 305-405ms, 415-515ms, and 610-710ms. For the posterior region, latency intervals included 105-155ms, 170-220ms, 225-305ms, 315-365ms, 355-405ms, 435-535ms, 560-710ms. Temporal context (2) by spatial context (2) by

electrodes repeated measures ANOVAS were conducted in frontal, central, and posterior regions separately, with Geisser-Greenhouse corrections when appropriate. Only trials with correct recognition memory responses were included in ERP averages.

Results

Behavioral results.

The correctly recognized old pictures were collapsed across three confidence levels because of an insufficient number of moderate and somewhat confident judgments (Table 1). A 2 (temporal context) by 2 (spatial context) repeated measures ANOVA on the proportion of correctly recognized old pictures showed that both the main effects of temporal and spatial context and the interaction between them were not significant ($p>.05$), indicating that the manipulation of temporal and spatial context did not influence recognition accuracy. However, the repeated measures ANOVA on reaction time showed that there was a significant main effect of temporal context ($F(1, 22) =18.898$, $p<.001$), suggesting that it took significantly longer time to recognize an old target picture when the temporal context was different. Neither the main effect of spatial context nor the interaction was significant ($ps>.05$), indicating that the change of spatial context did not affect recognition reaction time.

ERP results.

For the frontal head region, the main effect of spatial context was significant for the 65-115ms ($F(1,22)=7.999$, $p=.01$), 160-260ms ($F(1,22)=8.849$, $p=.007$), 230-330ms ($F(1,22)=5.924$, $p=.024$), and 275-425ms ($F(1,22)=4.569$, $p=.044$) latency intervals, indicating that the correctly recognized old target pictures elicited more positive ERP waveforms when the spatial context remained the same across study and test during these latency intervals than when the spatial context of the target picture changed (Figure 5). The main effect of temporal context was

significant, beginning slightly later than the spatial effect, at the 160-260ms ($F(1,22)=8.564$, $p=.008$), 230-330ms($F(1,22)=14.456$, $p=.001$), 275-425ms intervals ($F(1,22)=10.222$, $p=.004$), and extending slightly later than the spatial effect, through the 420-520ms ($F(1,22)=6.919$, $p=.015$) latency intervals. These effects indicate that the correctly recognized old target pictures were more positive during these latency intervals when they were preceded by same temporal context stimuli than when the temporal context stimuli were changed. There was a significant interaction between temporal and spatial context during the 145-195ms latency interval ($F(1,22)=5.986$, $p=.023$). Follow-up paired sample t-tests indicated that when the temporal context was the same, there was no difference between the same and different spatial context conditions ($t(22)=-.183$, $p=.856$) from 145-195 ms in the frontal electrodes. However, when the temporal context images were different, the ERP waveform was more positive when the spatial context was the same than when it was different ($t(22)=4.442$, $p<.001$).

For the central head region, the main effect of spatial context was significant in the 65-115ms ($F(1,22)=7.497$, $p=.012$), 165-215ms ($F(1,22)=8.868$, $p=.007$), 230-280ms ($F(1,22)=7.900$, $p=.01$), and 255-305ms ($F(1,22)=4.387$, $p=.048$) latency intervals, indicating that the correctly recognized old target pictures elicited more positive ERP waveforms when the spatial context remained the same across study and test during these latency intervals (Figure 5). The main effect of temporal context was significant in 230-280ms ($F(1,22)=5.807$, $p=.025$) and 255-305ms ($F(1,22)=5.390$, $p=.03$) latency intervals, indicating that the correctly recognized old target pictures were more positive when they were preceded by the same temporal context during these latency intervals. There were no significant interactions between temporal and spatial context in any of the tested latency intervals in the central electrodes ($ps>.05$).

For the posterior head region, there was main effect of the spatial context during the 170-

220ms ($F(1,22)=5.693$, $p=.026$) and 355-405ms ($F(1,22)=4.466$, $p=.046$) latency intervals, indicating that the correctly recognized old target pictures elicited more positive ERP waveform when the spatial context remained the same across study and test during these latency intervals (Figure 5). Neither the main effect of the temporal context nor the interaction between temporal and spatial context were significant during any time interval in the posterior electrodes ($ps>.05$).

Discussion

In the ERP experiment, temporal and spatial contexts were manipulated to examine their effect on item representation. Behavioral results showed that it took significantly more time for participants to correctly recognize old target pictures when they were preceded by different temporal contexts between two presentations. In contrast, the change of spatial context did not influence the reaction time of picture recognition. Even though the manipulation of spatial context did not influence picture recognition behaviorally, it had robust effects on the ERP waveform. The ERP effects of spatial context were identified in all three regions (frontal, central, and posterior) and it started as early as 65ms latency and ended as late as 425ms latency. Different from spatial context, the ERP effects of temporal context were only observed in frontal and central regions. These effects started later than the ERP effects of spatial context (160ms latency in frontal region and 230ms latency in central region) and also ended later in the frontal region (520ms latency). During the 145-195ms latency interval in the frontal region, the effect of spatial context relied on temporal context; there was only an ERP effect of spatial context when the temporal context was different.

General Discussion

The present study investigated how temporal context is processed in hippocampal subfields, via fMRI, and whether temporal context is processed differently from non-temporal

context at a cognitive level, via ERP. The fMRI results showed that the representational similarity between two events decreases as a function of time in both hippocampal CA1 and DG/CA3 subfields, which for the first time directly demonstrates that the human hippocampus encodes the flow of time by changing its activation patterns. The result that CA1 encodes physical time is consistent with what has been found in previous studies. Since it is well established that CA1 also encodes spatial context (Moser, Kropff, & Moser, 2008), it seems temporal context does not differ from non-temporal context in terms of the involvement of CA1.

Most of the previous studies only focused on CA1 (MacDonald et al., 2011; Kraus et al., 2013; MacDonald et al., 2013; Pastalkova et al., 2008; Gill, Mizumori, & Smith, 2011). A few studies investigated CA1 and DG/CA3 and provided inconsistent evidence regarding to whether DG/CA3 is involved in temporal context processing. Kesner, Hunsaker, and Gilbert (2005) found that CA3 lesioned rats performed as well as controls to associate an object with an odor across time. Mankin et al.'s (2012) study showed that the firing patterns of CA3 neurons were highly stable across a few hours or even one-day interval, suggesting that CA3 does not encodes physical time. The evidence that supports the role of DG/CA3 in temporal context processing comes from both animal and human studies that used paradigms in which similar temporal context information need to be distinguished. For example, Farovik, Dupont, and Eichenbaum (2010) trained rats to learn a sequence of odors. They found that rats with CA3 lesions failed to distinguish studied from reversed sequence when the inter-odor interval was either short (3s) or long (10s). Azab, Stark, and Stark's (2014) showed that DG/CA3 is a general pattern separator which is sensitive to changes in both temporal and spatial information. Therefore, a possible role of DG/CA3 in temporal information processing would be that DG/CA3 is only involved when highly similar temporal contexts need to be distinguished. This explanation is consistent with

current findings. In the present study, two identical pictures were presented with an 8/10s or 28/30s inter-picture interval. DG/CA3 might be involved in separating these identical pictures occurring at similar time points.

The variety of multiple intervening events did not influence the temporal representation of CA1 or DG/CA3 in the present fMRI study. Compared to manipulating the similarity between temporal cues that immediately precede the target event in encoding and retrieval, the manipulating of the variety of multiple tasks that occurred between two target events is a relatively indirect way to change temporal context. In addition, the intervening tasks were not related to the target picture, thus these tasks may not effectively change the cognitive status. A more effective intervening task might be one that is related to pictures, in which case the cognitive status would be better manipulated when participants process the target picture.

In contrary to the fMRI experiment that focused specifically on the hippocampus, the ERP study provided a more general picture about how the brain processes temporal context and whether the temporal context is processed cognitively in the same way as non-temporal (i.e. spatial) context. The spatial context was associated with ERP effects in frontal, central, and posterior regions with the latency earlier than 425ms. The temporal context was associated with ERP effects in frontal and central regions with the latency interval around 160-520ms. These results indicate that comparing to spatial context the ERP effects of temporal context were more frontally distributed, which is consistent with patient studies and neuroimaging studies that showed the involvement of frontal lobe in temporal judgments (Milner, 1971; Milner et al., 1991; Cabeza et al., 1997; Suzuki et al., 2002). Both the ERP effects of temporal and spatial context showed similar latency intervals and overlapping distributions with the FN400, which may indicate that the same temporal and spatial contexts primed the recognition process of item

information. In other words, when the same context was presented during the second presentation of the target picture, these identical contexts eased the recognition process of the target. This priming effect was shown behaviorally by shorter reaction in same than different temporal context condition. However, there was no reaction time difference between same and different spatial context conditions. This is probably because the change of spatial context was more obvious to participants than temporal context and they were told to make old/new recognition judgement regardless of spatial position. Therefore, they were trying to avoid the interference created by the change of spatial positions on their behavioral response. There were no observed effects that were similar to parietal old/new effect. This is probably because in the present study the comparison was conducted between correctly recognized old pictures that were associated with same and different contexts, whereas parietal old/new effect is often observed when comparing correctly recollected old items to new items. In addition, behavioral results showed that the accuracy was same across same and different context conditions, suggesting that similar amount of contextual details were recollected. Therefore, there should not be any difference associated with parietal old/new effect.

The ERP results also showed that during the 145-195ms latency interval in the frontal region, the effect of spatial and temporal context interacted with each other. Spatial context only had influence on ERP waveform when the temporal context was different; temporal context only had influence on ERP waveform when the spatial context was different. This result suggests that spatial and temporal context did not work independently.

Taking together the results from the fMRI and ERP experiments, temporal context shared similar neural correlates as non-temporal context, even though temporal context is very different from non-temporal context. The involvement of both hippocampal CA1 and DG/CA3 subfields

provided critical evidence for the BIC theory and implicated that the BIC theory can also be applied to temporal context. The difference between temporal and spatial contexts seems to lie in the involved brain regions. The temporal context is more associated with frontal brain regions as opposed to spatial context. Future studies are needed to examine the role of frontal brain regions in processing temporal context.

Conclusion

The present study investigated the brain mechanisms underlying temporal context processing by using both fMRI and ERP techniques. The fMRI study showed that both CA1 and DG/CA3 were sensitive to the flow of physical time. However, the variety of environmental cues precedes target event did not influence temporal representation. The ERP study showed that temporal and spatial contexts had overlapping ERP effects except that the ERP effects of temporal context is more frontally distributed than spatial context. Therefore, even though temporal context is different from non-temporal context, it has similar neural correlates as other types of context in episodic memory.

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Table 1.

Accuracy and reaction time of old pictures in each condition.

	Same temporal/ same spatial		Same temporal/ different spatial		Different temporal/ same spatial		Different temporal/ different spatial	
	Accuracy	RT	Accuracy	RT	Accuracy	RT	Accuracy	RT
Old Pictures	96.2%	809ms	95.8%	811ms	95.3%	847ms	95.1%	848ms

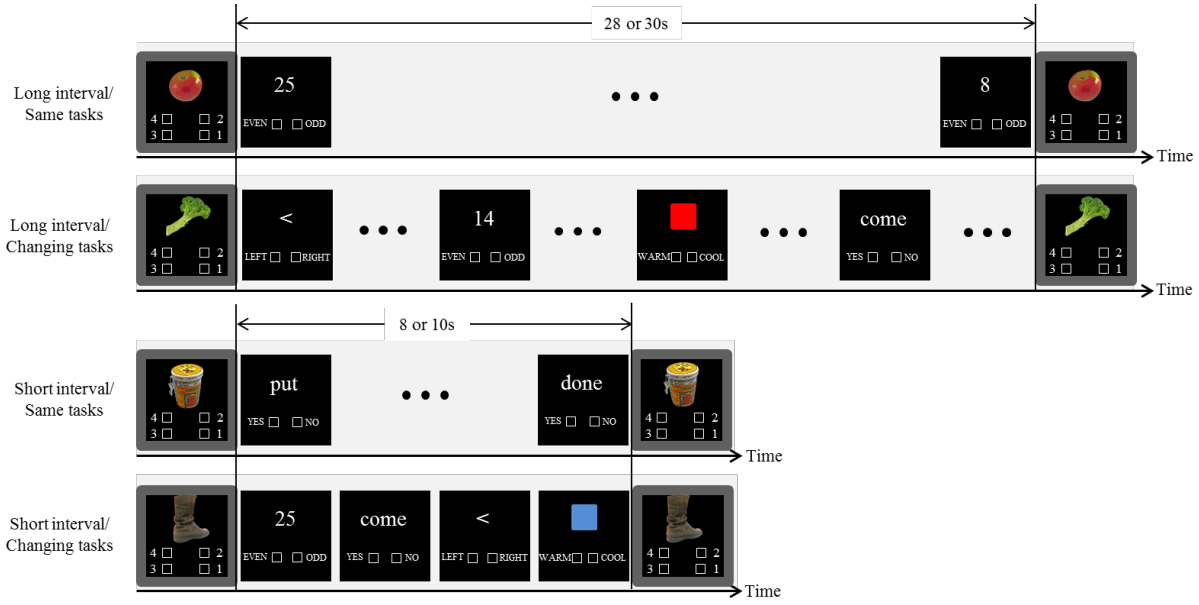

Figure 1. fMRI experimental procedure. Each picture was presented twice. The interval between two presentations was either short (8 or 10 s) or long (28 or 30 s). The tasks filled in the interval were either all four tasks or one of four tasks.

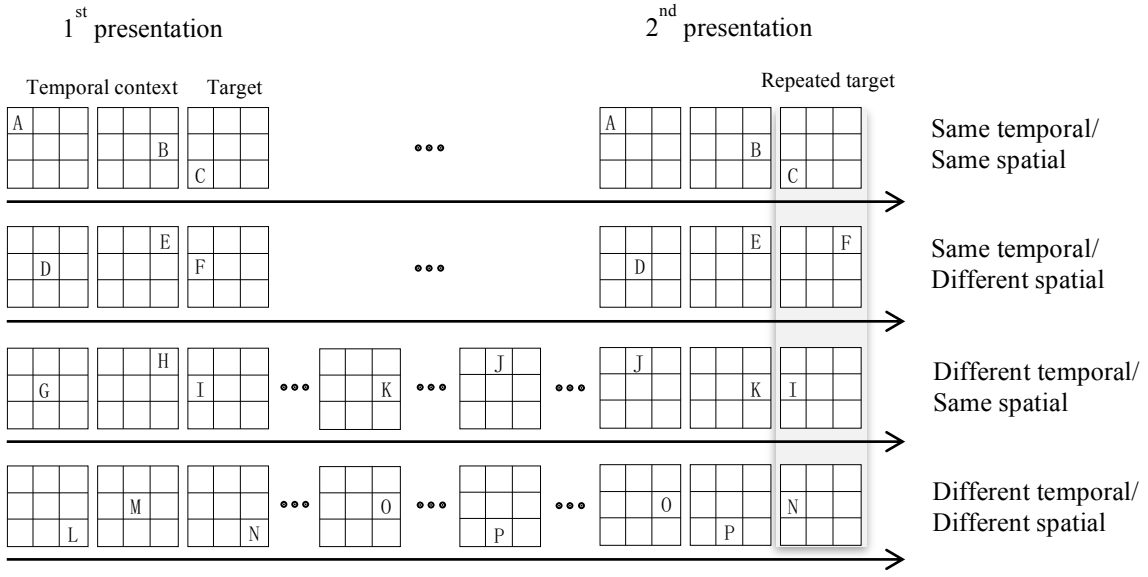

Figure 2. ERP experimental procedure. Each triplet will be presented twice. The target object will be repeated across two presentations. However, its temporal and spatial context will either remain the same or change in the second presentation.

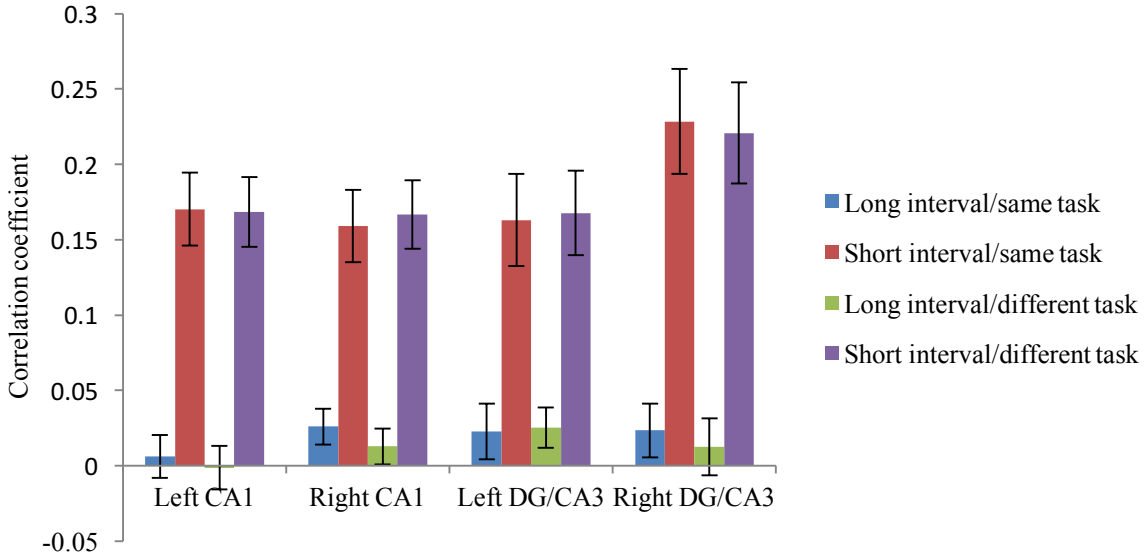

Figure 3. Corrected correlation coefficients between the two presentations of pictures in each of four conditions.

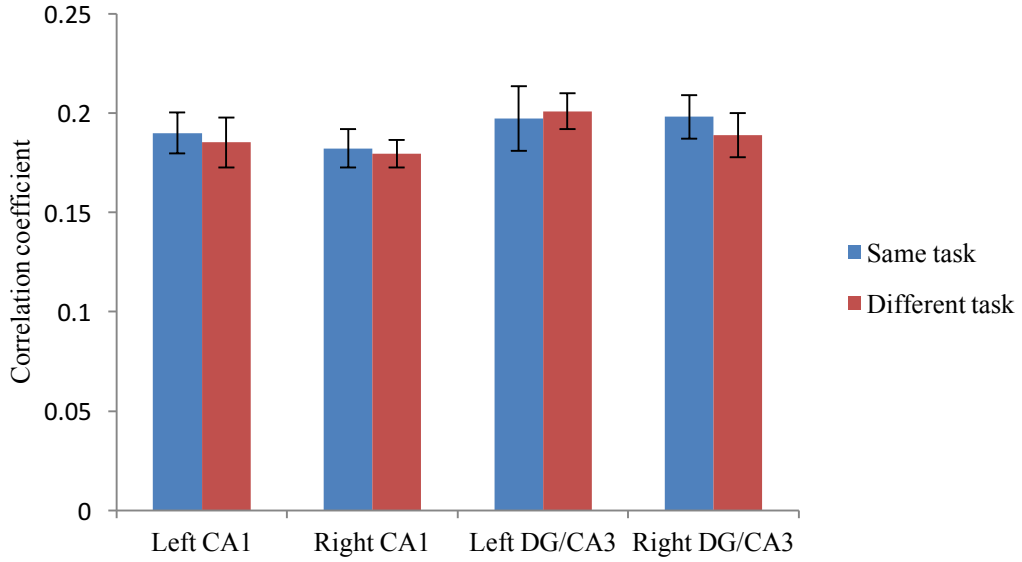

Figure 4. Uncorrected correlation coefficients between two presentations of pictures that are collapsed across.

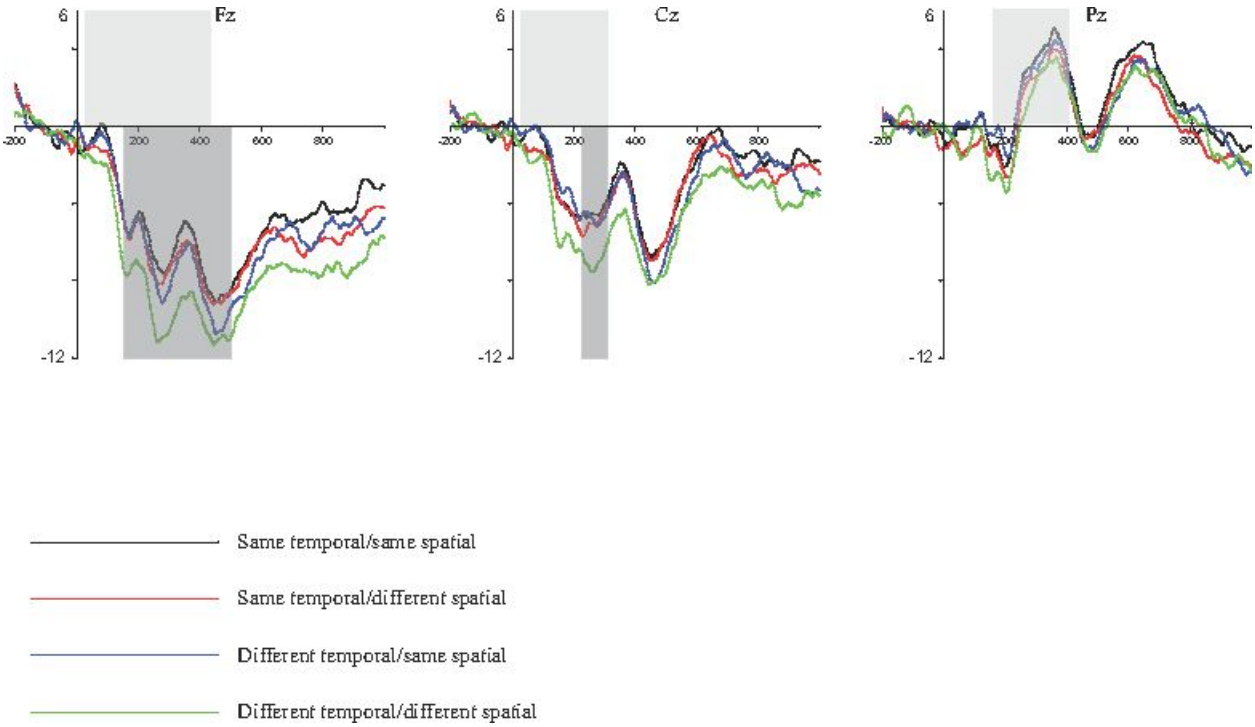

Figure 5. The ERP waveforms of correctly recognized old target pictures in four context manipulation conditions. All or most of latency intervals in the lighter areas showed a significant main effect of spatial context. All or most of latency intervals in the darker areas showed a significant main effect of temporal context.