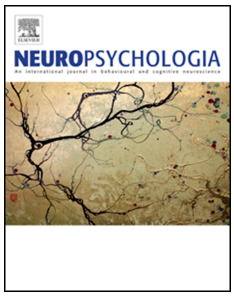

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PII: S0028-3932(19)30342-2

DOI: https://doi.org/10.1016/j.neuropsychologia.2019.107300

Reference: NSY 107300

To appear in: *Neuropsychologia*

Received Date: 27 June 2019

Revised Date: 4 December 2019

Accepted Date: 6 December 2019

Please cite this article as: Lee, A.C.H., Thavabalasingam, S., Alushaj, D., Cavdaroglu, B., Ito, R., The hippocampus contributes to temporal duration memory in the context of event sequences: A cross-species perspective, *Neuropsychologia* (2020), doi: https://doi.org/10.1016/j.neuropsychologia.2019.107300.

Article for "Memory, Consciousness, and Beyond: Special Issue in Honour of Endel Tulving"

The hippocampus contributes to temporal duration memory in the context of event sequences: a cross-species perspective

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Abstract

Although a large body of research has implicated the hippocampus in the processing of memory for temporal duration, there is an exigent degree of inconsistency across studies that obfuscates the precise contributions of this structure. To shed light on this issue, the present review article surveys both historical and recent cross-species evidence emanating from a wide variety of experimental paradigms, identifying areas of convergence and divergence. We suggest that while factors such as time-scale (e.g. the length of durations involved) and the nature of memory processing (e.g. prospective vs. retrospective memory) are very helpful in the interpretation of existing data, an additional important consideration is the context in which the duration information is experienced and processed, with the hippocampus being preferentially involved in memory for durations that are embedded within a sequence of events. We consider the mechanisms that may underpin temporal duration memory and how the same mechanisms may contribute to memory for other aspects of event sequences such as temporal order.

Keywords: Hippocampus, episodic memory, time, sequences, duration, order

1. Introduction

Temporal information is a highly important component of our memories, allowing us to remember when an event took place (temporal context), how recent an event occurred (temporal recency), the order in which events unfolded (temporal order), whether two events were experienced close or far apart in time (temporal distance) and relatedly, the amount of elapsed time during or between events (temporal duration). Given the importance of the hippocampus (HPC) to mnemonic processing, there has been much interest in understanding how this structure contributes to the temporal organization of memories (Clewett et al., 2019; Eichenbaum, 2013; Howard and Eichenbaum, 2015; Ranganath and Hsieh, 2016; Rondina and Ryan, 2017), with a myriad of studies having investigated the impact of hippocampal damage on different aspects of temporal memory as well as how patterns of neural activity in this structure, as measured by electrophysiology or functional neuroimaging, may code for temporal information. In the present article, we focus specifically on the contributions of the hippocampus to memory for temporal duration and seek to add to recent reviews that have explored this topic (MacDonald, 2014; Meck et al., 2013; Palombo and Verfaellie, 2017) by surveying an extensive range of cross-species research that has employed a variety of experimental approaches. This includes studies that have provided insight into the role of the hippocampus in trace conditioning (Büchel et al., 1999; Clark and Squire, 1998; Solomon et al., 1986) and classic timing paradigms (Clark and Isaacson, 1965; Meck et al., 1984; Richards, 1973; Shaw and Aggleton, 1994) in both animals and humans, animal electrophysiological investigations that have characterised the properties of hippocampal 'time' cells (MacDonald et al., 2011; Pastalkova et al., 2008), and a body of recent human functional magnetic resonance (fMRI) work that has examined changes in hippocampal activity in relation to the encoding and/or retrieval of duration-related information (Deuker et al., 2016; Ezzyat and Davachi, 2014; Thavabalasingam et al., 2018). Relevant evidence is organised broadly according to species (non-human vs. human) followed by behavioural paradigm

(in non-humans) or methodological approach (i.e. human neuropsychology vs. functional neuroimaging), and in order to convey the complexities and nuances of the existing literature, a reasonable degree of detail will be provided in each section. On the basis of this empirical evidence, we consider the conditions under which the hippocampus may preferentially be involved in subserving temporal duration memory and to facilitate this, Table 1 (non-human) and Table 2 (human) summarize the main details of pertinent studies (paradigm, length of durations assessed, key finding/s), with each study also categorized, as best as possible, according to the involvement of retrospective or prospective memory, and whether a demand was placed on sequence processing. Importantly, we argue for the importance of considering the role of the hippocampus as a sequence processor (Buzsáki and Tingley, 2018; Howard and Eichenbaum, 2015; Wallenstein et al., 1998) when considering the contributions of this structure to temporal duration memory. Finally, we discuss the potential mechanisms that may underpin hippocampal-dependent memory for durations, and propose that these mechanisms may also contribute to other forms of temporal memory with a particular focus on memory for temporal order.

2. Animal Evidence Supporting a Role for the Hippocampus in Temporal Duration Memory

Early evidence for the HPC being involved in time perception and memory in animals came from a series of seminal studies conducted by Meck et al. (1984). In one study, rats were trained to discriminate between two auditory signals that differed in duration (2 or 8 s) or rate. Post-acquisition, rats with bilateral lesions of the fimbria-fornix (FF), a structure with afferent and efferent projections to and from the HPC, demonstrated a shift in their perception of timing to shorter durations and slower rates. In subsequent studies, it was established that FF-lesioned rats were impaired in retaining signal duration memory across a 5 s delay, and responded earlier than the time of scheduled

reinforcement (20 s) in a peak-procedure task (Meck, 1984). Since then, the recruitment of the HPC for temporal memory has been probed and confirmed using many different types of time-sensitive paradigms that include trace conditioning, differential reinforcement of low rates of responding (DRL), temporal bisection, in addition to peak interval (PI) procedure, which will be discussed in this section (see Table 1).

2.1 The Hippocampus and Trace Conditioning

Trace conditioning is a widely used time-sensitive task, in which the presentation of a conditioned stimulus (CS) and an unconditioned stimulus (US) is separated in time by an empty trace interval of <40 seconds (Mackintosh, 1974), as opposed to the temporally contiguous presentation and simultaneous termination of the CS and US in classical Pavlovian delay conditioning (Clark and Squire, 1998; McEchron and Disterhoft, 1999). It is well established that classical delay conditioning can occur in the absence of hippocampal function, but that trace conditioning depends critically on the integrity of the HPC (Bangasser et al., 2006; Ito et al., 2005; McEchron et al., 1998; Solomon et al., 1986). Studies using eyeblink trace conditioning procedures, in which the presentation of a CS and onset of an unconditioned corneal air puff (US) is separated by a trace interval (typically 500 ms), have consistently demonstrated that rabbits with HPC lesions exhibit a characteristically shorter latency of conditioned eyeblink response (responded to the US earlier in the trace interval) compared to sham-lesioned animals in which the eyeblink response coincided with the time of US presentation, suggesting that the HPC is particularly necessary for temporal duration learning (Kim et al., 1995; Moyer et al., 1990; Port et al., 1986; Solomon et al., 1986). Moreover, rabbits that received complete HPC lesions *following* trace eyeblink conditioning demonstrated significant reductions in the retention of recently acquired trace conditioned responses as measured by inappropriately timed responses, but not of remotely acquired responses (Kim et al., 1995), supporting earlier theories that

the HPC is critical for the consolidation of temporal information in addition to spatial information (Rawlins, 1985; Solomon, 1980). Aspirative and excitotoxic lesions of the HPC have also been reported to impair trace fear conditioning (abolished freezing responses to CS), in which a 15 s auditory tone CS and a shock (US) is typically separated by a 30 s trace interval (Bangasser et al., 2006; McEchron et al., 1998), albeit the timing effects (shortened latency of CRs) observed with trace eyeblink conditioning are not typically present, as the timing of CR expression (freezing) is inherently variable, and not as tightly coupled to the onset of the US (Burman and Gewirtz, 2004).

In keeping with the growing recognition that the HPC is a functionally and anatomically heterogeneous structure along the septotemporal (dorsal-ventral) and transverse (Dentate Gyrus [DG], CA3, CA1 subfields) axes (Bannerman et al., 2004; Fanselow and Dong, 2010; Ito and Lee, 2016; Moser and Moser, 1998), attempts have been made to localize the subregions responsible for the representation of temporal duration memory. Selective manipulations of the dorsal HPC (dHPC) and ventral HPC (vHPC) in rats and rabbits have been coupled with trace fear conditioning paradigms, measuring freezing or heart rate as conditioned responses. Pre-training pharmacological disruptions of the dHPC have been shown to impair the acquisition of trace fear conditioned responses (McEchron et al., 2000; Quinn et al., 2005; Raybuck and Lattal, 2011) and post-training manipulations of the dHPC impair the retention of trace fear conditioned responses (Quinn et al., 2005, 2002), while sparing delay fear conditioning (McEchron et al., 2000; Quinn et al., 2002; Raybuck and Lattal, 2011). There is also evidence that vHPC manipulations (both transient pharmacological inactivation and excitotoxic lesion) impair the acquisition and expression of trace fear conditioning (Czerniawski et al., 2009; Yoon and Otto, 2007). Thus, lesion studies have implicated both dHPC and vHPC in the acquisition and retrieval of trace fear conditioning. However, a preferential role for the dHPC in trace eye blink conditioning has been reported in a single cell recording study by Weible et al. (2006), in which neuronal activity in the CA1 region of the dHPC

and vHPC was compared during trace eyeblink conditioning in the rabbit. It was found that dHPC CA1 exhibited activity that was more robust during the acquisition of trace conditioning, and during the trace interval, compared to neural activity in the vHPC (Weible et al., 2006). Recent evidence from Sellami et al. (2017) also corroborates the postulated relationship between the dHPC CA1 and temporal duration memory. In a trace fear conditioning task, optogenetic inactivation of the dorsal CA1 region in mice during a 40 s trace interval impaired acquisition of the CS-US pairing, revealing that the CA1 region of the dHPC specifically is critical in the representation of a temporal gap that allows for the temporal binding of discontiguous stimuli in memory (Sellami et al., 2017). Interestingly, convergent findings were observed by Kesner et al. (2005) in an object-odour association variant of the trace conditioning paradigm, in which rats were first exposed to an object and then after a 10s trace period, presented with an odour. Lesions of the dHPC CA1, but not CA3, impaired the ability of rats to form an association between the object and odour, with the presence of the trace period suggested to be critical to this deficit (Kesner et al., 2005). Finally, there is also evidence to suggest that the DG may also contribute to trace conditioning with, for example, the blockade of neurogenesis in the adult rat DG impairing eyeblink trace conditioning while leaving delay conditioning intact (Shors et al., 2001). Work in mice has, however, demonstrated that the extent of trace conditioning impairment is more closely related to the degree of excitotoxic damage to the dHPC CA1 rather than dHPC CA3, DG, and even overall dHPC lesion size, suggesting a preferential role of the CA1 subregion in trace conditioning (Tseng et al., 2004).

Despite the strength of the evidence implicating the HPC in duration processing in the trace eyeblink and fear conditioning literature, this putative role has been challenged by results from appetitive trace conditioning tasks in which there were no observed reductions in conditioned responding following HPC lesions (Kyd et al., 2008; Lin and Honey, 2011; Thibaudeau et al., 2009, 2007), suggesting that trace conditioning with an appetitive US, unlike an aversive US, is HPC-

independent. However, a more recent study by Tam and Bonardi (2012) that likewise employed an appetitive trace conditioning task demonstrated that while global levels of conditioned responding to both a delay and trace CS were comparable between dHPC-lesioned and control rats, a finer analysis of responding on a trial-by-trial basis revealed that dHPC-lesioned animals demonstrated earlier peak conditioned responding to the trace CS compared to controls in the early half of acquisition (Tam and Bonardi, 2012). Thus, the findings of this study highlight the fact that subtle HPC lesion-induced timing deficits could be masked when analysing global measures of trace conditioning (e.g., total number of conditioned responses), and speak to the need for finer, trial by trial analysis of temporal patterns of responding, as is possible with the use of PI procedures (see next section).

Taken together, studies of trace conditioning largely substantiate the HPC in representations of temporal duration memory. The question of whether there is regional specificity in the encoding and retention of temporal memory remains unresolved, as evidence for the involvement of both dorsal and ventral HPC in mediating trace conditioning exists. It should also be noted that the HPC dependency of trace conditioning may be related to the trace interval used, with longer intervals (> 500 ms in eyeblink conditioning and > 1 s in fear conditioning) requiring an intact HPC (Moustafa et al., 2013). However, consideration should be given to the fact that trace conditioning, particularly at longer trace intervals typically used in fear conditioning, promotes contextual conditioning, which is also dependent on HPC function (Maren et al., 1997; Phillips and LeDoux, 1994), and hence the observed effects of HPC lesions on trace conditioning may not exclusively reflect disruptions to duration memory.

2.2 The Hippocampus and Peak Interval Procedure

Some of the most compelling evidence for the role of the HPC in duration timing is derived from studies that use the PI procedure (Catania, 1970; Meck et al., 1984; Yin et al., 2017). In this

procedure, animals are initially trained in a fixed interval (FI) schedule of reinforcement in which the first response they emit after a fixed time interval is reinforced. Once a criterion level of responding is reached in the FI training, animals then proceed to the next phase of training, in which half of the trials within a FI training session becomes randomly replaced with 'probe trials', which usually last 3 times longer than the FI trials, and in which the animals are not reinforced. The introduction of probe trials (or peak trials) allows the investigation of 'response rates' after the expected reinforcement time. Initially, animals continue to respond with high rates after the FI schedule has passed but after a few sessions of training with the 'peak trials', the rate of responding drops, and generate a bell curve, when pooled (Balci et al., 2009). The peak of this curve indicates where animals have the highest expectation of reward. The temporal distance between the peak and the FI schedule is used as a substitute of animals' timing accuracy, while the spread of the curve indicates their timing precision (Gibbon, 1977). The spread of the curve typically shows linear scaling with peak times, in other words a wider spread for higher peak times. Single-trial-analysis is also conducted to uncover meaningful data that may be masked by the overall response curve analysis. Even though the averaged response rates in peak trials are shaped like a bell curve, response rates in individual trials resemble a boxcar, where the animals start and stop responding abruptly. It is possible to use a cumulative sum test (Church et al., 1994) to calculate these start and stop times (Balci et al., 2009; Gür et al., 2019; Matell and Portugal, 2007) and crucially, there needs to be high correlation between 'start' and 'stop' times for an effect to be timing related. Any alterations that are only in start times in individual trials are thought to index non-temporal change in behaviour, such as motivation and reward (Balci et al., 2010; Balcı et al., 2013; Taylor et al., 2007), while differences only in stop times could be associated with changes in response inhibition (Balci et al., 2009). The PI procedure has also been used in the context of trace Pavlovian conditioning paradigms to look at the temporal

control of conditioned responses, which usually produce similar responding patterns to the operant version of the task, as discussed earlier (e.g. Tam and Bonardi, 2012).

Early experiments revealed that animals with both pre-training (Meck, 1988) and post-training hippocampal area damage show a gradual leftward shift in peak times (responding earlier than scheduled time), indicating underestimation of durations (Meck et al., 1987; Olton et al., 1988), while sparing the spread of the curve (precision). This pattern of responding following hippocampal damage has led some to argue that the integrity of the HPC is not necessary for prospective duration memory, in which a subject is aware in advance that memory for a stimulus, in this case a specific duration, will be subsequently assessed (MacDonald, 2014). However, one of the caveats of early studies lies in the fact that the lesions were not restricted to the HPC, and included the FF and medial septal area, which entailed extensive damage of fibres of passage. Nevertheless, recent research have confirmed this finding with more selective hippocampal damage, providing strong evidence for the role of HPC in the PI procedure (Balci et al., 2009; Gür et al., 2019; Tam et al., 2015, 2013; Tam and Bonardi, 2012; Yin and Meck, 2014, but see Dietrich et al., 1997; Dietrich and Allen, 1998). Furthermore, recent work has identified a functional differentiation along the dorsal-ventral axis of the HPC in the learning and performance of a bi-peak procedure, in which mice are trained to respond to two concurrent target durations (i.e. 15 s, 45 s) on two different levers (Yin and Meck, 2014). Pre-training and post-training excitotoxic lesioning of the dHPC was found to induce a leftward shift in peak time (timing underestimation), accompanied by an earlier 'start' time and 'stop' time in single trials. In contrast, pre-training vHPC lesions caused a rightward shift in the peak curve, which further analysis attributed to the mice 'stopping' later. It was concluded that manipulations of the dHPC induced classic 'timing' deficits that uncover its key function in 'core timing mechanisms', while the pattern of timing alternations following vHPC manipulations was more in line with its role in motivational and contextual modulation of timing behaviour. Altogether, studies using peak

procedures provide concerted evidence that the HPC, and the dorsal aspect in particular, is critical in duration processing.

2.3. The Hippocampus and Differential Reinforcement of Low Rates of Responding

DRL is one other commonly used procedure to study timing, alongside peak procedure (Ferster and Skinner, 1957; Sidman, 1955; Skinner, 1938). It is a deceptively simple procedure in which animals are required to wait a fixed duration (schedule) before responding to obtain a reinforcer. Every response that is emitted resets the schedule timer. Thus, responding *after* the completion of the schedule is the best way to maximize reward acquisition in this task. The task creates a trade-off between waiting longer to increase the probability of getting reward and responding earlier to increase reward rate. The most commonly used measures of DRL performance is efficiency (number of reinforcers/responses), number of responses and average inter-response times (IRT). Distributions of IRTs at steady state resemble an inverse-gaussian distribution with an exponential component at lower IRTs. The exponential component is usually thought to be related to impulsivity and separate from timed responses, which are represented by the inverse gaussian component of the distribution. It is possible to calculate the most optimal waiting duration for DRL using these distributions based on timing uncertainty thanks to the scalar property of timing responses (Freestone and Church, 2016).

Hippocampal damage causes a reduction in efficiency measures, which is produced by leftward shifts in DRL IRT distributions, similar to its effect on peak procedure, for both pre-training lesions (Bannerman et al., 1999; Cho and Jeantet, 2010; Clark and Isaacson, 1965; Jaldow and OAkley, 1990; Jarrard and Becker, 1977; Pellegrino and Clapp, 1971; Rawlins et al., 1983; Schmaltz and Isaacson, 1966; Sinden et al., 1986; Woodward et al., 2018) and post-training lesions (Bannerman et al., 1999; Cho and Jeantet, 2010; Clark and Isaacson, 1965; Jaldow and OAkley, 1990; Jarrard and Becker, 1977; Pellegrino and Clapp, 1971; Rawlins et al., 1983; Schmaltz and

Isaacson, 1966a; Sinden et al., 1986; Woodward et al., 2018). This deficit in responding with HPC damage is ameliorated by giving a signal at either the half way point of the schedule (Rawlins et al., 1983) or at the schedule duration (Pellegrino and Clapp, 1971), indicating that the effect is not purely a behavioural inhibition deficit. Bannerman et al. (1999) observed that selective lesions of the dHPC or vHPC also produced the leftward shift in IRT distributions, albeit the effect was weaker compared to when the HPC was fully lesioned. It should also be noted, however, that in this study the efficiency scores for all groups (including the controls) were surprisingly low, indicating that learning may not have been optimal. Lesions of the CA3 and DG subfields have also been reported to induce a leftward shift, while CA1 lesions do not have an effect on performance (Bueno et al., 2006; Costa et al., 2005; Jarrard and Becker, 1977; Sinden et al., 1986). Similarly, Young and McNaughton (2000) observed via single cell recording that a cluster of CA1/CA3 neurons started firing at the beginning of a DRL trial and decayed slowly until a response was made, indicating the presence of a temporally relevant signal in these regions of the HPC (Young and McNaughton, 2000).

Although the majority of studies that have demonstrated a role for the HPC in DRL have used efficiency (number of pellets/responses) and the number of bar presses as their measures, these measures do not provide us with a full picture of the nature of observed timing deficits. In order to gain further insight into the role of the HPC in the temporal control over goal-directed responding, IRT distributions must be examined. As discussed earlier, the DRL is known to generate an IRT distribution that has an exponential non-timed component. It is therefore possible that previously observed changes in DRL responding is related to an alteration in this part of the IRT distribution, which is more indicative of deficits in impulsivity. In fact, studies that have reported IRT distributions have consistently observed an increase in impulsive responding in addition to a leftward shift as a result of HPC lesions (Cho and Jeantet, 2010; Costa et al., 2005; Jaldow and OAkley, 1990) whereas 5,7 -DHT lesions of median raphe nuclei that reduce the serotonin levels in HPC produce a

leftward shift without changing the impulsive responses (Fletcher, 1995). Thus, data from the DRL literature reveal that the HPC has a dual role in impulse control and the timing components of the DRL task. Interestingly, impairments in the timing component of the distribution is not observed if the scheduled duration is signalled with a cue (Cho and Jeantet, 2010; Fletcher, 1995). Thus, the dominant role of the HPC in the DRL task is in the temporal control of behaviour, and not behavioural inhibition (Braggio and Ellen, 1976; Cho and Jeantet, 2010; Rawlins et al., 1983).

One line of query regarding findings from DRL as well as PI research is whether the effects of hippocampal damage reflect a role for this structure in timing or memory for time. Classically, findings from the PI and DRL paradigms in rodents have been interpreted in the context of Scalar Expectancy Theory (Gibbon, 1977; Gibbon et al., 1984), which has three basic components suggested to be essential for timing: clock (pacemaker and accumulator), memory (working and reference) and decision (comparator). Although typical leftward shifts in response curves following hippocampal dysfunction may occur as a result of an increase in clock speed, this account can only explain data in which the time duration underestimation occurs after post-training HPC damage (Meck et al., 1987; Meck, 1988; Olton et al., 1988; Yin and Meck, 2014), and not pre-training damage (Gür et al., 2019; Tam et al., 2015, 2013; Tam and Bonardi, 2012; Yin and Meck, 2014), since animals receiving pre-training hippocampal damage should learn the timing duration with the new (post-lesion) clock speed. Thus, shifts in the memory component (memory translation constant - K) is a more likely explanation for the observed changes in HPC-lesioned animals (Allman et al., 2013; Yin and Troger, 2011). In fact, simulations of data collected from animals with pre-training damage of the HPC show that the results are more consistent with the change in K rather than clock speed (Gür et al., 2019) suggesting, therefore, that the HPC plays an important role for memory for duration information.

2.4. The Hippocampus and Temporal Bisection

The temporal bisection procedure is another interval timing task that has been used to assess timing ability (Church and Deluty, 1977). Subjects are initially trained with two reference durations that can be discriminated easily (e.g., 2 and 8 s) by pressing the lever associated with them. Unreinforced probe trials of intermediate durations (e.g., 2.4, 3.8, 4.2, 5.0 s, etc.) are then interspersed with these reference durations after successful learning (> 85% accuracy) and subjects must press either the short or long duration lever to continue the experiment. Preference for the long duration lever is plotted for each duration to obtain a psychometric curve and the midpoint at which preference for both options is 50% is called the point of subjective equality (PSE) or bisection point. Importantly, in contrast to the PI and DRL procedures, subjects do not need to know the exact duration of the stimuli, and only the relative duration compared to the reference durations. Relatively fewer experiments have investigated the role of the rodent HPC in temporal bisection, but FF lesions have been reported to produce a leftward shift in PSE, indicating underestimation of durations, in agreement with PI and DRL findings (Meck et al., 1984). Moreover, the hippocampal CA1 subfield has been associated with a larger P3-like event-related potential compared to the frontal cortex or cerebellum during the bisection task (Onoda et al., 2003) suggesting involvement of this region in temporal discrimination, although DG lesions have been observed to have no significant impact on behavioural performance (Bueno and Júnior, 2011).

2.5. Hippocampal time cell work

One of the most striking discoveries to emerge from recent electrophysiological recordings in the HPC is the existence of “time cells,” neurons from the CA1 region aptly named for their involvement in the encoding of temporally consecutive moments during an empty interval between two events (Gill et al., 2010; Kraus et al., 2013; MacDonald et al., 2013, 2011; Pastalkova et al., 2008). Akin to

place cells that encode an animal's spatial location with respect to its environment, pyramidal "time cell" neurons in the CA1, which were first reported by Pastalkova et al. (2008) and referred to as "episode neurons", have been shown to fire at specific moments in a temporal sequence to organize and represent temporal memories for events as well as the time of the durations between events (Eichenbaum, 2014; Modi et al., 2014). Evidence from trace eyeblink tasks in rabbits lent early support for the sensitivity of HPC CA1 cells to trace interval duration, with CA1 cells showing persistent firing during the interval period, particularly during early phases of conditioning, and even before the manifestation of behavioral CR (Solomon et al., 1986; McEchron & Disterhoft, 1997) (see also Suter et al., 2019 for related findings in the DG). McEchron et al., (2003) also revealed CA1 pyramidal neurons to fire maximally at a timepoint coupled to the end of the trace fear interval (and onset of US) during a post-acquisition test that measured responses to the CS alone. Furthermore, work by Moyer et al., (1996) found that the CA1 cells of brain slices taken from rabbits that had undergone trace fear conditioning 24 hrs prior to recording showed a transient increase that lasted up to 5 days post-acquisition. Taken together, early work indicated that discrete CA1 neurons mediate the encoding of specific time points throughout a duration.

The activity of time cells in the representation of durations was further investigated in a series of experiments by MacDonald and colleagues (2011, 2013), in which the activity of hippocampal CA1 neurons was assessed in rats after they learned to differentiate between event sequences comprising two distinct sensory events (i.e. object 1 with odour 1, object 2 with odour 2) separated by an empty delay period. During the delay interval, neurons would fire at distinct moments in succession so as to fill the entirety of the duration, and the firing patterns of the individual neurons demonstrated flexibility (i.e. "retimed") according to changes in the length of a delay (MacDonald et al., 2011). A follow-up study using a delayed matching-to-sample task requiring head-fixed rats to respond to a probe odour that matched a previously presented sample likewise demonstrated that

clusters of hippocampal CA1 cells encoded particular odour memories throughout a delay (MacDonald et al., 2013). This paradigm was critical in disentangling time-related neuronal activity from locomotion and intended movement, as previous studies of time cells frequently involved freely-moving animals, with distance travelled serving as a potential confounding factor in the encoding of duration given the HPC's role in spatial processing (Gill et al., 2010; Kraus et al., 2013; Pastalkova et al., 2008). Thus, this study provided evidence that the temporal encoding of durations mediated by CA1 neurons occurs independently of neuronal input from movement and spatial configuration. Of note, subsequent work also demonstrated that time cell firing is scalar in nature, with neurons firing later in a sequence firing for a longer period of time compared to those firing earlier on (Howard et al., 2014; Kraus et al., 2013) This is particularly interesting given the scalar property of behavioural responses in timing tasks, such as the PI and DRL paradigms reviewed earlier, and the impact of hippocampal dysfunction on such tasks.

Although early studies of hippocampal time cells focused primarily on the CA1's role in the encoding of temporal information, there has been recent evidence that the CA3 also contributes to temporal duration memory. Time cells and place cells are often co-localized within neuronal HPC populations including CA3 as well as CA1, and some neurons can dynamically encode both place and time properties, leading to speculation that a wider hippocampal circuit might be involved in the encoding of temporal duration memory (Eichenbaum, 2014). Indeed, recent evidence provides support for the prevalence of time cells within the CA3, and points to similarities in temporal patterns of firing between CA3 and CA1 time cells, indicating that the encoding of temporal duration memory is not restricted to the CA1 region (Salz et al., 2016). Evidence of time cells in regions other than the CA1 thus supports the possibility that the origin of timing signals is intrinsic within the hippocampal circuitry (see Section 4: Synthesizing Across the Animal and Human Literature for further discussion).

Importantly, electrophysiological evidence for the involvement of HPC cells in the signalling of temporal duration information has also been observed in non-human primates. In a temporal-order memory task involving macaques, researchers recorded neurons from the HPC and found evidence for an incremental timing signal that was used to map distinct stimuli along a temporal gradient (Naya and Suzuki, 2011). In addition to representing the temporal order of the sequence, hippocampal cells were also active during the delay imposed between presentations of the objects, increasing or decreasing in excitability so as to provide an indication of the elapsed time since the last stimulus presentation as well as an estimate of the time until the next stimulus presentation (Naya and Suzuki, 2011). Although this neural activity is not 'time cell-like' *per se* (i.e. an assembly of cells that fires at distinct time points throughout an interval), more recent work has reported the observation of time cell firing in the monkey HPC during the 1s delay period between the cue and test stimulus on each trial of a visual paired associate task (Cruzado et al., 2019).

2.6. Memory for Longer Temporal Durations

Taken together, the findings from animal research are remarkably unequivocal in implicating the HPC, and particularly its dorsal aspect, and CA1 and CA3 subfields, in mediating temporal duration memory and its control over Pavlovian and goal-directed behaviour. Converging evidence from the trace eyeblink conditioning, PI procedure, temporal bisection, and DRL literature indicates that HPC damage induces an underestimation of duration/intervals, leading to a leftward shift in temporal control over responding.

One very important caveat of the animal work, however, is the limited range of time durations/intervals that have been used. To our knowledge, the longest duration that has been tested with HPC lesions is ~50 s for peak procedure, ~20 s for DRL, and ~60 s for trace conditioning studies. Very few studies have directly examined the role of the HPC in processing longer duration

memory, likely because animals do not perform well in tasks involving longer durations. Nevertheless, Jacobs et al. (Jacobs et al., 2013) investigated the role of HPC in an odour-interval reward discrimination task using intervals in the order of minutes (1 – 12 min), and found that muscimol inactivation of the HPC impaired the ability of rats to discriminate between longer durations with smaller temporal differences (8 vs. 12 min), as opposed to shorter timescale durations (60 vs. 90 s) and larger temporal differences (e.g., 1 vs. 12 min), implicating the CA1 in temporal pattern separation. Additionally, Mankin et al. (2012) recorded from cells in the CA1 and CA3 cells as they were repeatedly exposed to familiar arenas over a time interval of 6, 24 or 30 hrs. They found that CA3 cell activity remained stable and highly correlated in the same environment over time (all intervals), indicating that the CA3 may code for attributes in the environment (e.g., context) outside of temporal information. In contrast, the degree of similarity in CA1 neuronal responses for the same spatial location in a familiar environment decreased over repeated exposure over all time intervals, indicating that the CA1 codes temporal information in the order of hours and days. In a subsequent study, Mankin et al. (2015) uncovered an even more prominent role of the CA2 population activity in temporal coding using the same task. Crucially, in a recent calcium imaging study, Mau et al. (2018) observed that sequences of CA1 neuron firing carried information not only in the order of seconds (i.e. across a 10 s interval) but also longer periods of time including minutes and even over days. Thus, there is growing support from the animal literature that hippocampal involvement in memory for durations is not limited to short time periods but applies across multiple time-scales.

TABLE 1 AROUND HERE

3. The Role of the Human Hippocampus in Temporal Duration Memory

A sizeable portion of relevant evidence from the human literature comes from patient neuropsychological research and fMRI studies in neurologically healthy participants, which have used behavioural paradigms that are comparable to those employed in animal studies, including trace conditioning (e.g. Büchel et al., 1999; Clark and Squire, 1998; McGlinchey-Berroth et al., 1997), temporal bisection (e.g. Caselli et al., 2009), and interval estimation or reproduction (e.g. Harrington et al., 2004; Perbal et al., 2001; Richards, 1973). Moreover, there has been a growing number of recent studies that has assessed temporal memory with novel experimental tasks, providing insight that is unique to the human literature (e.g. Deuker et al., 2016; Ezzyat and Davachi, 2014; Thavabalasingam et al., 2018) (see Table 2).

3.1 Neuropsychological Evidence

Consistent with the non-human animal conditioning work reviewed above, amnesic patients with hippocampal damage have been reported to demonstrate significant impairments (e.g. as reflected by fewer conditioned responses to the CS+ and shorter conditioned response peak latency compared to controls) in trace eyeblink conditioning at an interval of 1000 ms, with milder deficits observed at delays of 500 ms and 750 ms (Clark and Squire, 1998; McGlinchey-Berroth et al., 1997). Notably, the same patients were found to exhibit intact delay eyeblink conditioning (Clark and Squire, 1998; Gabrieli et al., 1995). One suggestion is that this difference in hippocampal dependency between delay and trace conditioning relates to their varying demands on declarative memory, with conscious knowledge of the temporal relationship between the CS and UCS being critical for the development of the conditioned response in trace, but not delay, conditioning (Clark and Squire, 1998). Of note, there is related evidence suggesting that hippocampal damaged amnesic patients are also impaired at probabilistic visual associative learning when delayed feedback is provided (Foerde et al., 2013). More specifically, Foerde and Shohamy (2013) asked participants to learn, via trial and error,

butterfly-flower image pairs within a probabilistic framework and found that amnesic patients were impaired when there was a 7s delay between participant response and feedback (i.e. 'correct' vs. 'incorrect') on each trial, but not when response and feedback were temporally close together (i.e. 1s delay). This work is of particular interest since the delayed feedback learning task shares characteristics with delay conditioning, with both paradigms requiring participants to exploit the relationship between two events separated in time.

Other work that may offer some insight into a potential role for the HPC in memory for short duration information is research that has assessed duration reproduction or discrimination in amnesic patients with hippocampal or wider MTL damage. In the light of the aforementioned trace conditioning findings and moreover the rodent DRL, PI, temporal bisection and time cell work reviewed here, one could conceivably expect patients with hippocampal damage to be impaired at reproducing or discriminating durations even in the order of seconds. Yet, existing evidence paints a picture that is far from clear. Richards (1973) conducted one of the earliest investigations into duration reproduction following MTL damage by administering a simple behavioural paradigm to Patient HM, who had extensive damage to MTL structures including the HPC. On each trial, the experimenter first produced a time interval by speaking the word 'start' followed 1 - 300 s later by 'stop' and after a brief delay, Patient HM was required to reproduce the interval in the same fashion. It was found that Patient HM only had difficulties reproducing intervals beyond 20s in duration and typically underestimated durations of this magnitude, suggesting that MTL damage only impacts the processing of longer durations within the time-scale of long-term memory. Subsequent studies in focal amnesic patients have reported data that are, in principle, consistent with this conclusion, although importantly, there is some discrepancy in the reported duration lengths for which intact performance is observed. For instance, Perbal et al. (2001) assessed participants' ability to reproduce the durations for which a blue square was presented on a computer monitor and found that patients

with unilateral temporal lobe resections exhibited intact performance up to 38 s. On the other hand, using a similar approach to that of Richards (1973), Shaw and Aggleton (1994) reported that a group of encephalitic patients demonstrated normal reproduction of temporal durations up to 96 s. Notably, while these two studies demonstrated intact duration reproduction of intervals greater than that reported by Richards (1973) in Patient HM (i.e. 20 s), neither assessed duration reproduction beyond 36 s and 96 s respectively, thus, offering no insight into potential impairments at longer durations. Speaking to this issue, Noulhiane et al. (2007) asked participants to estimate the durations of intervals at which a series of objects were presented during the projection of a documentary film and observed that patients with left but not right unilateral temporal lobe resections exhibited intact performance at durations below 3 minutes, but significantly overestimated durations that were in the range from 3 to 8 minutes. Similarly, in a recent study by Palombo et al. (2016), amnesic patients with focal MTL damage, and patients with circumscribed hippocampal damage, completed a time estimation task in which they viewed a video clip on each trial and were required to make a forced-choice judgment about the duration of the clip (e.g. 'was the video clip 40 s or 1 min 15 s in duration?'). Patients were significantly impaired (as reflected in proportion correct) at making temporal estimations for videos that were longer than 4 min in duration ('long' condition), but not those that were less than 90 s ('short' condition). Of note, patients with circumscribed hippocampal damage performed similarly to those with wider MTL lesions, suggesting that the observed deficits may be attributed to the disruption of hippocampal-dependent processing (Palombo et al., 2016).

While the patient studies described thus far suggest that MTL-damage leads to deficits in the processing of durations in the order of minutes but not seconds, there is research that has demonstrated impairments for shorter durations. This work has primarily assessed populations associated with more diffuse brain atrophy such as Alzheimer's disease (AD) (Caselli et al., 2009; Nichelli et al., 1993; Papagno et al., 2004; Rueda and Schmitter-Edgecombe, 2009) although there

has, to our knowledge, also been one study involving individuals with temporal lobe resections (Melgire et al., 2005). For example, Nichelli et al. (1993) had subjects reproduce a series of 1s time intervals demarcated by auditory beeps as well as estimate the time it took them to read aloud 5, 10, 20, or 40 digits appearing one at a time while concurrently keeping the rhythm of making a key press every second. Individuals with AD were impaired on both tasks, reproducing intervals that were greater in length and more variable compared to elderly controls and were less precise (i.e. greater variability in responses), although overall similar in accuracy, when estimating the time spent on each trial in the time estimation task. Converging with this, Papagno et al. (2004) found that AD patients were significantly poorer compared to controls when estimating the durations of trials lasting 15 or 50 s (with the most frequent error being duration overestimation) in the context of a visual attentional task, in which participants were required to press a key when a moving ball entered a target square, as well as a digit span task, in which participants were instructed to repeat a verbally presented sequence of digits. Similarly, Rueda and Schmitter-Edgecombe (2009) observed that AD patients significantly overestimated the time taken to read a series of visually presented digit sequences lasting 10 – 60 s in duration, and Caselli et al. (2009) reported that AD patients were more imprecise in their ability to make long vs. short judgments of interval durations ranging from 100 to 600 ms (short time bisection task) or from 1000 to 3000 ms (long time bisection task). Notably, findings in participants with mild cognitive impairment (MCI) have contrasted with those in AD, perhaps reflecting the relatively reduced extent of brain atrophy in the former (Coelho et al., 2016; Mioni et al., 2019; Rueda and Schmitter-Edgecombe, 2009). Using the same task as that in AD patients, Rueda and Schmitter-Edgecombe (2009) failed to observe a group effect in MCI cases, and likewise Coelho et al. (2016) found that MCI patients were not significantly different compared to controls when estimating the durations of empty intervals signalled by auditory beeps. Moreover, Mioni et al. (2019) administered a temporal bisection task incorporating neutral and emotional

stimuli to MCI cases (faces with differing emotional expressions) and failed to observe a significant difference in task performance between patients and healthy participants.

A few studies involving temporal lobe epilepsy patients with hippocampal atrophy have also found impairments in the reproduction and discrimination of short durations in the sub-second range (Ehrlé et al., 2001; Vidalaki et al., 1999). Vidalaki et al. (1999) observed that individuals with unilateral temporal lobe epilepsy exhibited deficits on a duration reproduction task involving visual durations from 500 ms to 8 s, as well as a temporal bisection paradigm in which participants were required to classify visual durations of 1 - 2 s in length as 'short' or 'long'. In particular, those with right hippocampal atrophy possessed larger Weber fractions on the reproduction task (defined as the standard deviation of responses divided by the mean of responses) as well as the bisection task (defined as the difference limen [DL] divided by the PSE, with the former referring to half the difference between the duration classified 75% of the time as long, and the duration classified 25% of the time as short). In contrast, patients with left hemisphere epilepsy only showed a shorter PSE in the bisection task. On the other hand, Ehrlé et al. (2001) found that temporal epilepsy patients with left hippocampal atrophy were significantly poorer compared to controls and right hippocampal atrophy patients at detecting a change in the interval timing of two successively presented rapid auditory sequences. Perhaps surprisingly, however, this impairment was specific to the condition with 80 ms intervals between each presented tone, with left hemisphere patients requiring a significantly higher threshold to detect a change, and performance was intact at other intervals up to 1000 ms. In contrast to this, Melgire et al. (2005) found that right rather than left unilateral temporal lobe resection patients demonstrated poorer precision on a time bisection task involving intervals from 50 to 200 ms, as reflected in greater DLs and Weber fractions.

Finally, although the vast majority of neuropsychological evidence has arisen from studies employing temporal duration estimation/reproduction tasks that are prospective in nature, Drane et al.

(2010) provided some insight into temporal lobe epilepsy patients' retrospective temporal memory by asking them to estimate the time periods (~15 min) that elapsed after a left and then right hemisphere amobarbital injection (or vice versa) prior to receiving an anterior temporal lobectomy. Right temporal lobe epilepsy patients significantly underestimated the amount of elapsed time following a right or left hemisphere injection compared to controls on a comparable task, irrespective of whether they were unaware (i.e. retrospective memory) or aware (i.e. prospective memory) of the upcoming temporal estimation task (by nature of whether an injection was received first or second in sequence). A similar pattern was observed for left hemisphere patients after a right hemisphere injection, although interestingly, estimation accuracy improved following a left hemisphere injection that was received second rather than first in sequence, suggesting potential differences between prospective and retrospective memory processing in the left hemisphere (Drane et al., 2010). Interestingly, contrary to these findings, studies in AD and MCI have failed to observe impairments in retrospective temporal memory in the order of minutes, with these patients being similar to controls in their ability to estimate the amount of time taken for an entire neuropsychological assessment session (Coelho et al., 2016; Heinik and Ayalon, 2010) or a specific task during neuropsychological assessment (i.e. clock drawing) (Coelho et al., 2016).

Overall, the patient findings covered here provide some evidence to suggest that the HPC is involved in the remembering of information about temporal duration. Crucially, however, there is a large degree of inconsistency across studies, with some demonstrating impairments for short durations (e.g. several milliseconds to a few seconds), and others only finding impairments at longer durations (e.g. tens of seconds to minutes). In addition to this, it is important to highlight that drawing definitive conclusions regarding human hippocampal contributions to temporal duration memory from existing patient neuropsychological data alone is challenging on two fronts. Firstly, much of the evidence arises from behavioural paradigms that do not focus purely on temporal

duration memory *per se*. For instance, while duration reproduction paradigms do contain a mnemonic component, they also place significant demands on other processes including timing perception and decision-making. Thus, poor performance on such tasks may arise from impairments in any one or more cognitive processes involved, and observed patient deficits on one paradigm but not another may reflect, in part, differences in the types of processes that these paradigms each recruit. Secondly, and perhaps more crucially, the wide variability in the underlying aetiology (e.g. encephalitis/AD/MCI/epilepsy/temporal lobe resection/stroke), extent (e.g. unilateral/bilateral; focal hippocampal/wider MTL and beyond; diffuse damage) and characterization (e.g. qualitative/quantitative/absence of scans) of patient lesions in the studies discussed, and moreover the unknown impact of such damage to wider brain network functioning in the reported cases (e.g. see Argyropoulos et al., 2019; Hayes et al., 2012; Henson et al., 2016; Rudebeck et al., 2013), renders specific attribution of observed deficits to the HPC almost impossible. In particular, while a number of studies have described patient deficits on duration estimation/reproduction tasks, the reported participants have typically possessed widespread damage. As such, the consideration of evidence from functional neuroimaging work in neurologically healthy participants alongside patient neuropsychological research is highly critical.

3.2 Neuroimaging Evidence

With regards to trace conditioning, Büchel et al. (1999) reported fMRI findings consistent with non-human animal and human amnesic patient work. Specifically, significant bilateral anterior hippocampal activity was observed during the earlier phases of acquisition of an auditory neutral CS and unpleasant US pair separated by 1000 ms, supporting a crucial role for the HPC in trace conditioning. Similarly, Knight et al. (2004) observed a comparable pattern of left anterior hippocampal activity during a trace conditioning paradigm that paired a visual stimulus with an

electric shock after a 10 s delay, and converging with the trace vs. delay conditioning hippocampal lesion literature, Cheng et al. (2008) demonstrated right hippocampal activity during an eye-blink trace conditioning task with a 500 ms delay contralateral to the eye to which the air puff was delivered, but did not observe any significant hippocampal involvement during a delay conditioning version of the task. Notably, the hippocampal activity in Cheng et al. (2008) was more posterior in location and moreover, was greater during the later rather than early phases of conditioning, the latter being attributed to the slower rate of acquisition of the conditioned response in comparison to earlier work that observed greater hippocampal activity during the earlier phases of acquisition (Büchel et al., 1999; Knight et al., 2004). As noted in the preceding section (3.2 Neuropsychological Evidence), probabilistic associative learning with delayed feedback can be considered to share similarities with trace conditioning, and reflective of this, greater bilateral hippocampal activity, predominantly in the anterior portion, has been reported during the learning of visual stimulus pairs with delayed, as opposed to immediate, trial-wise feedback (Foerde and Shohamy, 2011).

Somewhat contradictory to the patient work described earlier, however, the vast majority of fMRI studies investigating the neural correlates associated with interval reproduction and estimation have not found any human hippocampal involvement (e.g. Bueti et al., 2012; Coull et al., 2008; Pouthas et al., 2005; Teki and Griffiths, 2016). Although a detailed summary of this literature is beyond the scope of the present review, the key point to note here is that such work has often highlighted other structures as being important for such tasks, including the cerebellum, basal ganglia nuclei, dorsolateral prefrontal cortex, supplementary motor area, supramarginal gyrus and insula (e.g., for review see Grondin, 2010; Merchant et al., 2013; Nani et al., 2019). One exception, to our knowledge, is work by Harrington et al. (2004), who examined neural activity while participants compared one of two standard intervals (1200/1800 ms) on each trial with a subsequent interval that was slightly longer or shorter in duration. Both intervals were demarcated by auditory

tones, and were presented with a short 2800/2200 ms delay between them. Importantly, a crucial design characteristic of this study is that the BOLD response elicited by the presentation of the first interval on each trial (i.e. interval memory encoding) was decoupled from that associated with the participants determining the relative durations of the first and second intervals (i.e. decision phase). Significant anterior hippocampal activity was observed during the former, providing some support for the possibility that temporal duration information is encoded in memory. Nevertheless, the fact that the vast majority of fMRI studies have failed to observe hippocampal activity during temporal duration estimation/reproduction tasks raises significant doubt as to whether amnesic patient deficits on similar tasks, in particular those involving durations in the order of seconds, can be attributed specifically to hippocampal damage.

More recently, a number of fMRI studies have sought specifically to explore the involvement of the HPC and other brain structures in the mnemonic representation of time by using paradigms that have assessed retrospective temporal memory (Deuker et al., 2016; Ezzyat and Davachi, 2014; Lositsky et al., 2016; Nielson et al., 2015). For example, participants in Ezzyat and Davachi (2014) first encoded a series of object- or face-scene image pairs and were then asked to judge how far apart in time (i.e. 'very far/far/close/very close') they remembered pairs of items that were presented 8 s apart had occurred. On the other hand, Deuker et al. (2016) assessed participants' memory for the temporal proximity of objects experienced repeatedly within a navigable virtual reality environment, with these objects being situated ~2 – 30 s apart in time. Interestingly, both studies observed that multivoxel patterns of activity in the HPC reflected subjective, rather than objective, temporal memory, with items that participants remembered to have occurred closer together in time being associated with more similar patterns of hippocampal activity in the HPC. Not inconsistent with this, Lositsky et al. (2016) asked participants to estimate the durations between pairs of sound clips that were taken 2 minutes apart from a previously presented continuous 25-minute auditory narrative and

observed a significant relationship between duration estimation and multivoxel pattern activity change in an extensive region of activity that included among other regions (i.e. perirhinal cortex, amygdala, temporal pole), the right HPC. These findings suggest, therefore, that mnemonic representations in the HPC can contain information that reflects an individual's memory of the temporal distance between two events, even if these events were experienced seconds apart. Extending this concept to longer time-scales, Nielson et al. (2015) scanned participants while they retrieved and 'mentally relived' autobiographical memories in response to personal smart phone photographs taken over a period of ~1 month. Left anterior hippocampal activity reflected the temporal distance between events that occurred from 15 hours to 1 month apart, with the retrieval of memories closer in time being associated with more similar patterns of activity.

It is important to acknowledge that while existing fMRI work (Deuker et al., 2016; Ezzyat and Davachi, 2014; Lositsky et al., 2016) suggests that human HPC representations reflect subjective rather than objective retrospective temporal memory, methodological limitations associated with fMRI can render it challenging for this technique to provide definitive insight into the neural activity associated with objective temporal memory. In particular, since fMRI signal drift is inherently correlated with the passage of time, it can be difficult to capture signal change arising from the passage of time alone. Thus, previous studies have examined subjective temporal memory and its associated neural activity for pairs of events comprising a constant temporal interval, without providing a direct comparison with objective memory (Ezzyat and Davachi, 2014; Lositsky et al., 2016).

An important limitation of the aforementioned fMRI research is that it is unclear whether the observed changes in activity reflect the passage of time per se, or changes in the quality and/or quantity of externally experienced events. For instance, changes in contextual information, transitioning from one episode to another (including event segmentation), and fluctuations in the

number and structure of experienced (and remembered) events all likely have an impact on an individual's memory of the amount of time that has passed between two timepoints (e.g. Block, 1974; Boltz, 1995; Ezzyat and Davachi, 2014; Liverence and Scholl, 2012). While these factors may be considered to constitute the experience of time itself (Buzsáki and Tingley, 2018; Tsao et al., 2018), a key question is whether the human HPC represents the durations of empty intervals in the order of seconds, akin to those utilised in trace conditioning paradigms (e.g. Clark & Squire, 1998) and studies that have investigated the characteristics of hippocampal time cells (e.g. Macdonald et al., 2011). To investigate this, Barnett et al (2014) examined hippocampal activity during a short-term sequence memory task, in which participants were first presented on each trial with a sequence of four scenes (study phase) separated by varying intervals (mean 500, 1000, and 2000 ms) and were then required to determine whether a second sequence presented after a jittered 3.5 s delay (test phase) was identical or different (i.e. match-mismatch response) (Figure 1A). A distinctive feature of this paradigm compared to existing fMRI work exploring temporal duration processing is that participants were explicitly instructed to remember the durations of the empty intervals on each trial, with these intervals being embedded within a sequence of events (presentation of scene images). This is critical since the HPC is suggested to be important for sequence processing and the binding of temporally discrete events (e.g. Howard et al., 2005; Jensen and Lisman, 2005; Rawlins, 1985; Wallenstein et al., 1998), functions that are unlikely to be recruited in typical interval estimation/discrimination paradigms in which single intervals are often presented in association with basic sensory stimuli (e.g. auditory tones, visual shapes). It was found that hippocampal activity (in particular in the anterior region) was sensitive to changes in the durations of the three blank intervals, with greater activity during the test phase when the intervals remained the same (i.e. match trial) compared to when they were altered (i.e. mismatch trial) (Figure 1B). Although the interpretation of the direction of this change in activity was unclear given mismatch detection is typically associated

with increased, rather than decreased, hippocampal activity (e.g. Kumaran and Maguire, 2007, 2006), these data were interpreted as being suggestive of hippocampal processing of duration information in the order of seconds within the context of sequences of events (Barnett et al., 2014). To investigate this further, the same data were subsequently subjected to a multivariate analysis in which hippocampal pattern similarity between study and test activity was examined (Figure 1C), with the logic that hippocampal processing of duration information would be reflected in higher pattern similarity for match in comparison to mismatch trials (Thavabalasingam et al., 2018). This is indeed what was found (Figure 1C) suggesting, therefore, that hippocampal sequence memory representations can contain temporal duration information pertaining to empty intervals in the order of seconds (Thavabalasingam et al., 2018). Importantly, this hippocampal representation of duration information appears to occur not only for explicitly encoded duration information but also that processed implicitly. A follow-up study revealed a comparable finding using a task in which participants were instructed to monitor temporal order information (i.e. the order in which the scenes in each sequence were presented) while duration information was manipulated implicitly. Specifically, hippocampal study-test pattern similarity was greater for trials on which temporal order information was constant but duration information was altered (i.e. order match-duration match > order match-duration mismatch), even when participants did not report awareness of the latter (Figure 1C). In the light of the role of the HPC as a match-mismatch detector, a potential caveat of this work is that the observed changes in hippocampal study-test pattern similarity reflect a general match-mismatch signal rather than changes in temporal duration information. Control analyses, however, undermined this alternative interpretation - the magnitude of pattern similarity change did not correlate significantly with univariate signal change (thus ruling out the contribution of a univariate match-mismatch signal), and classification analyses failed to distinguish match from mismatch trials (thus ruling out a generic multivariate match-mismatch signal). Of note, converging

with these fMRI data, more recent patient work has revealed that patients with hippocampal damage are significantly impaired at remembering sequences of short durations but not individual durations (Palombo et al., 2019). Crucially, this finding cannot be explained by differences in memory load for total duration or pieces of information between sequences and individual durations, providing further evidence that the HPC plays an important role in temporal duration memory particularly within the context of event sequences.

FIGURE 1 AROUND HERE

A limitation of Barnett et al. (2014) and Thavabalasingam et al. (2018) is that these studies employed paradigms that assessed short-term memory for duration information, thus making the implications of this work to long-term memory unclear. To address this issue, Thavabalasingam et al. (2019) examined whether temporal duration information encoded within long-term memory could be decoded from hippocampal patterns of activity. Participants first learned four distinct sequences of scene images (Figure 2A), which varied with respect to scene identity and inter-stimulus intervals in a 2 x 2 factorial design. During fMRI scanning, participants' memory for these sequences was then assessed, first in a recognition memory task and then in a cued recall task, in which participants were instructed to mentally replay each sequence in as much visual and temporal detail as possible in response to an on-screen cue. Supportive of the idea that hippocampal long-term memory sequence representations contain temporal duration information, multivariate classification analyses revealed that each sequence was associated with a distinct pattern of activity in the anterior HPC (Figure 2B - C), with the most informative voxels being located in the CA1 subfield. Moreover, a classifier that was trained on the recognition memory fMRI data could successfully classify the four different sequences from the cued recall data, suggesting that the same anterior hippocampal representations

underpinned both recognition and cued recall memory. Crucially, classification according to scene or temporal duration information alone was unsuccessful, reinforcing the idea that the HPC processes temporal duration information in the context of event sequences, and represents the conjunction of temporal duration with other forms of sequence-specific information such as event details and temporal order (Thavabalasingam et al., 2019).

FIGURE 2 AROUND HERE

In summary, the aforementioned fMRI studies provide evidence that the human HPC contributes to temporal duration memory, with hippocampal involvement observed most commonly in experimental tasks in which participants are presented with sequences of events as opposed to single durations. Although correlational in nature, this work offers a degree of anatomical specificity that goes beyond patient neuropsychological studies, and furthermore, has adopted novel approaches to examine temporal duration memory, including the use of more naturalistic stimuli (e.g. Deuker et al., 2016; Lositsky et al., 2016), which go beyond the more basic behavioural paradigms that have been administered to animals and human patients.

TABLE 2 AROUND HERE

4. Synthesizing Across the Animal and Human Literature

By surveying the evidence from both animal and human research, it is evident that the HPC has a role to play in memory for temporal durations. What is also apparent, however, is that there is a sizable degree of variability in the reported findings across studies, which must be taken into account and explained adequately in any cohesive characterization of the involvement of the HPC in

temporal duration memory. To this end, one important distinction that has been made when considering hippocampal contributions to duration memory is that between prospective and retrospective memory. More specifically, it has been proposed that the HPC is predominantly involved in retrospective duration memory, with its involvement in prospective memory being limited for durations, particularly those in the range of seconds (MacDonald, 2014). Related to the latter, an additional division that has been proposed is that between shorter timescales in the order of seconds, and those in the order of minutes and beyond, with the HPC suggested to play a key role in memory for longer durations and corticostriatal circuits considered to be crucial for timing processing at shorter timescales. By considering both of these factors, the differential involvement of the HPC across a variety of experimental paradigms as reviewed above may be better understood. For instance, one can accommodate the suggestion that hippocampal damage in animals impacts but does not eliminate prospective duration memory as assessed by the PI and DRL procedures (MacDonald, 2014). Moreover, the relative lack of studies that have reported human hippocampal activity during interval discrimination/reproduction paradigms may be explained by the prospective nature of these tasks as well as the fact that they involve durations in the order of seconds. In contrast, hippocampal involvement is more consistently observed in both animals and humans in tasks that require the subjects to make a retrospective judgment of durations of previously experienced events and/or involve durations that are relatively longer, including trace conditioning (e.g. Clark and Squire, 1998; Moyer et al., 1990; Port et al., 1986; Solomon et al., 1986), discrimination of intervals in the order of minutes (e.g. Jacobs et al., 2013) and more recent human fMRI tasks (e.g. Deuker et al., 2016; Ezzyat and Davachi, 2014; Nielson et al., 2015).

Although the distinctions between prospective and retrospective temporal memory, as well as that between short and long time-scales are helpful in interpreting existing research, there are aspects of the literature that do not fall neatly within this framework (see Tables 1 and 2). In particular,

recent fMRI and amnesic patient studies demonstrating the importance of the human HPC to short- and long-term memory tasks involving durations in the order of seconds (Barnett et al., 2014; Thavabalasingam et al., 2018, Palombo et al., 2019) (see previous section) are not consistent with the idea that this structure is preferentially involved in retrospective duration memory and memory for durations at longer timescales. In the light of this, we suggest that an additional factor that needs to be considered when characterizing the role of the HPC in duration memory is whether such information is embedded within a sequence of events. Specifically, the HPC is preferentially involved in memory for temporal duration in the context of event sequences rather than individual temporal durations *per se* (Figure 3). Previous research findings point towards the notion that the HPC plays a special role in representing sequences in memory through linking events in space and time (Buzsáki and Tingley, 2018; Howard and Eichenbaum, 2015). For example, amnesic patients with hippocampal damage (e.g. Giovanello et al., 2003; Holdstock et al., 2005; Mayes et al., 2001, 2004) and HPC-lesioned rodents (e.g. Fortin et al., 2002; Kesner et al., 2002) have impairments in remembering associations between items such as is necessary for temporal order memory, but have a relatively preserved capacity to remember individual items. Similarly, there is data highlighting the importance of the HPC in associative memory for temporally discontinuous events (Clark and Squire, 1998; Rawlins, 1985; Wallenstein et al., 1998) with, for instance, greater human hippocampal activity being linked to the successful formation of memories that require the binding of temporally discontinuous stimuli (Hales and Brewer, 2010; Qin et al., 2007; Staresina and Davachi, 2009). Moreover, a number of cross-species studies have identified a crucial role for the HPC in context-specific sequence memory processing, in particular when sequences with overlapping information must be disambiguated (Kumaran and Maguire, 2006a, 2007). Thus, there is convergent evidence from a large body of animal and human work suggesting that the HPC represents sequences in the service of memory.

By viewing the temporal duration memory literature through the lens of the HPC as a sequence processor, seemingly disparate findings can perhaps be reconciled. More precisely, prior animal studies that have demonstrated hippocampal involvement in memory for durations in the order of seconds have typically employed tasks that require the learning of associations between events or stimuli that are temporally discontiguous and sequential in nature. For instance, hippocampal time cells have often been studied in the context of paradigms in which an animal must learn to link an initial event (e.g. presentation of an object or odour) with a subsequent event that takes place after a brief delay. The same principle applies to other hippocampal-dependent tasks, such as trace conditioning, where a CS must be associated with a discontinuous UCS (e.g. Disterhoft et al., 1986; Moyer et al., 1990; Sellami et al., 2017; Solomon et al., 1986), and the PI (e.g. Meck et al., 1984; Tam et al., 2013; Tam and Bonardi, 2012) and DRL procedures (Sinden et al., 1986; Young and McNaughton, 2000), in which animals must learn that reinforcement is contingent on responding after a specified interval. In human studies of duration estimation or reproduction, however, participants are typically required to focus on single durations on each trial, with these durations demarcated by basic sensory stimuli (e.g. auditory tone or visual image) or represented by a singular 'event'(e.g. duration of movie clip). Such tasks place minimal demand on hippocampal-dependent sequence processing and the binding of information across time, in particular when the durations are short and in the order of seconds. Consequently, it is perhaps not surprising that functional neuroimaging studies employing these paradigms have typically not observed significant hippocampal activity (e.g. Bueti et al., 2012, 2008; Coull et al., 2008; Pouthas et al., 2005; Teki and Griffiths, 2016). In contrast, more recent work has reported hippocampal involvement in association with paradigms that ask participants to make temporal duration memory judgements pertaining to sequences of events (e.g. a series of visual stimuli, everyday autobiographical events), regardless of whether these events were experienced over a period of seconds (Barnett et al., 2014; Deuker et al.,

2016; Ezzyat and Davachi, 2014; Thavabalasingam et al., 2019, 2018) or weeks (Nielson et al., 2015), or whether the memory judgements were prospective (Barnett et al., 2014; Thavabalasingam et al., 2018, 2019) or retrospective (Ezzyat & Davachi, 2014; Nielson et al., 2015; Deuker et al., 2016) in nature.

FIGURE 3 AROUND HERE

It is vital to note that while consideration of the HPC as a sequence processor may provide a plausible explanation as to when this structure contributes to duration memory, there remains a number of issues emanating from the literature, which require further research to resolve. One important question is whether the involvement of an event sequence is the single most critical determinant of HPC involvement in duration memory or whether this factor is another boundary condition that needs to be considered alongside the proposed distinctions between retrospective and prospective memory, and/or short vs. long durations. Undermining the former, there are studies in which hippocampal involvement has been demonstrated for prospective memory for single durations in the order of minutes (Jacobs et al., 2013; Palombo et al., 2016), suggesting that the absence of the requirement to remember a sequence of events does not necessarily render a duration memory task hippocampal independent. On the other hand, however, if one conceives time to not be an entity in of itself but rather a property that emerges from the experience of an unfolding flow of events (including external sensory stimulation, and changes in internal states), it may be argued that longer durations inherently contain multiple events, and that bridging across these (whether explicitly or implicitly) is necessary to perceive and remember the entire extent of a single longer duration. Regardless, it is evident that the complex pattern of findings in the literature (see Tables 1 and 2) makes it somewhat difficult to propose an all-encompassing framework and further research will be

necessary to fully understand the boundary conditions that govern the involvement of the HPC in temporal duration memory, ideally with a focus on methodologies and patient populations that allow for clear attribution of findings to the HPC itself (e.g. electrophysiology, fMRI, focal HPC lesions with accompanying volumetric and connectivity data).

Another outstanding question is whether there is differential involvement of the HPC to temporal duration memory along the long axis of this structure, with present research offering no clear answer to this issue. As reviewed earlier (Section 2. Animal Evidence Supporting a Role for the Hippocampus in Temporal Duration Memory), there is evidence supporting a role for both the dorsal and ventral rodent HPC in trace conditioning as well as the DRL procedure. Both regions have also been implicated in PI tasks, although there is some indication that the effects of dorsal vs. ventral manipulations are qualitatively different, reflecting distinct contributions to this paradigm. Moreover, although studies of time cells have typically examined cells in the rodent dorsal HPC, it is unknown whether cells that exhibit comparable properties are also present in the ventral portion. Similarly, existing human work does not provide definitive evidence on this issue. Human neuropsychological studies lack the anatomical specificity to offer insight into anterior (ventral in rodents) vs. posterior (dorsal in rodents) hippocampal involvement and a number of fMRI studies of temporal memory have examined hippocampal activity without paying specific attention to regional differences (Ezzyat & Davachi, 2014; Lositsky et al., 2016; Thavabalasingam et al., 2018). Moreover, those that have, have reported varying findings, with some reporting anterior hippocampal activity (e.g. Barnett et al., 2014; Büchel et al., 1999; Nielson et al., 2015; Thavabalasingam et al., 2019) and others more posterior hippocampal involvement (Cheng et al., 2008). Further research is necessary, therefore, to determine whether the ventral/anterior and dorsal/posterior regions of the HPC, alongside their differential anatomical connectivity, contribute in a qualitatively different manner to memory for temporal durations.

An additional ongoing topic of interest is whether the HPC generates its own timing signal or relies on other regions for this information in the context of memory processing, particularly at shorter time-scales. The observation of neurons with time cell-like properties in multiple HPC subregions suggests the possibility of an intrinsic hippocampal timing signal and indeed, some theoretical models have proposed a timing mechanism within the HPC itself (e.g. Grossberg and Merrill, 2007, 1992). As discussed previously (Section 2.3. The Hippocampus and Differential Reinforcement of Low Rates of Responding), however, the interpretation of findings from the PI and DRL paradigms in rodents in the context of Scalar Expectancy Theory (Gibbon, 1977; Gibbon et al., 1984) suggests that hippocampal dysfunction impacts memory for time in these tasks (Gür et al., 2019), and that the HPC receives timing information from elsewhere. Convergent with this, work using temporal discrimination and trace conditioning paradigms support a role for the HPC in the retention, rather than perception, of duration information (Jackson et al., 1998; Kim et al., 1995). Moreover, electrophysiological research has observed that the sequential firing of time cells during a delay period can be disrupted when input from medial entorhinal cortex is optogenetically inhibited, suggesting the importance of externally generated temporal information (Robinson et al., 2017), although notably the opposite has also been observed with a lesion approach, with excitotoxic damage to the same area not impacting time cell sequential firing (Sabariego et al., 2019). Beyond the HPC, a wide range of candidate regions for a timing signal have been suggested including the striatum, cerebellum, insula and prefrontal cortex, with the contribution of these regions dependent on the time-scale involved and the nature of the task at hand (e.g. automatic, cognitively demanding, motor-related) (e.g. Lewis and Miall, 2003). These regions have been proposed to interact with the HPC during temporal duration memory (e.g. Gu et al., 2015; MacDonald et al., 2014) and consistent with this, Barnett et al. (2014) observed increased functional connectivity between the HPC and these regions when participants were presented with novel as opposed to old duration information

(i.e. duration mismatch trials), suggesting that interaction between the HPC and timing regions supports the encoding of duration information.

Finally, related to this discussion of non-HPC contributions to the processing of duration memory, it is important to highlight that the firing properties of HPC neurons in relation to temporal information are not unique to this structure, with a number of studies having demonstrated similar patterns of neuronal firing in other regions of the brain. In particular, time cell-like firing has been reported in the striatum (Akhlaghpour et al., 2016; Jin et al., 2009; Mello et al., 2015), and medial and lateral prefrontal cortices (Tiganj et al., 2018, 2017) and furthermore, changes in population activity over an extended period of time have been observed in the medial prefrontal cortex (Hyman et al., 2012) as well as amygdala (Rashid et al., 2016). In the light of this work, an important endeavour going forwards is to investigate how these regions may also contribute to temporal duration memory and how these contributions are distinct from that of the HPC. One possibility is that the neural firing in each area supports temporal duration processing for the type of memory for which that region is specialised, for example, memory for complex conjunctive/relational information in the case of the HPC (whether long- or short-term, including episodic memory and working memory for conjunctive/relational information) (e.g. Lee et al., 2012; Olson et al., 2012). Thus, in other words, it is not that the HPC plays a unique role in the processing of temporal duration information *per se* but rather, codes for duration information as is relevant to its role in subserving memory for complex conjunctive/relational information.

5. Considering an Underlying Mechanism for Hippocampal Contributions to Temporal Duration Memory

If, as suggested above, the HPC does indeed encode and represent temporal information as part of its role in processing sequences of events, then a logical question is whether a common hippocampal

mechanism supports both the processing of duration as well as other sequence-related temporal information such as temporal order. Indeed, considering temporal order information specifically, there are neural, behavioural and theoretical reasons to suggest that order and duration information are subserved by the same mechanism. From a neural perspective, there is a wealth of evidence across species highlighting a critical role for the HPC in supporting temporal order memory (e.g. for review see Davachi and Dubrow, 2015; Eichenbaum, 2013; Wang and Diana, 2017). In brief, hippocampal damage impairs the ability to remember temporal order and hippocampal activity has been demonstrated to reflect different facets of temporal order memory, including for example, successful subsequent recognition, match-mismatch detection and information regarding specific events in their temporal positions within a sequence (e.g. Fortin et al., 2002; Hsieh et al., 2014; Kesner et al., 2002; Kumaran and Maguire, 2006b; Lehn et al., 2009; Manns et al., 2007; Mayes et al., 2001; Shimamura et al., 1990; Tubridy and Davachi, 2011). In addition to this, the temporal coding of sequences has been suggested to be supported by neural oscillations in the theta band (4 - 7 Hz) (Buzsáki and Draguhn, 2004; Hasselmo and Eichenbaum, 2005; Lisman and Idiart, 1995; Lisman and Jensen, 2013; O'Keefe and Recce, 1993; Skaggs et al., 1996) and theta oscillations have been observed in the processing of temporal order (Crivelli-Decker et al., 2018; Heusser et al., 2016; Hsieh et al., 2011). Interestingly, neural oscillations have also been proposed to be involved in memory for duration information (Buhusi and Meck, 2005; Matell and Meck, 2004, 2000), and prior work has suggested that the theta rhythm can contribute to the coding of time intervals (Gu et al., 2015; Hasselmo and Stern, 2014). Indeed, hippocampal theta has been demonstrated to be important in the acquisition of trace conditioning (Hoffmann and Berry, 2009), discriminating temporal durations on the order of seconds (Nakazono et al., 2015) and in interacting with classical timing regions during learning such as the cerebellum and striatum (Berke et al., 2004; Hoffmann and Berry, 2009).

From a behavioural perspective, a number of studies support the view that order and duration may be related components of an overall sequence representation processed by a common underlying mechanism. For example, memory for duration has been shown to be selectively disrupted by concurrent temporal order memory tasks (Brown and Smith-Petersen, 2014; Fortin et al., 2007) highlighting that both may share a similar set of specialized cognitive functions (Brown and Smith-Petersen, 2014; Elvevåg et al., 2004; Farrell, 2008). Furthermore, prior research has demonstrated that memory for temporal order is impacted by duration (Brunec et al., 2017; Chiba et al., 1994; Geiger and Lewandowsky, 2008; Kesner, 1990; Kwok and Macaluso, 2015; Lewandowsky et al., 2008), with order memory increasing as a function of the amount of temporal separation between the items presented within a sequence.

Thirdly, from a theoretical perspective, models emerging from the human memory literature have proposed a connection between temporal order and duration memory. Time-based models of human memory have emphasized that events occur along a temporal dimension (Brown et al., 2007, 2000), and further assume that memory for the order of events follows memory for the timing of those events. A similar set of models are retrieved-context models (Anderson and Bower, 1972; Howard and Kahana, 2002; Polyn et al., 2009). According to these models, when a sequence of stimuli is presented, each stimulus is associated with a gradually varying context state. Any two stimuli that were experienced in close proximity are subsequently associated indirectly by their similar context states. Thus, during the recall of a list of items – 1-2-3-4 – a successive item “4” will be maximally predicted by the retrieval of “3” because of their similar contexts with this effect gradually decreasing with items further away (e.g. retrieval of “1”) (see, however, Hintzman, 2016). Importantly, this definition of temporal context has been recently generalized so as to enable the mnemonic representation to carry information about the temporal relationships between stimuli, such as explicit timing information. For instance, in trace conditioning, a CS does not maximally predict

the UCS to occur immediately afterwards (as classic retrieved-context models would predict), but rather, will only maximally predict a subsequently occurring UCS after *n* seconds (Shankar and Howard, 2010). This updated model differs from prior models that also demonstrate a scalar property (Church, 1984; Gallistel and Gibbon, 2000; Gibbon, 1977; Oprisan et al., 2018) by assuming that temporal effects in episodic recall, such as recency and contiguity effects, share a common origin with the timing effects seen in paradigms such as trace conditioning and the observed impact of hippocampal lesions, and therefore, is consistent with previous theories that establish a connection between episodic memory and timing behaviour (Clark and Squire, 1998; Rawlins, 1985; Wallenstein et al., 1998). A further strength of this computational approach is that it provides a unique and necessary bridge between behaviour and neurophysiology, by proposing an all-encompassing framework that potentially accounts for both the timing-related behavioural and cell-recording findings reviewed here (Tables 1 and 2) (Howard et al., 2015; Howard and Eichenbaum, 2013). In support of a retrieved-context viewpoint, a neural signal has been demonstrated in the MTL in association with changing contextual representation (Folkerts et al., 2018; Howard et al., 2012; Manning et al., 2011) and importantly, has been shown to support temporal order memory for events (Jenkins and Ranganath, 2016; Manns et al., 2007). For instance, in a recent study participants encoded objects while performing a semantic judgment task and during test, judged the relative recency of pairs of studied items. Greater hippocampal activity pattern dissimilarity between pairs of items during encoding led to more accurate subsequent discrimination of relative recency (Jenkins and Ranganath, 2016). Crucially, prior data also supports the possibility that a changing context representation in the HPC can underpin duration memory. For instance, it has been shown that the more distinct two context representations are in the HPC, the more likely events will be subsequently remembered as being further apart in time (Deuker et al., 2016; Ezzyat and Davachi, 2014; Paz et al., 2010). In addition, the importance of contextual information to duration memory has also been

demonstrated behaviourally, with retrospective duration estimates during a navigational task being related to the recollection of contextual information (Brunec et al., 2017). Hippocampal contextual representations could, therefore, underpin sequence memory and provide important information about experienced events and their timing with respect to temporal order and duration.

Besides contextual representation, there are a number of other mechanisms that have been suggested to facilitate memory for temporal order (e.g. for review see Friedman, 1993). These include associative chaining, in which order is derived from the associations that are formed between successively experienced stimuli/events (e.g. Lewandowsky and Murdock, 1989), and memory strength, which decays as a function of time from the moment a stimulus/event is encoded and supports order judgements on the basis of recency (e.g. an event associated with a weaker memory would be judged to have occurred earlier than an event associated with greater memory strength) (e.g. Hinrichs, 1970; Hintzman, 2005). Importantly, although a detailed discussion of the merits and weaknesses of these and other theoretical accounts is beyond the present review, there is evidence linking the HPC to these mechanisms in support of temporal order memory (e.g. Dubrow and Davachi, 2014; Lieberman et al., 2017). Moreover, it is plausible that these same mechanisms could also contribute to duration memory with a longer interval between two events being encoded as a greater decay in memory strength or a weaker pairwise associative link. Needless to say, further research is necessary to investigate the potential contributions and limitations of these different mechanisms, with the possibility that a combination of these contributes to both temporal order and duration memory (e.g. DuBrow and Davachi, 2017; Lieberman et al., 2017).

Finally, although commonalities exist between duration and order memory, it is important to note that it has also been suggested that order and duration are subserved by largely separate, dedicated cognitive systems (e.g. Carr and Wilkie, 1997) and indeed, certain theoretical models, such as event-based theories, assign minimal or no importance to time in relation to order memory

(e.g. Burgess and Hitch, 2006; Farrell et al., 2011; Farrell and McLaughlin, 2007; Henson, 1998; Lewandowsky and Farrell, 2008). In addition to this, there are differences in the utility and expression of memory for order and duration. Previous work has demonstrated that individuals are more accurate at discriminating previously experienced events on the basis of order in comparison to duration information (Barnett et al., 2014; Brunec et al., 2017; Thavabalasingam et al., 2018), likely reflecting the greater saliency of the former in comparison to the latter. Moreover, subjective memory for duration is liable to be influenced by a number of factors. For instance, individuals tend to underestimate the travel time for a spatial route, with this compression in time being shown, for example, to be related to the familiarity and complexity of a route (Arnold et al., 2016; Bonasia et al., 2016; Jafarpour and Spiers, 2017). Furthermore, retrospective duration estimations and temporal compression in episodic memory retrieval can be impacted by the number and nature of the experienced events, including the degree of similarity between events, whether the events are goal-directed, the amount of perceptual information change, and the presence of event boundaries (e.g. Ezzyat and Davachi, 2014; Faber and Gennari, 2015; Jeunehomme et al., 2017; Jeunehomme and D'Argembeau, 2018).

Considering all of the above, therefore, it is conceivable that a similar but non-identical set of mechanisms may exist to support temporal order and duration information, as well as other forms of temporal memory, in support of a role for the HPC in processing sequences, but also more generally in the binding together and representation of different elements of experience (Buzsáki and Tingley, 2018; Clewett et al., 2019; Eichenbaum, 2000; Lee et al., 2012; Olsen et al., 2012; Yonelinas, 2013).

6. Conclusion

Converging animal and human evidence shows remarkable consistency in implicating the HPC in the processing of temporal information. Animal and patient lesion data provide strong causal evidence

linking the HPC to temporal duration memory, albeit there is some inconsistency in the literature concerning the range of time durations at which the HPC-dependency emerges, with some arguing that longer durations engage the HPC preferentially. More recent neurophysiological and brain imaging data, which offer superior anatomical specificity to early lesion/neuropsychological data, have confirmed and identified the HPC and its subfields (CA1, CA3) to be responsive and active during temporal duration coding and retrieval, especially under task conditions in which temporally discontinuous events were presented in sequence. It is proposed that conceptualising the HPC as a sequencer processor may offer some resolution to the disparate findings in the literature concerning HPC involvement in duration memory. According to this framework, tasks that place minimal demand on sequence processing and the temporal binding of information (e.g., task requiring retention of a single duration of an event or stimulus in each trial or when the durations are short and in the order of seconds) would not require the HPC. Clearly, further work is required to delineate potential qualitative differences in the contributions of the HPC along the long axis (anterior/posterior, dorsal/ventral) in temporal duration processing, and to further elucidate the exact mechanisms by which the HPC engages in duration memory and other forms of temporal information that are inherent to event sequences such as temporal order.

7. Acknowledgements

This work was funded by the Natural Sciences and Engineering Research Council of Canada (Canada Graduate Scholarship - Doctoral to ST, Canada Graduate Scholarship – Masters to DA; Discovery Grants to ACHL, RI) and a University of Toronto Connaught International Scholarship (to BC). We thank Maryam Sorkhou for help with manuscript editing.

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Figure Legends

Figure 1 – (A) Schematic representation of the match-mismatch paradigm employed by Barnett et al., (2014) in which participants were presented with a sequence of events (i.e. scene stimuli) during the study phase of each trial, and asked to judge whether a second sequence at test was identical (match) or different (mismatch), with the latter arising from a change in the interval durations between events, or the durations of the events themselves. (B) Mean percent signal change in the bilateral hippocampus across the different trial types as reported in Barnett et al. (2014). (C) Examination of pattern similarity in the bilateral hippocampus in Thavabalasingam et al. (2018), in which interval duration information was manipulated explicitly (reanalysis of Barnett et al., 2014 data) or implicitly in a similar sequence match-mismatch task. The analysis approach (left) and findings for explicit and implicit duration memory (right) are shown. All error bars denote standard error. * $p < 0.05$.

Figure 2 – (A) Schematic diagram of the paradigm used in Thavabalasingam et al. (2019). Participants were first required to learn four different sequences of scenes with scene content and temporal structure varying in a 2 x 2 factorial design. Memory for these sequences was then assessed during fMRI scanning using a recognition memory task, with single statistical maps being created for the entirety of each sequence. (B) A classifier was used to explore 4-way sequence classification (i.e. combination of image and temporal information), 2-way classification on the basis of image content only, or 2-way classification based on temporal information only, in the anterior hippocampus (aHPC), posterior hippocampus (pHPC) and parahippocampal place area (PPA) bilaterally. (C) Significant 4-way classification was observed in the aHPC only, whereas significant image classification was observed in the PPA alone. Significant temporal classification was not found in any of the regions of interest. Error bars denote standard error. Dashed lines in graphs indicate chance-level classification accuracy. * $p < 0.05$; ** $p < 0.01$.

Figure 3 – Schematic diagram illustrating some of the conditions for which the HPC is suggested to be involved in temporal duration memory, particularly when durations are in the order of seconds. The upper half depicts scenarios that do not require sequence processing, defined here as the binding of discontiguous, discriminable events, and hence, are HPC independent. These include remembering the duration of a single event (upper-top), remembering the relationship between two events that overlap in time and terminate simultaneously such as in delay conditioning (upper-middle), and remembering the duration of a single interval that is demarcated by two identical (e.g. two auditory beeps) or non-identical (e.g. auditory beep followed by visual stimulus) events, for which detailed memory is not necessary for task performance. The bottom half depicts scenarios that do require sequence processing and thus, are HPC dependent. These include remembering the durations of two distinct stimuli presented successively (top), remembering the temporal relationship between two non-identical events for which memory is necessary for task performance such as in trace conditioning, PI, DRL and paradigms often used to characterise time cells (lower-middle), and remembering the intervals between a series of non-identical events as assessed in recent duration match-mismatch paradigms (lower-bottom). Key: black box = filled duration; white box = empty interval; white letter = memory necessary for task performance; grey letter = memory unnecessary for task performance.

Table 1 – Overview of non-human evidence relevant to the role of the HPC in temporal duration memory, generally organized according to the paradigm employed and chronological order. Besides providing brief details of the paradigms and key findings, each study is also classified as best as possible according to whether it assessed prospective or retrospective duration memory, and whether the paradigm involved individual, temporally discontiguous events, that occurred within a sequence. Note that in some studies the classification of prospective vs. retrospective memory and event sequencing cannot be made with certainty as it is difficult to ascertain the exact cognitive processes engaged by the animals during the relevant task/s.

Reference	Paradigm	Duration length	Key finding	Prospective vs. Retrospective?	Sequence of events?
Trace Conditioning					
Meck et al., 1984	Duration/rate discrimination, peak procedure, in rats with fimbria-fornix lesions.	2, 8 s	Post-training fimbria-fornix lesions impaired temporal working memory, and decrease the 'remembered time of reinforcement'.	Retrospective	Yes
Port et al., 1986	Trace eyeblink conditioning in rabbits with dHPC lesions.	750 ms	Post-training dHPC lesions lengthened onset latency of conditioned responses.	Retrospective	Yes
Solomon et al., 1986	Trace eyeblink conditioning in rabbits with HPC lesions and multiunit dHPC CA1 recordings during acquisition.	500 ms	Pre-training HPC lesions impaired acquisition of CR in trace conditioning. HPC dHPC CA1 activity during trace interval of 500, but not 2000ms in early training.	Retrospective	Yes
Moyer et al., 1990	Trace eyeblink conditioning in rabbits with complete HPC	300 ms, 500 ms	Pre-training HPC lesions impaired trace conditioning at 500ms interval.	Retrospective	Yes

	lesions.				
Kim et al., 1995	Trace eyeblink conditioning in rabbits with complete HPC lesions.	500 ms	Lesioning HPC 1 day after learning (but not 30 days) disrupted trace CR.	Retrospective	Yes
Moyer et al., 1996	Recording of CA1 pyramidal neurons in rabbits brain slices after trace eyeblink conditioning.	500 ms	CA1 neurons showed transient increase in excitability up to 5 days after conditioning.	Retrospective	Yes
McEchron & Disterhoft, 1997	Trace eyeblink conditioning (tone + air puff) and single unit recording in rabbit dHPC CA1.	500 ms	Pyramidal dHPC CA1 cells encode discontiguous spatial and temporal information early in training.	Retrospective	Yes
McEchron et al., 1998	Trace fear conditioning (tone CS and foot shock US) in rats with HPC lesions.	30 s	Pre-training HPC lesions impaired trace fear conditioning.	Retrospective	Yes
McEchron et al., 2000	Trace fear (heart rate) conditioning in rabbits with dHPC lesions.	10 s	Pre-training dorsal HPC impaired acquisition of trace fear CR.	Retrospective	Yes
Shors et al., 2001	Trace and delay eyeblink conditioning in rats with decreased DG neurogenesis.	500 ms	Decreased DG neurogenesis impaired trace but not delay eyeblink conditioning.	Retrospective	Yes
Quinn et al., 2002	Trace fear conditioning in rats with dHPC lesions.	28 s	Post-training dHPC lesions impaired trace fear conditioning.	Retrospective	Yes
McEchron et al., 2003	Extracellular recording of rabbit CA1 neurons during	10 s, 20 s	A cluster of CA1 neurons encode trace interval duration.	Retrospective	Yes

	trace fear conditioning (heart rate).				
Tseng et al., 2004	Trace eyeblink conditioning in mice with dHPC lesions.	250 ms	Pre-training dHPC lesions impaired trace eyeblink conditioning, with volume of dHPC CA1 lesions more predictive of behavioural impairment compared to dHPC CA3, dHPC DG and overall dHPC damage.	Retrospective	Yes
Quinn et al., 2005	Trace fear conditioning in rats with NMDA receptor antagonist APV in the dHPC.	28 s	Pre-training dHPC APV impaired acquisition of trace fear CRs, post-training APV impaired the retention of trace fear CRs.	Retrospective	Yes
Bangasser et al., 2006	Trace fear conditioning in rats with HPC lesions.	30 s	Pre-training HPC lesions impaired trace conditioning.	Retrospective	Yes
Weible et al., 2006	Trace eyeblink conditioning with single cell recording in rabbit dHPC and vHPC CA1.	500 ms	dHPC CA1 showed more robust activity during acquisition and trace interval compared to vHPC.	Retrospective	Yes
Yoon and Otto, 2007	Trace fear conditioning with in rats with dHPC or vHPC lesions.	30 s	Pre- and post-training vHPC lesions impaired acquisition and expression of trace fear CR, post-training dHPC lesions impaired expression of CR.	Retrospective	Yes
Thibaudeau et al., 2007	Appetitive trace conditioning in rats with dorsal, ventral or complete HPC lesions.	2, 4 or 8 s	No impairment in appetitive trace conditioning by pre-training HPC lesions.	Retrospective	Yes
Kyd et al., 2008	Appetitive duration discrimination with fornix vs.	3 vs. 12 s	No impairment in duration discrimination with fornix or HPC	Retrospective	Yes

	HPC lesions.		lesions.		
Czerniawski et al., 2009	Trace fear conditioning in rats with dHPC vs. vHPC lesions.	30 s	Inactivation of vHPC, but not dHPC, impaired acquisition and expression of trace fear CRs.	Retrospective	Yes
Thibaudeau et al., 2009	Appetitive trace conditioning in rats with HPC lesion.	2 s	No impairment in appetitive trace conditioning.	Retrospective	Yes
Lin and Honey, 2011	Appetitive trace discrimination in rats with HPC lesion.	10 s vs. 40 s	HPC lesions impaired the acquisition of the 10s trace discrimination, but not 40s.	Retrospective	Yes
Raybuck and Lattal, 2011	Trace fear conditioning in mice with dHPC lesion.	30 s	Pre-training dHPC inactivation impaired trace fear conditioning.	Retrospective	Yes
Tam and Bonardi, 2012	Appetitive trace conditioning in rats with in dHPC lesion.	15 s	Pre-training dHPC lesion induced maximum CR at earlier time point.	Retrospective	Yes
Sellami et al., 2017	Trace fear conditioning in mice with optogenetically silenced dHPC CA1.	40 s	dHPC CA1 inactivation impaired trace conditioning.	Retrospective	Yes
Suter et al., 2019	In vivo electrophysiology during trace eyeblink conditioning in rabbits.	500 ms	Sustained dHPC DG neuronal responding (significant increase and decrease) during CS presentation and trace period.	Retrospective	Yes
PI Procedure					
Meck et al., 1987	PI procedure in rats with nucleus basalis magnocellularis (NBM) or medial septal area (MSA) lesions.	FI: 40 s, probe: 130 s	Rats with NBM lesions responded later in the peak interval, rats with MSA lesions responded earlier.	Prospective	Yes

Meck, 1988	PI procedure in rats with fimbria-fornix lesions.	20 s, 10 s	Lesioned rats show earlier responding (leftward shift) in peak trials.	Prospective	Yes
Olton et al., 1988	PI procedure in rats with frontal cortex (FC) or NBM or fimbria-fornix or MSA lesions.	FI: 10 s, 20 s probe: 120 s	Rats with FC and NBM lesions show rightward shift in peak trials, rats with FF or MSA show leftward shift.	Prospective	Yes
Dietrich et al., 1997	PI procedure in rats with HPC or subiculum lesions.	FI: 40 s, probe: 130 s	Null effect of HPC lesions on timing behaviour.	Prospective	Yes
Dietrich and Allen, 1998	PI procedure in rats with HPC or mPFC lesions.	FI: 40 s, probe: 130 s	Null effect of HPC or mPFC lesions on timing behaviour.	Prospective	Yes
Tam et al., 2013	PI procedure with gaps in rats with dHPC lesions.	FI: 15 s, 7.5 s Probe: 45 s, 37.5 s	dHPC lesioned rats showed greater rightward shifts compared to controls on gap trials. Impairment in no-gap trials disappears with training.	Prospective	Yes
Yin and Meck, 2014	PI procedure in mice with dHPC vs. vHPC lesions.	Target durations: 15 s, 45 s	Mice with dHPC lesions underestimate target durations (leftward shift); mice with vHPC lesions demonstrate rightward shift (related to the stop time increase in 45s target).	Prospective	Yes
Tam et al., 2015	PI procedure in rats with dHPC lesions.	FI: 15 s, 40 s Probe: 45 s, 80 s	Greater dHPC damage led to greater differences in observed peak time and reinforced duration.	Prospective	Yes
DRL					
Clark and Isaacson, 1965	DRL in rats with bilateral HPC lesions.	20 s	HPC lesions decrease efficiency of responding.	Prospective	Yes
Schmaltz and Isaacson,	DRL in rats with complete	20 s	HPC lesions decrease efficiency of	Prospective	Yes

1966a	HPC lesions.		responding.		
Schmaltz and Isaacson, 1966b	DRL in rats with complete HPC lesions.	20 s	Training animals in CRF after HPC lesions abolish the impairment seen in animals trained in CRF before the HPC lesions.	Prospective	Yes
Pellegrino and Clapp, 1971	Cued DRL in rats with bilateral amygdala, HPC or neocortex lesions.	20 s	HPC and amygdala lesions impaired performance on DRL task if animals are trained with a cue and cue is removed afterwards. No differences in animals that are not trained with cues.	Prospective	Yes
Braggio and Ellen, 1976	Cued DRL in rats with HPC lesions.	20 s	HPC lesions impaired temporal control, cued training rescues it.	Prospective	Yes
Jarrard and Becker, 1977	DRL in rats with damage to CA1 cell fields or CA3-septal connections.	20 s	CA3-septal connection necessary for DRL task, CA1 cell field lesion does not impair performance.	Prospective	Yes
Rawlins et al., 1983	DRL in rats with HPC or Cortical lesions.	12 s	HPC lesions impaired DRL performance. Adding a cue at halfway point decreases the impairment only in HPC group.	Prospective	Yes
Sinden et al., 1986	DRL in rats with complete HPC, CA3 or subiculum lesions.	12 s, 18 s	Complete HPC lesions impaired DRL performance when schedule is increased from 12 to 18s.	Prospective	Yes
Jaldow and Oakley, 1990	DRL in rats with neocortex or HPC lesions.	12 s	HPC lesions induce leftward shifts in IRT distributions.	Prospective	Yes
Bannerman et al., 1999	DRL in rats with complete, dHPC or vHPC lesions.	18 s	Complete HPC lesions produce strongest leftward shift in average IRT	Prospective	Yes

			distributions; selective lesions of dHPC and vHPC also produce leftward shift.		
Young and McNaughton, 2000	Single cell recording of CA1/CA3 neurons in rats performing DRL task.	15 s	Increase in CA1 and CA3 neuronal firing at beginning of DRL trial with gradual decline leading up to response.	Prospective	Yes
Costa et al., 2005	DRL in DG-lesioned rats.	20 s	DG-lesioned rats underestimated durations (leftward shift in peak times).	Prospective	Yes
Bueno et al., 2006	DRL in pre-training DG-lesioned rats.	20 s	DG lesion slowed acquisition; DG important for temporal discrimination.	Prospective	Yes
Cho and Jeantet, 2010	DRL in mice with HPC, PFC or striatum lesions.	10 s	HPC lesions caused less efficiency in timing of responses, PFC mice also impaired on task.	Prospective	Yes
Woodward et al., 2018	DRL in rats with prenatal traffic-related air pollution (TRAP) exposure.	20 s	Reduced DG neurogenesis; fewer lever presses in DRL task.	Prospective	Yes
Temporal Bisection					
Onoda et al., 2003	Event-related potentials (ERP) recorded from HPC in rats performing temporal bisection task.	2 s vs. 8 s	CA1 demonstrated significantly large P3-like ERP during temporal bisection.	Prospective	No
Bueno and Júnior, 2011	Temporal bisection procedure in DG-lesioned rats.	4 vs. 16 s	DG lesions do not impair performance.	Prospective	No
'Time cell' work					
Pastalkova et al., 2008	Recording of dHPC CA1 neurons in rats during treadmill running in between	Delay: 10 s, 20 s	"Time cell" assemblies in the HPC encode time during the delay.	Retrospective	Yes

	spatially alternating maze runs.				
Gill et al., 2010	dHPC CA1 neuronal recording in rats during the delay periods in between trials of reward retrieval task in a plus maze.	Delay: 18-25 s	dHPC CA1 neurons demonstrated discrete firing periods during delay, even from first day of learning.	Retrospective	Yes
MacDonald et al., 2011	Recording of dHPC CA1 cell activity in rats during the delay period of an object-delay-odor reward memory task.	Delay: 10 s	Presence of time cells: neurons fire successively during the delay and 'retime' according to changes in temporal parameters.	Retrospective	Yes
Kraus et al., 2013	Recording of HPC dHPC CA1 cells in rats during treadmill running in between spatially alternating maze runs.	5-16 s	Distinct HPC neurons integrate temporal information.	Retrospective	Yes
MacDonald et al., 2013	Recording of HPC dHPC CA1 cells in head-fixed rats during the delay period of an odour delayed match-to-sample task.	2-5 s	Clusters of CA1 cells encode odour memories during a delay.	Retrospective	Yes
Modi et al., 2014	Two-photon calcium imaging of mice dHPC CA1 HPC neurons during trace eyeblink conditioning.	250 ms	CA1 cells fire during a temporal gap to bridge paired stimuli.	Retrospective	Yes
Salz et al., 2016	Electrophysiological recording of rat dHPC CA1 and dHPC CA3 neurons during treadmill	20 s	Presence of time cells in dHPC CA3 as well as dHPC CA1.	Retrospective	Yes

	running in between spatially alternating maze runs.				
Mau et al., 2018	Calcium imaging of dHPC CA1 neurons in mice during treadmill running as part of traversing a rectangular track to retrieve a reward.	10 s recording compared across minutes, days	The same dHPC CA1 neurons that encode temporal information at short timescales also encode longer timescales.	Retrospective	Yes
Cruzado et al., 2019	Recording of HPC neurons in monkeys during delay period in between the cue and choice stimuli of a visual paired associate task.	1250 ms	Presence of time cells in the HPC.	Retrospective	Yes
Other					
Jackson et al., 1998	Temporal go/no-go task in rats with complete HPC lesions or mPFC lesions.	2 vs 8/10 s	Impairment following HPC lesions.	Prospective	Yes
Kesner et al., 2005	Object-trace-odour paired associate task in rats with dHPC CA1, dHPC CA3 or control lesions.	10 s	Impairment following dHPC CA1 but not dHPC CA3 or control lesions.	Retrospective	Yes
Naya and Suzuki, 2011	Single unit recording in HPC , entorhinal and perirhinal cortex in macaques performing a temporal-order memory task.	40 ms	Incremental timing signal in HPC represents stimuli according to temporal gradient.	Retrospective	Yes
Mankin et al., 2012	dHPC CA1 and dHPC CA3	6, 24, 30 hrs	dHPC CA1 codes temporal information	Retrospective	N/A

	cell recording in rats during repeated exposure to familiar arenas.		at large timescales (hours-days).		
Jacobs et al., 2013	Odour-interval reward discrimination task in rats with dHPC CA1 lesions.	1-12 min	dHPC CA1 inactivation impaired discrimination between longer durations with smaller temporal differences as opposed to short durations or large temporal differences.	Retrospective	No
Mankin et al., 2015	dCA2 cell recording in rats during repeated exposure to familiar arenas.	6, 18, 24, 30 hrs	Population of dCA2 neurons involved in temporal coding.	Retrospective	N/A

Table 2 – Overview of human evidence relevant to the role of the HPC in temporal duration memory, organized according to the type of task employed and chronological order. Studies are listed if they sought specifically to investigate the role of the HPC (and/or surrounding regions) in temporal duration memory, or have provided incidental relevant evidence. Besides providing brief details of the paradigms and key findings, each study is also classified as best as possible according to whether it assessed prospective or retrospective duration memory, and whether successful performance necessitated participants to process individual, temporally discontiguous events, and bind them together as a sequence.

Reference	Paradigm	Duration length	Key finding	Prospective vs. retrospective?	Sequence of events?
Conditioning					
Gabrieli et al., 1995	Delay eye-blink conditioning (tone with air puff) in MTL amnesic patients.	750 ms (from start of CS)	Intact conditioning.	Prospective	No
McGlinchey-Berroth et al., 1997	Trace eye-blink conditioning (tone with air puff) in MTL amnesic patients.	500, 750 & 1000 ms (from end of CS)	Impaired conditioning, with greater deficits at longer durations.	Prospective	Yes
Clark & Squire, 1998	Trace eye-blink conditioning (tone with air puff) in MTL amnesic patients. Delay eyeblink conditioning (tone with air puff) in MTL amnesic patients.	1000 ms (from end of CS) 1250 ms (from start of CS)	Impaired conditioning. Intact conditioning.	Prospective Prospective	Yes No
Büchel et al., 1999	Auditory trace conditioning (neutral tone with aversive tone) fMRI study.	1000 ms (from end of CS)	Bilateral anterior HPC activity during acquisition.	Prospective	Yes
Knight et al., 2004	Visual trace conditioning (visual shape with electric shock) fMRI study.	10 s (from end of CS)	Left anterior HPC activity early in acquisition.	Prospective	Yes

Cheng et al., 2008	Trace eye-blink conditioning (tone/white noise with air puff) fMRI study.	500 ms (from end of CS)	Greater right posterior HPC activity during trace vs. delay conditioning, with greater late vs. early trace conditioning acquisition activity.	Prospective	Yes
	Delay eye-blink conditioning (tone/white noise with air puff) fMRI study.	750 ms (from start of CS)	Reduced right posterior HPC activity compared to trace conditioning.	Prospective	No
Probabilistic learning					
Foerde and Shohamy, 2011	FMRI study of probabilistic associative learning with immediate or delayed feedback.	0 & 6 s	Bilateral HPC activity (predominantly anterior) for delayed (6 s) compared to immediate (0 s) feedback.	Prospective	Yes
Foerde and Shohamy, 2013	Probabilistic associating learning with immediate or delayed feedback in MTL amnesia patients.	1 & 6 s	Impaired learning for delayed (6 s) compared to immediate (1 s) feedback.	Prospective	Yes
Duration reproduction					
Richards, 1973	Reproduction of durations demarcated by verbal signals (‘stop’, ‘start’) in Patient HM.	1 – 300 s	Impaired reproduction beyond 20 s, with tendency to underestimate time.	Prospective	No
Nichelli et al., 1993	Reproduction of duration demarcated by auditory beep and visual square in AD patients.	1 s	Impaired reproduction by producing longer intervals.	Prospective	No
Shaw & Aggleton, 1994	Reproduction of durations demarcated by verbal signals (‘stop’, ‘start’) in MTL amnesic patients.	3 – 96 s	Intact reproduction at all durations.	Prospective	No

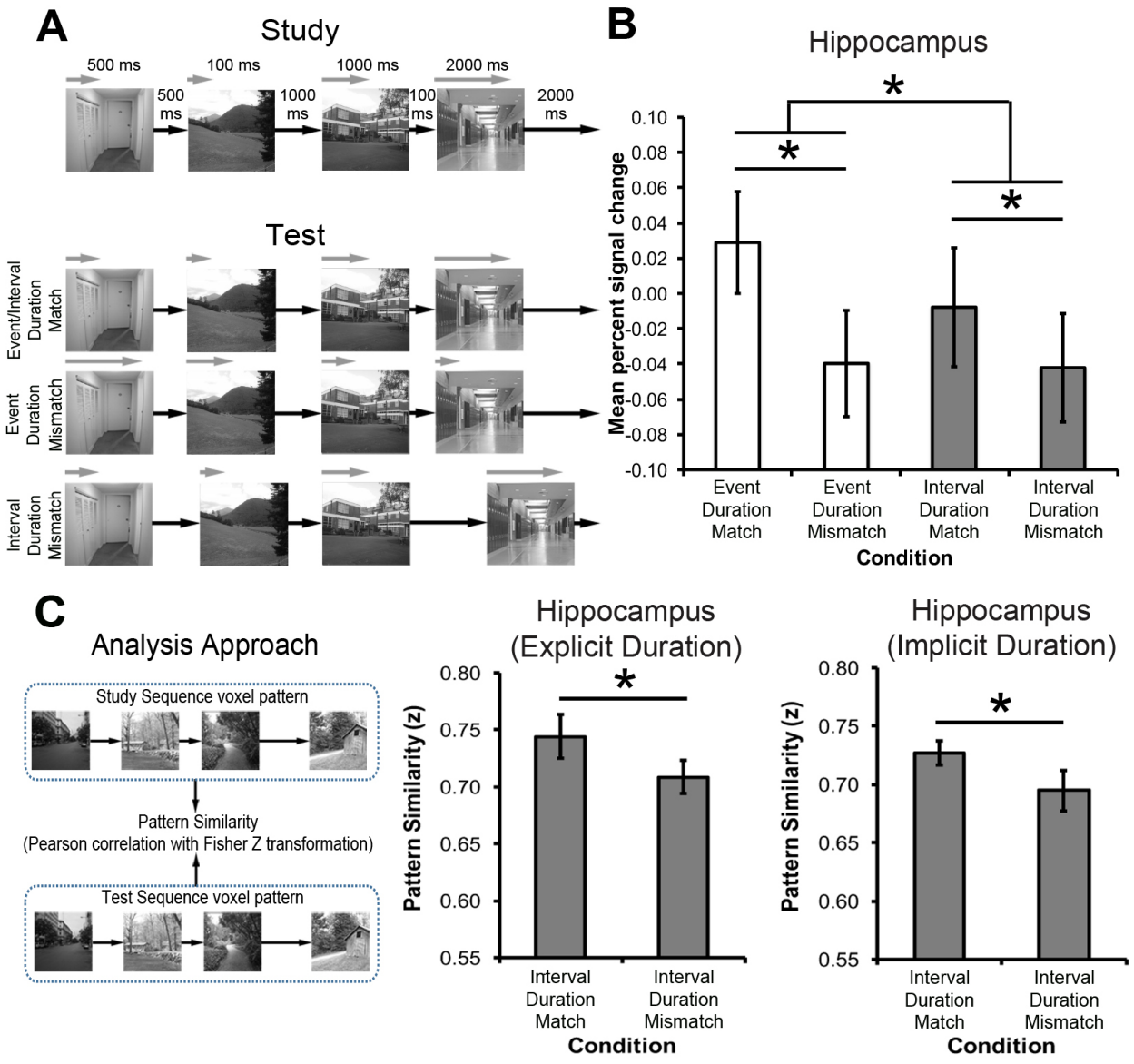
Vidalaki et al., 1999	Reproduction of durations of visually presented circle in unilateral temporal lobe epilepsy patients.	500 ms – 8 s	Impaired reproduction (greater Weber fractions) in patients with right but not left hemisphere patients.	Prospective	No
Perbal et al., 2001	Reproduction of durations of visually presented square in unilateral temporal lobe resection patients.	5, 14 & 38 s	Intact reproduction at all durations.	Prospective	No
Duration estimation					
Nichelli et al., 1993	Estimation of time needed to read aloud visually presented digits in AD patients.	~5 – 40 s	Impaired estimation (reduced precision in responses).	Prospective	No
Papagno et al., 2004	Estimation of time taken for each trial of a visual attention task (participants indicated when a ball entered a target square) in AD patients.	15 & 50 s	Impaired estimation (overestimation) of both durations.	Prospective	No
	Estimation of time taken for each trial of a verbal digit span task in AD patients.	15 & 50 s	Impaired estimation (overestimation) of both durations.	Prospective	No
Noulhiane et al., 2007	Estimation of time between object pictures presented during movie clip in unilateral temporal lobe resection patients.	1 – 8 min	Intact estimation in right resection patients at all intervals. Left resection patients impaired from 3 min.	Retrospective	Yes
Rueda & Schmitter-Edgecombe, 2009	Estimation of time taken to read visually presented digits in MCI patients.	10, 25, 45, & 60 s	Intact estimation of all durations.	Prospective	No
	Estimation of time taken to read	10, 25, 45, &	Impaired estimation	Prospective	No

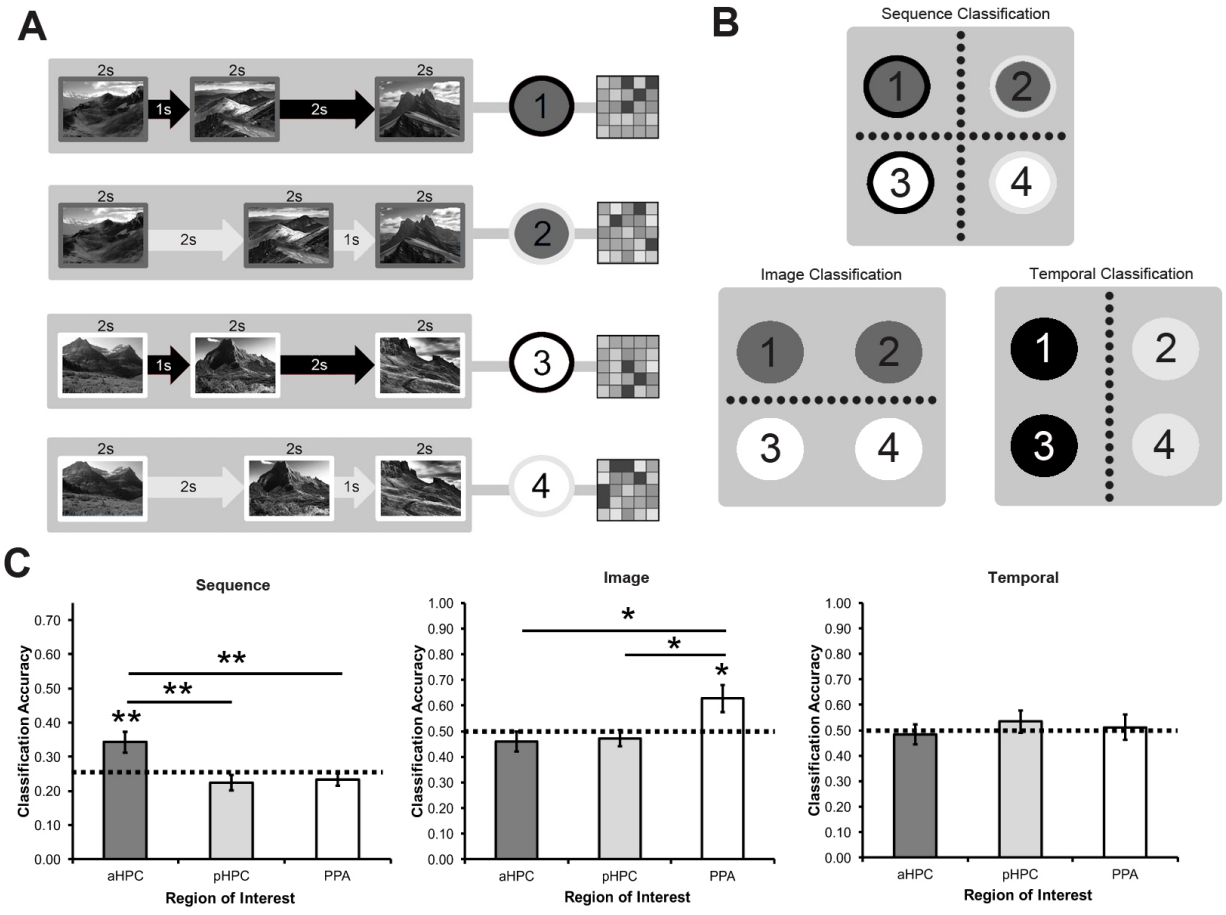
	visually presented digits in AD patients.	60 s	(overestimation) of all durations.		
Drane et al., 2010	Estimation of elapsed time following unilateral amobarbital injections in unilateral temporal lobe epilepsy patients.	~15 min	Impaired estimation (underestimation) in task-aware right hemisphere patients after left or right hemisphere injection.	Prospective	Yes
			Impaired estimation (underestimation) in task-unaware right hemisphere patients after left or right hemisphere injection.	Retrospective	Yes
			Impaired estimation (underestimation) in task-aware left hemisphere patients after right hemisphere injection but improved estimation after left hemisphere injection.	Prospective	Yes
			Improved estimation of task-unaware left hemisphere patients after left or right hemisphere injection	Retrospective	Yes
Heinik & Ayalon, 2010	Estimation of time taken for neuropsychological assessment in dementia patients (including AD) and MCI.	~40 min	Intact estimation in both	Retrospective	No
Ezzyat & Davachi, 2014	FMRI study of subjective temporal	8 s	Greater left HPC pattern	Retrospective	Yes

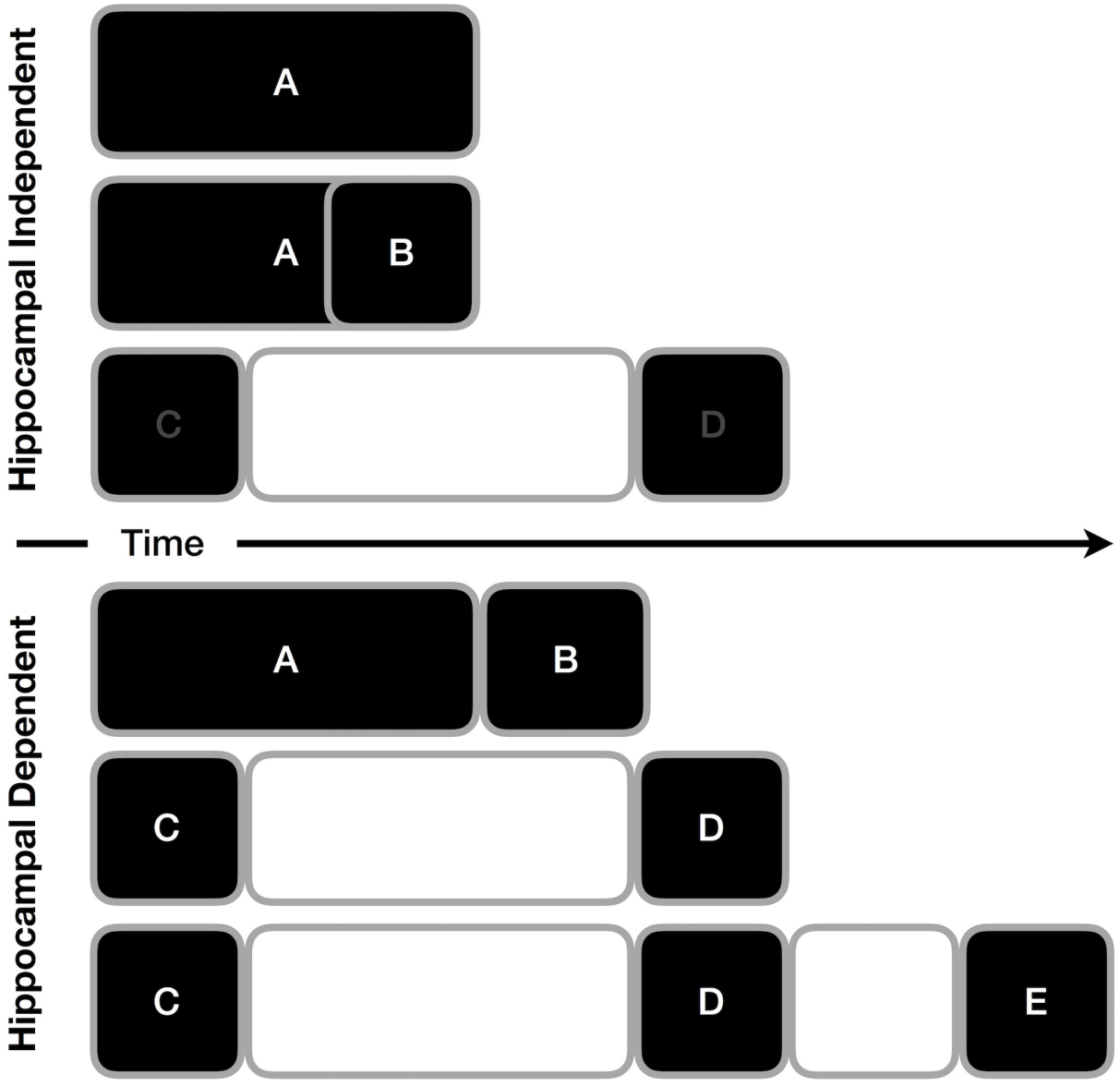
	distance between object-/face-scene pairs presented in a sequence.		similarity for stimuli judged to have occurred closer together in time.		
Deuker et al., 2016	FMRI study of subjective temporal distance between objects encountered along a navigational route within a virtual environment.	~2 – 30 s	Greater bilateral HPC pattern similarity for objects judged to have been encountered closer together in time. Significant correlation between pattern similarity and temporal distance in right anterior HPC.	Retrospective	Yes
Lositsky et al., 2016	FMRI study of estimation of durations between pairs of sound clips taken from a longer auditory narrative.	2 min	Significant correlation between duration estimation and multivoxel activity pattern change in right anterior HPC.	Retrospective	Yes
Palombo et al., 2016	Estimation of durations of movie clips in MTL amnesia patients.	Either ≤ 90 s or > 4 min	Intact estimation at ≤ 90 s, impaired estimation beyond 4 min (performance measured as proportion correct).	Prospective	No
Coelho et al., 2016	Estimation of empty interval demarcated by auditory beeps in MCI patients.	7, 32, & 58 s	Intact interval estimation.	Prospective	No
	Estimation of time taken to draw a clock or administer neuropsychological evaluation in MCI patients.	Minutes	Intact time estimation.	Retrospective	No
Temporal bisection & discrimination					
Vidalaki et al., 1999	Temporal bisection of durations of	1 – 2 s	Impaired bisection in right	Prospective	No

	visually presented circle in unilateral temporal lobe epilepsy patients.		(greater Weber fractions) and left (greater DLs) hemisphere patients.		
Ehrlé et al., 2001	Temporal irregularity discrimination of auditory sequences in MTL epilepsy patients with unilateral HPC sclerosis	80 – 1000 ms	Impaired performance in left but not right hemisphere patients for tones presented at 80 ms intervals (higher threshold needed to detect duration change). Intact performance at all other intervals.	Prospective	No
Harrington et al., 2004	FMRI study of discrimination of durations demarcated by two auditory tones	980 – 1470 ms or 1482 – 2185 ms	Right anterior HPC activity during encoding of durations	Prospective	No
Melgire et al., 2005	Temporal bisection of durations of an auditory tone in unilateral temporal lobe resection patients.	50 – 200 ms	Impaired bisection in right (greater DLs and Weber fractions) but not left unilateral temporal lobe resection patients.	Prospective	No
Caselli et al., 2009	Temporal bisection of durations demarcated by an auditory tone and visual white square in AD patients.	100 – 600 ms or 1000 – 3000 ms	Impaired bisection (reduced precision) across both duration ranges.	Prospective	No
Mioni et al., 2019	Temporal bisection of durations indicated by presentation of neutral and emotional face images in MCI patients.	400 – 1600 ms	Intact performance.	Prospective	No
Duration match-mismatch detection					
Barnett et al., 2014	FMRI study of explicit match-mismatch detection of sequences of	~500 – 2000 ms	Increased bilateral anterior HPC activity at retrieval for match	Prospective	Yes

	scene images with varying durations.		compared to mismatch trials.		
Thavabalasingam et al., 2018	FMRI study of explicit and implicit match-mismatch detection of sequences of scene images with varying durations.	~500 – 2000 ms	Mismatch trials associated with decreased bilateral HPC pattern similarity compared to match trials for both explicit and implicit manipulations.	Prospective	Yes
Palombo et al., in press	Match-mismatch detection of sequences of durations depicted by spinning pinwheels in MTL amnesic patients.	~500 – 2000 ms	Impaired match-mismatch detection.	Prospective	Yes
	Match-mismatch detection of individual durations depicted by spinning pinwheels in MTL amnesic patients.	~500 – 2000 ms	Intact match-mismatch detection.	Prospective	No
Other					
Nielson et al., 2015	FMRI study of autobiographical memory retrieval in response to personal photographs.	15 hrs – 1 month	More similar patterns of activity in left anterior HPC for memories of events that occurred closer together in time.	Retrospective	Yes
Thavabalasingam et al., 2019	FMRI study of recognition and free recall of sequences of scene images with varying durations.	1 & 2 s	Individual sequences associated with distinct multivoxel activity patterns in bilateral anterior HPC, with most informative voxels in CA1.	Prospective	Yes


A
Study
500 ms
100 ms
1000 ms
2000 ms
500 ms
1000 ms
100 ms
2000 ms
Test
Event/Interval Duration Match
Event Duration Mismatch
Interval Duration Mismatch
B
Hippocampus
Mean percent signal change
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
-0.06
-0.08
-0.10
Event Duration Match
Event Duration Mismatch
Interval Duration Match
Interval Duration Mismatch
Condition
C
Analysis Approach
Study Sequence voxel pattern
Pattern Similarity
(Pearson correlation with Fisher Z transformation)
Test Sequence voxel pattern
Hippocampus
(Explicit Duration)
Pattern Similarity (z)
0.80
0.75
0.70
0.65
0.60
0.55
Interval Duration Match
Interval Duration Mismatch
Condition
Hippocampus
(Implicit Duration)
Pattern Similarity (z)
0.80
0.75
0.70
0.65
0.60
0.55
Interval Duration Match
Interval Duration Mismatch
Condition


A
2s
1s
2s
1
2
3
4
B
Sequence Classification
Image Classification
Temporal Classification
C
Sequence
Image
Temporal
Classification Accuracy
Region of Interest
aHPC
pHPC
PPA
**
*


Hippocampal Independent
A
A
B
C
D
Time
Hippocampal Dependent
A
B
C
D
C
D
E

Highlights

- Cross-species evidence supports a role for the hippocampus in duration memory.
- Discrepancies in findings cloud the conditions governing hippocampal involvement.
- We suggest the importance of considering the hippocampus as a sequence processor.
- The hippocampus supports duration memory in the context of event sequences.
- Overlapping hippocampal mechanisms may support memory for duration and order.