Neural dynamics in sleep and memory

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Doctor of Philosophy in Neuroscience

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List of Abbreviations

AUC – Area under the curve

CT – Computed tomography

EEG – electroencephalography

EOG – electrooculography

IQR – Interquartile range

KDE – Kernel density estimation

LDA – Linear discriminant analysis

LME – Linear mixed-effects (model)

MRI – Magnetic resonance imaging

MTL – Medial temporal lobe

NREM – Non-rapid eye movement (sleep)

PCA – Principal component analysis

PC – Principal component

RT – Reaction time

SD – Standard deviation

SEM – Standard error of the mean

SO – Slow oscillation

tACS – Transcranial alternating current stimulation

tDCS – Transcranial direct current stimulation

TFR – Time-frequency representation

Abstract

Our ability to store and retrieve information in memory is supported by the complex activity of billions of neurons across trillions of synaptic connections. These neurons do not send and receive signals randomly; rather, they covary in structured ways over time and space. This gives rise to emergent electrophysiological properties, including neural oscillations and latent population trajectories. By exploring these emergent patterns, we can better understand how the brain uses neural dynamics at different scales to support memory function in wake and sleep. In this thesis, I focus on three related dynamic neural signals at distinct spatio-temporal scales: cortical spindles, hippocampal ripples, and unit-level latent population trajectories.

Spindles are characteristic sleep oscillations linked to memory function. The local expression of spindles is influenced by task-related endogenous cortical excitation before sleep. However, it is unclear whether spindle topographies respond to exogenous stimulation. In **Chapter 2**, I present a nap study in which I used non-invasive brain stimulation to experimentally excite local cortical sites before recording scalp electroencephalography (EEG) during subsequent sleep. The results show spindle rates track the excited cortical sites, indicating spindle topography is directed by cortical excitability before sleep. This contributes to our understanding of local spindle expression and establishes a new method for experimentally manipulating spindle topographies.

Next, I zoom in and examine hippocampal ripples. The hippocampus plays a functional role in indexing and reactivating associations; however, it is unknown whether ripple activity in wakefulness responds to associative memory load. **Chapter 3** describes an intracranial EEG (iEEG) study where participants performed associative and non-associative memory tasks in

an intermixed paradigm. The results showed higher ripple rates in associative retrieval and delay periods. Moreover, the amplitude and duration of ripple events were greater during the delay period after encoding memory items in the associative task. Together, this suggests hippocampal ripples track associative task demands during active memory retrieval and rest periods.

Subsequently, I zoom in further to explore the dynamic properties of unit-level population activity. During cued recall, population activity shifts to represent the associated target memory. Recalling a more stable or well-connected memory may result in faster "shifts" to express the target representation. Moreover, successful memory search may require the population activity to rapidly activate multiple representations before triggering the correct memory trace. Therefore, faster changes of the population activity may relate to memory success. In **Chapter 4**, I test how the rapid activity changes, reflected in the velocities of population trajectories, relate to memory behaviour, reinstatement, and ripple activity. My results reveal that peak velocities in trials are related to memory behaviour, representational reinstatement, and local ripples. This reveals correlations between properties of dynamic latent population activity and memory processing.

Finally, **Chapter 5** summarises and discusses the significance of the main findings, whilst highlighting limitations and future directions.

Together, this thesis makes methodological and theoretical progress that advances our understanding of the emergent dynamics of neural activity related to memory function in wake and sleep.

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Statement of Contributions

I collected all the data and performed all the analyses in the study presented in Chapter 2. This includes the data collection of a vast magnetic resonance imaging (MRI) data set (>80 hours of scanning) which is not detailed in this thesis but will be investigated by future researchers. The study described in Chapter 2 was later published in *SLEEP* (Thom & Staresina, 2025). I authored the Introduction and Discussion sections of Chapter 2 before submission. Following peer review, I revised these sections to incorporate additional results. Material in these sections, in the same or a similar format, also appears in the published version. For consistency and to preserve scientific accuracy, the Abstract, Methods, and Results sections in Chapter 2 are closely resemble the published version, with partial editorial contributions from Bernhard Staresina.

For the projects presented in Chapters 3 and 4, I developed the research questions, performed the analysis, and authored the chapters. The data set was initially collected as part of a previous study (Staresina et al., 2019), with neurosurgical procedures performed by Jan Boström and Florian Mormann, recruitment by Christian Egler, and data collection by Johannes Niediek, Thomas Reber, and Florian Mormann. Due to the long life cycle of intracranial projects, I did not directly collect the data presented in Chapters 3 and 4. Instead, I actively supported the collection of intracranial data for future studies by setting up a collaboration with Bristol Southmead Hospital. This involved multiple site visits and the collection of data from patients, which future researchers will analyse.

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Chapter 1: General Introduction

Prominent neurobiological models suggest that memory function relies on interactions between the hippocampus and cortex, where cortical sites process stimuli and integrate learned experiences into polymodal inputs, which are indexed in a code in the hippocampus (McClelland et al., 1995; Nadel et al., 2000; Teyler & DiScenna, 1986). This code is then reactivated during memory consolidation in wakeful rest and sleep, to stabilise the memory traces by reprocessing the learned information (Rasch & Born, 2013; van der Meer & Bendor, 2025). Moreover, during cued recall, the hippocampal code is reactivated through pattern completion, whereby partial information of the coded learned experience triggers the reinstatement of the associated information, which in turn reactivates cortical sites involved in processing the learned information. Through reactivation of memory traces via this hippocampal-cortical dialogue in memory consolidation and retrieval, the memory traces stabilise into long-term storage and integrate themselves with other learned information.

Although this account of memory function is intuitive, the electrophysiological dynamics underlying memory consolidation and retrieval remain to be fully understood. In this section, I introduce the role of the hippocampal-cortical dialogue in memory function, including the role of the hippocampal index, plasticity, and pattern completion. I then discuss the potential role of neural oscillations during sleep and wake in supporting the hippocampal-cortical dialogue and memory function. Finally, I explore how we can study the cognitive computations in memory by measuring the dynamic properties of unit-level population activity.

The hippocampal-cortical dialogue in memory

The Complementary Learning Systems theory argues the brain requires two learning systems: a "fast" system encoding individual experience for immediate retention, and a "slow" system which integrates information over time for long-term storage (McClelland et al., 1995; McClelland & Goddard, 1996). The theory postulates that the hippocampus and cortex support these "fast" and "slow" learning functions in mammals, and that a dialogue between the two facilitates the integration and transformation of rapidly encoded information in the hippocampus into long-term memory in the cortex. This theory has roots in models of neurobiological systems supporting memory function, which suggest the hippocampus plays a somewhat specialised role in indexing links between cortical sites responsible for processing associated stimuli and behaviours (Marr, 1971; Teyler & DiScenna, 1986).

Converging evidence suggests structures in the medial temporal lobe (MTL) are especially important for memory function. The MTL is a deep brain system of related structures, including the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex (Squire et al., 2004; Squire & Zola-Morgan, 1991). Specifically, the hippocampus is thought to play a role in the encoding, consolidating, and recollecting episodic memories (Diana et al., 2006; Moscovitch et al., 2016; Ranganath & Ritchey, 2012; Scoville & Milner, 1957; Tulving & Markowitsch, 1998; Yonelinas et al., 2019a). Episodic memory is a type of associative memory which refers to our ability to mentally travel back in time and retrieve "where", "what", and "when" information from an "episode" of experience (Tulving, 1972, 2002). This differs from semantic memory, a form of long-term memory for concepts and facts that are not linked to a specific experience (Tulving, 1972).

For instance, an episodic memory might involve a specific scene, such as two people enjoying an ice cream in a city plaza during golden hour. Storing such memories requires encoding associations between multiple high-level features, including the people, objects, and context. Anatomically, the hippocampus is in a unique position to process high-level associations due to its reciprocal connections with high-order associative areas, including the perirhinal, parahippocampal, and entorhinal cortices (Lavenex & Amaral, 2000). Moreover, functionally specialised processing streams that differentially participate in encoding items (e.g., ice creams) and their context (golden hour at the plaza) in episodic memory are thought to converge in the hippocampus (Davachi, 2006). Once these multi-element representations arrive in the hippocampus, it is believed that specific circuitry involving attractor dynamics can efficiently transform them into unique associative patterns (McClelland & Goddard, 1996; Treves & Rolls, 1994). This process then results in changes in the relative strengthening of the synaptic connections between the co-activated populations of hippocampal neurons representing the associated elements, such as the people eating the ice-creams on the plaza.

As well as efficiently encoding high-level associations, it is critical for a "fast" memory system to be able to separate distinct episodic memories when they share overlapping information. This requires unique combinations of elements which only differ slightly (e.g., two people eating ice cream on the plaza at a different time of day) to result in drastic changes to the associative hippocampal activity pattern. Computational models illustrate how the circuitry of dentate granule cells in the hippocampal formation supports this distinction by orthogonalising representations of the incoming inputs before associative binding (McClelland & Goddard, 1996; Rolls, 2016; Treves & Rolls, 1994).

Following successful encoding in the hippocampus, memory traces can be reactivated through pattern completion. This process involves presenting an incomplete activity pattern

associated with a stored memory via relevant cortical areas, including the entorhinal cortex (van Strien et al., 2009). This partial memory cue subsequently activates the corresponding distributed neural populations in the hippocampus. The resulting reactivation is then projected back through these same pathways, specifically via the entorhinal cortex and targeted cortical sites, to trigger activity associated with the specific features and items of the retrieved episode (Chrobak et al., 2000; McClelland & Goddard, 1996; Teyler & DiScenna, 1986).

This reactivation is considered critical for reflecting the reprocessing of the retrieved memory information. Pattern completion plays a role in cued recall scenarios where partial information serves as a retrieval cue (e.g., identifying the people eating the ice-creams at the plaza). Neuroimaging studies have shown hippocampal activity is strongly correlated with successful episodic memory retrieval and facilitates the reinstatement of cortical activation patterns characteristic of the encoded episode (Bosch et al., 2014; Ritchey et al., 2013; Staresina et al., 2012). Furthermore, intracranial recordings have shown that iEEG and neural firing activity in the hippocampus reinstate patterns of neural activity linked to remembered episodic representations during retrieval (Staresina et al., 2016, 2019). Convergent findings indicate hippocampal high-frequency activity in a cued-recall paradigm signals a functional switch in cortical field potential patterns from encoding the memory cue to representing the retrieved memory items. This reactivation is not only informational but also influences memory behaviour. For instance, Liu and colleagues used optogenetic stimulation to reactivate memory traces associated with fearful stimuli (Liu et al., 2012). This reliably evoked behavioural fear responses in rodents, highlighting the hippocampus's causal role in retrieving stored representations and reinstating their functional cognitive and behavioural impact via pattern completion.

As well as supporting active memory retrieval (e.g., during cued recall), hippocampal reactivation is thought to be essential for consolidating memories during rest. Consolidation refers to the process of stabilising and pruning encoded memories to facilitate the retention and integration of information within the brain. Wakeful rest (Wamsley, 2019) and sleep (Klinzing et al., 2019; Rasch & Born, 2013) are critical periods where the brain actively processes encoded information to support consolidation. Electrophysiological studies have demonstrated patterns of neural population activity linked to memories are reactivated during rest and sleep, with impacts on subsequent memory performance (Carr et al., 2011; Wilson & McNaughton, 1994). This reactivation is believed to support memory consolidation at both the systems and synaptic levels.

At a systems level, two-stage models propose that information initially encoded in the hippocampus is gradually integrated into cortical representations (Dudai, 2004; Frankland & Bontempi, 2005; McClelland et al., 1995). This process is informed by studies demonstrating that memory is initially heavily reliant on the hippocampus and becomes transformed, generalised, and integrated into long-term storage in the cortex. At a synaptic level, the reactivation of synaptic activity between associated hippocampal and cortical sites mechanistically modulates memory traces via long-term potentiation and long-term depression. Long-term potentiation is a neurophysiological process whereby increased synaptic activity strengthens synaptic connections, reinforcing the synaptic links representing associated features in memory (Bliss & Collingridge, 1993). Conversely, lack of reactivation and associated synaptic activity may lead to long-term depression, resulting in a reduction in synaptic strength between features of the memory over time (Bear & Malenka, 1994).

While the hippocampus and its memory trace reactivation are thought to play a crucial role in processing associative episodic memories, it may also support other forms of memory,

including motor sequence learning (Albouy et al., 2013). Research has shown that patients with hippocampal damage can still learn new sequential motor movements, such as those required for playing a musical instrument or touch-typing (Nissen & Bullemer, 1987; Reber & Squire, 1994; Schapiro et al., 2019). However, imaging experiments have linked the hippocampal activity with the learning of motor sequences and memory retention after sleep (Albouy et al., 2008, 2013; Schendan et al., 2003).

A recent study showed cortical activity patterns related to the motor learning sequence are reactivated during wakeful rest periods, and these reactivation events showed high signal variance in the motor, entorhinal, and hippocampal regions (Buch et al., 2021). In line with this, a study recording units in macaque motor cortex during a visual motor task found that neural co-firing patterns in primary motor cortex were reactivated during rest, and the rate of reactivation predicted task performance gains (Griffin et al., 2025). These findings suggest that components of motor learning may also benefit from the same hippocampal-cortical reactivation processes involved in episodic memory function (King et al., 2017).

Together, this suggests the hippocampal-cortical dialogue supports the encoding, consolidation, and retrieval of associative memories. However, it is not entirely clear how the brain mechanistically enables this dialogue. With billions of neurons and trillions of connections, how does the brain ensure efficient communication between distant neural populations to support cortico-cortical and hippocampal-cortical interactions? One candidate mechanism is neural oscillations. In the next section, I will introduce the role of neural oscillations in facilitating communication between neural populations during sleep and wake, serving the purpose of memory processing.

Neural oscillations and memory processing in sleep and wake

Neural oscillations recorded with scalp and iEEG reflect synchronous activity in local neural populations (Cohen, 2017). Popular theories, including the "Communication Through Coherence" hypothesis (Fries, 2005, 2015), argue that neural oscillations enable neural populations to communicate within and between regions by providing time windows where co-oscillating neural populations can interact efficiently. Additionally, complex interactions between oscillations at different spatio-temporal scales may boost informational signals travelling between neural populations involved in memory processing, and facilitate synaptic plasticity (Düzel et al., 2010; Fell & Axmacher, 2011). Oscillatory activity differs widely in sleep and wake. Here, I briefly introduce oscillations at different scales during sleep and wake, and their roles in memory consolidation and retrieval.

Non-rapid eye movement sleep (NREM) is characterised by its increased levels of oscillatory activity. These oscillations are believed to participate in active memory consolidation processes. During active consolidation, memory systems reactivate relevant memory activity patterns to strengthen their synaptic connections while integrating information into long-term memory (Klinzing et al., 2019; Rasch & Born, 2013; Staresina, 2024). Specifically, three primary oscillatory signatures in NREM sleep have been studied in relation to active consolidation: SOs, spindles, and ripples. These hierarchically nested oscillations have been found to interact to support the hippocampal-cortical dialogue and cortico-cortical connectivity in service of memory function (Rasch & Born, 2013; Staresina et al., 2015, 2023).

Slow Oscillations

Slow oscillations (SOs) are characterised by large-scale fluctuations (< 1Hz) in cellular excitability, switching between depolarised up-states and hyperpolarised down-states (Massimini et al., 2004). SOs are generated in cortical networks (Crunelli & Hughes, 2010) and often manifest as travelling waves, originating in frontal cortical sites and propagating to posterior cortex and deep brain regions, including thalamus, and hippocampus (Staresina et al., 2023; Steriade et al., 1993; Vyazovskiy & Harris, 2013). Local SOs, which are regionally specific to cortical sites, have also been observed (Nir et al., 2011). These global and local SOs create time windows of large-scale activity and inactivity among neural populations, with intracranial studies showing neural firing rates are linked to SO up-states and down-states (Nir et al., 2011; Staresina et al., 2023; Steriade et al., 2001). As well as reflecting neural activity, SO up- and down-states represent changes in cortical excitability. For example, Bergmann and colleagues used transcranial magnetic stimulation (TMS) targeting the cortical hand area to show motor-evoked responses were greater during SO up-states (Bergmann, Mölle, Schmidt, et al., 2012).

SOs have also been linked to memory processing. Following a memory task where participants learned associations between word pairs, SO up-states had higher amplitudes (Mölle et al., 2009) and marked time windows with increased inter-regional coherence in EEG frequency bands during learning and subsequent sleep (Mölle et al., 2004). Moreover, Huber and colleagues found local SO activity in motor cortices was affected by visuomotor learning before sleep and predicted sleep-related performance gains (Huber et al., 2004, 2006). EEG studies have also found that SOs facilitate cortico-cortical connectivity increases and are predictive of memory performance increases after sleep, suggesting SOs promote

memory consolidation by enabling long-range communication between distant cortical networks (Niknazar et al., 2022).

Spindles

Spindles are 12-16 Hz oscillations with a waxing and waning amplitude profile. They are generated through interactions between GABAergic neurons in the nucleus reticularis and glutamatergic thalamo-cortical projections. Spindle expression is focused around the central and parietal cortex and is projected widely across the brain, including deep brain areas and the hippocampus (Staresina et al., 2015). In this thesis, I differentiate between fast (12-16 Hz) and slow (8-12 Hz) spindles, focusing on the former since slow spindles have been shown to differ in their function, regional expression, and are less commonly represented in hippocampal-cortical dialogue (Mölle et al., 2011a; Staresina et al., 2015).

Increases in spindle amplitude and spindle rate have been linked to improvements in memory after sleep (Gais et al., 2002; Holz et al., 2012; Schabus et al., 2004). Cortical sites and activity patterns during task learning have also been found to reactivate around spindles (Bergmann, Mölle, Diedrichs, et al., 2012; Schreiner et al., 2021). Schreiner and colleagues used multivariate decoding to show learning-related cortical EEG patterns in an associative memory task reactivated around spindle events during subsequent sleep. Moreover, the strength of reactivation predicted memory performance after sleep (Schreiner et al., 2021). As well as supporting associative episodic memory, spindles have also been linked to memory consolidation for motor sequence learning tasks. The rate, duration, and amplitude of spindles have been shown to correlate with motor learning consolidation in young adults

(Fogel et al., 2017), while spindle-linked reactivation of cortical and subcortical areas related to a motor sequence task predicted post-sleep performance gains (Boutin et al., 2018).

Spindles are prime candidates for supporting memory consolidation due to their role in hippocampal-cortical synchronisation and synaptic plasticity. A study concurrently recording spindles in cortex and hippocampus showed hippocampal-cortical interactions were mediated by coupled inter-regional spindle events (Ngo et al., 2020). This mediation may promote the information transfer between regions necessary for memory consolidation. Spindles also directly enable synaptic plasticity by increasing neural firing activity and enhancing cofiring of neuron pairs to within 25 msec, which is close enough in time to promote synaptic plasticity (Dickey et al., 2021; Staresina et al., 2023). Moreover, biophysical experiments found that calcium influx, which kickstarts the molecular process of plasticity, can be induced with electrical stimulation at the spindle frequency and is predicted by the amplitude of spindle events (Niethard et al., 2018; Rosanova & Ulrich, 2005; Seibt et al., 2017).

Spindles and SOs do not occur randomly; instead, they are coupled. Spindles are temporally nested in SO up-states (Staresina et al., 2015), with specific phase alignment boosting spindle amplitudes (Fell & Axmacher, 2011). Spindle-SO coupling has also been shown to predict memory consolidation (Mikutta et al., 2019), while reactivation of cortical EEG patterns is greater around spindles coupled to SOs (Schreiner et al., 2021). This hierarchical coupling and phase alignment of SOs and spindles is thought to work together to enable cross-regional communication at different time resolutions with tight spindle synchronisation riding on larger SO fluctuations (Bergmann & Born, 2018; Fell & Axmacher, 2011).

Spindles also exhibit relatively high degrees of local specificity. This spatial topography is affected by cognitive task demands before sleep (Clemens et al., 2005, 2006; Cox et al., 2014;

Nir et al., 2011; Petzka et al., 2022). Recent work by Petzka and colleagues showed spindles during post-learning sleep are more prevalent at brain sites involved in prior learning (Petzka et al., 2022). The study found that the degree of overlap between cortical activity, measured as a reduction in alpha/beta frequency (6-20 Hz), during an associative episodic memory task and spindle rate topography predicted memory maintenance after sleep. Together, this suggests local cortical sites which are relevant for processing relevant memory information might be "tagged" during wake. Tagged sites then show greater local spindle expression in subsequent sleep as the spindles promote efficient communication within and between the hippocampus and the relevant cortical areas, supporting the reactivation and strengthening of memory traces during active memory consolidation (Petzka et al., 2022; Rasch & Born, 2013; Staresina, 2024).

Stimulating spindles

The functional role of spindles in memory consolidation is supported by studies which used non-invasive methods to stimulate spindle activity experimentally. For example, Cairney and colleagues used audio cues during sleep to influence spindles (Cairney et al., 2018). Sounds associated with certain memory items before sleep were replayed during sleep. When the experimenters played sounds associated with memory items, the sounds triggered an increase in spindle activity. Additionally, cortical EEG patterns related to encoding the cued memory items were reactivated around spindle events and predicted memory retention after sleep (Cairney et al., 2018; Ngo & Staresina, 2022).

Transcranial electrical stimulation is another non-invasive modulation technique which can be used to stimulate spindles. Transcranial electrical stimulation applies low-voltage currents

to the brain via scalp electrodes (Bestmann & Walsh, 2017). The current can be constant (transcranial direct current stimulation; tDCS) or can alternate at a specific frequency (transcranial alternating current stimulation; tACS; e.g., to simulate a SO at 1 Hz). Transcranial electric stimulation influences the excitatory/inhibitory balance of the targeted cortex (Nitsche & Paulus, 2000; Stagg et al., 2018; Stagg & Nitsche, 2011), which may in turn influence SO and spindle expression at the stimulated sites. Others have used transcranial electrical stimulation to modulate spindles, with various levels of success (Antonenko et al., 2013; Barham et al., 2016; Cellini & Mednick, 2019; Del Felice et al., 2015; Eggert et al., 2013; Koo et al., 2018; Ladenbauer et al., 2016, 2017; Lustenberger et al., 2016; Marshall et al., 2004, 2006, 2011; Mednick et al., 2013; Park et al., 2023; Sahlem et al., 2015). Note that these studies focused on artificially inducing spindles through SO-like or spindle-like alternating currents (tACS) or bursting direct currents (tDCS) during sleep.

Given that studies have shown task demands and cortical excitability during wake influence subsequent spindles (Clemens et al., 2005, 2006; Cox et al., 2014; Nir et al., 2011; Petzka et al., 2022), this raises the possibility of using tDCS to modulate cortical excitability during wakefulness and shift localised spindle expression during subsequent sleep. Furthermore, this manipulation could be used to examine the effects on related localised memory consolidation processes experimentally.

Ripples

Ripples are high-frequency gamma bursts (80-120 Hz in humans (Liu et al., 2022)), which are characteristic signatures of hippocampal activity. Hippocampal ripples are generated by a well-studied interaction between pyramidal cells and interneurons in the CA3 and CA1

subfields (Buzsáki, 2015). Ripples are primarily a signature of NREM sleep, where they are coupled with SOs and spindles (Staresina et al., 2015, 2023). This hierarchical nesting of oscillations is thought to allow the brain to communicate and consolidate memory information efficiently (Fell & Axmacher, 2011; Staresina, 2024). Specifically, ripples support memory consolidation by creating very narrow time windows of high synchrony between brain regions. During these narrow windows of coherence, the reactivation of neural activity patterns related to relevant memory can trigger memory traces across the brain and strengthen synaptic connections. Classic studies in rodents found ripples marked events where neural firing patterns from experiences during wake were temporally compressed and replayed in the hippocampus (Wilson & McNaughton, 1994) and cortical sites (Peyrache et al., 2009; Wilber et al., 2017). Moreover, the level of ripple activity and linked reactivation predicted memory performance after sleep (Carr et al., 2011; Ego-Stengel & Wilson, 2010; Girardeau et al., 2009).

Although ripples have primarily been studied in sleep, ripples may play a role in memory retrieval and consolidation during wake. Ripples have been detected in the wake in humans (Axmacher et al., 2008; Billeke et al., 2017; Chen et al., 2021) and have similar properties to those during sleep (Chen et al., 2021). Ripple activity during wake has since been linked to successful memory retrieval, increased hippocampal-cortical synchronisation, and the reactivation of sequential neural firing patterns around ripple events (Norman et al., 2019, 2021; Vaz et al., 2019, 2020). Together, this suggests ripples in the wake might play an important role in synchronising and reactivating information via the hippocampal-cortical dialogue in support of memory retrieval and consolidation during wakefulness.

As outlined earlier, the hippocampus is believed to play a key role in associating features in episodic memory (Diana et al., 2007; Moscovitch et al., 2016; Yonelinas et al., 2019). While

ripples have been linked to successful retrieval of visual memories (Norman et al., 2019), paired associations (Vaz et al., 2019, 2020), and autobiographical long-term memory (Norman et al., 2021), it remains unclear whether ripple activity plays a functional role in linking associated memory items in episodic memory; perhaps through their ability to synchronise cross-regional populations representing different high-level elements. If ripples are a mechanism which supports the hippocampus in reactivating associated memory traces during retrieval and offline consolidation, we might expect tasks with greater associative memory demands to elicit more hippocampal ripple activity.

Population trajectories

So far, I have described how hippocampal-cortical interactions are believed to reactivate memory traces during memory consolidation and retrieval, and how the necessary inter- and intra-regional communication is enabled by oscillations at different scales during wake and sleep. However, the nature of the reactivation process in the MTL remains elusive. As described previously, partial information of high-level features is thought to be input to the hippocampus via surrounding cortices, including the entorhinal cortex. Pattern completion in the hippocampus then reactivates the neural code linking the associated features and context. The hippocampus then reactivates the related cortical sites via outputs passing through the entorhinal cortex (Chrobak et al., 2000; McClelland & Goddard, 1996; Teyler & DiScenna, 1986). This suggests population activity in the hippocampal-entorhinal circuit dynamically shifts its representational pattern during successful cued recall. This shift in representational states can be studied as a dynamical system where population codes transform to search for and reinstate memory content.

Similar to spindles and ripples, which reflect synchronous fluctuations of neural activity across neural populations in space and time, population trajectories represent how activity covaries across time within a population of neurons. The brain is thought to represent and process information according to population codes (Ebitz & Hayden, 2021; Saxena & Cunningham, 2019), where high-dimensional activity patterns in large populations of neurons covary in structured ways, representing information in latent patterns of activity.

Take the motor cortex as an example. The primary motor area contains hundreds of millions of neurons. If we recorded each neuron, we could map the activity pattern into a multi-million-dimensional space, with each neuron's activity represented by a dimension. However, neural activity has been found to covary such that subspaces with drastically lower dimensionality can retain almost complete information of cognition and behaviour (Churchland & Cunningham, 2014; Cunningham & Yu, 2014; Gao & Ganguli, 2015; Georgopoulos et al., 1986). As neural activity unfolds over time, these low-dimensional patterns in population activity can be mapped onto trajectories through a subspace. Importantly, this low-dimensional nature of coordinated activity within and between neural populations, as well as their interactions and behaviours, is thought to reflect the computations supporting cognition and behaviour (Vyas et al., 2020).

Therefore, studying latent neural trajectories as dynamic systems allows us to test hypotheses about how their temporal evolution contributes to cognition and behaviour (Shenoy et al., 2013; Vyas et al., 2020). Within motor neuroscience, this approach has been key in examining how the geometric features inherent in low-dimensional neural trajectories support computations underlying behaviour (Churchland et al., 2012; Churchland & Cunningham, 2014; Saxena & Cunningham, 2019).

This perspective also extends to memory research. For example, in a task where monkeys needed to maintain information of an item in mind, population codes in the prefrontal cortex represented the item information in low-dimensional subspaces across the task, despite the single-unit dynamics of individually tuned neurons being heterogeneous (Murray et al., 2017), showing how latent population activity can support memory processing. Studies have also investigated the significance of population trajectory timing on behaviour itself (Colins Rodriguez et al., 2024; Wang et al., 2018), revealing that behavioural factors like movement speed can be encoded in the corresponding velocity of neural trajectories.

Considering this, relatively little is known about the dynamic features of neural trajectories in MTL populations during memory retrieval. If successful memory retrieval relies on the population activity changing to reinstate the recalled information, then the speed at which the activity changes, or the velocity of the trajectory, may track the likelihood of successful retrieval. For example, when successfully recalling a well-defined memory trace, the population activity may shift rapidly toward the target representation, since the dynamics of a system are governed by a complex function of its constituent wiring and excitability (Langdon et al., 2023). On the other hand, the shift in population activity may be slower when a memory trace is less defined or competing with other representations. This way, rapid velocities in the neural trajectories may not only relate to memory behaviour but also link to the representational stability of the memory trace and the degree of reinstatement. Moreover, successful memory search may require the population trajectories to rapidly visit multiple representations before triggering the correct target memory. By studying the latent trajectories in motion, we might uncover correlates between trajectory behaviour and memory behaviour. Moreover, trajectories may also relate to other memory retrieval processes, including local oscillations.

Aims of Thesis

In this thesis, I aim to shed light on dynamic electrophysiological processes involved in sleep and memory at varying scales. Specifically, I focus on three dynamic phenomena related to the consolidation and retrieval of memory: sleep spindle oscillations in the cortex, wake ripple oscillations in the hippocampus, and unit-level population trajectories in the hippocampal-entorhinal circuitry during pattern completion.

First, I use non-invasive tDCS to study local spindle topography and its relationship with memory consolidation. As previously described, sleep rhythms, including SOs and spindles, have localised topographies. This regional expression in spindles has been linked to cortical sites showing endogenous excitability during a learning task before sleep (Petzka et al., 2022). However, it remains unknown whether exogenous excitability can shift spindle topographies, and whether this has an influence on memory consolidation of learning tasks which are functionally localised to the regions of spindle expression. In Chapter 2, I test the hypothesis that spindles track experimentally excited cortical sites and mediate memory consolidation in a somewhat functionally localised visuomotor learning task. In a repeated-measure design, I used non-invasive tDCS to laterally excite the motor cortex before measuring scalp EEG during subsequent sleep. I show that anodal tDCS can be used to amplify local spindle topographies. The implications of these results are twofold. First, it provides insights into the neurophysiology of where and how spindles are expressed across the cortex, supporting the notion that local excitability before sleep may tag regions for spindle activity in sleep. Second, future research can utilise tDCS as a tool to manipulate local spindle topographies, thereby gaining a deeper understanding of their role in memory, health, and disease.

Next, I zoom in from scalp EEG to iEEG and neuronal recordings in the MTL. In Chapters 3 and 4, I explore the same rich intracranial data set to tackle two entirely separate sets of questions.

In Chapter 3, I investigate ripple activity in associative and non-associative memory processing. Hippocampal ripples have been linked to episodic memory retrieval (Norman et al., 2019, 2021; Vaz et al., 2019, 2020). During retrieval, ripples are thought to support the reactivation of memory traces by facilitating communication between the reactivated hippocampal code, which holds the associative links, and relevant cortical areas (Dickey et al., 2022). This would suggest ripple activity would be greater when memory demands are explicitly associative. In Chapter 3, I test this hypothesis by comparing ripple activity in encoding, retrieval, and delay periods between an associative and a non-associative memory task. I show that ripple activity is greater during memory retrieval and restful delay periods in an associative memory task, suggesting ripple activity is functionally related to associative memory demands.

Finally, in Chapter 4, I zoom in further to explore population activity at the neuronal level. A central computation in our models of memory function is pattern completion in the hippocampal-entorhinal circuitry, which remains poorly understood in humans. Interactions and dynamics in population trajectories provide insights into the computations of cognition (Vyas et al., 2020). Therefore, it is valuable to study the behaviour of neural trajectories during memory retrieval and pattern completion. Furthermore, linking patterns in dynamics between the micro-scale population activity and macro-scale oscillatory activity helps us better understand how these different formats of latent covariance collaborate in the service of memory function. In Chapter 4, I ask if the population trajectories are faster during successful retrieval and if this affects pattern completion. I also test whether peak velocities

of the trajectories are linked to ripple activity. To this end, I analysed unit and iEEG recordings in the hippocampal-entorhinal circuitry during an associative retrieval task. My results show trajectory velocities are related to memory behaviour, pattern completion, and ripple activity; and have implications relating the dynamic behaviour of population activity in the MTL to memory retrieval.

Chapter 2: Human sleep spindles track experimentally excited brain circuits

Abstract

Spindles are hallmark oscillations during NREM sleep. Together with slow SOs, they are thought to play a mechanistic role in the consolidation of learned information. The quantity and spatial distribution of spindles has been linked to brain activity during learning before sleep and to memory performance after sleep. If spindles are drawn to cortical areas excited through pre-sleep learning tasks, this begs the question whether the spatial distribution of spindles is flexible, and whether their regional expression can also be manipulated with experimental brain stimulation. We used excitatory tDCS to stimulate the left and right motor cortex in a repeated-measures experimental design. After stimulation, we recorded high-density EEG during sleep to test how local stimulation modulated the regional expression of sleep spindles. Indeed, we show that excitatory tDCS of local cortical sites before sleep biases the expression of spindles to the excited locations during subsequent sleep. No effects of localised tDCS excitation were seen for SOs. These results demonstrate that the spatial topography of sleep spindles is neither hard-wired nor random, with spindles being flexibly directed to exogenously excited cortical circuits.

Introduction

Sleep spindles are waxing and waning oscillations (12-16 Hz) generated in cortico-thalamic loops and expressed across the cortex during NREM sleep (Andrillon et al., 2011; Fernandez & Lüthi, 2020; Mak-McCully et al., 2017; Sarasso et al., 2014; Staresina et al., 2015; Staresina, 2024; Steriade, 2006). SOs are slower oscillations (~1 Hz) that reflect large increases and decreases in the excitation of populations (Massimini et al., 2004; Steriade, 2006; Vyazovskiy & Harris, 2013). Spindles, have been found to nest upstate of SOs, which together are believed to play a key role in the synaptic plasticity and inter-regional communication necessary for memory consolidation (Diekelmann & Born, 2010; Ngo et al., 2020; Niethard et al., 2018; Schreiner et al., 2021; Staresina et al., 2015). Biophysical experiments indicate that spindles facilitate the influx of calcium into synaptic dendrites, which begins the process of synaptic potentiation (Chittajallu et al., 1998). For instance, Rosanova and colleagues induced artificial spindle-like activity with intracellular electrical stimulation and found calcium levels increased (Rosanova & Ulrich, 2005), while Siebt and colleagues showed the power of spindles correlated with calcium influx (Seibt et al., 2017). Spindles also provide time windows of heightened hippocampal-cortical communication (Ngo et al., 2020), with recent studies showing they enhance the precision of neural co-firing at frequencies optimal for of short-term dependent plasticity (Dickey et al., 2021; Staresina et al., 2023). These properties make spindles uniquely suited for transmitting information across neural populations and consolidating it through synaptic plasticity. It is important to note, that we refer to fast-spindles as "spindles" here, distinguished from slow spindles, which have a slower frequency profile (8-12 Hz) and are less clearly linked to memory processing or hippocampal-cortical interactions (Mölle et al., 2011; Staresina et al., 2015).

The ability to synchronise memory systems and induce plasticity suggest spindles may play a mechanistic role in stabilising memory traces (Diekelmann & Born, 2010; Fernandez & Lüthi, 2020; Staresina, 2024; Ulrich, 2016). The quantity and quality of spindles have been linked to behavioural improvements in memory after sleep (Bergmann, Mölle, Diedrichs, et al., 2012; Cairney et al., 2018; Gais et al., 2002; Holz et al., 2012; Latchoumane et al., 2017; Mednick et al., 2013; Schabus et al., 2004; Schreiner et al., 2021). However, spindles are not uniformly distributed; instead, they display a spatial topography which varies with cognitive demands during wake (Clemens et al., 2005, 2006; Cox et al., 2014; Nir et al., 2011; Petzka et al., 2022; Piantoni et al., 2017; Tamaki et al., 2013). This topographical flexibility suggests that the local expression of spindles may support region-specific plasticity and learning. Recently, Petzka and colleagues investigated whether spindle topographies could adapt based on task demands (Petzka et al., 2022). They found spindle expression mirrored the topography of decreases in alpha/beta power observed during a learning task before sleep. The overlap between spindle topographies and the distribution of reductions in task-induced alpha/beta power was predictive of memory retention after sleep. Previous studies found decreases in alpha/beta power are related to increased cortical excitability, to increases in gamma power (>40 Hz), and to increases in single-unit firing activity (Bonnefond & Jensen, 2015, 2015; Haegens et al., 2011; Jensen et al., 2014; Lundqvist et al., 2024; Mathewson et al., 2011; Osipova et al., 2008; Samaha et al., 2017; Sauseng et al., 2009; Staresina et al., 2016; Voytek et al., 2010). It is easier to elicit the motor evoked potential with TMS when alpha power at the motor cortex is low (Sauseng et al., 2009). Moreover, alpha/beta power correlates with lower thresholds for TMS-induced phosphenes (Romei et al., 2008; Samaha et al., 2017). Therefore, spindles overlapping with task-related alpha/beta reductions (Petzka et al., 2022) may reflect a mechanism whereby the expression of spindles is flexible and tracks "hot spots" of cortical excitement during wakeful learning prior to sleep.

If spindles track regional cortical excitability, it should not matter whether cortical excitement is induced endogenously through particular learning tasks (Clemens et al., 2005, 2006; Petzka et al., 2022) or exogenously through experimental brain stimulation. Here we test this by directly exciting local regions with tDCS and tracking the expression of spindles and SOs in subsequent sleep. Previous attempts to modulate spindles with slow-oscillating or alternating transcranial stimulation yielded mixed results (Antonenko et al., 2013; Barham et al., 2016; Cellini & Mednick, 2019; Del Felice et al., 2015; Eggert et al., 2013; Koo et al., 2018; Ladenbauer et al., 2016, 2017; Lustenberger et al., 2016; Marshall et al., 2004, 2006, 2011; Mednick et al., 2013; Park et al., 2023; Sahlem et al., 2015). These studies attempted to artificially stimulate spindles by inducing pulsing or alternating currents. Rather than treating the system as a resonator, we used tDCS to directly alter the excitatory/inhibitory balance of regional cortical sites. Anodal-tDCS has been shown to increase cortical excitability in local circuits for over 90 mins after application, allowing us to alter boost excitation before sleep and observe its effects on regional sleep spindles (Agboada et al., 2019; Ho et al., 2016; Stagg et al., 2018; Stagg & Nitsche, 2011; Vignaud et al., 2018; Woods et al., 2016). Moreover, anodal-tDCS is thought to facilitate synaptic plasticity by increasing calcium uptake by N-Methyl-D-aspartic acid (NMDA) receptors and reducing inhibitory gamma-aminobutyric acid (GABA) levels (Bachtiar et al., 2015; Nitsche et al., 2003; Stagg et al., 2018). Influencing NMDA receptors and GABA modulates spindles (Fernandez & Lüthi, 2020; Jacobsen et al., 2001; Mednick et al., 2013). Therefore, tDCS may induce physiological aftereffects at cortical sites which modulate subsequent spindle expression. Moreover, to examine the potential effects of modulating local spindles on memory consolidation, we used a unilateral visuomotor finger-tapping task thought to be regionally localised to right motor cortex (Ambrus et al., 2016; Buch et al., 2021; Iwane et al., 2023; Witt et al., 2008) to observe changes in motor learning behaviour before and after sleep (Boutin et al., 2018; Fogel et al., 2017).

Our results indicate cortical excitability generated by tDCS can modulate the rate of spindles at targeted sites. Importantly, we did not find an effect of excitatory tDCS on the distribution of SOs. This serves as a control condition, suggesting the underlying state of cortical excitability during wakefulness which directs spindles, does not also influence SOs. Moreover, the effect of excitatory stimulation on spindle rates was specific to the targeted areas. These results suggest spindle topographies are neither hard-wired nor random but are influenced by pre-sleep cortical excitability and can be modified with external stimulation.

Methods

Participants

We collected data from 21 volunteers. One participant was excluded because of a technical issue and another due to inability to sleep, resulting in a final sample size of 19 (9 female; age, M = 25.00 years, SD = 4.37). Although the relatively small sample size is similar to other studies testing the effects of transcranial electric stimulation on sleep activity (Del Felice et al., 2015; Lustenberger et al., 2016), it remains a limitation of the current study. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) and were not proficient in playing a keyboard instrument. Participants were also screened to ensure they did not work nightshifts in the last month, were not pregnant, were non-smokers, did not take sleep-altering medication, and did not have a history of neurological or psychiatric disorders. Participants were asked to get up an hour earlier than usual on the day of the session. They were also asked to refrain from consuming alcohol or caffeine on the night before or the day of the sessions, respectively. All participants self-reported an ability to nap in the daytime. Written informed consent was provided by all

participants at the beginning of each session and participants were compensated a total of 150 GBP for their time. Protocols were approved by the local ethics committee (Central University Research Ethics Committee #R83711/RE002).

Procedure

Participants engaged in two day-long experimental sessions from 9:00–17:00, at least 5 days apart. **Figure 1A** illustrates the timeline of an experimental session. After providing written consent and being screened for MRI and tDCS safety, the participant washed and dried their hair and changed into scrubs. The experimenter then applied the EEG cap. At 10:00 the participant started with the computerized "localiser" and visuomotor finger-tapping tasks which lasted approximately 60 minutes (see **Tasks** for details).

After completing the computerized tasks, the experimenter removed the EEG cap, and the participant washed and dried their hair. At 11:30 AM, the participant underwent structural and functional MRI scans lasting 45 minutes. From 12:15 to 12:30, participant and experimenter ate lunch whilst watching a nature documentary. The documentary was randomly selected for each session and each participant. At 12:30, the experimenter applied the tDCS pads which took 10 minutes. A total of 1.5 hours elapsed between completing the tasks and the application of tDCS, allowing residual task-related activation to subside before stimulation.

Next, the tDCS was switched on and ran at 1mA for 20 minutes, during which time the experimenter and participant continued passively watching the nature documentary. After the stimulation, the tDCS pads were removed, the scalp was cleaned with alcohol, and the experimenter reapplied the EEG cap. Once the EEG cap was applied, the participant got

into bed and wore earplugs and an eye mask to sleep. The experimenter left the room, giving the participant 90 minutes to sleep.

At 15:00, the experimenter woke the participant and gave them five minutes to overcome sleep inertia. The participant then completed three more blocks of the visuomotor finger-tapping task to assess motor skill post-sleep. After completing the retest of the finger-tapping task, the EEG cap was removed, the participant washed and dried their hair before having another set of MRI scans which lasted approximately one hour. At 17:00 the participant changed back into their clothes and was thanked for their time.

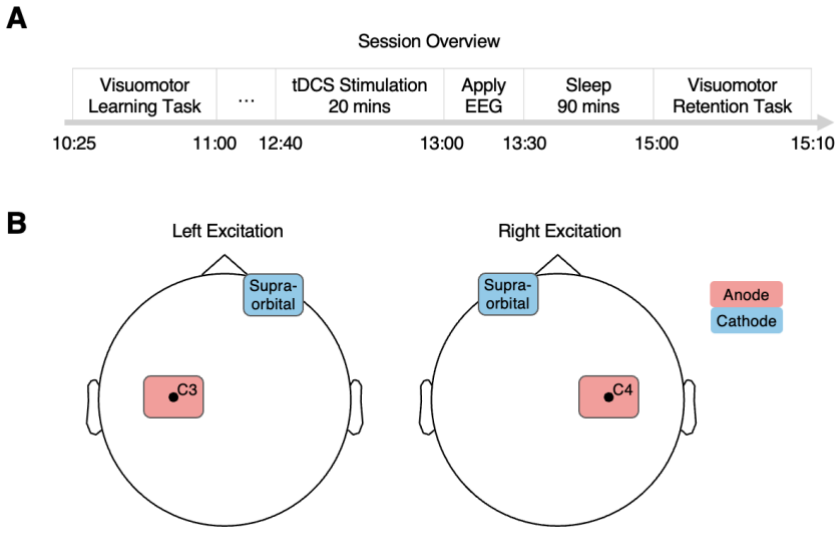

Figure 1. Session overview and tDCS montages. A) Overview of a session's schedule. Each participant conducted two sessions at least 5 days apart; one session with left excitation and one with right excitation (order counterbalanced across participants). **B)** tDCS montages for the left and right excitation conditions. Stimulation was set to 1mA for 20 minutes. A simulation of the distribution of voltage induced by the tDCS montages is shown in **Supplementary Figure 2**.

Tasks

The tasks were run using MATLAB 2021 (The Mathworks Inc., MA, USA) and Psychtoolbox (Brainard, 1997). The participant used an iMac keyboard and a 23.8-inch colour screen (1920x1080 resolution) which was positioned approximately 30 cm away. To keep the participant from looking at their fingers during the tasks, a cardboard box was placed over their left hand.

The first task was a visual localiser in which images were shown on the screen. The participant was instructed to press the down-arrow key if the same image was presented twice in a row. The images in each session were unique and consisted of two faces, two objects, two scenes, and two words. Each image was presented 55 times in total and was repeated twice in a row five times. Presentations lasted 1 sec, with a 0.5 sec fixation period and a random intertrial-interval jitter of between -0.1 and 0.1 secs. There were self-paced pauses after 75 image presentations which participant skipped by pressing the space bar.

Next, the participant learned the unilateral visuomotor finger-tapping task. First, they received instructions regarding the task design. The task consisted of blocks which contained a tapping phase and a resting phase (see **Supplementary Figure 1A-C**). During the tapping phase, four of the images from the localiser task would be presented in a sequence. Each image belonged to one category (face, object, scene, or word) and each category was linked to a number key at the top of the keyboard (1-face, 2-object, 3-scence, 4-word). The participant used their left hand to press the number keys, with one key assigned to each finger. The goal was to press the corresponding key as quickly as possible when an image was presented. For example, an image of George Clooney would require the participant to press key "1" since it is linked to the category "face". After pressing "1", the next image would be presented, which is a desert scene prompting the participant to press key "3" (linked to scene).

This would continue for 30 secs, pressing keys in the sequence as quickly and accurately as possible.

The participant was explicitly instructed that there was a four-part sequence which would repeat for the entire session. The sequences were "1-3-2-4" and "4-2-3-1" which are mirrors of each other, to match complexity. The image stimuli and tapping sequence used in session 1 and session 2 were counterbalanced between participants. After the tapping phase, the participant received feedback, which was displayed for 3 secs, on how many full four-part sequences ("1-3-2-4" or "4-2-3-1") they had pressed. They were instructed to maximise the number of full correct sequences over the course of the blocks.

After the tapping phase and feedback, there was a resting phase in which the participant performed a distraction task where they needed to count the number of times a fixation cross changed shades of grey. This resting phase kept the participant focused whilst allowing their left hand to rest. After the resting phase, the participant entered the number of fixation cross changes using their right hand and a separate keyboard from the one used in the tapping phase. That way their left hand remained in the same position, on the number keys for the entire task. The next block began once the number of fixation changes was entered.

The visuomotor finger-tapping task before the nap consisted of 23 blocks. Each block was made up of tapping phase, feedback, and resting phase. The participant was instructed to try as hard as they could throughout the learning blocks to perform well in the final test blocks which were identical to the learning blocks. The resting phase of the 10^{th} and 20^{th} blocks were extended to five minutes to allow the participant's left hands to significantly rest. Additionally, before starting with the learning blocks, the participant performed a practice block with different images and a different sequence. In total, the visuomotor finger-tapping task lasted approximately 40 minutes.

tDCS application

The coordinates of the stimulation sites (C3 and C4) were located with a measuring tape during the initial EEG capping. Before stimulation, the sites were marked using a red marker to guide the tDCS application. The tDCS system was a NeuroConn DC-Stimulator Plus (Neurocare Group AG, Germany) with 5 cm x 7 cm pads. After parting hair and cleaning the scalp with rubbing alcohol, we used Ten20 conductive paste to adhere the pads to the scalp as well as rubber bands. **Figure 1B** depicts how the anodal pad was placed at C3 or C4 with a vertical orientation while the cathodal pad was placed on the contralateral supraorbital cortex with a horizontal orientation. The tDCS ran at 1mA for 20 minutes whilst the participant and experimenter continued watching a nature documentary. We chose this montage because it has been shown to influence synaptic and cortical excitability in ipsilateral motor cortex (Agboada et al., 2019; Bachtiar et al., 2015; Vignaud et al., 2018; Woods et al., 2016). Since there was no sham condition, participants were informed they would receive stimulation in both sessions and that they may experience a tingling sensation around the electrode pads. The pad-placement and sensory stimulation of tDCS were linked to the stimulation condition. Therefore, participants were aware that the experiment had two conditions. However, participants did not know the importance of the pad-placement and it is unlikely differences in topical sensation at the time of stimulation influenced the topography of oscillatory events during subsequent sleep. However, future studies should employ a sham condition to disentangle the specificity of the effect of stimulation on sleep activity, compared to a no-stimulation baseline. It was not possible to blind the experimenter to whether C3 or C4 was being stimulated because the conditions required different pad-placements.

EEG data recording

EEG recordings were conducted using a 64-contact Brain Products ActiChamp system (Brain Products UK LTD, UK) recording at 1000 Hz. The cap used a standard 10-20 layout which was customised to have two electrooculography (EOG), two electromyography (EMG), and two mastoid contacts for sleep scoring. AFz was used as the ground electrode and Fz was the online reference. The impedance of the contacts was brought below 20 kOhm with Abralyt HiC gel. Lic2 electrode cream was used to attach the two EMG electrodes to the skin under the chin. Finally, bandage gauze was applied around the EEG cap to secure it during sleep.

Sleep scoring

Sleep scoring was performed on the raw data, split into in 30 sec epochs, by two deep learning models, Somnobot (SomnoBot, n.d.) and YASA (Vallat & Walker, 2021). A researcher, blind to the conditions, visually inspected the epochs and resolved discrepancies between the classifications of the two models according to the American Academy of Sleep Medicine guidelines (Berry et al., 2020).

EEG preprocessing and event detection

EEG data were analysed in MATLAB 2024b (The Mathworks Inc., MA, USA) using Fieldtrip functions (Oostenveld et al., 2011). The recordings were down-sampled to 200 Hz and the mastoid, EOG, and EMG contacts were removed. Artefacts were detected on each contact individually as events with an absolute amplitude over 2.5 SD from the mean or an

absolute amplitude over 100 μV. Artefacts were padded with 1 sec on either side and contacts whose signal was more than 10% artefactual were interpolated from neighbouring contacts using "ft_channelrepair" with the "weighted interpolation" method. After interpolating bad contacts, all contacts were re-referenced to the mean signal of all contacts. Re-referencing to the mean signal, rather than linked mastoids, is better suited for topographical analyses since it reduces the influence of any single lateralised mastoid contact which may otherwise bias the signal in all contacts toward a hemisphere.

Custom scripts based on established detection algorithms (Ngo et al., 2020) were used to detect spindle and SO events. Only non-artefactual data during N2 and N3 epochs were considered for event detection. To detect spindles, the EEG signal was first bandpass filtered between 12-16 Hz and the envelope was smoothed with a 0.2 sec root mean square kernel. A spindle event was identified when the smoothed envelope had an amplitude between 1.5-5 SD from the mean of the eligible data and had a duration between 0.5-3 secs. For the more conservative threshold criteria used in **Supplementary Figure 7**, the detection threshold was 1.75-5 SD from the mean.

To detect SOs, the signal was filtered to retain frequencies between 0.3 and 1.25 Hz. All points where the signal crossed zero were identified, and the candidate SO duration was measured as the interval between the two consecutive positive-gradient zero crossings. Candidate events lasting between 0.8 and 2 secs were then selected, and their amplitude was evaluated (both trough and trough-to-peak amplitude). Events were classified as SOs if both trough and trough-to-peak amplitudes were above the mean plus 1.5 SD of all candidate events. We also conducted our analysis on SOs using AASM detection guidelines (Berry et al., 2020), i.e., a trough-to-peak threshold of 75 μV (**Supplementary Figure 4**). Results were comparable to the main SO analysis using channel- specific thresholds (**Supplementary**

Figure 3). For all other analyses, we continued with SOs detected using channel-specific thresholds.

Behavioural and EEG statistical analysis

We used MATLAB 2024b (The Mathworks Inc., MA, USA) and the Fieldtrip toolbox (Oostenveld et al., 2011) to analyse the data.

In the visuomotor finger-tapping task, RTs were excluded which were below 0.05 secs and above 0.5 secs, to remove accidental presses and outliers. The first block of one session was excluded from the RT analyses because the participant did not press a correct key with an RT under 0.5 secs. Spindle and SO rates were calculated per session as the number of events divided by the total non-artefactual time spent in N2 or N3 (given in events per minute).

Cluster-based permutation tests were performed using "ft_timelockstatistics" in the Fieldtrip toolbox, using 1000 random permutations, a cluster-alpha threshold of $p < .05$ and a significance threshold of $p < .05$ (two-tailed). The data distribution was presumed to be normal, though this assumption was not verified.

To explore the effect of power spectra on skill retention (**Supplementary Figure 8**), we first calculated the fast Fourier transform of the signal for frequencies 0-30 Hz (steps of 0.5 Hz) in 4 sec windows (50% overlap) of N2 and N3 sleep. Next, we binned the power into 2 Hz bins and ran linear-mixed effect models (LMEs) with the equation 'Retention ~ Session + Stimulation Site + Spectral Power + (1|Participant Number)', where retention was the average performance in the three blocks after sleep minus the three blocks before sleep. A separate LME was run for each frequency bin and contact combination (15 bins x 57 contacts

= 855 combinations), whilst controlling for anodal-tDCS stimulation site and session number.

Results

Polysomnography and spindle events

Participants slept for an average of 78.74 mins (SD = 12.13) in each session. This included an average of 60.68 mins of N2 or N3 sleep (N2, M = 41.62 mins, SD = 12.95; N3, M = 19.07 mins, SD = 12.32). **Figure 2A** depicts a hypnogram from an example session with time spent in different sleep stages. LME models showed neither session number (1 vs. 2) nor stimulation condition (right vs. left excitation) had a significant effect on the total time or proportion of time spent in N2 and N3. Additionally, paired-samples t-tests showed neither session number (1 vs 2), nor excitation condition (left vs right) had a significant effect on spindle rates and counts and SO rates and counts at Cz. Further summary statistics of sleep stages are detailed in **Supplementary Table 1**.

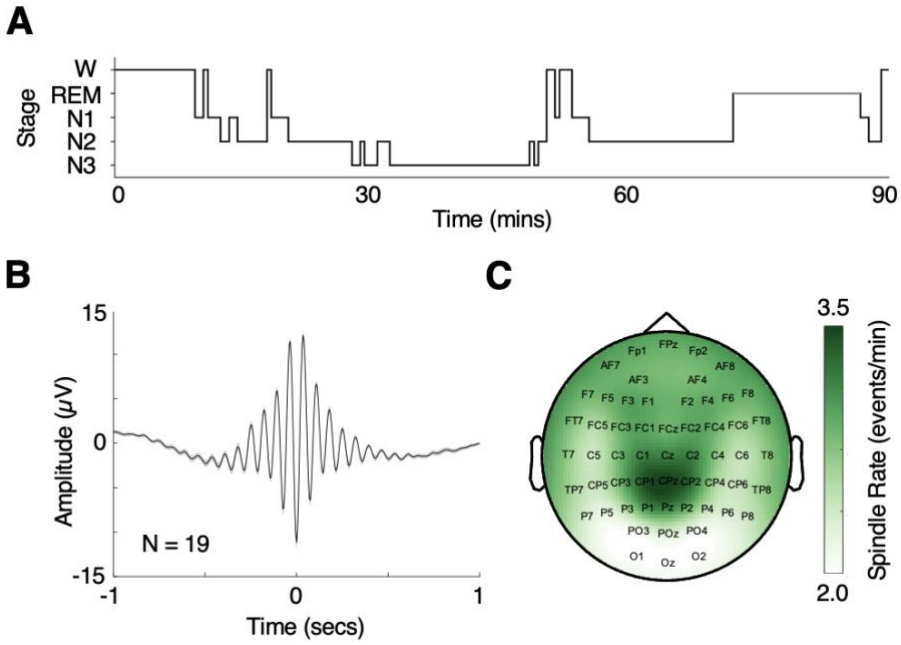

Figure 2. Sleep stages and spindle events. **A)** Example hypnogram showing time spent in different sleep stages. **B)** Grand average spindle from Cz contacts. Spindles were aligned to their largest trough and baseline corrected using the mean of the 2 sec window, before averaging across sessions (N = 2) and across participants (N = 19). Shading represents ±1 SEM. **C)** Average spindle rate topography. The topographies were averaged across left and right excitation sessions before averaging across participants.

Figure 2B shows the waxing and waning nature of the grand average spindle detected at Cz across participants. The spindle rate topography averaged across both excitation conditions was most dense around Cz and parietal areas (**Figure 2C**) and the spindle rates averaged 2.76 and 2.69 events/min at the C3/C4 target sites respectively (**Supplementary Table 2**).

Targeted tDCS stimulation increased local spindle rates

To quantify the effect of targeted, pre-sleep excitatory stimulation on subsequent spindle rates, we conducted a paired-samples t-test to compare the C4 minus C3 spindle rate contrast in sessions with left and right excitatory stimulation. If spindle rates are greater at excited sites, we would expect the C4 (right) minus C3 (left) contrast to be greater when C4 (right) is excited, compared to when C3 (left) is excited. **Figure 3A** confirms this, showing a significant difference in C4 minus C3 spindle rate contrasts between right excitation (M = 0.02, SD = 0.27) and left excitation conditions (M = -0.17, SD = 0.37), $t(18) = -2.55$, $p = .020$, $d = -0.58$, two-tailed). Visual inspection suggests that the difference in spindle rates between left and right stimulation conditions was more pronounced at C4 than at C3 (**Supplementary Figure 5A**). However, directly comparing C4 minus C3 to zero did not yield significant effects for either stimulation condition in isolation (both $p > .05$, two-tailed). This highlights the importance of differential spindle rate changes as a function of stimulation condition and region (i.e., significant 2-way interaction). Additionally, a paired-samples t-test was not significant for SO rate contrasts (**Supplementary Figures 3A & 4A**).

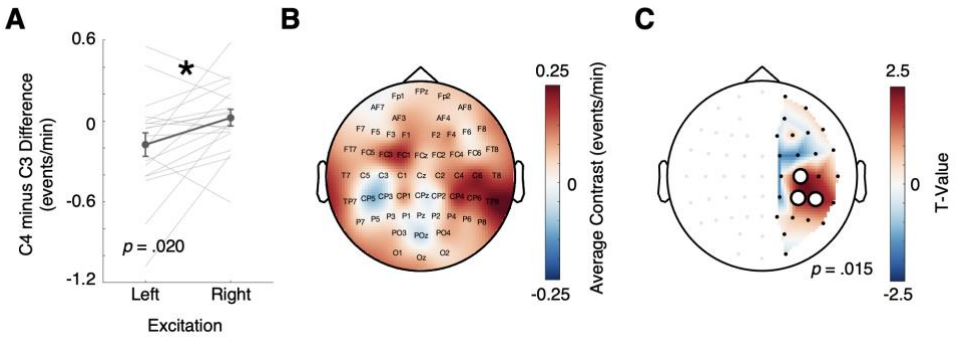

Figure 3. Spindle rates were influenced by lateralised tDCS stimulation. **A)** Significant contrast between spindle rates at C3 and C4 target sites in left and right excitation conditions. Lines represent individual participants. Error bars represent ±1 SEM. **B)** Average right excitation spindle rate topography minus left excitation spindle rate topography contrast across participants (N=19). **C)**. Right excitation minus left excitation contrast values from left hemisphere contacts were subtracted from right hemisphere contacts to create a measure of excitation-dependent spindle rate lateralisation. White circles depict a significant cluster, using cluster-based permutation tests.

To test the effect of all aforementioned factors on event rate, we used a 3-way repeated-measures ANOVA (factor 1 = event type (spindle/SO), factor 2 = stimulation condition (left/right excitation), factor 3 = EEG contact (C3/C4)). Results showed a significant main effect of event type ($F(1,18) = 12.13$, $p = .003$, $\eta_p^2 = .40$), with spindles having a greater rate than SOs (spindles, M = 2.73, SD = 0.36; SOs, M = 2.44, SD = 0.27; **Supplementary Figure 5**). Importantly, there was a significant 3-way interaction between event type, stimulation condition, and EEG contact ($F(1,18) = 5.59$, $p = .030$, $\eta_p^2 = .24$), confirming the effect of stimulation condition on event rate at the target contacts is specific to spindles and not SOs. Together, these results show spindle rates at targeted sites were significantly modulated using excitatory pre-sleep tDCS.

Next, we further investigated the regional specificity of the effect of excitatory stimulation on spindle rates. **Figure 3B** shows the topography of the contrast in spindle rates between

sessions with right excitatory stimulation (anode on C4) and left excitatory stimulation (anode on C3). To test the regional specificity of the effect of targeted lateral stimulation, we subtracted the right excitation minus left stimulation contrast of left hemisphere contacts from their right hemisphere mirror pairs (e.g., CP3 from CP4) and compared this lateralised contrast value to zero. **Figure 3C** shows a significant positive cluster including C3/C4, CP3/CP4, and CP5/CP6 (cluster-based permutation test, $p = .015$). The same analysis and test methods did not show any significant effects of lateralised tDCS on regional SO rates (**Supplementary Figures 3B-C & 4B-C**), nor did it affect the amplitudes or durations of the spindle events. These results demonstrate the boosting effect of targeted pre-sleep tDCS stimulation on spindle rate is localised to the target region and does not carry over to SOs.

To test the robustness of the findings, we repeated the analysis with z-scored spindle rates. Before taking the contrasts, we normalised spindle rates across the scalp EEG contacts within each session. **Supplementary Figure 6A** shows the paired-samples t-test with significant differences in z-scored C4 minus C3 spindle rate contrasts between left excitation (M = -0.35, SD = 0.67) right excitation (M = -0.01, SD = 0.65), $t(18) = -2.18$, $p = .042$, $d = -0.50$, two-tailed. **Supplementary Figures 6B-C** illustrate the corresponding right minus left excitation condition contrast, showing a significant cluster at C3/C4 and CP5/CP6 ($p = .043$). As a final control, we increased the threshold for detecting spindle events during event detection from mean plus 1.5 SD to mean plus 1.75 SD, thus making the detection criteria more conservative (**Supplementary Figure 7A**). Repeating the analysis with only the spindle events fulfilling the stricter criteria again led to similar results. The paired-samples t-test illustrated in **Supplementary Figure 7B** shows a significant difference in the C4-C3 contrast between left excitation (M = -0.15, SD = 0.27) and right excitation (M = 0.00, SD = 0.26) conditions, $t(18) = -2.72$, $p = .014$, $d = -0.62$, two-tailed. **Supplementary Figure 7C** displays the hemisphere contrasts of the right minus left excitation contrasts with a

significant positive cluster at C3/C4, CP5/CP6, and TP7/TP8. Together, these results suggest that the effect of targeted tDCS on spindle rate lateralisation is robust to normalisation and to more conservative thresholds for spindle events.

Lateralised excitatory stimulation did not significantly influence skill retention after sleep in a unilateral finger-tapping task

Sleep spindles have been linked to memory consolidation during sleep (Bergmann, Mölle, Diedrichs, et al., 2012; Boutin et al., 2018; Fogel et al., 2017; Petzka et al., 2022; Schreiner et al., 2021). By comparing the performance in the unilateral visuomotor finger-tapping task, we were able to examine if excitatory tDCS stimulation to the left or right motor cortex influenced skill retention after sleep and how this might be mediated by changes in local sleep spindles. First, we tested whether participants learned the task and retained skill after sleep (**Supplementary Figure 1D-E**). Then, we used two LME models to examine the effect of block and session on average reaction time (RT; secs) of correct key presses (model 1) and the number of correct four-part sequence responses (model 2), with participant included as a random intercept. Results indicated a significant main effect of block in both models, suggesting that RT decreased across blocks (β = -0.004, SE = 0.000, t(870) = -23.10, p < .001) and the number of correct four-part sequence responses increased across blocks (β = 0.332, SE = 0.017, t(871) = 19.00, p < .001). This reduction in RT and increase in correct sequence responses with successive blocks provides evidence of learning over time, as participants became faster and more accurate with practice. There was also a main effect of being in the second session on RT (β = -0.011, SE = 0.002, t(870) = -5.91, p < .001), indicating differences in RT between sessions. Similarly, the number of full sequences was greater in the second

session ($\beta = 0.761$, SE = 0.232, $t(871) = 3.65$, $p < .001$), suggesting performance was generally better in the second session.

To evaluate whether tDCS stimulation condition influenced motor skill retention in the visuomotor finger-tapping task, we tested for an interaction between performance metrics (mean RT of correct key presses and mean number of full correct sequence responses) across the three penultimate trials of the learning task and the mean performance metrics across the three trials following sleep, similar to Fogel and colleagues (Fogel et al., 2017). This analysis was conducted using two 2 × 2 repeated-measures ANOVAs. Performance was significantly better in the trials pre-sleep, compared to trials post-sleep (RT: $F(1,18) = 11.30$, $p = .003$, $\eta_p^2 = .61$; correct sequences: $F(1,18) = 15.01$, $p = .001$, $\eta_p^2 = .41$). However, there was no main effect of stimulation condition (RT: $F(1,18) = 0.05$, $p = .834$, $\eta_p^2 = .00$; correct sequences: $F(1,18) = 1.86$, $p = .189$, $\eta_p^2 = .05$) and no significant interaction effect between pre-sleep and post-sleep performance and right- versus left-excitatory tDCS stimulation conditions (RT: $F(1,18) = 0.18$, $p = .677$, $\eta_p^2 = .01$; correct sequences: $F(1,18) = 0.79$, $p = .387$, $\eta_p^2 = .04$). Therefore, the results do not provide evidence that tDCS stimulation condition influences skill retention and memory consolidation across sleep in the unilateral visuomotor finger-tapping task.

Although there was no effect of stimulation site on skill retention after sleep, it is possible that other oscillatory signatures were linked to skill retention of the visuomotor task. To explore this, we extracted spectral power at each contact from 0-30 Hz, in 2 Hz bins. We used an LME model to test the effect of spectral power on skill retention for each combination of frequency bin and contact, whilst controlling for stimulation site and session number (see **Methods** for details). **Supplementary Figure 8** shows an exploratory trend of 6-10 Hz power affecting skill retention across primarily frontal and fronto-central contacts.

Positive t-values and negative t-values indicate more retention when considering the number of correct sequences or the average RT per block, respectively. Note that these results are exploratory and the tests for significance were not corrected for multiple comparisons. This suggests, if anything, 6-10 Hz oscillations, and not localised spindles, may contribute to skill retention in the visuomotor task employed here and provides insight as to why modulating spindles at C3/C4 did not affect skill retention after sleep in our paradigm.

Discussion

We set out to test whether the local expression of sleep spindles is sensitive to cortical excitability during wakefulness. Our results demonstrate excitatory tDCS can modulate regional spindle rates in humans. Specifically, anodal-tDCS applied before a nap increased the number of spindles at the target site compared to the contralateral homologous region. The effect was specific to the target region, significantly influencing spindle rates at the stimulation sites (C3/C4) and neighbouring centroparietal sites (**Figure 3A-C**). While our results show no significant difference in spindle rates between left and right hemisphere stimulation, the effect appears stronger in the right hemisphere (C4). Given that our unilateral motor task likely engaged the right motor cortex, it's possible that task-related activity prior to sleep influenced the stimulation effect. Although we had a 90-minute wash-out period, the lack of a sham stimulation condition and balanced left and right-handed tasks/participants makes it unclear whether this potential right-hemisphere bias stemmed from the combination of right stimulation and right-lateralised local learning before sleep. Future studies should employ a sham stimulation control and use balanced motor tasks targeting both hemispheres to more accurately disentangle these factors. SO rates have also

been shown to track learning-related sites (Huber et al., 2004; Nir et al., 2011; Vyazovskiy et al., 2011), however, the effect of anodal-tDCS was specific to spindles. The significant interaction shows tDCS was greater for spindles rates than SO rates (**Supplementary Figure 4**), ruling out that stimulation does not have a global broadband effect. These results indicate spindle topographies are flexible and are affected by pre-sleep cortical excitability, which can be directly influenced using non-invasive brain stimulation.

The spatial specificity in our results aligns with previous work showing spindle expression tracks the topography of endogenous cortical excitability during a learning task. While previous work (Petzka et al., 2022) showed spindle topographies adapt to match task-induced activation patterns, our results extend this by revealing spindles also track regional exogenous excitability induced through artificial external stimulation. Together, these findings suggest the deployment of sleep spindles is adaptive and biased towards regions that are excited before sleep.

Unlike previous attempts which used oscillatory stimulation to modulate sleep spindles (Antonenko et al., 2013; Barham et al., 2016; Cellini & Mednick, 2019; Del Felice et al., 2015; Eggert et al., 2013; Koo et al., 2018; Ladenbauer et al., 2016, 2017; Lustenberger et al., 2016; Marshall et al., 2004, 2006, 2011; Mednick et al., 2013; Park et al., 2023; Sahlem et al., 2015), we focused on modifying the excitability of the underlying cortical circuits with constant excitatory stimulation using a well-tested tDCS protocol (Agboada et al., 2019; Stagg et al., 2018; Woods et al., 2016). Specifically, the tDCS protocol used here has been shown to modulate cortical excitability and increase the amplitude of motor evoked potentials in motor cortex up to 90 minutes after stimulation (Agboada et al., 2019). The success of this method suggests that targeting the underlying synaptic and physiological state of cortical regions (Bachtiar et al., 2015; Chittajallu et al., 1998; Stagg et al., 2018) and thus "tagging" them for

later endogenous spindle deployment may be more fruitful than attempting to entrain specific bursts with their frequency profiles.

Despite successfully modulating local spindles around motor areas, we did not find evidence for behavioural influences of excitatory tDCS on a left-handed finger-tapping task which we believed to locally recruit right motor areas around C4. There are several limitations that need to be considered. Firstly, the strength and duration of the stimulation regimen may not have been sufficient to impact subsequent behaviour. Secondly, it is possible that the relationship between local spindle activity and regional memory consolidation is non-linear, making it difficult to predict how manipulating spindles would affect learning retention. Thirdly, our task may not have been optimised to benefit from increased spindle rates in the targeted regions. Interestingly, **Supplementary Figure 8** suggests that oscillatory signals outside the fast spindle range (6-10 Hz) may be more relevant for skill consolidation during sleep. Finally, it is difficult to obtain a measure of motor learning after sleep without introducing additional practice opportunities, which can mask true changes in retention. This issue limits the number of trials we can include in our post sleep test, making the results vulnerable to outliers. To overcome these limitations, alternative paradigms like standard declarative memory tasks could be used, even if they don't provide the same level of circumscribed cortical localisation as finger-tapping.

Nevertheless, our findings have several potential applications. The ability to guide spindles using targeted non-invasive brain stimulation may be valuable for targeted neurorehabilitation, particularly when regional plasticity needs modulating. Brain-computer interfaces during sleep which look to modify activity patterns in the sleeping brain may be able to use targeted excitation to bias local sleep oscillations and thus effect sleep quality and, or memory performance. Additionally, this work provides a foundation for investigating the

effect of targeted stimulation before sleep on the expression and characteristics of sleep oscillations. Future work may explore other sleep oscillations, stimulation protocols, and application methods to refine our understanding of the spatiotemporal dynamics of sleep oscillations.

In conclusion, our results demonstrate that pre-sleep cortical excitability can shape the topographical expression of sleep spindles in humans, suggesting a flexible system which responds to exogenous as well as endogenous excitation of cortical sites. These finding lay the groundwork for future work to investigate regionally specific sleep-dependent memory processing and developing targeted interventions for manipulating regional sleep oscillations in research and the clinic.

Chapter 3: Region- and task-specificity of human awake ripples

Abstract

Ripples are a prominent signature of hippocampal field potentials during sleep and are believed to mechanistically facilitate memory function by synchronising neural activity between memory systems. Recent investigations have begun to explore the role of ripples during wakefulness, with some studies detecting wake ripple activity in non-hippocampal regions. It remains unclear to what extent ripples are a prominent signal in wake, especially in the non-hippocampal areas. In our first analysis, we asked whether we could detect ripple signals in the hippocampus and entorhinal cortex using a data-driven approach. We found a prevalence of peaks in gamma power in the ripple-band in the hippocampus, but not in the entorhinal cortex, during memory retrieval. In our second analysis, we asked whether ripple activity tracks the explicit associative demands of a memory task. Ripple activity during wake has specifically been shown to predict the retrieval of episodic memories. Since the hippocampus is thought to play a role in linking associative information during recollection, we tested whether ripple activity differed between associative and non-associative memory tasks. Our results show ripple activity is greater during associative retrieval and delay periods. Additionally, the delay ripples during the associative task had greater amplitudes and durations. This suggests ripples may play a specific role in hippocampal memory function involving the maintenance and retrieval of associated information. Together, we show local hippocampal ripples are a prominent signal during memory retrieval, and their expression and characteristics track associative memory demands.

Introduction

Hippocampal ripples are high-frequency gamma oscillations which orchestrate cross-regional information transfer in service of memory function (Buzsáki, 2015; Klinzing et al., 2019; Norman et al., 2021; Vaz et al., 2019). However, not all memory is equal. Some tasks require the recollection of associated context and information, while others can be achieved by simply recognising the novelty of information (Yonelinas, 2002). To better understand the role of ripples in memory function, we take advantage of a data set with macro-level iEEG recordings from human MTL, to investigate ripple activity in human wake and its relationship with associative and non-associative memory encoding, maintenance, and retrieval.

Ripples are characterised as macro-scale iEEG bursts (140-200 Hz in rodents, 80-120 Hz in humans) generated through an interplay between pyramidal cells and interneurons in the CA3 and CA1 hippocampal subfields (Buzsáki, 2015). Since their initial characterisation in rodents (Buzsáki et al., 1992), ripples have been widely studied across species (Buzsáki et al., 2013) including humans (Bragin et al., 1999; Quyen et al., 2010; Staresina et al., 2015). Commonly observed during NREM, ripples show temporal coordination with other sleep-related rhythms, including SOs and spindles (Sirota et al., 2003; Staresina et al., 2015, 2023). Through their hierarchical nesting with sleep-rhythms, ripples are believed to facilitate interactions between the hippocampus and neocortex (Jadhav et al., 2016; Ngo et al., 2020), supporting the two-stage model of memory consolidation (Buzsáki, 1989; Girardeau & Zugaro, 2011; Klinzing et al., 2019), where information is consolidated to cortex from hippocampus through reactivation during rest (Diekelmann & Born, 2010; Dudai et al., 2015; Jadhav et al., 2016).

Wake ripple events in hippocampus and non-hippocampal cortex

While ripple activity and associated consolidation mechanisms are primarily observed in sleep and rest, human ripples have also been identified in active wake (Axmacher et al., 2008; Billeke et al., 2017; Chen et al., 2021), where they relate to memory retrieval (Chen et al., 2021; Kunz et al., 2024; Norman et al., 2019, 2021; Vaz et al., 2019, 2020). However, this is still a relatively new direction, and it remains unclear to what extent ripples during wake are equivalent to ripples during sleep. Chen and colleagues compared ripples in task, rest, and sleep and found ripple attributes including duration, and amplitude were relatively consistent between wake and sleep, while the rate of events was greater during NREM (Chen et al., 2021). However, unlike NREM ripples, which are coupled to spindles and SOs, wake ripples are not clearly coupled to other electrophysiological signatures. This raises the question of whether awake ripples are a physiological signal or a result of detection algorithms detecting pseudo-ripple events in broad-band gamma activity (Liu et al., 2022).

This is a particular concern for studies which identified ripples in non-hippocampal areas during wake. The neural circuitry which underpins hippocampal ripples has been explored in depth (Buzsáki, 2015), while it remains unclear whether wake ripples can be generated or detected in non-hippocampal sites. Studies in wake humans have identified ripples in non-hippocampal areas (Axmacher et al., 2008; Dickey et al., 2022; Sakon & Kahana, 2022). Sakon & Kahana (2022) detected ripples in human entorhinal and parahippocampal cortex, while Dickey et al. (2022) found ripples in inferior parietal cortex. Yet, the studies did not test whether gamma bursts in the ripple frequency band were a prominent feature of the non-hippocampal iEEG signal during wake on a single-trial level. Since an algorithm that detects ripples through peaks in frequency power will even detect events in noise, it remains to be

established whether reported non-hippocampal ripples in wake humans are a signal or an artefact of ripple-detecting algorithms.

Taken together, it is unclear if human hippocampal ripples detected during wake retrieval reflect discrete increases in ripple-band activity rather than broad gamma increases, or if ripple-activity is also a feature of non-hippocampal iEEG during wake. In our first analysis we address these ambiguities by explicitly testing whether power peaks across the broad gamma range (30-200 Hz) are prevalent in the ripple-band (80-120 Hz) of iEEG signals in hippocampus and entorhinal cortex, while showing how ripple-like bursts can be detected in noise. This allows us to directly test whether ripple signals are a prominent feature of iEEG in hippocampal and non-hippocampal cortex during wake retrieval.

Associative and non-associative memory

Episodic memory refers to the ability to mentally travel back in time and reimagine information which was previously experienced (Tulving, 1972, 2002). It is possible the role of ripples in episodic memory retrieval (Kunz et al., 2024; Norman et al., 2019, 2021; Vaz et al., 2019, 2020) reflects their ability to synchronise neural activity between hippocampus and cortex. It is widely accepted that the hippocampus plays a key role in processing episodic memory (Moscovitch et al., 2016; Ranganath & Ritchey, 2012; Scoville & Milner, 1957; Tulving & Markowitsch, 1998; Yonelinas et al., 2019). The Complementary Learning Systems framework suggests the hippocampus rapidly stores associations between elements in an episode, while neocortex holds distributed representations of items and features (McClelland et al., 1995; Norman & O'Reilly, 2003).

However, not all episodic memory is equal. The dual process view (Yonelinas, 1994, 2002) suggests two processes support episodic memory which rely on overlapping, yet distinct systems. The "recollection system" includes the hippocampus and is important for storing and actively reactivating contextual links between elements in an episode (Diana et al., 2007). While the "familiarity system", is responsible for differentiating new from old information and does not necessarily require the hippocampus since it can be achieved through non-associative mechanisms such as habituation. This dual process view partially stems from neuropsychological evidence showing different forms of amnesia affecting recollection and familiarity behaviour result from selective damage to the hippocampus or surrounding cortex (Aggleton et al., 2005; Bowles et al., 2007; Diana et al., 2007; Yonelinas et al., 1998, 2010). This suggests the hippocampus and associated ripples may play a greater role in synchronising and integrating information across representations in cortex during memory tasks which require associative linking, storage, and active recollection.

To study the effect of associative and non-associative task demands on ripple activity, we can examine the role of ripple activity at each stage of a memory trace: encoding, offline maintenance, and retrieval.

Few studies have explicitly studied ripple activity during encoding. A recent intracranial study showed no difference in ripple rates during encoding of memory items which were later remembered (Sakon et al., 2024). If ripples serve to synchronise activity between associated representations, then we might expect ripples to be less important during encoding when the memory information does not need to be synchronised because it is being simultaneously displayed. However, high-frequency activity (~>60 Hz) has been linked to successful associative encoding (Burke et al., 2014), which indicates there may be an effect of associative demands on ripple activity at encoding since their frequency bands overlap.

On the other hand, memory retrieval has been explicitly linked to ripple activity (Norman et al., 2019; Vaz et al., 2019, 2020). According to the Complementary Learning Systems framework, the hippocampus integrates and reactivates the associated cortical patterns during retrieval (Norman & O'Reilly, 2003) and ripples are thought to play an important role in this integration by creating time windows to synchronise activity between associated representations. In line with this, Vaz and colleagues found sequences of single-unit activity related to memory items were replayed around ripples in humans during retrieval (Vaz et al., 2020). Moreover, a recent study showed single-units in the MTL which were tuned to associated pairs of places and objects were more likely to coacctivate around ripples during retrieval of the association (Kunz et al., 2024). This suggests ripples provide a potential mechanism for supporting reactivation in retrieval, through hippocampal-cortical synchronisation.

As well as supporting retrieval, ripples occurring during offline states are thought to play a key role in memory consolidation during offline periods, with the number and duration of ripples during rest predicting memory performance (Ego-Stengel & Wilson, 2010; Fernández-Ruiz et al., 2019; Girardeau et al., 2009; Jadhav et al., 2012). Ripples may achieve this by orchestrating unit-level reactivation, whereby cell-assembly firing patterns linked to a memory-relevant items or events reactivate around ripples (Carr et al., 2011; Diba & Buzsáki, 2007; Foster & Wilson, 2006). In line with the need to consolidate connected associations into cortex, offline reactivation has a greater effect on associative memory compared to non-associative memory (Peyrache et al., 2009; Tambini et al., 2017). If offline ripples guide unit-level reactivation for the consolidation of associative memories, one might expect the quantity and quality of ripples during offline periods to reflect associative memory demands. Our final analysis explores this by testing the effect of associative vs non-associative memory demands on ripple rate and features during offline delay periods in the memory tasks.

In the present study we investigate the nature of ripple activity during memory processing. Firstly, we ask whether the ripple signal reported during retrieval is detectable using a bottom-up approach and compare the localisation of activity between entorhinal cortex and hippocampus. We then ask whether associative, vs non-associative, memory demands are linked to ripple activity during encoding, delay periods, and retrieval. To investigate the relationship between ripples and different forms of memory, we had participants perform an associative and non-associative memory task. Although both tasks may have included episodic recollection, only the associative task required participants to encode, retain, and recollect context-bound information, while the non-associative task could be performed using familiarity judgments. Our study is therefore uniquely designed to test whether ripple activity tracks associative compared to non-associative memory demands.

Methods

The data set and paradigm in the present study have been previously reported, and therefore some of the methodological details here are paraphrased with permission from Staresina et al. (2019). Additionally, some of the methods are later repeated in Chapter 4 which looks at the same data whilst asking an entirely different set of questions.

Participants

Nine patients undergoing iEEG monitoring for epilepsy participated in the study (four female, age: M = 36.72 years old, SD = 8.84). Written informed consent was obtained from all participants. The implantation scheme was determined according to clinical needs to

localise seizure onset zones. The present study did not influence the electrode implantation in any way and was conducted according to the ethical guidelines from the University of Bonn's Medical Institutional Review Board.

Task

Participants conducted associative and non-associative memory tasks in an intermixed design.

In associative encoding trials, pairs of items and scenes were displayed for three seconds. While the scene was always trial-unique, the item was chosen with 50% chance from a set of two items. The set of two items remained the same throughout the session (e.g., "key" and "apple"). Participants were asked to imagine a scenario with the presented item-scene pair and judge whether the scenario was plausible using the arrow keys (left = "plausible", right = "implausible", down = "don't know"). This encouraged participants to engage with the stimuli. After a delay period with a fixation cross, participants conducted a set of retrieval trials. In retrieval trials, the scenes from the encoding trials (memory cue) were presented for three seconds. After three seconds elapsed, participants were prompted to use the arrow keys to indicate which item was paired with the scene (left, right), or state they had forgotten (down). After giving the response, participants were shown a feedback screen for 500 msec with a green or red arrow pointing at the correct response (left or right) if correctly remembered not, respectively. The retrieval scenes were presented in a random order. Each block contained 10 encoding trials, a 30-second delay, and 10 retrieval trials. Each participant conducted eight blocks across the session (80 encoding/retrieval trials in total).

In non-associative encoding trials, images of scenes were presented for two seconds. Participants were then prompted to judge whether the scene was pleasant (left), unpleasant

(right), or they didn't know (down). After a delay period with a fixation cross, participants conducted a set of retrieval trials. In each retrieval trial, a scene was shown that was either a scene from the encoding trials, or a novel scene. After the scene was shown for two seconds, participants used arrow keys to respond to a prompt, indicating the scene was old (left), new (right), or that they didn't know (down). Participants were then shown a 500 msec feedback screen similar to that in the associative task. Each session contained four non-associative encoding-delay-retrieval blocks, each with 20 encoding trials, a delay, and 40 retrieval trials (50% old, 50% novel).

All trials were preceded by a 500 msec fixation cross and followed by a black screen with a jittered random duration between 100-400 msec. All responses were self-paced and timed out after 10 seconds (counted as "don't know" response). To create an intermixed design across the session, a non-associative block was always preceded by two associative blocks.

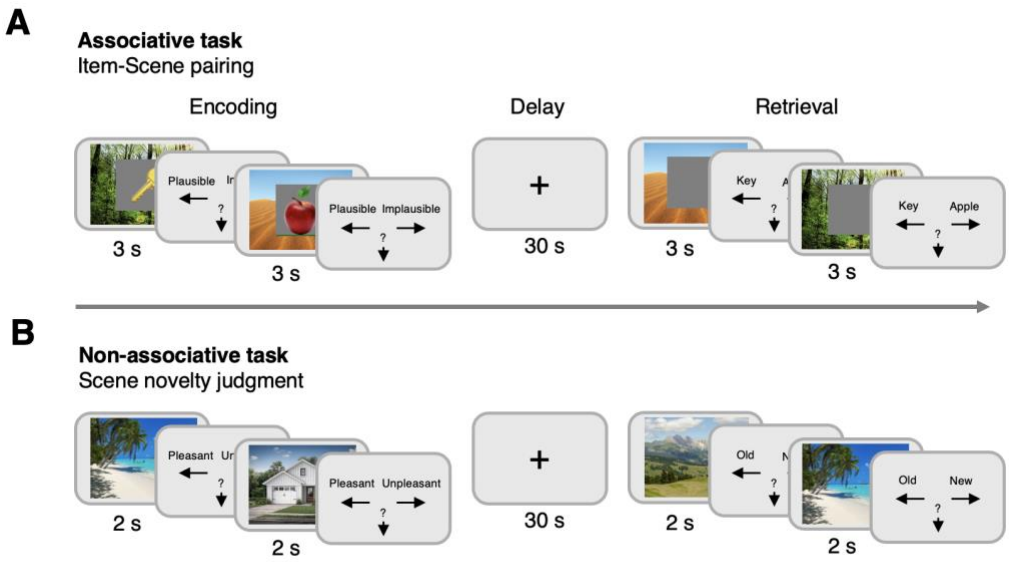

Figure 1. Memory tasks. A) Associative memory task design. In encoding trials, item-scene pairs were shown for three seconds before participants were prompted with a plausibility response. After a delay, participants conducted a set of retrieval trials. In retrieval trials, a scene was presented for three seconds before participants were prompted to identify the corresponding paired item. **B)** Non-associative memory task design. In encoding trials, images of scenes were presented for two seconds. Participants then judged the pleasantness of the scenes. After a delay, participants were shown scenes for two seconds. The scenes were either from the encoding set, or new. Participants were then asked to identify whether the scene was old or new.

Electrophysiological recordings

A T1 weighted MRI showing an example implanted intracranial depth electrode is depicted in **Figure 2A**. A 256-channel Neuralynx Atlas system (Bozeman, MT, USA) amplified the signal from the depth electrodes (AdTech, Racine, WI, USA) that was sampled at 32 kHz with a 0.1-9000 Hz filter. The iEEG signal from macro contacts was down sampled to 1000 Hz.

In total we included 33 hippocampal and 13 entorhinal macro iEEG contacts. Each participant had at least two hippocampal contacts and one entorhinal contact (contacts per

participant: Hippocampal contacts: M = 3.67, SD = 1.87; Entorhinal contacts: M = 1.44, SD = 0.53). We did not include iEEG contacts in the pathological hemisphere in the case that the epileptic activity was clinically localised in a hemisphere. The iEEG signals from the most medial macro contacts on the depth electrodes were re-referenced with the closest white matter contact. A notch filter removed line noise between 49-51 Hz (and harmonics at 99-101, 149-151, and 199-201 Hz).

Macro-electrode locations were linked to hippocampus or entorhinal cortex using post-implantation CT scans co-registered with pre-implantation MRI scans.

Artefact detection

To detect amplitude artefacts in the iEEG data, the signal was first bandpass filtered between 0.3-150 Hz and artefactual events were detected where the signal exceeded the median ± 4 IQR. Gradient artefacts were defined as timepoints where the first derivative of the iEEG signal exceeded the median ± 4 IQR of the first-derivative values. Amplitude-and-gradient events were events where both amplitude and gradient exceeded the median ± 4 IQR. To detect high-frequency burst artefacts which could be mistaken for ripples, a 150 Hz high-pass filter was applied to the signal. Windows with an envelope exceeding median ± 4 IQR for at least 100 msec were detected as high frequency burst events. Finally, we applied interictal discharge detection from Ung et al. (2017) to classify interictal spikes as artefacts. Artefact events were buffered with a 300 msec time window on either side and removed from ripple detection analyses.

Gamma-peak detection

Our approach for gamma-peak detection was designed to be sensitive to burst-like activity across all gamma frequencies, while also being sensitive to burst activity that may be heterogeneous between trials and therefore affected by cross-trial averaging before burst detection (Lundqvist et al., 2016). To reduce the influence of any pre-processing steps, artefactual events were not excluded from gamma-peak detection. To detect gamma-peaks, the iEEG data were first segmented from -1.5 to 3 seconds after cue onset in retrieval trials, pooled from both tasks (including a one second time buffer to mitigate edge effects in time-frequency representation (TFR) analysis). A multi-taper convolution method was used to compute the TFR, using Hanning tapers. We included frequencies between 30-200 Hz with a 1 Hz frequency resolution and 10 msec temporal resolution. A fixed window of 100 msec was used for the Fast Fourier Transforms. Resulting power values were corrected to represent the relative power change compared to the -0.5-0 second pre-stimulus window. The TFRs in each trial were smoothed with a 50-msec and 20 Hz Gaussian kernels. For each trial, gamma-peaks were detected as events in the relative TFR, which exceeded one SD from the mean of the power in the time-frequency space. The local maxima of the peaks were taken as the time-frequency coordinates of the gamma-peaks. These coordinates were then averaged across trials for each contact to create a density map of gamma-peaks (see **Figure 2B-D**).

Ripple detection

Ripples were detected offline on artefact-free iEEG data using custom algorithms (Ngo et al., 2020). To detect ripples, the iEEG signal was bandpass filtered between 80-120 Hz. The root-mean-square envelope was smoothed with a 20 msec moving mean, and ripple events were characterised as having an envelope which was at least one SD above the mean, while lasting between 38-300 msec and having between three and nine cycles. For each contact, ripple detection was conducted across the entire session. **Supplementary Figure 9** shows the grand average ripple across subjects and the average ripple for each subject.

Analysis

Analysis during encoding and retrieval windows were conducted up until 2 seconds post-stimulus onset, as this is the time which is shared between associative and retrieval trials. For the ripple rate analyses in (**Figure 3**), rates in each contact were z-scored with the mean and SD from the concatenated trials included in the respective comparison. For example, in **Figure 3A** the ripple rates were z-scored using the mean and SD from all concatenated encoding trials (-0.5-2 seconds; both tasks).

Statistical analysis was conducted using MATLAB 2024b (The Mathworks Inc., MA, USA) with functions from Fieldtrip version 20241219 (Oostenveld et al., 2011).

We used LMEs to account for the presence of multiple channels within each participant. For statistical comparisons between conditions, the LME formula was "Variable ~ Condition + (1|Participant)", while comparisons to zero used the formula "Variable ~ 1 + (1|Participant)".

Cluster-based permutation tests were conducted across channels and treated them as independent. All cluster-based permutation testing was conducted with 1000 permutations. An alpha threshold of 0.05 was used to determine if results were significant. To account for the fact that channels are not independent and are nested in participants, all cluster-based permutation test analyses are complemented with an LME analysis averaging over the time/frequency window of interest.

Results

Memory behaviour

First, we tested whether participants had above-chance memory in the tasks. Accuracy was significantly above chance-level (0.5) in both associative and non-associative tasks (Associative: M = 0.81, SD = 0.11, $t(8) = 8.74$, $p < .001$, $d = 2.91$, two-tailed; Non-associative: M = 0.91, SD = 0.04, $t(8) = 29.74$, $p < .001$, $d = 9.91$, two-tailed). We also compared remembering behaviour in associative and non-associative tasks. A paired-samples t-test showed lower accuracy in the associative task (Non-associative: M = 0.91, SD = 0.04, Associative: M = 0.81, SD = 0.11, $t(8) = -3.16$, $p = .013$, $d = -1.05$, two-tailed). The relatively low proportion of trials with incorrect responses (Associative M = 0.18, SD = 0.11; Non-associative: M = 0.09, SD = 0.04; N = 9 participants) and timeout or "don't know" responses (Associative: M = 0.01, SD = 0.02; Non-associative: M = 0.01, SD = 0.02; N = 9 participants) limited our ability to conduct analyses comparing remembered and forgotten conditions.

Gamma-peaks in the ripple frequency band are prevalent in hippocampal, but not entorhinal, iEEG during memory retrieval

First, we used a bottom-up analysis to investigate the nature of the iEEG signal in hippocampus and entorhinal cortex during memory retrieval. Specifically, we wanted to test whether there was evidence of a higher concentration of gamma-peaks in the ripple-band (80-120 Hz) of the power spectrum when examining the broad gamma range (30-200 Hz) during memory retrieval.

After detecting gamma-peaks in trials and averaging over trials for each contact (see **Methods**), gamma-peak densities were smoothed over frequency bins with a 20 Hz Gaussian smoothing kernel. Gamma-peak density for each frequency band was then averaged over the 0-2 s window after the memory cue was presented, and frequency-specific densities were mean-corrected across all gamma frequencies (30-200 Hz). All associative and non-associative retrieval trials were included in the analysis. **Figure 2B** shows the density of hippocampal gamma-peaks in the ripple-band (80-120 Hz) was significantly greater than the mean across the full gamma range (N = 33; cluster-based permutation testing, $p < .05$; two-tailed). On the other hand, entorhinal contacts showed the opposite effect, where the density of gamma-peaks in the ripple-band was significantly lower than the mean across the full gamma range (**Figure 2B**, N = 13; cluster-based permutation testing, $p < .05$; two-tailed). An LME analysis controlling for the presence of multiple channels within each participant compared the average mean-corrected gamma peak density in the 80-120 Hz range to zero (not smoothed across time or frequency). The LME results showed a significant positive effect in hippocampal contacts (M = 1.20, SD = 1.18; $\beta = 1.082$, SE = 0.289, $t(32) = 3.75$, $p < .001$) and a significant negative effect for entorhinal contacts (M = -0.56, SD = 0.62; $\beta = -0.558$, SE = 0.176, $t(12) = -3.18$ $p = .008$).

The difference in ripple-band gamma-peak density is further visualised in **Figure 2C-D**, which show the average density of gamma peaks across contacts for hippocampal and entorhinal contacts across the whole retrieval time window and gamma frequency range. Together, these results reveal that gamma-peaks are prevalent in the ripple band in hippocampal contacts, but not in entorhinal contacts.

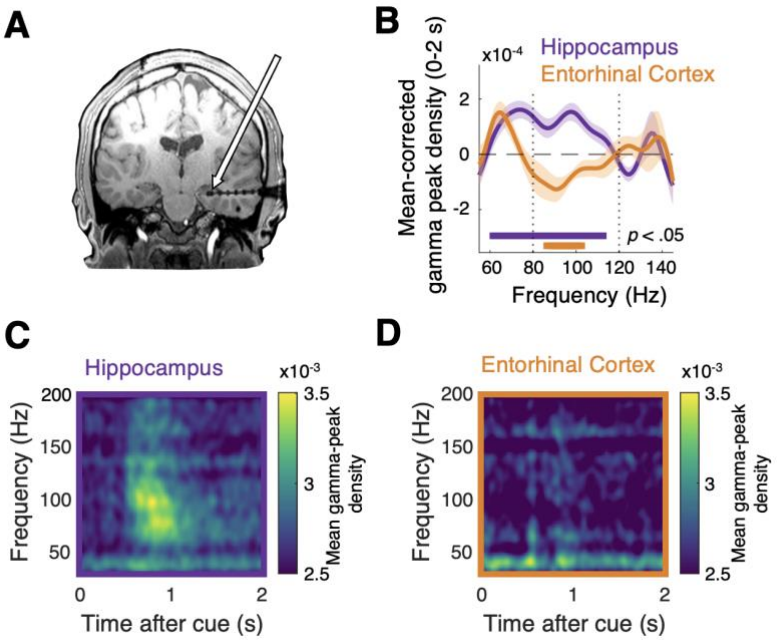

Figure 2. Peaks in gamma in the hippocampus and entorhinal cortex during memory retrieval. A) T1-weighted MRI showing an implanted iEEG electrode. **B)** Mean-corrected gamma-peak density over frequency bands in the hippocampus and entorhinal cortex during retrieval. For details on how gamma-peaks were detected, see **Methods**. Purple and orange lines represent the mean for the hippocampal and entorhinal contacts, respectively (Hippocampus: N = 33 contacts; Entorhinal cortex: N = 13 contacts). Shading is SEM. Horizontal coloured bars represent significant clusters using cluster-based permutation tests ($p < .05$; two-tailed), comparing the mean-corrected average gamma-peak densities in hippocampal (purple) and entorhinal (orange) contacts to zero. Vertical dashed lines show the 80 Hz and 120 Hz boundaries of the ripple-band used in our later analysis. **C)** Average gamma-peak density during retrieval time across hippocampal contacts (N = 33). Density is smoothed along the frequency axis with a 20 Hz Gaussian kernel, and along the time axis with a 200 msec Gaussian smoothing kernel. **D)** Same as **C)**, but for entorhinal contacts (N = 13).

Finally, we show that ripple-like events can be detected even when there is no signal by detecting ripples in white noise. **Supplementary Figure 9C** shows the grand average ripple of ripples detected in participants after the hippocampal iEEG signal was replaced with white noise (randomly generated signal with SD of 5 μV). However, after repeating the gamma-peak detection analysis on the white noise signals we see no indication of a prevalence of gamma-peaks in the ripple-band (**Supplementary Figure 10**). This demonstrates how ripple-like events can be detected in noise due to a detection algorithm's criteria and the mere presence of detected ripple-like events does imply they are a prevalent signature in the signal.

Ripple activity is greater in the delay and retrieval periods during the associative memory task

Next, we sought to test whether ripple activity differs between associative and non-associative memory demands. Since our previous results (**Figure 2**) show evidence of greater hippocampal gamma-peak density in the ripple-band (80-120 Hz), we used a custom algorithm (see **Methods**) to detect ripples in hippocampal contacts, as it is more sensitive to the properties of ripples. These ripples are referred to throughout the rest of the analysis.

We then compared the ripple rates around the time of stimulus or cue onset in encoding and retrieval trials between associative and non-associative tasks. Two-tailed cluster-based permutation testing showed normalised ripple rates were greater around one second after cue onset in associative retrieval trials, compared to non-associative trials (**Figure 3C**, $p < .05$, two-tailed). However, the associative memory condition was not found to influence the ripple rate during encoding (**Figure 3A**, cluster-based permutation test, $p > .05$, two-tailed). An LME analysis controlling for the presence of multiple channels within each participant revealed the associative memory condition had a significant positive effect on the average

unsmoothed normalised ripple rate between 0-2 s during retrieval trials (Associative: M = 4.14 * 10^{-3}, SD = 4.15 * 10^{-3}; Non-associative: M = 0. 89 * 10^{-3}, SD = 0.20 * 10^{-3}; β = 3.246 * 10^{-3}, SE = 0.683 * 10^{-3}, $t(64) = 4.75$, $p < .001$). This effect was not significant ($p > .05$) in encoding trials (Associative: M = 2.08 * 10^{-3}, SD = 2.21 * 10^{-3}, Non-associative: M = 1.95 * 10^{-3}, SD = 3.16 * 10^{-3}; β = 0.126 * 10^{-3}, SE = 0.661 * 10^{-3}, $t(64) = 0.19$, $p = .850$).

To determine if the effect was specific to retrieval, we first averaged the normalised ripple rates from 0-2 s post-stimulus onset during encoding and retrieval periods for associative and non-associative trials. We then subtracted the mean normalised ripple rate during non-associative trials from the mean during associative trials for encoding and retrieval periods separately. An LME analysis revealed being in the retrieval task phase had a positive effect on the difference between associative and non-associative ripple rate (Encoding contrast: M = 0.00, SD = 0.04; Retrieval contrast: M = 0.04, SD = 0.06; β = 3.095 * 10^{-3}, SE = 1.031 * 10^{-3}, $t(64) = 3.00$, $p = .004$).

While the ripple activity during encoding and retrieval periods could in principle reflect differences in the visual stimuli and the type of decision-making processes, the delay periods were identical between the two conditions. Therefore, a difference in ripple activity during delay periods would reflect a response to the associative demands of the memory task. To test whether associative task demands modulated ripple activity during delay periods we used an LME analysis. The results show there was positive effect of the associative condition on the normalised unsmoothed ripple rate in associative delay periods (Associative delay: M = 0.10, SD = 0.20; Non-associative delay: M = -0.20, SD = 0.40; β = 0.300, SE = 0.076, $t(64) = 3.94$, $p < .001$).

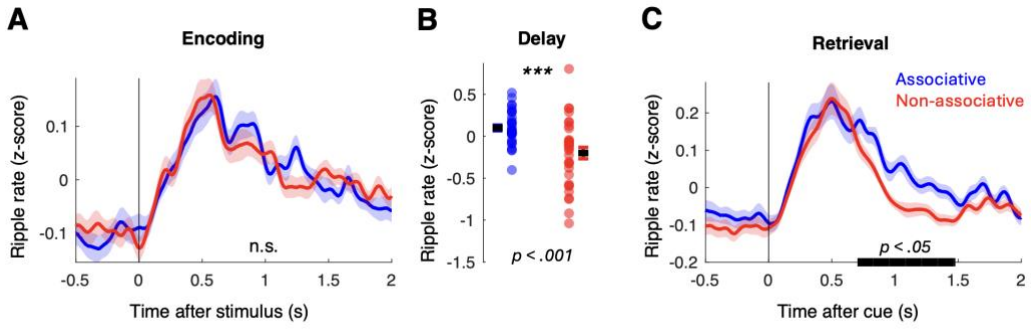

Figure 3. Ripple activity during memory encoding, delay, and retrieval periods of associative and non-associative tasks. A) Z-scored ripple rate locked to the presentation of the encoding stimuli. Blue and red lines show the mean normalised ripple rates across hippocampal contacts (N = 33) during associative (blue) and non-associative (red) encoding trials. All encoding trials were used for each condition. Shading represents SEM. "N.S." represents a lack of significant clusters when comparing associative and non-associative ripple rates using cluster-based permutation testing in the -0.5-2 s window (p < .05; N = 33; two-tailed). **B)** Comparison of normalised ripple rates in associative and non-associative delay periods. Points are individual contacts. Black dashes and error bars are mean and SEM over contacts (N = 33). Triple asterisk (***) indicates a significant LME model effect of associative condition on normalised ripple rate during delay periods (p < .001). **C)** Same as **A)** but locked to the onset of the memory cue in remembered retrieval trials. The black bar indicates a significant difference between associative and non-associative ripple rates, as determined by cluster-based permutation testing (p < .05, N = 33; two-tailed).

Finally, we investigated whether the ripples during associative and non-associative delays exhibited qualitative differences (**Figure 4**). First, we compared the durations of the ripples. An LME showed a significant positive effect of the associative condition on the duration of ripples during delay periods (Associative delay: M = 58.97 msec, SD = 19.45; Non-associative delay: M = 57.85 msec, SD = 18.23; β = 1.020, SE = 0.468, $t(64)$ = 2.18, p = .029). Next, we tested whether ripple amplitude was affected by the associative condition. Amplitude was taken as the maximum of the ripple envelope (see **Methods**). The LME showed the associative condition positively affected ripple amplitudes in delay periods

(Associative delay: M = 3.61 μV, SD = 1.63; Non-associative delay: M = 3.42 μV, SD = 1.37; β = 0.117, SE = 0.036, $t(64)$ = 3.26, p = .001). Finally, an LME showed no evidence of a significant effect (p > .05) of the associative condition on ripple frequencies in delay periods (Associative delay: M = 91.90 Hz, SD = 5.88; Non-associative delay: M = 92.02 Hz, SD = 5.71; β = 0.046, SE = 0.140, $t(64)$ = 0.33, p = .744).

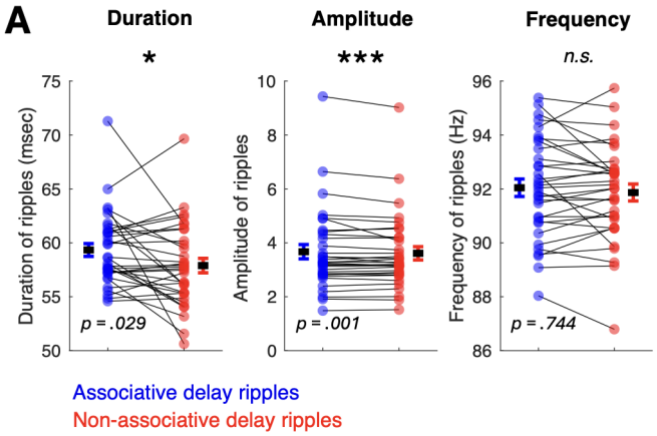

Figure 4. Ripple features during delay periods of associative and non-associative tasks. A) Comparison of mean duration, amplitude, and frequency of ripples in associative and non-associative delay periods. Points and lines are individual contacts. Black dashes and error bars are mean and SEM over contacts (N = 33). Asterisk (*) and triple asterisk (***) indicate significant effects of associative condition on ripple features in LME (p < .05 and p = .001 respectively). "N.S." represents a lack of a significant effect (p > .05).

Together, this suggests ripple activity is affected by the associative memory condition during memory retrieval and delay periods, with greater ripple rates, durations, and amplitudes tracking associative task demands.

Discussion

In this study, we investigated the prominence of ripples in wake iEEG signals and their relationship to associative memory demands. First, we tested for ripple-like gamma-peaks during memory retrieval in hippocampal and non-hippocampal contacts. Our results show gamma-peaks in the ripple-band are prominent in hippocampal, but not entorhinal, iEEG during memory retrieval. Next, we compared ripple activity in an intermixed paradigm. We found the quantity and quality of hippocampal ripples during retrieval and delay periods tracked explicit associative memory demands, suggesting ripples play a role in associative memory function.

The results of our first analysis showed ripples were detectable in the hippocampus during retrieval using bottom-up methods. After detecting power peaks in the broad gamma range (30-200 Hz) on a single-trial basis, we showed the gamma-peak density hippocampus significantly increases in the ripple-band (80-120 Hz) around retrieval (**Figure 2B**). This supports the notion that ripple events occur during wake retrieval that are not detected due to broadband gamma increases. Previous studies have also shown that high-frequency gamma activity is related to memory retrieval (Burke et al., 2014; Treder et al., 2021). However, these studies averaged over trials. We show in **Figure 2C-D** that the density of single-trial gamma-peaks averaged over trials can appear as a gamma cloud. This way, if many ripple events are averaged over trials, they may appear as a high-frequency gamma cloud around retrieval, while hiding the burst-like nature of the signal at the single-trial level. Thus, our results suggest the high-frequency gamma effect of retrieval may be a result of trial-averaged ripple events, as has been proposed by others (Lundqvist et al., 2016; Tong et al., 2021). Future studies could explicitly test this by observing whether a non-ripple high gamma effect persists after removing discrete ripple events from the iEEG.

Our initial analysis also shows there is a lack of ripple-like gamma peaks in the entorhinal cortex (**Figure 2B&D**). The entorhinal cortex is a direct input and output of the hippocampus (Witter et al., 2017). Therefore, if a ripple signal were prominent in non-hippocampal regions during wake retrieval, one would expect it to be easily detectable in the entorhinal cortex. Since we show this is not the case, our results suggest ripples in the wake may be localised to the hippocampus. This has implications for studies examining ripple activity outside the hippocampus in wake. An algorithm which detects ripple events by thresholds of the ripple-band envelope can detect suitable events that have the characteristics of ripples in noise. When plotted and characterised, these pseudo-ripple events found in noise appear to have the properties of ripples (as we demonstrate in **Supplementary Figure 9C**). However, our gamma-peak detection method showed no prevalence of ripple-like bursts in the noise (**Supplementary Figure 10**). Therefore, our results highlight the importance of ensuring that bursting events within the ripple range of the gamma spectrum are overrepresented in the iEEG signal of interest before using more sensitive ripple-detection algorithms, so as not to detect pseudo-ripples in areas with no clear ripple signal falsely.

Next, we show how ripple activity is greater during retrieval of the associative memory task, compared to the non-associative task (**Figure 3C**). If ripples are important for synchronising hippocampus and cortex for the reactivation of associated memory elements during retrieval (e.g., place and items (Kunz et al., 2024)), then we would expect more ripple activity during associative retrieval. Therefore, our results support the notion that ripples serve as a mechanism to integrate associated information during episodic recollection (Davachi, 2006; Diana et al., 2007). Additionally, these results suggest hippocampal processes (including ripples) play a greater role in retrieval requiring recollection and not only familiarity, supporting the dual process framework (Yonelinas, 2002). Future studies could explore this

in more detail, using receiver operating characteristics to quantify the level of familiarity vs recollection granularly during retrieval trials.

As well as higher ripple activity during retrieval, we found greater ripple rates during the delay periods in the associative task (**Figure 3B**). If hippocampal processing in delay periods is important for connecting information between episodic elements and consolidating these relationships into a long-term store, we might expect associative memory delay periods to express more ripple activity to support the stabilisation of the associated links. This memory-dependent difference in ripple rate may be facilitated by short-term fluctuations in acetylcholine. Acetylcholine is a neurotransmitter which is thought to regulate hippocampal activity and ripple activity during rest. Low levels of acetylcholine promote hippocampal output signals to the cortex (Gais & Born, 2004; Hasselmo, 1999; Hasselmo & McGaughy, 2004), and high levels have been found to impair ripples (Vandecasteele et al., 2014; Zhang et al., 2021). Recent work shows acetylcholine levels can be tracked at the level of minutes and seconds (Reimer et al., 2016). New directions could explore how levels of acetylcholine during delay periods change with memory demands (high load vs low load, associative vs non-associative) and investigate whether this drives differences in the expression of ripples.

Interestingly, our results showed no evidence for a difference in ripple rates during encoding periods for associative and non-associative memory tasks (**Figure 3A**). This may be due to the nature of the task. Hippocampal engagement has been shown to track spatial and temporal distances between linked information (Staresina & Davachi, 2009). In this study, the item and scene were overlaid, reducing the need for active binding during the encoding phase. Similarly, an intracranial study that found an effect of hippocampal ripple coupling with cortex at retrieval, did not find the same effect at encoding (Vaz et al., 2019), while another showed no increase in ripple rates at encoding for stimuli that were later remembered

(Sakon et al., 2024). This supports other studies which have shown the hippocampus can play a functional role in memory consolidation and retrieval, even when initial task learning is less hippocampus dependent (Sawangjit et al., 2018). For example, Schapiro and colleagues showed patients with hippocampal damage were unimpaired in learning a motor memory task but did not benefit from hippocampus-related sleep dependent memory consolidation, unlike matched controls (Schapiro et al., 2019).

The quality, as well as the quantity of ripples has been found to track memory demands and cognitive states (Buzsáki, 2015; Chen et al., 2021; Fernández-Ruiz et al., 2019). Specifically, longer ripples have been linked to greater memory demands and increased memory consolidation in rodents (Fernández-Ruiz et al., 2019). Our results show that human ripple features are similarly affected by memory demands, with greater event amplitudes and durations during associative delay periods (**Figure 4**). Although we were unable to test for differences in memory consolidation due to the ceiling effects and the block design of the task, we show that the ripple activity was greater during associative delay periods and that the ripples were qualitatively larger and longer.

Offline ripples in rodents have been shown to relate to the reactivation of neural populations that represent specific task-relevant information (Carr et al., 2011; Diba & Buzsáki, 2007; Foster & Wilson, 2006). Therefore, ripples during delay periods of tasks with associative demands may be related to a particular increase in units tuned to the associated items (i.e., reactivations of paired memory item representations; similar to Kunz et al., (2024)). Future experiments with stimulus-tuned units could explicitly test this, while linking it with performance to determine if ripple-linked reactivation during delays is important for associative memory consolidation in wake.

There may also be a link between the relevance of ripples in associative memory and memory decline with age. Studies exploring memory decline with age have shown that recollection is affected to a greater degree than familiarity (Koen & Yonelinas, 2014). Recent evidence from rodent models also shows that the rate of wake ripple expression reduces with age (Cowen et al., 2020). If ripples are more involved in hippocampal recollective memory processes, as our results suggest, then a reduction in ripple expression with age may mechanistically drive the decline in recollective memory with age.

Finally, it is important to address two key limitations of the study: the differences in stimuli between tasks and the small sample size. Firstly, as well as including an associative link, the associative task also differed from the non-associative task in the domain of the stimuli presented. The non-associative task contained images of scenes, while the associative task included images of items and scenes. There is evidence to suggest the hippocampus is particularly active in the perception and processing of scene information (Aly et al., 2013; Hodgetts et al., 2017; Lee et al., 2005), which may lead to biased hippocampal involvement in the tasks. However, if the exclusive involvement of scene stimuli and scene discrimination increased hippocampal ripple activity, one would expect greater activity in the non-associative task (no item or grey box in the middle of the screen). However, we find the opposite (**Figure 3C)** with ripple activity remaining the same during encoding between tasks and increasing in the associative task at retrieval. Additionally, there was no significant difference during encoding (**Figure 3A**). Moreover, any difference in the stimuli does not account for the effect of the associative task on ripple activity during delay periods, since the delay periods were identical between tasks. Therefore, it is unlikely that the difference in ripple activity was the result of the nature of the stimulus domain.

Secondly, it is important to note that although the small number of participants (N = 9) is not uncommon for iEEG studies, it makes it difficult to draw strong conclusions from the results. Future efforts could take advantage of multi-centre data sets to increase the number of participants and address this issue.

In conclusion, we demonstrate how bottom-up methods detect a prominent gamma-peak signal in the ripple band in hippocampal, but not entorhinal, contacts during retrieval, suggesting that the ripple signal during wake may be regionally localised and demonstrating the value of validating algorithmically detected ripples with data-driven approaches. We also found ripple activity during retrieval was greater in an associative memory task, supporting the notion that hippocampal processes, including ripples, support associative memory. Finally, we demonstrate the quantitative and qualitative effects of memory demands on ripples in delay periods. Together, this suggests wake ripple activity reflects associative memory demands in humans.

Chapter 4: Velocities of neural trajectories relate to memory retrieval

Abstract

Imagine bumping into someone at the supermarket. It takes a moment for you to realise she is an old classmate from school. In the blink of an eye, your brain perceived their face, searched your memory, and retrieved information about them. At a neural level, the activity of neural populations shifted from encoding perceptual information to reinstating memory representations. Each stage of this dynamic recall process requires population activity to rapidly move through representational subspaces which encode perceptual and memory information. If memory traces are stronger, and/or memory search is faster, this would reflect on the dynamic behaviour of the trajectories themselves. Here, we explore this by testing how the velocities of latent population activity behave when we remember or forget an episodic memory linked to a memory cue. Moreover, we investigate how rapid velocities of neural trajectories relate to representational reinstatement of memory information and to macro-scale ripple events. We test this in a data set including neuronal recordings and macro iEEG from the human MTL. Our results show that peak velocities in low-dimensional population trajectories are greater during successful memory retrieval, compared to unsuccessful retrieval. Peak velocities also predict the degree of representational reinstatement during retrieval and coincided with hippocampal ripple activity. This suggests the dynamic properties of neural trajectories are related to memory processing and shows how studying population trajectories as dynamic systems in motion may help us better understand the nature of neural computations underlying memory function and cognition.

Introduction

Some memories come rushing back to mind. Other times, a memory is stuck "on the tip of our tongue", or we forget it entirely. How is this difference reflected in the behaviour of underlying neural activity? Does neural activity shift faster when we successfully recall information? Here, we explore this by looking at the dynamic properties of neural activity patterns during memory retrieval.

Mounting evidence suggests that the hippocampus links representations of cues with associated memories (Lisman, 1999; Wallenstein et al., 1998). As perceptual information of the cue reaches the hippocampus, the pattern completion process is thought to reinstate a rich representation of the cue whilst activating linked memory representations across cortex (Goode et al., 2020; McNaughton & Morris, 1987; Norman & O'Reilly, 2003; Teyler & DiScenna, 1986), with the entorhinal cortex acting as an interface between hippocampus and cortex (Chrobak, 2000; O'Reilly & Norman, 2002). Supporting evidence from cued recall paradigms shows hippocampal activation precedes reinstatement of retrieved memory representations in the hippocampus, entorhinal cortex, and temporal cortex (Staresina et al., 2016, 2019; Treder et al., 2021; Yaffe et al., 2014). This reinstatement is promoted by high-frequency (80-120 Hz) hippocampal bursts of macro-scale population activity, known as ripples (Buzsáki et al., 1987; Vaz et al., 2019, 2020), which promote cross-regional synchrony between the hippocampus and cortex (Buzsáki et al., 1987; Buzsáki, 2015; Ngo et al., 2020; Rasch & Born, 2013). Thus, the population activity in the hippocampus and cortex, facilitated by ripples, shifts to represent the retrieved information to guide future cognition and behaviour. This transient shift in population activity, representing the retrieved information, lends itself to being studied as a dynamic system.

Studying neural population activity as a dynamic system enables us to investigate how population activity may give rise to cognition and behaviour through its temporal evolution (Shenoy et al., 2013; Vyas et al., 2020). Motor neuroscience has adopted this framework to investigate how the geometric properties of low-dimensional neural trajectories (Cunningham & Yu, 2014; Williamson et al., 2019) mechanistically underpin neural computations underlying behaviour (Churchland et al., 2012; Churchland & Cunningham, 2014; Saxena & Cunningham, 2019). This has also been applied to the memory domain. For example, Murray and colleagues (Murray et al., 2017) demonstrated that task-relevant memory information was encoded in low-dimensional subspaces, allowing the information to be reliably decoded across time, despite the heterogeneous single unit dynamics. Studies have also tested the importance of the temporal characteristics of population trajectories on behaviour (Colins Rodriguez et al., 2024; Wang et al., 2018). For example, Colins Rodriguez and colleagues found that the velocity of a reaching movement was encoded in the velocity of the population trajectory (Colins Rodriguez et al., 2024), revealing how the dynamic properties of population trajectories themselves encode information related to behaviour. Another study recorded neural populations in the prefrontal cortex of monkeys while they estimated the length of time windows (Meirhaeghe et al., 2021). Analysis revealed that the velocities of neural trajectories were faster during short-time-window approximation, suggesting that the dynamic properties of the trajectory reflect cognitive processing.

Like movement and time estimation, cued recall is a dynamic process (Staresina & Wimber, 2019). The cue initiates an internal search, followed by the reinstatement of retrieved memory information and the preparation of a response (Staresina et al., 2019; Treder et al., 2021). At each stage, neural ensembles must be able to internally decode the relevant information (e.g., the cue or the reinstated information) to guide further processing. The transient phases of low-dimensional neural trajectories may be important for this internal representation of

information. In a classic odour experiment, Mazor and Laurent found that the identity and concentration of odours were most separable during highly transient phases of the population trajectory, rather than during periods where the trajectories reached fixed points (Mazor & Laurent, 2005). A fixed point only occurred during sustained stimulus presentation and was not necessary for decoding. Since neural populations go on to internally decode and act on the representation of the memory (for example, to prepare a response), it is possible that trajectories with faster, more exaggerated, transient states have a higher chance of resulting in successful memory retrieval and may result in higher levels of pattern completion (Rabinovich et al., 2008).

Not much is known about the dynamic properties of trajectories in the MTL during memory behaviour. If representational reinstatement is important for successful memory retrieval (O'Reilly & Norman, 2003), then trajectories will shift during retrieval to reinstate relevant information. The speed at which the trajectory shifts (i.e. its velocity profile) may track memory success. If a memory trace is well-defined, then the strength of the underlying circuitry may rapidly pull the trajectory to represent memory-specific information, resulting in high velocities in the trajectory. Therefore, rapid velocities may relate to the quality of the reinstatement of the memory trace itself as well as memory behaviour. Moreover, if the retrieval process is not all-or-nothing, but rather an accumulation of evidence for the target memory, and this evidence accumulates quicker in a correctly remembered trial, then we might expect fast velocities in the neural trajectories representing a rapid accumulation of memory-specific information in remembered trials. Additionally, the search for the correct memory representation may require the neural activity to probe multiple memory traces before finding the correct one. Here, faster movements through neural subspaces may reflect a greater chance at triggering the correct memory trace and reinstating the memory. This way,

rapid changes in the velocity profiles of neural trajectories in the MTL likely relate to memory processing and behaviour.

In the present study, we take advantage of a rich human data set including single-unit, multi-unit, and iEEG recordings in the human MTL to investigate recollection in motion. Specifically, we ask how the peak velocities of low-dimensional population trajectories in the hippocampus and entorhinal cortex relate to the dynamic unfolding of memory retrieval. To achieve this, we test the relationship of trajectory velocities with memory retrieval by asking whether there are differences in peak neural trajectory velocities during remembered and forgotten memory retrieval in a cued memory paradigm. We then test the relationship between the magnitude of peak and representational reinstatement and link high velocity events with hippocampal ripples in time.

Our results show that peak velocities of low-dimensional population trajectories are linked to participants successfully recalling paired items and greater representational reinstatement. Additionally, peak velocities in population trajectories co-occur with hippocampal ripples. Together, this suggests the dynamic characteristics of neural trajectories in the human hippocampus and entorhinal cortex are linked to memory processing.

Methods

The data set and paradigm in the present study have been previously reported and partially overlaps with the data explored in Chapter 3. Therefore, some of the methodological details here are paraphrased with permission from Staresina et al. (2019) and are repeated from Chapter 3 for consistency.

Participants

16 epilepsy patients (nine female; age, M = 36.08 years, SD = 10.01) participated in the study. The patients were implanted with depth electrodes for clinical monitoring and localisation of seizure onset zones. The study had no influence on the localisation nor the timing of the implantation. Participants provided informed written consent from each participant, and the study was conducted according to the ethical guidelines of the University of Bonn's Medical Institutional Review Board.

Task

The task sessions consisted of an associative and a non-associative memory task, presented in an intermixed block design. In the present study, we only analysed the associative memory task (**Figure 1A**). In each block of the associative memory task, participants were presented with an image of a scene overlaid with an image of an item. The scenes were trial-unique while the item was one of two items. The two items remained unchanged throughout the session. A 500-msec fixation cross preceded all trials, and a blank screen appeared after each trial to add between 100 and 400 msec of inter-trial jitter. During encoding trials, the scene-item pairs were presented for three seconds, after which participants were asked to use the arrow keys to provide a self-paced plausibility judgment of an imagined scenario that combined the scene and the item. Each block contained 10 encoding trials, followed by a 30-second delay where participants fixated on a fixation cross. Following the delay, participants performed 10 retrieval trials. During retrieval trials, the scenes were shown without the paired item for three seconds. After three seconds, participants used the arrow keys to indicate which item was paired with the scene or gave a "do not know" response. Responses were

self-paced. Feedback was given after retrieval trials either by colouring the chosen arrow green (if correct) for 500 msec or colouring the correct arrow red (if incorrect or unknown). Each session consisted of eight blocks, totalling 80 encoding and 80 retrieval trials. Each participant completed one session.

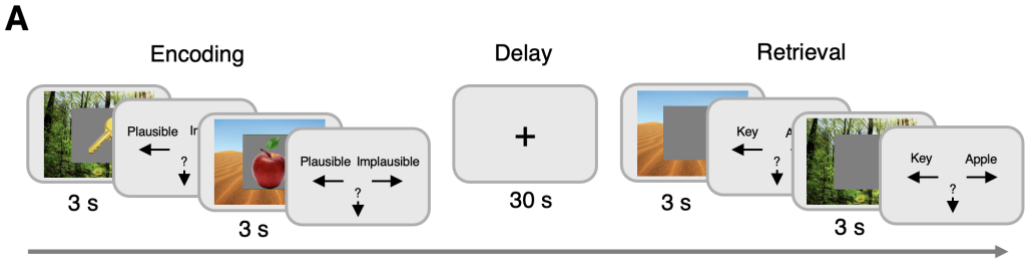

Figure 1. Associative Memory Task. A) Schematic of a block in the associative memory task. During the encoding phase, item-scene pairs were presented for three seconds. Participants then gave a plausibility response using the left, right, or down arrow key. Each block contained 10 item-scene pairs. Following a 30-second delay with a fixation cross, participants were presented with the scene for three seconds before they could use the arrow keys to indicate which item was paired with the scene during encoding.

Electrophysiological recordings

Microwire bundles with eight recording electrodes and one reference electrode (AdTech, Racine, WI, USA) extended approximately 4 mm from the end of the depth electrodes. A 256-channel Neuralynx Atlas system (Bozeman, MT, USA) amplified the signal that was sampled at 32 kHz with a 0.1-9000 Hz filter. Spike detection and sorting required a 300-3000 Hz bandpass filter, and units were manually categorised as single-units, multi-units, or artefacts using features including refractory periods, spike shape, and inter-spike intervals.

Macro-electrode and microwire locations were linked to the hippocampus or the entorhinal cortex using post-implantation CT scans co-registered with pre-implantation MRI scans.

Nine of the 16 participants had hippocampal iEEG macro contacts (33 total contacts; Mean contacts per participant = 3.67, SD = 1.87). Only hippocampal iEEG contacts were used for ripple analyses, while hippocampal and entorhinal units were included together in unit-level analyses. The iEEG signal was down sampled to 1000 Hz. We did not include contacts in the pathological hemisphere in the case that the epileptic activity was clinically localised in a hemisphere.

Pre-processing and ripple detection

The iEEG signals from the most medial macro contacts on the depth electrodes were re-referenced with the closest white matter contact. A notch filter removed line noise between 49-51 Hz (and harmonics at 99-101, 149-151, and 199-201 Hz).

Ripples were detected offline on artefact-free iEEG data using custom algorithms (Ngo et al., 2020). To detect amplitude artefacts in the iEEG data, the signal was first bandpass filtered between 0.3 and 150 Hz, and artefactual events were detected where the signal exceeded the median ± 4 IQR. Gradient artefacts were defined as timepoints where the first derivative of the iEEG signal exceeded the median ± 4 IQR of the first-derivative values. Amplitude-and-gradient events were events where both amplitude and gradient exceeded the median ± 4 IQR. To detect high-frequency burst artefacts which could be mistaken for ripples, a 150 Hz high-pass filter was applied to the signal. Windows with an envelope exceeding median ± 4 IQR for at least 100 msec were detected as high-frequency burst events. Finally, we applied interictal discharge detection Ung et al. (2017) to classify interictal spikes

as artefacts. All artefacts were padded with ±300 msec, and this data was excluded from ripple event detection, but not TFR analyses.

To detect ripples, the iEEG signal was bandpass filtered between 80 and 120 Hz. The root-mean-square envelope was smoothed with a 20 msec moving mean, and ripple events were characterised as having an envelope which was at least one SD above the mean, while lasting between 38-300 msec and having between three and nine cycles. For each participant, ripple detection was conducted across the entire session.

Analysis

We retained single and multi-units from hippocampus and entorhinal cortex with an average firing rate over 0.05 Hz across the session, resulting in a total of 225 hippocampal and 159 entorhinal units (Hippocampus: mean per participant = 14.06, SD = 9.28; Entorhinal cortex: mean per participant = 9.94, SD = 6.73). All units (single-unit, multi-unit, hippocampal, and entorhinal) were pooled for the remaining analyses. Spiking rates with a sample rate of 1000 Hz were smoothed using a 50-msec Gaussian kernel to create continuous signals (except for the exemplar trial in **Figure 2A,** which is shown using a 500-msec Gaussian smoothing kernel for visualisation). 50 msec was chosen as it was previously used by Staresina et al. (2019).

The analysis focused on the time window between 0- and 3-seconds post-stimulus onset, during the time of encoding or retrieval, but before response. Our goal was to study the dynamics in the latent trajectories of population activity. To uncover the latent trajectories of the population activity (Cunningham & Yu, 2014; Williamson et al., 2019), spiking activity during encoding and retrieval trials was concatenated into a unit-by-time matrix and z-scored

over time to give equal weighting to units with different baseline firing rates. The matrix was reduced to the top four principal components (PCs), using principal component analysis (PCA). Four PCs were chosen because they were the lowest dimensionality that still resulted in a significant cluster in the encoding-retrieval cross-decoding analysis (**Figure 3A**), indicating that item-specific representations were retained with the top four components across participants. Incorrect and "do not know" responses were pooled as "forgotten" in all analyses.

The velocities were derived from each trial's population trajectory X(t) such that:

$$v(t) = dX/dt = X(t+1) - X(t)$$

The magnitude of the velocity at each timepoint in each trial was given by:

$$||v(t)|| = \sqrt{(\sum_{i=1}^{d} v_i^2(t))}$$

where d = number of PCs.

Note that the main results, comparing the magnitude of peak trajectory velocities in remembered and forgotten trials (**Figure 2C**), were robust to the number of dimensions chosen (See **Results**). To ensure sufficient trials could be used for comparison between remembered and forgotten retrieval trials, four participants were excluded from the comparison of the peak velocities and the encoding-retrieval cross-decoding in remembered and forgotten trials, as they had fewer than 10 forgotten trials (similar to previous analyses Staresina et al. (2019)). Since there are more remembered trials, if we performed PCA on all trials, the PCA components would be biased towards representing patterns in variance in remembered trials. To account for this and not bias the PCA analysis toward remembered trials, the peak velocities used to compare between remembered and forgotten conditions (**Figure 2C**) are taken from a PCA reduction containing an equal amount of remembered

and forgotten trials, via random subsampling. In contrast, all other analyses examining peak velocities in only remembered trials use peak velocities taken from a PCA reduction containing all trials since remembered and forgotten conditions are not being directly compared.

Encoding-retrieval cross-decoding analyses (**Figure 3**) were conducted on spiking rates with a 500-msec average-window smoothing kernel. The data for all encoding and retrieval trials (0-3 s) were then concatenated into a unit x time matrix, before being z-scored across time. PCA then reduced the data dimensionality along the unit-axis to the top four PCs. The matrix was split back into trials (PC x trial x time). To maximise differences across trials, we then z-scored the data across trials. For each time-by-time combination, a linear discriminant analysis (LDA) classifier was trained on all encoding trials (40 trials for each item-class) and tested on only remembered retrieval trials, using the "mv_classify_timextime" function in MVPA-light (Treder, 2020).

All cluster-based permutation tests were performed with 1000 permutations, and an alpha threshold of 0.05 was used to determine whether the results were statistically significant. The peak decoding probability of each trial for the correlation in **Figure 3B** was the peak decoding probability during retrieval after averaging the time-by-time probabilities over the encoding time-axis.

For TFR analyses (**Figure 4C**), time windows were extracted ± 2 seconds around the peak velocities in each trial with an additional 500 msec buffer to account for edge artefacts. We used Fieldtrip's "mtmconvol" function with a Hanning taper and a frequency range from 0-250 Hz in 1 Hz steps, a time resolution of 10 msec steps, a minimum window length of 100 msec, and a minimum of five cycles per frequency. To maintain temporal resolution, the number of cycles is scaled with the frequency. The statistical analyses for the TFR results

were exploratory and not cluster corrected. After averaging across trials, the spectral power for each frequency band was z-scored across the ± 2-second window for each iEEG contact, before averaging over contacts for each participant. All analyses were conducted in MATLAB 2024b (The Mathworks Inc., MA, USA) with functions from Fieldtrip version 20241219 (Oostenveld et al., 2011).

Results

Memory behaviour

Memory performance was significantly above chance (50%) with a mean accuracy of 79.06% (SD = 10.59%; one-sample t-test against 50% chance: $t(15) = 10.98$, $p < .001$, $d = 2.74$, two-tailed).

Peak velocities in neural trajectories are greater during successful memory retrieval

As neural firing patterns dynamically unfold, the latent population trajectories twist and turn through the subspace. This is shown in **Figure 2A**, which depicts an example neural trajectory in a retrieval trial. However, the velocity with which the trajectory moves through the latent space is not constant, rather it speeds up and slows down as the trajectory evolves. If a small number of timepoints exhibit exceptionally high velocities, these high velocity moments may reflect events of interest for memory retrieval including rapid state transitions.

To determine if a small number of timepoints exhibited exceptionally high velocities, we compared the mean magnitudes of the top 100 velocities in each trial, from a total of 3000

timepoints (0-3 s at 1000 Hz) to those of the next largest 100 velocities. After averaging over trials for each subject, we compared the mean magnitudes with a two-tailed paired sample t-test. The results show the averages of the top 100 trial velocities, are significantly greater than those of the next top 100 velocity timepoints (Top100: M = 2.44, SD = 1.36; Next100: M = 1.45, SD = 0.58; $t(15) = 4.08$, $p = .001$, $d = 1.02$). We also tested whether the distribution of the velocities was positively skewed with a one sample t-test. The results indicate velocity values are significantly positively skewed (M = 12.39, SD = 20.22, $t(15) = 2.45$, $p = 0.027$, $d = 0.61$, one sample t-test, two-tailed; see **Supplementary Figure 11**). Together, this demonstrates a small number timepoints have exceptionally high trajectory velocities. Accordingly, the remaining analyses target the peak velocities (maximum value per trial) to isolate these moments of rapid neural trajectory movement. **Figure 2B** shows a kernel density estimation (KDE) with a 50-msec kernel visualising the distribution of these peak velocity moments in remembered trials.

We then tested whether remembered retrieval trials had greater peak velocities when compared to forgotten trials. **Figure 2C** shows peak velocities in remembered trials are greater than those in forgotten trials (two-tailed paired-samples t-test: $t(11) = 3.52$, $p = 0.005$, $d = 1.01$, Remembered: M = 0.81, SD = 0.10, Forgotten: M = 0.74, SD = 0.11).

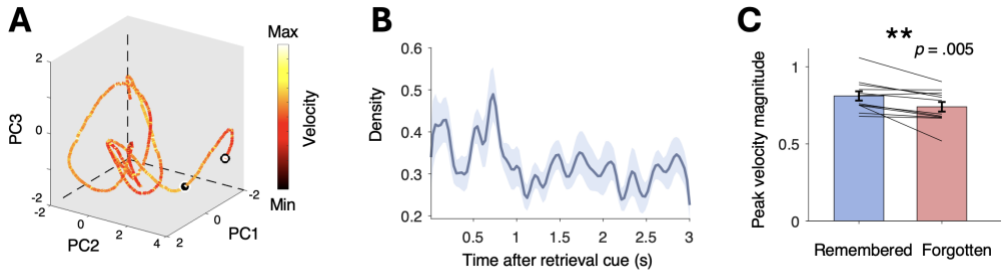

Figure 2. Peak velocities in neural trajectories. A) Exemplar of a neural trajectory during a retrieval trial, projected onto a three-PC subspace. Colour represents the velocity of the trajectory at a given time. The white marker is the cue onset, while the black marker shows the time of peak velocity. **B)** KDE plot of peak velocity timings in remembered trials. KDE used a 50-msec kernel. Shading is SEM. Line is group-level mean (N=16). For a plot of the KDE of velocities from trajectories that include the pre-cue fixation period, see **Supplementary Figure 12**. **C)** Paired-samples t-test across participants shows the magnitude of the peak velocity is greater in remembered compared to forgotten trials. Lines show individual participants. Bars represent group-level means (N = 12). Error bars indicate SEM. Double asterisk (**) shows significance ($p < .01$).

Next, we performed control analyses to determine if the differences in peak velocity reflect overall differences in trajectory magnitude and unit activity amplitude between remembered and forgotten trials. First, we ran the same analysis as depicted in **Figure 2C**, while scaling the trajectories so the mean trajectory magnitude was equal between remembered and forgotten trials in each participant. A paired sample t-test showed a significantly greater peak velocity magnitude in remembered trials, even when scaling the trajectories to match between conditions (Remembered: M = 0.82, SD = 0.11, Forgotten: M = 0.74, SD = 0.12, $t(11) = 2.46$, $p = 0.032$, $d = 0.71$, two-tailed). We then compared maximum firing rates in remembered and forgotten retrieval trials. Similar to the velocity analysis, firing rates were normalised using a z-score of task activity across remembered and forgotten trials. The unit activity was then averaged across units, and the maximum activity was found for each trial.

We then averaged the peak activity across trials for each participant. A two-tailed paired sample t-test revealed no significant difference ($p > .05$) between the maximum unit activity in remembered and forgotten trials (Remembered: M = 1.42, SD = 0.63, Forgotten: M = 1.43, SD = 0.73, $t(11) = -0.16$, $p = 0.873$, $d = -0.05$). Next, we compared the average z-scored firing rate at the time of the peak velocity in remembered and forgotten trials. The unit activity around peak trajectory velocity times in remembered and forgotten trials is visualised in **Supplementary Figure 13**. There was no significant difference ($p > .05$) in the average z-scored unit activity at the peak trajectory velocity times in remembered and forgotten trials (Unit activity at max velocity: Remembered M = 0.61, Forgotten M = 0.64, SD = 0.35, $t(11) = -0.53$, p = 0.607, $d = -0.15$, two-tailed paired sample t-test). Taken together, we did not find evidence of a memory effect on the maximum unit activity in trials nor unit activity at peak trajectory velocity times.

To test whether this result was sensitive to hyperparameters, we compared the peak velocity magnitudes in remembered vs forgotten trials when using five PCA dimensions (instead of four). We also tested whether the effect was similar using a 100-msec Gaussian smoothing on the data (rather than 50-msec). Finally, we tested the effect of remembered vs forgotten retrieval using the mean of the top 100 velocities in each trial, rather than using the single maximum value, to account for the potential sensitivity of using one peak velocity. All these variations showed a similar effect when conducting paired-sample t-tests with greater velocity magnitudes in remembered trials: Five PCs: Remembered: M = 0.90, SD = 0.18, Forgotten: M = 0.81, SD = 0.13 , $t(11) = 2.32$, $p = 0.041$, $d = 0.67$; 100 msec Gaussian smoothing: Remembered: M = 0.43, SD = 0.08, Forgotten: M = 0.40, SD = 0.07, $t(11) = 2.10$, $p = 0.060$, $d = 0.61$, Mean of top 100 velocities: Remembered: M = 0.48, SD = 0.06, Forgotten: M = 0.46, SD = 0.07, $t(11) = 2.25$, $p = 0.046$, $d = 0.65$; all t-tests were two-tailed).

Peak velocities in remembered trials predict peak reinstatement

Are item-specific latent population activity patterns during encoding reinstated during remembered retrieval? To test for reinstatement at retrieval, we trained LDA classifiers to predict the item identity (of the two items used) using population activity in encoding trials (40 trials for each item) for each time point. **Figure 3A** shows significant encoding-retrieval reinstatement across participants ($p < .05$, two-tailed cluster-based permutation testing). For this analysis, firing activity was smoothed with a 500-msec moving mean kernel, before being reduced to the top four PCs (see **Methods**). We then tested the classifiers for each encoding time point on the activity patterns during successfully remembered retrieval trials at each time point, resulting in a time-by-time matrix of area-under-the-curve (AUC) values. This encoding-retrieval decoding analysis was performed for each participant before comparing with the chance level (AUC = 0.5).

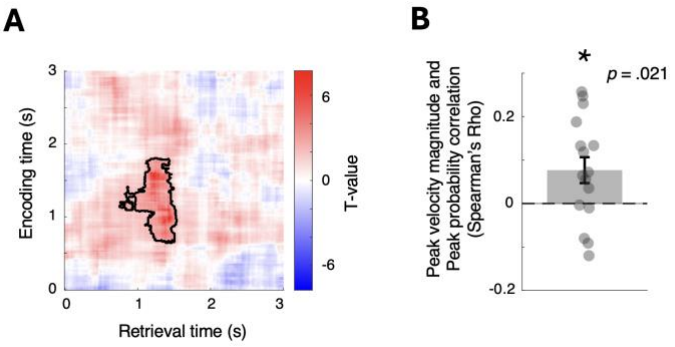

Figure 3. Encoding-retrieval representational reinstatement is linked to the magnitude of peak velocities. A) Reinstatement of item-specific encoding representation around retrieval time, in remembered trials. T-values compare the LDA classification AUC against 0.5. Black contours represent significant clusters, $p < .05$, two-tailed cluster-based permutation testing. **C**) Group-level comparison of Spearman correlations between peak velocity magnitude and peak probability during successful retrieval against zero. Correlation values were calculated across all remembered retrieval trials. Points show individual participants. Bar represents group mean (N = 16). Error bar is SEM. Asterisk (*) shows significance ($p < .05$).

Are peak velocities greater when memory traces are more stable? To test this, we asked whether the magnitude of peak velocities predicted reinstatement in remembered trails. LDA classifiers trained on encoding trials were tested on individual remembered retrieval trials, resulting in a time-by-time matrix of probability values for the correct paired item. The probability values were then averaged across encoding time (0-3 s) to give a value of the reinstatement across retrieval time for each trial. We correlated the peak values in reinstatement during retrieval with the peak population activity velocities across remembered trials for each participant. **Figure 3B** shows that Spearman's Rho between peak reinstatement and peak velocity magnitude was significantly positive across participants (one-sample t-test: M = 0.08, SD = 0.12, $t(15) = 2.57$, $p = 0.021$, $d = 0.64$, two-tailed).

Together, these results suggest activity patterns in the hippocampal and entorhinal population activity reinstate item-specific encoding representations during subsequent retrieval, and this reinstatement is greater during successful retrieval. Furthermore, the magnitude of the peak reinstatement during remembered retrieval trials is greater when the peak velocities of the population vectors are greater.

Peak velocities co-occur with ripple events

To investigate whether peak neural trajectories had a temporal relationship with ripples, we first detected ripples in hippocampal contacts (**Figure 4A**). Note only hippocampal iEEG contacts were used for detected ripples, while hippocampal and entorhinal units were included in unit analyses. Across the nine participants with hippocampal macro iEEG contacts, there were an average of 7627.11 ripples detected per participant (SD = 4328.85). The ripple events were converted to a ripple rate across the session, which we normalised

using the z-score. **Figure 4B** shows the normalised ripple rate time locked to the peak velocities during retrieval trials (remembered and forgotten trials; 250 msec moving mean smoothing kernel). Ripple rates were averaged across contacts within a participant before performing statistical analysis across participants. There was a significant increase in the normalised ripple rate around the timing of peak trajectory velocity ($p < .05$, two-tailed cluster-based permutation testing).

To determine whether this effect was spurious and test if it was local to the human ripple band (80-120 Hz), we ran an exploratory TFR analysis. First, the spectral power was extracted in the time-locked TFR for each contact. To control for general increases in ripple activity across retrieval trials, we subtracted the mean TFR time locked to shuffled max velocity times (randomly shuffled across trials) from the original TFR signal. Spectral power was then smoothed with a 250-msec moving mean kernel and z-scored for each frequency band (see **Methods**). After averaging the real TFRs across contacts for each participant, we found a significant positive uncorrected cluster in the ripple frequency range around the time of peak velocity in the real condition, compared to the shuffled condition (**Figure 4C**, $p < .05$, two-tailed permutation testing).

Together, these results suggest that the timepoints of peak velocity in population trajectories co-occur with hippocampal ripple activity during cued memory retrieval.

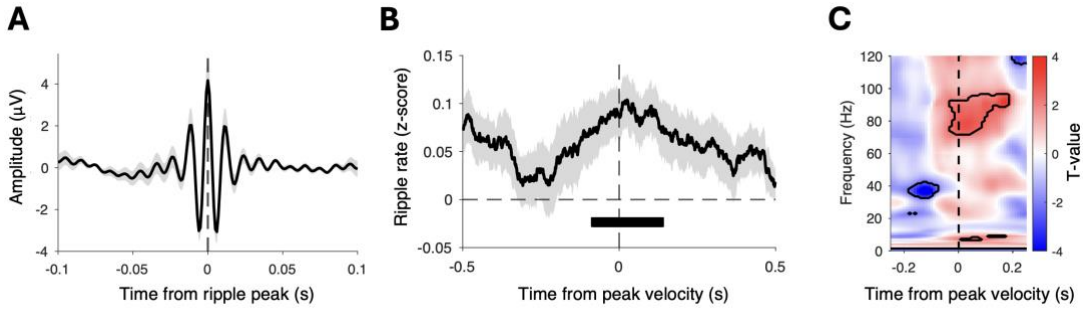

Figure 4. Peak velocities are linked to the timing of ripple activity. A) Mean iEEG signal centred at the peak of the ripple events. Averaged across channels within each participant, before averaging across participants (N = 16). iEEG was baseline corrected by subtracting from -100 to -50 milliseconds before the ripple peak. Shading represents SEM. **B)** Mean z-scored ripple rate around times of peak velocity in all retrieval trials (N = 16). Black bar represents $p < .05$ cluster-based permutation testing (two-tailed). Ripple rates were first z-scored for each channel, then plotted around the peak velocity time point, and then averaged within subjects. Shading represents SEM. **C)** T-values of spectral power around peak velocity times in trials, compared to shuffled peak velocity times (among trials) across subjects (N = 16). Black borders represent significant clusters uncorrected ($p < .05$, uncorrected permutation testing, two-tailed).

Discussion

We set out to test whether the velocities of population trajectories are linked to memory retrieval. Our results reveal that the peak velocities of low-dimensional population trajectories in the hippocampus and entorhinal cortex are related to successful memory retrieval. Specifically, the peak velocities in trajectories during successful cued memory retrieval were faster compared to unsuccessful retrieval (**Figure 2C**). Furthermore, the magnitude of the peak velocities in remembered retrieval trials positively correlated with the degree of representational reinstatement on the single-trial level (**Figure 3B**) while the timings of peak velocities cooccurred with hippocampal ripples (**Figure 4**). Together, this

suggests the dynamic nature of population trajectories is linked to memory processing, offering a new perspective on studying static neural activity codes.

Our first result shows that peak trajectory velocities are faster during remembered retrieval (**Figure 2C**). This demonstrates that the dynamic properties of the latent trajectory differ with memory behaviour. It is important to note that, since the latent trajectory is a low-dimensional representation of the unit activity, properties of the unit activity, such as amplitude, will influence the trajectory dynamics. We did not find evidence that remembered and forgotten trials differed in unit activity amplitude during retrieval or around peak velocity times, suggesting the difference in peak trajectory velocities reflects temporal dynamics rather than simple differences in unit activity. However, future efforts should directly explore the relationship between cognitive correlates of unit-activity, such as amplitude or coherence and dynamics in latent trajectories, as well as the direct relationship between unit activity and trajectories during different cognitive processes. For example, studies could use experimental stimulation methods to alter trajectory properties whilst keeping average unit activity stable, or vice versa, and measure the relative impact on memory function.

Although speculative, trajectory velocities may be linked to successful pattern completion. If the cue results in pattern completion during successful retrieval, this may unleash a highly dynamic cascade of activity, resulting in sharp transitions of the trajectory. Additionally, if the population trajectory's movements reflect the active searching process for the target memory, a faster-moving trajectory might be able to search more memory information and have a higher chance of reactivating paired representations containing information of the paired associate. This way, the role of greater peak trajectory velocities in successful retrieval may be two-fold: fast movements in the trajectories may be caused by enhanced pattern completion during successful retrieval, whilst themselves facilitating memory performance

through enhancing the bandwidth of memory search. Future efforts could utilise computational models of pattern completion, such as Hopfield Networks (Hopfield, 1982; Krotov & Hopfield, 2016), to directly investigate how successful pattern completion is reflected in the velocities of neural trajectories.

Secondly, we found trials with faster peak velocities showed increased encoding-retrieval cross-decoding (**Figure 3B**). Trials with higher encoding-retrieval similarity may have connections between neural ensembles involved in item-specific representations which are stronger, primed, or more plentiful. Thus, these trials may result in a faster evolution of the neural population trajectory, as the target memory information is more readily available, or the pattern completion process is more efficient. We might expect the trajectory to have faster movements during the efficiently processed trials as the population activity rapidly transitions from processing the cue to reinstatement and response preparation. Additionally, highly transient states are times of high representational separability (Mazor & Laurent, 2005; Rabinovich et al., 2008), so information of the memory cue and retrieved item may be more easily interpretable by internal neural computations in trials with faster trajectories, resulting in richer reinstatement of encoding-like activity. Although trajectories with faster movements may reflect efficient memory processing, we should remain cautious when interpreting these findings since our understanding of the relationship between unit activity and trajectory dynamics remains limited.

Finally, we found that the timepoints of peak trajectory velocities coincided with hippocampal ripples (**Figure 4**). Hippocampal ripples are thought to play a key role in broadcasting information between the MTL and the cortex during memory consolidation and retrieval (Buzsáki, 2015; Vaz et al., 2019). Previous studies have shown that ripple activity increases during successful retrieval (Norman et al., 2019; Vaz et al., 2019) and have found

sequences of unit activity in the cortex replaying around ripples (Vaz et al., 2020). If trajectory velocity is related to pattern completion, then ripples may coincide with high velocity times to facilitate widespread cortical reinstatement. It is important to note that our measure of encoding-retrieval cross-decoding does not capture the complete picture of pattern completion, since retrieved information may have been transformed or might not resemble encoding activity as it serves the purpose of guiding a response.

Additionally, the macro-level population synchrony during ripples affects single- and multi-unit firing (Staresina et al., 2023; Tong et al., 2021). Thus, ripple activity likely perturbs the unit-level activity, pushing and pulling the population trajectories. These perturbations may be reflected in turn as fast transient shifts in the unit-level population trajectory. This way, ripples may encourage successful memory retrieval by "jolting" neural population activity, encouraging it to move more rapidly through latent spaces, increasing the likelihood of triggering task-relevant pattern completion.

As is the case with intracranial studies in humans, the resolution of the neuronal recordings and the relatively small number of memory trials were a limitation factor (Parvizi & Kastner, 2018). This prevented us from exploring the nature of the trajectories in greater detail. It would have been exciting to test whether the peak velocities occur when the trajectories are moving towards fixed attractor points representing the memory items. One could also explicitly test how dynamics in neural trajectories reflect memory search. For example, are the movements of trajectories along neural subspaces which represent certain memory information more rapid compared to movements in subspaces representing task-irrelevant information?

Additionally, greater trial and neuronal resolution would enable us to test the cognitive role of other geometric measures of trajectories, such as tortuosity and curvature. Recordings

from a larger subset of participants would also allow us to ask whether the velocities of population vectors may be less smooth in people with cognitive decline or neuropsychological disorders. Thus, together with the dynamic systems framework, future improvements in our ability to record and analyse larger neural data sets may help us better understand how the nature of neural dynamics plays a mechanistic role in human memory function in health and disease.

Here, we have shown how the velocities of trajectories in the hippocampus and entorhinal cortex are linked to memory retrieval, highlighting the perspective that studying neural population activity evolving through time gives rise to behaviour, which shows promise for investigating the neural computations of human memory function.

Chapter 5: General discussion

In this thesis, I explore the behaviour of neural oscillations and population trajectories related to memory function. I begin at the macro-scale, examining sleep spindles with scalp-EEG, where I tested if external experimental stimulation could bias spindle topography during subsequent sleep, and what effect this had on motor learning. Zooming in, I investigated how hippocampal ripple activity responded to associative memory task demands, using iEEG recordings. Finally, I focus on the dynamic behaviour of latent population activity during memory retrieval in unit-level recordings. In this section, I summarise my main findings and discuss their broader significance in relation to the literature and each other. I also address relevant limitations and highlight promising future directions.

Spindles track excited sites

The spatial topography of spindles has been linked to local cortical excitability during a memory task before sleep (Petzka et al., 2022). The level of overlap between excitability before sleep and after sleep predicted memory consolidation. This indicates localised cortical excitability before sleep might "tag" regions for later spindle expression. However, it remains unclear whether cortical excitability during wakefulness is sufficient to direct local spindle expression. In Chapter 2, I asked whether the local application of excitatory tDCS to local cortical sites before sleep influences the topography of sleep spindles. Moreover, I tested whether experimentally modulating local spindles in the lateral motor cortex impacted memory consolidation in a lateralised motor sequence learning task. The results show spindles flexibly track cortical sites stimulated with anodal-tDCS during prior wakefulness.

These results have several implications. First, it provides supporting evidence that spindle topographies are neither hard-wired nor random but are instead guided by regional cortical excitability. This complements existing findings that spindles track endogenously excited sites (Petzka et al., 2022). Notably, the results show that this excitability can be manipulated exogenously with non-invasive electrical stimulation methods. Together, this opens avenues for the future study of local sleep spindles in sleep. Linking cortical excitability induced by tDCS to spindle rates enables researchers to connect neuromechanical changes resulting from tDCS with the mechanisms that govern spindles. For example, functional connectivity between the thalamus and the primary motor cortex was found to increase after tDCS was applied using a similar montage to that used in Chapter 2 (Polanía et al., 2012). Therefore, the modulation in local spindle rates through tDCS may result from increased thalamo-cortical connectivity, linking functional connectivity with local spindle expression.

Spindles are thought to play a critical role in promoting synaptic plasticity changes in the cortex (Fernandez & Lüthi, 2020). So far, it has been challenging to study the effect of local spindles on plasticity in humans with experimental manipulation. My results suggest tDCS stimulation could be paired with other methods, including non-invasive imaging, to study the effects of local spindles on cortical plasticity experimentally. For example, MRI can be used to measure how memory and learning affect local changes in white matter, as well as tractography and local functional connectivity (Behrens et al., 2003; Cousins et al., 2016; Sampaio-Baptista & Johansen-Berg, 2017). For example, in a recent study, Brodt and colleagues used diffusion tensor imaging to show plasticity changes could be detected in the cortex one hour after learning (Brodt et al., 2018). If local spindles have immediate effects on the synaptic plasticity in brain circuits, one can measure these with similar MRI metrics. To this end, I collected an MRI data set including diffusion and resting state scans in the paradigm described in Chapter 2, before and after tDCS stimulation and sleep. Future work

on this data (in the lab) will investigate the effect of local spindle manipulations on diffusion and functional connectivity metrics to test whether experimentally manipulated localised spindle expression mediates an effect on regional metrics of cortical plasticity changes.

While spindles were locally modulated around the lateralised motor cortex with tDCS, the results showed no significant effects of spindle modulation on changes in learning behaviour in the left-handed visuo-motor finger-tapping task, which we believed to be somewhat functionally localised to the right motor cortex. Multiple factors could have caused the lack of a behavioural effect. The stimulation parameters, including amplitude and duration, as well as the change in spindle rate with stimulation, may not have been significant enough to have a measurable behavioural impact. Moreover, the task may not have benefited from spindle increases in motor areas. Instead of relying on memory tasks with localised cortical activity patterns, such as motor tasks, future studies could utilise declarative memory tasks that have already been linked to memory improvements after sleep (e.g., Petzka et al., 2022). By correlating the spatial topography with cortical excitation during the task, one could study the effects of local spindle manipulation via exogenous stimulation on memory consolidation.

Additionally, the precise distribution of electrical fields induced by tDCS in the brain is difficult to estimate. Models suggest tDCS stimulation patterns are somewhat heterogeneous and chaotic, with the most significant effects on excitability sometimes occurring between the anode/cathode sites (Neuling et al., 2012). Future work attempting to manipulate spindle topographies may benefit from using fine-grained methods, such as high-definition tDCS, in which a ring of cathodes surrounds an anode, creating a fine-grained focal excitatory effect (Müller et al., 2022).

Although I did not find an effect of tDCS on SO topographies, the ability to shift spindle topographies is valuable for future work studying the spatial-temporal nesting relationship

between SOs and spindles. SOs and spindles are coupled in time, with spindles preferentially occurring in the upstate of SOs (Staresina et al., 2015). Since SOs are travelling waves that propagate across the cortex (Massimini et al., 2004), the temporal alignment of spindle-SO coupling is influenced by a complex interaction between the SOs and spindles in time and space. This way, my results demonstrate that tDCS can be used to bias spindle topographies and investigate the impact spindle topographies have on SO-spindle coupling in local circuits.

Ripples reflect associative memory demands

Ripples have been linked to episodic memory retrieval and are thought to play a mechanistic role in enabling communication between the hippocampus and cortical sites to reactivate linked memory traces. However, no study has directly compared ripple activity between memory tasks with differing associative demands. In Chapter 3, my results support the findings in the literature, showing increased burst activity in the ripple band during retrieval in hippocampal but not entorhinal contacts. This suggests the phenomenon may be somewhat localised in the hippocampus. Moreover, the primary results demonstrate that hippocampal ripple activity is greater during memory retrieval in an associative memory task, suggesting ripples play a greater role in processing information during associative memory retrieval, supporting theories that hippocampal activity is linked to associative memory function (Davachi, 2006; Diana et al., 2007).

Note, to link the ripple activity directly to memory behaviour, the results would need to show ripple rates were affected by retrieval outcome (remembered or forgotten) or that ripple rates during delay periods predict performance in subsequent retrieval. The ability to test for a behavioural effect of ripple activity was limited due to behavioural ceiling effects (especially

in non-associative tasks) and the small sample size. Future studies using more difficult paradigms with more intermixed blocks of trials could investigate how ripple activity influences memory behaviour in associative and non-associative tasks, and how the memory effect of ripples may differ depending on the type of task.

The hippocampus links associated items, and ripple-linked reactivation during offline rest is important for reactivating and stabilising memory traces (Davachi, 2006; McClelland et al., 1995; Rasch & Born, 2013). Moreover, longer ripple durations during rest and sleep have been linked to memory consolidation in rodents and increased hippocampal-cortical interaction (Fernández-Ruiz et al., 2019; Ngo et al., 2020). Together, this suggests the quality as well as quantity of ripples may change according to the associative demands of the task. Notably, the results in Chapter 3 show ripple activity during offline delay periods was affected by the memory demands, with higher ripple rates and larger and longer ripple events in the associative memory task. This demonstrates how encoding and retaining links between memory items affect subsequent brain activity during rest.

The change in delay period ripple activity between tasks also suggests that ripple expression during rest is influenced by mechanisms operating on short-time scales, in the range of minutes or seconds. One candidate mechanism controlling the ripple rates is fluctuations in acetylcholine. High concentrations of the neurotransmitter reduce ripple activity in rodents (Zhang et al., 2021), while higher levels increase hippocampal-cortical interactions (Gais & Born, 2004). Therefore, the brain may reduce acetylcholine levels dynamically in response to increased associative encoding, thus preparing for more ripple activity in subsequent rest. To test whether acetylcholine mediates the effect on ripples, future work could measure how acetylcholine varies during memory encoding and delay periods in varying memory demands.

This would provide a better understanding of how the brain "tags" specific rest periods for increased ripple activity.

This carry-over effect from the memory task to the offline delay is not trivial since the associative and non-associative task blocks were intermixed. The difference in ripple rate and duration reflects greater reactivation and active memory consolidation processes. To test this, future studies could employ a design similar to that used by Kunz and colleagues (Kunz et al., 2024). In their study, neurons were categorised in the MTL according to whether they responded selectively to a place or an item. At the same time, epilepsy patients navigated and collected items in a video game. They found associated neurons coactivated around ripples during the encoding and retrieval of an item-place pair in the game. Moreover, the level of cofiring around ripples decreased with learning. A similar paradigm could also be used to study the level of reactivation during rest and see whether the increased ripple rate in associative offline periods mediates memory retention between encoding and retrieval.

Population dynamics reflect memory processes

The firing activity of neurons in populations covaries in structured ways. This means neural activity can be mapped onto latent population trajectories in low-dimensional subspaces (Cunningham & Yu, 2014; Ebitz & Hayden, 2021). These population trajectories twist and turn as they move around the neural subspace over time. If memory items are represented as specific points or planes in latent activity space, the dynamic behaviour of the population trajectory as it moves through space may be linked to memory behaviour. In Chapter 4, I investigated the dynamic properties of population trajectories in the hippocampal-entorhinal circuit during cued memory recall. Specifically, I tested how peak velocities of the population

vector related to memory behaviour. My results showed population trajectories had greater peak velocities when participants remembered the cued memory item. Additionally, the magnitude of the velocities correlated with the trial-level representational reinstatement. This offers a new perspective on studying population activity as a dynamic system and reveals how kinematic properties of the latent trajectory relate to memory behaviour and reactivation.

Although the velocities are purely descriptive, they may reflect the underlying cognitive process of memory search. My results show that item identity can be decoded during retrieval from latent trajectories in hippocampal-entorhinal circuitry. This implies the item identity is represented along at least one dimension (since I used an LDA classifier), but it may also be separated along multiple dimensions or along dynamic dimensions which shift (e.g., Panichello & Buschman, 2021; Rabinovich et al., 2008). The brain is believed to use this type of representational separation in low-dimensional subspaces to process information, for example, keeping competing memory items separated (Miller et al., 2024; Panichello & Buschman, 2021). Since greater velocities in remembered trials and trials with greater reinstatement reflect faster movements, twists, and turns in the population trajectory, this may increase the chances of a trajectory finding and shifting along the item-defining dimension that is relevant for memory recall. On the other hand, if the circuit is primed to reactivate the item activity, greater velocities may reflect a faster shift in the neural representation toward the recalled item. Future work could help elucidate the link between velocities and memory-related representational shifts by examining the directionality around peak velocities and testing whether they occur at moments when the trajectory is moving along the item-separating dimension, toward the target representation.

Population trajectories enable us to measure a latent activity code that contains information about temporal coherence, structure, and relationships between the firing patterns of

individual units within the population. Therefore, they represent a transformed low-dimensional version of activity. However, it is notable to account for the fact that the activity of population trajectories reflects latent information from the underlying unit activity. Therefore, properties of unit activity directly influence population trajectories. To account for this, I found no evidence of unit-level activity accounting for the memory effect on peak velocities. Future work should investigate how the dynamics of latent trajectories are differentially shaped by properties of unit activity, including coherence and amplitude. This will help understand how unit activity gives rise to latent dynamics and would enable research into the relative contributions of unit activity and dynamics in memory processing.

In addition to linking population trajectory dynamics to unit firing, it is also valuable to link them to activity in macro iEEG contacts near the populations of interest. This relationship is remarkably underexplored. A recent study explored the link between macro iEEG and latent population trajectories in the primary cortex of monkeys (Gallego-Carracedo et al., 2022). They found that iEEG contacts were correlated with latent population activity in gamma frequencies (>50 Hz). This suggests ripples (80-120 Hz) may be linked to latent population dynamics. In Chapter 4, I tested this and showed hippocampal ripples co-occur around peak velocity times. The result indicates there is a link between iEEG ripple activity and latent population velocities. If we imagine the neural trajectory navigating a subspace, the local high-frequency activity related to ripples may "jolt" the population trajectories rapidly, resulting in rapid movements that facilitate the reactivation of the relevant memory trace. Since iEEG signals and population trajectories both reflect underlying unit-activity (Gallego et al., 2017; Pesaran et al., 2018), it is valuable for future work to map the relationships between iEEG, latent trajectory, and unit-level activity patterns. This can be expanded to include all the neural dynamics covered in my thesis, at multiple scales.

Emergent properties at multiple scales

Population trajectories, ripples, and spindles are all reflections of dynamic patterns in electrical fields at different spatial and temporal scales. Miller and colleagues describe how the processes of cognition and behaviour cannot be fully understood by examining the reduction of individual neural signatures in isolation (Miller et al., 2024). Instead, brain functions like memory and sleep can only be understood as emergent properties of brain activities many parts. For example, if we studied the neural firing rates of single neurons in isolation, we would not see how low-dimensional population codes can be used to retain memory information (Murray et al., 2017). Similarly, we would not see how local synchrony of many neurons creates the emergent signal of neural oscillations, which support inter- and intra-regional communication between populations (Fries, 2005).

Considering my results and this emerging property perspective, one might imagine how cortical excitability biases local spindle topography, which in turn influences local spindle-ripple coupling and affects the behaviour of latent trajectories in the hippocampus. Moreover, when remembering an associative memory in wakefulness, the hippocampus could require more ripple activity to manipulate latent trajectories during pattern completion in the hippocampus, which in turn reactivates local activity patterns in the cortex that were strengthened by local spindles the night before. Note that this is not to imply a causal relationship between the influential role of any phenomenon and another, but rather to demonstrate how emergent properties of neural dynamics at different scales can work together to support memory function in wake and sleep. To this end, the results of my thesis shed light on various emerging properties, furthering our understanding of brain activity during sleep and memory.

Final conclusions

Neural activity is highly structured in space and time. Studying the dynamic patterns in neural activity provides an opportunity to gain a deeper understanding of how the brain supports memory and sleep. Cortical and hippocampal neural oscillations in memory and sleep facilitate cortico-cortical and hippocampal-cortical communication, while latent population trajectories reflect cognitive processing in action.

In this thesis, I set out to investigate the relationship between these emergent neural dynamics in sleep and memory at three levels. Starting at the macro-scale, with scalp-EEG, I showed that exogenous excitation of cortical sites influences the spatial distribution of sleep spindles. This demonstrates that spindle topography is neither fixed nor random and is influenced by cortical excitability. Next, I zoomed in and explored hippocampal ripple activity with iEEG recordings. Ripple activity tracked associative memory demands, indicating ripple activity serves a role in linking associated items during episodic retrieval. Finally, I used unit-level recordings to demonstrate that the velocities of latent population trajectories differ during remembered and forgotten recollection and relate to reinstatement and ripple activity. This shows how the dynamic properties of latent trajectories may offer a new perspective for studying unit activity in memory processing and its relationship to iEEG signals.

As well as contributing to our theoretical understanding of neural dynamics at multiple scales, this work contributes by establishing a new method for experimentally manipulating local sleep spindles, which enables new lines of scientific research exploring the physiological basis and cognitive importance of spindle topographies.

Together, this thesis expands our understanding of the physiological and cognitive factors that affect local spindles, hippocampal ripples, and population trajectory dynamics, supporting memory function and sleep.

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Supplementary material

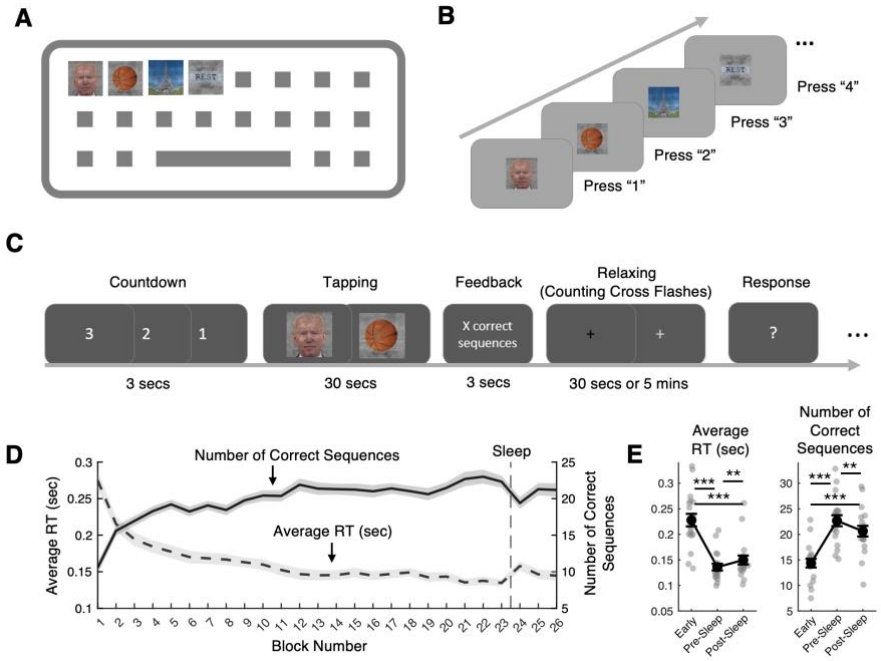
Session	Metric	Mean	SD	Min	Max
Both	Time N1 (mins)	12.41	8.70	2.50	44.00
	Time N2 (mins)	41.62	12.95	18.00	63.50
	Time N3 (mins)	19.07	12.32	0.00	45.50
	Time N2/3 (mins)	60.68	16.69	23.00	91.50
	Time REM (mins)	5.64	8.16	0.00	29.00
	Total Sleep Time (mins)	78.74	12.13	49.50	100.00
	Proportion N1	0.17	0.13	0.03	0.66
	Proportion N2	0.53	0.14	0.26	0.78
	Proportion N3	0.24	0.15	0.00	0.55
	Proportion N2/3	0.76	0.15	0.34	0.97
	Proportion REM	0.07	0.10	0.00	0.35
1	Time N1 (mins)	12.42	7.83	3.50	37.00
	Time N2 (mins)	41.97	9.85	18.00	59.00
	Time N3 (mins)	19.89	12.42	0.00	45.50
	Time N2/3 (mins)	61.87	15.65	26.00	87.50
	Time REM (mins)	5.47	6.10	0.00	19.50
	Total Sleep Time (mins)	79.76	12.27	50.50	100.00
	Proportion N1	0.17	0.12	0.04	0.52
	Proportion N2	0.53	0.13	0.26	0.69
	Proportion N3	0.24	0.14	0.00	0.53
	Proportion N2/3	0.77	0.13	0.37	0.93
	Proportion REM	0.07	0.07	0.00	0.21
2	Time N1 (mins)	12.39	9.71	2.50	44.00

	Time N2 (mins)	41.26	15.74	20.00	63.50
	Time N3 (mins)	18.24	12.50	0.00	40.00
	Time N2/3 (mins)	59.50	18.01	23.00	91.50
	Time REM (mins)	5.82	9.98	0.00	29.00
	Total Sleep Time (mins)	77.71	12.24	49.50	99.00
	Proportion N1	0.17	0.15	0.03	0.66
	Proportion N2	0.52	0.15	0.28	0.78
	Proportion N3	0.24	0.16	0.00	0.55
	Proportion N2/3	0.76	0.16	0.34	0.97
	Proportion REM	0.07	0.12	0.00	0.35

Supplementary Table 1. Summary sleep statistics.

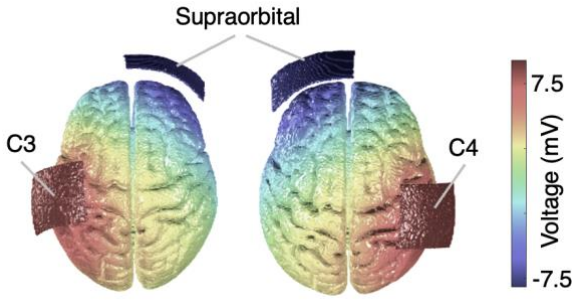
Metric	Session	Contact	Mean	SD	Min	Max
Spindle Rate	Both	C3	2.76	0.40	2.15	3.92
		C4	2.69	0.31	2.16	3.40
		Cz	3.16	0.53	1.96	4.24
		All	2.69	0.54	0.29	4.53
	1	C3	2.77	0.39	2.25	3.92
		C4	2.67	0.25	2.28	3.14
		Cz	3.19	0.56	1.96	4.05
		All	2.71	0.55	0.29	4.35
	2	C3	2.76	0.41	2.15	3.81
		C4	2.71	0.37	2.16	3.40
		Cz	3.13	0.51	2.17	4.24
		All	2.67	0.54	0.90	4.53
Number of Events	Both	C3	165.82	45.81	67	268
		C4	162.00	44.54	62	258
		Cz	191.61	61.35	58	350
		All	161.21	49.99	24	355
	1	C3	168.21	38.42	102	258
		C4	164.68	45.00	74	258
		Cz	195.37	58.10	95	350
		All	164.36	45.40	24	355
	2	C3	163.42	53.15	67	268
		C4	159.32	45.15	62	240
		Cz	187.84	65.81	58	328
		All	158.06	54.03	49	343

Supplementary Table 2. Summary spindle statistics for C3, C4, and Cz.

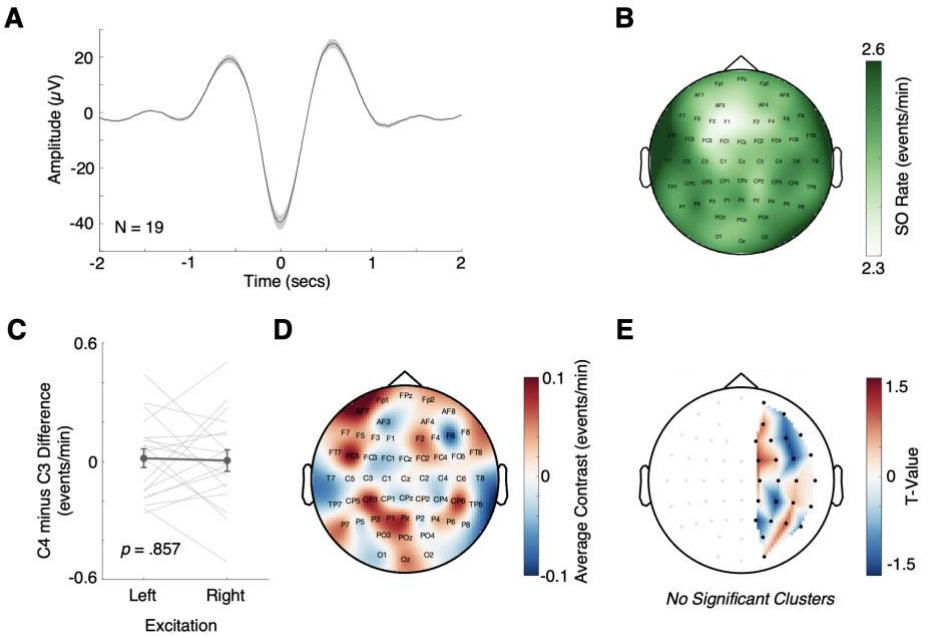


Supplementary Figure 1. Overview of visuomotor finger-tapping task. **A)** An image category was assigned to each of the four number keys in the top row of the keyboard. The participant received explicit instructions to use one finger per key. The assignment was always 1-Face, 2-Object, 3-Scene, 4-Word, although the images were unique to each session and were counterbalanced across subjects. **B)** Pressing the image category key would progress the task to the next image. **C)** Overview of a block. After a countdown, the participant tapped for 30 secs before receiving feedback on the number of correct four-part sequences they achieved. They then relaxed their hand and counted the number of times the fixation cross changed brightness for 30 secs (5 mins after block 10 and block 20) and finally responded how many flashes they counted with their right hand on a separate keyboard. There were 23 blocks in total during the learning task and three blocks after sleep. **D)** Learning over blocks. Mean number of correct sequences (solid line) and mean average RT (dashed line) over blocks. Sessions were treated as independent (N = 38). Shading indicates ±1 SEM. **E)** Comparison of mean values of average RT and number of correct sequences across early blocks (blocks 1-3), pre-sleep blocks (blocks 21-23), and post-sleep blocks (blocks 24-26). The values were averaged across sessions for each subject before comparing early, pre-sleep, and post-sleep performance. Paired-sample t-tests showed significant decreases in average RT and increases in number of correct sequences from early (average RT: M = 0.23, SD = 0.05; number of correct sequences: M = 14.37, SD = 3.70) to pre-sleep (average RT: M = 0.14, SD = 0.03; number of correct sequences: M = 22.67, SD = 4.68) blocks (average RT: $t(18) = 10.09$, $p < .001$, $d = 2.32$,

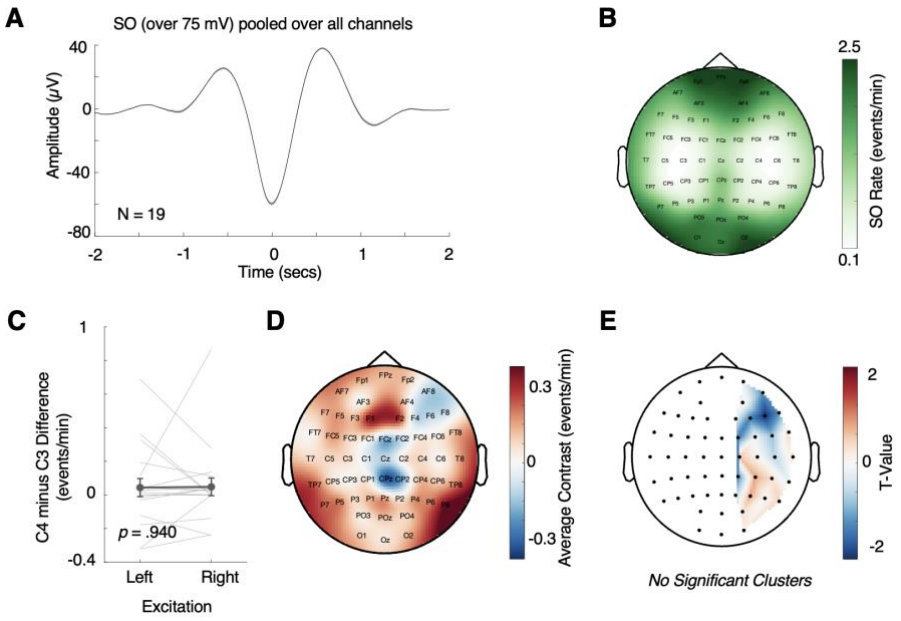
two-tailed; number of correct sequences: $t(18) = -9.72$, $p < .001$, $d = -2.23$, two-tailed). Performance became worse in post-sleep blocks (average RT: M = 0.15, SD = 0.04; number of correct sequences: M = 20.62, SD = 4.53), compared to pre-sleep blocks (average RT: $t(18) = -3.36$, $p = .004$, $d = -0.77$, two-tailed, paired-sample; number of correct sequences: $t(18) = 3.87$, $p = .001$, $d = 0.89$, two-tailed, paired-sample), while post-sleep performance remained significantly better than performance during early blocks (average RT: $t(18) = 9.87$, $p < .001$, $d = 2.27$, two-tailed, paired-sample; number of correct sequences: $t(18) = -9.20$, $p < .001$, $d = -2.11$, two-tailed, paired-sample).



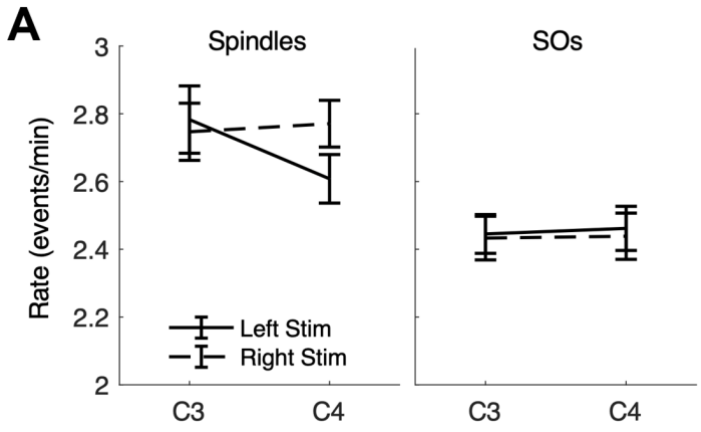
Supplementary Figure 2. Simulation of tDCS voltage effects. **A)** Simulation using ROAST (Huang et al., 2019) of the distribution of voltage caused by 1mA tDCS stimulation for 20 mins during left excitatory and right excitatory stimulation. The simulation was conducted using a template brain.



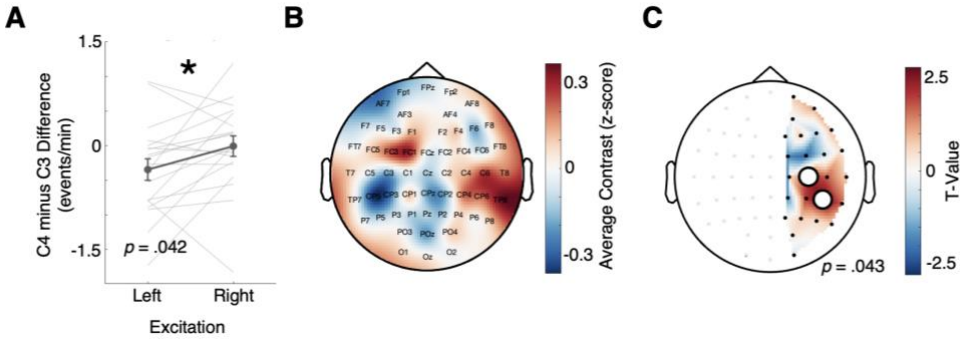
Supplementary Figure 3. No evidence of tDCS stimulation influencing the lateralisation of SO rates. A-E) Same as **Figure 2B-C** and **Figure 3A-C** with SO rates. Lines represent individual participants. Error bars represent ±1 SEM. T-test was paired-sample and two-sided. Cluster-based permutation tests were tested as $p < .05$ significance.



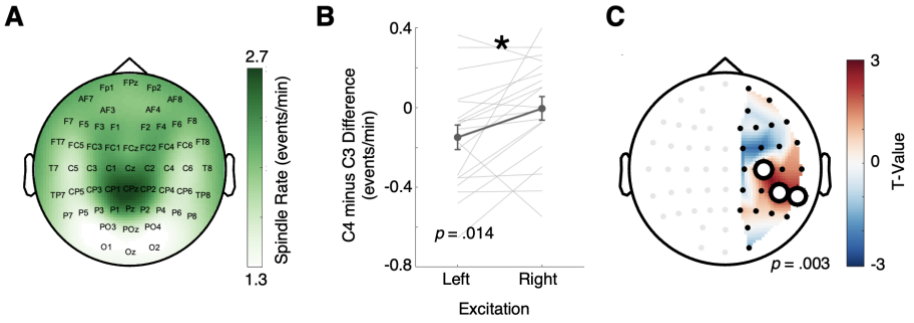
Supplementary Figure 4. No evidence of tDCS stimulation influencing the lateralisation of SO rates, using >75 μV threshold. A) Grand average SO pooled across all contacts. SOs were aligned to their largest trough and baseline corrected using the mean of the 2 sec window, before averaging across sessions (N = 2) and across participants (N = 19). Shading represents ±1 SEM. **B-E)** Same as **Figure 3B-E**. Lines represent individual participants. Error bars represent ±1 SEM. T-test was paired-sample and two-sided. Cluster-based permutation tests were tested as $p < .05$ significance.



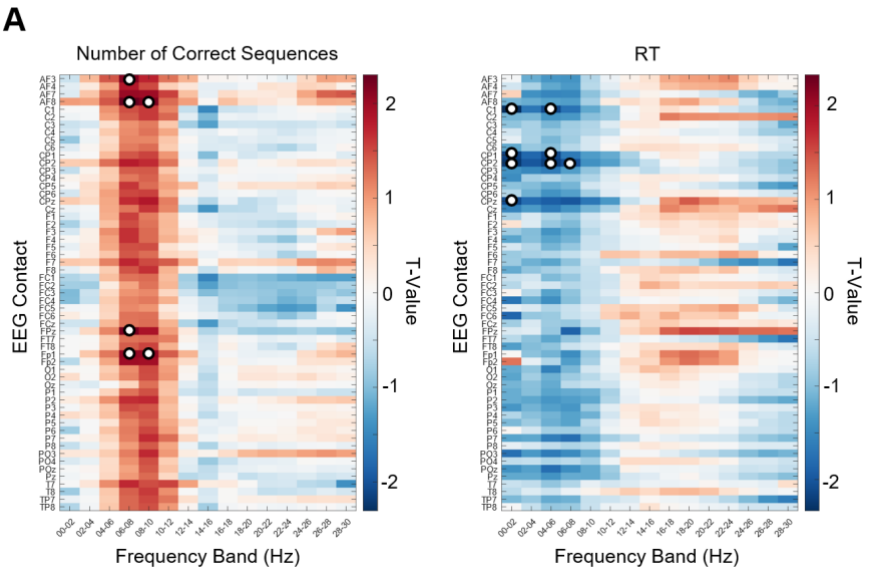
Supplementary Figure 5. 3-way ANOVA and interaction between event type, stimulation condition, and contact. A) The mean event rates across subjects, split by event type, contact, and stimulation condition. Error bars indicate ±1 SEM. The main effect of event type was significant, $F(1,18) = 12.13$, $p = .003$, $\eta_p^2 = .40$, with spindles having a greater rate than SOs (spindles, M = 2.73, SD = 0.36; SOs, M = 2.44, SD = 0.27). The 3-way interaction between event type, stimulation condition, and contact was significant ($F(1,18) = 5.59$, $p = .030$, $\eta_p^2 = .24$).



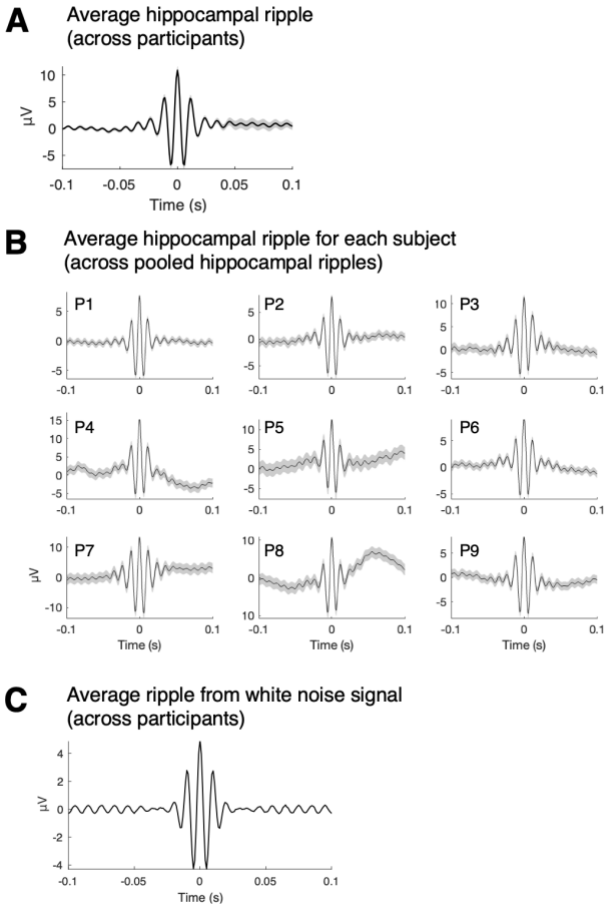
Supplementary Figure 6. Z-scored spindle rates were influenced by lateralised tDCS stimulation. A-C) Same as **Figure 3** with z-scored spindle rates (normalised within each session before subtracting and creating contrasts). Error bars represent ±1 SEM. Lines represent individual participants. White circles highlight significant clusters, $p < .05$.



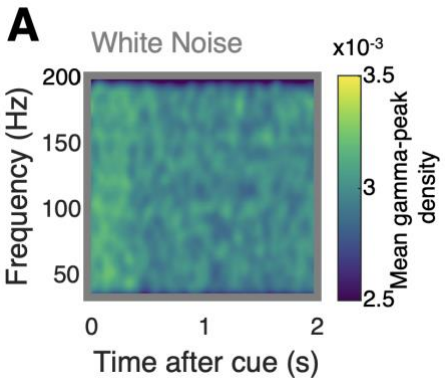
Supplementary Figure 7. Spindle rates with more conservative thresholds were influenced by lateralised tDCS stimulation. A-C) Same as **Figures 2C, 3A, & 3C** with spindle rates using a detection threshold of mean + 1.75 SD (rather than mean + 1.5 SD). Lines represent individual participants. Error bars represent ±1 SEM. White circles highlight significant clusters, $p < .05$.



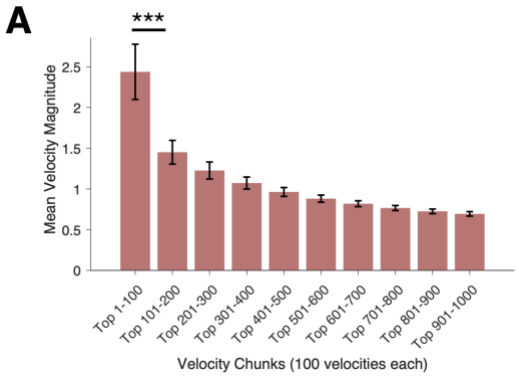
Supplementary Figure 8. Exploration of relationship between spectral power in N2 / N3 sleep and visuomotor skill retention after sleep. A) The t-values for the effect of spectral power on skill retention from exploratory LME models with the equation 'Retention ~ Session + Stimulation Site + Spectral Power + (1|Participant Number)'. One LME model was employed for each EEG contact-frequency bin combination (see **Methods** for details). Positive and negative t-values indicate better retention after sleep for the number of correct sequences and RT, respectively. White circles represent significance ($p < .05$), not corrected for multiple comparisons.



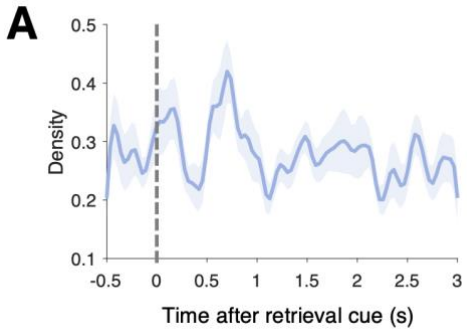
Supplementary Figure 9. Grand average ripple and average ripple for each participant. A) Mean iEEG signal centred at peak of the ripple events across the entire session. Singla was averaged across hippocampal contacts and baseline-corrected by subtracting the mean between -250 and -150 msec before the ripple peak. Mean was taken within each participant, before averaging across participants (N = 9). Shading represents SEM. **B)** Same as **A)** but for each participant, averaged across all ripples, pooled over contacts (N = total ripples). The number of hippocampal contacts and total ripples throughout the session were as follows: P1: 6 contacts, 14284 ripples; P2: 3 contacts, 6201 ripples; P3: 4 contacts, 7395 ripples; P4: 2 contacts, 3522 ripples; P5: 2 contacts, 4151 ripples; P6: 2 contacts, 5789 ripples; P7: 6 contacts, 15173 ripples; P8: 6 contacts, 8167 ripples; P9: 2 contacts; 3922 ripples. **C)** Same as **A)** but showing grand average pseudo-ripple detected from white noise channels across participants (Hippocampal contacts with signal replaced by randomly generated signal with SD of 5 μV).



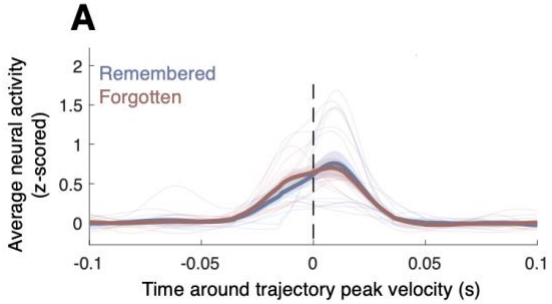
Supplementary Figure 10. Gamma-peak density from white noise channels. A) Average gamma-peak density during retrieval time across white noise contacts (N = 33; Hippocampal contacts with signal replaced by randomly generated signal with SD of 5 μV). This analysis replicated the hippocampal analysis (Chapter 3 Figure 2C with the iEEG signal for each contact replaced with white noise. Density is smoothed along the frequency axis with a 20 Hz Gaussian kernel, and along the time axis with a 200 msec Gaussian smoothing kernel.



Supplementary Figure 11. Mean velocity magnitude of sorted velocity value chunks. A) Mean magnitude of sorted velocity values (chunked into groups of 100). Values were averaged within chunks and then across trials within participants, before comparing across participants. Bars are group-level means (N = 16). Error bars are SEM. Triple asterisk represents significance (p = .001)



Supplementary Figure 12. KDE distribution of peak velocities including pre-cue 500 msec fixation period. A) KDE plot of peak velocity timings in remembered trials. Trajectories of the velocities in this plot are from a PCA reduction which included the 500 msec pre-cue fixation period (unlike the main analyses). KDE used a 50-msec kernel. Shading is SEM. Line is group-level mean (N=16).



Supplementary Figure 13. Neural activity around peak trajectory velocity timepoints in remembered and forgotten retrieval. A) Mean z-scored firing rate of pooled z-scored hippocampal and entorhinal units, around the time of memory cue in remembered (blue) and forgotten (red) trials. Thin lines represent individual participants. (N = 12 participants). Shading represents SEM.