

**Regulating Memory Persistence: Peripheral Nerve Stimulation Across the Forgetting
Continuum**

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DECLARATION

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

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SUMMARY

Understanding how memories are formed, retained or forgotten is central to cognitive neuroscience. According to contemporary models, remembering and forgetting depend on control mechanisms that govern the accessibility, stability and updating of memory representations (Akers et al., 2014; Anderson et al., 1994; Berry et al., 2024; Davis & Zhong, 2017; Hardt & Sossin, 2019). These mechanisms selectively modulate engram accessibility in a context-sensitive manner, enabling adaptive behaviour by reducing interference, prioritising goal-relevant information and supporting flexible updating of memory traces (Davis & Zhong, 2017; Ryan & Frankland, 2022). Forgetting is therefore an active and regulated process.

Building on this framework, in **chapter 1**, I propose that forgetting exists along a regulatory continuum. At one end, *hyperforgetting* reflects accelerated loss of information as seen in preclinical Alzheimer's disease (AD), epilepsy and brain injury. Whereas *hypoforgetting* reflects insufficient attenuation of memories, contributing to maladaptive persistence in conditions such as post-traumatic stress disorder (PTSD) and addiction. Across this spectrum, pathological forgetting is framed not solely as failure of encoding or consolidation, but as dysregulation of memory control systems governing plasticity and engram accessibility.

This unified theoretical account of memory control integrates active forgetting theory, with predictive processing accounts and neuromodulatory models. Accordingly, memory control reflects adaptive model updating driven by prediction error signals guiding selective stabilisation or suppression of memory traces (Bayer et al., 2025; Sinclair & Barense, 2019), with disruptions to this regulation implicated in disorders across the forgetting spectrum (Kube et al., 2020; Ruzzoli et al., 2016). Central to this regulatory architecture is the locus coeruleus-noradrenergic (LC-NA) system, which modulates hippocampal and cortical circuits involved in attention, arousal, synaptic tagging and consolidation (Dahl, Bachman, et al., 2023; Dahl et al., 2020; Poe et al., 2020), functioning as a plasticity gatekeeper and prediction-error signaller (Berridge & Waterhouse, 2003; Groves et al., 2025; Mather et al., 2016; Sara, 2009). Its integration with intrinsic forgetting mechanisms and oscillatory dynamics (Costanzi et al., 2021; Sara, 2015) further positions it as a core component of memory control architecture.

Peripheral nerve stimulation targeting afferents such as the trigeminal, vagus, or greater occipital nerve, has emerged as a non-invasive method for accessing central neuromodulatory pathways. Such approaches engage LC-NA activity and modulate hippocampal and amygdala circuits (L. Chen et al., 2025; Luckey, McLeod, et al., 2023; Alireza Majdi et al., 2025); influencing central plasticity systems, neural activity within memory-related networks, and behavioural memory outcomes (Liu et al., 2025; Vanneste et al., 2020).

Building on this foundation, **chapters 2, 3 and 5** investigate whether greater occipital nerve stimulation using direct current (GON-tDCS) can bias memory control mechanisms and modulate outcomes across the forgetting continuum. Although prior research shows enhanced consolidation (Luckey, McLeod, et al., 2023; Vanneste et al., 2020), GON-tDCS' effects on reconsolidation, active forgetting, emotional memory persistence and hyperforgetting phenotypes such as accelerated long-term forgetting (ALF) remain unexplored. As such, this thesis novelly demonstrates that GON-tDCS does not globally enhance memory. Rather, it modulates plasticity trajectories depending on (i) memory stage, (ii) memory type and (iii) baseline neural state - consistent with a dynamic memory control model.

In **chapter 2**, an experimental investigation of reconsolidation reveals dissociable effects of stimulation on memory strengthening versus retrieval-induced forgetting. GON-tDCS was associated with enhanced reconsolidation-related stabilisation processes, while no statistically significant effects were observed for retrieval-induced forgetting, suggesting its delineated effects on memory and forgetting within the memory control system.

In **chapter 3**, in an aversive learning paradigm, stimulation during acquisition reduces later autonomic fear expression, alongside attenuated pupil dilation (a proxy of LC-NA activity). In contrast to prior demonstrations of enhanced memory, this novel finding indicates that GON-tDCS can attenuate maladaptive expression of emotional memories, potentially via altered synaptic tagging, consolidation or integration dynamics. Modulating memory control systems may therefore reduce persistence of emotional memory traces.

In **chapter 4**, I review the literature on the synaptic strength processes that influence engram cell accessibility, and which are dysregulated in disorders across the forgetting spectrum. I focus on how these mechanisms relate to conditions where ALF presents as a symptom, as well as for conditions on the other end of the forgetting spectrum.

In **chapter 5**, in preclinical AD, GON-tDCS did not reduce ALF. Instead, cognitive effects were state-dependent and differed compared to healthy older adults. Critically, peripheral nerve stimulation interacted with baseline oscillatory dynamics, shaping plasticity and memory outcomes.

Collectively, this thesis proposes a unified framework in which peripheral nerve stimulation biases memory plasticity by interacting with LC-NA dependent gating systems that regulate persistence along the forgetting continuum. Memory outcomes depend on stimulation timing, memory stage, memory type and intrinsic oscillatory dynamics. By integrating theoretical models and experimental neuromodulation, this work demonstrates that GON-tDCS does not universally enhance memory; instead, it shifts plasticity dynamics toward greater memory persistence or forgetting depending on context.

LIST OF PUBLICATIONS

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Adcock, K., **Arulchelvan, E.**, Shields, N., & Vanneste, S. (2026). Towards precision medicine for otology and neurotology: Machine learning applications and challenges. *Hearing Research*, 469, 109473. <https://doi.org/10.1016/j.heares.2025.109473>

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Kennedy, L., Sanagavaram, A., **Arulchelvan, E.**, Vanneste, S., & Leroi, I. (2025). Greater occipital nerve stimulation for cognitive impairment in Parkinson’s disease: A two-stage feasibility and tolerability study. *HRB Open Research*, 8, 124. <https://doi.org/10.12688/hrbopenres.14230.1>

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Byczynski, G., **Arulchelvan, E.**, & Vanneste, S. (2024). Comment on: Frontal HD-tACS enhances behavioural and EEG biomarkers of vigilance in continuous attention task. *Brain Stimulation*, 17(6), 1331–1332. <https://doi.org/10.1016/j.brs.2024.07.001>

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
AD	Alzheimer's disease
ALF	Accelerated Long-term Forgetting
AMCI	Amnesic Mild Cognitive Impairment
APP	Amyloid Precursor Protein
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory-II
COWAT	Controlled Oral Word Association Test
CS	Conditioned Stimuli
ECG	Electrocardiogram
EMDR	Eye Movement Desensitisation and Reprocessing
ERP	Electrophysiological Response Potential
FMRI	Functional Magnetic Resonance Imaging
GLM	General Linear Model
GON-tACS	Non-invasive Greater Occipital Nerve Stimulation using Alternating Current
GON-tDCS	Non-invasive Greater Occipital Nerve Stimulation using Direct Current
HPA	Hypothalamic-Pituitary-Adrenal
HR	Heart Rate
HSAM	Highly Superior Autobiographical Memory
IFG	Inferior Frontal Gyrus
LC	Locus Coeruleus
LC-NA	Locus Coeruleus-Noradrenaline
LTD	.Long-term Depression
LTP	Long-term Potentiation
MMN	Mismatch Negativity
MMSE	Mini Mental State Exam
NA	Noradrenaline
OCD	Obsessive-compulsive Disorder
PD	Parkinson's disease
PRP	Plasticity Related Proteins
PTSD	Post-traumatic Stress Disorder
REM	Rapid Eye Movement Sleep
RoF	Return of Fear
SCD	Subjective Cognitive Decline

SCR	Skin Conductance Response
SNAQ	Snake Questionnaire
SWS	Slow Wave Sleep
TACS	Transcranial Direct Current Stimulation
TBI	Traumatic Brain Injury
TDCS	Transcranial Alternating Current Stimulation
TES	Transcranial Electrical Stimulation
TMS	Transcranial Magnetic Stimulation
US	Unconditioned Stimulus

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CHAPTER ONE: GENERAL INTRODUCTION¹

1.1 Introduction: Why Memory Control Matters

Memory is often evaluated in terms of its success (retention) and failure (forgetting). Yet this binary framing obscures a central neurobiological reality: the nervous system did not evolve to maximise storage capacity, it evolved to optimise behavioural adaptability. In this sense, remembering and forgetting are not necessarily opposing states but complementary processes within a regulated system that governs the accessibility, stability, and updating of stored memory representations.

At the cellular level, memories are encoded in distributed neural ensembles known as engrams (Josselyn & Tonegawa, 2020; Ryan & Frankland, 2022). Following encoding, these representations undergo consolidation i.e. a set of neurobiological processes that stabilise memory traces over time. Consolidation operates across multiple temporal and anatomical scales. Synaptic (cellular) consolidation involves rapid and slower activity-dependent changes in synaptic strength, including protein synthesis and structural modifications within hippocampal and neocortical circuits (Dudai et al., 2015; García-Martínez et al., 2023). These early synaptic changes support the longer-term stabilisation of memory traces. Over time, through systems consolidation, these traces are reorganised across distributed neural networks, and gradually embedded within broader neocortical ensembles. Through these coordinated synaptic and systems-level processes, newly encoded memories become more stable and resistant to interference or forgetting.

Several theoretical models have sought to characterise this consolidation process, each emphasising (though to differing degrees) the role of the hippocampus. Standard consolidation theory proposes that the hippocampus initially binds information into coherent memory traces, which progressively become hippocampus-independent as they are reorganised into neocortical networks (García-Martínez et al., 2023; Mameniškienė et al., 2020). In contrast, multiple trace theory argues that episodic memories continue to rely on medial temporal lobe structures, with each retrieval generating additional hippocampal–neocortical traces. Unified models reconcile aspects of both accounts, suggesting that while early consolidation requires coordinated hippocampal–neocortical

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The author of this thesis is the first author on these publications.

activity, later retrieval remains supported by hippocampal indexing and long-range projections (Mameniškienė et al., 2020).

In line with these approaches, for much of the twentieth century, forgetting was conceptualised primarily as passive decay of these memory traces, trace interference, or retrieval failure (Dudai et al., 2015; Ebbinghaus, 2013). Under this model, long-term memory loss was typically attributed to incomplete consolidation or structural damage to stored traces. However, converging evidence from molecular neuroscience, optogenetics, behavioural paradigms, and computational modelling has substantially revised this view. Forgetting is now understood, in many cases, as an active and biologically orchestrated process mediated by specific molecular and circuit-level mechanisms (Berry et al., 2024; Davis & Zhong, 2017; Ryan & Frankland, 2022).

Rather than reflecting erasure of an engram, forgetting often appears to involve altered accessibility. Accordingly, memory traces may persist in latent form, but become suppressed, weakened or contextually gated. For instance, behavioural work on retrieval-induced forgetting demonstrates that recalling one memory can actively suppress competing traces (Anderson et al., 1994). Rodent studies further show that optogenetic stimulation of engram cells can reinstate seemingly “forgotten” memories, indicating that the underlying trace can remain intact (Ryan & Frankland, 2022). Together, these findings suggest that memory is governed by control processes that regulate which memory traces remain accessible and which are attenuated.

This regulatory perspective reframes forgetting as functionally adaptive. At the systems level, this regulation prevents interference, supports abstraction and generalisation, and enables behavioural flexibility (Guskjolen & Cembrowski, 2023). Forgetting irrelevant information is therefore computationally beneficial, as excessive persistence may impede behavioural adaptation just as much as excessive information loss. In other words, forgetting, in this light, is not a failure of memory systems or consolidation, but a functional component of adaptive cognition.

Mechanistically, this balance is evident at the level of synaptic plasticity. Memory formation begins with activity-dependent synaptic plasticity. Long-term potentiation (LTP), mediated primarily through NMDA receptor activation and AMPA receptor insertion, increases the likelihood of coordinated neuronal reactivation (Kennedy, 2013). Calcium-dependent kinase cascades initiate transcriptional changes and local protein synthesis, producing structural spine modifications that stabilise synaptic efficacy. However, consolidation is not synonymous with memory permanence. Even during early stabilisation, synapses remain labile. Depotentiation and long-term depression (LTD) can reverse LTP through NMDA-dependent AMPA receptor internalisation (particularly of GluA2-containing subunits) thereby weakening connectivity between engram cells (Berry et al., 2024; Ryan & Frankland, 2022). Strengthening and weakening processes are therefore mechanistically intertwined.

Beyond glutamatergic signalling, GABAergic activity modulates excitatory plasticity thresholds, shaping whether potentiation or depression predominates (Kennedy, 2013). Actin cytoskeletal remodelling further alters spine morphology and synaptic persistence, while glial mechanisms (including microglial-mediated synaptic pruning and astrocytic modulation) further regulate engram stability (Berry et al., 2024). Adult hippocampal neurogenesis has also been implicated in circuit reorganisation and memory clearance, with increased neurogenesis promoting forgetting through network remodelling (Akers et al., 2014). Additionally, Rac1-dependent signalling cascades, among others, promote actin remodelling and synaptic weakening and appear evolutionarily conserved across species (Davis & Zhong, 2017). Thus, these mechanisms operate as intrinsic components of circuit maintenance and optimisation.

These regulatory processes are advantageous, given that biological systems operate under constraints of metabolic costs, storage capacity and interference, whereby persistent retention of outdated information would impair abstraction and behavioural updating. Thus, forgetting has an adaptive function, regulated by memory control systems and determined by stability-plasticity dynamics.

However, these dynamics are vulnerable to disruption. As such, forgetting may not simply stem from aberrant consolidation mechanisms, but rather, from dysregulated forgetting processes. For example, it is plausible that if destabilising processes (due to neurodegeneration, inflammatory signalling, altered neuromodulation, or aberrant network excitability) disproportionately exceed stabilising mechanisms, aberrant forgetting may occur. In line with this, pathological forgetting may thus reflect dysregulation within this memory control architecture.

1.2 Accelerated Long-term Forgetting (ALF) and The Forgetting Continuum

ALF describes a memory phenotype in which individuals exhibit relatively intact encoding and short-delay recall but demonstrate disproportionate forgetting across extended retention intervals, typically over days to weeks (Elliott et al., 2014). The term ‘accelerated long-term forgetting’ was first coined by Blake and colleagues (Blake et al., 2000) to characterise cases of ‘long-term amnesia’ in patients with epilepsy (Elliott et al., 2014). Early work primarily identified ALF in patients with temporal lobe epilepsy, but it has since been documented in transient epileptic amnesia, extratemporal and genetic generalized epilepsies (García-Martínez et al., 2023; Mameniškienė et al., 2020). Beyond epilepsy, ALF has also been observed in traumatic brain injury (TBI), limbic encephalitis, stroke, 22q11.2 deletion syndrome, and neurodegenerative disorders such as Alzheimer’s disease (AD) or Parkinson’s disease (PD) have also exhibited signs of ALF (García-Martínez et al., 2023; Savage et al., 2019; van der Werf et al., 2016; Witt & Helmstaedter, 2021).

Despite two decades of research, the mechanisms underlying ALF remain debated (Audrain & McAndrews, 2019; García-Martínez et al., 2023; Geurts et al., 2019; Hoefeijzers et al., 2013; Mameniškienė et al., 2020; Mayes et al., 2019; Rodini et al., 2022). These approaches typically

disagree on certain factors such as: (i) Is ALF *qualitatively* or *quantitatively* different to classic amnesia, and does it reflect impaired acquisition or consolidation? (ii) Are structural abnormalities - particularly hippocampal pathology - necessary or sufficient to produce ALF? (iii) Is ALF driven by overt seizures or subclinical epileptiform activity?

While each account captures part of the phenomenon, they fail to explain its transdiagnostic occurrence. Moreover, ALF is observed in individuals without clear hippocampal damage, seizure activity, or overt acquisition or consolidation deficits. This suggests that the critical mechanism must be one that is dysregulated across diverse neurological and psychiatric conditions.

In Arulchelvan & Vanneste (Arulchelvan & Vanneste, 2026a), I propose that ALF may arise not solely from impaired memory maintenance (e.g., consolidation failure), but from hyperactive intrinsic forgetting mechanisms. Emerging evidence indicates that forgetting is not merely due to passive decay but an active, biologically regulated process operating in parallel (and often in opposition) to consolidation (Castillo Díaz et al., 2021; Dalto et al., 2025). Memory persistence may therefore reflect a dynamic equilibrium between stabilising and weakening forces within a homeostatic system (Davis & Zhong, 2017). From this perspective, ALF reflects a shift in this balance towards excessive weakening.

Given that hyperactive forgetting processes could act at different stages of memory processing, this framework accommodates heterogeneous findings in the ALF literature. In some individuals, hyperactive forgetting processes may disrupt early stabilisation, mimicking encoding or consolidation deficits; in others, they may accelerate later-stage weakening, producing apparently intact short-term retention followed by disproportionate long-term loss. Such variability may explain inconsistent associations between ALF and acquisition or consolidation performance across studies (Hoefjeijzers et al., 2013).

At the mechanistic level, forgetting involves active molecular pathways. Rac1 activation, actin cytoskeleton remodelling, and AMPA receptor endocytosis contribute to synaptic weakening (Berry et al., 2024; Davis & Zhong, 2017). These pathways are tightly regulated under normal conditions. However, disease-related alterations (such as neuroinflammation, dopaminergic depletion, or aberrant excitatory-inhibitory balance) could amplify weakening processes.

Different pathologies may therefore converge on shared downstream mechanisms. In Parkinson's disease, dopaminergic deficits may reduce synaptic tagging efficiency and stabilisation probability, biasing circuits toward destabilisation (Kouli et al., 2018; Noyes et al., 2021). In Alzheimer's disease, amyloid- β and tau pathology compromise synaptic integrity and may potentiate LTD-like processes (Hsieh et al., 2006; Kaldun et al., 2021; Ohno, 2023). In epilepsy, recurrent excitatory bursts may induce maladaptive homeostatic scaling, promoting progressive synaptic downscaling and impairing network level activity (Stampanoni Bassi et al., 2019). Although the

pathologies differ, each may ultimately be driven by (or contribute to) synaptic pathways that ultimately accelerate engram weakening.

This reinterpretation of ALF as a consequence of hyperactive forgetting situates it at one end of a broader continuum. Under this view, if forgetting pathways are excessively activated or insufficiently counterbalanced by stabilisation signals, engram accessibility may decline more rapidly than is behaviourally optimal. Conversely, insufficient weakening may produce maladaptive memory persistence. Importantly, many molecular pathways implicated in forgetting also support adaptive updating of memories and behavioural flexibility (Ryan & Frankland, 2022). The issue, therefore, is not the presence of forgetting mechanisms per se, but their calibration: whereby hyperforgetting and hypoforgetting may share mechanistic substrates but differ in regulatory bias. In other words, I propose that ALF is positioned on one side of a forgetting continuum, with evidence suggesting converging mechanisms across the two sides of this forgetting spectrum (Figure 1.1) (See also Chapter 4 for a deeper discussion on ALF and a unifying perspective on the neurobiology of forgetting). Furthermore, this continuum model proposes that neuromodulatory systems responsible for gating plasticity may play a central role in determining position along this continuum.

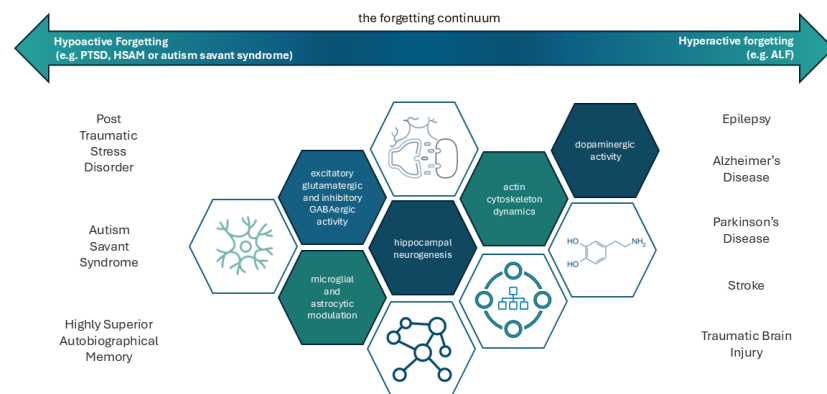


Figure 1.1| Proposed Shared Neurobiological Pathways Underlying the Forgetting Continuum. The proposed shared neurobiological pathways that underlie conditions of both hypoactive and hyperactive forgetting. These conditions can be conceptualised as existing along the forgetting continuum.

1.3 Hypoforgetting and Maladaptive Persistence: The Other End of the Continuum

If ALF (i.e. hyperforgetting) represents excessive attenuation of memory traces, the converse phenotype (hypoforgetting) is reflective of maladaptive persistence. At this end of the regulatory spectrum, memories remain resistant to updating, may have heightened accessibility or be disproportionately influential in guiding behaviour. Clinically, such aberrant persistence factors into conditions including PTSD, addiction, obsessive-compulsive disorder (OCD), and certain anxiety disorders (Costanzi et al., 2021).

Looking at PTSD specifically, it is characterised by intrusive recollections, hyperarousal, avoidance, and negative alterations in mood and cognition (American Psychiatric Association, 2013). Among these features, cognitive models of PTSD suggest that intrusive memories may lie at the centre of PTSD symptomology and act as the driver of these other symptoms (Iyadurai et al., 2019).

Neurobiologically, acute trauma exposure engages stress-responsive neuromodulatory systems that bias memory formation toward durability. Noradrenergic activation originating in the locus coeruleus enhances amygdala responsivity, which in turn modulates hippocampal-dependent encoding and consolidation processes (McGaugh, 2013; Roozendaal & McGaugh, 2011). Concurrent glucocorticoid release interacts with noradrenergic signalling to further potentiate consolidation of emotionally arousing events (Roozendaal et al., 2009). Human neuroimaging studies demonstrate that greater amygdala activation during emotional encoding predicts stronger long-term retention, mediated by amygdala–hippocampal interactions (Dolcos et al., 2004). In PTSD, heightened amygdala reactivity and altered medial prefrontal regulation are consistently observed, alongside hippocampal involvement in contextual processing (Pitman et al., 2012). Together, these findings support the view that traumatic memories may be preferentially stabilised at encoding through stress-related neuromodulation of limbic circuitry, leading to strengthened consolidation of emotionally salient memories (Brohawn et al., 2010; McIntyre et al., 2012).

However, emerging accounts also suggest that intrusive memories may stem to some degree from deficient active forgetting processes (Berry et al., 2024). Active forgetting refers to the intentional or unintentional suppression or weakening of unwanted memories, rather than their passive decay (Fawcett et al., 2024). Converging work has identified neural circuits and molecular pathways that support such attenuation, particularly top-down inhibitory control exerted by the prefrontal cortex over the hippocampus (Anderson & Hanslmayr, 2014; Anderson & Hulbert, 2021; Lu et al., 2023; Meyer & Benoit, 2022). In healthy individuals, these mechanisms enable the suppression of emotional memories and reduce its subsequent accessibility. Individuals with PTSD however, demonstrate impairments in these active forgetting abilities. Laboratory paradigms assessing retrieval suppression consistently show reduced capacity to downregulate unwanted memories, accompanied by altered activity in prefrontal–hippocampal circuits (Catarino et al., 2015; Costanzi et al., 2021; Stramaccia et al., 2021; Sullivan et al., 2019; Waldhauser et al., 2018).

These contrasting patterns are further supported by neuroimaging evidence derived from the Neurosynth database (Yarkoni et al., 2011), which I used to compare typical functional magnetic resonance imaging (fMRI) activity patterns associated with PTSD versus with memory suppression. As shown in Figure 1.2, the top row depicts an automated meta-analysis of 106 PTSD-related studies, whereas the bottom row depicts an automated meta-analysis of 314 suppression-related studies. Suppression-related studies in the Neurosynth meta-analysis are domain-general, rather than memory-specific, encompassing tasks such as motor inhibition. However, converging evidence indicates that domain-general inhibitory control mechanisms can operate across both overt actions

and internal memory processes (Anderson et al., 2025; Wessel & Anderson, 2024). Thus, the inverse activity patterns observed (i.e. reduced engagement in control-related regions in PTSD relative to increased engagement during suppression in healthy individuals), support the view that deficient memory control processes may contribute to PTSD symptomology.

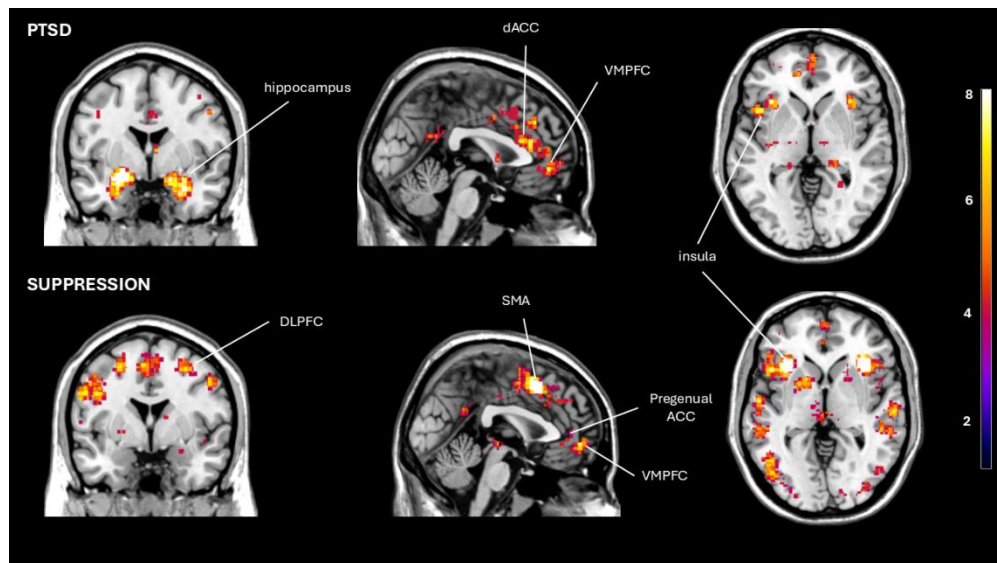


Figure 1.2 | Exemplar brain activity patterns for PTSD versus memory suppression. These images are examples of typical fMRI activity patterns in PTSD versus memory suppression. These activity patterns were generated using the Neurosynth database and MRIcron for visualisation. The top row represents an automated meta-analysis of 106 PTSD-related studies, and the bottom row represents an automated meta-analysis of 314 suppression-related studies. Lighter colours indicate higher z-score according to a uniformity test. *Abbreviations include:* post-traumatic stress disorder (PTSD); dorsal Anterior Cingulate Cortex (dACC); ventromedial prefrontal cortex (VMPFC); dorsolateral prefrontal cortex (DLPFC); supplementary motor area (SMA) and pregenual anterior cingulate cortex (pregenual ACC).

Indeed, disrupted memory control has been linked to intrusive symptom severity and resilience outcomes following trauma (Mary et al., 2020). Such findings suggest that, beyond strengthened encoding, PTSD may involve insufficient engagement of inhibitory mechanisms that would normally attenuate or suppress traumatic memory traces. Importantly, emerging evidence indicates that these control processes are modifiable. Training individuals to suppress unwanted thoughts has been shown to reduce persistence of fear-related imagery and improve anxiety and mood symptoms, particularly in those with elevated post-traumatic stress (Mamat & Anderson, 2023; Mamat et al., 2024; Varma et al., 2024). Strengthening active forgetting capacities may therefore hold therapeutic value (Arulchelvan & Vanneste, 2026b).

Addiction or substance-use disorder provides another example of hypoforgetting (Arulchelvan & Vanneste, 2025a). In these conditions, learning and memory processes are impacted. For those

with substance use disorder, seeing a drug-related cue can trigger an intense memory, leading to drug-seeking behaviour and potential relapse. Essentially, these individuals are plagued by an inability to forget these strong drug-associated memories. In other words, addiction-associated cues acquire disproportionate motivational salience and remain strongly encoded even after prolonged abstinence (Everitt & Robbins, 2016; Perry et al., 2014). Neurobiologically, dopaminergic signalling within mesolimbic circuits promotes late-phase synaptic plasticity and synaptic tagging mechanisms that enhance consolidation of reward-associated memories, embedding cue-drug associations within striatal and cortical networks (Everitt & Robbins, 2016; Hyman et al., 2006). However, in addition to enhanced consolidation, deficient active forgetting processes have been implicated in these conditions, with evidence of impaired forgetting on lab-based tasks (Chen & Gao, 2023; Stramaccia et al., 2021).

At first glance, hyperforgetting (e.g., ALF) and hypoforgetting (e.g., PTSD or addiction) may appear oppositional. However, as outlined above, both can emerge from dysregulation of shared plasticity pathways. Thus, pathological forgetting phenotypes may stem from altered plasticity gain rather than distinct biological systems. As such, what determines whether a memory is strengthened, destabilised, or attenuated? Predictive processing frameworks offer a computational architecture for understanding memory updating in these memory control processes.

1.4 Predictive Processing as a Unifying Computational Framework

The terms ‘predictive coding’ and ‘predictive processing’ are often used interchangeably, though they can denote distinct concepts (Sprevak & Smith, 2023). Following prior work, I adopt predictive processing as a broad umbrella term that stems from earlier, more narrow, predictive coding accounts (Clark, 2013; Kube et al., 2020).

Predictive coding characterizes the brain as a “prediction machine”, continuously generating hypotheses about the world and updating them through a weighted integration of prior expectations, incoming sensory input (interoceptive and exteroceptive), and the discrepancy between the two (Clark, 2013; Kube et al., 2020). This discrepancy - termed *prediction error* - reflects the mismatch between expected and actual input and may be positive or negative depending on whether sensory input exceeds or falls short of predictions (Keller & Masic-Flogel, 2018).

Crucially, both predictions and sensory inputs are assigned *precision* (i.e., confidence), which determines the impact of resulting prediction errors. Under typical conditions, sufficiently large and precise prediction errors drive belief updating, enabling flexible and adaptive behaviour. Accurate predictions, constructed from memories and current input, are therefore fundamental for decision-making organisms (Kraemer & Golding, 1997; Richards & Frankland, 2017; Ryan & Frankland, 2022).

Broader predictive processing frameworks, particularly *active inference* (Friston, 2010; Friston et al., 2016), extend these principles beyond perception to action. Within this account, perception is

shaped by prior expectations and their a priori probabilities, and highly precise priors can bias updating in favour of expectations over sensory evidence (Kube et al., 2020). Importantly, prediction error minimization can occur not only through belief revision but also through action: by sampling the environment in ways that confirm prior expectations, effectively making “priors become reality” (Berg et al., 2022). In line with Bayesian brain accounts, active inference thus conceptualises both perception and decision-making as processes that reduce uncertainty by minimising prediction errors. Throughout this thesis, *predictive processing* refers to this broader framework in which both cognition and action are prediction error driven.

Within this framework, memory is central to prediction. Past experiences provide the basis for generating expectations about the future, rendering memory and prediction inextricably linked. However, predictive systems may become biased when priors (particularly memory-informed ones) are assigned excessive precision, leading to updating that’s driven more by prior beliefs than by prediction error signals. Indeed, the overlap between memory and prediction is reflected in neural activity, with the hippocampus being a central brain region involved in both processes (Barron et al., 2020). In recent years, there is an amalgamation of research that is highlighting how memory control processes (i.e. our capacity to retain or forget information) in both natural and pathological forgetting are driven by predictive processing mechanisms.

For example, in a recent rodent study demonstrating that natural forgetting is a form of adaptive engram plasticity, the authors notably highlight how this forgetting plasticity operates as a function of an error-driven learning model, where prediction errors determine whether an engram is strengthened or weakened (O’Leary et al., 2023). Put differently, in this rodent study, the signal from prediction errors determined whether a memory was forgotten or retained. Likewise in humans, when investigating whether a fear memory was retained or forgotten, another study innovatively demonstrated how reconsolidation requires the occurrence of a prediction error (Sevenster et al., 2013). For more details on the role of prediction errors in reconsolidation, the reader is directed to a review by (Exton-McGuinness et al., 2015). These studies provide novel evidence in both rodents and humans that, whether we remember or forget information relies on prediction error signals

Pathological forgetting can thus be conceptualised as dysregulated precision-weighted updating within this computational architecture. Accordingly, hyperforgetting may reflect excessive precision assigned to prediction errors or chronically reduced precision of priors, leading to repeated destabilisation and progressive weakening of representations. Conversely, hypoforgetting may reflect rigid and over-precise priors that resist modification, even in the presence of contradictory evidence. Forgetting, in this sense, is not merely due to decay, but an emergent property of maladaptive inference dynamics. See Figure 1.3 for a graphical representation of this proposed model of pathological forgetting.

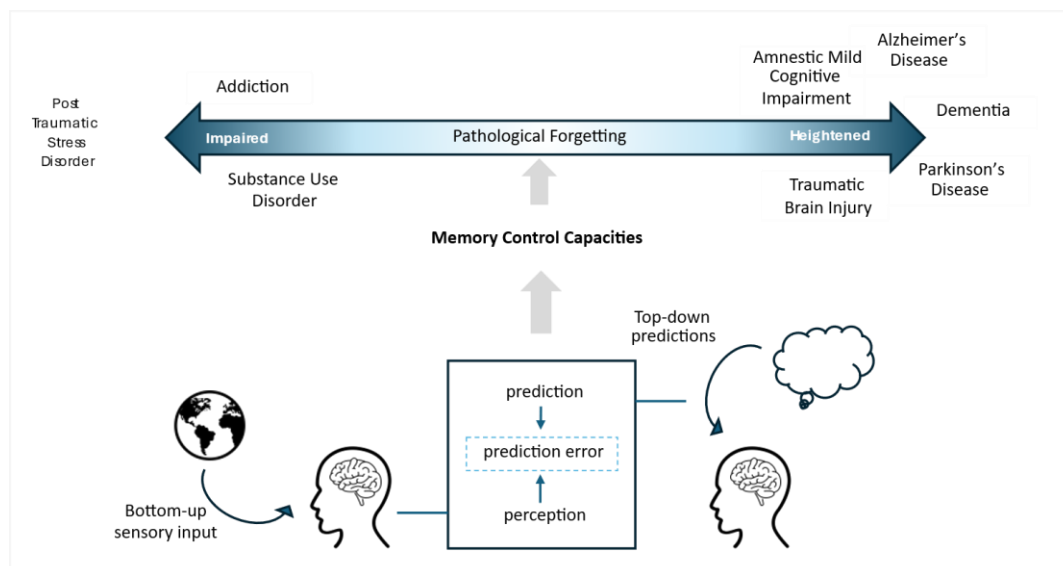


Figure 1.3 | Proposed View of Pathological Forgetting. Exemplar representation of how predictive coding processes are proposed to influence conditions of pathological forgetting, where symptoms can range from heightened forgetting on one end of the scale, to impaired forgetting on the other.

This perspective integrates behavioural, molecular, and clinical findings within a unified framework. For example, in PTSD, threat-related priors may be assigned excessive precision, rendering prediction errors insufficient to modify the traumatic representation. Indeed in PTSD, both heightened emphasis of predictions or prior expectations and reduced salience given to prediction errors were found to contribute to memory control capacities and these patients' ability to intentionally forget information (Leone et al., 2022). By contrast, in ALF, priors may fail to achieve sufficient post-encoding stabilisation, leading to disproportionate weakening over time.

At the electrophysiological level, prediction error processing can be indexed using electrophysiological response potential (ERP) markers such as the mismatch negativity (MMN) and P300 component. The MMN amplitude is argued to reflect the brain's automatic detection of deviations from expected sensory input, in other words the precision-weighted prediction error (Bangel et al., 2017; Hodson et al., 2024; Näätänen, 1995; Schmidt et al., 2013). Likewise, the P300 has been indicated as a marker of prediction errors, and associated with attentional updating and the conscious evaluation of unexpected events (Nieuwenhuis et al., 2005; Yasoda-Mohan & Vanneste, 2024), making both reliable indicators of predictive processing in the brain.

Alterations in MMN and P300 amplitudes and latencies have been observed across clinical populations characterised by hypo or hyperforgetting. For instance, reduced MMN amplitude or increased MMN latency has been reported in addiction-related disorders (He et al., 2018; Motlagh et al., 2018; Ramlakhan et al., 2018), and neurodegenerative conditions in association with cognition and rates of forgetting (Brønnick et al., 2010; Cheng et al., 2021; Gao et al., 2018; Laptinskaya et al., 2018; Tsolaki et al., 2017). Conversely, in PTSD, both increased or reduced MMN amplitude has been observed and associated with PTSD symptomology (Bangel et al., 2017; Ge et al., 2011;

Menning et al., 2008; Morgan & Grillon, 1999), which may suggest an imbalance between priors and sensory information, where some individuals cannot forget traumatic memories due to hyper-precise predictions, and others because of deficient prediction error abilities.

In terms of the P300 response, for cases of hyperforgetting, increased P300 latency, and some initial evidence of reduced P300 amplitude was reported in those with various stages of AD and PD (Howe et al., 2014; Papadaniil et al., 2016; Tsolaki et al., 2017; Xu et al., 2022). Notably, these aberrant predictive processing markers were associated with disease progression, with the P300 differences becoming more exaggerated as cognitive impairment advanced. On the other hand, in cases of diminished forgetting, differential P300, P3a or P3b amplitude responses were found depending on stimuli characteristics. Specifically, in those with substance use disorder or PTSD, increased P300 or P3a amplitude was observed in response to trauma- or drug-related stimuli respectively, whereas decreased P300 or P3b amplitude was reported in response to non-drug or -trauma stimuli respectively (Johnson et al., 2013; Luijten et al., 2016; Petit et al., 2015). Given the association between P300 amplitude and precision, this may suggest that addiction- or trauma-related stimuli are afforded greater precision by the brain in those with PTSD or addiction, which is associated with increased amplitude, whereas non-trauma related stimuli are down-weighted, associated with decreased amplitude.

These findings support the idea that disrupted predictive processing (indexed through MMN and P300 responses) may underlie both excessive forgetting and persistence of maladaptive memories. At the neurobiological level, these inferential dynamics are implemented through synaptic plasticity mechanisms, with NMDA receptor-dependent processes playing a central role in encoding and updating probabilistic representations (Barron et al., 2020). Neuromodulatory systems regulate the precision-weighting of prediction errors. Noradrenaline has been implicated in signalling unexpected uncertainty, effectively increasing the gain on prediction errors and promoting model revision (Sara, 2009). Consistent with this, reduced noradrenaline has been associated with greater precision of prior beliefs and slower learning rates under uncertainty (Lawson et al., 2021). Acetylcholine has been linked to sensory precision, upregulating bottom-up signals and enhancing the influence of predictable sensory input (Hodson et al., 2024; Moran et al., 2013; Sedley et al., 2016). Dopamine is strongly associated with reward prediction error signalling and learning, contributing to the precision of action policies and value updating (O'Leary et al., 2023; Ryan & Frankland, 2022; Yasoda-Mohan & Vanneste, 2024).

Importantly, these neurotransmitter systems do not operate in isolation. Dopaminergic effects on memory and forgetting are modulated by glutamatergic, GABAergic, cholinergic, and serotonergic interactions (Castillo Díaz et al., 2021), and neuromodulators dynamically interact across cortical hierarchies, differentially shaping precision-weighted prediction errors across brain regions and levels of abstraction (Hodson et al., 2024). Neuromodulators (such as glutamate, GABA serotonin, acetylcholine, dopamine and noradrenaline) also play a role in the production of both the MMN and

P300 ERPs (Garrido et al., 2009; Harms et al., 2021; Kenemans & Kähkönen, 2011; Murphy et al., 2011; Nieuwenhuis et al., 2005; Yasoda-Mohan & Vanneste, 2024). Thus, neuromodulatory systems may gate whether memories are stabilised or destabilised by modulating precision-weighting. Dysregulation of these systems could therefore influence outcomes along the forgetting continuum.

Thus, this chapter proposes that neuromodulatory systems gate whether memories are stabilised or destabilised by regulating precision-weighting through plasticity mechanisms. Consequently, dysregulation of these systems influences memory persistence outcomes along the forgetting continuum. In particular, I posit that the locus coeruleus-noradrenergic system, is anatomically and functionally positioned to coordinate large-scale plasticity gating across these cortical and hippocampal networks

1.5 Neuromodulatory Gating of Memory Plasticity

The locus coeruleus-noradrenergic (LC-NA) system is centrally positioned to regulate prediction error signalling and plasticity. It modulates arousal, attention, uncertainty processing, synaptic plasticity thresholds, and large-scale network coordination (Berridge & Waterhouse, 2003; Sara, 2009). Its widespread projections and temporally precise firing modes position it as a candidate gatekeeper of engram stabilisation and destabilisation.

The locus coeruleus is a small nucleus in the pontine brainstem containing the majority of central noradrenergic neurons (Sara, 2009). Despite its compact size, it projects diffusely to the hippocampus, amygdala, prefrontal cortex, sensory cortices, thalamus, cerebellum, and spinal cord (Berridge & Waterhouse, 2003). This anatomical reach allows it to modulate distributed neural ensembles simultaneously. LC neurons exhibit two principal firing modes: tonic firing, which reflects global arousal state and behavioural flexibility, and phasic firing, characterised by brief bursts which occur in response to salient or unexpected events (Aston-Jones et al., 1999; Vazey et al., 2018).

Phasic LC activation increases signal-to-noise ratios in target regions, enhancing processing of behaviourally relevant stimuli (Sara, 2015). Tonic hyperactivity, in contrast, is associated with distractibility and reduced task engagement. This dual-mode architecture allows the LC to regulate both global network state and event-specific plasticity. At the synaptic level, noradrenaline influences plasticity through β -adrenergic receptor activation, modulating intracellular cyclic AMP pathways and protein kinase A signalling. These processes increase the probability of LTP, and promote synaptic tagging and capture mechanisms (Mather et al., 2016).

According to synaptic tagging theory, weakly activated synapses can be stabilised if neuromodulatory signals supply plasticity-related proteins within a critical time window (Frey & Morris, 1997). Noradrenergic release acts as a modulatory permission signal that determines which synapses consolidate (Mather et al., 2016). Importantly, noradrenaline does not uniformly enhance memory. Its effects are context-dependent and nonlinear. While moderate noradrenergic engagement

promotes plasticity, excessive or diminished noradrenergic tone can negatively impact prefrontal cortical stability and amplify neural noise (Dahl et al., 2022). Thus, LC output appears to tune plasticity thresholds rather than simply increase retention.

This threshold-tuning function aligns with my continuum model of forgetting. I propose that LC activity does not uniformly enhance memory, but rather regulates the conditions under which memory traces are stabilised, destabilised, or updated. Both excessive and insufficient noradrenergic signalling may disrupt this calibration. Insufficient LC engagement may fail to support synaptic tagging and consolidation, leaving engrams vulnerable to decay or destabilisation. Conversely, excessive or poorly timed LC activity may amplify neural gain in ways that either reinforce or destabilise existing representations.

Predictive processing frameworks provide a computational lens for interpreting LC function. The LC has been proposed to encode unexpected uncertainty, signalling situations in which environmental contingencies shift in unanticipated ways (Lawson et al., 2021; Sara, 2009). Under such conditions, phasic LC bursts increase gain on cortical processing, amplifying prediction error signals. Within hierarchical inference models, neuromodulators are thought to encode precision-weighting signals that determine the influence of sensory evidence on internal models (Groves et al., 2025). Noradrenaline, in particular, may signal uncertainty about current predictions, increasing the impact of bottom-up prediction errors.

In line with this, within a memory context, recent accounts suggest that LC–hippocampal interactions facilitate memory updating when prediction errors signal model inadequacy (Groves et al., 2025). This implies that LC activation may determine whether reactivated memories undergo destabilisation and updating. If prediction errors are accompanied by phasic LC engagement, destabilisation thresholds may be crossed. Without sufficient LC-mediated precision weighting, retrieval may fail to trigger reconsolidation. LC activity may therefore determine whether a memory remains stable, becomes labile, or is reinforced.

Beyond synaptic mechanisms, LC activity also shapes large-scale network oscillations. Noradrenergic signalling influences hippocampal theta rhythms, cortical gamma activity, and the coordination of hippocampal sharp-wave ripples (Sara, 2015). These oscillatory patterns are critical for memory consolidation and systems integration. During slow-wave sleep, hippocampal sharp-wave ripples support the replay of recently encoded experiences, facilitating their integration into cortical networks (Dudai et al., 2015). Noradrenaline levels fluctuate across sleep stages, remaining low during slow-wave sleep and increasing during REM. Disruptions to LC firing (such as those observed in epilepsy or early neurodegeneration) may therefore impair the oscillatory coordination required for stable consolidation (Krohn et al., 2023).

This framework has direct implications for pathological forgetting. In preclinical AD, degeneration of the locus coeruleus precedes overt hippocampal atrophy (Dahl et al., 2024),

suggesting that reduced noradrenergic tone may impair synaptic tagging and consolidation thresholds, biasing circuits toward destabilisation. Similarly, in PD, LC degeneration occurs alongside dopaminergic loss (Zarow et al., 2003), potentially altering the balance of plasticity regulation.

By contrast, PTSD is associated with heightened noradrenergic reactivity, particularly in response to trauma reminders (Pitman et al., 2012), which may contribute to the persistence of emotionally salient memories. Pharmacological modulation of β -adrenergic receptors has shown some promise in supporting traumatic memory reconsolidation (Pigeon et al., 2022), further supporting the role of noradrenergic gating. In epilepsy, altered LC-hippocampal interactions have been implicated during seizure activity (Larsen et al., 2023). Despite their clinical differences, these conditions converge on a common principle: dysregulation of LC-mediated plasticity gating may modulate memory outcomes across the continuum of forgetting. Moreover, given how LC activity interacts with intrinsic oscillatory dynamics, baseline oscillatory state may also constrain how neuromodulatory inputs influence plasticity outcomes.

Taken together, the LC-NA system possesses several properties consistent with a regulator of memory persistence. It modulates synaptic stabilisation thresholds, encodes unexpected uncertainty and precision weighting within predictive inference, coordinates oscillatory dynamics essential for consolidation, and is implicated across multiple disorders characterised by pathological forgetting. Within the theoretical framework of this thesis, it is proposed that LC-mediated plasticity gating determines whether engrams are stabilised or updated. Accordingly, if pathology emerges when this gating mechanism becomes dysregulated, interventions that can target this mechanism may hold promise for modulating plasticity and memory outcomes across the forgetting continuum. The next section therefore examines peripheral nerve stimulation as a potential translational method to probe and manipulate this plasticity gate.

1.6 Peripheral Nerve Stimulation

Peripheral nerve stimulation has emerged as a viable approach for indirectly engaging central neuromodulatory systems in humans. Several cranial and cervical nerves contain afferent fibres that project to brainstem relay nuclei which maintain reciprocal connections with neuromodulatory centres such as the LC (Luckey, Adcock, et al., 2023). Through these ascending pathways, stimulation of peripheral nerves can influence neuromodulatory tone and thereby alter neural processes underlying cognition and memory (Fiorentini et al., 2025). Among the nerves most frequently studied are the vagus nerve, trigeminal nerve, and greater occipital nerve, each providing sensory input to brainstem nuclei involved in arousal regulation and neuromodulatory signalling.

The functional influence of peripheral stimulation on central neuromodulatory systems is largely mediated through projections to the nucleus tractus solitarius and the trigeminocervical complex (Luckey, Adcock, et al., 2023). These nuclei integrate sensory input from cranial and cervical

afferents and maintain dense projections to multiple neuromodulatory centres, including the LC. Activation of these pathways can therefore influence LC firing patterns and alter noradrenergic signalling throughout widespread cortical and subcortical regions.

For instance, studies on transcutaneous vagus nerve stimulation and trigeminal nerve stimulation demonstrate how these approaches engage brainstem nuclei and downstream neurotransmitter projections implicated in learning and memory (L. Chen et al., 2023; Alireza Majdi et al., 2025; Semminck et al., 2024; Szeska et al., 2025). Similarly, stimulation of the greater occipital nerve can modulate brain activity, support synaptic plasticity processes and influence cognitive, memory and motor function (Asamoah et al., 2019; Hulseley et al., 2019; Jacobs et al., 2015; Luckey, McLeod, et al., 2023; Vanneste et al., 2020). Together, these findings indicate that peripheral nerve stimulation can influence neuromodulatory circuits that play a key role in regulating memory plasticity.

Previous work from our laboratory has demonstrated that non-invasive stimulation of the greater occipital nerve can influence cognitive processes relevant to memory. For example, alternating current stimulation applied to the greater occipital nerve (GON-tACS) has been shown to enhance attentional engagement and memory encoding, while direct current stimulation (GON-tDCS) has been associated with improvements in consolidation processes (Arulchelvan & Vanneste, 2025b; Luckey, McLeod, et al., 2023; Luckey et al., 2022; Vanneste et al., 2020). These findings might suggest that greater occipital nerve stimulation globally enhances memory through encoding or consolidation benefits.

However, within the LC-mediated plasticity gating framework, noradrenergic signalling regulates whether synaptic changes associated with learning are stabilised or weakened. This process is thought to operate through synaptic tagging and capture mechanisms, whereby neuromodulatory input determines which synapses receive the molecular resources required for long-term stabilisation (Dahl et al., 2020; Frey & Morris, 1997).

This perspective has important implications for understanding the behavioural effects of peripheral nerve stimulation. If stimulation influences LC activity and downstream neuromodulatory signalling, it may alter the probability that recently encoded representations undergo stabilisation. From this standpoint, the memory enhancement effects reported in the above peripheral nerve stimulation studies by our lab may reflect selective biasing of plasticity thresholds rather than uniform amplification of mnemonic processes.

Framing these effects within the forgetting continuum provides a more comprehensive account of how neuromodulatory systems influence memory outcomes. For instance, memory processing unfolds across multiple phases (including encoding, consolidation, reconsolidation, and retrieval) with each characterised by distinct plasticity or neural mechanisms (Dudai et al., 2015). As outlined earlier in this chapter, forgetting processes can act on memory outcomes at each of these stages, and

the regulatory processes underlying forgetting are determined by interactions between intrinsic plasticity mechanisms, predictive inference processes, and neuromodulatory signals.

Within this broader context, peripheral nerve stimulation may provide a useful experimental tool for probing the regulatory architecture underlying memory persistence or forgetting. By engaging neuromodulatory systems at specific stages of memory processing, it becomes possible to perturb the gating processes that determine whether memories are stabilised, modified, or attenuated.

Thus, peripheral nerve stimulation's effect on neuromodulatory engagement during each phase may therefore produce different outcomes. For example, does peripheral nerve stimulation at the time of reconsolidation support stabilisation or de-stabilisation processes? For fear-based memories (which tend to be resistant to forgetting), can peripheral nerve stimulation attenuate their memory persistence? For individuals with hyperforgetting (such as those with ALF), can peripheral nerve stimulation bias plasticity outcomes and support memory persistence?

If LC-NA signalling contributes to precision-weighted prediction error processing and synaptic stabilisation, then experimentally biasing this system should alter outcomes for memories across this forgetting spectrum. In this sense, peripheral nerve stimulation may function less as a general enhancer of memory performance, and more as a selective modulator of the processes that regulate memory dynamics. It provides a controlled, non-invasive method for experimentally perturbing one component of this system (the neuromodulatory gate). The experimental work presented in the following chapters employs greater occipital nerve stimulation as a translational tool to examine whether neuromodulatory engagement can bias the mechanisms that determine whether memory traces persist or weaken over time.

1.7 Aims of the Thesis

The theoretical framework developed in this chapter proposes that memory persistence along the forgetting continuum is governed by neuromodulatory plasticity mechanisms that regulate the balance between stabilisation and attenuation of engrams. Within this framework, peripheral nerve stimulation provides a potential method for experimentally biasing these mechanisms in humans.

The overarching aim of this thesis is to investigate how non-invasive stimulation of the greater occipital nerve (which modulates the LC-NA system) interacts with memory control processes and forgetting outcomes. To address this aim, the thesis examines memory plasticity across multiple stages of processing and across different types of forgetting.

Chapter 2 aims to investigate whether GON-tDCS influences reconsolidation and retrieval-induced forgetting processes. By experimentally dissociating these mechanisms, the chapter seeks to determine whether stimulation selectively biases stabilisation and/or destabilisation processes during memory reactivation.

Chapter 3 aims to examine whether GON-tDCS during acquisition influences the persistence and expression of emotionally salient associative memories. This chapter tests the hypothesis that neuromodulatory engagement during learning can alter the later expression of fear-related memory responses.

Chapter 4 aims to expand on chapter 1 by reviewing the evidence for how the symptom of ALF (which presents across various neuropsychiatric disorders) may stem from hijacked intrinsic forgetting processes, and the neurobiological pathways that may underlie this. In doing so, it aims to highlight how dysregulation in these processes is also evident in conditions across the forgetting spectrum, further strengthening the neurobiological basis for this conceptual model.

Chapter 5 aims to evaluate the continuum model of pathological forgetting by examining potential preclinical stages of AD, including subjective cognitive decline and amnesic mild cognitive impairment. This study investigates whether GON-tDCS can influence rates of ALF in this population and whether stimulation effects are moderated by baseline neural oscillatory state.

Together, these chapters aim to provide empirical insight into the mechanisms through which neuromodulatory systems regulate memory persistence and forgetting. By integrating behavioural, physiological, and neuromodulatory perspectives, this thesis seeks to advance a unified account of memory control in which pathological forgetting reflects dysregulation of plasticity gating processes rather than simple failure of storage or retrieval.

CHAPTER TWO: GON-TDCS, RECONSOLIDATION AND RETRIEVAL-INDUCED FORGETTING²

2.1 Introduction

Once information is encoded, for it to be stored as a more stable, longer-lasting memory, it undergoes a process of consolidation (Squire et al., 2015). However, the maintenance of memories is a dynamic and active process (Nader, 2015). Accordingly, reactivation of a consolidated memory can trigger the process of reconsolidation. Thus, while acquisition, consolidation, retrieval (and recently forgetting) are acknowledged as stages in the memory process, over the last few decades, accumulating research has identified another critical stage: reconsolidation (Alberini & LeDoux, 2013; de Oliveira Alvares & Do-Monte, 2021; Nader, 2015). Reconsolidation refers to the phenomenon whereby consolidated memories can enter a labile state when reactivated, during which time they can be further strengthened or are sensitive to disruption (Alberini & LeDoux, 2013; Lee et al., 2017; Sandrini et al., 2015; Sinclair & Barense, 2019). In particular, it is increasingly accepted how the act of retrieval itself can initiate this process of reconsolidation (Alberini & LeDoux, 2013; Lee et al., 2017; Sandrini et al., 2015; Tronson & Taylor, 2007; Vavrková et al., 2020).

Retrieval refers to accessing information that is stored in our long-term memory, often through the use of cues (Roediger & Butler, 2011). Using tDCS montages that target peripheral nerves, only one study to date previously examined peripheral nerve stimulation's impact on retrieval. In that study however, tDCS to the Greater Occipital Nerve (GON-tDCS) was applied at the time of retrieval and found no significant effect, moreover it did not look specifically at reconsolidation (Vanneste et al., 2020). One means through which reconsolidation can be assessed is through the use of retrieval practice. Retrieval practice involves repeatedly retrieving previously learnt information with the intention of improving our memory for them. While the benefits of retrieval practice are well-established, no studies to-date have investigated whether peripheral nerve stimulation using tDCS can enhance reconsolidation via retrieval practice.

From a neurobiological perspective, GON-tDCS represents a particularly appropriate intervention for modulating reconsolidation processes. Although non-invasive neurostimulation techniques such as tDCS were initially conceptualised as exerting their effects through direct transcranial modulation of cortical activity, accumulating evidence indicates that stimulation applied to the head or neck can act through indirect transcutaneous peripheral nerve pathways (Asamoah et al., 2019; van Boekholdt et al., 2021; Vöröslakos et al., 2018; Woods et al., 2016). For example, when stimulation is applied over the C2 nerve dermatome, a substantial proportion of current is argued to pass through the greater occipital nerve. These greater occipital nerve afferents converge onto neurons in the spinal trigeminal

² This chapter incorporates material which has been published in the following article:

Arulchelvan, E., Steltzner, C., & Vanneste, S. (2026). *Peripheral nerve stimulation using tDCS can enhance reconsolidation but cannot mitigate retrieval-induced forgetting.* *Biological Psychology*.
<https://www.sciencedirect.com/science/article/pii/S0301051126000426>

The author of this thesis is the first author of this publication.

nucleus caudalis within the trigeminocervical complex, which synapse on to brainstem nuclei such as the nucleus tractus solitarius, subsequently activating LC-NA projections across cortical and subcortical regions (Goadsby et al., 2008; Luckey, Adcock, et al., 2023).

Noradrenergic and dopaminergic signalling from the LC and ventral tegmental area play central roles in memory reconsolidation, influencing hippocampal synaptic plasticity and the re- or destabilisation of reactivated memory traces (Hansen, 2017; Haubrich et al., 2020; Pigeon et al., 2022; Sara, 2009). Consistent with this framework, recent work from our laboratory has demonstrated that GON-tDCS supports memory consolidation and retention via locus coeruleus-mediated noradrenergic modulation of hippocampal activity (Luckey, McLeod, et al., 2023; Vanneste et al., 2020). Accordingly, GON-tDCS' neuromodulatory mechanisms position it as an intuitive non-invasive stimulation technique to modulate memory reactivation processes. Thus, this experiment aimed to novelly test whether GON-tDCS could enhance memory reconsolidation. Specifically, it sought to investigate whether GON-tDCS could enhance memory of previously consolidated information using a paradigm involving retrieval practice.

As mentioned above, reconsolidation can both strengthen memories, or render them more susceptible to interference (Alberini & LeDoux, 2013; Lee et al., 2017; Sandrini et al., 2015). Related to this, established research has highlighted how the act of retrieval can both support the maintenance of certain memories or induce forgetting of others, with this phenomenon aptly termed *retrieval-induced forgetting* (Anderson et al., 1994; Hulbert & Anderson, 2020; Miller, 2021; Murayama et al., 2014). Retrieval-induced forgetting, a form of active forgetting, is often investigated through the use of cue-target paradigms where retrieval of some items from memory (e.g. A-B cue-target pairs) will enhance their retention, while also inhibiting the retention of other related items (especially those associated with the same cue, e.g. A-C pairs). However, critically, prior research has not only neglected to specifically investigate whether peripheral nerve stimulation can enhance reconsolidation via retrieval practice, but likewise it has failed to examine whether it can prevent retrieval-induced forgetting.

Across drosophila and rodents, the dopaminergic system has been implicated in regulating the persistence or forgetting of memories (Berry et al., 2024; Castillo Díaz et al., 2021). In rodents, it has been shown that blocking specific dopamine receptors in the medial prefrontal cortex impaired retrieval-induced forgetting (Gallo et al., 2022). Supporting this, in humans one study demonstrated how dopamine availability impacted retrieval-induced forgetting. Specifically, genetic markers associated with greater levels of prefrontal cortical dopamine predicted increased rates of retrieval-induced forgetting (Wimber et al., 2011).

Thus, these studies suggest that dopamine facilitates adaptive forgetting of competing memories in prefrontal-mediated memory control. Given GON-tDCS has been shown to modulate dopaminergic as well as noradrenergic activity (Luckey, McLeod, et al., 2023), it is conceivable that it may also alter forgetting dynamics during retrieval. However, prior behavioural work by our lab suggests a more selective pattern: previously we observed that GON-tDCS enhanced consolidation

but did not modulate forgetting rates in older adults (Luckey et al., 2020). This raises an important open question: does peripheral nerve stimulation strengthen memories during reconsolidation without altering inhibitory forgetting processes, or can it influence both?

The present study aimed to address this gap by testing whether GON-tDCS modulates memory during reconsolidation triggered by retrieval practice. Specifically, I examined whether stimulation enhances retention of previously consolidated information following reactivation, and whether it alters retrieval-induced forgetting of competing memories. Based on prior findings (Luckey, McLeod, et al., 2023; Luckey et al., 2020), I hypothesized that GON-tDCS would enhance reconsolidation via retrieval practice but would not significantly modulate retrieval-induced forgetting.

Importantly, retrieval practice and retrieval-induced forgetting have clinical implications in conditions such as schizophrenia or preclinical stages of AD (Ebert & Anderson, 2009; Hanseeuw et al., 2012; Jantzi et al., 2019). Moreover, whether the declarative components of memories can be modulated through reconsolidation-based neurostimulation approaches is likewise relevant for conditions such as PTSD or addiction-related disorders (Alberini & LeDoux, 2013; Lee et al., 2017; Sandrini et al., 2015). Thus, investigating these questions will not only help with our mechanistic understanding of peripheral nerve stimulation's impact on memory processes, but also may outline future therapeutic avenues worth investigating.

2.2 Methods

2.2.1 Participants

Forty participants were recruited to participate in this study. Participants were screened to ensure normal or corrected-to-normal vision, no transcranial electrical stimulation (tES) contraindications including no neurological or psychiatric diagnoses, no taking of neuropsychiatric medications or prescription stimulants, and no chronic use of illicit drugs. Participants were native English speakers, with no prior familiarity or exposure to Arabic language or Swahili (due to task stimuli).

Validated measures including the Beck Depression Inventory-II (BDI-II)(Beck et al., 1996), Beck Anxiety Inventory (BAI)(Beck et al., 1988) and Mini Mental State Exam (MMSE)(Mitchell, 2017) were administered to each participant at the start of visit one to measure cognition, anxiety or depression levels. If standard cut-off values were exceeded on these measures, participants were excluded from participating. For example, based on standard procedures, participants were excluded from participating if they scored >20 on the BDI-II indicating moderate/ severe depression, >16 on the BAI indicating moderate/ severe anxiety, or >24 on the MMSE indicating probable mild cognitive impairment (Bardhoshi et al., 2016; Mitchell, 2017; Whisman & Richardson, 2015).

Alongside these measures, demographic variables were also collected to ensure that any between-group behavioural differences were specifically due to the effects of the stimulation. In addition, given that sleep can impact consolidation, participants were asked to indicate the quality (out of 10) and length (hours) of their sleep the night before each session. This enabled us to ensure that if there were any differences between groups after receiving stimulation, that this was not due to a sleep-specific benefit.

One participant was excluded from participating for exceeding the BAI cut-off score. One other participants' data was excluded due to software malfunction resulting in incomplete data. This resulted in 38 participants' data being analysed (11 males and 27 females: mean age 20.42 years, SD = 2.21 years) (See Table 2.1 for demographic information and control measure results).

An a priori power analysis was performed in G*Power (Faul et al., 2009) to estimate the sample size necessary to detect a significant difference in memory between active and sham conditions, assuming a medium effect size derived from previous literature on peripheral nerve stimulation (Luckey, McLeod, et al., 2023; Luckey et al., 2020; Vanneste et al., 2020). Results indicated that 38 participants would yield 93% power to detect effects at $\alpha = .05$. Allowing for an expected 5% attrition rate, the planned sample size was set at 40 participants.

Table 2.1. Average Control Measures of the Stimulation Groups.

	Active	Sham		
<i>N</i>	18	20		
			χ^2	<i>p</i>
Sex	Male (N = 4)	Male (N = 7)	.75	.386

	Female (N = 14) Female (N = 13)			
Gender	Man (N = 4)	Man (N = 5)	1.01	.604
	Woman (N = 14)	Woman (N = 14)		
	Non-binary (N = 0)	Non-binary (N = 1)		
Handedness	LH (N = 3)	LH (N = 4)	.07	.791
	RH (N = 15)	RH (N = 16)		
Sleep quality			8.92	.259
Sleep quality			12.58	.083
			F	p
Age	20.5 (2.73)	20.35 (1.69)	.04	.838
MMSE	29.22 (0.88)	29.15 (1.09)	.05	.825
BDI	4.72 (3.25)	4.5 (0.95)	.03	.859
BAI	4.17 (3.28)	4.35 (4.39)	.02	.886
Sleep length	6.9 (0.71)	7.8 (1.5)	5.10	*
(hours: night prior to Day 1)				
Sleep length	7.64 (1.17)	7.07 (1.19)	2.24	.143
(hours: night between Day 1 and 2)				

*Abbreviations include: Left-handed (LH), Right-handed (RH), Mini Mental State Exam (MMSE), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). * $p < .05$*

2.2.2 Materials

2.2.2.1 GON-tDCS

Non-invasive stimulation of the greater occipital nerve using direct current (GON-tDCS) was delivered using a specially developed, battery-powered, constant-current stimulator with a maximum output of 10mA (<http://www.neuroconn.de>) via a pair of saline-soaked surface sponges (35 cm²) on the scalp. Stimulation parameters (electrode location, stimulation intensity, ramp up/ down details and sham conditions) were in line with prior research (Luckey, McLeod, et al., 2023; Luckey et al., 2020; Vanneste et al., 2020). Electrodes were placed on the left and right C2 nerve dermatome, and impedance under each electrode was maintained under 10 kΩ.

In Session 2, participants were randomly assigned to one of two groups: active GON-tDCS or sham GON-tDCS. For active GON-tDCS, stimulation ramped up for 30 seconds, a constant current of 1.5 mA intensity was applied during each of the 3 study phases of the task (i.e. 375 seconds × 3 blocks), and stimulation ramped down for 5 seconds. For sham GON-tDCS, placement of the electrodes was identical to active GON-tDCS. At the start of each study phase, stimulation ramped

up for 30 seconds, was applied for 15 seconds only (to mimic the sensation), and ramped down for 5 seconds. No stimulation was applied during rest or testing phases for either group, and no stimulation was applied during Session 1 or Day 2 for either group. See Figure 2.1 for the stimulus protocol.

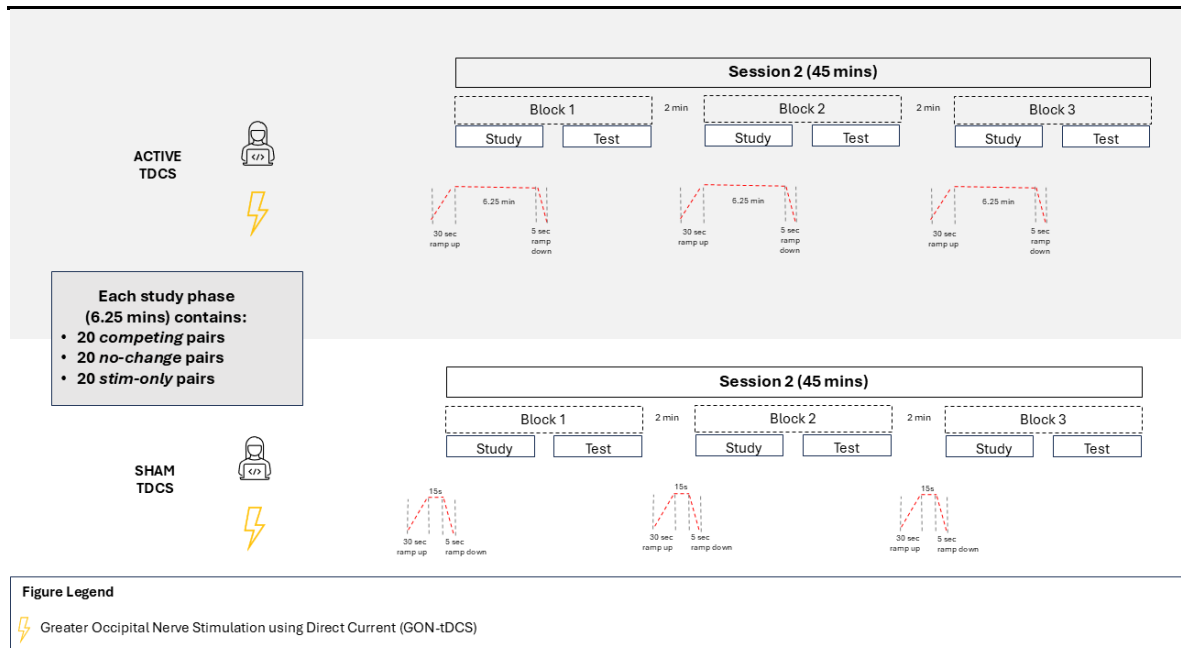


Figure 2.1 | Session 2 Stimulation Protocol. In Session 2, active stimulation was applied for each of the three study phases, while sham stimulation ramped up and down immediately prior to each study phase to mimic the sensation.

2.2.2.2 Paired Association Task

Participants completed a computerized Swahili-English word association task, using word-pairs from Nelson & Dunlosky's (1994) study. The task was adapted from a well-established paradigm by Karpicke & Roediger (2008), and amended following standard interference-based and retrieval-induced forgetting paradigms (Anderson & Neely, 1996). The task was designed using PsychoPy software. In Session 1, participants learned 60 randomly presented Swahili-English cue-target pairs. These pairs were made up of 3 lists of 20 cue-target pairs (termed *original* pairs, *competing* pairs and *no-change* pairs). In Session 2 on Day 1, 60 Swahili-English cue-target pairs were also presented. However, this list varied slightly. Twenty of these pairs had the same Swahili cue but a different English target to the *original* pairs. These were termed *competing* pairs). For example, lozi-almond (*original* pair shown in Session 1) versus lozi-oval (*competing* pair shown in Session 2). Another 20 pairs were the exact same cue-target pairs as Session 1 (i.e. the *no-change* pairs), and the remaining 20 were novel cue-target pairs (termed *stim-only* pairs because they were only presented for learning during Session 2 where stimulation was applied)(See Figure 2.2 for task design and examples of the

stimuli sets). The presentation of these word pairs at each session was randomized, meaning participants were unaware that the pairs they were learning were made up of 3 separate lists.

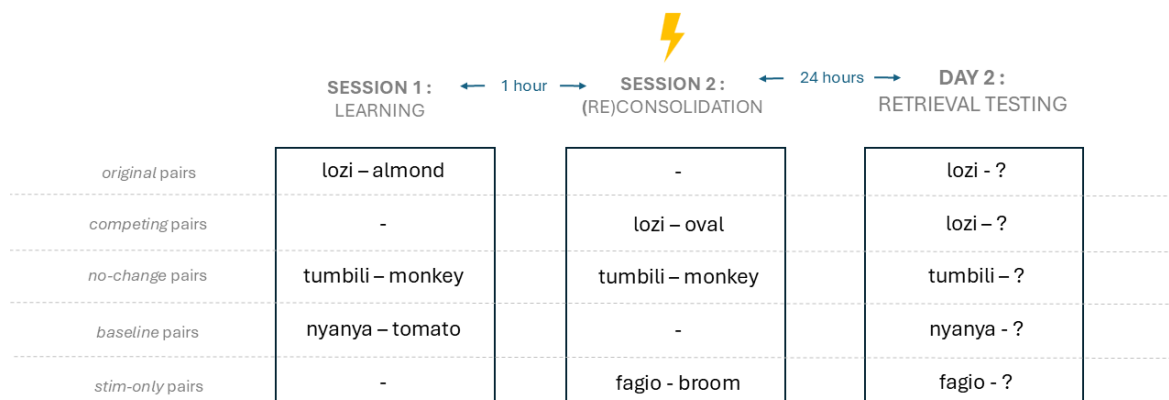


Figure Legend

 Greater Occipital Nerve Stimulation using Direct Current (GON-tDCS)

Figure 2.2 | Task Design and Stimuli Sets. In Session 1, *original*, *no-change* and *baseline* pairs were randomly presented. In Session 2, *competing*, *no-change* and *stimulation-only* pairs were randomly presented. These sessions were separated by a 1-hour break. The following day, participants returned for a retrieval test of all of these pairs.

The task in both Session 1 and Session 2 followed the same format but with slightly different instructions. It involved 3 blocks, each with a study and test phase. In the study phase, each Swahili-English word pair (e.g. Bustani – Garden) were shown on screen for 5s at a time, with the Swahili word on top, and English translation underneath, with a 1s break in between each pair (i.e. $(5s \times 60 \text{ pairs}) + (1s \times 60 \text{ pairs}) = 360s$). Words were presented in black on a white background. A 30s rest separated the study phase from the test phase. The test phase followed standard retrieval practice format. Here, each Swahili cue word was randomly presented on screen for 8s (with a 1s break in between each), and the participant was tasked with typing the English translation. If no response was given, the computer program automatically moved onto the next Swahili cue. This cycle was repeated twice more. Any correctly recalled pairs from the 1st and 2nd testing phases were dropped from being tested in subsequent test phases (but were still presented in all 3 study phases). This meant that the study phase was always 360s per block, with 3 blocks in total. However, the length of the retrieval test phase varied for each participant depending on how many words they had correctly learned in the previous block. Word order was randomized in each phase and block. Cumulative rates of learning were calculated across the 3 test phases. In Session 1, participants were instructed to try to learn as many pairs as possible. In Session 2, the instructions varied slightly in that participants were informed that some of the pairs may be the same or different to those presented in the earlier session, but their task was still to try to learn as many pairs as possible.

When participants returned for the final visit the next day, they completed only 2 retrieval testing-phase blocks of the task. In the first block, they were asked to recall the English targets of the Swahili cues that were presented in Session 1 the previous day. Sixty cues were randomly presented in this block from the *original*, *no-change* and *baseline* pairs. In the second block, they were asked to recall the English targets of the Swahili cues that had been presented in Session 2 the previous day. In this block, 40 Swahili cues were randomly presented from the *competing* and *stim-only* pairs. When each Swahili cue was presented on screen, their task was to type the correct English translation. There were no review of word-pairs and no stimulation on this visit. The structure of this word-association paradigm is presented in Figure 2.2 and Figure 2.3.

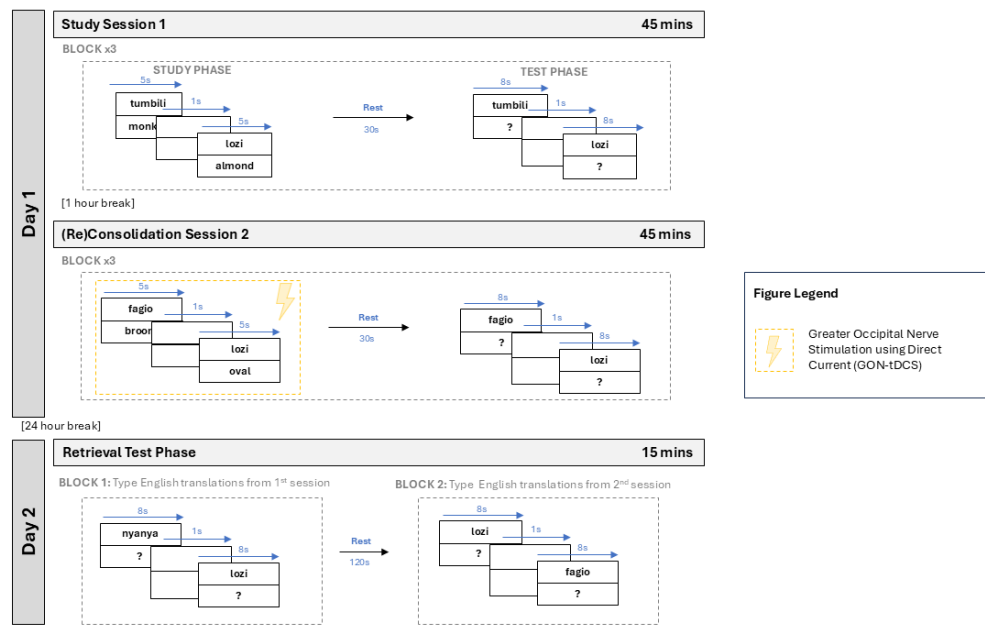


Figure 2.3 | Trial Design. In Session 1, there were 3 blocks each consisting of a study and test phase. In the study phase, Swahili-English word pairs were presented on screen for 5s with a 1s blank screen in between. A 30s rest period followed, before the retrieval test phase began. In the test phase, the Swahili word was shown on screen for 8s while the participants were tasked with typing the English translation, with a 1s blank screen in between each stimuli. Session 2 followed the same format, except active or sham stimulation was applied at each of the study phases. 24 hours later, participants returned for the retrieval test phase. There were 2 blocks, where participants were asked to type the English translations to the Swahili cues they learned the day prior, either in the first or second session, respectively.

As such, *original* and *baseline* pairs were used to test baseline learning in Session 1 for the two stimulation groups, with no differences between stimulation groups expected. Given prior research which demonstrated no effect of GON-tDCS on acquisition (Luckey, McLeod, et al., 2023; Luckey et al., 2020), it was also expected that there would be no differences between the stimulation groups in learning rates for *competing* and *stim-only* pairs in Session 2.

To compare consolidation rates, on Day 2 memory retrieval for the different pair lists was tested. It was expected that consolidation for the *baseline* and *original* pairs would not differ between groups. Whereas, given GON-tDCS' effects on consolidation (Luckey, McLeod, et al., 2023; Luckey et al., 2020), it was hypothesised that on Day 2, memory retrieval for the *competing* and *stim-only* pairs would be greater for the active group than the sham group.

The *no-change* pairs were presented during both Session 1 and Session 2. Critically, these pairs served to test whether GON-tDCS' could enhance memory by boosting reconsolidation via retrieval practice. Reconsolidation can render a memory labile upon reactivation or retrieval. Both reconsolidation and retrieval can support the maintenance of certain memories or induce forgetting of others. Given that the *original* and *competing* pairs involved the use of the same Swahili cues but different English translations (i.e. lozi-almond versus lozi-oval), these pairs served to assess whether GON-tDCS could support the maintenance and reconsolidation of memories by minimising retrieval-induced forgetting. In other words, if retrieval for both *original* and *competing* pairs were greater for the active group than the sham group on Day 2, this would suggest enhanced reconsolidation due to GON-tDCS. Conversely, if from Day 1 to Day 2 more *competing* pairs were forgotten than the *original* pairs (with no differences between stimulation groups), this would indicate retrieval-induced forgetting was not mitigated by GON-tDCS.

2.2.2.3 tES Exit Questionnaire

To assess possible side effects of GON-tDCS, post-stimulation participants completed the tES Exit Questionnaire (Brunoni et al., 2011). It asked participants to rate (using a 4-point scale from 1 = absent to 4 = severe) the extent to which they might have felt symptoms (incl. headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentrating, or acute mood changes). If any were experienced, participants were asked to indicate (yes/no) whether they believed each symptom was related to the application of GON-tDCS. To determine if the stimulation was well-blinded, an item asked participants to guess, based on their experience, which stimulation they believed they had received (active or non-active).

2.2.3 Procedure

This study was designed as a double-blind, placebo-controlled, randomized parallel group study. It was granted ethical approval by the Research Ethics Committee of the School of Psychology at Trinity College Dublin (Approval number: SPREC052022-08) and conducted in accordance with the ethical guidelines of the Helsinki declaration (1964).

Participation involved three visits to Trinity College Dublin. Session 1 and Session 2 were conducted on Day 1 (with a 1-hour break in between the two). 24 hours later, participants returned for the Day 2 session, which took place at the same time as their Session 1 the day prior. In Session 1, participants completed control assessments incl. a sleep questionnaire, the MMSE, BAI, and BDI-

II, followed by a computer-based word-association task. In Session 2, participants returned and completed a related computer-based word-association task, whilst receiving active or sham GON-tDCS. A second researcher administered the stimulation, ensuring that the researcher who instructed the participant and conducted the analysis was blind to the stimulation protocol. At the end of this session, participants completed the stimulation exit questionnaire. Participants returned the following day to test memory performance. At the end of this session, they completed a final sleep-based questionnaire and were debriefed. Upon completion, participants could choose to be reimbursed monetarily for travel compensation, or to receive course credits where relevant.

2.2.4 Statistical Analyses

All analyses were conducted using JASP (version 0.19.1.0).

2.2.4.1 Paired Association Task

On Day 1, cumulative learning rates (percentage of correctly learnt words from blocks one to three) were calculated for each of the *original*, *competing*, *no-change*, *baseline* and *stim-only* pair lists. On Day 2, the percentage of correctly recalled words from each list of pairs were calculated to examine memory recall. Forgetting rates i.e. percentage of pairs from each list that were forgotten were calculated by subtracting Day 1 scores from Day 2. To assess Session 1 learning rates, 3 one-way ANOVAs were conducted with the pair list of interest as the dependent variable and stimulation group (active/ sham) as the independent variable. To assess Session 2 learning rates, 3 one-way ANOVAs were likewise conducted with the pair list of interest as the dependent variable and stimulation group (active/ sham) as the independent variable.

To compare memory recall on Day 2 between the stimulation groups, 5 one-way ANOVAs were conducted with recall rate for pair list of interest as the dependent variable and stimulation group (active/ sham) as the independent variable.

To compare forgetting rates from Day 1 to Day 2 between the stimulation groups, 5 one-way ANOVAs were conducted with the forgetting rate for the pair list of interest as the dependent variable and stimulation group (active/ sham) as the independent variable.

To investigate whether GON-tDCS could mitigate retrieval-induced forgetting, a repeated measures ANOVA was conducted with stimulation group (active/sham) as the between-subjects variable and retrieval rates on Day 2 (for the *original* pairs and *competing* pairs) as the within-subject variables. If significance was obtained, a post-hoc analysis was applied to compare the different conditions using a Bonferroni correction. Additionally, a repeated measures ANOVA with stimulation group (active/ sham) as the between-subjects variable and forgetting rates of *original* and *competing* pairs as the within-subjects variables was conducted.

2.2.4.2 Control Measures

One-way ANOVAs were conducted to examine whether there was a difference between the stimulation groups (active vs sham) for age (years), average sleep quality and length (hours) on the night prior to Day 1 and the night between Day 1 and Day 2 sessions, and MMSE, BDI, and BAI scores. Chi-square (χ^2) tests were calculated to compare if there was a difference between the active and sham group for sex, gender and handedness.

2.2.4.3 tES Exit Questionnaire

To analyse whether participants were blinded to their stimulation group, χ^2 tests compared the stimulation participants received (active vs sham) to what they thought they received (active vs non-active). A MANOVA was conducted to compare whether there was any difference between groups for experiencing common stimulation side-effects.

2.3 Results

2.3.1 Paired Association Task

The main aim of this research was to determine whether GON-tDCS delivered via tDCS influences memory performance by enhancing reconsolidation following retrieval practice and/or by modulating retrieval-induced forgetting, thereby clarifying which memory processes are behaviourally sensitive to stimulation. However firstly, baseline levels of learning were assessed, and tests were run to validate GON-tDCS' effects on consolidation (but not acquisition or forgetting).

2.3.1.1 Baseline learning and memory levels, and validating prior research

There were no significant differences between the groups in learning rates for any of the stimuli (i.e. *original* and *baseline* pairs) presented only during Session 1 (when no stimulation was applied). These results demonstrate equal baseline rates of learning for the two groups (see Table 2.2a).

Table 2.2a. Summary of ANOVA Results for Session 1 (Learning)

	Active	Sham	F	<i>p</i>	ω^2
original pairs	68.06 (19.19)	59.25 (17.87)	2.16	.15	.030
competing pairs					
no-change pairs	65.57 (21.34)	59.25 (19.15)	0.92	.35	.000
baseline pairs	66.67 (19.93)	59.00 (25.27)	1.06	.31	.002
stim-only pairs					

Notes. This table contains average percentage (and standard deviation) of learning rates for the active and sham groups.

As expected, at Session 2 (when active/ sham stimulation was applied), there were also no significant differences between the groups in learning rates for *competing* and *stim-only* pair lists. See Table 2.2b for these results.

Table 2.2b. Summary of ANOVA Results for Session 2 (Re)(Consolidation)

	Active	Sham	F	<i>p</i>	ω^2
original pairs					
competing pairs	74.44 (18.93)	63.50 (24.98)	2.28	.14	.032
no-change pairs	90.28 (12.30)	80.00 (17.92)	4.15	.049	.077

baseline pairs

stim-only pairs	77.50 (19.67)	63.25 (26.02)	3.57	.07	.063
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Notes. This table contains average percentage (and standard deviation) of recall rates for the active and sham groups.

Furthermore, as expected, on Day 2, there were significant differences between groups in memory retrieval only for the pair lists that had been presented during Session 2 the day prior (when active/sham stimulation was applied), with the active group correctly remembering more of *competing* and *stim-only* pair lists than the sham group. See Table 2.2c for the full results of these statistical tests. These results are in line with prior research, and validate how GON-tDCS does not enhance acquisition of newly learnt information, but rather boosts consolidation processes.

Table 2.2c. Summary of ANOVA Results for Day 2 (Retrieval)

	Active	Sham	F	<i>p</i>	ω^2
original pairs	55.28 (19.81)	46.25 (14.41)	2.62	.11	.041
competing pairs	52.78 (20.09)	38.50 (21.91)	4.54	.040	.085
no-change pairs	80.83 (15.65)	69.50 (17.54)	4.38	.044	.082
baseline pairs	52.50 (19.19)	42.75 (20.87)	2.23	.14	.031
stim-only pairs	64.17 (18.25)	49.25 (24.51)	4.44	.042	.083

Notes. This table contains average percentage (and standard deviation) of retrieval rates for the active and sham groups.

In addition, as expected, there were no significant differences between groups in the forgetting rates of each of the lists of word pairs. See Table 2.2d for these results. This further supports the argument that GON-tDCS enhances memory through upregulating consolidation, not by upregulating acquisition or downregulating forgetting processes.

Table 2.2d. Summary of ANOVA Results for Forgetting Rates.

	Active	Sham	F	<i>p</i>	ω^2
original pairs	-12.78 (9.24)	-13.00 (10.93)	.00	.95	.000
competing pairs	-21.68 (10.29)	-25.00 (13.38)	.73	.40	.000

no-change pairs	-9.44 (7.84)	-10.50 (8.72)	.15	.70	.000
baseline pairs	-14.17 (10.74)	-16.25 (8.72)	.44	.51	.000
stim-only pairs	-13.33 (9.70)	-14.00 (9.40)	.05	.83	.000

Notes. This table contains average percentage (and standard deviation) of forgetting rates for the active and sham groups.

2.3.1.2 Can GON-tDCS enhance reconsolidation

The abovementioned results indicate that improved memory in response to GON-tDCS may stem from upregulated consolidation (and not downregulated forgetting). However, this study sought to novelly investigate whether GON-tDCS could enhance memory by boosting reconsolidation via retrieval practice. Critically and interestingly, in Session 2, there was a significant difference between groups in learning of the *no-change* pairs ($F(1, 36) = 4.15, p = .049, \omega^2 = .077$), with the active group ($M = 90.28, SD = 12.30$) remembering significantly more of the *no-change* pairs than the sham group ($M = 80.00, SD = 17.92$) (See Figure 2.4b). This result of $\omega^2 = .077$ suggests that this was a moderate effect. This was the only list of pairs in Session 2 where there was a significant difference between groups (see Table 2.2b). Given that the *no-change* pairs had also been presented in Session 1 (where there were no significant differences between groups, see Figure 2.4a), this suggests that for previously consolidated information, GON-tDCS can upregulate retrieval practice, further boosting reconsolidation of this information. This boost in reconsolidating the *no-change* pairs, subsequently led to significantly enhanced retrieval on Day 2, as outlined in Table 2.2c and Figure 2.4c. See supplementary materials for additional analyses checking for outliers and verifying GON-tDCS' effect on reconsolidation.

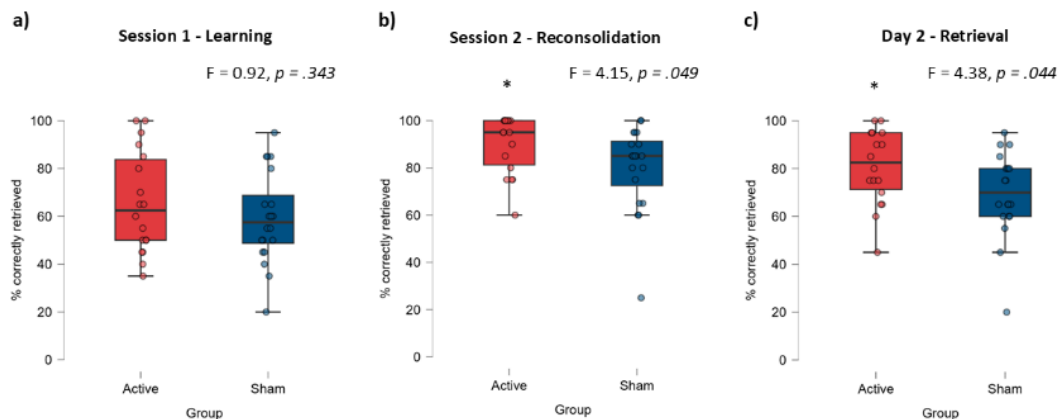


Figure 2.4 | Effect of Reconsolidation and Stimulation. **A** There were no significant differences between the active and sham groups in the retrieval of *no-change* pairs in Session 1. **B** However, when these pairs were presented again in Session 2 where active or sham stimulation was applied, there was a significant difference between the groups, with the active group retrieving more *no-change* pairs than the sham group. **C** Similarly, on Day 2, the active group retrieved significantly more *no-change* pairs than the sham group, demonstrating GON-tDCS' memory enhancement effect on retrieval practice.

2.3.1.3 Can GON-tDCS mitigate retrieval-induced forgetting during reconsolidation?

On Day 2, when comparing active and sham groups and looking at memory recall rates for the *original* and *competing* pairs, no significant effect of stimuli type was found ($F(1, 36) = 3.40, p = .073, \omega^2 = .013$) (See Figure 2.5a). Although there was no significant effect for stimuli, this difference was most pronounced for *competing* stimuli, where the sham group recalled less on average. Interestingly however, there was a significant difference between the groups ($F(1, 36) = 4.48, p = .041, \omega^2 = .045$), with the active group remembering more pairs (*Original Pairs*: $M = 55.28, SD = 19.81$; *Competing Pairs*: $52.78, SD = 20.09$) than the sham group (*Original Pairs*: $M = 46.25, SD = 14.41$; *Competing Pairs*: $38.50, SD = 21.10$) on Day 2.

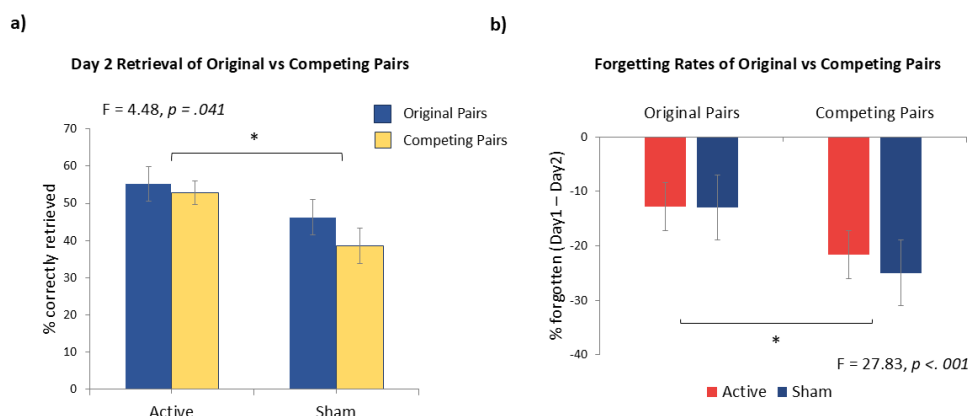


Figure 2.5 | Retrieval-induced Forgetting Rates. **A** The active group retrieved significantly more *original* and *competing* pairs on Day 2 than the sham group. There was no significant difference in retrieval between the *original* and *competing* pairs, suggesting GON-tDCS had a general memory enhancement effect that may have stemmed from increased consolidation or downregulated retrieval-induced forgetting. **B** Given both active and sham groups forgot significantly more *competing* pairs than *original* pairs, this suggests that GON-tDCS had no impact on mitigating retrieval-induced forgetting of *competing* pairs.

This suggests that GON-tDCS had a general memory enhancement effect. To test whether this memory enhancement effect stemmed (to some degree) from mitigating retrieval-induced forgetting, forgetting rates of these *original* vs *competing* stimuli were analysed for the two groups. Here, there

was a significant large effect of stimuli ($F(1, 36) = 27.83, p < .001, \omega^2 = .176$), whereby from Day 1 to Day 2, *competing* pairs were forgotten (Active: $M = -21.67$, $SD = 10.29$; Sham: $M = -25.00$, $SD = 13.38$) more than *original* pairs (Active: $M = -12.78$, $SD = 9.76$; Sham: $M = -13.00$, $SD = 10.93$), regardless of group (see Figure 2.5b). In addition, there was no significant effect of group ($F(1, 36) = 0.336, p = .565, \omega^2 = .000$). Thus, the results of these two analyses together novelly highlight how both groups forgot more *competing* pairs from Day 1 to Day 2. In other words, GON-tDCS had no impact on retrieval-induced forgetting, but rather it enhanced reconsolidation and retrieval of both *original* and *competing* pairs.

2.3.2 Control Measures

Between the active and sham GON-tDCS groups, there was no significant difference in their sex ($\chi^2(1, N = 38) = .75, p = .386$), gender ($\chi^2(2, N = 38) = 1.01, p = .604$), age ($F(1, 36) = .04, p = .838, \omega^2 = .000$), handedness ($\chi^2(1, N = 38) = .07, p = .791$), or scores on the MMSE ($F(1, 36) = 0.05, p = .825, \omega^2 = .000$), BDI ($F(1, 36) = .03, p = .859, \omega^2 = .000$) or BAI ($F(1, 36) = .02, p = .886, \omega^2 = .000$) measures. There was however a significant difference between groups in the hours of sleep on the night prior to participants' first day of participation ($F(1, 36) = 5.10, p = .030, \omega^2 = .097$). However, while this was a moderate effect size, on average participants slept 7.35 hours (Active: $M = 6.9$ hours, $SD = .71$; Sham: $M = 7.8$ hours, $SD = 1.45$). Furthermore, there was no significant difference between groups in the quality of sleep that night ($\chi^2(7, N = 38) = 8.92, p = .259$). Moreover, with regards to consolidation and stimulation effects, the hours and quality of sleep on the night between sessions was of more concern to the research question than the night prior to Session 1 (due to stimulation), and there were no significant differences between groups on quality of sleep ($\chi^2(7, N = 38) = 12.58, p = .083$) or hours of sleep ($F(1, 36) = 2.24, p = .143, \omega^2 = .032$) on that night. See Table 2.1 for average scores of these measures for each group.

2.3.3 tES Exit Questionnaire

A MANOVA revealed a non-significant main effect of stimulation group (active vs sham) for the various tES side effects (Wilks' $\lambda = .813, F(7, 30) = 0.99, p = .458$) (See Figure 2.6a). In particular, there were no measurable differences in scalp pain, neck pain or acute mood change symptoms, and no significant differences in the remaining symptoms (of headache, tingling, itching, burning, skin redness, sleepiness or trouble concentrating). All stimulation sessions were well tolerated, and no major stimulation related complications were noted. Blinding of stimulation conditions was effective as there was no significant difference between which groups participants thought they were in (active vs non-active) compared to their actual groups (active vs sham) ($\chi^2(1, N = 38) = 1.79, p = .180$) (see Figure 2.6b). In the active group, 33.33% of participants believed they received the non-active stimulation, while 66.67% believed they received the active stimulation. In the sham group, 45% of

participants thought they received the active stimulation, with the remaining 55% believing they received the sham stimulation.

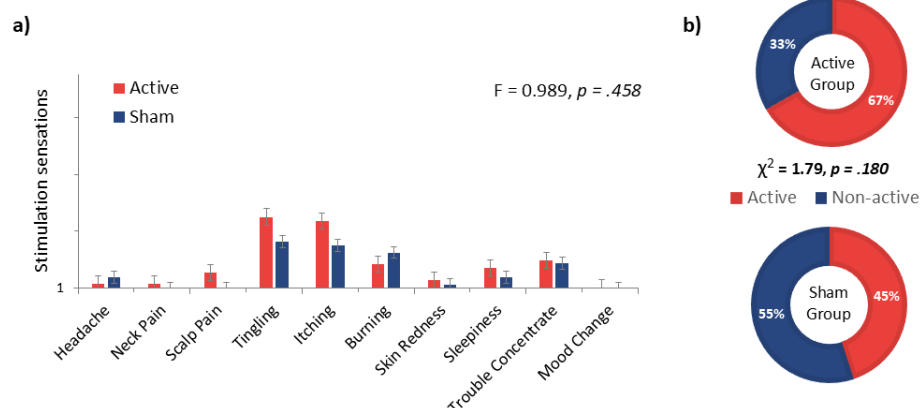


Figure 2.6 | Stimulation Sensations and Stimulation Blinding. **A** There were no measurable differences between active and sham stimulation for neck pain, scalp pain and mood change stimulation sensations, and no significant differences found between active and sham stimulation for the remaining stimulation sensations. **B** There was no significant difference found between the stimulation that participants received (active/ sham) versus what they believed they received (active/ non-active).

2.4 Discussion

Reconsolidation refers to the process by which a previously consolidated memory, rendered labile upon retrieval, undergoes restabilisation. During this process, the memory can be strengthened further or become vulnerable to disruption (Alberini & LeDoux, 2013; de Oliveira Alvares & Do-Monte, 2021; Lee et al., 2017; Sandrini et al., 2015; Sinclair & Barense, 2019). However, no prior research has investigated whether non-invasive peripheral nerve stimulation approaches can enhance memory by modulating these reconsolidation-stage processes. Thus, the main aims of this research were to investigate whether peripheral nerve stimulation could enhance reconsolidation, through boosting retrieval practice and/or mitigating retrieval-induced forgetting.

Firstly, results of this study show that GON-tDCS can strengthen memory reconsolidation via retrieval practice. To demonstrate this, *no-change* pairs were presented in Session 1 (during three encoding and retrieval phases). In Session 2, these same *no-change* pairs were presented (again during three encoding and retrieval phases, however with active or sham stimulation applied at the times of encoding). This session served as a reconsolidation phase for these stimuli, whereby the intention was to test whether stimulation could enhance reconsolidation of these pairs through retrieval practice. Memory retrieval for these pairs was then tested when participants returned on Day 2.

As expected, there were no significant differences between active and sham groups in learning of the *no-change* pairs on Session 1, confirming equivalent learning pre-stimulation. However, there were significant differences between the groups at the reconsolidation stage in Session 2, and when memory was tested 24 hours later, with the active group retrieving more *no-change* pairs at both time points than the sham group. These results highlight how peripheral nerve stimulation can bolster reconsolidation leading to sustained memory benefits 24 hours later. It is important to note that a statistically significant group difference was observed for the *no-change* pairs in Session 2 (see Tables 2.2a and 2.2b). Thus, this novelly highlights how during reconsolidation, peripheral nerve stimulation applied at the time of studying previously consolidated information, strengthens retrieval practice, and leads to sustained memory retrieval. These findings align with the idea that reactivated memories enter a transiently plastic state during which GON-tDCS appears to have amplified the strengthening effect typically produced by retrieval practice, leading to sustained memory benefits observed 24 hours later.

At the time of reconsolidation, memories are rendered labile - meaning they can either be further strengthened or are likewise sensitive to disruption (Alberini & LeDoux, 2013; Lee et al., 2017; Sandrini et al., 2015). Furthermore, the act of retrieval can both support the maintenance of certain memories or induce forgetting of others (Hulbert & Anderson, 2020; Murayama et al., 2014). Thus, the second aim of this research was to investigate whether peripheral nerve stimulation could modulate retrieval-induced forgetting.

To investigate this, participants first learned *original* cue-target pairs in Session 1. In Session 2, the same cues were paired with *competing* targets under active or sham stimulation. On Day 2,

memory retrieval for both *original* and *competing* pairs was assessed. Indeed, on Day 2, although the active group showed overall better memory than the sham group, forgetting rates did not differ between groups. Across participants, *competing* pairs were forgotten more than *original* pairs, demonstrating a typical retrieval-induced forgetting pattern. However, stimulation did not reduce or exacerbate this effect. These findings indicate that GON-tDCS was associated with enhanced memory performance during reconsolidation. However, no statistically significant effects were observed for retrieval-induced forgetting measures.

This dissociation is theoretically informative. Retrieval-induced forgetting is thought to arise from prefrontal inhibitory control processes that suppress competing memory traces (Levy & Anderson, 2002; Wimber et al., 2015; Wimber et al., 2008). In contrast, reconsolidation-related strengthening is more closely linked to hippocampal plasticity mechanisms (Kim et al., 2021; Osorio-Gómez et al., 2023; Schroeder et al., 2023). The present results therefore may suggest that peripheral nerve stimulation preferentially influenced hippocampal–memory stabilisation processes rather than prefrontal inhibitory control mechanisms.

These findings extend previous work demonstrating that GON-tDCS enhances consolidation but not acquisition, retrieval, or forgetting (Luckey et al., 2022; Vanneste et al., 2020). The present study identifies reconsolidation as an additional memory stage sensitive to this form of peripheral nerve stimulation. Importantly, no statistically significant effects were observed for retrieval-induced forgetting, consistent with earlier findings that likewise found that GON-tDCS does not alter forgetting rates in older adults (Luckey et al., 2020).

In terms of the putative mechanism behind this neurostimulation approach, originally, non-invasive neurostimulation approaches employing tDCS or tACS were applied to the head with the aim of modulating brain activity and influencing behaviour (Woods et al., 2016). However, in recent years, research continues to build highlighting how these neurostimulation approaches can exert their effects not only through direct *transcranial* pathways to the brain, but also through indirect *transcutaneous* peripheral nerve pathways (Asamoah et al., 2019; van Boekholdt et al., 2021; Vöröslakos et al., 2018). These peripheral nerves include the vagus nerve, trigeminal nerve and greater occipital nerve. This peripheral nerve route to modulating memory has been validated by prior research (L. Chen et al., 2025; Clark et al., 1999; Jacobs et al., 2015; Luckey, McLeod, et al., 2023). In this transcutaneous route, when stimulation is applied non-invasively to the head or neck, peripheral nerves located just under the skin are argued to receive a greater proportion of the electrical current stimulation than deeper brain regions located beneath the skull (van Boekholdt et al., 2021).

Indeed, in rodents, peripheral nerve stimulation has been shown to activate deep brain regions such as the hippocampus or brainstem nuclei (L. Chen et al., 2025; Hulsey et al., 2017), and blocking these peripheral nerve routes subsequently blocks brainstem nuclei activity in response to stimulation (Alireza Majdi et al., 2025). This highlights how these peripheral nerve pathways behind transcutaneous stimulation are essential in activating deeper brain regions (Luckey, Adcock, et al., 2023; Majdi et al., 2024). Furthermore, neurotransmitter activity has been implicated in the

mechanism(s) through which these peripheral nerves have been shown to modulate brain activity, support synaptic plasticity processes and influence cognitive, memory and motor function (Asamoah et al., 2019; Hulseley et al., 2016; Hulseley et al., 2019; Luckey, McLeod, et al., 2023; Luckey et al., 2022). Specifically, research conducted by our lab on stimulating the greater occipital nerve has demonstrated that GON-tDCS supports consolidation and retention of memories through a LC-NA pathway that facilitates hippocampal activation (Luckey, McLeod, et al., 2023; Vanneste et al., 2020).

Thus, in light of the above literature, in this present study, it is postulated that GON-tDCS strengthens existing memories by upregulating neuromodulatory input to hippocampal circuits during memory reactivation. This interpretation is consistent with prior demonstrations that GON-tDCS increases markers of LC-NA and dopaminergic activity (Luckey, McLeod, et al., 2023; Vanneste et al., 2020), both of which are known to facilitate synaptic plasticity and memory stabilisation (Hansen, 2017). However, given that the present study did not include direct neurophysiological measurements, future research is warranted to confirm whether this same mechanism (or others) underlie GON-tDCS' effects on reconsolidation.

In parallel, forgetting is not a passive process, but involves active inhibition mediated by medial prefrontal and dorsolateral prefrontal cortical regions on downstream hippocampal memory traces (Levy & Anderson, 2002; Wimber et al., 2015; Wimber et al., 2008). Moreover, dopamine is reported to play a critical role in prefrontal inhibitory control during retrieval-induced forgetting (Berry et al., 2024; Castillo Díaz et al., 2021; Gallo et al., 2022; Wimber et al., 2011). Thus, the absence of GON-tDCS' effect on retrieval-induced forgetting is notable. One possibility is that GON-tDCS' neuromodulatory effects are biased toward hippocampal and brainstem pathways rather than prefrontal control networks. This compares to a recent neurostimulation study which demonstrated that disrupting prefrontal activity can reduce retrieval-induced forgetting. In that study, high-definition tDCS over the medial prefrontal cortex decreased forgetting of competing memories by altering inhibitory control signals (Khan et al., 2024). Specifically, in response to stimulation, beta desynchronization in fronto-parietal networks during retrieval practice was associated with stronger suppression of competitors, suggesting dynamic communication changes as inhibitory processes unfold.

Following this logic, GON-tDCS may enhance memory strengthening without substantially influencing the top-down inhibitory mechanisms required for adaptive forgetting. Indeed, prior studies by our lab have demonstrated how GON-tDCS increases activity in hippocampal regions and specifically theta-gamma coupling in medial temporal cortical regions (Luckey, McLeod, et al., 2023; Vanneste et al., 2020), which is widely acknowledged as a core mechanism for memory processing enabling the encoding, retrieval and organisation of information in time (Colgin, 2015; Jensen & Colgin, 2007; Köster et al., 2014). However, future research combining GON-tDCS with neuroimaging will be required to confirm whether this mechanism contributes to the present results.

Interestingly, contemporary perspectives suggest that predictive coding serves as a core computational model for memory updating and retrieval, where the brain constantly generates

hierarchical predictions and uses prediction error to determine whether a memory should be updated or suppressed (Bayer et al., 2025; de Oliveira Alvares & Do-Monte, 2021; Sinclair & Barense, 2019; Vaverková et al., 2020). According to the predictive coding viewpoint, the brain constantly forms predictions about memory content based on prior experience and uses prediction errors (mismatches between expected and actual inputs) to decide whether or not to destabilise existing memories for reconsolidation or suppress competing memories (Sinclair & Barense, 2019). Theta-gamma coupling in hippocampal–cortical networks has been proposed as a mechanism supporting this updating process (Köster, 2024; Köster & Gruber, 2022), while neuromodulators from the locus coeruleus such as noradrenaline and dopamine signal the salience of prediction errors (Groves et al., 2025).

In parallel, GON-tDCS has previously been associated with increased hippocampal activity and enhanced theta-gamma coupling (Luckey, McLeod, et al., 2023; Vanneste et al., 2020), raising the possibility that stimulation amplified neural dynamics supporting prediction-error-driven memory updating. In contrast, retrieval-induced forgetting is more closely linked to beta-band activity in prefrontal control networks associated with inhibitory suppression of competing traces (Khan et al., 2024). The present dissociation between enhanced reconsolidation and unchanged retrieval-induced forgetting is therefore consistent with the notion that GON-tDCS primarily influenced prediction-error–driven updating mechanisms rather than inhibitory control processes, although this remains to be directly tested.

When interpreting the current findings, it is important to consider the limitations that exist within the research. Although some of the significant findings here involve large effect sizes, others range from small to moderate effect sizes. Thus, while these findings provide initial support for how peripheral nerve stimulation can support reconsolidation processes, additional research should validate these claims. In line with this, in addition to the analyses included in the supplementary materials, to further verify the existence of the reconsolidation effect (and to rule out general neurostimulation effects as an alternative explanation of the results in the present study), future research could also include a no-retrieval/ stimulation-only control group for comparison, whereby no learning occurs in Session 2, and only GON-tDCS is applied. Additionally, the study's sample consisted of young healthy individuals, as such the generalisability of the findings need to be confirmed with future research. This is especially the case in order to investigate the potential translational applicability of these results.

For example, given that reconsolidation processes involving retrieval practice or retrieval-induced forgetting are implicated in conditions such as schizophrenia or preclinical stages of Alzheimer's disease (Ebert & Anderson, 2009; Hanseeuw et al., 2012; Jantzi et al., 2019), the ability to modulate these processes may have clinical applications, but next steps should firstly include additional validation of these neurostimulation results. Additionally, reconsolidation-based interventions have been widely studied in conditioned fear and cue-reactivity models relevant to PTSD (Astill Wright et al., 2021; Noël, 2023), and behavioural reconsolidation modification procedures are being investigated for reducing cue-induced craving in addiction models or substance use disorders (B.

Chen et al., 2025; Yue et al., 2025). However, less is known about whether declarative memory components of these disorders can be similarly updated (Kim et al., 2021). The present findings may therefore be particularly relevant for understanding how stimulation could influence reconsolidation of hippocampal-dependent associative memories, such as autobiographical or contextual elements linked to traumatic or substance-related experiences. Thus, investigating these questions will not only help with our mechanistic understanding of peripheral nerve stimulation's impact on memory processes, but also may outline future therapeutic avenues worth investigating.

2.4.1 Conclusion

This chapter provides novel evidence through an experimental investigation of reconsolidation, of GON-tDCS' delineated effects on memory and active forgetting processes within the memory control system. Essentially, GON-tDCS had no impact on inhibitory control processes that suppress competing memory traces. However, it appeared to enhance reconsolidation through hippocampal-memory stabilisation processes. These findings further demonstrate that this stimulation approach supports consolidation, but not acquisition or forgetting processes. Beyond advancing mechanistic understanding, this preliminary work suggests the potential translational relevance of peripheral nerve stimulation for disorders marked by memory dysfunction such as Alzheimer's, as well as PTSD or addiction-related disorders.

Indeed, with respect to PTSD, and in parallel to reconsolidation, emotional memories are another instance where memory control systems come into play, and where consolidation or forgetting processes may impact memory persistence. Specifically, fear learning and extinction processes can involve both stabilisation and destabilisation processes, which can impact clinical outcomes in conditions such as PTSD, anxiety or addiction-related disorders. Moreover, extinction processes also involve the learning of competing memories. Given that GON-tDCS did not impact active forgetting processes in this chapter, one might expect that it would not be able to support the forgetting of emotional or traumatic memories. However, it has also been argued that appropriate integration and consolidation of information is essential for the processing of fear memories, and may explain sustained fear responses in clinical conditions such as anxiety or PTSD (Dalglish, 2004; Foa et al., 2006; Foa & Kozak, 1986). In light of this, GON-tDCS may in fact attenuate the persistence of emotional memories through its ability to upregulate hippocampal-stabilisation processes.

Thus, in the subsequent chapter, I sought to investigate whether GON-tDCS could modulate the persistence of emotional memories. Whereas the last chapter focused on the declarative aspect of memory, this experiment sought to investigate GON-tDCS' impact on implicit fear indices during conditioning. Moreover, it measured pupil dilation as a proxy of LC-NA activity to confirm its neuromodulatory mechanism.

CHAPTER THREE: GON-TDCS ATTENUATES AVERSIVE MEMORIES AND MODULATES NORADRENALINE³

3.1 Introduction

Learning to predict danger, while balancing the inhibition of previous threat responses are fundamental processes that underpin adaptive behaviour. Associative fear conditioning and extinction learning provide central experimental models for studying how defensive responses are acquired, modified, and suppressed, as well as for developing interventions for anxiety and trauma-related disorders (Milad et al., 2014; Szeska et al., 2022). Extinction is not simply forgetting; similar to fear learning, it is an active process that depends on plasticity in a distributed circuit including the amygdala, hippocampus, and ventromedial prefrontal cortex (Battaglia et al., 2020; Krabbe et al., 2018). Through the extinction process, a novel safety memory is formed that competes with, rather than erases, the original fear memory. A key limitation of traditional extinction-based treatments (such as exposure therapy), is that this safety memory often remains fragile and context-dependent, rendering it vulnerable to relapse phenomena such as spontaneous recovery, reinstatement and renewal (the so-called ‘return of fear’) (Dunsmoor et al., 2015; Vervliet et al., 2013). Consequently, identifying strategies that enhance the durability of extinction and reduce relapse risk remains a critical objective of clinical neuroscience.

In parallel, therapeutic approaches that seek to modify the original traumatic memory trace, rather than solely promoting competing safety learning, have gained increasing attention. Following exposure to a traumatic event, an individual may develop PTSD, a condition characterised by persistent and intrusive recollections, hyperarousal and avoidance of trauma-related cues (American Psychiatric Association, 2013; Iyadurai et al., 2019). Contemporary models propose that traumatic memories in PTSD are inadequately integrated within broader memory networks and are instead stored in dysregulated, emotionally-charged form, contributing to their pathological persistence (Chamberlin, 2019). From this perspective, interventions that facilitate adaptive reprocessing of traumatic memories and attenuate their emotional salience may offer advantages over approaches that rely exclusively on forming new safety associations. Eye Movement Desensitisation and Reprocessing (EMDR) therapy for instance, has demonstrated efficacy in alleviating PTSD symptoms by enabling controlled re-experiencing of traumatic material in the absence of overwhelming fear responses (Arulchelvan & Vanneste, 2025a; Bisson et al., 2013; Chamberlin, 2019). These developments have fuelled growing interest in strategies that alter or update fear memory representations rather than merely suppressing their expression (Dunsmoor et al., 2015).

³ This chapter incorporates material from the following article which is under review for the journal *Brain Stimulation*:

Arulchelvan, E., Byczynski, G., Welch, C., & Vanneste, S. (2026). *Attenuating Fear Responses to Aversive Stimuli and Modulating Noradrenaline with Greater Occipital Nerve Stimulation.*

The author of this thesis is the first author of this publication.

A promising avenue for such modulation lies in targeting neuromodulatory systems that govern emotional memory encoding and consolidation (Dunsmoor et al., 2015). In particular, noradrenergic (NA) activity arising from the LC, exerts a powerful influence over attentional allocation, arousal, synaptic plasticity and the strength of emotionally salient memories (Cahill & McGaugh, 1998; Huang & Clewett, 2024). The LC-NA system interacts with amygdala-cortical circuits to bias whether conditioned fear responses are strengthened, generalised, or suppressed, and it plays a critical role in gating plasticity during extinction and subsequent retrieval (Clewett et al., 2018; Giustino & Maren, 2018; Huang & Clewett, 2024; Krabbe et al., 2018; Szeska et al., 2020). Modulating noradrenergic tone at behaviourally relevant time points may therefore alter the trajectory of fear memory consolidation and the retention of extinction learning. However, despite theoretical promise, pharmacological approaches targeting this system have yielded inconsistent results and are often limited by side effects (Dunsmoor et al., 2015).

In contrast, non-invasive peripheral nerve stimulation has emerged as a viable method for modulating central neurotransmitter systems without the risks associated with intracranial stimulation or systemic pharmacotherapy. Both transcutaneous vagus nerve stimulation and trigeminal nerve stimulation can engage brainstem nuclei and downstream neurotransmitter projections implicated in emotional learning and memory (Calderon-Williams et al., 2024; L. Chen et al., 2023; Alireza Majdi et al., 2025; Seminck et al., 2024; Szeska et al., 2025). In rodent models, vagus nerve stimulation applied at the time of extinction can reduce fear and anxiety symptoms, improve generalisation of extinction, and alleviate PTSD-like symptoms (Noble et al., 2017; Noble et al., 2019; Souza et al., 2022). Human studies have demonstrated more heterogeneous effects, with outcomes appearing sensitive to stimulation timing, parameters, and the specific stage of learning being targeted (Burger et al., 2018; Burger et al., 2017; D'Agostini et al., 2025; Szeska et al., 2020; Zhang et al., 2025).

Similarly, as mentioned in the preceding chapters, GON-tDCS and GON-tACS can influence attention, associative memory encoding, and consolidation in humans, with evidence suggesting that these effects are mediated through engagement of LC-NA pathways and subsequent modulation of hippocampal and cortical plasticity (Arulchelvan & Vanneste, 2025b; Luckey, Adcock, et al., 2023; Luckey, McLeod, et al., 2023; Vanneste et al., 2020). These findings and the results of chapter 2, position GON-tDCS as a novel and mechanistically plausible tool for influencing emotional memory processes, including those underlying fear acquisition and persistence.

Complementing these neuromodulatory theories, psychophysiological measures offer sensitive indices of conditioned responding and extinction dynamics. Skin conductance response (SCR) is a well-established marker of sympathetic arousal to threat cues; heart rate (HR) dynamics index autonomic balance and defensive orienting; and pupillometry has emerged as a temporally precise proxy for LC-NA activity in humans (Geršak, 2020; Murphy et al., 2014; Viglione et al., 2023). Additionally, pupil dilation during conditioned stimulus presentation correlates with central noradrenergic responsiveness and with electrophysiological markers of attention and memory

encoding (Dahl et al., 2020; Murphy et al., 2014; Reimer et al., 2016), and has been used to index the neuromodulatory consequences of peripheral stimulation (Seminck et al., 2024; Vanneste et al., 2020). Together, these measures provide complementary windows into the autonomic and neuromodulatory changes associated with fear acquisition, extinction and retention.

Despite converging theoretical and empirical support for the role of LC-NA modulation in fear learning, the application of occipital nerve stimulation within the context of fear learning has not yet been studied. Moreover, it is argued that appropriate integration of information is essential for the processing of fear memories, and may explain sustained fear responses in clinical conditions such as anxiety or PTSD (Daggleish, 2004; Foa et al., 2006; Foa & Kozak, 1986). In other words, incomplete consolidation of emotional memories may lead to the persistence of fear responses. As such, given evidence that GON-tDCS can engage LC-relevant networks and enhance associative memory consolidation, it is plausible that GON-tDCS applied during fear acquisition could bias subsequent extinction and retention in clinically meaningful ways (potentially through consolidation mechanisms).

Accordingly, this chapter tested the hypothesis that GON-tDCS administered during fear acquisition would facilitate subsequent extinction learning and attenuate the retention of fear responses. I employed a typical aversive conditioning paradigm and examined multiple physiological indices (pupil diameter, SCR and HR) to capture both momentary arousal, autonomic regulation and putative noradrenergic engagement during conditioning and to assess how these signals relate to fear extinction and retention 24 hours later. By integrating a mechanistically informed neuromodulation approach with multimodal psychophysiological assessment, this experiment aimed to clarify whether peripheral nerve stimulation can be leveraged to modify fear memories and reduce the persistence of maladaptive fear, thereby informing potential augmentation strategies for therapeutic interventions.

3.2 Methods

3.2.1 *Participants*

Participants were screened to ensure normal or corrected-to-normal vision, no tES contraindications, no neurological or psychiatric diagnoses, no current use of neuropsychiatric medications or prescription stimulants, no chronic use of illicit drugs and no ophidiophobia (fear of snakes) due to the nature of the task stimuli.

Demographic items (age, sex, gender, handedness etc) were collected for each participant. Validated measures including the BDI-II and BAI, MMSE and Snake Questionnaire (SNAQ) (Lang et al., 1970; Polák et al., 2020) were administered to each participant at the start of visit one to measure cognition, anxiety or depression levels and ophidiophobia. The BDI-II and BAI were used to exclude individuals above a moderate/severe category of depression (20+) or anxiety (16+), and the MMSE was used to exclude participants who scored < 24. Given that these factors can impact learning and memory outcomes, these measures were also recorded to exclude the possibility that any behavioural differences between the groups were due to underlying differences in anxiety, depression or cognition levels and to ensure that any between-group behavioural differences were specifically due to the effects of the stimulation. Due to the nature of the visual stimuli (photos of snakes), the SNAQ was also used to exclude participants who scored >23, as this would indicate clinical fear of snakes.

36 participants were recruited to participate in this study. However, 4 participants were excluded due to software malfunctions, and 2 participants were excluded due to exceeding a cut-off score on a control measure. Thus, 30 participants were included in the final analysis (16 males and 14 females: mean age 21.4 years, SD = 2.93 years). Participants provided written, informed consent. Participants were given course credit where relevant.

3.2.2 *Materials*

3.2.2.1 *Aversive Learning Task*

Participants completed a computerised aversive learning paradigm following typical fear conditioning task designs (Lonsdorf et al., 2017). The conditioned stimuli (CS) consisted of 4 aversive visual cues (photos of 4 snakes) taken from the Open Biological Negative Image Set (OBNIS) database (Shirai & Watanabe, 2022). The unconditioned stimulus (US) consisted of an aversive auditory sound of a human scream from the International Affective Digitized Sounds Expanded (IADS-E) database (Yang et al., 2018). Prior research has demonstrated the effectiveness of human screams as aversive anxiety-inducing stimuli (Beaurenaut et al., 2020). The task was designed using PsychoPy software and presented on a 27" screen.

On Day 1, the aversive learning task consisted of a fear acquisition phase separated into two blocks. The task consisted of 4 conditioned stimuli (i.e. aversive visual cues of photos of snakes) and an unconditioned stimulus (i.e. an aversive sound of a human scream). The unconditioned stimulus

is abbreviated to US throughout this paper and is conditioned stimuli are referred to as CS^{+1} , CS^{-1} , CS^{+2} and CS^{-2} , where the $^{+}$ or $^{-}$ symbol denote whether they predict the presence or absence of the US, and the ^{1} or ^{2} reflect whether they were presented in Block 1 or Block 2 of the task on Day 1.

For example, in Block 1, two snake stimuli (CS^{+1} , CS^{-1}) were presented for 6s each, separated by a jittered (10-12s) inter-stimulus interval of a fixation cross. The CS^{+1} and CS^{-1} were each presented 12 times (i.e. 24 trials) in pseudorandomised order. The unconditioned stimulus (US: scream) was presented on 75% of the CS^{+1} trials, with the presentation of this auditory US coinciding with the final 3 seconds of the visual CS^{+1} cue. As per fear conditioning guidelines (Lonsdorf et al., 2017), the pseudorandomised presentation of these CS stimuli began with the CS^{-} , and ended on a reinforced CS^{+} not an unreinforced CS^{+} , with randomised presentation of CS^{+1} and CS^{-1} in between (with the exception that no more than 2 consecutive trials of the same stimulus would occur). Block 2 followed the same format but with two different snake stimuli (CS^{+2} , CS^{-2}). During this block, half of the participants were also randomly assigned to receive the active or sham stimulation. As such, each block lasted approximately 6.75 mins.

Day 2 consisted of the fear extinction phase, return of fear (RoF) phase and fear retention test phase. In the extinction phase, the four snake stimuli (CS^{+1} , CS^{-1} , CS^{+2} , CS^{-2}) were presented for 6s each in pseudorandom order (where the same stimulus was presented no more than 2 consecutive times), however the US (scream) was not presented for either of either of the CS^{+} stimuli, to extinct the association between snake imagery and scream. The interstimulus interval jittered between 10-12s. Each snake was presented 6 times This was repeated 6 times (i.e. 24 trials). In the RoF phase, the US (scream) was presented alongside a neutral visual cue (circle) for 3s, with an interstimulus interval of 500ms with the goal to introduce the fear response with the US. This was repeated 5 times (i.e. 5 trials). In the retention phase, the four snake stimuli (CS^{+1} , CS^{-1} , CS^{+2} , CS^{-2}) were presented for 6s each in pseudorandom order, with no US (scream) presented with the CS^{+} stimuli. The interstimulus interval jittered between 10-12s. This was repeated 3 times (i.e. 12 trials). The trial design is schematically represented in Figure 3.1.

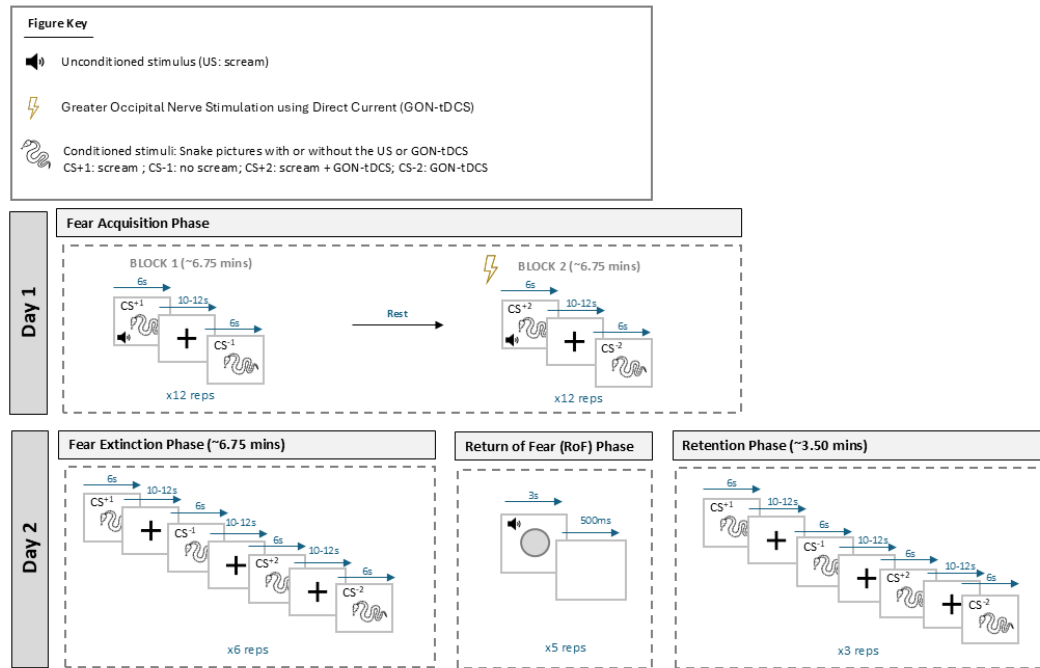


Figure 3.1 | Trial Design. This figure presents a summary of the trial design across the two consecutive days, and the various blocks of the fear paradigm.

3.2.2.2 GON-tDCS

GON-tDCS was applied using the same device and electrode placement as in chapter 2. On Day 1, for Block 2 of the aversive learning paradigm, participants were randomly assigned to one of two groups: active GON-tDCS or sham GON-tDCS. For active GON-tDCS, stimulation ramped up for 30 seconds and a constant current of 1.5 mA intensity was applied for the duration of the block (i.e. 415 seconds), after which the stimulation was ramped down for 5 seconds. For sham GON-tDCS, placement of the electrodes was identical to active GON-tDCS. At the start of this block, stimulation ramped up for 30 seconds, was applied for 15 seconds (to mimic the sensation of the active group), and then immediately ramped down for 5 seconds. No stimulation was applied during Block 1 on Day 1 for either group, and no stimulation was applied during Day 2 for either group. See Figure 3.2 for the stimulus protocol.

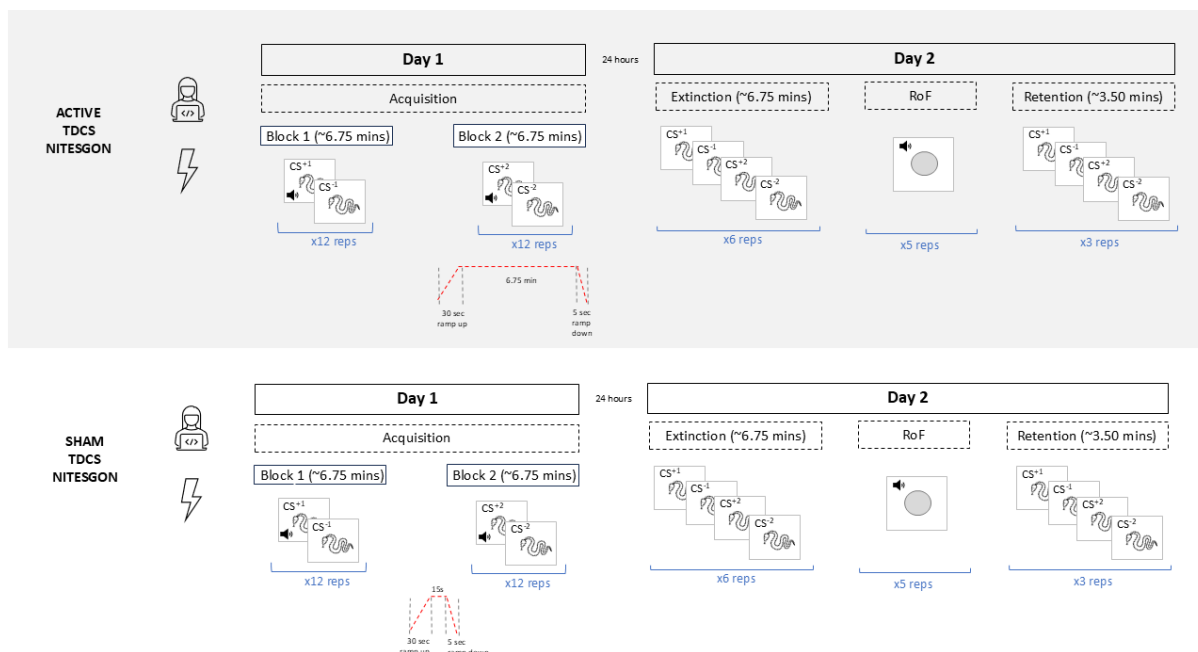


Figure 3.2 | Fear Paradigm and Stimulus Protocol. This figure graphically represents the task structure across 24 hours, including the stimulation protocol for the active and sham groups.

3.2.2.3 Neurophysiological Measures

Participants were instructed to avoid any caffeine and nicotine in the hour before their sessions, and to avoid any alcohol the night before the sessions. HR, SCR, and pupil dilation were simultaneously recorded during the task. HR and SCR were recorded using BioSemi ActiveTwo system with a sampling rate of 4096 Hz. An EyeLink 1000 Plus eye tracker (SR Research, Canada) recorded pupil data from the right eye with a sampling rate of 1,000 Hz. Heart rate data were recorded using conductance gel and electrodes placed 2cm below the left and right clavicle with reference electrodes placed on the lower left and right abdomen/ribcage. SCR was measured using BioSemi ActiveTwo EDA/GSR Sensor Electrode Set (two high-quality Ag/AgCl sintered electrodes with low offset voltage and conductance gel) placed on the index and middle fingers of the left hand. Data from days 1 and 2 were processed for each participant individually.

3.2.2.4 Data Preprocessing

Electrocardiogram (ECG) signals were cleaned using NeuroKit2 (Makowski et al., 2021) which included filtering and artifact correction, and R-peaks were detected to compute HR. HR was calculated for the full event epoch. HR was computed as the mean beats per minute per trial. SCR signals were similarly pre-processed with NeuroKit2, including smoothing and phasic-tonic decomposition (Makowski et al., 2021). For each trial, the maximum phasic response (i.e. SCR peak) was extracted. Epochs shorter than 20 samples or with constant signals were excluded.

Pupillometry data were pre-processed by screening data for blinks and extreme values. Blinks were identified as samples where pupil size measurements ≤ 0 or z-scores < -3 relative to a rolling mean and standard deviation. Detected artifacts were expanded ± 20 samples and replaced with linear interpolation. The resulting pupil traces were then smoothed using a Savitsky-Golay filter (window length = 51 samples, polynomial order = 3). For each trial, epochs were extracted from stimulus onset to 6s post-onset and z-score normalized. Pupil size data were used to compute peak pupil dilation and latency to peak dilation. Trials with any missing data (e.g., loss of eye detection, participant movement out of camera view) were excluded.

All processing and analyses were automated via custom Python scripts, and results were aggregated for subsequent statistical analysis at the trial level.

3.2.2.5 *tES Exit Questionnaire*

To assess possible side effects of GON-tDCS, participants completed the tES Exit Questionnaire (i.e. the same questionnaire administered in chapter 2). To determine if the stimulation was well-blinded, an item asked participants to guess, based on their experience, which stimulation they believed they had received (active or non-active).

3.2.3 **Procedure**

This study was designed as a double-blind, placebo-controlled, randomized parallel group study. It was granted ethical approval by the Research Ethics Committee of the School of Psychology at Trinity College Dublin (Approval number: SPREC052022-08) and conducted in accordance with the ethical guidelines of the Declaration of Helsinki (1964).

Participation involved two visits on two consecutive days to Trinity College Dublin. The two sessions were spaced 24 hours apart. In Session 1 participants completed control assessments including the MMSE, BAI, BDI-II, and the validated Snake Questionnaire (SNAQ) (Lang et al., 1970; Polák et al., 2020) to assess ophidiophobia. Following this, ECG electrodes, galvanic skin response electrodes and stimulation electrodes were placed. Participants were given 7 minutes prior to the task to allow for adaptation and stabilization of the heartrate and skin response, and to calibrate the eye tracker.

For the task, participants were instructed to attend to the screen and listen to the auditory sounds presented through the headphones. They were informed that no stimulation would be applied for block 1 of the task, but that after block 1 the researcher would re-enter the room, assess the participant comfort, and begin stimulation (active/sham) for block 2. A third researcher administered all stimulation, to maintain double blinding of the primary researcher who carried out the subsequent analysis. At the end of this session, the participant completed a tES Exit Questionnaire (Brunoni et al., 2011).

Participants returned the following day, where the same neurophysiological measures were recorded, and they completed Day 2 of the aversive learning paradigm.

3.2.4 *Statistical Analyses*

All statistical tests were carried out using SPSS (version 28), and significance was set at $p < 0.05$.

3.2.4.1 *Fear Conditioning Paradigm and Neurophysiological Measures*

To determine the effect of stimulation on neurophysiological measures in a fear conditioning paradigm, four generalised linear models (GLMs) were conducted with group and block as predictors, and HR, SCR, peak pupil dilation and latency to peak pupil dilation as the respective response variables. For each test, if the interaction effect was significant, post-hoc analyses were conducted using a Bonferroni correction.

3.2.4.2 *Control Measures*

One-way ANOVAs were conducted to examine whether there was a difference between the stimulation groups (active vs sham) for age (years), and MMSE, BDI, BAI and SNAQ scores. χ^2 tests were calculated to compare if there was a difference between the active and sham group for sex, gender and handedness.

3.2.4.3 *tES Exit Questionnaire*

To analyse whether participants were blinded to their stimulation group, χ^2 tests compared the stimulation participants received (active vs sham) to what they thought they received (active vs non-active). A MANOVA was conducted to compare whether there was any difference between groups for experiencing common stimulation side-effects.

3.3 Results

3.3.1 Fear Conditioning

Table 3.1a and 3.1b summarise the results for the fear responses (i.e. mean and standard error of each of the neurophysiological measures) for the active and sham groups at each of the fear conditioning blocks, including post-hoc Bonferroni corrected pairwise comparisons.

Table 3.1a Summary of Post-Hoc Analyses from GLMs for Heart Rate and SCR

	Heart Rate (BPM)			SCR	
	Active	Sham	p_{bonf}	Active	Sham
Day 1					
Block 1	75.25 (.83)	75.58 (.81)	<i>n.s.</i>	394.57 (51.82)	507.46 (48.39)
Block 2	73.44 (.84)	75.61 (.81)	<i>n.s.</i>	461.38 (50.46)	399.50 (48.39)
Day 2					
Extinction	70.94 (.76)	79.52 (.91)	***	266.56 (45.27)	370.10 (54.59)
Return of Fear	68.83 (1.69)	75.36 (2.00)	<i>n.s.</i>	170.12 (101.75)	337.10 (125.45)
Retention	73.57 (1.07)	79.38 (1.29)	*	330.69 (64.02)	486.97 (77.21)

Notes. This table contains average fear response (and standard error) of each of the neurophysiological measures for the active and sham groups at each of the fear conditioning blocks. Post-hoc comparisons were conducted using Bonferroni correction when interaction effects were significant (i.e. for heart rate, but not for SCR data). Abbreviations include Generalized Linear Models (GLMs), beats per minute (BPM), and skin conductance response (SCR). *n.s.* = not significant. * $p < .05$; *** $p < .001$.

Table 3.1b Summary of Post-Hoc Analyses from GLMs for Pupil Peak Dilation and Latency to Peak

	Pupil Peak Dilation			Latency to Peak Dilation	
	Active	Sham	p_{bonf}	Active	Sham
Day 1					
Block 1	0.00 (.11)	0.00 (.12)	<i>n.s.</i>	2.89 (.11)	2.79 (.11)

Block 2	-0.15 (.11)	0.08 (.12)	<i>n.s.</i>	2.83 (.11)	2.74 (.11)
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Day 2

Extinction	-0.43 (.11)	0.26 (.13)	**	2.39 (.11)	2.73 (.12)
Return of Fear	-0.24 (.16)	0.21 (.18)	<i>n.s.</i>	2.88 (.23)	2.84 (.27)
Retention	-0.36 (.11)	0.22 (.13)	*	2.56 (.15)	2.99 (.17)

Notes. This table contains average fear response (and standard error) of each of the neurophysiological measures for the active and sham groups at each of the fear conditioning blocks. Post-hoc comparisons were conducted using Bonferroni correction when interaction effects were significant (i.e. for peak pupil dilation data, but not for latency to peak dilation data). Abbreviations include Generalized Linear Models (GLMs). *n.s.* = not significant. * $p < .05$; ** $p < .01$.

3.3.1.1 Heart Rate

A GLM with block and group as predictors revealed a significant block $\times$ group interaction ($\chi^2(4) = 29.39, p < .001$; Figure 3.3a). The main effect of group was also significant ($\chi^2(1) = 39.79, p < .001$), whereas the main effect of block did not reach significance ($\chi^2(4) = 8.26, p = .06$). Post-hoc Bonferroni comparisons indicated that the active group exhibited significantly lower heart rates than the sham group during the extinction block (Active: $M = 70.94, SE = .76$, Sham: $M = 79.52, SE = .91$; $p_{bonf} < .001$; Figure 3.3b) and retention block (Active: $M = 73.57, SE = 1.07$; Sham: $M = 79.38, SE = 1.29, p_{bonf} = .02$; Figure 3.3c).

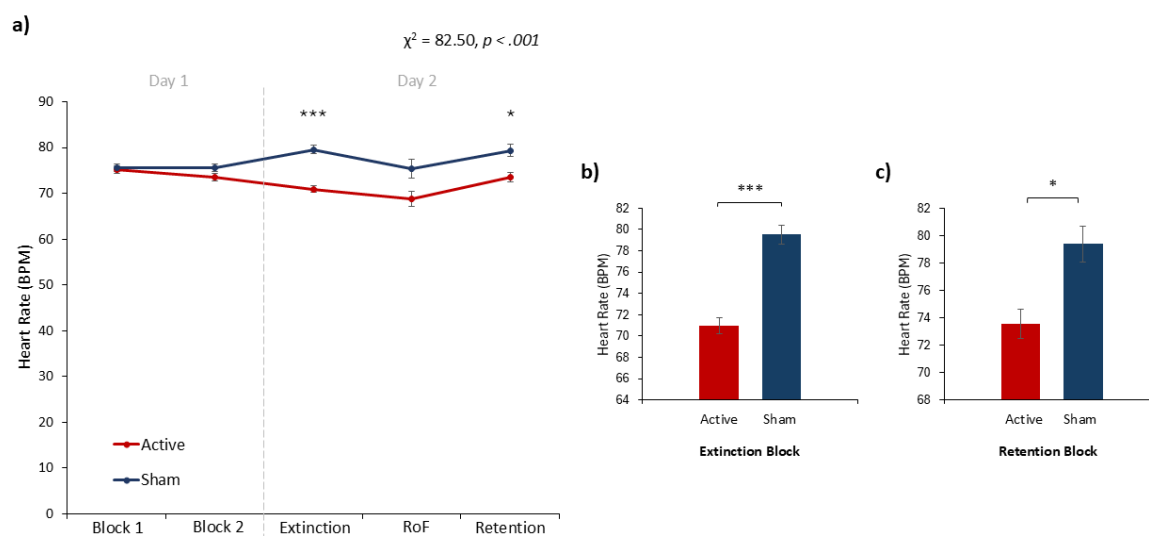


Figure 3.3 | Heart Rate Responses (BPM). A When looking at heart rate data i.e. beats per minute (BPM), there was a significant block $\times$ group interaction. The main effect of group was also significant, whereas the main effect of block did not reach significance. Post-hoc Bonferroni comparisons indicated that the active group had significantly lower heart rates than the sham group during the **B** extinction block and **C** retention block.

3.3.1.2 Peak Pupil Dilation and Latency to Peak Dilation

Baseline differences were found between groups for the pupil dilation data during block 1 on Day 1. As such, the GLM was conducted using corrected peak pupil data (see supplementary methods). When looking at peak pupil dilation, the GLM with block and group as predictors revealed a significant block $\times$ group interaction ($\chi^2(4) = 10.92, p = .027$; Figure 3.4a). The main effect of group was also significant ($\chi^2(1) = 22.19, p < .001$), whereas the main effect of block did not reach significance ($\chi^2(4) = .65, p = .96$). Post-hoc Bonferroni comparisons indicated that the active group had significantly smaller peak pupil dilations than the sham group during the extinction block (Active: $M = -4.29$, $SE = 1.12$, Sham: $M = 2.63$, $SE = 1.30$; $p_{\text{bonf}} = .002$; Figure 3.4b) and retention block (Active: $M = -3.57$, $SE = 1.12$; Sham: $M = 2.18$, $SE = 1.30$, $p_{\text{bonf}} = .035$; Figure 3.4c).

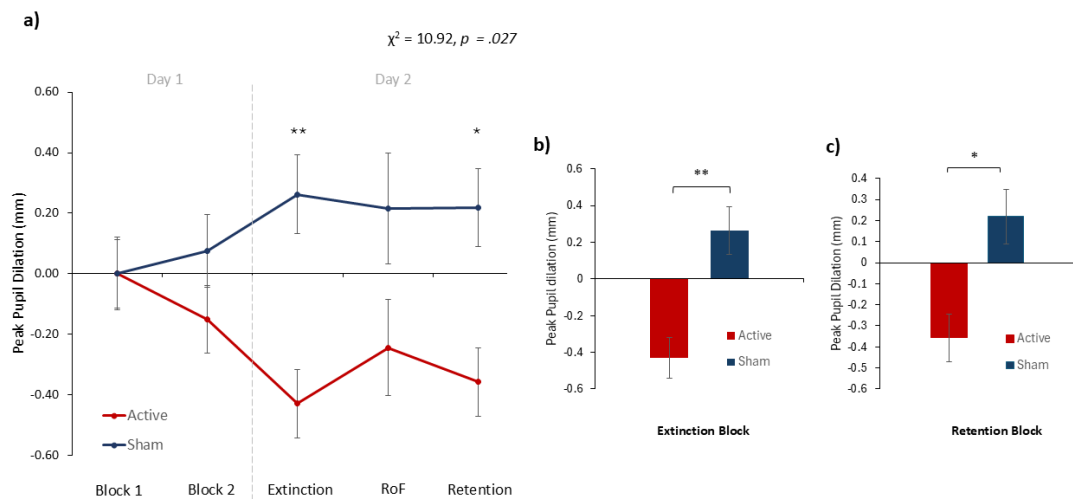


Figure 3.4 | Peak Pupil dilation Responses (mm). A When looking at peak pupil dilation between the groups across the blocks, there was a significant block $\times$ group interaction. The main effect of group was also significant, whereas the main effect of block did not reach significance. Post-hoc Bonferroni comparisons indicated that the active group had significantly smaller peak pupil dilations than the sham group during the **B** extinction block and **C** retention block.

When considering latency to peak pupil dilation, a GLM with block and group as predictors revealed no significant effect of block ($\chi^2(4) = 7.49, p = .11$), group ($\chi^2(1) = 1.17, p = .280$) or interaction effect ($\chi^2(4) = 7.33, p = .12$) (Figure 3.5a).

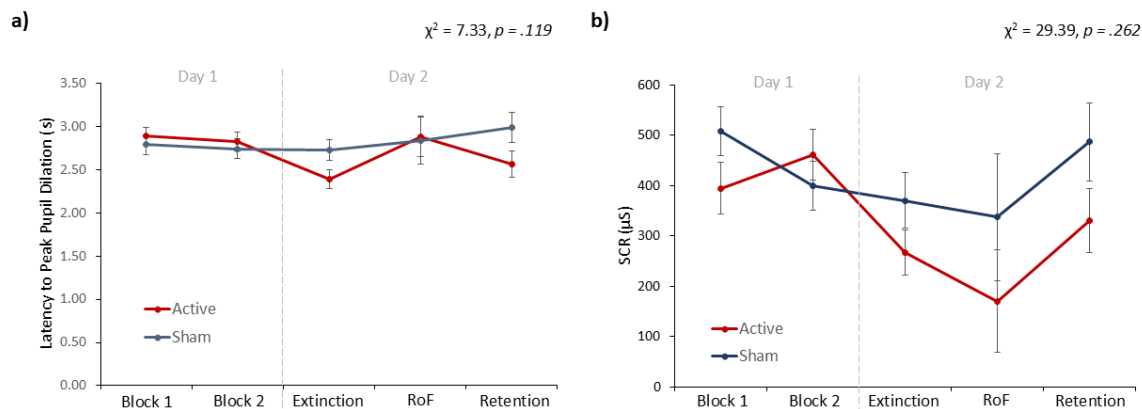


Figure 3.5 | Latency to Peak Pupil Dilation (s) and Skin Conductance Responses (μS). **A** There were no significant differences in latency to peak pupil dilation between groups, no effect of block and no interaction effect. **B** The active group had significantly lower skin conductance responses than the sham group overall (with no effect of block, and no interaction effect).

3.3.1.3 Skin Conductance

A GLM with block and group as predictors revealed a significant effect of block ($\chi^2(4) = 11.32, p = 0.023$), and group ($\chi^2(1) = 4.47, p = 0.034$) but no significant interaction effect ($\chi^2(4) = 5.25, p = 0.26$; Figure 3.5b). Specifically, the active group ($M = 324.66, SE = 29.48$) had significantly lower SCRs than the sham group ($M = 420.29, SE = 34.27$). See Table 3.1a for more details.

3.3.2 Control Measures

Between the active and sham GON-tDCS groups, there was no significant difference in sex ($\chi^2(1, N = 30) = .15, p = .70$), gender ($\chi^2(1, N = 30) = .15, p = .70$), age ($F(1, 28) = .04, p = .85$), handedness ($\chi^2(1, N = 30) = .02, p = .89$), or scores on the MMSE ($F(1, 28) = 0.36, p = .552$), BDI ($F(1, 28) = .51, p = .48$), BAI ($F(1, 28) = 3.41, p = .075$) or SNAQ ($F(1, 28) = 0.33, p = .57$) measures. These results are summarised in Table 3.2.

Table 3.2. Average control measures of stimulation groups.

Active	Sham

<i>N</i>			χ^2	<i>p</i>
	16	14		
Sex	Male (N = 8)	Male (N = 8)	.15	.696
	Female (N = 8)	Female (N = 6)		
Gender	Man (N = 8)	Man (N = 8)	.15	.696
	Woman (N = 8)	Woman (N = 6)		
Handedness	LH (N = 2)	LH (N = 2)	.02	.886
	RH (N = 14)	RH (N = 12)		
	M (SD)	M (SD)	F	<i>p</i>
Age	21.5 (3.14)	21.29 (2.79)	.04	.846
MMSE	29.25 (0.78)	29.43 (.85)	.36	.552
BDI	4.38 (4.92)	5.86 (6.38)	.51	.479
BAI	2.25 (2.18)	4.65 (3.93)	3.41	.075
SNAQ	6.69 (2.12)	7.43 (4.62)	.33	.569

*Abbreviations include: Left-handed (LH), Right-handed (RH), Mini Mental State Exam (MMSE), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Snake Anxiety Questionnaire (SNAQ). * $p < .05$*

3.3.3 *tES Exit Questionnaire*

A MANOVA revealed a non-significant main effect of stimulation group (active vs sham) for the various tES side effects (Wilks' $\lambda = .042$, $F(5,1) = 4.60$, $p = .34$). In particular, there were no measurable differences in neck pain, skin redness, acute mood changes or other symptoms, and no significant differences in the remaining symptoms (of headache, scalp pain, tingling, itching, burning, sleepiness or trouble concentrating). All stimulation sessions were well tolerated, and no major stimulation related complaints were reported. There was no significant difference between which groups participants thought they were in (active vs non-active) compared to their actual groups (active vs sham) ($\chi^2(1, N = 30) = 3.27$, $p = .070$). In the active group: 31.25% of participants believed they received the non-active stimulation, while 68.75% believed they received the active stimulation. In the sham group: 35.71% of participants thought they received the active stimulation, and 64.29%

believed they received the sham stimulation. **Although the analysis did not provide evidence for a statistically significant difference between groups, the observed numerical differences and sample size mean that the possibility of a true group difference cannot be excluded. As such, these findings should be interpreted with caution.** See Figure 3.6a and 3.6b for stimulation sensations and blinding between groups.

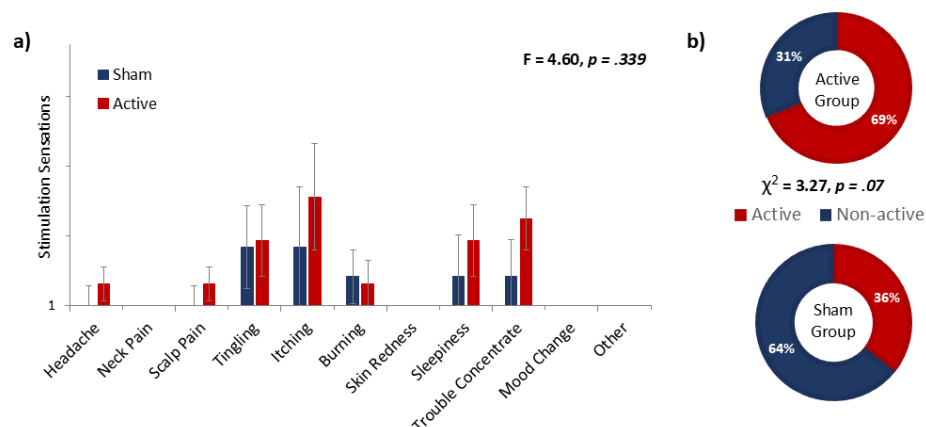


Figure 3.6 | Stimulation Sensations and Blinding. **A** There were no measurable differences between active and sham stimulation for neck pain, skin redness, acute mood changes or other symptoms, and no significant differences in the remaining symptoms (of headache, scalp pain, tingling, itching, burning, sleepiness or trouble concentrating). **B** There was no significant difference between which groups participants thought they were in (active vs non-active) compared to their actual groups (active vs sham).

3.4 Discussion

These findings challenge the notion that neurostimulation administered during fear acquisition inevitably strengthens fear memories. Instead, I provide novel evidence that targeted stimulation at the time of encoding significantly attenuates subsequent fear expression across autonomic indices (SCR and HR), and pupil dilation (suggesting a LC-NA mechanism). Moreover, I demonstrate that stimulation applied during this encoding window leads to sustained retention of attenuated fear responses 24 hours later. These results provide initial evidence that the acquisition phase is not merely a passive encoding window, but a critical intervention point at which neural plasticity can be biased towards safety or weakened threat encoding. This reveals a previously underexplored opportunity for early intervention strategies that prevent pathological fear formation rather than solely modifying it after consolidation.

Participants completed a two-day fear conditioning paradigm. On Day 1, they underwent two blocks of fear acquisition, where two aversive visual cues (snakes) were presented in each block, with one of them paired with an aversive auditory stimulus (human scream). Active or sham GON-tDCS was applied during the second block. Physiological measures (pupil diameter, SCR and HR) were recorded to capture both momentary arousal, autonomic regulation and putative noradrenergic engagement during conditioning. Day 2 comprised of a Fear Extinction phase, Return of Fear (RoF) phase, and Fear Retention phase. The same physiological measures were recorded.

HR analyses revealed no baseline differences between active and sham groups during block 1 or block 2 on Day 1, indicating comparable initial sympathetic arousal and no immediate stimulation effects. However, 24 hours later, the active group showed significantly lower HR during extinction and retention. This suggests that stimulation applied during the fear encoding window, facilitated later extinction learning and yielded more persistent attenuation of fear responding after fear reinstatement. In contrast, SCR showed no interaction between stimulation group and conditioning block, although the active group exhibited overall lower SCR across phases. Given similar baseline SCR, this may reflect a general anxiolytic effect of GON-tDCS not tied to specific stimuli or learning phases.

In addition to refining our understanding of when fear memories are malleable, this study adds critical insight into our mechanistic understanding of how noradrenergic activity contributes to the formation and persistence of fear memories. Pupil dilation, a known proxy for noradrenergic activity (Geršak, 2020; Murphy et al., 2014; Viglione et al., 2023), was modulated by GON-tDCS in this study. Specifically, the active group had significantly smaller peak pupil dilations than the sham group during extinction and retention phases. These results parallel the HR findings, and suggest that GON-tDCS modulates LC-NA activity in conjunction with fear memory processing. This mechanism may be through reducing arousal and/or attention.

Although arousal and attention are supported by shared LC-NA circuitry, they may also represent distinct processes. Namely, pupil amplitude is closely tied to autonomic arousal and sympathetic activation, correlating with HR and SCR responses to emotional stimuli (Bradley et al., 2008; Chang

et al., 2025; Murphy et al., 2011). Conversely, latency to peak pupil dilation may more closely reflect top-down attentional engagement and cognitive control (Kang et al., 2014; Oliva & Anikin, 2018). The presence of group differences in peak dilation, but not latency, might suggest that GON-tDCS preferentially dampens arousal-driven LC-NA activity, rather than modulating LC-NA driven attentional control mechanisms. However, because peak dilation can also index attentional processes (Alnæs et al., 2014; Cohen et al., 2015), and because LC arousal influences attention (Huang & Clewett, 2024), these interpretations are not mutually exclusive. In fact, in a prior study, I have shown that GON-tACS during a memory task can modulate LC-NA activity (as assessed through salivary α -amylase levels) and influence attention networks in the brain (Arulchelvan & Vanneste, 2025b). Additional research studies by our lab have demonstrated that GON-tDCS likewise modulates LC-NA activity (as measured through pupil diameter) (Luckey, McLeod, et al., 2023; Vanneste et al., 2020). However critically, in these studies, increased and not decreased pupil diameter was observed in the active group, which is the inverse of the results in the present study. Thus, while it is plausible that GON-tDCS effects were through arousal mechanisms, or that subtle attentional effects did occur here but were not captured by latency measures, this interpretation cannot fully account for the pupil diameter results in the present study.

Instead, an alternative and more viable interpretation is that peripheral nerve stimulation when administered during the fear encoding window reliably and durably diminishes implicit reactions to learned threat, through pre-emptively altering consolidation dynamics in line with the behavioural tagging theory (originating from the synaptic tag and capture model). According to this theory, learning events create transient synaptic tags that require subsequent capture of plasticity-related proteins (PRPs), in order for this to stabilise into a long-term memory (Frey & Morris, 1997; Moncada et al., 2015). Given that neuromodulatory release from the LC directs this process (Moncada, 2017; Takeuchi et al., 2016), applying GON-tDCS at the time of fear learning may promote widespread tag setting across multiple neural circuits, thereby increasing competition among synapses for a limited pool of PRPs. In line with the emotional tagging hypothesis (Bergado et al., 2011; Dunsmoor et al., 2022; Richter-Levin & Akirav, 2003), this ‘dilution’ could reduce the probability that amygdala fear-related synapses successfully capture PRPs, weakening long-term fear memory consolidation. Thus, GON-tDCS at fear encoding may mitigate fear persistence by shifting PRP allocation away from fear-tagged synapses towards non-fear pathways.

The behavioural tagging research suggests a critical time window spanning minutes to hours before and after the learning event where the tag and capture of these proteins can occur (Dunsmoor et al., 2022). Prior work by our lab is consistent with this theory, and demonstrated a retroactive memory effect of GON-tDCS (Luckey, McLeod, et al., 2023). These results may suggest that there is a post fear encoding window whereby application of GON-tDCS can continue to have beneficial effects on fear retention. Providing future research can clarify the potential time boundaries of this encoding window with respect to fear-related stimuli, it may open the door for translational research to investigate preventative treatments after trauma exposure or prophylactic use of peripheral nerve

stimulation in high-risk populations (e.g. emergency workers). Indeed, initial research into this looks promising as only one recent study (to the best of my knowledge) has applied transcutaneous peripheral nerve stimulation of the vagus nerve immediately after fear acquisition and found sustained reductions in fear responses (measured through SCR and neural activity) (Zhang et al., 2025). These results suggest a potential strategy for reducing pathological fear formation if intervention occurs at or immediately following traumatic exposure.

The findings of the present study may seem counterintuitive in light of previous research by our lab. Specifically, our lab has previously demonstrated that GON-tDCS enhances consolidation processes of associative memories (Luckey, McLeod, et al., 2023; Luckey et al., 2022; Vanneste et al., 2020). However, one interpretation of the current study is that this same stimulation technique appears to disrupt consolidation of fear memories. This raises an interesting question about these seemingly contradictory results. However, rather than stimulation disrupting consolidation of fear memories, perhaps its' ability to diminish fear responses actually stems from supporting consolidation and appropriate integration of fear memories.

This supposition would be in line with clinical research and theory investigating emotional processing, fear memories and PTSD. For example, in Foa & Kozak's (1986) Emotional Processing Theory, they argue that the persistence of fear is due in part to cognitive biases in information processing at various stages (including encoding). Their theory asserts that appropriate integration of information is essential for the processing of fear memories, and may explain sustained fear responses in clinical conditions such as anxiety or PTSD (Dalgleish, 2004; Foa et al., 2006; Foa & Kozak, 1986). Additional theoretical approaches elaborate further and converge on a similar argument. Specifically, these viewpoints argue that traumatic memories are fragmented in nature (likely due to extreme emotional arousal at the time of encoding) due to the central nervous system's failure to adequately synthesise sensory aspects of the traumatic memory into a cohesive schema and autobiographical memory (Dalgleish, 2004; Ehlers & Clark, 2000; Rubinstein et al., 2025; van der Kolk, 2000; van Der Kolk & Fisler, 1995). The result is that while efforts to integrate continue, this traumatic material remains stored in an active form of memory, contributing to the intrusive nature of these memories, and reexperiencing symptoms characteristic of traumatic disorders such as PTSD (Dalgleish, 2004; Horowitz, 1976).

It is therefore argued that in order for these symptoms to resolve, the traumatic information needs to be appropriately assimilated and integrated into one's long-term autobiographical memory database (Dalgleish, 2004; Ehlers & Clark, 2000). As such, it is plausible that GON-tDCS applied at the time of fear acquisition, in fact supports consolidation of fear responses, through facilitating appropriate integration of fear-inducing stimuli. Given that the current study was conducted in a healthy sample, it will be necessary for this proposition to be tested further in clinical groups to assess whether indeed this is the mechanism through which GON-tDCS led to sustained attenuated fear responses, and whether it has any translational value as a potential therapeutic avenue.

In parallel, in the present study, given GON-tDCS attenuated autonomic indices of fear, it can be said to weaken the emotional memory. However, it remains to be tested whether it impacts contingency awareness, and not just the affective aspect of the memory. Given how CS-US contingency awareness can influence fear learning and responses (Lonsdorf et al., 2017), in the present study, contingency instructions (about CS-US pairings) were not presented to participants. This means that only implicit fear responses, and not explicit responses were recorded. As such, future research should examine whether this peripheral nerve stimulation approach can also modulate explicit beliefs and expectancies, particularly given prior findings that vagus nerve stimulation during extinction modulates explicit but not implicit fear indices (Burger et al., 2017).

3.4.1 Conclusion

Summarising the above, neurostimulation during fear acquisition did not exacerbate fear learning; instead, it reliably reduced psychophysiological fear responses. This study provides novel evidence that non-invasive GON-tDCS administered during fear acquisition can attenuate LC-NA activity and diminish fear responses during extinction and retention 24 hours later. These findings suggest that the encoding phase constitutes a sensitive period during which neural plasticity can be biased away from threat representation. These results align with models of memory formation which emphasise synaptic tagging, and indicate that early neuromodulatory intervention may offer a promising preventative avenue for reducing the development of maladaptive fear memories, potentially through upregulating memory consolidation and integration dynamics. This represents a novel advancement towards the sustained attenuation of implicit autonomic responses to threat.

The persistence of emotional or traumatic memories is characteristic of clinical conditions such as PTSD. As outlined in chapter 1, PTSD is proposed to lie at one end of the forgetting continuum, with cases of ALF for example, at the other end. Although chapter 1 briefly introduced this forgetting model, it did not go into too much detail on the proposed shared neurobiological mechanisms that underlie hypoactive or hyperactive forgetting. As such, the next chapter, chapter 4, will review the literature on some of the synaptic regulation and remodelling pathways that influence engram cell accessibility. In particular, it will focus on how these relate to conditions where ALF presents as a symptom, however it will then discuss how these same mechanisms are dysregulated across the psychiatric disorders that exist along the forgetting spectrum.

CHAPTER FOUR: A DEEPER DIVE ON ALF AND THE FORGETTING CONTINUUM⁴

4.1 An alternative unifying perspective of ALF

Although ALF was first identified in cases of epilepsy (Elliott et al., 2014; García-Martínez et al., 2023; Mameniškienė et al., 2020), since then, individuals with TBI, limbic encephalitis, stroke, 22q11.2 deletion syndrome, and neurodegenerative disorders such as AD or PD have also exhibited signs of ALF (García-Martínez et al., 2023; Savage et al., 2019; van der Werf et al., 2016; Witt & Helmstaedter, 2021).

As outlined in chapter 1 of this thesis, no consensus has been found as to the exact mechanism(s) underlying ALF, and no clear cause has been identified. However, if as I posit in chapter 1, ALF does indeed stem to some degree from over-active forgetting processes, what might be the mechanism underlying these?

Based on recent and emerging perspectives which summarise research across flies, rodents and humans (Castillo Díaz et al., 2021; Dalto et al., 2025; Davis & Zhong, 2017; Noyes et al., 2021), I propose that disrupted biochemical and molecular pathways may accelerate intrinsic forgetting processes that underlie ALF. In line with this, while various neuropsychiatric conditions may have different pathologies, I outline how these can impact molecular and biochemical factors which may lead to the same downstream cognitive symptom, ALF.

Furthermore, as outlined in chapter 1, I propose that ALF is positioned on one side of a forgetting continuum, with evidence suggesting converging mechanisms across the two sides of the forgetting spectrum (see Figure 1.1). Chapter 1 briefly summarised some of these mechanisms, however in this chapter, I will provide greater detail as to the proposed driving factor behind these, and the molecular and biochemical pathways that are implicated in these processes. I will then discuss how the various neuropathologies of these disorders may accelerate (or inhibit) the brain's biological forgetting processes.

4.2 A Prediction-Based Mechanism Behind Forgetting

Broadly speaking, information learning and memory storage induce neuroplastic changes within and between cells in the brain forming a memory trace. These neuronal ensembles underlying the memory trace are also known as engrams, and may include non-neuronal glial cells such as microglia and astrocytes (Ryan & Frankland, 2022). One recent perspective argues that non-pathological forgetting serves an adaptive purpose by helping the brain to actively unlearn irrelevant information, with this achieved through circuit remodelling which modifies engram cell accessibility from an

⁴ This chapter incorporates material which has been published in the following article:

Arulchelvan, E., & Vanneste, S. (2025). Accelerated long-term forgetting across neuropsychiatric disorders: A review of mechanisms and a neurobiological perspective of forgetting, Neuroscience & Biobehavioural Reviews, 180, 106461. <https://doi.org/10.1016/j.neubiorev.2025.106461>

The author of this thesis is the first author on this publication.

accessible state, to an inaccessible one (Ryan & Frankland, 2022). In other words, forgetting can be viewed in itself as a form of neuroplasticity, i.e. an active process of unlearning. According to this theoretical framework, this active, bidirectional process of forgetting can be modulated by expectancy violation (Ryan & Frankland, 2022). Essentially, when an organism's expectations about its environment are violated, this generates a mismatch between expectations and reality, and this mismatch (or misprediction) is termed a prediction error. This prediction error can then trigger forgetting processes, so that an organism can adaptively update its model (i.e. expectations) about the environment.

Interestingly, a recent human study has provided support for this theory. In this study, when expectancies about previously presented visual stimuli were violated, memory for those items was impaired (Kim et al., 2014; Ryan & Frankland, 2022). Notably, only items which generated large prediction errors for the participants were subsequently forgotten. Not only that, but the authors observed how forgetting of items negatively correlated with fMRI activity in the parahippocampal gyrus and temporal fusiform cortex, which (using an fMRI-based pattern classifier) was inferred as reduced engram cell reactivation (Kim et al., 2014). In other words, visual items that generated stronger predictions led to larger prediction errors when these expectations were violated, which correlated with reduced engram cell accessibility, greater memory-trace weakening, and greater rates of forgetting for these expectancy-violating, prediction error-driving items. If mismatches between our expectations and environment trigger forgetting of information, what molecular and biochemical pathways underlie these processes?

4.3 Engram Cell Accessibility and the Neurobiology of Forgetting

In the last decade, as research into engrams has advanced, our understanding of the neurobiology of memory and active forgetting has progressed. Through this, several biochemical and molecular pathways have been implicated in these processes, which likely modulate engram accessibility via synaptic regulation and remodelling (Berry et al., 2024; Dalto et al., 2025; Guskjolen & Cembrowski, 2023; Ryan & Frankland, 2022). Interestingly, despite the growing research on intrinsic forgetting processes, the literature on ALF still predominantly debates whether ALF is a consequence of early or late-stage consolidation deficits. There is no review which specifically explores how the symptom of ALF (which presents across various neuropsychiatric disorders) may stem from hijacked intrinsic forgetting processes, and the neurobiological pathways that may underlie this. Thus, this next section will summarise the synaptic strength mechanisms that contribute to engram cell accessibility and how this relates to forgetting processes. Critically, it will then highlight recent clinical research which demonstrates how aberrations in these pathways are evident across neuropsychiatric conditions where ALF presents as a symptom.

4.3.1 Engram Cell Accessibility: Synaptic Regulation and Remodelling.

Across species, memories are encoded in engrams through synaptic regulation and remodelling, which refer to the processes that modulate the structure and function of synapses, including their formation, maintenance, and plasticity. In other words, when synaptic strength is altered, engram accessibility is reduced, resulting in forgetting (Ryan & Frankland, 2022). Several factors can influence the synaptic strength processes underlying engram accessibility and forgetting. In particular, these include factors such as neurotransmission, receptor functioning, microglial and astrocytic modulation, actin cytoskeleton dynamics, hippocampal neurogenesis, and dopaminergic activity (see Supplementary Table 2 in Appendix III for a summary of these). It is worth noting that these mechanisms don't necessarily act in isolation, and there are likely other processes that also operate in tandem. The subsequent sections will discuss these factors in more detail and how they relate to engram accessibility and forgetting outcomes.

4.3.2 Synaptic Regulation and Remodelling: Neurotransmission and Receptor Functioning

4.3.2.1 Excitatory Glutamatergic Activity and Inhibitory GABAergic Activity.

Glutamatergic synapses, the primary excitatory connections in the brain, are crucial for learning and memory. They facilitate communication between neurons through the release of glutamate, which then activates receptors on the receiving neuron. This process, particularly involving NMDA (N-methyl-D-aspartate) receptors and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) type 2 subunit (GluA2)-containing receptors, is essential for synaptic plasticity, learning and memory processes (Kennedy, 2013). Notably, as several reviews summarise, NMDA-R activity and GluA2 AMPA-R endocytosis can facilitate forgetting through weakening engram-to-engram synaptic connectivity, with evidence that this occurs through deconstructing the synaptic architecture that was built during consolidation (Berry et al., 2024; Guskjolen & Cembrowski, 2023; Ryan & Frankland, 2022). Adding to this, this glutamatergic synaptic regulation can also be modulated by inhibitory GABAergic activity (Kennedy, 2013).

Notably, engram accessibility may not only be reduced via decreasing the strength in excitatory synaptic inputs, but also by increasing synaptic inhibition. For example, one potential mechanism of silencing these cells could be to strengthen inhibitory GABAergic inputs onto excitatory engram cells (Ryan & Frankland, 2022). Indeed, there has been suggestions that a given engram ensemble may consist of specific inhibitory cells that mirror excitatory ensembles, and which function to maintain the engram's homeostatic activation (Ryan & Frankland, 2022). Supporting this, impaired disinhibition of engram cells has been shown to result in forgetting in certain types of memories (Ryan & Frankland, 2022). As such, this excitation-inhibition balance may be a mechanism for forgetting, although this remains to be directly tested.

In healthy individuals, research into active forgetting mechanisms has highlighted how the ability to actively forget or suppress memories is associated with enhanced DLPFC activity and

downregulated activity in memory-related brain regions such as the hippocampus (Anderson & Hanslmayr, 2014; Anderson & Hulbert, 2021; Costanzi et al., 2021). At the cellular level, the roles of pyramidal glutamatergic neurons and GABAergic interneurons have been implicated in these inhibitory control pathways from the prefrontal cortex to downstream hippocampal and amygdala regions (Costanzi et al., 2021). Specifically, both direct and indirect cellular pathways from inhibitory regions to memory-related regions have been outlined. In the direct circuit, efferent pathways from the prefrontal cortex consists largely of glutamatergic projections to memory-related regions such as the hippocampus. The activity of this inhibitory control network originates from firing of excitatory glutamatergic neurons and their direct excitation of inhibitory GABAergic neurons in downstream memory-related regions (Costanzi et al., 2021). In the indirect route, hippocampal and amygdala activity is indirectly modulated through prefrontal glutamatergic projections to subcortical regions such as the ventral tegmental area, locus coeruleus and basal forebrain. From there, dopaminergic, noradrenergic and acetylcholine axons project to the hippocampus and amygdala in this indirect inhibitory control pathway (Costanzi et al., 2021).

Notably, the role of GABAergic activity and these active forgetting pathways has been supported by neuroimaging research. For example, in one study, elevated hippocampal GABA levels was associated with increased negative coupling between prefrontal cortical and hippocampal regions alongside greater downregulation during successful retrieval suppression (Schmitz et al., 2017). This also highlights how alongside inhibitory control of prefrontal regions, the activity of GABAergic interneurons local to the hippocampus play a key role in active forgetting processes (Schmitz et al., 2017).

4.3.3 Synaptic Regulation and Remodelling: Microglial and Astrocytic Modulation

Microglia and astrocytes are two types of glial cells in the central nervous system which aim to modulate neuroinflammation and ensure proper brain function. While microglia operate as the brain's immune cells, astrocytes support neuronal survival and synaptic regulation, and maintain the blood brain barrier (Vainchtein & Molofsky, 2020). With regards to memory and forgetting, engram cell ensembles are modified by microglial-dependent mechanisms, whereby weak synaptic connections are pruned by microglia (Ryan & Frankland, 2022). In other words, microglia-dependent synapse elimination can both reduce engram accessibility and increase forgetting (Guskjolen & Cembrowski, 2023). Thus, these mechanisms have been shown to underlie natural forgetting in rodents (Ryan & Frankland, 2022). Interestingly, many lifestyle factors can regulate microglia activation, thus microglia-dependent forgetting may stem from several potential distal causes (Madore et al., 2020; Ryan & Frankland, 2022).

In terms of astrocytes, one way in which these glial cells can contribute to forgetting is through regulating synapse dynamics via activity-dependent elimination of excitatory synapses (Guskjolen & Cembrowski, 2023). Moreover, astrocytes can also affect engram accessibility and contribute to forgetting through their interaction with glutamatergic receptors. For example, astrocytes can induce

NMDA-dependent long-term depression through postsynaptic GluA2 AMPAR endocytosis (Guskjolen & Cembrowski, 2023; Navarrete et al., 2019). Thus, glial cells' ability to modulate synaptic remodelling can impact engram accessibility and subsequently forgetting. This glial-based remodelling of engram ensembles is a slow process, operating over timeframes of days or weeks (Ryan & Frankland, 2022). Another mechanism that impacts synaptic reorganisation over similar timeframes is hippocampal neurogenesis-mediated forgetting.

4.3.4 Synaptic Regulation and Remodelling: Hippocampal Neurogenesis

Hippocampal neurogenesis has been proposed as a mechanism for disrupting engram circuits in the brain, resulting in forgetting (Davis & Zhong, 2017). At the synaptic level, this could occur when new neurons integrate into existing hippocampal circuits and compete with established cells for input and output connectivity and new synaptic connections likewise compete with existing synaptic connections (Ryan & Frankland, 2022). Indeed, there is evidence that new adult-generated neurons can replace existing synaptic connections and regulate forgetting (Adlaf et al., 2017; Akers et al., 2014). Put differently, reconfiguration can alter the synaptic weight between engram cells, reducing the likelihood of engram cell reactivation, resulting in forgetting (Guskjolen & Cembrowski, 2023; Ryan & Frankland, 2022).

4.3.5 Synaptic Regulation and Remodelling: Actin Cytoskeleton Dynamics

Most cellular activities rely on the dynamic remoulding of the actin cytoskeleton (Lee & Dominguez, 2010). These actin cytoskeleton dynamics are tightly regulated by various signalling pathways including those involving Rho GTPases (like Rho, Rac1, and Cdc42) and other regulatory proteins (Berry et al., 2024; Lee & Dominguez, 2010). Importantly, these cytoskeleton dynamics can also alter existing synapse size in direct association with changes in synaptic strength (Berry et al., 2024). Moreover, it is believed that memories have distinct actin cytoskeleton pathways for their erasure (Berry et al., 2024). Thus, cytoskeleton remodelling has been suggested as a key mediator of both learning and forgetting through synaptic mechanisms (Berry et al., 2024). *Drosophila* research highlights Rac1 and Cdc42's roles as regulators of active forgetting (Shuai et al., 2010; Zhang et al., 2016). Theoretically speaking, these Rho GTPases could also regulate forgetting in mammals due to their known ability to modulate dendritic spine morphology (Berry et al., 2024). Supporting this, in mammals, Rac1 has been shown to regulate forgetting processes (Berry et al., 2024; Ryan & Frankland, 2022). For example, in rodents, Rac1 activity accelerates forgetting, whereas its inhibition prevents intrinsic forgetting, leading to memory persistence (Jiang et al., 2016; Liu et al., 2016). As such, Rac1 activity has been outlined as a key controller of the brain's memory management system, enabling its adaptive intrinsic forgetting processes, likely through altering engram accessibility (Ryan & Frankland, 2022; Wang et al., 2023).

However, this suggests that there must be a receptor-based mechanism that enables Rac1 activity to modulate engram accessibility in response to both the organism's internal state and its external environment (Ryan & Frankland, 2022). Dopaminergic signalling has been outlined as one such factor that influences Rac1 activity and likely engram accessibility (Ryan & Frankland, 2022).

4.3.6 Synaptic Regulation and Remodelling: Dopaminergic Activity

In recent years, the central role of dopamine in intrinsic forgetting processes has been highlighted. In particular, when dopaminergic receptors on postsynaptic engram cells are activated, forgetting is induced via a signalling cascade that results in engram cell actin cytoskeleton restructuring, and synaptic regulation and remodelling through pathways involving the modulation of small G-proteins such as Rac1 or Cofilin (Davis & Zhong, 2017; Noyes et al., 2021). In *Drosophila*, while the same dopaminergic neurons that encode a memory are regulators of forgetting, dopamine also influences both learning and forgetting through acting on different receptors (Berry et al., 2024).

Specifically, memory acquisition is driven through dopamine acting on D1 receptors, while forgetting is influenced by dopamine acting on DAMB receptors. Similarly, in mammals, dopamine and D1 receptors are also strongly implicated in intrinsic forgetting processes (Berry et al., 2024). Likewise, the role of dopamine and forgetting in humans has also been reported. For example, higher levels of forgetting have been observed in individuals with higher levels of prefrontal cortical dopamine (due to a loss-of-function allele for catechol-O-methyltransferase (COMT)) (Berry et al., 2024; Noyes et al., 2021). Similarly, while no ALF has been reported in healthy ageing (Studer, Heinemann, et al., 2024), healthy older adults can show increases in dopamine levels with age (Grogan et al., 2015). Adding to this, genetic variations of dopaminergic receptors or transporters have been found to correlate with enhanced forgetting in older (but not younger) adults (Ryan & Frankland, 2022). This suggests that dopamine bioavailability may contribute to whether ALF presents in older adults (Ryan & Frankland, 2022). Related to this, the interactions between sleep and dopamine-based forgetting signals have also been highlighted.

There are several stages in sleep including deep sleep, rapid eye movement (REM) or slow-wave sleep (SWS), each of which can impact neural activity, and have well-documented effects on learning and memory in flies, rodents and humans (Berry et al., 2024). However, there is inconsistent evidence linking sleep as a causative factor behind ALF, with research highlighting how ALF can occur within hours regardless of sleep (Stähli et al., 2022). Nevertheless, sleep disturbances have been associated with ALF. For example, although ALF is typically not evident in healthy older adults, in one study, when ALF was observed in these individuals, there was an association between this and greater sleep fragmentation i.e. more intra-sleep awakenings (Mary et al., 2013). Given that rates of learning did not differ between young and older adults in this study, it is possible that the intra-sleep awakenings in older adults disrupted typical sleep cycles and SWS sleep, contributing to ALF (Mary et al., 2013).

Typically, in healthy individuals, sleep-related memory benefits are proposed to stem from enhanced consolidation processes that are facilitated via sleep. However, an equally plausible (and

not mutually exclusive) explanation is that sleep blocks intrinsic forgetting of newly-formed memory-traces (Berry et al., 2024). In other words, sleep may modulate memory persistence by balancing consolidation and forgetting signals. Interestingly, one means through which this may be achieved is through sleep's ability to block ongoing dopamine-driven forgetting signals, which could alter engram cells' synaptic strength and accessibility (Berry et al., 2024). Indeed dopamine plays a role in both REM sleep and SWS (Grogan et al., 2015), and the activity of certain dopaminergic neurons are modulated by behavioural states such as sleep (Berry et al., 2024; Ryan & Frankland, 2022). In addition, structural and functional research highlight how synaptic downscaling which occurs through sleep may encourage engram degradation and forgetting (Berry et al., 2024; Ryan & Frankland, 2022). Thus, ALF may be driven by synaptic regulation and remodelling processes that are impacted by dopaminergic signalling and sleep disruptions, which alter engram cell accessibility.

As such, dopamine has been suggested for its bidirectional role in both learning and forgetting processes (Castillo Díaz et al., 2021). Moreover, in line with the idea that forgetting may stem from prediction errors (i.e. mismatches between our expectations and environment), fly and rodent research increasingly implicates dopaminergic signalling in expectancy violation processes (Ryan & Frankland, 2022). Essentially, dopamine which is known to mediate prediction errors, may trigger both forgetting and de-forgetting processes (Ryan & Frankland, 2022).

4.4 How These Forgetting Pathways Relate to ALF in Neuropsychiatric Conditions

The prior sections outline a perspective where mismatches between expectations and environment may trigger forgetting, in part through dopaminergic signalling and altered engram accessibility. Additionally, it suggests that ALF may stem from hyperactive forgetting processes, rather than purely consolidation deficits. Following this logic, if ALF is indeed a form of over-active forgetting processes, and forgetting itself is prediction-error driven, then in neuropsychiatric conditions where ALF presents as a symptom, one would expect aberrations in the molecular and biochemical pathways proposed to underlie forgetting. In line with this, the next section will list the neuropsychiatric conditions where ALF has been observed, and critically outline the evidence demonstrating disruptions in these forgetting-related pathways. Examples of these abnormal synaptic regulation and remodelling pathways that may contribute to engram accessibility across the forgetting continuum are also summarised in Supplementary Tables 3a and 3b in Appendix III.

4.4.1 ALF in Alzheimer's disease and Parkinson's Disease

Symptoms of ALF have been observed across various stages of AD in both animal models and humans, and in presymptomatic individuals with a higher genetic risk for developing the disease (Ohno, 2023; Rodini et al., 2022; Ruggeri et al., 2024; Weston et al., 2018). Moreover, ALF in AD may indeed result from issues with engram cell accessibility. For example, there is accumulating evidence in mouse models of AD that engram cell reactivation can recover forgotten memories (Ryan

& Frankland, 2022), suggesting how information is not irreversibly forgotten but rather temporarily inaccessible. Notably, there are several ways in which the pathophysiology of AD can interact with and disrupt the synaptic regulation and remodelling mechanisms that support engram cell accessibility outlined above.

AD is characterised by increasing levels of intercellular amyloid- β plaques and intracellular tau tangles in association with neurodegeneration in memory-related brain regions such as the hippocampus, with the spread of these proteins increasing throughout the brain as the disease progresses and forgetting symptoms also escalate (Kaldun et al., 2021). $A\beta_{42}$, derived from amyloid precursor protein (APP), constitutes a key component of $A\beta$ plaques, and is believed to influence the molecular disease pathways (Kaldun et al., 2021). In fact, when rates of ALF were tested after a 3-month delay in cognitively healthy individuals with subjective memory difficulties, forgetting rates were increased for subjects with abnormal CSF $A\beta_{42}$ values (García-Martínez et al., 2023; Tort-Merino, Valech, et al., 2021). In additional research, ALF was likewise identified in asymptomatic individuals at high risk of developing AD (i.e. APOE $\epsilon 4$ carriers), with forgetting rates correlating with abnormal levels of the CSF $A\beta_{42}$ /ptau ratio (García-Martínez et al., 2023; Ohno, 2023; Tort-Merino, Laine, et al., 2021). These studies further highlight how ALF may represent an early clinical indicator of AD, and is related with the pathophysiology of the disease. Thus, if ALF stems from disrupted engram cell accessibility due to impaired synaptic remodelling and regulation mechanisms, one would expect the pathophysiology of AD to disrupt these processes.

Indeed, there are several ways in which $A\beta$ levels can influence these forgetting mechanisms. One such process is actin cytoskeleton dynamics via Rac1-mediated forgetting, with several studies demonstrating how Rac1 activation may contribute to ALF in preclinical AD (Ohno, 2023). For example, $A\beta$ expression activates Rac1, with Rac1 levels elevated alongside accelerated forgetting in mouse models of AD and in AD patients (Ohno, 2023; Ryan & Frankland, 2022). Conversely, while heightened Rac1 activity may contribute to ALF in AD, it has been suggested that deficient Rac1-mediated forgetting processes may give rise to behavioural inflexibility that is characteristic of autism spectrum disorder (Dong et al., 2016; Ryan & Frankland, 2022; Wang et al., 2023). However, of relevance for ALF, in both fly and mouse models of AD, inhibiting Rac1 reduces forgetting (Ryan & Frankland, 2022; Wu et al., 2019).

In the previous section of this chapter, it was discussed how sleep (in part through blocking dopaminergic forgetting signals) can alter engram cell accessibility and impact forgetting through synaptic remodelling and regulation processes. Interestingly, another way in which $A\beta$ pathology may impact forgetting mechanisms is through disrupted sleep patterns. For example, disruptions in the sleep-wake cycle were shown to influence $A\beta$ and tau accumulation and AD pathology in mice and humans (Holth et al., 2019; Madore et al., 2020). Furthermore, in humans, changes in sleep-wake cycles are evident prior to symptom onset in preclinical AD (Musiek et al., 2018), and in flies, sleep can rescue accelerated forgetting symptoms driven by $A\beta$ pathology (Kaldun et al., 2021).

ALF in AD may also stem from disrupted neurotransmission and receptor functioning. For example, increased A β levels impairs synaptic transmission through endocytosis of GluA2-containing AMPARs from the postsynaptic membrane (similar to that which mediates natural forgetting)(Hsieh et al., 2006; Ohno, 2023), and blocking this GluA2 endocytosis prevents forgetting in mouse models of AD (Dong et al., 2015; Ryan & Frankland, 2022). Moreover, microglial-dependent synaptic elimination contributes to synapse loss in early stages of AD (Ryan & Frankland, 2022). These factors can also act in tandem, with lifestyle factors such as sleep disruptions known to impact microglial inflammatory responses and consequently neurodegeneration (Madore et al., 2020).

ALF has likewise been reported in individuals with other neurodegenerative conditions such as PD (García-Martínez et al., 2023; Rodini et al., 2022). PD is characterised by a pathological and progressive loss of dopaminergic neurons, predominantly in the substantia nigra (Kouli et al., 2018). Although it also involves interactions between other factors such as neurodegeneration, protein accumulation, oxidative stress and neuroinflammation, leading to the production of motor and cognitive problems (Kouli et al., 2018). These factors can alter synaptic processes and modulate engram accessibility, potentially contributing to forgetting symptoms (as discussed previously). Thus, the fact that these processes are impacted in the pathophysiology of PD implicates these mechanisms in the production of ALF symptoms in these patients.

4.4.2 ALF in Post-stroke or Acquired Brain Injury

ALF symptoms have also been observed in transient ischemic attack, minor stroke, and thalamic stroke patients (Geurts et al., 2019; Lammers et al., 2022; Tu et al., 2014). Moreover, abnormal forgetting processes have been shown to contribute to ALF symptoms in animal models of stroke. For example, excessive post-stroke hippocampal neurogenesis was shown to contribute to ALF in mice, and inhibiting this hippocampal circuitry remodelling reduced improved long-term memory performance (Cuartero et al., 2019; Ryan & Frankland, 2022).

In addition to ALF in patients with acquired brain injury due to stroke, ALF has been observed in patients with acquired brain injury due to trauma, resections, encephalitis or hypoxic encephalopathy (Studer, G., et al., 2024). Similarly, in children with traumatic brain injury, ALF was associated with diffuse subcortical injuries (Lah et al., 2017). Across these conditions, the damage to the brain hasn't always been in the hippocampus, the presumed seat of accelerated long-term forgetting. This further highlights how hippocampal damage specifically is not the sole driver of ALF symptoms. However, ALF in these disorders may stem from disrupted synaptic regulation and remodelling which underlie engram accessibility. In particular, acquired brain injury can lead to downstream pathological changes in axonal injury, excitotoxicity, inflammation and oxidative stress (Jamjoom et al., 2021).

For example, levels of excitatory glutamate can increase acutely post brain injury, with more severe damage inducing greater levels of excitotoxicity and worse outcomes (Zhang et al., 2001). Neuroinflammation via microglial activity that peaks in shorter and longer timescales post brain

injury has also been observed (Simon et al., 2017). Likewise markers of inflammation and oxidative stress increase (Licastro et al., 2016). Furthermore, production of amyloid precursor protein (APP) accelerates after acquired brain injury due to stroke or trauma (Johnson et al., 2013). APP is, as the name suggests, a precursor to A β plaques which accumulate in the brains of individuals with Alzheimer's disease (AD). In other words, it can contribute to its pathophysiology. Traumatic brain injury has also been found to induce tau aggregation and spreading, and tau pathology is characteristic of chronic traumatic encephalopathy (Edwards et al., 2020). Thus, escalation of each of these factors which are known to disrupt homeostatic synaptic mechanisms likely contribute to engram accessibility, resulting in the ALF symptoms observed across these disorders.

4.4.3 ALF in 22q11.2 Deletion Syndrome

22q11.2 deletion syndrome is a condition where part of an individual's chromosome 22 (at a location known as 22q11.2) is micro-deleted (i.e. missing) (Lackey & Muzio, 2023). This genetic mutation can have several phenotypic presentations, with individuals at higher risk of developing neuropsychiatric disorders, including autism spectrum disorder, seizures, epilepsy, early-onset Parkinson's disease, schizophrenia, attention-deficit hyperactivity disorder, intellectual disability, and anxiety disorders (Lackey & Muzio, 2023; Zinkstok et al., 2019). Moreover, ALF has been observed in children and adolescents with 22q11.2 deletion syndrome (Stähli et al., 2022).

The pathophysiology of 22q11.2 likely involves multiple complex processes. However, if ALF is viewed as a consequence of disrupting the synaptic mechanisms that alter engram accessibility, there are several ways in which the pathophysiology of 22q11.2 deletion syndrome may contribute to these mechanisms. Firstly, several of the neurotransmitter systems implicated are relevant for the proposed mechanisms of ALF. For example, altered dopamine transmission and signalling balance between glutamate and GABA has been identified in the pathophysiology of 22q11.2 deletion syndrome (Zinkstok et al., 2019). As mentioned previously, these neurotransmitter signals have been discussed for their roles in regulating engram accessibility. Additionally, how sleep regulates forgetting processes has previously been discussed in this review. Thus, it is worth noting how sleep disturbances are more frequent in children with 22q11.2 deletion syndrome (Stähli et al., 2022).

4.4.4 ALF in Epilepsy

As outlined earlier in this thesis, much of the initial research on ALF was conducted in epileptic patients. However, the original mechanisms behind ALF insufficiently addressed its potential pathophysiology. That being said, if ALF is viewed as a consequence of disrupting the synaptic mechanisms that alter engram accessibility, there are several ways in which the pathophysiology of epilepsy may contribute to these mechanisms. For example, perhaps the question is not whether seizures cause ALF. Instead, one possibility is that an imbalance between excitatory and inhibitory neurotransmitters, which is characteristic of epilepsy and precedes seizure onset (Akyuz et al., 2021;

Shariff et al., 2024; Sumadewi et al., 2023), is a driving factor behind ALF in epilepsy. Following this logic, it may explain why resolving seizures doesn't necessarily help ALF symptoms (García-Martínez et al., 2023), if excitatory and inhibitory neurotransmission remains imbalanced.

Furthermore, several of the synaptic regulation and remodelling mechanisms that may underlie ALF are disrupted by the pathophysiology of epilepsy. For example, SWS in healthy people has been found to positively correlate with sleep-related memory benefits (Atherton et al., 2016). However, for epilepsy patients, interestingly there tends to be an inverse relationship between sleep and ALF (Mameniškienė et al., 2020). For example, for epilepsy patients with ALF – as the amount of SWS increased, any memory-benefit decreased. It has been suggested that this differential outcome stems from greater electrographic epileptiform activity that's evident during SWS (Atherton et al., 2016).

Additionally, levels of neuroinflammation which contribute to neuronal hyperexcitability are elevated in epilepsy (Rana & Musto, 2018). Oxidative stress plays a role (Akyuz et al., 2021; Sumadewi et al., 2023). Additionally, epilepsy-triggered molecular changes (including altered neurogenesis) have been observed in the hippocampus (Sumadewi et al., 2023). Thus, altered engram accessibility that stems from these aberrant synaptic mechanisms may result in cognitive symptoms such as ALF in epileptic patients. It may also explain why some but not all individuals with epilepsy present with ALF, as there may be thresholds behind these mechanisms that have to be met before cognitive symptoms present.

Moreover, the role of other neurotransmitters (most notably dopamine) have been implicated in epilepsy (Akyuz et al., 2021) and may also influence the likelihood of ALF presenting. Dopamine, dopaminergic neurons and receptors have in particular been identified as an attractive forgetting mechanism due to their roles in initiating signalling cascades involving actin cytoskeleton dynamics of engram cells that can alter synaptic changes induced during acquisition or consolidation (Noyes et al., 2021). In epilepsy, initial evidence has demonstrated how dopaminergic medications can have an anti-convulsant effect (Akyuz et al., 2021). Although not yet investigated, it is possible that in light of the above mechanistic interpretations, these dopaminergic-based interventions could also alleviate ALF symptoms. This remains an open question for future research.

Another interesting consideration is the relationship between seizure activity, synaptic plasticity mechanisms and network connectivity in the brain. For example, in one study mentioned previously, rates of ALF were not associated with seizure activity nor the site of epileptic focus (Audrain & McAndrews, 2019). However, the presence of seizures between testing points was predictive of worse resting state functional connectivity between the hippocampus and lateral temporal cortex. Moreover, rates of ALF in these epileptic patients were associated with reduced resting-state functional connectivity between these regions (Audrain & McAndrews, 2019).

Given how homeostatic synaptic plasticity processes have been proposed to drive network organization in the brain (Stampanoni Bassi et al., 2019), the evidence of altered resting-state connectivity in epileptic patients may suggest two things. The first being that seizure activity impairs synaptic regulation and remodelling processes, disrupting network level connectivity, consequently

contributing to cognitive symptoms such as ALF. The second being that seizure activity is driven by abnormal synaptic regulation and remodelling processes, which disrupts network level connectivity and contributes to cognitive symptoms such as ALF. These remain outstanding points worth investigating.

4.5 A Deeper Dive on the Neurobiology of the Forgetting Continuum

Building on the above logic, and as introduced in chapter 1, ALF may exist on one side of a forgetting continuum. In other words, if ALF represents a cognitive symptom that originates from *hyperactive* forgetting processes, a logical conclusion is that *hypoactive* forgetting processes may result in opposing cognitive symptoms. Thus, conditions where individuals either can't or don't forget information (such as PTSD, autism savant syndrome, or highly superior autobiographical memory (HSAM)) may exist on the opposing end of this scale. Following this logic, if these conditions represent two sides of the same scale, one expects the same synaptic mechanisms to underlie these.

4.5.1 The Forgetting Continuum and Shared Aberrant Synaptic Mechanisms

Indeed, there are several lines of research that implicate shared disrupted synaptic mechanisms such as neurotransmission, glial cell modulation, hippocampal neurogenesis, actin cytoskeleton dynamics and dopaminergic activity across conditions at both ends of the forgetting continuum. This next section will briefly outline this evidence with respect to the 3 conditions mentioned above (i.e. PTSD, autism savant syndrome and HSAM). Each of these conditions can be characterised by downregulated forgetting processes. While there is a vast amount of research investigating potential mechanisms of PTSD, most of the research on the latter two conditions consists of case reports and small-scale studies. Thus, I will clarify where there is a large body of evidence to support this perspective, or where tentative conclusions are being made, and outline what remains to be confirmed.

PTSD can develop in some individuals, after experiencing a traumatic event, or a series of traumatic events (Fujikawa et al., 2024). It is a condition characterised by intrusive, fear-related autobiographical memories that are hard to forget. However not all individuals exposed to trauma subsequently develop the condition. Consequently, researchers have investigated what might lead some individuals to be more resilient to trauma, and what might contribute to making these memories 'unforgettable' for others. Although there remains debate as to the exact mechanisms underlying PTSD, there is recent accumulating evidence underscoring the aberrant forgetting mechanisms that may influence engram accessibility in individuals with PTSD.

One mechanistic theory of PTSD proposes that inhibitory control deficits in suppressing episodic memories underlie intrusive memories in PTSD patients. According to this viewpoint, resilience to PTSD can stem from sufficient inhibitory control mechanisms that appropriately suppress traumatic

memories. As briefly summarised in chapter 1, in healthy individuals, there is an abundance of research into active forgetting mechanisms that have implicated DLPFC regions in inhibitory control processes (Anderson & Hulbert, 2021). In other words, in healthy individuals, the ability to actively forget or suppress memories is associated with enhanced DLPFC activity and downregulated activity in memory-related brain regions such as the hippocampus (Anderson & Hanslmayr, 2014; Anderson & Hulbert, 2021; Costanzi et al., 2021).

Conversely, neurophysiological research has found diverging activity patterns in the brains of trauma-exposed individuals with or without PTSD, and healthy controls when participants completed an active forgetting task. For example, in one study, in healthy (i.e. trauma-exposed but without PTSD, or non-exposed) individuals, memory suppression attempts were associated with reduced functional coupling between inhibitory control and memory systems, but no such reduction in connectivity was observed in PTSD individuals (Mary et al., 2020). In particular, in healthy individuals, the suppression of intrusive memories stemmed from right anterior DLPFC regulation of the hippocampus and precuneus (two regions known for their roles in the re-experiencing of traumatic memories) (Mary et al., 2020). These findings have been supported by other studies of trauma-exposed individuals with or without PTSD, with fMRI analysis highlighting reduced activity in DLPFC regions during memory suppression attempts, suggesting deficient inhibitory control mechanisms (Berry et al., 2024; Catarino et al., 2015; Costanzi et al., 2021; Iqbal et al., 2023; Sullivan et al., 2019).

Notably in PTSD, in addition to dysfunctional inhibitory control processes (as outlined above), there is increasing suggestion that abnormal glutamatergic and GABAergic neurotransmission are central factors in trauma-related disorders (Iqbal et al., 2023). In fact, in one review of preclinical and clinical studies, and neuroimaging and pharmacological research, the reduced functioning of the GABAergic system in relation to the inhibitory PFC-hippocampal network was observed in individuals with PTSD (Huang et al., 2023). In particular, in PTSD, levels of cortical GABA increase which impairs the DLPFC inhibition of downstream hippocampal and amygdala regions. Alongside this, reduced GABA receptors in these memory-related regions contribute to impaired processing of fear memories. Moreover, in individuals with PTSD, deficits in synthesising GABAergic metabolites in memory related regions such as the amygdala, has been associated with impaired forgetting of fear-related memories and increased PTSD symptom severity (Iqbal et al., 2023). Further implicating GABAergic activity in the pathophysiology of PTSD: reduced GABA levels post-trauma in fact predicts PTSD development (Huang et al., 2023).

While the role of GABA has historically been acknowledged in PTSD, more recent evidence is also highlighting how aberrant glutamatergic neurotransmission plays a role in the pathophysiology of PTSD (Averill et al., 2017). For example, in one human study using in vivo and postmortem evidence, there was increased density of cortical metabotropic glutamate receptor 5 (mGluR5) in individuals with PTSD compared to healthy controls (Holmes et al., 2017). There was also indications of aberrant glucocorticoid functioning in PTSD patient samples compared to controls

(Holmes et al., 2017). Further evidence from human studies demonstrate how altered glutamate neurotransmission in PTSD impacts grey matter changes through several mechanisms incl. through impaired glial function or altered dendritic morphology and density (Averill et al., 2017).

This is important because it again highlights how these synaptic mechanisms often operate in tandem, with bidirectional effects. For example, traumatic stress itself can induce glutamatergic-driven excitotoxicity which disrupts astrocytic and glial cell function (Iqbal et al., 2023). Meanwhile, disrupted glial cell function can lead to increased extrasynaptic glutamate levels and subsequently excitotoxicity which alters dendritic morphology and density (Averill et al., 2017). Adding to this, there has been suggestions that the hypothalamic-pituitary-adrenal (HPA) regulation of fear-related behaviours and memories may be mediated to a greater extent by glutamatergic neurons than GABAergic neurons (Huang et al., 2023). As a result, pharmacological studies are investigating drugs that can target these processes (such as ketamine) to ameliorate PTSD symptomology, with promising early results (Averill et al., 2017).

Interestingly, accumulating research is also highlighting how the therapeutic benefits of these drugs involve not only their effects on neurotransmission, but other forgetting-related synaptic mechanisms such as hippocampal neurogenesis and astrocytic and microglial activation. For example, in one recent study, using a rodent model of PTSD, astrocytes and microglia of the prefrontal cortex were shown to play a crucial role in the acute stress response via cerebral homeostatic mechanisms (Valenza et al., 2024). Specifically, a signalling cascade beginning with glial and astrocyte activation and involving downstream neuroinflammatory changes in cytokines and proteins was evident in rodents that were vulnerable (but not resilient) to acute traumatic stress. Moreover ketamine - a drug which largely affects glutamatergic NMDA receptors - was shown to rescue these pathological changes, and support intrinsic homeostatic processes in the brain (Valenza et al., 2024). Similar findings were reported by another study which administered memantine to stress-exposed mice that developed PTSD-like behaviours (Ishikawa et al., 2019). Memantine is an NMDA receptor antagonist, which functions similar to ketamine. In this study, administration of memantine supported forgetting of traumatic memories in mice whilst also improving PTSD anxiety-related behaviours (Ishikawa et al., 2019). However critically, the authors further demonstrated that these beneficial effects stemmed from memantine-induced hippocampal neurogenesis.

Hippocampal neurogenesis has itself been investigated as a potential viable target for improving PTSD symptoms. In a recent rodent study, several methods were used to try to promote hippocampal neurogenesis as a means of weakening the original trauma-related memory engram and reducing PTSD-like behaviours in adult mice (Fujikawa et al., 2024). Notably, the authors demonstrated that in rodents, interventions that target hippocampal neurogenesis-mediated forgetting were a viable mechanism for improving PTSD symptoms (Fujikawa et al., 2024). Building on and connecting these results, a recent human study proposes that hippocampal neurogenesis mechanisms underlie therapeutic effects of either exposure therapy or ketamine in PTSD patients (Zilcha-Mano et al., 2023). In this study of two clinical trials, not only were these interventions most effective for

individuals with greater levels of hippocampal volume pre-treatment, but they were also associated with increased right hippocampal volume during treatment. The authors argue that this increased hippocampal volume likely stemmed from enhanced neurogenesis similar to what's been demonstrated in rodents (Zilcha-Mano et al., 2023). Thus, these studies highlight the potential therapeutic value of targeting active forgetting mechanisms such as hippocampal neurogenesis, whilst also suggesting that factors such as hippocampal volume may have predictive value in identifying individuals most likely to benefit from these treatments (Fujikawa et al., 2024; Ishikawa et al., 2019; Zilcha-Mano et al., 2023).

In addition to the above mechanisms, dopamine dysfunction has also recently been implicated in PTSD pathophysiology. For example, a recent review of animal and human research summarises the preliminary evidence for this, including recent case studies and clinical trials indicating dopaminergic agonists may be viable and effective treatment options (Ney et al., 2021). Interestingly, one means through which the authors argue that dopamine impacts forgetting of traumatic memories in PTSD is through its associations with prediction error signalling (Ney et al., 2021). Supporting this, recent perspectives likewise suggest that prediction-error mechanisms may drive engram accessibility not only in healthy individuals, but also in cases of pathologic forgetting such as those with PTSD (Arulchelvan & Vanneste, 2025a; O'Leary et al., 2023; Ryan & Frankland, 2022).

Other conditions of heightened memory persistence (i.e. where individuals exhibit a lack of forgetting) include autism savant syndrome and HSAM. It is worth noting that individuals present with these conditions far less often than PTSD, and as such our pathophysiological understanding of these conditions is somewhat limited by this (Mazzoni et al., 2019; Song et al., 2019). Adding to the complexity, not all individuals with autism spectrum disorder are diagnosed with savant syndrome (Song et al., 2019). Nevertheless, from what has been observed through case studies and small-scale studies, there is evidence to suggest that shared disrupted synaptic regulation and remodelling mechanisms may contribute to the persistence of memories in these conditions.

Autism spectrum disorder encompasses a range of early-onset neurodevelopmental disorders (Song et al., 2019). For a percentage of these individuals, they may also exhibit exceptional skills or talents in certain areas – most commonly in memory abilities. The co-occurrence of exceptional skills in certain domain(s) alongside neurodevelopmental difficulties, is referred to as savant syndrome (Song et al., 2019). In one recent case study of an adolescent with savant syndrome and exceptional memory, potential cellular mechanisms were elucidated. Using urinary induced pluripotent stem cells, and techniques such as RNA-sequencing and Western blot analysis, associations between dysregulated genetic expression, abnormal cellular and synaptic morphology and disrupted electrophysiological functioning in autism savant syndrome were identified (Song et al., 2019). In particular, the derived neurons exhibited increased frequency of spontaneous excitatory postsynaptic currents, suggesting a greater synaptic release probability, and showed markedly elevated expression of PAX6, TBR1, and FOXP2. Prior research implicates TBR1 and FOXP2 genes in cellular and dendritic morphology thus it was postulated that overexpression of these genes may contribute to

both the enlarged cell body and dendritic spines and reduced spine density observed in the derived neurons of this individual (Song et al., 2019).

Additionally, GAD65, an enzyme involved in the synthesis of GABA, was downregulated in this individual's urinary induced pluripotent stem cells compared to a healthy control. GAD65's synthesis of GABA is essential for several functions including synaptic plasticity processes, and regulating neural network excitability (Kash et al., 1997; Lange et al., 2014). Thus, the GAD65 pathway might be one mechanism contributing to the increased frequency in excitatory signals that was observed in this case study (Song et al., 2019). Moreover, given GAD65's regulation of GABAergic inhibition, and its association with conditioned fear generalization and hyperexcitability of the amygdala and hippocampus, it may also be implicated in the pathophysiology of conditions such as PTSD (Lange et al., 2014; Müller et al., 2015). However, this is just one case study, and this potential mechanism in individuals with autism savant syndrome or conditions such as PTSD warrants further investigation.

Generally speaking, genetic and molecular studies have widely confirmed the altered synaptic structure and function in the pathophysiology of autism spectrum disorder (Nisar et al., 2022). Moreover, dysfunction in glutamate signalling and imbalances between excitatory and inhibitory neurotransmission have been implicated in various phenotypes of autism spectrum disorder (Choudhury et al., 2012; Nisar et al., 2022). In particular, aberrations in metabotropic glutamate receptors (including mGluR1 and mGluR5) have frequently been observed in autism-related disorders (Nisar et al., 2022). Specifically, alterations in mGluR5 functioning and higher expression of mGluR5 protein has been reported in various brain regions of individuals with autism spectrum disorders. Notably, these studies don't report if these individuals also had savant syndrome. However, given how savant syndrome and PTSD can both be characterised by downregulated forgetting, it is interesting to note how increased density of cortical mGluR5 was also observed in individuals with PTSD compared to controls (as previously discussed in this chapter)(Holmes et al., 2017).

Interestingly, with respect to autism spectrum disorder, a recent study of both humans and animal models propose that mGluR5 density may not be the central factor involved in the pathophysiology of the condition (Galineau et al., 2023). In this study, glutamatergic synapse abnormalities were shown to evolve with age, with increased mGluR5 densities in most cortex and subcortical areas in adulthood. Consequently, their findings suggest that increased density of these receptors may be a downstream consequence of adaptation to glutamatergic dysfunctions that occur earlier in the disease progression (Galineau et al., 2023). Although no studies have specifically tied this glutamatergic dysfunction to downregulated forgetting in autism savant syndrome, given the evidence linking glutamatergic mechanisms to forgetting outcomes, it is an interesting perspective for future investigations.

Another related theory of the pathophysiology of autism is the excitation-inhibition (E/I) imbalance theory, with accumulating research highlighting the increased E/I ratio in autism (Oya et al., 2023). This is important, because as outlined earlier in this chapter, this is one mechanism of

forgetting that may contribute to the synaptic regulation and remodelling that underlies engram cell accessibility. Critically, a recent study added further insight into the astrocytic and dopaminergic regulation of this E/I balance in the anterior cingulate cortex of humans with autism spectrum disorder (Oya et al., 2023). In this study using an advanced magnetic resonance spectroscopy protocol, increased glutamate, glutamine (a metabolite of glutamate) and myo-inositol (a marker of astrocytic activation) levels were found in the anterior cingulate cortex of adults with autism spectrum disorder, but not healthy controls. Additionally, increased binding of dopamine to D1 receptors in the ACC negatively correlated with glutamine levels, suggesting dopamine's role in regulating the synthesis of glutamine/glutamate. Furthermore, a correlation between elevated myo-inositol levels and glutamine levels was observed in patients with autism spectrum disorder in this study. Given astroglia's role in glutamine synthesis under normal homeostatic conditions, this finding may support the proposition that disruption to these processes is involved in the pathogenesis of autism spectrum disorder (Gzielo & Nikiforuk, 2021; Nagai et al., 2021; Oya et al., 2023).

There was also an association between glutamine and myo-inositol levels in the anterior cingulate cortex and symptomology of autism spectrum disorder. Specifically, they were associated with the attention switching subscale of the Autism Quotient measure. This is particularly interesting given how not only is the anterior cingulate cortex associated with attentional control (Nelson & Dunlosky, 1994), but also with active forgetting in healthy individuals (Crespo-García et al., 2022). In one recent study, our adaptive ability to intentionally forget (i.e. selectively suppress) information critically depended on the dorsal anterior cingulate cortex (Crespo-García et al., 2022). Specifically, using EEG and fMRI analysis, this study demonstrated how the dorsal anterior cingulate cortex acts as a central gatekeeper, signalling to DLPFC regions when unwanted memories need to be proactively suppressed, or reactively when directed forgetting attempts are unsuccessful. Importantly, successful forgetting in these healthy individuals was associated with functional connectivity from the dorsal anterior cortex, to the right DLPFC, and from there to the hippocampus (Crespo-García et al., 2022).

As such, the anterior cingulate cortex is not only a key instigator of attention control, but also in triggering top-down inhibitory control in intentional forgetting. Essentially, E/I imbalance in anterior cingulate cortex has been implicated in the pathogenesis of autism, and associated with attentional control, but not yet investigated in cases of downregulated forgetting such as autism savant syndrome. However, given its role in models of motivated forgetting, while not yet validated, it is plausible that it may also be implicated across the pathological forgetting spectrum.

Indeed, supporting this, similar brain activity has been implicated in other conditions of downregulated forgetting, such as HSAM. HSAM can be described as the rare ability to rapidly remember highly detailed autobiographical memories (Talbot et al., 2025). This ability is so extreme it is often described as a form of “uncontrollable remembering” by HSAM individuals (Brandt & Bakker, 2018). Thus, intuitively, perhaps downregulated forgetting processes contributes to the persistence of memories for these individuals. Although the rarity of such cases limits our

understanding of the exact mechanisms involved, there is some evidence that abnormal activity in regions associated with forgetting are implicated in HSAM.

Notably, a recent systematic review of 20 experimental studies elucidates how no structural neuroanatomical differences were observed in HSAM individuals (Talbot et al., 2025). However, abnormal hippocampal resting-state connectivity was frequently reported in cases of HSAM versus controls. Moreover, during retrieval, overactivation of regions central to the autobiographical memory network such as the precuneus was observed in HSAM individuals. This is especially interesting as, outlined earlier in this chapter, motivated forgetting of intrusive memories has previously been associated with right anterior DLPFC regulation of the hippocampus and precuneus (Mary et al., 2020). Further implicating abnormal activation of forgetting-related brain regions in HSAM individuals, the authors observed decreased functional connectivity between regions such as the anterior cingulate cortex and the prefrontal cortex and hippocampus (Talbot et al., 2025). As discussed previously, the anterior cingulate cortex has been discussed for its role in directed forgetting in healthy individuals (Crespo-García et al., 2022), and for its proposed role in the regulation of forgetting in autism savant syndrome. Thus, the disrupted functional connectivity between the anterior cingulate cortex and regions implicated in the inhibitory control of memories, suggests converging mechanisms may contribute to downregulated forgetting processes across these conditions.

No research to-date has investigated whether neurotransmission or biological mechanisms also contribute to downregulated forgetting in HSAM (Talbot et al., 2025). However, given the significant crosstalk that exists between the neural networks and synaptic processes discussed throughout this perspective, it stands to reason the same mechanisms that are proposed to underlie ALF, may also contribute to cases of downregulated forgetting. Following this logic, this would position conditions of accelerated forgetting and downregulated forgetting on two ends of a forgetting spectrum, with shared mechanisms underlying them all.

4.6 Conclusion

ALF is a multifaceted cognitive symptom observed across a diverse array of neuropsychiatric disorders. Historically, explanations for ALF have been dominated by debates over whether it reflects subtle encoding failures, disrupted consolidation, hippocampal dysfunction, or seizure-related activity. However, none of these factors fully explain its prevalence or variability across clinical populations. This review chapter advances an alternative perspective: that ALF may, at least in part, arise from the dysregulation of intrinsic forgetting mechanisms - processes that operate in parallel to memory consolidation to regulate memory persistence. Drawing on emerging literature across animal models and human studies, I highlight how forgetting is not simply a passive decay of memory traces but an active, neurobiologically mediated process involving synaptic remodelling, neurotransmitter balance, glial modulation, hippocampal neurogenesis, and dopaminergic signalling. Notably, these

pathways are disrupted across many of the conditions in which ALF manifests, including Alzheimer's disease, Parkinson's disease, epilepsy, stroke, TBI, and 22q11.2 deletion syndrome.

By reframing ALF as potentially resulting from hyperactive forgetting (rather than purely impaired consolidation) this chapter reviews the potential neurobiological pathways involved in this novel conceptual model that may explain the shared cognitive symptomatology across diverse pathologies. Viewing ALF within a broader "forgetting continuum", with hypoactive forgetting states such as PTSD, autism savant syndrome, and HSAM at the opposite pole, further underscores the centrality of these shared mechanisms. It encourages future research to investigate how disease-specific molecular and cellular disruptions converge on shared neurobiological mechanisms of forgetting. Such an approach could inform the development of targeted interventions aimed at modulating forgetting pathways to alleviate ALF symptoms and improve cognitive outcomes across neuropsychiatric populations.

Building on this review chapter and the preceding empirical chapters, the next chapter of this thesis (Chapter 5) aims to investigate GON-tDCS' ability to modulate memory outcomes at specific point on the continuum model of pathological forgetting. This chapter will apply GON-tDCS to healthy older adults, as well as individuals with preclinical stages of AD including subjective cognitive decline and amnesic mild cognitive impairment. At these preclinical stages of AD, subjective memory complaints can often precede overt signs of ALF. Thus, this chapter investigates whether GON-tDCS can influence forgetting outcomes in healthy and preclinical samples, and how neural oscillatory state impacts stimulation's efficacy and predicts memory outcomes.

CHAPTER FIVE: STATE-DEPENDENT EFFECTS OF GON-TDCS IN PRECLINICAL AD⁵

5.1 Introduction

tES is widely proposed as a means of modulating cognition, yet its behavioural effects remain inconsistent and mechanistically unresolved. tDCS, the most extensively studied approach, has been reported to enhance learning and memory (Galli et al., 2019; Indahlastari et al., 2021; Nitsche et al., 2008; Woods et al., 2016). but effect sizes are highly variable across individuals and contexts (Horvath et al., 2015; Huo et al., 2021; Indahlastari et al., 2021). This heterogeneity has limited both theoretical progress and translational development, and suggests that dominant assumptions about how tDCS influences cognition remain incomplete. Two key explanations for this variability have been proposed: (1) whether stimulation acts primarily through direct cortical modulation or indirect peripheral pathways and (2) whether its efficacy depends on the underlying neural state at the time of stimulation.

With regards to the first, biophysical modelling and in vivo measurements indicate that much of the applied current is attenuated by scalp and skull (Vöröslakos et al., 2018), challenging the plausibility of direct cortical excitation as the primary mechanism. Instead, converging evidence suggests that tES may engage peripheral cranial and cervical nerves, thereby influencing ascending neuromodulatory systems that regulate large-scale brain networks (Asamoah et al., 2019; van Boekholdt et al., 2021; Vanneste et al., 2020; Vöröslakos et al., 2018). Among these, recruitment of the LC-NA system has been proposed as a key pathway through which tES may affect cognition (Luckey, Adcock, et al., 2023; Majdi et al., 2023). At the same time, a growing body of work indicates that stimulation effects are strongly state-dependent, such that endogenous oscillatory activity and neuromodulatory tone can determine whether stimulation enhances, disrupts, or fails to modulate performance (Bradley et al., 2022; Silvanto et al., 2008; Vergallito et al., 2022; Wansbrough et al., 2024; Zagha & McCormick, 2014).

Such state-dependence may account for the substantial heterogeneity reported in the cognitive tDCS literature (Bradley et al., 2022), yet it has rarely been tested directly in populations undergoing age-related or pathological neural change. This is notable because older adults and individuals with cognitive impairment often show more variable, and sometimes inconsistent, cognitive responses to tDCS than younger or healthy groups (Emonson et al., 2019; Fromm et al., 2025; Li et al., 2024). Moreover, neural oscillations, which index both brain state and neuromodulatory function, are systematically altered in AD and its preclinical stages such as subjective cognitive decline (SCD) and amnestic mild cognitive (aMCI) (Beppi et al., 2021; Weiss et al., 2023).

⁵ This chapter incorporates material from the following article which is under review for the journal *Communications Medicine*:

Arulchelvan, E., Rubio, I., Jeffrey-Carrick, M., & Vanneste, S. (2026) *State-dependency drives divergent memory effects of peripheral nerve stimulation across healthy and pathological ageing.*

The author of this thesis is the first author of this publication.

For example, whereas reduced post-learning alpha and beta activity predicts improved long-term memory in healthy individuals (Bencze et al., 2025), preclinical stages of AD exhibit distinct oscillatory alterations, including altered encoding dynamics (Hayes et al., 2017) and non-linear increases in beta-gamma activity associated with amyloid burden (Gaubert et al., 2019). These findings suggest that individuals at risk for AD operate in a fundamentally altered neural state, which could further shape responsiveness to stimulation.

The LC-NA system provides a plausible mechanistic link between peripheral nerve stimulation, brain state, and memory. The LC is among the earliest sites of pathology in AD (Dahl, Bachman, et al., 2023; Jacobs et al., 2021; Mather, 2025), with evidence for altered structural integrity and functional connectivity in preclinical stages (Bell et al., 2023; Gong et al., 2023). Noradrenergic projections originating from the LC regulate hippocampal plasticity, cortical dynamics, and memory performance (Bell et al., 2023; Dahl, Kulesza, et al., 2023; Mather & Harley, 2016; Noei et al., 2022; Robison et al., 2023; Sara, 2015; Unsworth & Robison, 2017), and early LC degeneration may be accompanied by compensatory increases in noradrenergic activity (Krohn et al., 2023; Noei et al., 2022). Given the inverted U-shaped relationship between noradrenergic tone and cognitive performance (Arnsten, 2011; Monte-Silva et al., 2010; Vijayraghavan et al., 2007), these changes raise the possibility that individuals at risk for AD may lie near the boundaries of an optimal neuromodulatory range, with consequences for both neural state and the behavioural efficacy of stimulation.

I therefore tested the hypothesis that the cognitive effects of peripheral nerve stimulation are fundamentally constrained by neural state, and that this constraint differs between older adults with or without preclinical AD. To test this, I used greater occipital nerve stimulation delivered via direct current (GON-tDCS), an approach proposed to engage LC-NA pathways and previously shown to enhance long-term memory in healthy individuals (Luckey, McLeod, et al., 2023; Luckey et al., 2020; Vanneste et al., 2020). However, this approach has not been investigated in preclinical or clinical samples. As such, I extended prior research by applying this stimulation and comparing healthy older adults with individuals with preclinical AD (incl. SCD and aMCI) on an associative memory task, with follow-up assessments at 7 and 28 days to index long-term retention and rates of ALF. Resting-state electroencephalography was acquired before and after stimulation to characterise oscillatory state and its modulation by GON-tDCS.

By applying a stimulation approach that targets the LC-NA system, alongside testing how baseline neural state and post-learning neural state shapes the behavioural effects of peripheral nerve stimulation, this study addresses a central limitation of the tES literature and highlights a critical factor for understanding variability in stimulation outcomes.

5.2 Methods

5.2.1 *Participants*

Seventy-two individuals between the ages of 50 and 86 participated in this study ($M = 65.99$, $SD = 7.39$), consisting of 40 preclinical participants (with SCD or aMCI) and 30 controls. Participants were recruited through community outreach, including the distribution of study information in community settings, such as local community centres and public libraries, and through St James's Memory Clinic. Preclinical participants were eligible if they met the following criteria: ≥ 50 years; subjective memory difficulties or a diagnosis of probable aMCI; Mini Mental State Examination score > 21 ; adequate visual and auditory acuity; capacity to understand and sign informed consent; no evidence of cognitive decline or dementia that is not Alzheimer's disease related; no presence of any neurological, psychiatric or cardiac diseases or significant brain damage; no history of epileptic seizures in the past 2 years; no psychoactive or blood pressure medication use; stable AChI medication > 3 months; no abuse of alcohol or drugs in the last 12 months; English as the native language; no knowledge of the Swahili language; no enrolment in an ongoing investigational medicinal product study. The eligibility criteria for healthy controls were the same except for no subjective memory difficulties or no diagnosis of probable aMCI.

5.2.2 *Materials*

5.2.2.1 *Word-Association Task*

Participants completed a computerized Swahili-English word association task, based on a well-established paradigm by Karpicke & Roediger (Karpicke & Roediger, 2008), and consisting of 25 Swahili-English word pairs (e.g. lozi – almond) from previously published norms (Nelson & Dunlosky, 1994). The task was programmed in Visual Studio software using C# and presented on a 27-inch screen positioned at eye level. On the first day, the task consisted of 3 blocks (each with a study and test phase), with a 2-minute rest between each block. In block 1, in the study phase each Swahili-English word pair was presented simultaneously on screen for 10s, and participants were instructed to try to learn the English translation for each Swahili cue. The study phase was followed by a 30 second rest period. During the test phase, each Swahili cue was shown on screen for 16s, and the participant's task was to try type the correct English translation. After the 16s, the task automatically moved onto the next Swahili cue.

In the second and third block, the study phases followed the same format, followed by the 30s rest period. However, the test phases varied slightly. In these blocks, any correctly recalled pairs from the 1st and 2nd testing phases were dropped from being tested in subsequent test phases (but were still presented in all 3 study phases). This meant that the study phase was always 250s per block (10s x 25 pairs), with 3 blocks in total. However, the length of the test phase varied for each participant depending on how many words they had correctly recalled in the previous block. Word order was

randomized in each phase and block. To assess learning rates/ short-term memory on Day 1, cumulative learning rates across the 3 blocks were calculated.

When participants returned 7 and 28 days later, the task consisted only of 1 test phase. This following the same format as above, where each of the 25 Swahili cues were presented on screen for 16s and the participant's task was to try type the correct English translation within that timeframe.

5.2.2.2 GON-tDCS

GON-tDCS was applied using the same device and electrode placement as in chapters 2 and 3. Participants were randomly assigned to one of two stimulation groups: active GON-tDCS or sham GON-tDCS. For active GON-tDCS, stimulation ramped up for 30 seconds, a constant current of 1.5 mA intensity was applied during each of the 3 study phases of the task (i.e. 255 seconds $\times$ 3 blocks), and stimulation ramped down for 5 seconds. For sham GON-tDCS, placement of the electrodes was identical to active GON-tDCS. At the start of each study phase, stimulation ramped up for 30 seconds, was applied for 15 seconds only (to mimic the sensation), and ramped down for 5 seconds. No stimulation was applied during rest or testing phases for either group, and no stimulation was applied during the follow up visits on day 7 or 28. See Figure 5.1 for the stimulus protocol.

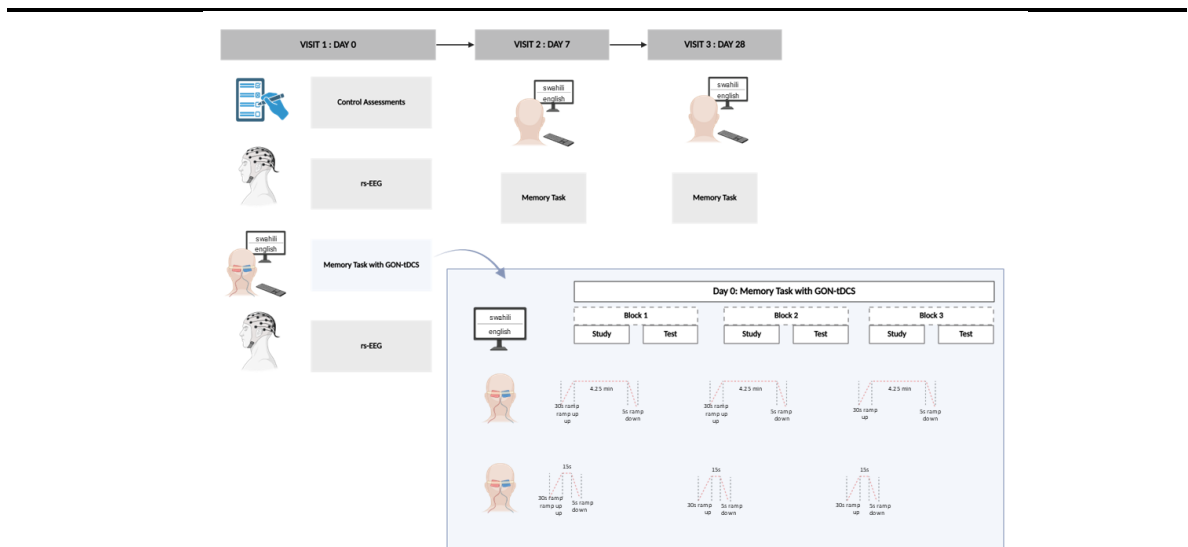


Figure 5.1 | Study Design and Stimulation Protocol. Figure 1 presents the study design on the first visit and follow up visits 7 and 28 days later, as well as the stimulation protocol administered in conjunction with a Swahili-English word association task. Abbreviations include resting-state electroencephalography (rs-EEG) and greater occipital nerve stimulation using direct current stimulation (GON-tDCS).

5.2.2.3 Rs-EEG

Resting-state EEG data were collected from each participant immediately before and after stimulation on day 1. The data were collected using 64 Ag/AgCl electrodes in standard 10-20

montage using a Biosemi Active. Two system (Amsterdam, Netherlands). Data were collected at 4096 Hz and processed offline. Eyes-closed recordings for approximately 5 minutes (both before and after stimulation) were obtained while participants sat upright in a comfortable chair in a darkened room. Participants were instructed not to drink alcohol (24hrs prior) or caffeinated beverages (1hr prior) to EEG recording (Logan et al., 2002; Siepmann & Kirch, 2002; Volkow et al., 2000). During the recording, participants were asked to sit relatively still, and to avoid excessive jaw clenching/ movement or excessive movement of eyes, head, arms or legs. Alertness was monitored online by assessing slowing of the alpha rhythm and the appearance of sleep spindles, in order to avoid possible increases in theta power due to drowsiness. None of the participants included in the present study showed such EEG changes during recording.

EEG preprocessing was conducted using EEGLAB v2023.1 (Delorme & Makeig, 2004). Recordings were down sampled to 500 Hz, and re-referenced to the average. Data were band-pass filtered using a basic finite impulse response (FIR) filter, lower edge = 0.55 Hz and upper edge = 44 Hz. The EEG data were then plotted for careful inspection for artifacts. Artifacts were identified by careful visual inspection and all segments containing eye blinks, eye movements, jaw tension, teeth clenching or body movements were removed. In addition, artifacts were addressed using a combination of frequency filtering, notch filtering, rejection of contaminated time intervals, removal of characteristic artifact topographies, independent component analysis, and model-based correction of stereotyped temporal artifacts. In addition, an independent component analysis was conducted to further verify whether all artifacts were excluded. Six participants data were removed during preprocessing due to extreme noise/ interference in the EEG data, resulting in 64 participants EEG data being analysed. After artifact rejection, the average EEG duration was compared across groups (control group and, preclinical group). No significant between-group differences were observed ($F = 0.74, p = 0.52$).

Standardized low-resolution brain electromagnetic tomography (sLORETA; <http://www.uzh.ch/keyinst/loreta.htm>) is a functional imaging method that estimates standardized current density with zero localization error under specific electrophysiological and neuroanatomical constraints (Pascual-Marqui, 2002). I used sLORETA to estimate the intracerebral sources underlying scalp-recorded activity in the following frequency bands beta (13–30 Hz) frequency band. The sLORETA algorithm solves the inverse problem, that is, the estimation of neuronal electrical sources from extracranial measurements, by assuming similar orientations and strengths for neighbouring neuronal sources represented by adjacent voxels. The solution space and lead-field matrix used here were those implemented in the LORETA-Key software. This software incorporates revised realistic electrode coordinates (Jurcak et al., 2007) and the lead field described by Fuchs et al. (Fuchs et al., 2002), computed using the boundary element method on the MNI-152 template (Montreal Neurological Institute, Canada). The sLORETA-Key anatomical template partitions the neocortical MNI-152 volume, including the hippocampus and anterior cingulate cortex (ACC), into 6,239 voxels of $5 \times 5 \times 5$ mm, based on probabilities derived from the Daemon Atlas. Co-registration uses the

appropriate transformation from MNI-152 space to Talairach and Tournoux space. Anatomical labelling of significant clusters was performed using the built-in sLORETA toolbox.

Although sLORETA has lower spatial resolution than functional MRI and is restricted to cortical grey matter and the hippocampus (Mulert et al., 2004), its validity has been supported by comparisons with structural MRI (Worrell et al., 2000), positron emission tomography (Pae et al., 2003; Pizzagalli et al., 2004; Zumsteg et al., 2005) and functional MRI (Mulert et al., 2004; Vitacco et al., 2002). Additional support comes from studies showing concordance between sLORETA localization and findings from invasive recordings in epilepsy (Zumsteg, Lozano, & Wennberg, 2006; Zumsteg, Lozano, Wieser, et al., 2006) and cognitive event-related potential studies (Volpe et al., 2007).

Furthermore, a region-of-interest was calculated for the beta frequency band (13–30 Hz), log-transformed current density values were averaged across all voxels within the region of interest. The ROIs included the left inferior frontal gyrus based on the a priori hypothesis.

5.2.2.4 Control Measures and tES Exit Questionnaire

Demographic information (age, gender, handedness, and education in years) were collected for each participant to ensure that any between-group behavioural differences were specifically due to the effects of the stimulation. To assess subjective memory difficulties in the pre-clinical group, these participants also completed the SMQ (Bennett-Levy & Powell, 1980). To confirm no differences between groups in cognition and memory, participants also completed validated control measures incl. the BAI (Beck et al., 1988) and BDI-II (Beck et al., 1996), CVLT-II (Yi, 2011) and the COWAT (Bauer & Malek-Ahmadi, 2023). Post-stimulation, participants completed the tES Exit Questionnaire (i.e. the same questionnaire administered in chapter 2) to assess possible side effects of GON-tDCS. To determine if the stimulation was well-blinded, an item asked participants to guess, based on their experience, which stimulation they believed they had received (active or non-active).

5.2.3 Procedure

This experiment was designed as a double-blind, placebo-controlled, parallel group study. It was granted ethical approval by the Research Ethics Committee of the School of Psychology at Trinity College Dublin (Approval number: SPREC102021-23) and conducted in accordance with the ethical guidelines of the Helsinki declaration (1964).

Participation involved 3 visits to the university over the course of 28 days. The second visit was scheduled for 7 days after the first (+/- 2 days), and the final visit was scheduled 28 days after the first (+/- 2 days).

In Session 1, participants completed control assessments incl. the BAI, BDI-II, CVLT-II, and the COWAT. After a 40-minute break, resting-state EEG was collected, the participant completed the word association task while receiving active or sham GON-tDCS, and resting-state EEG was

collected again immediately after. A second researcher administered the stimulation, ensuring that the researcher who instructed the participant and conducted the analysis was blind to the stimulation protocol. At the end of this session, participants completed the stimulation exit questionnaire. Participants returned 7 and 28 days later to test memory performance on the word association task. See Figure 5.1 for the experimental procedure. Upon completion, participants were reimbursed monetarily for travel compensation.

5.2.4 *Statistical Analyses*

All statistical tests on behavioural, demographic and cognitive measures were carried out using SPSS (version 28), and significance was set at $p < 0.05$.

5.2.4.1 *Word Association Task*

Learning rates and memory recall were calculated as percentages of the total amount of pairs that were presented. Forgetting rates were calculated by subtracting the percentage of words remembered on day 7 from the percentage of words remembered at day 28. A 2×2 ANCOVA was conducted to determine the effect of condition (preclinical vs control) and stimulation (active vs sham) on learning on day 1. A 2×2 ANCOVA was conducted to determine the effect of condition (preclinical vs control) and stimulation (active vs sham) on memory recall on day 7, while controlling for initial learning on day 1. A 2×2 ANCOVA was conducted to determine the effect of condition (pre-clinical vs control) and stimulation (active vs sham) on memory recall on day 28, while controlling for initial learning on day 1. A 2×2 ANOVA was conducted to determine the effect of condition (preclinical vs control) and stimulation (active vs sham) on forgetting rates between day 7 and day 28. For each test, if the interaction effect was significant, post-hoc analyses were conducted using a Bonferroni correction.

Subjective memory complaints can precede objective impairment in AD, with AD-related pathology already detectable at the stage of SCD (Hayes et al., 2017). In particular, individuals with SCD show reduced LC integrity and altered functional connectivity (Bell et al., 2023; Gong et al., 2023), and early LC degeneration may be accompanied by compensatory increases in noradrenergic activity (Krohn et al., 2023; Noei et al., 2022). In parallel, there is a known inverted-U shaped relationship between noradrenergic tone and cognitive performance, whereby too much or too little noradrenaline is linked with poorer cognition than moderate levels (Baldi & Bucherelli, 2005; Nieuwenhuis et al., 2005). A recent study in rodents and healthy individuals further demonstrated that noradrenaline tunes functional connectivity between brain regions, with moderate levels creating the most efficient, coordinated brain state for performance (Tong et al., 2025). Given this inverted U-shaped relationship between noradrenergic tone and cognitive performance, these findings raise the possibility that individuals with SCD operate closer to the limits of an optimal noradrenergic

range. Under this account, the memory effects of GON-tDCS, which is proposed to act via LC–NA mechanisms, may vary as a function of underlying neuropathology and subjective cognitive status.

Thus, to further understand how subjective memory levels impacted memory outcomes for the preclinical group specifically, two GLMs were conducted. The first GLM was conducted to examine the effect of stimulation on memory recall on Day 7, when controlling for baseline learning on day 1 and subjective memory levels. The second GLM was conducted to examine the effect of stimulation on memory recall on day 28, when controlling for baseline learning rates and subjective memory levels.

5.2.4.2 *Rs-EEG*

Pre- to post-stimulation changes were compared between the preclinical and control groups under both active and sham stimulation conditions. Whole-brain analyses were performed using a non-parametric permutation test, which estimates the empirical null distribution of the maximum statistic by randomization (Nichols & Holmes, 2002). This approach controls for multiple comparisons across all voxels and frequency bands and does not assume Gaussianity (Nichols & Holmes, 2002). Voxel-wise comparisons were conducted in sLORETA using the logarithm of the F-ratio, with significance assessed using 5,000 permutations.

For the region-of-interest analysis, I performed a repeated-measures ANOVA with group (preclinical versus control) and stimulation condition (active versus sham) as independent variables and the change in beta-band log-transformed current density (pre- minus post-stimulation) as the dependent variable. In addition, Pearson correlation analyses were performed separately in the preclinical and control groups to assess the association between changes in beta-band log-transformed current density and memory performance at days 7 and 28.

To test whether stimulation-related changes in neural state carried prospective information about later memory, I fitted a linear regression model in the healthy group only, using the pre- to post-stimulation change in left inferior frontal gyrus (IFG) beta-band log-transformed current density as the predictor and associative memory performance at Day 7 as the outcome variable. Model performance was evaluated using 10-fold cross-validation across the 30 healthy participants. Predictive performance was summarized using the correlation between predicted and observed Day 7 memory scores, mean absolute error (MAE), and root mean squared error (RMSE).

To assess whether baseline neural state contained information about group-related differences prior to stimulation, I trained a random forest classifier using baseline left IFG beta-band log-transformed current density to classify participants as preclinical or healthy control. This approach was chosen because random forests provide a flexible and robust ensemble-based classification framework that can accommodate complex predictor relationships with relatively limited parameter tuning (Biau & Scornet, 2016; Breiman, 2001). Classification performance was evaluated using stratified 10-fold cross-validation across 64 participants. Model performance was summarized using overall accuracy, Cohen's kappa, weighted F1 score, area under the receiver operating characteristic

curve (ROC-AUC), and the confusion matrix. Class-specific precision and recall were also reported for the preclinical and healthy groups.

5.2.4.3 Control Measures and tES Exit Questionnaire

χ^2 tests were conducted to compare if there was a difference between the active and sham stimulation and healthy control and preclinical conditions for gender and handedness. In addition, two-way ANOVAs were computed to see if there was a difference between the stimulation groups and healthy control and preclinical conditions for age, education level, the BDI, BAI, MMSE, CVLT-II, or the COWAT. For the preclinical group, a one-way ANOVA was used to test for a difference in SML score.

To analyse whether participants were blind to their stimulation group, χ^2 tests compared the stimulation participants received (active vs sham) to what they thought they received (active vs non-active) for both the healthy control and preclinical participants. A MANOVA was conducted to compare whether there was any difference between active and sham stimulation groups for experiencing common stimulation side-effects. A MANOVA was conducted to compare whether there was any difference between healthy control and preclinical participants for experiencing common stimulation side-effects.

5.3 Results

5.3.1 Control Measures

Seventy-two individuals between the ages of 50 and 86 participated in this study ($M = 65.99$, $SD = 7.39$), consisting of 40 preclinical participants (with SCD or aMCI) and 30 controls. In the control condition, 15 participants received active stimulation, and 15 received sham. In the preclinical condition, 20 participants received active stimulation, and 20 received sham. In the pre-clinical condition, there were no significant differences between the active or sham stimulation for scores on the SMQ ($F(1, 37) = .08$, $p = .79$; Figure 5.2a). See Table 5.1 for the condition and stimulation group means and standard deviations of the below control measures.

There was no significant interaction between the effects of stimulation and condition on age ($F(1, 66) = 0.14$, $p = .80$; Figure 5.2b). Simple main effects analysis showed that stimulation did not have a significant effect on age ($p = .559$), and condition also did not have a significant effect ($p = .12$). There was no significant interaction between the effects of stimulation and condition on education ($F(1, 66) = 0.00$, $p = .96$; Figure 5.2c). Simple main effects analysis showed that stimulation did not have a significant effect on education ($p = .652$), but condition did have a significant effect ($p < .001$).

There was no significant interaction between the effects of stimulation and condition on BDI scores ($F(1, 66) = 0.14$, $p = .71$; Figure 5.2d). Simple main effects analysis showed that stimulation did not have a significant effect on BDI scores ($p = .37$), but condition did have a significant effect ($p < .001$). There was no significant interaction between the effects of stimulation and condition on BAI scores ($F(1, 66) = 0.06$, $p = .81$; Figure 5.2e). Simple main effects analysis showed that stimulation did not have a significant effect on BAI scores ($p = .86$), but condition did have a significant effect ($p < .001$). There was no significant interaction between the effects of stimulation and condition on CVLT-II scores ($F(1, 66) = 2.40$, $p = .13$; Figure 5.2f). Simple main effects analysis showed that stimulation did not have a significant effect on CVLT-II scores ($p = .73$), but condition did have a significant effect ($p < .001$). There was no significant interaction between the effects of stimulation and condition on COWAT scores ($F(1, 66) = 0.13$, $p = .72$; Figure 5.2g). Simple main effects analysis showed that stimulation did not have a significant effect on COWAT ($p = .40$), but condition did have a significant effect ($p < .001$).

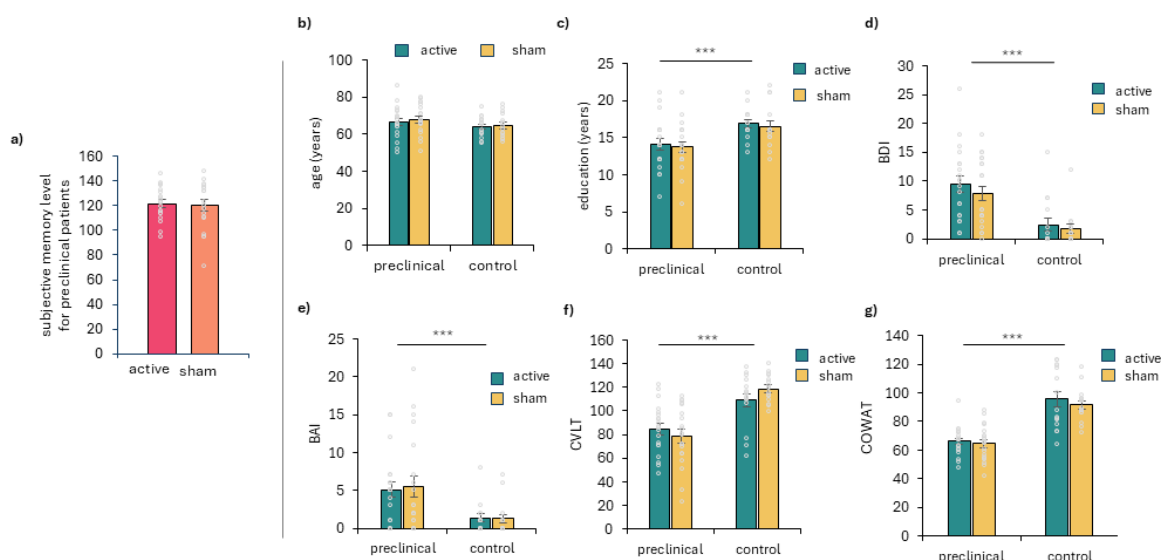


Figure 5.2 | Control Measures. Results of the cognitive and psychological control measures for the active and sham stimulation groups that includes **A** subjective memory scores for preclinical participants, **B** age (years), **C** education (years), **D** beck depression inventory (BDI), **E** beck anxiety inventory (BAI), **F** California verbal learning test (CVLT) and **G** controlled oral word association task (COWAT) for the preclinical and control participants.

When examining the proportion of pre-clinical and control participants (and the active or sham stimulation groups), there were no significant differences in their gender (control: $\chi^2(1, N = 30) = 1.29, p = .26$; preclinical: $\chi^2(1, N = 40) = 1.67, p = .19$; combined: $\chi^2(1, N = 70) = 0.60, p = .81$), or handedness (control: $\chi^2(1, N = 30) = 1.03, p = .31$; preclinical: $\chi^2(1, N = 39) = 0.29, p = .59$; combined: $\chi^2(1, N = 69) = 0.00, p = .97$). Figure 5.3a presents the percentage of participants who were male or female, and 5.3b presents those right-handed or left-handed in the condition (control or preclinical) or stimulation (active or sham) groups.

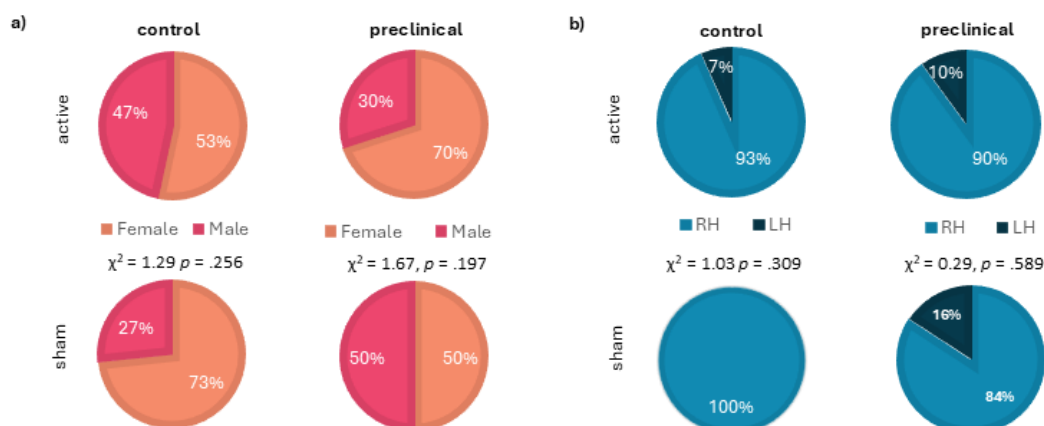


Figure 5.3 | Gender and Handedness of Participants. The proportion of participants in the control and preclinical conditions and active and sham groups that were **A** male or female and **B** right-handed (RH) or left-handed (LH).

Table 5.1 Summary of ANOVA results for control measures

	preclinical participants		control participants		P-value	
	active (n = 20)	sham (n = 20)	active (n = 15)	sham (n = 15)	group	condition G×C ¹
Age (years)	66.45 ± 8.56	67.95 ± 7.89	64.07 ± 5.76	64.67 ± 6.37	0.559	0.117
Education (years)	14.05 ± 3.50 ^{ab}	13.75 ± 3.26 ^b	16.87 ± 2.10 ^a	16.5 ± 2.89 ^{ab}	0.652	<0.001
BDI	9.45 ± 6.35 ^a	7.85 ± 5.82 ^a	2.47 ± 4.32 ^b	1.80 ± 3.03 ^b	0.372	<0.001
BAI	5.10 ± 4.56 ^{ab}	5.55 ± 6.36 ^a	1.33 ± 2.06 ^b	1.27 ± 2.22 ^b	0.858	<0.001
CVLT	84.65 ± 20.90 ^b	78.55 ± 25.12 ^b	109.07 ± 22.31 ^a	118.73 ± 11.96 ^a	0.727	<0.001
COWAT	66.20 ± 10.08 ^b	64.50 ± 12.31 ^b	95.60 ± 21.17 ^a	91.47 ± 12.12 ^a	0.395	<0.001

Abbreviations include: Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), California Verbal Learning Test (CVLT), Controlled Oral Word Association Test (COWAT).

Values are means ± SD. ^{a-b}Means in a row without a common superscript letter differ ($P < 0.05$) as analysed by two-way ANOVA. ¹G × C = stimulation group × memory condition interaction effect.

5.3.2 *Word Association Task*

5.3.2.1 *No Effect of GON-tDCS on Memory Encoding*

Previously, our lab has demonstrated that GON-tDCS, which operates through a LC-NA mechanism, has no effect on memory encoding in healthy younger and older adults (Luckey, McLeod, et al., 2023; Luckey et al., 2020; Vanneste et al., 2020). As such, my first aim was to extend these findings with a preclinical group, to confirm GON-tDCS likewise has no effect on initial learning in these participants. In doing so, if I observed any differences in long-term memory outcomes, I could confirm this was due to memory maintenance or consolidation processes, and not upregulated encoding. As expected, there was no significant interaction effect between memory condition and stimulation on learning on day 1, ($F(1, 66) = 2.11, p = .15, \eta^2 = .03$). Simple main effects analysis showed that there was also no significant effect of stimulation ($p = .81$) and condition ($p = .07$) on learning on day 1. These results extend and validate prior research demonstrating no online effects of GON-tDCS on encoding.

5.3.2.2 *No Evidence of ALF and No Effect of GON-tDCS on Forgetting Rates of Preclinical and Control Participants*

ALF is one of the earliest detectable cognitive deficits in preclinical stages of AD (Ohno, 2023). As such, the next question was to confirm whether the preclinical participants exhibited increased rates of ALF than the control participants, and whether GON-tDCS could mitigate how many words participants forgot between day 7 and day 28. There was no significant interaction effect between condition and stimulation on forgetting rates between day 7 and day 28, ($F(1, 66) = 0.81, p = 0.372, \eta^2 = .01$). Simple main effects analysis showed that stimulation had no significant effect on forgetting rates ($p = .987$), and condition also had no significant effect ($p = .932$). These results suggest that ALF was not detectable in the preclinical participants, and that stimulation had no effect on long-term forgetting rates.

5.3.2.3 *Divergent Long-term Memory Effects of GON-tDCS on Preclinical Participants versus Controls*

While GON-tDCS does not enhance encoding, research has demonstrated that GON-tDCS enhances long-term memory through upregulating consolidation processes (Luckey, McLeod, et al., 2023; Luckey et al., 2020; Vanneste et al., 2020). Based on these findings, my next aim was to investigate whether the memory benefits of this same stimulation approach extend to preclinical AD patients, and whether the effects differ compared to healthy controls due to state-dependency. After controlling for baseline learning rates on day 1, there was a significant interaction effect between condition and stimulation on memory recall on Day 7, ($F(1, 65) = 11.91, p < .001, \eta^2 = .16$). Simple main effects analysis showed that stimulation had a significant effect on memory recall on Day 7 ($p = .009$), and condition also had a significant effect ($p < .001$). Bonferroni corrected post-hoc analyses

showed that for the control participants, those who received active stimulation ($M = 41.24$, $SD = 15.86$) had significantly increased memory recall on Day 7 compared to those who received sham stimulation ($M = 25.99$, $SD = 9.31$; $p_{\text{bonf}} < .001$). Post-hoc analysis also showed that for the preclinical participants, there was no significant difference in memory recall on Day 7 for the active ($M = 24.40$, $SD = 18.40$) or sham stimulation ($M = 22.20$, $SD = 19.14$; $p_{\text{bonf}} = 1.00$). See Figure 5.4a.

Similarly, on day 28, after controlling for baseline learning rates on day 1, there was a significant interaction effect between condition and stimulation on memory recall ($F(1, 65) = 14.77$, $p < .001$, $\eta^2 = .19$). Simple main effects analysis showed that stimulation had significant effect on memory recall on Day 28 ($p = .007$), and condition also had a significant effect ($p < .001$). Bonferroni-corrected post-hoc analysis showed that for the control participants, those who received active stimulation ($M = 35.86$, $SD = 20.56$) had significantly increased memory recall on Day 28 compared to those who received sham stimulation ($M = 19.07$, $SD = 9.63$; $p_{\text{bonf}} < .001$). Post-hoc analysis showed that for the preclinical participants, there was no significant difference in memory recall on Day 28 for the active ($M = 17.60$, $SD = 14.76$) or sham stimulation ($M = 17.00$, $SD = 15.07$; $p_{\text{bonf}} = 1.00$). See Figure 5.4c.

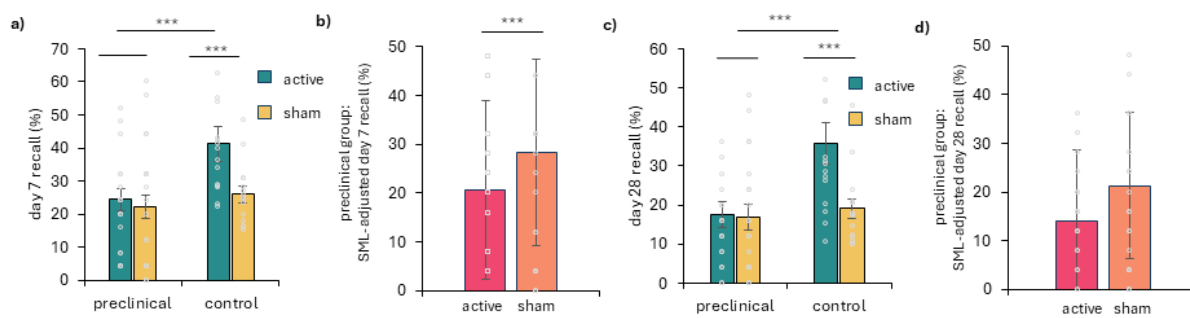


Figure 5.4 | Memory Outcomes of GON-tDCS. **A** memory recall on day 7 for preclinical and control conditions and active and sham stimulation. **B** subjective memory loss (SML) adjusted recall on day 7 for the preclinical group. **C** memory recall on day 28 for preclinical and control conditions and active and sham stimulation. **D** subjective memory loss (SML) adjusted recall on day 28 for the preclinical group.

5.3.2.4 Subjective Memory

An additional analysis was conducted to examine whether subjective memory complaints influenced GON-tDCS results in the preclinical group specifically. Indeed, when initial learning rates and subjective memory levels were controlled for, there was a significant main effect of stimulation on memory on Day 7 ($F(1, 8.32) = 14.69$, $p = .005$, $\eta^2 = .64$), with the active group ($M = 20.66$, $SD = 18.39$) remembering significantly less than the sham group ($M = 28.33$, $SD = 19.14$; Figure 5.4b). However, when looking at the preclinical group on day 28, when subjective memory levels and baseline learning rates were controlled for, there was no significant main effect of stimulation ($F(1,$

6.59) = 4.03, $p = .09$, $\eta^2 = .38$)(active: $M = 14.00$, $SD = 14.76$; sham: $M = 21.32$, $SD = 15.07$) on memory recall (Figure 5.4d).

5.3.3 *Rs-EEG*

5.3.3.1 *State-dependent Effects of GON-tDCS on Memory*

Pre- to post-stimulation changes in beta activity diverged by condition. In controls, active stimulation was associated with reduced beta synchronization in the left IFG extending into the precentral gyrus ($F(1,15) = 3.10$, $p < 0.05$, $\eta^2 = 0.18$; see Figure 5.5a), whereas the preclinical participants showed the opposite pattern, with increased beta synchronization in the same frontocentral region following active stimulation ($F(1, 15) = 2.65$, $p < 0.05$, $\eta^2 = 0.15$; see Figure 5.5b). No significant pre-to-post changes were observed following sham stimulation in either the preclinical group or the control group (preclinical: $F(1, 19) = 0.78$, $p = .69$; controls: $F(1, 15) = 1.04$, $p = .54$). Consistent with this, a region-of-interest analysis of the change in log-transformed current density in the left IFG from pre- to post-stimulation revealed a significant main effect of condition ($F(1, 60) = 4.91$, $p = 0.03$, $\eta^2 = 0.19$; Figure 5.5c), reflecting a decrease in control participants ($M = -0.10$, $SD = 0.23$) and an increase in preclinical participants ($M = 0.088$, $SD = 0.34$). There was no main effect of stimulation (active versus sham; $F(1, 60) = 0.16$, $p = 0.69$), but there was a significant condition-by-stimulation interaction ($F(1, 60) = 4.79$, $p = 0.033$, $\eta^2 = 0.07$). Contrast analyses showed that under active stimulation, the healthy and preclinical participants differed significantly ($F(1, 60) = 16.87$, $p < 0.001$, $\eta^2 = 0.22$), with decreased current density in healthy controls ($M = -0.14$, $SD = 0.19$) and increased current density in preclinical participants ($M = 0.15$, $SD = 0.13$). No such difference between conditions was observed in the sham group ($F(1, 60) = 1.35$, $p = 0.25$), where values were comparable in controls ($M = -0.05$, $SD = 0.23$) and preclinical participants ($M = 0.02$, $SD = 0.18$).

In healthy controls, greater reductions in log-transformed current density were associated with better memory performance at day 7 ($r = -0.55$, $p = 0.002$; Figure 5.5d) and day 28 ($r = -0.53$, $p = 0.003$; Figure 5.5e), indicating that larger post-stimulation decreases in beta activity predicted stronger long-term retention. By contrast, no significant associations were observed in the preclinical condition (day 7: $r = 0.011$, $p = 0.95$, Figure 5.5f; day 28: $r = 0.001$, $p = 0.99$, Figure 5.5g). The strength of these correlations differed significantly between conditions at both day 7 ($Z = 2.39$, $p = 0.008$) and day 28 ($Z = 2.25$, $p = 0.012$), further indicating that the relationship between stimulation-induced beta change and memory outcome was specific to healthy ageing.

In 10-fold cross-validation across 30 healthy participants, the model showed a predictive relationship between beta change and later memory outcome (correlation coefficient = -0.42 ; mean absolute error = 9.59; root mean squared error = 13.53). The fitted model indicated that larger reductions in left IFG beta were associated with better 7-day memory performance, consistent with the observation that beta decreases in healthy ageing track more favourable long-term retention.

These findings suggest that stimulation-induced beta modulation in the healthy brain is not only associated with later memory, but carries modest prospective information about consolidation-related outcome.

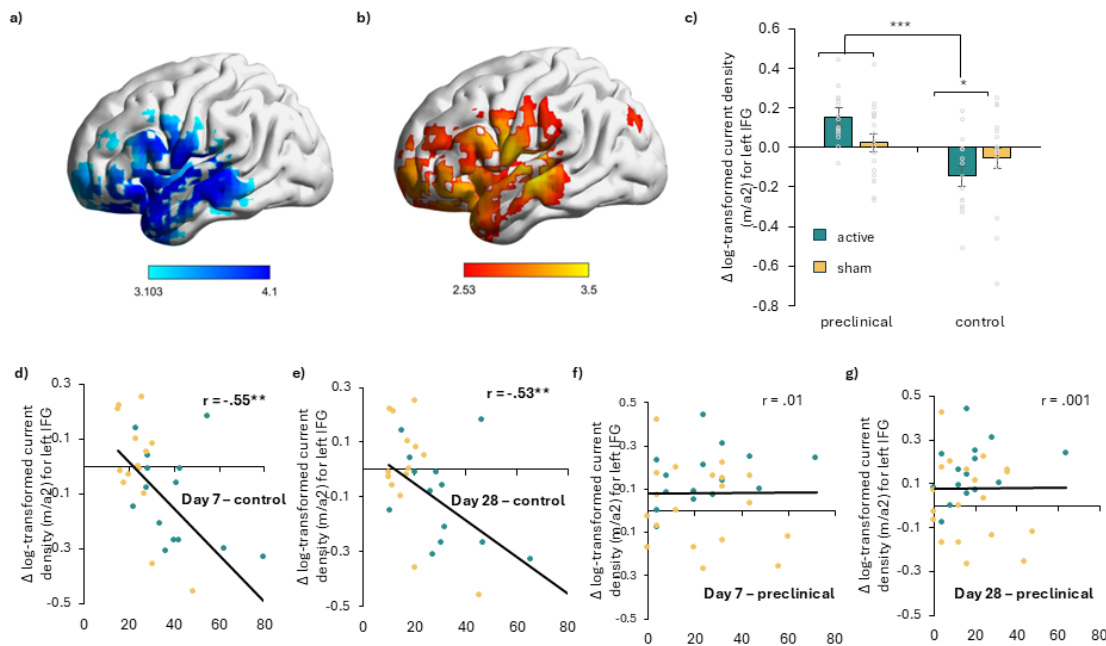


Figure 5.5 | State-dependent Effects of GON-tDCS. **A** reduced beta synchronization in the left IFG extending into the precentral gyrus in control participants. **B** increased beta synchronization in the left IFG extending into the precentral gyrus in preclinical participants **C** the change in log-transformed current density (from pre to post stimulation) for the left IFG for preclinical and control conditions and active and sham stimulation. **D – G** Correlation results between the change in the log-transformed current density for the left IFG and memory recall on **D** day 7 and **E** day 28 for the control participants, and **F** day 7 and **G** day 28 for the preclinical participants.

5.3.3.2 Predicting Stimulation Response from Baseline Neural State

To assess whether pre-stimulation neural state carried predictive information, I trained a random forest classifier to distinguish clinical from healthy participants using baseline left IFG beta activity. In stratified 10-fold cross-validation across 64 individuals, the model correctly classified 41 participants, corresponding to an overall accuracy of 64.1% ($\kappa = 0.29$, weighted F1 = 0.64, ROC area = 0.70). Classification performance was modest in both groups, with 19 of 34 clinical participants correctly identified (recall = 0.56, precision = 0.70) and 22 of 30 healthy participants correctly identified (recall = 0.73, precision = 0.60). The confusion matrix indicated bidirectional misclassification, although errors were more frequent for clinical participants being classified as healthy (15 cases) than for healthy participants being classified as clinical (8 cases). Together, these findings indicate that baseline left IFG beta contains measurable information about underlying group-related neural state before stimulation is applied. This analysis provides proof of principle that pre-

stimulation oscillatory markers may contribute to prospective models aimed at identifying those most likely to benefit from GON-tDCS.

5.3.4 tES Exit Questionnaire

There was no significant effect of condition (controls vs preclinical) for the various tES side effects (Wilks' $\lambda = .92$, $F(7, 62) = .73$, $p = .64$; Figure 5.6a). There was no significant effect of stimulation group (active vs sham) for the various tES side effects (Wilks' $\lambda = .91$, $F(8, 61) = .80$, $p = .61$; Figure 5.6b). In particular, there were no measurable differences in neck pain, skin redness, or acute mood change symptoms, and no significant differences in the remaining symptoms (of headache, tingling, scalp pain, itching, burning, sleepiness or trouble concentrating). All stimulation sessions were well tolerated, and no major stimulation related complications were noted.

Blinding of stimulation conditions was effective as there was no significant difference between which groups controls and preclinical participants thought they were in (active vs non-active) compared to their actual groups (active vs sham) (preclinical: $\chi^2(1, N = 39) = 0.30$, $p = .58$; controls: $\chi^2(1, N = 30) = 0.00$, $p = 1.00$; total: $\chi^2(1, N = 69) = 0.14$, $p = .71$) (see Figure 5.6c and 5.6d).

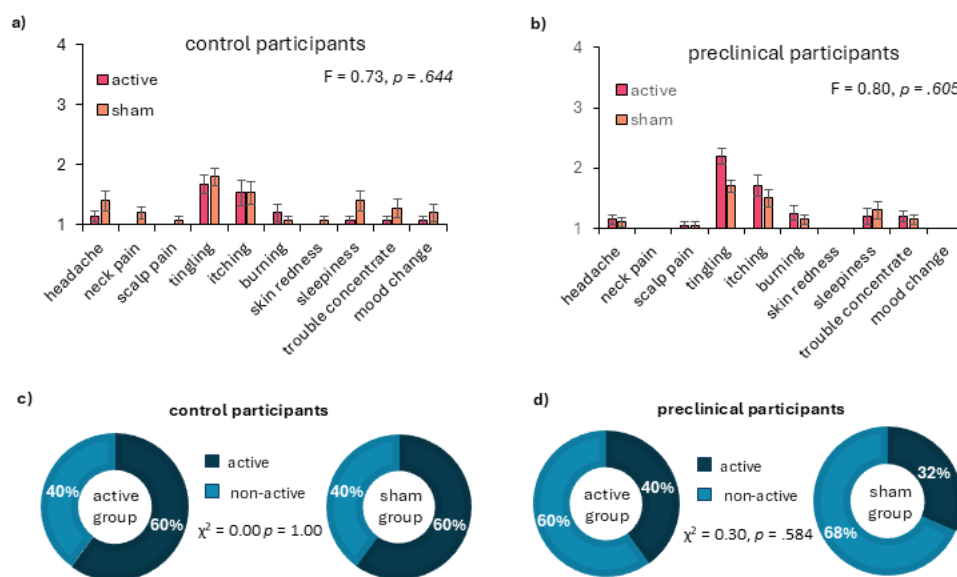


Figure 5.6 | Blinding and Stimulation Sensations. Stimulation sensations for the active and sham stimulation groups in the **A** control and **B** preclinical participants. **C – D** Proportion of participants who believed they received active versus non-active stimulation compared to what they actually received (active or sham), in the **C** control and **D** preclinical conditions.

5.4 Discussion

The present findings show that the effects of greater occipital nerve stimulation on memory are not uniformly facilitatory, but depend on the neural state into which stimulation is delivered. In healthy older adults, stimulation enhanced associative memory retention at 7 and 28 days without affecting initial learning. Whereas in preclinical Alzheimer's disease, it did not improve retention overall and, when subjective memory complaints were taken into account, it was associated with poorer 7-day recall.

These divergent behavioural outcomes were accompanied by opposite changes in frontocentral beta activity. Greater occipital nerve stimulation reduced beta synchronization in healthy ageing but increased it in preclinical participants, and only beta reductions predicted subsequent memory. Extending prior demonstrations of memory benefit in healthy individuals (Luckey, McLeod, et al., 2023; Luckey et al., 2020; Vanneste et al., 2020), the present study shows that the same stimulation protocol can produce beneficial, null, or adverse mnemonic outcomes depending on ageing or pathology-related brain state.

These findings extend state-dependent accounts of non-invasive brain stimulation by showing that the same stimulation protocol can produce qualitatively different outcomes across ageing trajectories. Previous work has argued that stimulation effects depend on ongoing neural activity and task engagement, and that this dependence may underlie some of the variability that characterizes the tES literature (Bradley et al., 2022; Silvanto et al., 2008; Vergallito et al., 2022). The present results bring this principle into a clinically relevant context by showing that state dependence is not only a feature of moment-to-moment task engagement, but also of pathological brain state. In this view, heterogeneity in stimulation outcomes may reflect systematic differences in network dynamics rather than experimental noise alone.

The electrophysiological findings provide novel information as to the nature and impact of this state dependence. In healthy ageing, stimulation shifted post-learning beta activity in the direction previously associated with successful long-term retention, and the magnitude of beta reduction predicted later recall. In preclinical participants, the same stimulation produced the opposite beta response and no memory benefit. Notably, beta modulation did not merely accompany the behavioural dissociation; it tracked its direction, magnitude and group specificity, making it the most immediate candidate marker of the neural state that gates stimulation outcome. More broadly, convergent work indicates that beta activity is not a unitary rhythm, but a context-sensitive signature of prefrontal control that can index maintenance, inhibitory control, interference suppression, or network reconfiguration depending on task demands (Bencze et al., 2025; Fang et al., 2023; Hanslmayr et al., 2014; Schmidt et al., 2019; Wen et al., 2024). The present findings are consistent with that account, suggesting that stimulation outcome depends less on the nominal protocol itself than on whether it moves ongoing dynamics towards or away from a memory-permissive state.

Importantly, these differences are unlikely to be explained by nonspecific effects of stimulation. GON-tDCS did not alter initial learning, arguing against an account based on enhanced encoding,

and the intervention was well tolerated and effectively blinded across groups, making explanations based on discomfort or expectancy less likely. Instead, the data point more specifically to differences in how post-learning neural state is perturbed by stimulation. This interpretation is reinforced by the fact that only the healthy group showed the pattern of beta modulation associated with improved later retention.

The preclinical pattern is consistent with the idea that individuals at risk for Alzheimer's disease exhibit an altered oscillatory and neuromodulatory regime. Preclinical AD has been associated with atypical beta-gamma activity, altered encoding-related responses, and early locus coeruleus vulnerability (Dahl, Bachman, et al., 2023; Gaubert et al., 2019; Hayes et al., 2017; Jacobs et al., 2021; Kim et al., 2026; Krohn et al., 2023; Noei et al., 2022). Within that context, the opposite beta response observed here suggests that stimulation engages a system already operating under altered constraints. Rather than normalising network dynamics, stimulation may in some individuals further displace them from an optimal operating range, which could explain the absence of benefit and the transient impairment observed when subjective memory complaints were taken into account. The preclinical pattern therefore appears to reflect a boundary condition on efficacy, with evidence for adverse effects under some symptom-defined conditions rather than a uniform impairment effect.

A plausible mechanistic account is that these effects are shaped by differences in locus coeruleus-noradrenergic function. Peripheral stimulation has been proposed to engage LC-linked pathways (Luckey, McLeod, et al., 2023; Vanneste et al., 2020), and preclinical Alzheimer's disease is associated with early LC vulnerability, altered functional connectivity and disrupted neuromodulatory regulation (Dahl, Bachman, et al., 2023; Gong et al., 2023; Krohn et al., 2023; Mather, 2025). Within this framework, healthy older adults may remain in a regime in which stimulation supports consolidation-related signalling, whereas preclinical participants may lie closer to a dysregulated range in which the same input is ineffective or counterproductive. This is compatible with broader evidence that cognitive performance follows a non-linear relationship with catecholaminergic tone (Baldi & Bucherelli, 2005; Monte-Silva et al., 2010; Nieuwenhuis et al., 2005; Vijayraghavan et al., 2007), and with work showing that LC activity can shift cortical state across distinct network configurations (Noei et al., 2022).

In parallel, although ALF is acknowledged as one of the earliest detectable cognitive symptoms in preclinical AD (Ohno, 2023), the present study did not find evidence of ALF in preclinical participants. Instead, I observed no significant difference in forgetting rates of control and preclinical participants who received sham stimulation. However, while prior studies have reported ALF in individuals with SCD, they have likewise found that these forgetting rates were greatest for participants with increased AD pathology (e.g. A β plaques) (García-Martínez et al., 2023; Ohno, 2023; Tort-Merino, Laine, et al., 2021; Tort-Merino, Valech, et al., 2021). Thus, it is possible in the present study that AD-pathology in preclinical participants were minimal as of yet, and thus symptoms of ALF were not yet detectable. Moreover, I found that GON-tDCS had no effect on ALF generally, or for preclinical or control participants specifically.

Notably, while ALF differences between control and preclinical participants were not detectable in the present study, the present findings point to an alternative potential route for stratification. Stimulation-induced changes in beta activity not only distinguished healthy and preclinical participants, but in healthy ageing also carried prospective information about later memory outcome, with greater reductions in left IFG beta predicting better 7-day retention in cross-validated regression. In parallel, baseline left IFG beta provided modest cross-validated discrimination between clinical and healthy participants, indicating that pre-stimulation oscillatory state already contains measurable information about group-related neural vulnerability before stimulation is applied. Together, these findings suggest that dynamic and baseline beta markers may index complementary aspects of stimulation susceptibility. The former reflecting whether stimulation shifts the brain towards a memory-permissive state, and the latter capturing the broader neural context into which stimulation is delivered.

Some limitations should be acknowledged. First, the involvement of the LC–NA pathway is inferred rather than directly demonstrated in the present study. However, this interpretation is supported by prior work from our group and others showing that occipital nerve-targeted direct current stimulation can activate LC–NA circuitry and enhance memory performance in both humans and animals (Luckey, Adcock, et al., 2023; Luckey, McLeod, et al., 2023; Majdi et al., 2023; A. Majdi et al., 2025; Vanneste et al., 2020). Second, the preclinical group combined individuals with SCD and aMCI, likely increasing heterogeneity in disease stage. However, this grouping was intended to reflect an at-risk continuum, given evidence that subjective memory complaints precede aMCI and are linked to later cognitive decline, dementia, and early AD-related brain changes (Hayes et al., 2017; S. M. Wang et al., 2021; X. T. Wang et al., 2021). Future studies combining peripheral stimulation with direct measures of noradrenergic function, stage-sensitive biomarkers, and prospective stratification will be important for testing mechanism and refining clinical relevance.

5.4.1 Conclusion

In summary, identical peripheral stimulation produced beneficial, null, or adverse memory-related outcomes depending on the underlying brain state. By linking this behavioural divergence to opposite post-learning beta responses, the present study provides a testable framework for understanding variability in neuromodulation and supports the development of biomarker-informed stimulation strategies in ageing and preclinical AD. More broadly, these findings indicate that variability in neuromodulation is a consequence of the state-dependent nature of brain stimulation, whereby identical stimulation can produce beneficial, null or adverse effects depending on the underlying neural context. This principle is likely to extend beyond memory to other state-sensitive domains, including attention, perception and motor control. Framed in this way, the future of neuromodulation is unlikely to lie in one-size-fits-all protocols, but in adaptive interventions that are tailored to the neural state of the individual brain

CHAPTER SIX: GENERAL DISCUSSION

6.1 Summary

The present thesis sought to advance our understanding of how memory persistence is regulated within the human brain by reconceptualising pathological forgetting as an active, adaptive and dynamically controlled process. Moving beyond traditional dichotomies that frame remembering and forgetting as opposing outcomes, this work proposed that both processes are governed by a regulatory architecture that determines the accessibility, stability and updating of memory representations. This thesis began by integrating theoretical developments in memory literature to emphasise that memory control outcomes are not solely dependent on stabilisation processes, but instead emerge from the dynamic interplay between mechanisms that support persistence and those that promote forgetting. Building on this framework, the empirical chapters employed peripheral nerve stimulation as a tool to experimentally probe this regulatory system, specifically investigating whether its effects on memory are driven by enhancement of memory stabilisation processes or the modulation of forgetting mechanisms, and to further elucidate the reasons for variability in stimulation outcomes.

Chapter 1 established the conceptual foundation for this work by building on classical and contemporary models of memory. Traditional frameworks have long conceptualised forgetting as a passive consequence of decay, interference or retrieval failure (Dudai et al., 2015; Ebbinghaus, 2013). However, converging evidence from molecular neuroscience, behavioural paradigms and computational modelling has led to a paradigm shift, wherein forgetting is increasingly understood as an active and biologically orchestrated process (Berry et al., 2024; Davis & Zhong, 2017; Ryan & Frankland, 2022). Within this emerging framework, forgetting does not necessarily reflect erasure of memory traces, but rather changes in their accessibility, often mediated by inhibitory control, synaptic remodelling and neuromodulatory signalling.

Building on this literature, chapter 1 introduced the forgetting continuum, which conceptualised memory dysfunction along a spectrum ranging from hyperforgetting (e.g. ALF) to hypoforgeting (e.g. maladaptive persistence in PTSD and addiction). This framework shifts focus from isolated deficits in encoding or consolidation toward dysregulation within a broader memory control system, offering a unified account that accommodates forgetting symptomology observed across neurological and psychiatric conditions.

Chapter 1 further integrated predictive processing accounts, proposing that memory control reflects adaptive model updating driven by prediction error signals (Kube et al., 2020; Sinclair & Barense, 2019). Within this framework, forgetting serves a functional role by suppressing outdated representations and facilitating behavioural flexibility. Central to this regulatory architecture is the LC-NA system, which modulates attention, arousal, synaptic plasticity and is therefore well positioned to influence memory persistence (Mather et al., 2016; Sara, 2009).

In terms of the stimulation literature, there is widespread heterogeneity in tDCS' effects on cognition and memory (Horvath et al., 2015; Huo et al., 2021; Indahlstari et al., 2021). Given this, this thesis aimed to investigate if tDCS' variable memory effects could be better understood in light

of the theoretical proposition made here. As such, chapters 2, 3 and 5 empirically tested whether GON-tDCS, an approach that engages the LC-NA pathway, has delineated effects on memory persistence versus forgetting dynamics, and how factors such as state-dependency interacts with GON-tDCS to determine memory outcomes.

Specifically, chapter 2 demonstrated that GON-tDCS enhances reconsolidation processes, strengthening memory stabilisation following reactivation. However, GON-tDCS does not mitigate retrieval-induced forgetting mechanisms, suggesting that stabilisation and active forgetting are dissociable processes within the memory control system. Furthermore, it suggests that GON-tDCS has delineated effects on reconsolidation and active forgetting dynamics.

Chapter 3 investigated how GON-tDCS impacted emotional memory formation and persistence. Critically, it found that GON-tDCS can attenuate the persistence of emotional memories. Although this might appear to suggest that GON-tDCS can enhance forgetting of these emotional memories, in line with theoretical models of PTSD, I argue that in this case, the attenuation of emotional memories may be achieved through GON-tDCS' effects on synaptic tag and capture processes and through supporting consolidation and integration dynamics. Moreover, this chapter outlined how GON-tDCS also reduced pupil dilation, suggesting modulation of noradrenergic activity, and supporting the argument of a LC-NA mechanism.

In chapter 4, the potential mechanisms underlying excessive or impaired forgetting at either end of the continuum are explored. Building on chapter 1, forgetting is framed as an active, adaptive process driven in part by prediction errors, which alter the accessibility of memory traces (engrams). Beginning with a focus on ALF, this chapter reviews the literature to highlight various neurobiological mechanisms (such as synaptic remodelling, neurotransmitter balance (glutamate, GABA, dopamine), glial cell activity, neurogenesis, and cytoskeletal changes) that regulate this process. Evidence for disruptions in these processes are discussed across conditions along the forgetting continuum including AD, PD, epilepsy, stroke, traumatic brain injury, PTSD, Autism Savante syndrome and HSAM.

Chapter 5 examined GON-tDCS' effects in individuals with preclinical AD or healthy controls. As expected, GON-tDCS had no effect on memory encoding. Moreover, this chapter demonstrated that there were no differences in ALF between preclinical participants and healthy controls, and GON-tDCS had no impact on rates of ALF. Additionally, this chapter critically observed that GON-tDCS upregulated memory consolidation only in healthy controls, and that its effects are strongly state-dependent. These results highlight that stimulation outcomes are constrained by underlying brain states, with oscillatory activity shaping responsiveness to neuromodulation. In particular, it highlighted how baseline beta activity and beta oscillatory dynamics can potentially predict individuals at risk of developing AD, as well as GON-tDCS responders and non-responders.

Taken together, these findings demonstrate that peripheral nerve stimulation does not exert uniform effects on memory. Rather, it interacts with a dynamic and context-sensitive memory control system, with outcomes shaped by memory stage, memory type and intrinsic neural state. This

supports a shift away from viewing memory as a static storage system and toward understanding it as an adaptive process governed by ongoing regulatory mechanisms.

6.2 Novel Contribution of this Thesis

Building on the empirical and theoretical synthesis outlined above, this thesis makes several novel contributions to the literature on memory, forgetting and neuromodulation.

First, this work builds on the emerging view that forgetting is not as a passive failure of memory, but an active and adaptive process (Berry et al., 2024; Davis & Zhong, 2017; Ryan & Frankland, 2022). Critically, the present thesis extends this perspective by situating forgetting within a broader system of memory control, in which memory persistence is determined by the dynamic interaction between stabilisation and weakening processes. Moreover, this thesis demonstrates across multiple experimental contexts that modulation of memory outcomes can arise through selective influences on these interacting processes.

Second, the thesis introduces and develops the forgetting continuum as a unifying theoretical framework. By conceptualising hyperforgetting and hypoforgetting as opposing outcomes of a shared regulatory system, this model integrates phenomena that are typically studied in isolation. This provides a parsimonious account of memory dysfunction across neurological and psychiatric conditions and shifts the focus toward dysregulation of shared plasticity and memory control mechanisms.

Third, this work contributes to the integration of predictive processing with neurobiological models of memory control. By framing forgetting as a mechanism of model updating driven by prediction error, this thesis bridges computational and biological accounts of memory. This integration provides a potential mechanistic explanation for why forgetting occurs and how it contributes to adaptive behaviour.

Fourth, this thesis includes a novel review which specifically explores how the symptom of ALF (which presents across various neuropsychiatric disorders) may stem from hijacked intrinsic forgetting processes, and the neurobiological pathways that may underlie this. Furthermore, it summarises these synaptic strength mechanisms that contribute to engram cell accessibility and how this relates to forgetting processes not just for conditions where ALF presents as a symptom, but for other disorders across the forgetting continuum.

Fifth, this thesis provides novel empirical evidence across 3 chapters that peripheral nerve stimulation has selective effects on memory processes that depend on context and neural state. Specifically, it supports the argument that memory strengthening and active forgetting are dissociable processes with GON-tDCS enhancing reconsolidation but not impacting retrieval-induced forgetting. It also highlighted how GON-tDCS can attenuate emotional memory expression, potentially through supporting memory consolidation and integration. In addition, it novelly demonstrated how GON-tDCS has dissociable effects on forgetting and consolidation processes in preclinical AD and healthy

older adults, further supporting the argument that memory persistence and forgetting are governed by divergent synaptic plasticity and neuromodulatory mechanisms.

Notably, chapter 5 identified state-dependency as a core principle governing the effects of neuromodulation on memory. Not only did it demonstrate how baseline beta activity and post-learning beta dynamics play a decisive role in determining responsiveness to stimulation, but it outlined how these state-dependent effects have critical implications for the efficacy of stimulation protocols in preclinical groups. This has important implications for both experimental design and clinical translation, suggesting that individual differences in neural state must be accounted for in order to optimise intervention outcomes. This is consistent with evidence from other neuromodulation techniques, such as transcranial magnetic stimulation (TMS) where cognitive brain state, oscillatory brain state, and recent brain state history, as well as factors such as baseline excitability predict responsiveness to TMS (Sack et al., 2024; Silvanto et al., 2008). Furthermore, in particular, the present work provides preliminary support for how baseline and dynamic beta markers may index complementary aspects of stimulation susceptibility. The former reflecting whether stimulation shifts the brain towards a memory-permissive state, and the latter capturing the broader neural context into which stimulation is delivered. These results may enable a biomarker-based approach to predicting which individuals are at risk of developing AD, as well those likely to respond or not respond to GON-tDCS.

Taken together, this thesis proposes a new conceptual framework for understanding the regulatory architecture that underlies memory control processes, and provides evidence for how GON-tDCS can upregulate LC-NA activity, has divergent effects on memory persistence and forgetting dynamics, and how state-dependency is a critical factor in the variability in tDCS outcomes.

6.3 Limitations, Future Directions and Clinical Implications

Although this work makes several novel contributions, some limitations within this thesis should be acknowledged. Importantly, building on the findings and limitations of this thesis, several key directions for future research emerge. These directions span methodological, theoretical and translational domains, reflecting the interdisciplinary nature of this work.

6.3.1 *The LC-NA Mechanism of GON-tDCS*

The first limitation of the present thesis is in relation to the indirect characterisation of GON-tDCS' proposed LC-NA system. For example, in chapter 3, GON-tDCS' LC-NA mechanism was inferred through measuring pupil dilation. However, this serves as an indirect proxy measure of noradrenergic activity (Geršak, 2020; Murphy et al., 2014; Viglione et al., 2023). Similarly, chapter 5 included preclinical AD participants who can typically exhibit LC degeneration (Bell et al., 2023; Dahl, Bachman, et al., 2023; Gong et al., 2023; Jacobs et al., 2021; Mather, 2025); however, this degeneration or LC-NA dysfunction can only be inferred here as no measures of LC degeneration or noradrenaline activity were recorded in this study. The absence of direct LC neural measurements

limits the ability to draw definitive conclusions regarding specific circuits and neurotransmitter systems involved. However, prior research has demonstrated that greater occipital nerve stimulation modulates LC-NA activity influencing learning and memory processes (Arulchelvan & Vanneste, 2025b; Luckey, McLeod, et al., 2023; Vanneste et al., 2020). Thus, an important next step will be to further validate this mechanism when applying this stimulation technique across the forgetting continuum, for example by combining neuromelanin-sensitive MRI techniques with additional indirect noradrenaline proxy measures such as salivary α -amylase. This is particularly salient given that the theoretical framework advanced in this thesis places neuromodulatory control at the centre of memory regulation.

6.3.2 The Predictive Processing Component of the Forgetting Continuum

Secondly, this thesis proposes a continuum model of forgetting where dysregulation in synaptic plasticity processes may contribute to symptoms of memory persistence or accelerated forgetting across a range of psychiatric disorders. It suggests that these forgetting outcomes may depend on a dynamic interaction between engram stabilisation or attenuation, which are determined by predictive coding processes and LC-NA activity. Notably, this theoretical perspective incorporates predictive processing as it relates to memory control at the conceptual level. However, this thesis did not experimentally test this component of the theory. Moreover, empirical work directly linking prediction error signals to forgetting mechanisms remains limited. However, as I outline in (Arulchelvan & Vanneste, 2025a), there is recent emerging evidence that therapeutic approaches (such as tDCS, TMS, EMDR or neurofeedback) are seeing initial success in improving pathological forgetting symptoms across various disorders by targeting predictive processes (Askovic et al., 2020; Bu et al., 2019; C. Y. Chen et al., 2023; Gu et al., 2022; Lamprecht et al., 2004; Tillman et al., 2023). Nevertheless, this is still a very nascent research area. As such, future research in humans could measure ERP markers of prediction errors to further confirm if/ how these relate to forgetting across the continuum, and whether stimulation approaches such as GON-tDCS can modulate these in association with memory or forgetting outcomes.

6.3.3 The Potential Translational Application of GON-tDCS Across the Forgetting Continuum

In line with this, another critical future direction is the translation of these findings into clinical populations. The continuum framework provides a novel lens through which to conceptualise a range of disorders characterised by maladaptive persistence or accelerated forgetting, and highlights how synaptic plasticity, neuromodulatory factors and prediction error processes may influence engram accessibility and underlie the symptoms at either end of the spectrum. The studies in chapters 2 and 3 were conducted in healthy adults, whereas chapter 5 focused on individuals with preclinical AD versus healthy older adults. While this combination provides initial insight into both normative and pathological memory processes, it does not capture the full spectrum of populations relevant to the forgetting continuum proposed in this thesis. Similarly, although emotional memory persistence was assessed in chapter 3, this was done in healthy adults. As a result, the extent to which the observed

effects of peripheral nerve stimulation generalise across clinical populations remains an open question. Future research should extend these paradigms to diverse and clinically relevant cohorts, enabling a more comprehensive test of the continuum framework.

For example, these findings may have translational applications for individuals with PTSD, where intrusive memories are thought to persist due to their heightened accessibility and poor integration into memory networks (Dalgleish, 2004; Foa et al., 2006; Foa & Kozak, 1986). Typically for these individuals, traditional therapeutic approaches including exposure therapy aim to reduce the emotional impact of these memories through repeated reactivation and extinction. However, the present findings suggest that GON-tDCS may provide a complementary or synergistic approach by modulating the strength, accessibility and integration of such memories, which may enhance the efficacy of existing treatments. These potential translational applications warrant future investigation in clinical samples. This framework and stimulation protocol also has implications for addiction and compulsive disorders, where maladaptive persistence of reward-related memories contributes to relapse. Thus, if interventions like GON-tDCS can attenuate the persistence of emotional memories, perhaps it can likewise modulate persistence of reward-related memories given the common neural circuits in the brain and synaptic plasticity mechanisms. Thus, whether this stimulation technique has translational implications for addiction or compulsive related disorders is worth investigating in future research.

6.3.4 Personalised Neuromodulation Approaches and Baseline Oscillatory Activity

Another important next step will be to incorporate the integration of multimodal neuroimaging techniques. For example, combining peripheral nerve stimulation with real-time neuroimaging methods such as fMRI, EEG or MEG where possible, would allow for more precise characterisation of the neural mechanisms underlying observed behavioural effects in this thesis. Related to this, one of the most promising avenues for future research based on this work is the development of precision or personalised neuromodulation approaches. The state-dependent effects observed in chapter 5 highlight that baseline and dynamic neural activity play a critical role in determining responsiveness to stimulation.

This suggests that future interventions should move beyond standardised protocols and instead tailor stimulation parameters to individual neural profiles. Advances in real-time neuroimaging and electrophysiology make it increasingly feasible to implement closed-loop systems, in which stimulation is dynamically adjusted based on ongoing brain activity (Soleimani et al., 2023). Such approaches have the potential to enhance efficacy while reducing variability. Based on the findings in chapter 5, a future direction could explore whether closed-loop GON-tDCS targeting beta activity is a feasible preventative option for individuals at-risk of AD and prior to them experiencing subjective memory difficulties.

In summary, while the present thesis advances a novel framework for understanding factors that govern memory persistence across the forgetting continuum, it also underscores the need for more precise, mechanistic and translational approaches. Addressing these challenges will be essential for fully understanding the boundary conditions that limit the efficacy of neuromodulation as a tool for modifying human memory.

6.4 Conclusion

The present thesis set out to advance understanding of how memory persistence is regulated within the human brain by challenging the traditional view of forgetting as a passive failure of memory. Instead, it proposed the view that forgetting is an active, adaptive, and dynamically controlled process that operates in concert with mechanisms of memory stabilisation. Across four chapters, this work demonstrated that memory outcomes emerge from the interaction between processes that strengthen, weaken, and update memory representations, and that GON-tDCS has disassociated effects on these processes.

A central contribution of this thesis is the articulation of memory as a regulated system, in which persistence is not fixed but continuously shaped by neural dynamics, neuromodulatory influences, predictive processing and contextual factors. This shifts the focus from memory outcomes being determined by isolated deficits in encoding or consolidation, towards broader dysregulation of memory control across both health and disease. Empirically, the findings show that GON-tDCS does not globally enhance memory, but rather interacts selectively with specific memory processes. In healthy adults it enhanced reconsolidation but did not mitigate active forgetting, and it attenuated emotional memory expression. However, it had no impact on ALF. Instead, it enhanced long-term retention in healthy older adults but not preclinical AD participants in a manner that is highly dependent on baseline neural state. These findings highlight the importance of considering both the memory type and stage, and the intrinsic state of the system being modulated.

More broadly, this thesis contributes to an emerging shift in cognitive neuroscience toward mechanism-based and systems-level accounts of behaviour. Within this integrated account, forgetting is not simply a loss of information, but a necessary and functional component of adaptive cognition, enabling the updating of internal models, the reduction of interference, and the prioritisation of behaviourally relevant information. At the same time, the findings highlight the inherent complexity of modulating memory in humans.

In conclusion, this thesis advances a novel and integrative account of memory persistence as a dynamically regulated process, and establishes the groundwork for future research aimed at understanding, and ultimately harnessing, the mechanisms that govern when we remember, and when we forget.

REFERENCES

- Adlaf, E. W., Vaden, R. J., Niver, A. J., Manuel, A. F., Onyilo, V. C., Araujo, M. T., Dieni, C. V., Vo, H. T., King, G. D., Wadiche, J. I., & Overstreet-Wadiche, L. (2017). Adult-born neurons modify excitatory synaptic transmission to existing neurons. *eLife*, 6, e19886. <https://doi.org/10.7554/eLife.19886>
- Akers, K. G., Martinez-Canabal, A., Restivo, L., Yiu, A. P., De Cristofaro, A., Hsiang, H.-L., Wheeler, A. L., Guskjolen, A., Niibori, Y., Shoji, H., Ohira, K., Richards, B. A., Miyakawa, T., Josselyn, S. A., & Frankland, P. W. (2014). Hippocampal Neurogenesis Regulates Forgetting During Adulthood and Infancy. *Science (New York, N.Y.)*, 344(6184), 598-602. <https://doi.org/doi:10.1126/science.1248903>
- Akyuz, E., Polat, A. K., Eroglu, E., Kullu, I., Angelopoulou, E., & Paudel, Y. N. (2021). Revisiting the role of neurotransmitters in epilepsy: An updated review. *Life Sciences*, 265, 118826. <https://doi.org/https://doi.org/10.1016/j.lfs.2020.118826>
- Alberini, C. M., & LeDoux, J. E. (2013). Memory reconsolidation. *Current Biology*, 23(17), R746-R750. <https://doi.org/10.1016/j.cub.2013.06.046>
- Alnæs, D., Sneve, M. H., Espeseth, T., Endestad, T., van de Pavert, S. H. P., & Laeng, B. (2014). Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. *Journal of Vision*, 14(4), 1-1. <https://doi.org/10.1167/14.4.1>
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. https://www.ncbi.nlm.nih.gov/books/NBK207191/box/part1_ch3.box16/
- Anderson, M. C., Bjork, R. A., & Bjork, E. L. (1994). Remembering can cause forgetting: retrieval dynamics in long-term memory. *J Exp Psychol Learn Mem Cogn*, 20(5), 1063-1087. <https://doi.org/10.1037//0278-7393.20.5.1063>
- Anderson, M. C., Crespo-Garcia, M., & Subbulakshmi, S. (2025). Brain mechanisms underlying the inhibitory control of thought. *Nature Reviews Neuroscience*, 26(7), 415-437. <https://doi.org/10.1038/s41583-025-00929-y>
- Anderson, M. C., & Hanslmayr, S. (2014). Neural mechanisms of motivated forgetting. *Trends in Cognitive Sciences*, 18(6), 279-292. <https://doi.org/https://doi.org/10.1016/j.tics.2014.03.002>
- Anderson, M. C., & Hulbert, J. C. (2021). Active Forgetting: Adaptation of Memory by Prefrontal Control. *Annual Review of Psychology*, 72(Volume 72, 2021), 1-36. <https://doi.org/https://doi.org/10.1146/annurev-psych-072720-094140>
- Anderson, M. C., & Neely, J. H. (1996). Chapter 8 - Interference and Inhibition in Memory Retrieval. In E. L. Bjork & R. A. Bjork (Eds.), *Memory* (pp. 237-313). Academic Press. <https://doi.org/https://doi.org/10.1016/B978-012102570-0/50010-0>
- Arnsten, A. F. T. (2011). Catecholamine Influences on Dorsolateral Prefrontal Cortical Networks. *Biological Psychiatry*, 69(12), e89-e99. <https://doi.org/https://doi.org/10.1016/j.biopsych.2011.01.027>
- Arulchelvan, E., & Vanneste, S. (2025a). Pathological forgetting from a predictive processing perspective. *Neuroscience & Biobehavioral Reviews*, 172, 106109. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2025.106109>
- Arulchelvan, E., & Vanneste, S. (2025b). Transcutaneous electrical stimulation enhances episodic memory encoding via a noradrenaline-attention network, with associated neuroinflammatory changes. *Brain Stimulation*, 18(1), 191-207. <https://doi.org/https://doi.org/10.1016/j.brs.2025.01.008>
- Arulchelvan, E., & Vanneste, S. (2026a). Accelerated long-term forgetting across neuropsychiatric disorders: A review of mechanisms and a neurobiological perspective of forgetting. *Neuroscience & Biobehavioral Reviews*, 180, 106461. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2025.106461>
- Arulchelvan, E., & Vanneste, S. (2026b). Targeting active forgetting with non-invasive stimulation: toward novel treatments for intrusive memories in PTSD. *International Review of Psychiatry*, 1-23. <https://doi.org/10.1080/09540261.2026.2631028>

- Asamoah, B., Khatoun, A., & Mc Laughlin, M. (2019). tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. *Nature Communications*, 10(1), 266. <https://doi.org/10.1038/s41467-018-08183-w>
- Askovic, M., Watters, A. J., Coello, M., Aroche, J., Harris, A. W. F., & Kropotov, J. (2020). Evaluation of Neurofeedback for Posttraumatic Stress Disorder Related to Refugee Experiences Using Self-Report and Cognitive ERP Measures. *Clinical EEG and Neuroscience*, 51(2), 79-86. <https://doi.org/10.1177/1550059419849170>
- Astill Wright, L., Horstmann, L., Holmes, E. A., & Bisson, J. I. (2021). Consolidation/reconsolidation therapies for the prevention and treatment of PTSD and re-experiencing: a systematic review and meta-analysis. *Translational Psychiatry*, 11(1), 453. <https://doi.org/10.1038/s41398-021-01570-w>
- Aston-Jones, G., Rajkowski, J., & Cohen, J. (1999). Role of locus coeruleus in attention and behavioral flexibility. *Biol Psychiatry*, 46(9), 1309-1320. [https://doi.org/10.1016/s0006-3223\(99\)00140-7](https://doi.org/10.1016/s0006-3223(99)00140-7)
- Atherton, K. E., Nobre, A. C., Lazar, A. S., Wulff, K., Whittaker, R. G., Dhawan, V., Lazar, Z. I., Zeman, A. Z., & Butler, C. R. (2016). Slow wave sleep and accelerated forgetting. *Cortex*, 84, 80-89. <https://doi.org/https://doi.org/10.1016/j.cortex.2016.08.013>
- Audrain, S., & McAndrews, M. P. (2019). Cognitive and functional correlates of accelerated long-term forgetting in temporal lobe epilepsy. *Cortex*, 110, 101-114. <https://doi.org/https://doi.org/10.1016/j.cortex.2018.03.022>
- Averill, L. A., Purohit, P., Averill, C. L., Boesl, M. A., Krystal, J. H., & Abdallah, C. G. (2017). Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies. *Neurosci Lett*, 649, 147-155. <https://doi.org/10.1016/j.neulet.2016.11.064>
- Baldi, E., & Bucherelli, C. (2005). The Inverted “U-Shaped” Dose-Effect Relationships in Learning and Memory: Modulation of Arousal and Consolidation. *Nonlinearity in Biology, Toxicology, Medicine*, 3(1), nonlin.003.001.002. <https://doi.org/10.2201/nonlin.003.01.002>
- Bangel, K. A., van Buschbach, S., Smit, D. J. A., Mazaheri, A., & Olf, M. (2017). Aberrant brain response after auditory deviance in PTSD compared to trauma controls: An EEG study. *Sci Rep*, 7(1), 16596. <https://doi.org/10.1038/s41598-017-16669-8>
- Bardhoshi, G., Duncan, K., & Erford, B. T. (2016). Psychometric Meta-Analysis of the English Version of the Beck Anxiety Inventory. *Journal of Counseling & Development*, 94(3), 356-373. <https://doi.org/https://doi.org/10.1002/jcad.12090>
- Barron, H. C., Auksztulewicz, R., & Friston, K. (2020). Prediction and memory: A predictive coding account. *Prog Neurobiol*, 192, 101821. <https://doi.org/10.1016/j.pneurobio.2020.101821>
- Battaglia, S., Garofalo, S., Pellegrino, G. d., & Starita, F. (2020). Revaluing the Role of vmPFC in the Acquisition of Pavlovian Threat Conditioning in Humans. *The Journal of Neuroscience*, 40(44), 8491-8500. <https://doi.org/10.1523/jneurosci.0304-20.2020>
- Bauer, K., & Malek-Ahmadi, M. (2023). Meta-analysis of Controlled Oral Word Association Test (COWAT) FAS performance in amnesic mild cognitive impairment and cognitively unimpaired older adults. *Applied Neuropsychology: Adult*, 30(4), 424-430. <https://doi.org/10.1080/23279095.2021.1952590>
- Bayer, H., Bertoglio, L. J., Maren, S., & Stern, C. A. J. (2025). Windows of change: Revisiting temporal and molecular dynamics of memory reconsolidation and persistence. *Neuroscience & Biobehavioral Reviews*, 174, 106198. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2025.106198>
- Beaurenaut, M., Tokarski, E., Dezechache, G., & Grèzes, J. (2020). The ‘Threat of Scream’ paradigm: a tool for studying sustained physiological and subjective anxiety. *Scientific Reports*, 10(1), 12496. <https://doi.org/10.1038/s41598-020-68889-0>
- Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, 56(6), 893-897. <https://doi.org/10.1037/0022-006X.56.6.893>
- Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. F. (1996). Comparison of Beck Depression Inventories-IA and-II in Psychiatric Outpatients. *Journal of Personality Assessment*, 67(3), 588-597. https://doi.org/10.1207/s15327752jpa6703_13
- Bell, T. R., Elman, J. A., Beck, A., Fennema-Notestine, C., Gustavson, D. E., Hagler, D. J., Jack, A. J., Lyons, M. J., Puckett, O. K., Toomey, R., Franz, C. E., & Kremen, W. S. (2023). Rostral-

- middle locus coeruleus integrity and subjective cognitive decline in early old age. *J Int Neuropsychol Soc*, 29(8), 763-774. <https://doi.org/10.1017/s1355617722000881>
- Bencze, D., Marián, M., Szöllösi, Á., Simor, P., & Racsmany, M. (2025). Increase in slow frequency and decrease in alpha and beta power during post-learning rest predict long-term memory success. *Cortex*, 183, 167-182. <https://doi.org/10.1016/j.cortex.2024.11.012>
- Bennett-Levy, J., & Powell, G. E. (1980). The Subjective Memory Questionnaire (SMQ). An investigation into the self-reporting of 'real-life' memory skills. *British Journal of Social and Clinical Psychology*, 19(2), 177-188. <https://doi.org/https://doi.org/10.1111/j.2044-8260.1980.tb00946.x>
- Beppi, C., Ribeiro Violante, I., Scott, G., & Sandrone, S. (2021). EEG, MEG and neuromodulatory approaches to explore cognition: Current status and future directions. *Brain Cogn*, 148, 105677. <https://doi.org/10.1016/j.bandc.2020.105677>
- Berg, M., Feldmann, M., Kirchner, L., & Kube, T. (2022). Oversampled and undersolved: Depressive rumination from an active inference perspective. *Neuroscience & Biobehavioral Reviews*, 142, 104873. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2022.104873>
- Bergado, J. A., Lucas, M., & Richter-Levin, G. (2011). Emotional tagging—A simple hypothesis in a complex reality. *Progress in Neurobiology*, 94(1), 64-76. <https://doi.org/https://doi.org/10.1016/j.pneurobio.2011.03.004>
- Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, 42(1), 33-84. [https://doi.org/https://doi.org/10.1016/S0165-0173\(03\)00143-7](https://doi.org/https://doi.org/10.1016/S0165-0173(03)00143-7)
- Berry, J. A., Guhle, D. C., & Davis, R. L. (2024). Active forgetting and neuropsychiatric diseases. *Molecular Psychiatry*, 29(9), 2810-2820. <https://doi.org/10.1038/s41380-024-02521-9>
- Biau, G., & Scornet, E. (2016). A random forest guided tour. *TEST*, 25(2), 197-227. <https://doi.org/10.1007/s11749-016-0481-7>
- Bisson, J. I., Roberts, N. P., Andrew, M., Cooper, R., & Lewis, C. (2013). Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database of Systematic Reviews*(12). <https://doi.org/10.1002/14651858.CD003388.pub4>
- Blake, R. V., Wroe, S. J., Breen, E. K., & McCarthy, R. A. (2000). Accelerated forgetting in patients with epilepsy: evidence for an impairment in memory consolidation. *Brain*, 123 Pt 3, 472-483. <https://doi.org/10.1093/brain/123.3.472>
- Bradley, C., Nydam, A. S., Dux, P. E., & Mattingley, J. B. (2022). State-dependent effects of neural stimulation on brain function and cognition. *Nature Reviews Neuroscience*, 23(8), 459-475. <https://doi.org/10.1038/s41583-022-00598-1>
- Bradley, M. M., Miccoli, L., Escrig, M. A., & Lang, P. J. (2008). The pupil as a measure of emotional arousal and autonomic activation. *Psychophysiology*, 45(4), 602-607. <https://doi.org/10.1111/j.1469-8986.2008.00654.x>
- Brandt, J., & Bakker, A. (2018). Neuropsychological investigation of "the amazing memory man". *Neuropsychology*, 32(3), 304-316. <https://doi.org/10.1037/neu0000410>
- Breiman, L. (2001). Random Forests. *Machine Learning*, 45(1), 5-32. <https://doi.org/10.1023/A:1010933404324>
- Brohawn, K. H., Offringa, R., Pfaff, D. L., Hughes, K. C., & Shin, L. M. (2010). The Neural Correlates of Emotional Memory in Posttraumatic Stress Disorder. *Biological Psychiatry*, 68(11), 1023-1030. <https://doi.org/https://doi.org/10.1016/j.biopsych.2010.07.018>
- Brønnick, K. S., Nordby, H., Larsen, J. P., & Aarsland, D. (2010). Disturbance of automatic auditory change detection in dementia associated with Parkinson's disease: A mismatch negativity study. *Neurobiol Aging*, 31(1), 104-113. <https://doi.org/10.1016/j.neurobiolaging.2008.02.021>
- Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizziero, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol*, 14(8), 1133-1145. <https://doi.org/10.1017/s1461145710001690>
- Bu, J., Young, K. D., Hong, W., Ma, R., Song, H., Wang, Y., Zhang, W., Hampson, M., Hendler, T., & Zhang, X. (2019). Effect of deactivation of activity patterns related to smoking cue reactivity on nicotine addiction. *Brain*, 142(6), 1827-1841. <https://doi.org/10.1093/brain/awz114>

- Burger, A. M., Van Diest, I., van der Does, W., Hysaj, M., Thayer, J. F., Brosschot, J. F., & Verkuil, B. (2018). Transcutaneous vagus nerve stimulation and extinction of prepared fear: A conceptual non-replication. *Scientific Reports*, 8(1), 11471. <https://doi.org/10.1038/s41598-018-29561-w>
- Burger, A. M., Verkuil, B., Fenlon, H., Thijs, L., Cools, L., Miller, H. C., Vervliet, B., & Van Diest, I. (2017). Mixed evidence for the potential of non-invasive transcutaneous vagal nerve stimulation to improve the extinction and retention of fear. *Behaviour Research and Therapy*, 97, 64-74. <https://doi.org/https://doi.org/10.1016/j.brat.2017.07.005>
- Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neurosciences*, 21(7), 294-299. [https://doi.org/https://doi.org/10.1016/S0166-2236\(97\)01214-9](https://doi.org/https://doi.org/10.1016/S0166-2236(97)01214-9)
- Calderon-Williams, D. R., de Souza, R. R., Tseng, C. T., Abdi, H., Sandoval-Flores, A., Ploski, J. E., Thorn, C. A., & McIntyre, C. K. (2024). Optogenetic inhibition of the locus coeruleus blocks vagus nerve stimulation-induced enhancement of extinction of conditioned fear in rats. *Learn Mem*, 31(12). <https://doi.org/10.1101/lm.053958.124>
- Castillo Díaz, F., Caffino, L., & Fumagalli, F. (2021). Bidirectional role of dopamine in learning and memory-active forgetting. *Neuroscience & Biobehavioral Reviews*, 131, 953-963. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2021.10.011>
- Catarino, A., Küpper, C. S., Werner-Seidler, A., Dalgleish, T., & Anderson, M. C. (2015). Failing to forget: inhibitory-control deficits compromise memory suppression in posttraumatic stress disorder. *Psychol Sci*, 26(5), 604-616. <https://doi.org/10.1177/0956797615569889>
- Chamberlin, D. E. (2019). The Predictive Processing Model of EMDR. *Front Psychol*, 10, 2267. <https://doi.org/10.3389/fpsyg.2019.02267>
- Chang, Y.-H., Yep, R., & Wang, C.-A. (2025). Pupil size correlates with heart rate, skin conductance, pulse wave amplitude, and respiration responses during emotional conflict and valence processing. *Psychophysiology*, 62(1), e14726. <https://doi.org/https://doi.org/10.1111/psyp.14726>
- Chen, B., Gan, H., Yang, L., Yan, X., Lv, X., Zhang, X., & Bu, J. (2025). A novel imagery-based retrieval-extinction training for intervention in nicotine addiction. *BMC Medicine*, 23(1), 568. <https://doi.org/10.1186/s12916-025-04386-3>
- Chen, C. Y., Liu, Y. H., & Muggleton, N. G. (2023). Use of the P300 event-related potential component to index transcranial direct current stimulation effects in drug users. *IBRO Neurosci Rep*, 14, 122-128. <https://doi.org/10.1016/j.ibneur.2023.01.001>
- Chen, L., Deng, Z., Asamoah, B., & Laughlin, M. M. (2023). Trigeminal nerve direct current stimulation causes sustained increase in neural activity in the rat hippocampus. *bioRxiv*, 2023.2012.2012.571341. <https://doi.org/10.1101/2023.12.12.571341>
- Chen, L., Sun, Q., Seminck, N., Huang, H., Asamoah, B., & Laughlin, M. M. (2025). Investigating the effect of non-invasive trigeminal nerve stimulation on memory consolidation: Insights from animal and human studies. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 18(1), 487. <https://doi.org/10.1016/j.brs.2024.12.795>
- Chen, Y., & Gao, X. (2023). Intentional forgetting in excessive behavior: direct suppression and thought substitution. *Addiction Research & Theory*, 31(6), 468-475. <https://doi.org/10.1080/16066359.2023.2210839>
- Cheng, C. H., Chang, C. C., Chao, Y. P., Lu, H., Peng, S. W., & Wang, P. N. (2021). Altered mismatch response precedes gray matter atrophy in subjective cognitive decline. *Psychophysiology*, 58(6), e13820. <https://doi.org/10.1111/psyp.13820>
- Choudhury, P. R., Lahiri, S., & Rajamma, U. (2012). Glutamate mediated signaling in the pathophysiology of autism spectrum disorders. *Pharmacology Biochemistry and Behavior*, 100(4), 841-849. <https://doi.org/https://doi.org/10.1016/j.pbb.2011.06.023>
- Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav Brain Sci*, 36(3), 181-204. <https://doi.org/10.1017/s0140525x12000477>
- Clark, K. B., Naritoku, D. K., Smith, D. C., Browning, R. A., & Jensen, R. A. (1999). Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nature Neuroscience*, 2(1), 94-98. <https://doi.org/10.1038/4600>
- Clewett, D. V., Huang, R., Velasco, R., Lee, T. H., & Mather, M. (2018). Locus Coeruleus Activity Strengthens Prioritized Memories Under Arousal. *J Neurosci*, 38(6), 1558-1574. <https://doi.org/10.1523/jneurosci.2097-17.2017>

- Cohen, N., Moyal, N., & Henik, A. (2015). Executive control suppresses pupillary responses to aversive stimuli. *Biological Psychology*, 112, 1-11. <https://doi.org/https://doi.org/10.1016/j.biopsycho.2015.09.006>
- Colgin, L. L. (2015). Theta-gamma coupling in the entorhinal-hippocampal system. *Curr Opin Neurobiol*, 31, 45-50. <https://doi.org/10.1016/j.conb.2014.08.001>
- Costanzi, M., Cianfanelli, B., Santirocchi, A., Lasaponara, S., Spataro, P., Rossi-Arnaud, C., & Cestari, V. (2021). Forgetting Unwanted Memories: Active Forgetting and Implications for the Development of Psychological Disorders. *J Pers Med*, 11(4). <https://doi.org/10.3390/jpm11040241>
- Crespo-García, M., Wang, Y., Jiang, M., Anderson, M. C., & Lei, X. (2022). Anterior Cingulate Cortex Signals the Need to Control Intrusive Thoughts during Motivated Forgetting. *The Journal of Neuroscience*, 42(21), 4342-4359. <https://doi.org/10.1523/jneurosci.1711-21.2022>
- Cuartero, M. I., de la Parra, J., Pérez-Ruiz, A., Bravo-Ferrer, I., Durán-Laforet, V., García-Culebras, A., García-Segura, J. M., Dhaliwal, J., Frankland, P. W., Lizasoain, I., & Moro, M. Á. (2019). Abolition of aberrant neurogenesis ameliorates cognitive impairment after stroke in mice. *The Journal of Clinical Investigation*, 129(4), 1536-1550. <https://doi.org/10.1172/JCI120412>
- D'Agostini, M., Vanden Bossche, L., Burger, A. M., & Van Diest, I. (2025). Transcutaneous Auricular Vagus Nerve Stimulation Does Not Accelerate Fear Extinction: A Randomized, Sham-Controlled Study. *Psychophysiology*, 62(1), e14754. <https://doi.org/https://doi.org/10.1111/psyp.14754>
- Dahl, M. J., Bachman, S. L., Dutt, S., Düzel, S., Bodammer, N. C., Lindenberger, U., Kühn, S., Werkle-Bergner, M., & Mather, M. (2023). The integrity of dopaminergic and noradrenergic brain regions is associated with different aspects of late-life memory performance. *Nature Aging*, 3(9), 1128-1143. <https://doi.org/10.1038/s43587-023-00469-z>
- Dahl, M. J., Kulesza, A., Werkle-Bergner, M., & Mather, M. (2023). Declining locus coeruleus–dopaminergic and noradrenergic modulation of long-term memory in aging and Alzheimer’s disease. *Neuroscience & Biobehavioral Reviews*, 153, 105358. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2023.105358>
- Dahl, M. J., Mather, M., Sander, M. C., & Werkle-Bergner, M. (2020). Noradrenergic Responsiveness Supports Selective Attention across the Adult Lifespan. *The Journal of Neuroscience*, 40(22), 4372-4390. <https://doi.org/10.1523/jneurosci.0398-19.2020>
- Dahl, M. J., Mather, M., & Werkle-Bergner, M. (2022). Noradrenergic modulation of rhythmic neural activity shapes selective attention. *Trends in Cognitive Sciences*, 26(1), 38-52. <https://doi.org/10.1016/j.tics.2021.10.009>
- Dahl, M. J., Werkle-Bergner, M., & Mather, M. (2024). Neuromodulatory systems in aging and disease. *Neuroscience & Biobehavioral Reviews*, 162, 105647. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2024.105647>
- Dalgleish, T. (2004). Cognitive Approaches to Posttraumatic Stress Disorder: The Evolution of Multirepresentational Theorizing. *Psychological Bulletin*, 130(2), 228-260. <https://doi.org/10.1037/0033-2909.130.2.228>
- Dalto, J. F., Medina, J. H., & Pastor, V. (2025). Molecular Underpinnings of Memory Persistence and Forgetting. *J Neurochem*, 169(5), e70089. <https://doi.org/10.1111/jnc.70089>
- Davis, R. L., & Zhong, Y. (2017). The Biology of Forgetting—A Perspective. *Neuron*, 95(3), 490-503. <https://doi.org/https://doi.org/10.1016/j.neuron.2017.05.039>
- de Oliveira Alvares, L., & Do-Monte, F. H. (2021). Understanding the dynamic and destiny of memories. *Neuroscience & Biobehavioral Reviews*, 125, 592-607. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2021.03.009>
- Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*, 134(1), 9-21. <https://doi.org/10.1016/j.jneumeth.2003.10.009>
- Dolcos, F., LaBar, K. S., & Cabeza, R. (2004). Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron*, 42(5), 855-863. [https://doi.org/10.1016/s0896-6273\(04\)00289-2](https://doi.org/10.1016/s0896-6273(04)00289-2)
- Dong, T., He, J., Wang, S., Wang, L., Cheng, Y., & Zhong, Y. (2016). Inability to activate Rac1-dependent forgetting contributes to behavioral inflexibility in mutants of multiple autism-

- risk genes. *Proc Natl Acad Sci U S A*, 113(27), 7644-7649. <https://doi.org/10.1073/pnas.1602152113>
- Dong, Z., Han, H., Li, H., Bai, Y., Wang, W., Tu, M., Peng, Y., Zhou, L., He, W., Wu, X., Tan, T., Liu, M., Wu, X., Zhou, W., Jin, W., Zhang, S., Sacktor, T. C., Li, T., Song, W., & Wang, Y. T. (2015). Long-term potentiation decay and memory loss are mediated by AMPAR endocytosis. *The Journal of Clinical Investigation*, 125(1), 234-247. <https://doi.org/10.1172/JCI77888>
- Dudai, Y., Karni, A., & Born, J. (2015). The Consolidation and Transformation of Memory. *Neuron*, 88(1), 20-32. <https://doi.org/10.1016/j.neuron.2015.09.004>
- Dunsmoor, J. E., Murty, V. P., Clewett, D., Phelps, E. A., & Davachi, L. (2022). Tag and capture: how salient experiences target and rescue nearby events in memory. *Trends in Cognitive Sciences*, 26(9), 782-795. <https://doi.org/https://doi.org/10.1016/j.tics.2022.06.009>
- Dunsmoor, J. E., Niv, Y., Daw, N., & Phelps, E. A. (2015). Rethinking Extinction. *Neuron*, 88(1), 47-63. <https://doi.org/10.1016/j.neuron.2015.09.028>
- Ebbinghaus, H. (2013). Memory: a contribution to experimental psychology. *Ann Neurosci*, 20(4), 155-156. <https://doi.org/10.5214/ans.0972.7531.200408>
- Ebert, P. L., & Anderson, N. D. (2009). Proactive and retroactive interference in young adults, healthy older adults, and older adults with amnesic mild cognitive impairment. *Journal of the International Neuropsychological Society*, 15(1), 83-93. <https://doi.org/10.1017/S1355617708090115>
- Edwards, G., 3rd, Zhao, J., Dash, P. K., Soto, C., & Moreno-Gonzalez, I. (2020). Traumatic Brain Injury Induces Tau Aggregation and Spreading. *J Neurotrauma*, 37(1), 80-92. <https://doi.org/10.1089/neu.2018.6348>
- Ehlers, A., & Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy*, 38(4), 319-345. [https://doi.org/https://doi.org/10.1016/S0005-7967\(99\)00123-0](https://doi.org/https://doi.org/10.1016/S0005-7967(99)00123-0)
- Elliott, G., Isaac, C. L., & Muhlert, N. (2014). Measuring forgetting: A critical review of accelerated long-term forgetting studies. *Cortex*, 54, 16-32. <https://doi.org/https://doi.org/10.1016/j.cortex.2014.02.001>
- Emonson, M. R. L., Fitzgerald, P. B., Rogasch, N. C., & Hoy, K. E. (2019). Neurobiological effects of transcranial direct current stimulation in younger adults, older adults and mild cognitive impairment. *Neuropsychologia*, 125, 51-61. <https://doi.org/10.1016/j.neuropsychologia.2019.01.003>
- Everitt, B. J., & Robbins, T. W. (2016). Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On. *Annu Rev Psychol*, 67, 23-50. <https://doi.org/10.1146/annurev-psych-122414-033457>
- Exton-McGuinness, M. T. J., Lee, J. L. C., & Reichelt, A. C. (2015). Updating memories—The role of prediction errors in memory reconsolidation. *Behavioural Brain Research*, 278, 375-384. <https://doi.org/https://doi.org/10.1016/j.bbr.2014.10.011>
- Fang, Z., Schuhmann, T., Oever, S. T., Sack, A., & Leunissen, I. (2023). Modulating inhibitory control non-invasively with transcranial alternating current stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 16(1), 127. <https://doi.org/10.1016/j.brs.2023.01.044>
- Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, 41(4), 1149-1160. <https://doi.org/10.3758/BRM.41.4.1149>
- Fawcett, J. M., Taylor, T. L., Megla, E., & Maxcey, A. M. (2024). Active intentional and unintentional forgetting in the laboratory and everyday life. *Nature Reviews Psychology*, 3(10), 652-664. <https://doi.org/10.1038/s44159-024-00352-7>
- Fiorentini, G., Massé, E., Ficarella, S. C., & Torromino, G. (2025). Peripheral transcutaneous electrical stimulation to improve cognition: a review of the main effects in healthy humans and in mildly cognitively impaired patient populations. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 137, 111290. <https://doi.org/https://doi.org/10.1016/j.pnpbp.2025.111290>
- Foa, E. B., Huppert, J., & Cahill, S. (2006). Emotional processing theory: An update. *Pathological anxiety: Emotional processing in etiology and treatment*, 3-24.

- Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: Exposure to corrective information. *Psychological Bulletin*, 99(1), 20-35. <https://doi.org/10.1037/0033-2909.99.1.20>
- Frey, U., & Morris, R. G. M. (1997). Synaptic tagging and long-term potentiation. *Nature*, 385(6616), 533-536. <https://doi.org/10.1038/385533a0>
- Friston, K. (2010). The free-energy principle: a unified brain theory? *Nature Reviews Neuroscience*, 11(2), 127-138. <https://doi.org/10.1038/nrn2787>
- Friston, K., FitzGerald, T., Rigoli, F., Schwartenbeck, P., O'Doherty, J., & Pezzulo, G. (2016). Active inference and learning. *Neuroscience & Biobehavioral Reviews*, 68, 862-879. <https://doi.org/10.1016/j.neubiorev.2016.06.022>
- Fromm, A. E., Trujillo-Llano, C., Grittner, U., Meinzer, M., Flöel, A., & Antonenko, D. (2025). Increased variability in response to transcranial direct current stimulation in healthy older compared to young adults: A systematic review and meta-analysis. *Brain Stimul*, 18(4), 1257-1265. <https://doi.org/10.1016/j.brs.2025.06.005>
- Fuchs, M., Kastner, J., Wagner, M., Hawes, S., & Ebersole, J. S. (2002). A standardized boundary element method volume conductor model. *Clin Neurophysiol*, 113(5), 702-712. <http://www.ncbi.nlm.nih.gov/pubmed/11976050>
- Fujikawa, R., Ramsaran, A. I., Guskjolen, A., de la Parra, J., Zou, Y., Mocle, A. J., Josselyn, S. A., & Frankland, P. W. (2024). Neurogenesis-dependent remodeling of hippocampal circuits reduces PTSD-like behaviors in adult mice. *Mol Psychiatry*, 29(11), 3316-3329. <https://doi.org/10.1038/s41380-024-02585-7>
- Galineau, L., Arlicot, N., Dupont, A.-C., Briend, F., Houy-Durand, E., Tauber, C., Gomot, M., Gissot, V., Barantin, L., Lefevre, A., Vercouillie, J., Roussel, C., Roux, S., Nadal, L., Mavel, S., Laumonnier, F., Belzung, C., Chalon, S., Emond, P., . . . Bonnet-Brilhault, F. (2023). Glutamatergic synapse in autism: a complex story for a complex disorder. *Molecular Psychiatry*, 28(2), 801-809. <https://doi.org/10.1038/s41380-022-01860-9>
- Galli, G., Vadillo, M. A., Sirota, M., Feurra, M., & Medvedeva, A. (2019). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) on episodic memory. *Brain Stimul*, 12(2), 231-241. <https://doi.org/10.1016/j.brs.2018.11.008>
- Gallo, F. T., Zanoni Saad, M. B., Silva, A., Morici, J. F., Miranda, M., Anderson, M. C., Weisstaub, N. V., & Bekinshtein, P. (2022). Dopamine Modulates Adaptive Forgetting in Medial Prefrontal Cortex. *J Neurosci*, 42(34), 6620-6636. <https://doi.org/10.1523/jneurosci.0740-21.2022>
- Gao, L., Chen, J., Gu, L., Shu, H., Wang, Z., Liu, D., Yan, Y., & Zhang, Z. (2018). Effects of Gender and Apolipoprotein E on Novelty MMN and P3a in Healthy Elderly and Amnesic Mild Cognitive Impairment [Original Research]. *Frontiers in Aging Neuroscience*, 10. <https://doi.org/10.3389/fnagi.2018.00256>
- García-Martínez, M., Sánchez-Juan, P., & Butler, C. R. (2023). A review of accelerated long-term forgetting in Alzheimer's disease: Current situation and prospects. *Neuropsychology*, 37(6), 673-682. <https://doi.org/10.1037/neu0000827>
- Garrido, M. I., Kilner, J. M., Stephan, K. E., & Friston, K. J. (2009). The mismatch negativity: A review of underlying mechanisms. *Clinical Neurophysiology*, 120(3), 453-463. <https://doi.org/10.1016/j.clinph.2008.11.029>
- Gaubert, S., Raimondo, F., Houot, M., Corsi, M.-C., Naccache, L., Diego Sitt, J., Hermann, B., Oudiette, D., Gagliardi, G., Habert, M.-O., Dubois, B., De Vico Fallani, F., Bakardjian, H., Epelbaum, S., & Initiative, A. s. D. N. (2019). EEG evidence of compensatory mechanisms in preclinical Alzheimer's disease. *Brain*, 142(7), 2096-2112. <https://doi.org/10.1093/brain/awz150>
- Ge, Y., Wu, J., Sun, X., & Zhang, K. (2011). Enhanced mismatch negativity in adolescents with posttraumatic stress disorder (PTSD). *Int J Psychophysiol*, 79(2), 231-235. <https://doi.org/10.1016/j.ijpsycho.2010.10.012>
- Geršak, G. (2020). Electrodermal activity - a beginner's guide. *Elektrotehniški Vestnik/Electrotechnical Review*, 87, 175-182.
- Geurts, S., van der Werf, S. P., Kwa, V. I. H., & Kessels, R. P. C. (2019). Accelerated long-term forgetting after TIA or minor stroke: A more sensitive measure for detecting subtle memory dysfunction? *Cortex*, 110, 150-156. <https://doi.org/10.1016/j.cortex.2018.04.002>

- Giustino, T. F., & Maren, S. (2018). Noradrenergic Modulation of Fear Conditioning and Extinction [Review]. *Frontiers in Behavioral Neuroscience, Volume 12* - 2018. <https://doi.org/10.3389/fnbeh.2018.00043>
- Goadsby, P. J., Bartsch, T., & Dodick, D. W. (2008). Occipital Nerve Stimulation for Headache: Mechanisms and Efficacy. *Headache: The Journal of Head and Face Pain*, 48(2), 313-318. <https://doi.org/https://doi.org/10.1111/j.1526-4610.2007.01022.x>
- Gong, L., Zhang, B., & Alzheimer's Disease Neuroimaging, I. (2023). The intrinsic locus coeruleus functional connectivity change in older adults with subjective memory complaint. *Alzheimer's & Dementia*, 19(S3), e060620. <https://doi.org/https://doi.org/10.1002/alz.060620>
- Grogan, J., Bogacz, R., Tsivos, D., Whone, A., & Coulthard, E. (2015). Dopamine and Consolidation of Episodic Memory: Timing Is Everything. *Journal of Cognitive Neuroscience*, 27(10), 2035-2050. https://doi.org/10.1162/jocn_a.00840
- Groves, I., Grella, S. L., Harley, C. W., Hardt, O., & Nadel, L. (2025). How prediction error drives memory updating: role of locus coeruleus–hippocampal interactions. *Trends in Neurosciences*, 48(11), 865-876. <https://doi.org/https://doi.org/10.1016/j.tins.2025.09.003>
- Gu, J., Li, D., Li, Z., Guo, Y., Qian, F., Wang, Y., & Tang, L. (2022). The Effect and Mechanism of Transcranial Direct Current Stimulation on Episodic Memory in Patients With Mild Cognitive Impairment. *Front Neurosci*, 16, 811403. <https://doi.org/10.3389/fnins.2022.811403>
- Guskjolen, A., & Cembrowski, M. S. (2023). Engram neurons: Encoding, consolidation, retrieval, and forgetting of memory. *Molecular Psychiatry*, 28(8), 3207-3219. <https://doi.org/10.1038/s41380-023-02137-5>
- Gzielo, K., & Nikiforuk, A. (2021). Astroglia in Autism Spectrum Disorder. *International Journal of Molecular Sciences*, 22(21), 11544. <https://www.mdpi.com/1422-0067/22/21/11544>
- Hanseeuw, B. J., Seron, X., & Ivanoiu, A. (2012). Increased sensitivity to proactive and retroactive interference in amnesic mild cognitive impairment: New insights. *Brain and Cognition*, 80(1), 104-110. <https://doi.org/https://doi.org/10.1016/j.bandc.2012.04.002>
- Hansen, N. (2017). The Longevity of Hippocampus-Dependent Memory Is Orchestrated by the Locus Coeruleus-Noradrenergic System. *Neural Plasticity*, 2017, 2727602. <https://doi.org/10.1155/2017/2727602>
- Hanslmayr, S., Matuschek, J., & Fellner, M.-C. (2014). Entrainment of Prefrontal Beta Oscillations Induces an Endogenous Echo and Impairs Memory Formation. *Current Biology*, 24(8), 904-909. <https://doi.org/https://doi.org/10.1016/j.cub.2014.03.007>
- Hardt, O., & Sossin, W. S. (2019). Terminological and Epistemological Issues in Current Memory Research. *Front Mol Neurosci*, 12, 336. <https://doi.org/10.3389/fnmol.2019.00336>
- Harms, L., Parras, G. G., Michie, P. T., & Malmierca, M. S. (2021). The Role of Glutamate Neurotransmission in Mismatch Negativity (MMN), A Measure of Auditory Synaptic Plasticity and Change-detection. *Neuroscience*, 456, 106-113. <https://doi.org/https://doi.org/10.1016/j.neuroscience.2020.01.046>
- Haubrich, J., Bernabo, M., & Nader, K. (2020). Noradrenergic projections from the locus coeruleus to the amygdala constrain fear memory reconsolidation. *eLife*, 9. <https://doi.org/10.7554/eLife.57010>
- Hayes, J. M., Tang, L., Viviano, R. P., van Rooden, S., Ofen, N., & Damoiseaux, J. S. (2017). Subjective memory complaints are associated with brain activation supporting successful memory encoding. *Neurobiol Aging*, 60, 71-80. <https://doi.org/10.1016/j.neurobiolaging.2017.08.015>
- He, J., Zheng, Y., Nie, Y., & Zhou, Z. (2018). Automatic detection advantage of network information among Internet addicts: behavioral and ERP evidence. *Sci Rep*, 8(1), 8937. <https://doi.org/10.1038/s41598-018-25442-4>
- Hodson, R., Mehta, M., & Smith, R. (2024). The empirical status of predictive coding and active inference. *Neuroscience & Biobehavioral Reviews*, 157, 105473. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2023.105473>
- Hoefeijzers, S., Dewar, M., Della Sala, S., Zeman, A., & Butler, C. (2013). Accelerated long-term forgetting in transient epileptic amnesia: An acquisition or consolidation deficit? *Neuropsychologia*, 51(8), 1549-1555. <https://doi.org/https://doi.org/10.1016/j.neuropsychologia.2013.04.017>

- Holmes, S. E., Girenti, M. J., Davis, M. T., Pietrzak, R. H., DellaGioia, N., Nabulsi, N., Matuskey, D., Southwick, S., Duman, R. S., Carson, R. E., Krystal, J. H., Esterlis, I., Group, t. T. S. B. S., Friedman, M., Kowall, N., Brady, C., McKee, A., Stein, T., Huber, B., . . . Serlin, G. (2017). Altered metabotropic glutamate receptor 5 markers in PTSD: In vivo and postmortem evidence. *Proceedings of the National Academy of Sciences*, 114(31), 8390-8395. <https://doi.org/doi:10.1073/pnas.1701749114>
- Holth, J. K., Fritsch, S. K., Wang, C., Pedersen, N. P., Cirrito, J. R., Mahan, T. E., Finn, M. B., Manis, M., Geerling, J. C., Fuller, P. M., Lucey, B. P., & Holtzman, D. M. (2019). The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science (New York, N.Y.)*, 363(6429), 880-884. <https://doi.org/doi:10.1126/science.aav2546>
- Horowitz, M. J. (1976). *Stress response syndromes*. Jason Aronson.
- Horvath, J. C., Forte, J. D., & Carter, O. (2015). Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 8(3), 535-550. <https://doi.org/10.1016/j.brs.2015.01.400>
- Howe, A. S., Bani-Fatemi, A., & De Luca, V. (2014). The clinical utility of the auditory P300 latency subcomponent event-related potential in preclinical diagnosis of patients with mild cognitive impairment and Alzheimer's disease. *Brain and Cognition*, 86, 64-74. <https://doi.org/https://doi.org/10.1016/j.bandc.2014.01.015>
- Hsieh, H., Boehm, J., Sato, C., Iwatsubo, T., Tomita, T., Sisodia, S., & Malinow, R. (2006). AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. *Neuron*, 52(5), 831-843. <https://doi.org/10.1016/j.neuron.2006.10.035>
- Huang, J., Xu, F., Yang, L., Tuolihong, L., Wang, X., Du, Z., Zhang, Y., Yin, X., Li, Y., Lu, K., & Wang, W. (2023). Involvement of the GABAergic system in PTSD and its therapeutic significance. *Front Mol Neurosci*, 16, 1052288. <https://doi.org/10.3389/fnmol.2023.1052288>
- Huang, R., & Clewett, D. (2024). The Locus Coeruleus: Where Cognitive and Emotional Processing Meet the Eye. In M. H. Papesch & S. D. Goldinger (Eds.), *Modern Pupillometry: Cognition, Neuroscience, and Practical Applications* (1 ed.). Springer Cham. <https://doi.org/https://doi.org/10.1007/978-3-031-54896-3>
- Hulbert, J. C., & Anderson, M. C. (2020). Does retrieving a memory insulate it against memory inhibition? A retroactive interference study. *Memory*, 28(3), 293-308. <https://doi.org/10.1080/09658211.2019.1710216>
- Hulse, D. R., Hays, S. A., Khodaparast, N., Ruiz, A., Das, P., Rennaker, R. L., & Kilgard, M. P. (2016). Reorganization of Motor Cortex by Vagus Nerve Stimulation Requires Cholinergic Innervation. *Brain Stimulation*, 9(2), 174-181. <https://doi.org/https://doi.org/10.1016/j.brs.2015.12.007>
- Hulse, D. R., Riley, J. R., Loerwald, K. W., Rennaker, R. L., Kilgard, M. P., & Hays, S. A. (2017). Parametric characterization of neural activity in the locus coeruleus in response to vagus nerve stimulation. *Experimental Neurology*, 289, 21-30. <https://doi.org/https://doi.org/10.1016/j.expneurol.2016.12.005>
- Hulse, D. R., Shedd, C. M., Sarker, S. F., Kilgard, M. P., & Hays, S. A. (2019). Norepinephrine and serotonin are required for vagus nerve stimulation directed cortical plasticity. *Experimental Neurology*, 320, 112975. <https://doi.org/https://doi.org/10.1016/j.expneurol.2019.112975>
- Huo, L., Zhu, X., Zheng, Z., Ma, J., Ma, Z., Gui, W., & Li, J. (2021). Effects of Transcranial Direct Current Stimulation on Episodic Memory in Older Adults: A Meta-analysis. *J Gerontol B Psychol Sci Soc Sci*, 76(4), 692-702. <https://doi.org/10.1093/geronb/gbz130>
- Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu Rev Neurosci*, 29, 565-598. <https://doi.org/10.1146/annurev.neuro.29.051605.113009>
- Indahlastari, A., Hardcastle, C., Albizu, A., Alvarez-Alvarado, S., Boutzoukas, E. M., Evangelista, N. D., Hausman, H. K., Kraft, J., Langer, K., & Woods, A. J. (2021). A Systematic Review and Meta-Analysis of Transcranial Direct Current Stimulation to Remediate Age-Related Cognitive Decline in Healthy Older Adults. *Neuropsychiatr Dis Treat*, 17, 971-990. <https://doi.org/10.2147/ndt.S259499>

- Iqbal, J., Huang, G.-D., Xue, Y.-X., Yang, M., & Jia, X.-J. (2023). The neural circuits and molecular mechanisms underlying fear dysregulation in posttraumatic stress disorder [Review]. *Frontiers in Neuroscience, Volume 17* - 2023. <https://doi.org/10.3389/fnins.2023.1281401>
- Ishikawa, R., Uchida, C., Kitaoka, S., Furuyashiki, T., & Kida, S. (2019). Improvement of PTSD-like behavior by the forgetting effect of hippocampal neurogenesis enhancer memantine in a social defeat stress paradigm. *Molecular Brain, 12*(1), 68. <https://doi.org/10.1186/s13041-019-0488-6>
- Iyadurai, L., Visser, R. M., Lau-Zhu, A., Porcheret, K., Horsch, A., Holmes, E. A., & James, E. L. (2019). Intrusive memories of trauma: A target for research bridging cognitive science and its clinical application. *Clin Psychol Rev, 69*, 67-82. <https://doi.org/10.1016/j.cpr.2018.08.005>
- Jacobs, H. I., Riphagen, J. M., Razat, C. M., Wiese, S., & Sack, A. T. (2015). Transcutaneous vagus nerve stimulation boosts associative memory in older individuals. *Neurobiol Aging, 36*(5), 1860-1867. <https://doi.org/10.1016/j.neurobiolaging.2015.02.023>
- Jacobs, H. I. L., Riphagen, J. M., Ramakers, I. H. G. B., & Verhey, F. R. J. (2021). Alzheimer's disease pathology: pathways between central norepinephrine activity, memory, and neuropsychiatric symptoms. *Molecular Psychiatry, 26*(3), 897-906. <https://doi.org/10.1038/s41380-019-0437-x>
- Jamjoom, A. A. B., Rhodes, J., Andrews, P. J. D., & Grant, S. G. N. (2021). The synapse in traumatic brain injury. *Brain, 144*(1), 18-31. <https://doi.org/10.1093/brain/awaa321>
- Jantzi, C., Mengin, A. C., Serfaty, D., Bacon, E., Elowe, J., Severac, F., Meyer, N., Berna, F., & Vidailhet, P. (2019). Retrieval practice improves memory in patients with schizophrenia: new perspectives for cognitive remediation. *BMC Psychiatry, 19*(1), 355. <https://doi.org/10.1186/s12888-019-2341-y>
- Jensen, O., & Colgin, L. L. (2007). Cross-frequency coupling between neuronal oscillations. *Trends in Cognitive Sciences, 11*(7), 267-269. <https://doi.org/https://doi.org/10.1016/j.tics.2007.05.003>
- Jiang, L., Mao, R., Zhou, Q., Yang, Y., Cao, J., Ding, Y., Yang, Y., Zhang, X., Li, L., & Xu, L. (2016). Inhibition of Rac1 Activity in the Hippocampus Impairs the Forgetting of Contextual Fear Memory. *Mol Neurobiol, 53*(2), 1247-1253. <https://doi.org/10.1007/s12035-015-9093-6>
- Johnson, J. D., Allana, T. N., Medlin, M. D., Harris, E. W., & Karl, A. (2013). Meta-analytic review of P3 components in posttraumatic stress disorder and their clinical utility. *Clin EEG Neurosci, 44*(2), 112-134. <https://doi.org/10.1177/1550059412469742>
- Josselyn, S. A., & Tonegawa, S. (2020). Memory engrams: Recalling the past and imagining the future. *Science (New York, N.Y.), 367*(6473), eaaw4325. <https://doi.org/doi:10.1126/science.aaw4325>
- Jurcak, V., Tsuzuki, D., & Dan, I. (2007). 10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems. *Neuroimage, 34*(4), 1600-1611. <https://doi.org/10.1016/j.neuroimage.2006.09.024>
- Kaldun, J. C., Lone, S. R., Humbert Camps, A. M., Fritsch, C., Widmer, Y. F., Stein, J. V., Tomchik, S. M., & Sprecher, S. G. (2021). Dopamine, sleep, and neuronal excitability modulate amyloid- β -mediated forgetting in *Drosophila*. *PLOS Biology, 19*(10), e3001412. <https://doi.org/10.1371/journal.pbio.3001412>
- Kang, O. E., Huffer, K. E., & Wheatley, T. P. (2014). Pupil Dilation Dynamics Track Attention to High-Level Information. *PLOS ONE, 9*(8), e102463. <https://doi.org/10.1371/journal.pone.0102463>
- Karpicke, J. D., & Roediger, H. L., 3rd. (2008). The critical importance of retrieval for learning. *Science (New York, N.Y.), 319*(5865), 966-968. <https://doi.org/10.1126/science.1152408>
- Kash, S. F., Johnson, R. S., Tecott, L. H., Noebels, J. L., Mayfield, R. D., Hanahan, D., & Baekkeskov, S. (1997). Epilepsy in mice deficient in the 65-kDa isoform of glutamic acid decarboxylase. *Proc Natl Acad Sci U S A, 94*(25), 14060-14065. <https://doi.org/10.1073/pnas.94.25.14060>
- Keller, G. B., & Mries-Flogel, T. D. (2018). Predictive Processing: A Canonical Cortical Computation. *Neuron, 100*(2), 424-435. <https://doi.org/10.1016/j.neuron.2018.10.003>
- Kenemans, J. L., & Kähkönen, S. (2011). How Human Electrophysiology Informs Psychopharmacology: from Bottom-up Driven Processing to Top-Down Control. *Neuropsychopharmacology, 36*(1), 26-51. <https://doi.org/10.1038/npp.2010.157>

- Kennedy, M. B. (2013). Synaptic Signaling in Learning and Memory. *Cold Spring Harb Perspect Biol*, 8(2), a016824. <https://doi.org/10.1101/cshperspect.a016824>
- Khan, A., Ti, C. H. E., Yuan, K., Crespo Garcia, M., Anderson, M. C., & Tong, R. K.-Y. (2024). Medial Prefrontal Cortex Stimulation Reduces Retrieval-Induced Forgetting via Fronto-parietal Beta Desynchronization. *The Journal of Neuroscience*, 44(37), e0189242024. <https://doi.org/10.1523/jneurosci.0189-24.2024>
- Kim, A. J., Morales, S., Senior, J., & Mather, M. (2026). Electroencephalography, pupillometry, and behavioral evidence for locus coeruleus-noradrenaline system related tonic hyperactivity in older adults. *Neurobiology of Aging*, 159, 15-32. <https://doi.org/https://doi.org/10.1016/j.neurobiolaging.2025.11.008>
- Kim, G., Kwon, M., Kang, W., & Lee, S. H. (2021). Is Reconsolidation a General Property of Memory? *Front Hum Neurosci*, 15, 643106. <https://doi.org/10.3389/fnhum.2021.643106>
- Kim, G., Lewis-Peacock, J. A., Norman, K. A., & Turk-Browne, N. B. (2014). Pruning of memories by context-based prediction error. *Proceedings of the National Academy of Sciences*, 111(24), 8997-9002. <https://doi.org/doi:10.1073/pnas.1319438111>
- Köster, M. (2024). The theta-gamma code in predictive processing and mnemonic updating. *Neuroscience & Biobehavioral Reviews*, 158, 105529. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2023.105529>
- Köster, M., Frieze, U., Schöne, B., Trujillo-Barreto, N., & Gruber, T. (2014). Theta–gamma coupling during episodic retrieval in the human EEG. *Brain Research*, 1577, 57-68. <https://doi.org/https://doi.org/10.1016/j.brainres.2014.06.028>
- Köster, M., & Gruber, T. (2022). Rhythms of human attention and memory: An embedded process perspective [Review]. *Frontiers in Human Neuroscience*, Volume 16 - 2022. <https://doi.org/10.3389/fnhum.2022.905837>
- Kouli, A., Torsney, K. M., & Kuan, W.-L. (2018). *Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis (Chapter 1)* (G. J. Stoker TB, Ed.). Brisbane (AU): Codon Publications. <https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018>
- Krabbe, S., Gründemann, J., & Lüthi, A. (2018). Amygdala Inhibitory Circuits Regulate Associative Fear Conditioning. *Biological Psychiatry*, 83(10), 800-809. <https://doi.org/https://doi.org/10.1016/j.biopsych.2017.10.006>
- Kraemer, P. J., & Golding, J. M. (1997). Adaptive forgetting in animals. *Psychonomic Bulletin & Review*, 4(4), 480-491. <https://doi.org/10.3758/BF03214337>
- Krohn, F., Lancini, E., Ludwig, M., Leiman, M., Guruprasath, G., Haag, L., Panczyszyn, J., Düzel, E., Hämmerer, D., & Betts, M. (2023). Noradrenergic neuromodulation in ageing and disease. *Neuroscience & Biobehavioral Reviews*, 152, 105311. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2023.105311>
- Kube, T., Berg, M., Kleim, B., & Herzog, P. (2020). Rethinking post-traumatic stress disorder – A predictive processing perspective. *Neuroscience & Biobehavioral Reviews*, 113, 448-460. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2020.04.014>
- Lackey, A. E., & Muzio, M. R. (2023). *DiGeorge Syndrome*. StatPearls. Retrieved June 23, 2025 from <https://www.ncbi.nlm.nih.gov/books/NBK549798/>
- Lah, S., Black, C., Gascoigne, M. B., Gott, C., Epps, A., & Parry, L. (2017). Accelerated Long-Term Forgetting Is Not Epilepsy Specific: Evidence from Childhood Traumatic Brain Injury. *Journal of Neurotrauma*, 34(17), 2536-2544. <https://doi.org/10.1089/neu.2016.4872>
- Lammers, N. A., Lugtmeijer, S., de Haan, E. H. F., & Kessels, R. P. C. (2022). Accelerated Long-Term Forgetting: Prolonged Delayed Recognition as Sensitive Measurement for Different Profiles of Long-Term Memory and Metacognitive Confidence in Stroke Patients. *Journal of the International Neuropsychological Society*, 28(4), 327-336. <https://doi.org/10.1017/S1355617721000527>
- Lamprecht, F., Köhnke, C., Lempa, W., Sack, M., Matzke, M., & Münte, T. F. (2004). Event-related potentials and EMDR treatment of post-traumatic stress disorder. *Neurosci Res*, 49(2), 267-272. <https://doi.org/10.1016/j.neures.2004.02.013>
- Lang, P. J., Melamed, B. G., & Hart, J. (1970). A psychophysiological analysis of fear modification using an automated desensitization procedure. *J Abnorm Psychol*, 76(2), 220-234. <https://doi.org/10.1037/h0029875>
- Lange, M. D., Jüngling, K., Paulukat, L., Vieler, M., Gaburro, S., Sosulina, L., Blaesse, P., Sreepathi, H. K., Ferraguti, F., & Pape, H.-C. (2014). Glutamic Acid Decarboxylase 65: A Link

- Between GABAergic Synaptic Plasticity in the Lateral Amygdala and Conditioned Fear Generalization. *Neuropsychopharmacology*, 39(9), 2211-2220. <https://doi.org/10.1038/npp.2014.72>
- Laptinskaya, D., Thurm, F., Küster, O. C., Fissler, P., Schlee, W., Kolassa, S., von Arnim, C. A. F., & Kolassa, I.-T. (2018). Auditory Memory Decay as Reflected by a New Mismatch Negativity Score Is Associated with Episodic Memory in Older Adults at Risk of Dementia [Original Research]. *Frontiers in Aging Neuroscience*, 10. <https://doi.org/10.3389/fnagi.2018.00005>
- Larsen, L. E., Caestecker, S., Stevens, L., van Mierlo, P., Carrette, E., Boon, P., Vonck, K., & Raedt, R. (2023). Hippocampal seizures differentially modulate locus coeruleus activity and result in consistent time-locked release of noradrenaline in rat hippocampus. *Neurobiology of Disease*, 189, 106355. <https://doi.org/10.1016/j.nbd.2023.106355>
- Lawson, R. P., Bisby, J., Nord, C. L., Burgess, N., & Rees, G. (2021). The Computational, Pharmacological, and Physiological Determinants of Sensory Learning under Uncertainty. *Current Biology*, 31(1), 163-172.e164. <https://doi.org/10.1016/j.cub.2020.10.043>
- Lee, J. L. C., Nader, K., & Schiller, D. (2017). An Update on Memory Reconsolidation Updating. *Trends in Cognitive Sciences*, 21(7), 531-545. <https://doi.org/10.1016/j.tics.2017.04.006>
- Lee, S. H., & Dominguez, R. (2010). Regulation of actin cytoskeleton dynamics in cells. *Mol Cells*, 29(4), 311-325. <https://doi.org/10.1007/s10059-010-0053-8>
- Leone, G., Postel, C., Mary, A., Fraisse, F., Vallée, T., Viader, F., de La Sayette, V., Peschanski, D., Dayan, J., Eustache, F., & Gagnepain, P. (2022). Altered predictive control during memory suppression in PTSD. *Nature Communications*, 13(1), 3300. <https://doi.org/10.1038/s41467-022-30855-x>
- Levy, B. J., & Anderson, M. C. (2002). Inhibitory processes and the control of memory retrieval. *Trends in Cognitive Sciences*, 6(7), 299-305. [https://doi.org/10.1016/S1364-6613\(02\)01923-X](https://doi.org/10.1016/S1364-6613(02)01923-X)
- Li, S., Tang, Y., Zhou, Y., & Ni, Y. (2024). Effects of Transcranial Direct Current Stimulation on Cognitive Function in Older Adults with and without Mild Cognitive Impairment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Gerontology*, 70(5), 544-560. <https://doi.org/10.1159/000537848>
- Licastro, F., Hrelia, S., Porcellini, E., Malaguti, M., Di Stefano, C., Angeloni, C., Carbone, I., Simoncini, L., & Piperno, R. (2016). Peripheral Inflammatory Markers and Antioxidant Response during the Post-Acute and Chronic Phase after Severe Traumatic Brain Injury. *Front Neurol*, 7, 189. <https://doi.org/10.3389/fneur.2016.00189>
- Liu, X., Yang, C., Wang, X., Wang, Z., Liao, H., Liu, H., Zhang, M., Zhang, L., & Wang, H. (2025). Associations between peripheral nerve stimulation and cognitive performance: insights from healthy individuals and various disease pathologies. *Front Aging Neurosci*, 17, 1518198. <https://doi.org/10.3389/fnagi.2025.1518198>
- Liu, Y., Du, S., Lv, L., Lei, B., Shi, W., Tang, Y., Wang, L., & Zhong, Y. (2016). Hippocampal Activation of Rac1 Regulates the Forgetting of Object Recognition Memory. *Curr Biol*, 26(17), 2351-2357. <https://doi.org/10.1016/j.cub.2016.06.056>
- Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron*, 33(5), 827-840. [https://doi.org/10.1016/s0896-6273\(02\)00612-8](https://doi.org/10.1016/s0896-6273(02)00612-8)
- Lonsdorf, T. B., Menz, M. M., Andreatta, M., Fullana, M. A., Golkar, A., Haaker, J., Heitland, I., Hermann, A., Kuhn, M., Kruse, O., Meir Drexler, S., Meulders, A., Nees, F., Pittig, A., Richter, J., Römer, S., Shiban, Y., Schmitz, A., Straube, B., . . . Merz, C. J. (2017). Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neuroscience & Biobehavioral Reviews*, 77, 247-285. <https://doi.org/10.1016/j.neubiorev.2017.02.026>
- Lu, F., Yang, W., & Qiu, J. (2023). Neural bases of motivated forgetting of autobiographical memories. *Cognitive Neuroscience*, 14(1), 15-24. <https://doi.org/10.1080/17588928.2022.2136150>
- Luckey, A. M., Adcock, K., & Vanneste, S. (2023). Peripheral nerve stimulation: A neuromodulation-based approach. *Neuroscience & Biobehavioral Reviews*, 149, 105180. <https://doi.org/10.1016/j.neubiorev.2023.105180>

- Luckey, A. M., Adcock, K., & Vanneste, S. (2023). Peripheral nerve stimulation: A neuromodulation-based approach. *Neurosci Biobehav Rev*, 149, 105180. <https://doi.org/10.1016/j.neubiorev.2023.105180>
- Luckey, A. M., McLeod, L. S., Huang, Y., Mohan, A., & Vanneste, S. (2023). Making memories last using the peripheral effect of direct current stimulation. *eLife*, 12, e75586. <https://doi.org/10.7554/eLife.75586>
- Luckey, A. M., McLeod, L. S., Huang, Y., Mohan, A., & Vanneste, S. (2023). Making memories last using the peripheral effect of direct current stimulation. *Elife*, 12. <https://doi.org/10.7554/eLife.75586>
- Luckey, A. M., McLeod, S. L., Mohan, A., & Vanneste, S. (2022). Potential role for peripheral nerve stimulation on learning and long-term memory: A comparison of alternating and direct current stimulations. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 15(3), 536-545. <https://doi.org/10.1016/j.brs.2022.03.001>
- Luckey, A. M., McLeod, S. L., Robertson, I. H., To, W. T., & Vanneste, S. (2020). Greater Occipital Nerve Stimulation Boosts Associative Memory in Older Individuals: A Randomized Trial. *Neurorehabil Neural Repair*, 34(11), 1020-1029. <https://doi.org/10.1177/1545968320943573>
- Luijten, M., Kleinjan, M., & Franken, I. H. A. (2016). Event-related potentials reflecting smoking cue reactivity and cognitive control as predictors of smoking relapse and resumption. *Psychopharmacology*, 233(15), 2857-2868. <https://doi.org/10.1007/s00213-016-4332-8>
- Madore, C., Yin, Z., Leibowitz, J., & Butovsky, O. (2020). Microglia, Lifestyle Stress, and Neurodegeneration. *Immunity*, 52(2), 222-240. <https://doi.org/10.1016/j.immuni.2019.12.003>
- Majdi, A., Asamoah, B., & Mc Laughlin, M. (2023). Reinterpreting published tDCS results in terms of a cranial and cervical nerve co-stimulation mechanism [Hypothesis and Theory]. *Frontiers in Human Neuroscience*, Volume 17 - 2023. <https://doi.org/10.3389/fnhum.2023.1101490>
- Majdi, A., Asamoah, B., & Mc Laughlin, M. (2024). Understanding novel neuromodulation pathways in tDCS: brain stem recordings in rats during trigeminal nerve direct current stimulation. *Translational Psychiatry*, 14(1), 456. <https://doi.org/10.1038/s41398-024-03158-6>
- Majdi, A., Chen, L., Larsen, L. E., Raedt, R., & Laughlin, M. M. (2025). tDCS cranial nerve Co-stimulation: Unveiling brainstem pathways involved in trigeminal nerve direct current stimulation in rats. *Brain Stimulation*, 18(2), 171-184. <https://doi.org/https://doi.org/10.1016/j.brs.2025.01.025>
- Majdi, A., Chen, L., Larsen, L. E., Raedt, R., & Laughlin, M. M. (2025). tDCS cranial nerve Co-stimulation: Unveiling brainstem pathways involved in trigeminal nerve direct current stimulation in rats. *Brain Stimul*, 18(2), 171-184. <https://doi.org/10.1016/j.brs.2025.01.025>
- Makowski, D., Pham, T., Lau, Z. J., Brammer, J. C., Lespinasse, F., Pham, H., Schölzel, C., & Chen, S. H. A. (2021). NeuroKit2: A Python toolbox for neurophysiological signal processing. *Behavior Research Methods*, 53(4), 1689-1696. <https://doi.org/10.3758/s13428-020-01516-y>
- Mamat, Z., & Anderson, M. C. (2023). Improving mental health by training the suppression of unwanted thoughts. *Science Advances*, 9(38), eadh5292. <https://doi.org/doi:10.1126/sciadv.adh5292>
- Mamat, Z., Levy, D. A., & Bayley, P. J. (2024). Reconsidering thought suppression and ironic processing: implications for clinical treatment of traumatic memories [Opinion]. *Frontiers in Psychology*, Volume 15 - 2024. <https://doi.org/10.3389/fpsyg.2024.1496134>
- Mameniškienė, R., Puteikis, K., Jasionis, A., & Jatužis, D. (2020). A Review of Accelerated Long-Term Forgetting in Epilepsy. *Brain Sciences*, 10(12), 945. <https://www.mdpi.com/2076-3425/10/12/945>
- Mary, A., Dayan, J., Leone, G., Postel, C., Fraisse, F., Malle, C., Vallée, T., Klein-Peschanski, C., Viader, F., de la Sayette, V., Peschanski, D., Eustache, F., & Gagnepain, P. (2020). Resilience after trauma: The role of memory suppression. *Science (New York, N.Y.)*, 367(6479). <https://doi.org/10.1126/science.aay8477>

- Mary, A., Schreiner, S., & Peigneux, P. (2013). Accelerated long-term forgetting in aging and intra-sleep awakenings [Original Research]. *Frontiers in Psychology*, Volume 4 - 2013. <https://doi.org/10.3389/fpsyg.2013.00750>
- Mather, M. (2025). Autonomic dysfunction in neurodegenerative disease. *Nature Reviews Neuroscience*, 26(5), 276-292. <https://doi.org/10.1038/s41583-025-00911-8>
- Mather, M., Clewett, D., Sakaki, M., & Harley, C. W. (2016). Norepinephrine ignites local hotspots of neuronal excitation: How arousal amplifies selectivity in perception and memory. *Behav Brain Sci*, 39, e200. <https://doi.org/10.1017/s0140525x15000667>
- Mather, M., & Harley, C. W. (2016). The Locus Coeruleus: Essential for Maintaining Cognitive Function and the Aging Brain. *Trends Cogn Sci*, 20(3), 214-226. <https://doi.org/10.1016/j.tics.2016.01.001>
- Mayes, A. R., Hunkin, N. M., Isaac, C., & Muhlert, N. (2019). Are there distinct forms of accelerated forgetting and, if so, why? *Cortex*, 110, 115-126. <https://doi.org/https://doi.org/10.1016/j.cortex.2018.04.005>
- Mazzoni, G., Clark, A., De Bartolo, A., Guerrini, C., Nahouli, Z., Duzzi, D., De Marco, M., McGeown, W., & Venneri, A. (2019). Brain activation in highly superior autobiographical memory: The role of the precuneus in the autobiographical memory retrieval network. *Cortex*, 120, 588-602. <https://doi.org/https://doi.org/10.1016/j.cortex.2019.02.020>
- McGaugh, J. L. (2013). Making lasting memories: Remembering the significant. *Proceedings of the National Academy of Sciences*, 110(supplement_2), 10402-10407. <https://doi.org/doi:10.1073/pnas.1301209110>
- McIntyre, C. K., McGaugh, J. L., & Williams, C. L. (2012). Interacting brain systems modulate memory consolidation. *Neuroscience & Biobehavioral Reviews*, 36(7), 1750-1762. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2011.11.001>
- Menning, H., Renz, A., Seifert, J., & Maercker, A. (2008). Reduced mismatch negativity in posttraumatic stress disorder: a compensatory mechanism for chronic hyperarousal? *Int J Psychophysiol*, 68(1), 27-34. <https://doi.org/10.1016/j.ijpsycho.2007.12.003>
- Meyer, A.-K., & Benoit, R. G. (2022). Suppression weakens unwanted memories via a sustained reduction of neural reactivation. *eLife*, 11, e71309. <https://doi.org/10.7554/eLife.71309>
- Milad, M. R., Rosenbaum, B. L., & Simon, N. M. (2014). Neuroscience of fear extinction: Implications for assessment and treatment of fear-based and anxiety related disorders. *Behaviour Research and Therapy*, 62, 17-23. <https://doi.org/https://doi.org/10.1016/j.brat.2014.08.006>
- Miller, R. R. (2021). Failures of memory and the fate of forgotten memories. *Neurobiology of Learning and Memory*, 181, 107426. <https://doi.org/https://doi.org/10.1016/j.nlm.2021.107426>
- Mitchell, A. J. (2017). The Mini-Mental State Examination (MMSE): Update on Its Diagnostic Accuracy and Clinical Utility for Cognitive Disorders. In A. J. Larner (Ed.), *Cognitive Screening Instruments: A Practical Approach* (pp. 37-48). Springer International Publishing. https://doi.org/10.1007/978-3-319-44775-9_3
- Moncada, D. (2017). Evidence of VTA and LC control of protein synthesis required for the behavioral tagging process. *Neurobiol Learn Mem*, 138, 226-237. <https://doi.org/10.1016/j.nlm.2016.06.003>
- Moncada, D., Ballarini, F., & Viola, H. (2015). Behavioral Tagging: A Translation of the Synaptic Tagging and Capture Hypothesis. *Neural Plast*, 2015, 650780. <https://doi.org/10.1155/2015/650780>
- Monte-Silva, K., Liebetanz, D., Grundey, J., Paulus, W., & Nitsche, M. A. (2010). Dosage-dependent non-linear effect of L-dopa on human motor cortex plasticity. *J Physiol*, 588(Pt 18), 3415-3424. <https://doi.org/10.1113/jphysiol.2010.190181>
- Moran, R. J., Campo, P., Symmonds, M., Stephan, K. E., Dolan, R. J., & Friston, K. J. (2013). Free Energy, Precision and Learning: The Role of Cholinergic Neuromodulation. *The Journal of Neuroscience*, 33(19), 8227-8236. <https://doi.org/10.1523/jneurosci.4255-12.2013>
- Morgan, C. A., 3rd, & Grillon, C. (1999). Abnormal mismatch negativity in women with sexual assault-related posttraumatic stress disorder. *Biol Psychiatry*, 45(7), 827-832. [https://doi.org/10.1016/s0006-3223\(98\)00194-2](https://doi.org/10.1016/s0006-3223(98)00194-2)
- Motlagh, F., Ibrahim, F., Rashid, R., Shafiabady, N., Seghatoleslam, T., & Habil, H. (2018). Acute effects of methadone on EEG power spectrum and event-related potentials among heroin

- dependents. *Psychopharmacology*, 235(11), 3273-3288. <https://doi.org/10.1007/s00213-018-5035-0>
- Mulert, C., Pogarell, O., Juckel, G., Rujescu, D., Giegling, I., Rupp, D., Mavrogiorgou, P., Bussfeld, P., Gallinat, J., Moller, H. J., & Hegerl, U. (2004). The neural basis of the P300 potential. Focus on the time-course of the underlying cortical generators. *Eur Arch Psychiatry Clin Neurosci*, 254(3), 190-198. <https://doi.org/10.1007/s00406-004-0469-2>
- Müller, I., Çalışkan, G., & Stork, O. (2015). The GAD65 knock out mouse - a model for GABAergic processes in fear- and stress-induced psychopathology. *Genes Brain Behav*, 14(1), 37-45. <https://doi.org/10.1111/gbb.12188>
- Murayama, K., Miyatsu, T., Buchli, D., & Storm, B. C. (2014). Forgetting as a consequence of retrieval: a meta-analytic review of retrieval-induced forgetting. *Psychol Bull*, 140(5), 1383-1409. <https://doi.org/10.1037/a0037505>
- Murphy, P. R., O'Connell, R. G., O'Sullivan, M., Robertson, I. H., & Balsters, J. H. (2014). Pupil diameter covaries with BOLD activity in human locus coeruleus. *Hum Brain Mapp*, 35(8), 4140-4154. <https://doi.org/10.1002/hbm.22466>
- Murphy, P. R., Robertson, I. H., Balsters, J. H., & O'Connell, R. G. (2011). Pupillometry and P3 index the locus coeruleus–noradrenergic arousal function in humans. *Psychophysiology*, 48(11), 1532-1543. <https://doi.org/https://doi.org/10.1111/j.1469-8986.2011.01226.x>
- Musiek, E. S., Bhimasani, M., Zangrilli, M. A., Morris, J. C., Holtzman, D. M., & Ju, Y.-E. S. (2018). Circadian Rest-Activity Pattern Changes in Aging and Preclinical Alzheimer Disease. *JAMA Neurology*, 75(5), 582-590. <https://doi.org/10.1001/jamaneurol.2017.4719>
- Näätänen, R. (1995). The mismatch negativity: a powerful tool for cognitive neuroscience. *Ear Hear*, 16(1), 6-18.
- Nader, K. (2015). Reconsolidation and the Dynamic Nature of Memory. *Cold Spring Harb Perspect Biol*, 7(10), a021782. <https://doi.org/10.1101/cshperspect.a021782>
- Nagai, J., Yu, X., Papouin, T., Cheong, E., Freeman, M. R., Monk, K. R., Hastings, M. H., Haydon, P. G., Rowitch, D., Shaham, S., & Khakh, B. S. (2021). Behaviorally consequential astrocytic regulation of neural circuits. *Neuron*, 109(4), 576-596. <https://doi.org/10.1016/j.neuron.2020.12.008>
- Navarrete, M., Cuartero, M. I., Palenzuela, R., Draffin, J. E., Konomi, A., Serra, I., Colié, S., Castaño-Castaño, S., Hasan, M. T., Nebreda, Á. R., & Esteban, J. A. (2019). Astrocytic p38 α MAPK drives NMDA receptor-dependent long-term depression and modulates long-term memory. *Nature Communications*, 10(1), 2968. <https://doi.org/10.1038/s41467-019-10830-9>
- Nelson, T. O., & Dunlosky, J. (1994). Norms of Paired-Associate Recall During Multitrial Learning of Swahili-English Translation Equivalents. *Memory*, 2(3), 325-335. <https://doi.org/10.1080/09658219408258951>
- Ney, L. J., Akhurst, J., Bruno, R., Laing, P. A. F., Matthews, A., & Felmingham, K. L. (2021). Dopamine, endocannabinoids and their interaction in fear extinction and negative affect in PTSD. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 105, 110118. <https://doi.org/https://doi.org/10.1016/j.pnpbp.2020.110118>
- Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp*, 15(1), 1-25. <https://doi.org/10.1002/hbm.1058> [pii]
- Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychol Bull*, 131(4), 510-532. <https://doi.org/10.1037/0033-2909.131.4.510>
- Nisar, S., Bhat, A. A., Masoodi, T., Hashem, S., Akhtar, S., Ali, T. A., Amjad, S., Chawla, S., Bagga, P., Frenneaux, M. P., Reddy, R., Fakhro, K., & Haris, M. (2022). Genetics of glutamate and its receptors in autism spectrum disorder. *Molecular Psychiatry*, 27(5), 2380-2392. <https://doi.org/10.1038/s41380-022-01506-w>
- Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., Fregni, F., & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*, 1(3), 206-223. <https://doi.org/https://doi.org/10.1016/j.brs.2008.06.004>
- Noble, L. J., Gonzalez, I. J., Meruva, V. B., Callahan, K. A., Belfort, B. D., Ramanathan, K. R., Meyers, E., Kilgard, M. P., Rennaker, R. L., & McIntyre, C. K. (2017). Effects of vagus nerve stimulation on extinction of conditioned fear and post-traumatic stress disorder

- symptoms in rats. *Translational Psychiatry*, 7(8), e1217-e1217. <https://doi.org/10.1038/tp.2017.191>
- Noble, L. J., Meruva, V. B., Hays, S. A., Rennaker, R. L., Kilgard, M. P., & McIntyre, C. K. (2019). Vagus nerve stimulation promotes generalization of conditioned fear extinction and reduces anxiety in rats. *Brain Stimulation*, 12(1), 9-18. <https://doi.org/https://doi.org/10.1016/j.brs.2018.09.013>
- Noei, S., Zouridis, I. S., Logothetis, N. K., Panzeri, S., & Totah, N. K. (2022). Distinct ensembles in the noradrenergic locus coeruleus are associated with diverse cortical states. *Proceedings of the National Academy of Sciences*, 119(18), e2116507119. <https://doi.org/doi:10.1073/pnas.2116507119>
- Noël, X. (2023). A critical perspective on updating drug memories through the integration of memory editing and brain stimulation [Mini Review]. *Frontiers in Psychiatry*, 14. <https://doi.org/10.3389/fpsy.2023.1161879>
- Noyes, N. C., Phan, A., & Davis, R. L. (2021). Memory suppressor genes: Modulating acquisition, consolidation, and forgetting. *Neuron*, 109(20), 3211-3227. <https://doi.org/10.1016/j.neuron.2021.08.001>
- O'Leary, J. D., Bruckner, R., Autore, L., & Ryan, T. J. (2023). Natural forgetting reversibly modulates engram expression. In: Cold Spring Harbor Laboratory.
- Ohno, M. (2023). Accelerated long-term forgetting: A sensitive paradigm for detecting subtle cognitive impairment and evaluating BACE1 inhibitor efficacy in preclinical Alzheimer's disease. *Front Dement*, 2, 1161875. <https://doi.org/10.3389/frdem.2023.1161875>
- Oliva, M., & Anikin, A. (2018). Pupil dilation reflects the time course of emotion recognition in human vocalizations. *Scientific Reports*, 8(1), 4871. <https://doi.org/10.1038/s41598-018-23265-x>
- Osorio-Gómez, D., Miranda, M. I., Guzmán-Ramos, K., & Bermúdez-Rattoni, F. (2023). Transforming experiences: Neurobiology of memory updating/editing. *Front Syst Neurosci*, 17, 1103770. <https://doi.org/10.3389/fnsys.2023.1103770>
- Oya, M., Matsuoka, K., Kubota, M., Fujino, J., Tei, S., Takahata, K., Tagai, K., Yamamoto, Y., Shimada, H., Seki, C., Itahashi, T., Aoki, Y. Y., Ohta, H., Hashimoto, R.-i., Sugihara, G., Obata, T., Zhang, M.-R., Suhara, T., Nakamura, M., . . . Higuchi, M. (2023). Increased glutamate and glutamine levels and their relationship to astrocytes and dopaminergic transmissions in the brains of adults with autism. *Scientific Reports*, 13(1), 11655. <https://doi.org/10.1038/s41598-023-38306-3>
- Pae, J. S., Kwon, J. S., Youn, T., Park, H. J., Kim, M. S., Lee, B., & Park, K. S. (2003). LORETA imaging of P300 in schizophrenia with individual MRI and 128-channel EEG. *NeuroImage*, 20(3), 1552-1560. <https://doi.org/10.1016/j.neuroimage.2003.08.001>
- Papadaniil, C. D., Kosmidou, V. E., Tsolaki, A., Tsolaki, M., Kompatsiaris, I. Y., & Hadjileontiadis, L. J. (2016). Cognitive MMN and P300 in mild cognitive impairment and Alzheimer's disease: A high density EEG-3D vector field tomography approach. *Brain Res*, 1648(Pt A), 425-433. <https://doi.org/10.1016/j.brainres.2016.07.043>
- Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Methods Find Exp Clin Pharmacol*, 24 Suppl D, 5-12. <https://www.ncbi.nlm.nih.gov/pubmed/12575463>
- Perry, C. J., Zbukvic, I., Kim, J. H., & Lawrence, A. J. (2014). Role of cues and contexts on drug-seeking behaviour. *British Journal of Pharmacology*, 171(20), 4636-4672. <https://doi.org/https://doi.org/10.1111/bph.12735>
- Petit, G., Cimochovska, A., Cevallos, C., Cheron, G., Kornreich, C., Hanak, C., Schroder, E., Verbanck, P., & Campanella, S. (2015). Reduced processing of alcohol cues predicts abstinence in recently detoxified alcoholic patients in a three-month follow up period: an ERP study. *Behav Brain Res*, 282, 84-94. <https://doi.org/10.1016/j.bbr.2014.12.057>
- Pigeon, S., Lonergan, M., Rotondo, O., Pitman, R. K., & Brunet, A. (2022). Impairing memory reconsolidation with propranolol in healthy and clinical samples: a meta-analysis. *Journal of Psychiatry and Neuroscience*, 47(2), E109-E122. <https://doi.org/10.1503/jpn.210057>
- Pitman, R. K., Rasmusson, A. M., Koenen, K. C., Shin, L. M., Orr, S. P., Gilbertson, M. W., Milad, M. R., & Liberzon, I. (2012). Biological studies of post-traumatic stress disorder. *Nature Reviews Neuroscience*, 13(11), 769-787. <https://doi.org/10.1038/nrn3339>

- Pizzagalli, D. A., Oakes, T. R., Fox, A. S., Chung, M. K., Larson, C. L., Abercrombie, H. C., Schaefer, S. M., Benca, R. M., & Davidson, R. J. (2004). Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Molecular Psychiatry*, 9(4), 393-405. <https://doi.org/10.1038/sj.mp.4001469>
- Poe, G. R., Foote, S., Eschenko, O., Johansen, J. P., Bouret, S., Aston-Jones, G., Harley, C. W., Manahan-Vaughan, D., Weinshenker, D., Valentino, R., Berridge, C., Chandler, D. J., Waterhouse, B., & Sara, S. J. (2020). Locus coeruleus: a new look at the blue spot. *Nature Reviews Neuroscience*, 21(11), 644-659. <https://doi.org/10.1038/s41583-020-0360-9>
- Polák, J., Sedláčková, K., Landová, E., & Frynta, D. (2020). Faster detection of snake and spider phobia: revisited. *Heliyon*, 6(5), e03968. <https://doi.org/https://doi.org/10.1016/j.heliyon.2020.e03968>
- Ramlakhan, J. U., Zomorodi, R., Downar, J., Blumberger, D. M., Daskalakis, Z. J., George, T. P., Kiang, M., & Barr, M. S. (2018). Using Mismatch Negativity to Investigate the Pathophysiology of Substance Use Disorders and Comorbid Psychosis. *Clin EEG Neurosci*, 49(4), 226-237. <https://doi.org/10.1177/1550059418760077>
- Rana, A., & Musto, A. E. (2018). The role of inflammation in the development of epilepsy. *Journal of Neuroinflammation*, 15(1), 144. <https://doi.org/10.1186/s12974-018-1192-7>
- Reimer, J., McGinley, M. J., Liu, Y., Rodenkirch, C., Wang, Q., McCormick, D. A., & Tolia, A. S. (2016). Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. *Nature Communications*, 7(1), 13289. <https://doi.org/10.1038/ncomms13289>
- Richards, B. A., & Frankland, P. W. (2017). The Persistence and Transience of Memory. *Neuron*, 94(6), 1071-1084. <https://doi.org/https://doi.org/10.1016/j.neuron.2017.04.037>
- Richter-Levin, G., & Akirav, I. (2003). Emotional tagging of memory formation—in the search for neural mechanisms. *Brain Research Reviews*, 43(3), 247-256. <https://doi.org/https://doi.org/10.1016/j.brainresrev.2003.08.005>
- Robison, M. K., Ralph, K. J., Gondoli, D. M., Torres, A., Campbell, S., Brewer, G. A., & Gibson, B. S. (2023). Testing locus coeruleus-norepinephrine accounts of working memory, attention control, and fluid intelligence. *Cognitive, Affective, & Behavioral Neuroscience*, 23(4), 1014-1058. <https://doi.org/10.3758/s13415-023-01096-2>
- Rodini, M., De Simone, M. S., Caltagirone, C., & Carlesimo, G. A. (2022). Accelerated long-term forgetting in neurodegenerative disorders: A systematic review of the literature. *Neuroscience & Biobehavioral Reviews*, 141, 104815. <https://doi.org/https://doi.org/10.1016/j.neubiorev.2022.104815>
- Roediger, H. L., III, & Butler, A. C. (2011). The critical role of retrieval practice in long-term retention. *Trends in Cognitive Sciences*, 15(1), 20-27. <https://doi.org/10.1016/j.tics.2010.09.003>
- Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nat Rev Neurosci*, 10(6), 423-433. <https://doi.org/10.1038/nrn2651>
- Roozendaal, B., & McGaugh, J. L. (2011). Memory modulation. *Behav Neurosci*, 125(6), 797-824. <https://doi.org/10.1037/a0026187>
- Rubinstein, D., Abargil, M., Duek, O., & Harpaz-Rotem, I. (2025). RESET post-traumatic stress disorder: clinical protocol integrating reconsolidation, exposure, short-term emotional transformation. *European Journal of Psychotraumatology*, 16(1), 2540141. <https://doi.org/10.1080/20008066.2025.2540141>
- Ruggeri, M., Monica, R., Carmela, G., & and Blundo, C. (2024). Accelerated long-term forgetting: from subjective memory decline to a defined clinical entity. *Aging, Neuropsychology, and Cognition*, 31(6), 1058-1069. <https://doi.org/10.1080/13825585.2024.2317924>
- Ruzzoli, M., Pirulli, C., Mazza, V., Miniussi, C., & Brignani, D. (2016). The mismatch negativity as an index of cognitive decline for the early detection of Alzheimer's disease. *Sci Rep*, 6, 33167. <https://doi.org/10.1038/srep33167>
- Ryan, T. J., & Frankland, P. W. (2022). Forgetting as a form of adaptive engram cell plasticity. *Nature Reviews Neuroscience*, 23(3), 173-186. <https://doi.org/10.1038/s41583-021-00548-3>
- Sack, A. T., Paneva, J., Kütthe, T., Dijkstra, E., Zwienenberg, L., Arns, M., & Schuhmann, T. (2024). Target Engagement and Brain State Dependence of Transcranial Magnetic Stimulation: Implications for Clinical Practice. *Biological Psychiatry*, 95(6), 536-544. <https://doi.org/https://doi.org/10.1016/j.biopsych.2023.09.011>

- Sandrini, M., Cohen, L. G., & Censor, N. (2015). Modulating reconsolidation: a link to causal systems-level dynamics of human memories. *Trends in Cognitive Sciences*, 19(8), 475-482. <https://doi.org/10.1016/j.tics.2015.06.002>
- Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience*, 10(3), 211-223. <https://doi.org/10.1038/nrn2573>
- Sara, S. J. (2015). Locus Coeruleus in time with the making of memories. *Current Opinion in Neurobiology*, 35, 87-94. <https://doi.org/https://doi.org/10.1016/j.conb.2015.07.004>
- Savage, S., Hoefelz, S., Milton, F., Streatfield, C., Dewar, M., & Zeman, A. (2019). The evolution of accelerated long-term forgetting: Evidence from the TIME study. *Cortex*, 110, 16-36. <https://doi.org/https://doi.org/10.1016/j.cortex.2017.09.007>
- Schmidt, A., Diaconescu, A. O., Komater, M., Friston, K. J., Stephan, K. E., & Vollenweider, F. X. (2013). Modeling ketamine effects on synaptic plasticity during the mismatch negativity. *Cereb Cortex*, 23(10), 2394-2406. <https://doi.org/10.1093/cercor/bhs238>
- Schmidt, R., Herrojo Ruiz, M., Kilavik, B. E., Lundqvist, M., Starr, P. A., & Aron, A. R. (2019). Beta Oscillations in Working Memory, Executive Control of Movement and Thought, and Sensorimotor Function. *The Journal of Neuroscience*, 39(42), 8231-8238. <https://doi.org/10.1523/jneurosci.1163-19.2019>
- Schmitz, T. W., Correia, M. M., Ferreira, C. S., Prescott, A. P., & Anderson, M. C. (2017). Hippocampal GABA enables inhibitory control over unwanted thoughts. *Nature Communications*, 8(1), 1311. <https://doi.org/10.1038/s41467-017-00956-z>
- Schroeder, M. N., Fullio, C. L., Ballarini, F., & Moncada, D. (2023). Modulation of memory reconsolidation by adjacent novel tasks: timing defines the nature of change. *Communications Biology*, 6(1), 1288. <https://doi.org/10.1038/s42003-023-05666-5>
- Sedley, W., Friston, K. J., Gander, P. E., Kumar, S., & Griffiths, T. D. (2016). An Integrative Tinnitus Model Based on Sensory Precision. *Trends in Neurosciences*, 39(12), 799-812. <https://doi.org/10.1016/j.tins.2016.10.004>
- Seminck, N., Khatoun, A., Kerstens, S., Nuttin, B., & Mc Laughlin, M. (2024). External stimulation of the trigeminal nerve causes pupil dilation in healthy volunteers, suggesting locus coeruleus modulation. *Brain Stimul*, 17(3), 678-680. <https://doi.org/10.1016/j.brs.2024.05.008>
- Sevenster, D., Beckers, T., & Kindt, M. (2013). Prediction Error Governs Pharmacologically Induced Amnesia for Learned Fear. *Science (New York, N.Y.)*, 339(6121), 830-833. <https://doi.org/doi:10.1126/science.1231357>
- Shariff, S., Nouh, H. A., Inshutiyimana, S., Kachouh, C., Abdelwahab, M. M., Nazir, A., Wojtara, M., & Uwishema, O. (2024). Advances in understanding the pathogenesis of epilepsy: Unraveling the molecular mechanisms: A cross-sectional study. *Health Sci Rep*, 7(2), e1896. <https://doi.org/10.1002/hsr2.1896>
- Shirai, R., & Watanabe, K. (2022). Open biological negative image set. *Royal Society Open Science*, 9(1). <https://doi.org/10.1098/rsos.211128>
- Shuai, Y., Lu, B., Hu, Y., Wang, L., Sun, K., & Zhong, Y. (2010). Forgetting Is Regulated through Rac Activity in *Drosophila*. *Cell*, 140(4), 579-589. <https://doi.org/10.1016/j.cell.2009.12.044>
- Siepmann, M., & Kirch, W. (2002). Effects of caffeine on topographic quantitative EEG. *Neuropsychobiology*, 45(3), 161-166. <https://doi.org/10.1159/000054958>
- Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends in Cognitive Sciences*, 12(12), 447-454. <https://doi.org/10.1016/j.tics.2008.09.004>
- Simon, D. W., McGeachy, M. J., Bayır, H., Clark, R. S., Loane, D. J., & Kochanek, P. M. (2017). The far-reaching scope of neuroinflammation after traumatic brain injury. *Nat Rev Neurol*, 13(3), 171-191. <https://doi.org/10.1038/nrneurol.2017.13>
- Sinclair, A. H., & Barense, M. D. (2019). Prediction Error and Memory Reactivation: How Incomplete Reminders Drive Reconsolidation. *Trends in Neurosciences*, 42(10), 727-739. <https://doi.org/10.1016/j.tins.2019.08.007>
- Soleimani, G., Nitsche, M. A., Bergmann, T. O., Towhidkhan, F., Violante, I. R., Lorenz, R., Kuplicki, R., Tsuchiyagaito, A., Mulyana, B., Mayeli, A., Ghobadi-Azbari, P., Mosayebi-Samani, M., Zilverstand, A., Paulus, M. P., Bikson, M., & Ekhtiari, H. (2023). Closing the loop between

- brain and electrical stimulation: towards precision neuromodulation treatments. *Translational Psychiatry*, 13(1), 279. <https://doi.org/10.1038/s41398-023-02565-5>
- Song, J., Yang, X., Zhou, Y., Chen, L., Zhang, X., Liu, Z., Niu, W., Zhan, N., Fan, X., Khan, A. A., Kuang, Y., Song, L., He, G., & Li, W. (2019). Dysregulation of neuron differentiation in an autistic savant with exceptional memory. *Molecular Brain*, 12(1), 91. <https://doi.org/10.1186/s13041-019-0507-7>
- Souza, R. R., Powers, M. B., Rennaker, R. L., McIntyre, C. K., Hays, S. A., & Kilgard, M. P. (2022). Timing of vagus nerve stimulation during fear extinction determines efficacy in a rat model of PTSD. *Scientific Reports*, 12(1), 16526. <https://doi.org/10.1038/s41598-022-20301-9>
- Sprevak, M., & Smith, R. (2023). An Introduction to Predictive Processing Models of Perception and Decision-Making. *Topics in Cognitive Science*, n/a(n/a). <https://doi.org/https://doi.org/10.1111/tops.12704>
- Squire, L. R., Genzel, L., Wixted, J. T., & Morris, R. G. (2015). Memory consolidation. *Cold Spring Harb Perspect Biol*, 7(8), a021766. <https://doi.org/10.1101/cshperspect.a021766>
- Stähli, N. E., Bigi, S., Grunt, S., Lidzba, K., & Studer, M. (2022). Systematic Review of Accelerated Long-term Forgetting in Children and Adolescents With Neuropediatric Diseases. *Neurol Clin Pract*, 12(6), e210-e220. <https://doi.org/10.1212/cpj.0000000000200081>
- Stampanoni Bassi, M., Iezzi, E., Gilio, L., Centonze, D., & Buttari, F. (2019). Synaptic Plasticity Shapes Brain Connectivity: Implications for Network Topology. *Int J Mol Sci*, 20(24). <https://doi.org/10.3390/ijms20246193>
- Stramaccia, D. F., Meyer, A. K., Rischer, K. M., Fawcett, J. M., & Benoit, R. G. (2021). Memory suppression and its deficiency in psychological disorders: A focused meta-analysis. *J Exp Psychol Gen*, 150(5), 828-850. <https://doi.org/10.1037/xge0000971>
- Studer, M., G. A., N., G., K., G., K., H., & and Heinemann, D. (2024). Accelerated long-term forgetting in patients with acquired brain injury. *Brain Injury*, 38(5), 377-389. <https://doi.org/10.1080/02699052.2024.2311349>
- Studer, M., Heinemann, D., Gutbrod, K., & Henke, K. (2024). Forgetting is comparable between healthy young and old people. *Sci Rep*, 14(1), 31176. <https://doi.org/10.1038/s41598-024-82570-w>
- Sullivan, D. R., Marx, B., Chen, M. S., Depue, B. E., Hayes, S. M., & Hayes, J. P. (2019). Behavioral and neural correlates of memory suppression in PTSD. *J Psychiatr Res*, 112, 30-37. <https://doi.org/10.1016/j.jpsychires.2019.02.015>
- Sumadewi, K. T., Harkitasari, S., & Tjandra, D. C. (2023). Biomolecular mechanisms of epileptic seizures and epilepsy: a review. *Acta Epileptologica*, 5(1), 28. <https://doi.org/10.1186/s42494-023-00137-0>
- Szeska, C., Pünjer, H., Riemann, S., Meinzer, M., & Hamm, A. O. (2022). Stimulation of the ventromedial prefrontal cortex blocks the return of subcortically mediated fear responses. *Translational Psychiatry*, 12(1), 394. <https://doi.org/10.1038/s41398-022-02174-8>
- Szeska, C., Richter, J., Wendt, J., Weymar, M., & Hamm, A. O. (2020). Promoting long-term inhibition of human fear responses by non-invasive transcutaneous vagus nerve stimulation during extinction training. *Scientific Reports*, 10(1), 1529. <https://doi.org/10.1038/s41598-020-58412-w>
- Szeska, C., Ventura-Bort, C., Giraudier, M., & Weymar, M. (2025). A vagal route to memory: evidence from invasive and non-invasive electrical vagus nerve stimulation studies and areas for future clinical application [Mini Review]. *Frontiers in Human Neuroscience*, Volume 19 - 2025. <https://doi.org/10.3389/fnhum.2025.1595737>
- Takeuchi, T., Duzkiewicz, A. J., Sonneborn, A., Spooner, P. A., Yamasaki, M., Watanabe, M., Smith, C. C., Fernández, G., Deisseroth, K., Greene, R. W., & Morris, R. G. M. (2016). Locus coeruleus and dopaminergic consolidation of everyday memory. *Nature*, 537(7620), 357-362. <https://doi.org/10.1038/nature19325>
- Talbot, J., Convertino, G., De Marco, M., Venneri, A., & Mazzoni, G. (2025). Highly Superior Autobiographical Memory (HSAM): A Systematic Review. *Neuropsychology Review*, 35(1), 54-76. <https://doi.org/10.1007/s11065-024-09632-8>
- Tillman, G. D., Morris, E. E., Bass, C., Turner, M., Watson, K., Brooks, J. T., Rawlinson, T., Kozel, F. A., Kraut, M. A., Motes, M. A., & Hart, J., Jr. (2023). P3a amplitude to trauma-related stimuli reduced after successful trauma-focused PTSD treatment. *Biol Psychol*, 182, 108648. <https://doi.org/10.1016/j.biopsycho.2023.108648>

- Tong, C., Li, W., Zou, Y., Xia, Y., Pei, M., Zhang, K., Luo, Y., & Liang, Z. (2025). Norepinephrine-mediated arousal fluctuations drive inverted U-shaped functional connectivity dynamics. *Nature Communications*, 16(1), 11318. <https://doi.org/10.1038/s41467-025-66436-x>
- Tort-Merino, A., Laine, M., Valech, N., Olives, J., León, M., Ecay-Torres, M., Estanga, A., Martínez-Lage, P., Fortea, J., Sánchez-Valle, R., Rami, L., & Rodríguez-Fornells, A. (2021). Accelerated long-term forgetting over three months in asymptomatic APOE $\epsilon 4$ carriers. *Annals of Clinical and Translational Neurology*, 8(2), 477-484. <https://doi.org/https://doi.org/10.1002/acn3.51245>
- Tort-Merino, A., Valech, N., Laine, M., Olives, J., León, M., Ecay-Torres, M., Estanga, A., Martínez-Lage, P., Fortea, J., Molinuevo, J. L., Sánchez-Valle, R., Rodríguez-Fornells, A., & Rami, L. (2021). Accelerated long-term forgetting in individuals with subjective cognitive decline and amyloid- β positivity. *International Journal of Geriatric Psychiatry*, 36(7), 1037-1049. <https://doi.org/https://doi.org/10.1002/gps.5539>
- Tronson, N. C., & Taylor, J. R. (2007). Molecular mechanisms of memory reconsolidation. *Nature Reviews Neuroscience*, 8(4), 262-275. <https://doi.org/10.1038/nrn2090>
- Tsolaki, A. C., Kosmidou, V., Kompatsiaris, I. Y., Papadaniil, C., Hadjileontiadis, L., Adam, A., & Tsolaki, M. (2017). Brain source localization of MMN and P300 ERPs in mild cognitive impairment and Alzheimer's disease: a high-density EEG approach. *Neurobiol Aging*, 55, 190-201. <https://doi.org/10.1016/j.neurobiolaging.2017.03.025>
- Tu, S., Miller, L., Piguet, O., & Hornberger, M. (2014). Accelerated forgetting of contextual details due to focal medio-dorsal thalamic lesion. *Front Behav Neurosci*, 8, 320. <https://doi.org/10.3389/fnbeh.2014.00320>
- Unsworth, N., & Robison, M. K. (2017). A locus coeruleus-norepinephrine account of individual differences in working memory capacity and attention control. *Psychonomic Bulletin & Review*, 24(4), 1282-1311. <https://doi.org/10.3758/s13423-016-1220-5>
- Vainchtein, I. D., & Molofsky, A. V. (2020). Astrocytes and Microglia: In Sickness and in Health. *Trends in Neurosciences*, 43(3), 144-154. <https://doi.org/10.1016/j.tins.2020.01.003>
- Valenza, M., Facchinetti, R., Torazza, C., Ciarla, C., Bronzuoli, M. R., Balbi, M., Bonanno, G., Popoli, M., Steardo, L., Milanese, M., Musazzi, L., Bonifacino, T., & Scuderi, C. (2024). Molecular signatures of astrocytes and microglia maladaptive responses to acute stress are rescued by a single administration of ketamine in a rodent model of PTSD. *Translational Psychiatry*, 14(1), 209. <https://doi.org/10.1038/s41398-024-02928-6>
- van Boekholdt, L., Kerstens, S., Khatoun, A., Asamoah, B., & Mc Laughlin, M. (2021). tDCS peripheral nerve stimulation: a neglected mode of action? *Molecular Psychiatry*, 26(2), 456-461. <https://doi.org/10.1038/s41380-020-00962-6>
- van der Kolk, B. (2000). Posttraumatic stress disorder and the nature of trauma. *Dialogues in Clinical Neuroscience*, 2(1), 7-22. <https://doi.org/10.31887/DCNS.2000.2.1/bvdkolk>
- van Der Kolk, B. A., & Fisler, R. (1995). Dissociation and the fragmentary nature of traumatic memories: Overview and exploratory study. *Journal of Traumatic Stress*, 8(4), 505-525. <https://doi.org/https://doi.org/10.1002/jts.2490080402>
- van der Werf, S. P., Geurts, S., & de Werd, M. M. E. (2016). Subjective Memory Ability and Long-Term Forgetting in Patients Referred for Neuropsychological Assessment [Original Research]. *Frontiers in Psychology*, Volume 7 - 2016. <https://doi.org/10.3389/fpsyg.2016.00605>
- Vanneste, S., Mohan, A., Yoo, H. B., Huang, Y., Luckey, A. M., McLeod, S. L., Tabet, M. N., Souza, R. R., McIntyre, C. K., Chapman, S., Robertson, I. H., & To, W. T. (2020). The peripheral effect of direct current stimulation on brain circuits involving memory. *Science Advances*, 6(45), eaax9538. <https://doi.org/doi:10.1126/sciadv.aax9538>
- Varma, M. M., Zeng, S., Singh, L., Holmes, E. A., Huang, J., Chiu, M. H., & Hu, X. (2024). A systematic review and meta-analysis of experimental methods for modulating intrusive memories following lab-analogue trauma exposure in non-clinical populations. *Nature Human Behaviour*, 8(10), 1968-1987. <https://doi.org/10.1038/s41562-024-01956-y>
- Vavrková, Z., Milton, A. L., & Merlo, E. (2020). Retrieval-Dependent Mechanisms Affecting Emotional Memory Persistence: Reconsolidation, Extinction, and the Space in Between [Review]. *Frontiers in Behavioral Neuroscience*, Volume 14 - 2020. <https://doi.org/10.3389/fnbeh.2020.574358>

- Vazey, E. M., Moorman, D. E., & Aston-Jones, G. (2018). Phasic locus coeruleus activity regulates cortical encoding of salience information. *Proceedings of the National Academy of Sciences*, 115(40), E9439-E9448. <https://doi.org/doi:10.1073/pnas.1803716115>
- Vergallito, A., Feroldi, S., Pisoni, A., & Romero Lauro, L. J. (2022). Inter-Individual Variability in tDCS Effects: A Narrative Review on the Contribution of Stable, Variable, and Contextual Factors. *Brain Sciences*, 12(5), 522. <https://www.mdpi.com/2076-3425/12/5/522>
- Vervliet, B., Craske, M. G., & Hermans, D. (2013). Fear extinction and relapse: state of the art. *Annu Rev Clin Psychol*, 9, 215-248. <https://doi.org/10.1146/annurev-clinpsy-050212-185542>
- Viglione, A., Mazziotti, R., & Pizzorusso, T. (2023). From pupil to the brain: New insights for studying cortical plasticity through pupillometry. *Front Neural Circuits*, 17, 1151847. <https://doi.org/10.3389/fncir.2023.1151847>
- Vijayraghavan, S., Wang, M., Birnbaum, S. G., Williams, G. V., & Arnsten, A. F. T. (2007). Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. *Nature Neuroscience*, 10(3), 376-384. <https://doi.org/10.1038/nn1846>
- Vitacco, D., Brandeis, D., Pascual-Marqui, R., & Martin, E. (2002). Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. *Hum Brain Mapp*, 17(1), 4-12. <https://doi.org/10.1002/hbm.10038>
- Volkow, N. D., Logan, J., Fowler, J. S., Wang, G. J., Gur, R. C., Wong, C., Felder, C., Gatley, S. J., Ding, Y. S., Hitzemann, R., & Pappas, N. (2000). Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. *Am J Psychiatry*, 157(1), 75-80. <https://doi.org/10.1176/ajp.157.1.75>
- Volpe, U., Mucci, A., Bucci, P., Merlotti, E., Galderisi, S., & Maj, M. (2007). The cortical generators of P3a and P3b: a LORETA study. *Brain Res Bull*, 73(4-6), 220-230. <https://doi.org/10.1016/j.brainresbull.2007.03.003>
- Vöröslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernández-Ruiz, A., Kozák, G., Kincses, Z. T., Iványi, B., Buzsáki, G., & Berényi, A. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nature Communications*, 9(1), 483. <https://doi.org/10.1038/s41467-018-02928-3>
- Waldhauser, G. T., Dahl, M. J., Ruf-Leuschner, M., Müller-Bamouh, V., Schauer, M., Axmacher, N., Elbert, T., & Hanslmayr, S. (2018). The neural dynamics of deficient memory control in heavily traumatized refugees. *Scientific Reports*, 8(1), 13132. <https://doi.org/10.1038/s41598-018-31400-x>
- Wang, S. M., Han, K. D., Kim, N. Y., Um, Y. H., Kang, D. W., Na, H. R., Lee, C. U., & Lim, H. K. (2021). Late-life depression, subjective cognitive decline, and their additive risk in incidence of dementia: A nationwide longitudinal study. *PLoS One*, 16(7), e0254639. <https://doi.org/10.1371/journal.pone.0254639>
- Wang, W., Wang, Z., Cao, J., Dong, Y., & Chen, Y. (2023). Roles of Rac1-Dependent Intrinsic Forgetting in Memory-Related Brain Disorders: Demon or Angel. *Int J Mol Sci*, 24(13). <https://doi.org/10.3390/ijms241310736>
- Wang, X. T., Wang, Z. T., Hu, H. Y., Qu, Y., Wang, M., Shen, X. N., Xu, W., Dong, Q., Tan, L., & Yu, J. T. (2021). Association of Subjective Cognitive Decline with Risk of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis of Prospective Longitudinal Studies. *J Prev Alzheimers Dis*, 8(3), 277-285. <https://doi.org/10.14283/jpad.2021.27>
- Wansbrough, K., Tan, J., Vallence, A.-M., & Fujiyama, H. (2024). Recent advancements in optimising transcranial electrical stimulation: reducing response variability through individualised stimulation. *Current Opinion in Behavioral Sciences*, 56, 101360. <https://doi.org/https://doi.org/10.1016/j.cobeha.2024.101360>
- Weiss, E., Kann, M., & Wang, Q. (2023). Neuromodulation of Neural Oscillations in Health and Disease. *Biology*, 12(3), 371.
- Wen, W., Grover, S., Hazel, D., Berning, P., Baumgardt, F., Viswanathan, V., Tween, O., & Reinhart, R. M. G. (2024). Beta-band neural variability reveals age-related dissociations in human working memory maintenance and deletion. *PLOS Biology*, 22(9), e3002784. <https://doi.org/10.1371/journal.pbio.3002784>
- Wessel, J. R., & Anderson, M. C. (2024). Neural mechanisms of domain-general inhibitory control. *Trends in Cognitive Sciences*, 28(2), 124-143. <https://doi.org/10.1016/j.tics.2023.09.008>

- Weston, P. S. J., Nicholas, J. M., Henley, S. M. D., Liang, Y., Macpherson, K., Donnachie, E., Schott, J. M., Rossor, M. N., Crutch, S. J., Butler, C. R., Zeman, A. Z., & Fox, N. C. (2018). Accelerated long-term forgetting in presymptomatic autosomal dominant Alzheimer's disease: a cross-sectional study. *Lancet Neurol*, 17(2), 123-132. [https://doi.org/10.1016/s1474-4422\(17\)30434-9](https://doi.org/10.1016/s1474-4422(17)30434-9)
- Whisman, M. A., & Richardson, E. D. (2015). Normative Data on the Beck Depression Inventory – Second Edition (BDI-II) in College Students. *Journal of Clinical Psychology*, 71(9), 898-907. <https://doi.org/https://doi.org/10.1002/jclp.22188>
- Wimber, M., Alink, A., Charest, I., Kriegeskorte, N., & Anderson, M. C. (2015). Retrieval induces adaptive forgetting of competing memories via cortical pattern suppression. *Nature Neuroscience*, 18(4), 582-589. <https://doi.org/10.1038/nn.3973>
- Wimber, M., Bäuml, K.-H., Bergström, Z., Markopoulos, G., Heinze, H.-J., & Richardson-Klavehn, A. (2008). Neural Markers of Inhibition in Human Memory Retrieval. *The Journal of Neuroscience*, 28(50), 13419-13427. <https://doi.org/10.1523/jneurosci.1916-08.2008>
- Wimber, M., Schott, B. H., Wendler, F., Seidenbecher, C. I., Behnisch, G., Macharadze, T., Bäuml, K. H. T., & Richardson-Klavehn, A. (2011). Prefrontal dopamine and the dynamic control of human long-term memory. *Translational Psychiatry*, 1(7), e15-e15. <https://doi.org/10.1038/tp.2011.15>
- Witt, J. A., & Helmstaedter, C. (2021). Neuropsychological Evaluations in Limbic Encephalitis. *Brain Sci*, 11(5). <https://doi.org/10.3390/brainsci11050576>
- Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., Cohen, L. G., Fregni, F., Herrmann, C. S., Kappenman, E. S., Knotkova, H., Liebetanz, D., Miniussi, C., Miranda, P. C., Paulus, W., Priori, A., Reato, D., Stagg, C., Wenderoth, N., & Nitsche, M. A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology*, 127(2), 1031-1048. <https://doi.org/https://doi.org/10.1016/j.clinph.2015.11.012>
- Worrell, G. A., Lagerlund, T. D., Sharbrough, F. W., Brinkmann, B. H., Busacker, N. E., Cicora, K. M., & O'Brien, T. J. (2000). Localization of the epileptic focus by low-resolution electromagnetic tomography in patients with a lesion demonstrated by MRI. *Brain Topogr*, 12(4), 273-282. <https://doi.org/10.1023/a:1023407521772>
- Wu, W., Du, S., Shi, W., Liu, Y., Hu, Y., Xie, Z., Yao, X., Liu, Z., Ma, W., Xu, L., Ma, C., & Zhong, Y. (2019). Inhibition of Rac1-dependent forgetting alleviates memory deficits in animal models of Alzheimer's disease. *Protein Cell*, 10(10), 745-759. <https://doi.org/10.1007/s13238-019-0641-0>
- Xu, H., Gu, L., Zhang, S., Wu, Y., Wei, X., Wang, C., Xu, Y., & Guo, Y. (2022). N200 and P300 component changes in Parkinson's disease: a meta-analysis. *Neurol Sci*, 43(12), 6719-6730. <https://doi.org/10.1007/s10072-022-06348-6>
- Yang, W., Makita, K., Nakao, T., Kanayama, N., Machizawa, M. G., Sasaoka, T., Sugata, A., Kobayashi, R., Hiramoto, R., Yamawaki, S., Iwanaga, M., & Miyatani, M. (2018). Affective auditory stimulus database: An expanded version of the International Affective Digitized Sounds (IADS-E). *Behavior Research Methods*, 50(4), 1415-1429. <https://doi.org/10.3758/s13428-018-1027-6>
- Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nat Methods*, 8(8), 665-670. <https://doi.org/10.1038/nmeth.1635>
- Yasoda-Mohan, A., & Vanneste, S. (2024). Development, Insights and Predisposing Factors of the Brain's Predictive Coding System to Chronic Perceptual Disorders—A Life-Course Examination. *Brain Sciences*, 14(1), 86. <https://www.mdpi.com/2076-3425/14/1/86>
- Yi, A. (2011). California Verbal Learning Test (California Verbal Learning Test-II). In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 475-476). Springer New York. https://doi.org/10.1007/978-0-387-79948-3_1112
- Yue, J.-L., Wang, R.-J., Chen, S.-J., Lin, X., Fang, Q., Guo, X.-J., Sun, Y.-K., Yuan, K., Bao, Y.-P., Shi, J., Xue, Y.-X., Wu, P., & Lu, L. (2025). Effect of conditioned stimuli-triggered memory retrieval-extinction in patients with methamphetamine use disorder. *Translational Psychiatry*, 15(1), 249. <https://doi.org/10.1038/s41398-025-03474-5>
- Zagha, E., & McCormick, D. A. (2014). Neural control of brain state. *Current Opinion in Neurobiology*, 29, 178-186. <https://doi.org/https://doi.org/10.1016/j.conb.2014.09.010>

- Zarow, C., Lyness, S. A., Mortimer, J. A., & Chui, H. C. (2003). Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. *Arch Neurol*, 60(3), 337-341. <https://doi.org/10.1001/archneur.60.3.337>
- Zhang, H., Zhang, X., Zhang, T., & Chen, L. (2001). Excitatory amino acids in cerebrospinal fluid of patients with acute head injuries. *Clin Chem*, 47(8), 1458-1462.
- Zhang, X., Li, Q., Wang, L., Liu, Z.-J., & Zhong, Y. (2016). Cdc42-Dependent Forgetting Regulates Repetition Effect in Prolonging Memory Retention. *Cell Reports*, 16(3), 817-825. <https://doi.org/10.1016/j.celrep.2016.06.041>
- Zhang, X., Sun, Y., Zhao, C., Yu, F., Li, J., Zhao, Z., & Ai, S. (2025). Transcutaneous vagus nerve stimulation modulates fear memory extinction and neural responses in humans. *Cerebral Cortex*, 35(8). <https://doi.org/10.1093/cercor/bhaf224>
- Zilcha-Mano, S., Duek, O., Suarez-Jimenez, B., Zhu, X., Lazarov, A., Helpman, L., Korem, N., Malka, M., Harpaz-Rotem, I., & Neria, Y. (2023). Underlying Hippocampal Mechanism of Posttraumatic Stress Disorder Treatment Outcome: Evidence From Two Clinical Trials. *Biological Psychiatry Global Open Science*, 3(4), 867-874. <https://doi.org/https://doi.org/10.1016/j.bpsgos.2023.01.005>
- Zinkstok, J. R., Boot, E., Bassett, A. S., Hiroi, N., Butcher, N. J., Vingerhoets, C., Vorstman, J. A. S., & van Amelsvoort, T. (2019). Neurobiological perspective of 22q11.2 deletion syndrome. *Lancet Psychiatry*, 6(11), 951-960. [https://doi.org/10.1016/s2215-0366\(19\)30076-8](https://doi.org/10.1016/s2215-0366(19)30076-8)
- Zumsteg, D., Lozano, A. M., & Wennberg, R. A. (2006). Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. *Clinical Neurophysiology*, 117(7), 1602-1609. <https://doi.org/https://doi.org/10.1016/j.clinph.2006.04.008>
- Zumsteg, D., Lozano, A. M., Wieser, H. G., & Wennberg, R. A. (2006). Cortical activation with deep brain stimulation of the anterior thalamus for epilepsy. *Clinical Neurophysiology*, 117(1), 192-207. <https://doi.org/https://doi.org/10.1016/j.clinph.2005.09.015>
- Zumsteg, D., Wennberg, R. A., Treyer, V., Buck, A., & Wieser, H. G. (2005). H215O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. *Neurology*, 65(10), 1657-1660. <https://doi.org/10.1212/01.wnl.0000184516.32369.1a>

APPENDICES

8.1 Appendix I: Supplementary Material for Chapter Two

8.1.1 *Outlier Analyses on Reconsolidation (i.e. No-Change) Pairs*

For the *no-change* pairs, potential outliers for retrieval rates were assessed using standardized Z-scores (i.e. values $> +3$ or < -3): identifying one participant in the sham group who had Z-scores < -3 . Notably, this occurred during and after the administration of sham stimulation. However, their retrieval rates for these pairs on Session 1 (before stimulation) fell within the normal Z-score range (-3 to $+3$). Their scores on control measures were all within standard cut-off values, and their learning and retrieval rates of all other pairs were all within the expected Z-score range as well. Additionally, when this outlier is removed, results remain significant at Session 2: $t(35) = 1.79, p = .041$; and Day 2: $t(35) = 1.82, p = .039$, but not Session 1: $t(35) = 0.67, p = .509$; in line with main results. This pattern suggests that the extreme values on the *no-change* pairs at Session 2 and Day 2 reflect a valid response to the sham intervention, rather than measurement error or a data entry mistake.

8.1.2 *Validating GON-tDCS' Reconsolidation Effects*

To verify GON-tDCS' effect on the reconsolidation process, I examined performance within the sham group for the *no-change* pairs across Sessions 1 and 2 on Day 1. Critically, participants in the sham group showed significant improvement in Session 2 relative to Session 1, despite receiving sham stimulation. A paired-samples t-test comparing performance on the *no-change* word pairs in the sham group between Session 1 ($M = 59.25, SD = 19.15$) and Session 2 ($M = 80.00, SD = 17.92$) revealed a significant improvement, $t(19) = 7.69, p < .001$, Cohen's $d = 1.72$, indicating that retrieval alone during Session 2 produced a reconsolidation effect.

8.2 Appendix II: Supplementary Material for Chapter Three

8.2.1 Baseline differences between groups

To ensure no baseline differences between groups in heart rate (HR), skin conductance response (SCR) and pupil data (peak and latency to peak): linear mixed models were conducted with group as the fixed factor and each physiological measure as the dependent measures. There were no significant differences between groups in baseline results (i.e. Block 1 Day 1) for skin conductance response (SCR), heart rate (HR) or latency to peak dilation (See Supplementary Table 1). There was however a significant difference between groups in baseline responses for peak pupil dilation (See Supplementary Table 1). As such, peak pupil dilation data was corrected by calculating the difference between active or sham stimulated items and baseline items (i.e. CS-2 – CS-1, and CS+2 – CS+1) at each of the blocks.

Supplementary Table 1. Linear Mixed Model Analyses of Baseline Measures

	Baseline Differences Between Groups			
	Active	Sham	F	<i>p</i>
Heart Rate (BPM)	75.25 (.86)	75.58 (.84)	.08	<i>n.s.</i>
SCR	394.58 (49.74)	507.46 (46.45)	2.75	<i>n.s.</i>
Peak Pupil Dilation	2.29 (.05)	1.96 (.05)	20.43	***
Latency to Peak Dilation	2.89 (.11)	2.79 (.12)	.35	<i>n.s.</i>

Notes. This table contains results from linear mixed model analyses assessing baseline differences between active and sham groups. Average fear response (and standard error) of each of the neurophysiological measures for the active and sham groups during block 1 on day 1 are reported above. Abbreviations include beats per minute (BPM), and skin conductance response (SCR). *n.s.* = not significant. *** $p < .001$

8.3 Appendix III: Supplementary Material for Chapter Four

Supplementary Table 2. Proposed Synaptic Regulation and Remodelling Mechanistic Pathways Influencing Engram Accessibility and Forgetting.

Synaptic Regulation and Remodelling Mechanisms		How These Mechanisms May Impact Engram Accessibility and Adaptive Forgetting
Neurotransmission and Receptor Functioning		Excitatory glutamatergic activity and inhibitory GABAergic activity may impact engram accessibility and forgetting via: • NMDAR activity and GluA2 AMPAR endocytosis. • Excitation-inhibition (E/I) balance. • Pyramidal glutamatergic neurons & GABAergic interneurons implicated in memory control networks in the brain (i.e. facilitates active forgetting via DLPFC's downregulation of regions such as the hippocampus and amygdala).
Microglial and Modulation	Astrocytic	Glial cells may impact engram accessibility and forgetting by: • Microglia-driven pruning of weak synaptic connections. • Activity-dependent elimination of excitatory synapses by astrocytes. • Astrocytic-induced NMDA-dependent long-term depression through postsynaptic GluA2 AMPAR endocytosis.
Hippocampal Neurogenesis	Engram accessibility	and adaptive forgetting processes can be modulated by: • Integration of new neurons in existing hippocampal circuits that complete for input/ output connectivity with new and existing synaptic connections. • Hippocampal circuitry reconfiguration which alters synaptic weight between engram cells, reducing likelihood of engram cell reactivation and accessibility.
Actin Cytoskeleton Dynamics	Engram cell accessibility and forgetting	are regulated through actin cytoskeleton dynamics via: • Signalling pathways including Rho GTPases (e.g. Rho, Rac1 and Cdc42) and other proteins which alter synapse size and strength or modulating dendritic spine morphology. These processes are impacted by dopaminergic neurotransmission and receptor functioning.
Dopaminergic Activity	Activation of specific dopamine receptors	regulate forgetting processes via: • Actin cytoskeleton restructuring • Synaptic regulation and remodelling (involving the modulation of small G-proteins such as Rac1 or Cofilin) In humans: • Dopamine bioavailability may contribute to ALF in ageing. Dopaminergic signalling: • In sleep may prevent forgetting via synaptic regulation and remodelling processes • May trigger forgetting via prediction error and expectancy violation processes.

Abbreviations include: Gamma-aminobutyric acid (GABA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), N-methyl-D-aspartate receptor (NMDAR), dorsolateral prefrontal cortex (DLPFC), and Accelerated Long-term Forgetting (ALF).

Supplementary Table 3a. Summary of Abnormal Synaptic Regulation and Remodelling Pathways That May Contribute to Engram Accessibility Across the Forgetting Continuum.

	Excitatory Glutamatergic Activity Inhibitory GABAergic Activity	and Microglial Modulation	AstrocyticHippocampal Neurogenesis	Actin Dynamics	CytoskeletonDopaminergic Activity
<i>Hyperactive Forgetting e.g. Accelerated Long-term Forgetting (ALF)</i>					
AD and PD	Aβ levels = endocytosis of GluA2-containing AMPARs	- Sleep disruptions = - microglial inflammatory responses - Microglial-dependent synaptic elimination = - forgetting		- Aβ expression activates Rac1 - Rac1 = forgetting - Inhibiting Rac1 reduces forgetting	- Dopaminergic signalling impacted via sleep. Sleep disruptions influence Aβ pathology and ALF symptoms. - Dopaminergic neurodegeneration associated with PD symptomatology.
Stroke/TBI	Glutamate & excitotoxicity post-injury	Inflammation and oxidative stress post stroke/ injury	Post stroke excessive hippocampal neurogenesis = forgetting (inhibiting this improved memory)	- APP (precursor of Aβ) and tau post-injury. - Aβ expression may activate Rac1, forgetting	
22q.11.2 deletion syndrome	Glutamate & GABA imbalance				Abnormal dopamine transmission and sleep disturbances
Epilepsy	- Glutamate & GABA imbalance = epileptic activity ↓ resting-state activity in memory networks in the brain (which rely on pyramidal glutamatergic neurons & GABAergic)	- neuroinflammation = neuronal hyperexcitability - Oxidative stress	Hippocampal neurogenesis		- Abnormal dopamine transmission - Dopaminergic medications = anti-convulsant effect

Abbreviations include: Accelerated Long-term Forgetting (ALF), Alzheimer's disease (AD), Parkinson's disease (PD), amyloid-beta (Aβ), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), amyloid precursor protein (APP), traumatic brain injury (TBI), gamma-aminobutyric acid (GABA), and N-methyl-D-aspartate (NMDA).

Supplementary Table 3b. Summary of Abnormal Synaptic Regulation and Remodelling Pathways That May Contribute to Engram Accessibility Across the Forgetting Continuum.

	Excitatory Glutamatergic Activity	Inhibitory GABAergic/Microglial and Astrocytic Modulation	Hippocampal Neurogenesis	Dopaminergic Activity
<i>Hypoactive Forgetting (e.g. PTSD, HSAM or autism savant syndrome)</i>				
PTSD	- Abnormal GABA levels and receptor functioning - cortical metabotropic glutamate receptor 5 (mGluR5) - traumatic stress = glutamatergic-driven excitotoxicity - Dysregulation of memory control network in the brain (which rely on pyramidal glutamatergic neurons & GABAergic) - NMDA receptor antagonists (e.g. ketamine/ memantine) can rescue neuroinflammatory changes = forgetting of traumatic memories	- Acute stress response = prefrontal cortical astrocytic and microglia activation & downstream cytokine signalling cascade - Altered glutamate neurotransmission = impaired glial function - excitotoxicity = impaired astrocytic & glial cell function	- NMDA receptor antagonists help through hippocampal neurogenesis - Hippocampal neurogenesis-targeted interventions = improve PTSD symptoms	Abnormal dopamine transmission & prediction error signalling
Autism savant syndrome	- frequency of spontaneous excitatory postsynaptic currents - Abnormal GAD65 regulation of GABA inhibition - Glutamatergic dysfunction (perhaps through abnormal mGluR5 expression & functioning) in autism - Glutamate & GABA imbalance in anterior cingulate cortex in autism	Astrocytic & dopaminergic regulation of Glutamate & GABA imbalance in anterior cingulate cortex in autism spectrum disorder		Astrocytic & dopaminergic regulation of Glutamate & GABA imbalance in anterior cingulate cortex.
HSAM	- Abnormal activity in inhibitory control and memory networks (that rely on pyramidal glutamatergic neurons & GABAergic) which incl.: - Abnormal hippocampal rs-connectivity - activation of precuneus during retrieval ↓ functional connectivity between anterior cingulate cortex & PFC & hippocampus			

Abbreviations include: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), gamma-aminobutyric acid (GABA), Post Traumatic Stress Disorder (PTSD), Highly Superior Autobiographical Memory (HSAM), and N-methyl-D-aspartate (NMDA).