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Accelerated long-term forgetting across neuropsychiatric disorders: A review of mechanisms and a neurobiological perspective of forgetting

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ABSTRACT

Accelerated long-term forgetting (ALF) is the rapid loss of newly-learnt information, typically noticeable after ~30 min, and observed across diverse neuropsychiatric disorders including epilepsy, Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury, stroke, and genetic conditions such as 22q11.2 deletion syndrome. Traditionally, ALF has been attributed to impaired memory consolidation or acquisition, with emphasis on hippocampal dysfunction or epileptic activity. However, these explanations are insufficient, as ALF also occurs in individuals without hippocampal damage or seizure activity. This review critiques these historical perspectives and proposes a unifying framework: that ALF may, to some degree, stem from hyperactive intrinsic forgetting mechanisms, rather than solely impaired consolidation. Drawing from recent research on memory engrams, synaptic plasticity, and forgetting, the review highlights the role of synaptic remodelling, neurotransmission, glial cell activity, actin cytoskeleton dynamics, hippocampal neurogenesis, and dopaminergic signalling in modulating engram accessibility, and thus memory persistence. Disruption in these pathways – evident across multiple neuropsychiatric conditions – may converge to produce ALF as a shared cognitive symptom. This reframing suggests that ALF may in part represent a maladaptive form of active forgetting, driven by disease-specific disruptions to otherwise adaptive neurobiological processes. Furthermore, ALF is framed as one end of a broader "forgetting continuum," with downregulated forgetting contributing to memory persistence (in conditions such as PTSD, autism savant syndrome, or highly superior autobiographical memory) on the other. Understanding ALF through this lens may unify its presence across diverse conditions and open avenues for targeted therapeutic interventions that aim to modulate memory persistence by addressing the brain's intrinsic forgetting machinery.

1. Introduction

Accelerated long-term forgetting (ALF) is a symptom that has been identified across a wide range of neuropsychiatric disorders. As the term suggests, it refers to the tendency to forget information after ~30 min at a faster rate than expected, despite normal encoding or initial consolidation (Elliott et al., 2014). In other words, although information is learnt and remembered when tested up to 30 min later, this information is forgotten at a faster rate than expected over subsequent minutes, hours, days, weeks or even months. The term 'accelerated long-term forgetting' was first coined by Blake and colleagues (Blake et al., 2000) to describe cases of what were originally referred to as 'long-term amnesia' in patients with epilepsy (Elliott et al., 2014). Most of this original research on ALF in patients with epilepsy was largely observed in those with temporal lobe epilepsy, but subsequently, further cases were observed in those with transient epileptic amnesia, and extra-temporal and genetic generalized epilepsies (García-Martínez et al., 2023; Mameniškienė et al., 2020). Since then, individuals with traumatic brain injury (TBI), limbic encephalitis, stroke, 22q11.2 deletion syndrome, and neurodegenerative disorders such as Alzheimer's disease (AD) or Parkinson's disease have also exhibited signs of ALF (García-Martínez et al., 2023; Savage et al., 2019; van der Werf et al., 2016; Witt and Helmstaedter, 2021).

Interestingly, although some studies and reviews have reported no evidence or inconsistent evidence of ALF across various memory-related disorders or disease stages, the use of recognition (rather than recall)

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tasks in these studies may have influenced these findings. For example, one study found no evidence of ALF in certain memory-related disorders (incl. TBI, amnesia, dementia, mild cognitive impairment, or multiple sclerosis) when recognition tests were used (Geurts et al., 2015). Similarly a systematic review of neurodegenerative disorders looked at studies of those with subjective memory decline, mild cognitive impairment, dementia or AD, as well as those with Parkinson's disease or Huntington's disease, and found conflicting evidence of ALF versus classic amnesia in different stages or conditions of memory impairment (Rodini et al., 2022). However, the authors note how the use of recall versus recognition tasks across these studies may have influenced these findings. Nevertheless, other studies have found evidence of ALF in various patient cohorts using either recall or recognition tasks (Hoefeijzers et al., 2013; Studer, G., et al., 2024; van der Werf et al., 2016). Elliot and colleagues note that the specific nature of the recognition tasks may have yielded these different results (Elliott et al., 2014). Moreover, another limitation in the literature on ALF is the variations in how ALF is defined and/or measured. As discussed in prior reviews, general methodological variations when testing for ALF may result in inconsistent results in these studies (Elliott et al., 2014; García-Martínez et al., 2023). These are important methodological considerations that future research must address when designing ALF studies.

However, methodological considerations when testing for ALF are not the focus of this review. Rather, the aim here is to review the predominant mechanistic theories that have been put forth for ALF, and to subsequently propose a unifying neurobiological theory. There has been several historical and current debates surrounding the exact mechanism (s) of ALF. These debates can be best described as follows: (i) Is ALF *qualitatively* or *quantitatively* different to classic amnesia? And does ALF stem from acquisition or consolidation deficits? (ii) Do structural issues underlie ALF? And is the hippocampus central to ALF? (iii) Does overt seizure activity or subclinical epileptic activity cause ALF?

This review will summarise research on the above mechanisms, and demonstrate how none of these questions adequately address the potential root cause of ALF. As Occam's Razor proposes, the simplest explanation is often the most likely. In other words, given how ALF presents as a symptom across a wide range of neuropsychiatric conditions, we argue that the driving mechanism behind this must be one which is abnormal across these various conditions. Interestingly (and in spite of its name) – the aforementioned approaches don't take into consideration the possibility that ALF may, to some degree, stem from over-active intrinsic forgetting processes. As Davis & Zhong eloquently argue, many systems with the brain and body operate based on homeostatic mechanisms (Davis and Zhong, 2017). Thus, an intuitive perspective on the brain's memory control processes is one which acknowledges how these processes are likely also regulated on a homeostatic basis.

Indeed, recent literature suggests that in parallel to memory maintenance processes (such as consolidation), the brain may also operate intrinsic forgetting processes (Castillo Díaz et al., 2021; Dalto et al., 2025; Davis and Zhong, 2017). In other words, our ability to remember or forget information may be regulated by processes in the brain that operate both in parallel and opposition, almost like a push-pull system (Castillo Díaz et al., 2021; Dalto et al., 2025). Thus, ALF may be a consequence not just of deficits in memory maintenance processes such as consolidation, but also of hyperactive forgetting processes. Theoretically speaking, instead of considering whether accelerated forgetting arises solely from deficits in acquisition or consolidation, an intuitive explanation might be that (as the name suggests) accelerated forgetting indeed stems to some degree from hyperactive forgetting processes. If this is the case, these forgetting processes could arguably ramp up at any stage in the memory process. In other words, in some individuals, these hyperactive forgetting processes may act on the acquisition or early consolidation phases, whereas in other cases, they may only accelerate later in the memory process. This could explain the conflicting results (which this review will later discuss) that differentially report how ALF is associated with poorer encoding or consolidation stage performance.

Moreover, we argue that there are two sides to this forgetting continuum. In other words, after demonstrating how *hyperactive* forgetting processes may underlie ALF symptoms in various disorders, we will highlight how *hypoactive* forgetting processes may contribute to the inability to forget information that is evident across other neuropsychiatric disorders such as post-traumatic stress disorder (PTSD), or other cases of heightened memory persistence such as highly superior autobiographical memory (HSAM) or autism savant syndrome.

As such, after reviewing how none of dominant theoretical approaches to ALF sufficiently address its potential root cause(s), we will propose unifying framework of forgetting, which positions ALF at one end of a forgetting continuum. Furthermore, we will summarise the evidence which suggests converging mechanisms across two sides of this forgetting spectrum.

2. Review of ALF mechanisms

2.1. Is ALF qualitatively or quantitatively different to classic amnesia? does ALF stem from acquisition or consolidation deficits?

Initially, questions arose as to whether ALF stemmed from subtle acquisition deficits or late-stage consolidation deficits (Geurts et al., 2019; Hoefeijzers et al., 2013). At the neurophysiological level, and generally speaking, consolidation processes are supported by both rapid and slow synaptic changes, in conjunction with wider systems-level changes in the brain (Dudai et al., 2015). This synaptic (i.e. cellular) consolidation describes how post-encoding stage, information is transferred into more stable long-term representations (i.e. memory traces) through local changes in the cellular synapses of a neural circuit that represents the memory (Dudai et al., 2015).

During rapid synaptic consolidation, synapses that are activated during learning (mainly in the hippocampus) produce new proteins and structural synaptic changes that support the maintenance of memories through slow synaptic restructuring (García-Martínez et al., 2023). In parallel to this, and over time, these synaptic connections underlying the memory are subsequently reorganised into larger neural ensembles throughout the brain via 'systems consolidation' (Dudai et al., 2015; García-Martínez et al., 2023). More recently, these memory-traces in the brain have been referred to as 'engrams' (Guskjolen and Cembrowski, 2023; Ryan and Frankland, 2022).

Several theoretical approaches of consolidation have been proposed, each which highlight (to varying degrees) the hippocampus' role in memory consolidation processes. The original, classic 'standard consolidation theory' proposes that the hippocampus plays a key role in initially binding information into memory traces via synaptic changes (García-Martínez et al., 2023; Mameniškienė et al., 2020). However, according to that theory, over time memories become independent of the hippocampus (and medial temporal lobe regions), with memory traces gradually reorganised into purely neocortical representations through systems consolidation (García-Martínez et al., 2023; Mameniškienė et al., 2020). A more recent evolution of this approach, termed 'multiple trace theory' argues that memories continue to rely on medial temporal lobe activity, with repeated retrievals generating multiple hippocampal-neocortical memory traces (García-Martínez et al., 2023; Mameniškienė et al., 2020). Both this theory and subsequent 'unified' theories propose that the hippocampus serves to index where memories are located across neocortical regions. However, the unified models argue that while initial synaptic consolidation requires both neocortical and hippocampal involvement, later consolidation and retrieval processes are facilitated through hippocampal-neocortical axonal projections (Mameniškienė et al., 2020).

Building on this, researchers have debated whether ALF is *qualitatively* or *quantitatively* distinct from classic amnesia syndromes. The qualitative viewpoint posits that ALF and classic amnesia have two distinct pathologies, where ALF deficits stem from disruptions of late-

stage consolidation or maintenance processes whereas amnesia originates from acquisition or early-stage consolidation deficits (García-Martínez et al., 2023; Mayes et al., 2019; Rodini et al., 2022). On the other hand, the quantitative viewpoint argues that ALF is a type of mild hippocampal amnesia where accelerated forgetting begins fairly quickly post-learning (or even at the time of encoding) but is so subtle that memory deficits are not evident until delayed testing points (García-Martínez et al., 2023; Mayes et al., 2019; Rodini et al., 2022). Some suggest that there is still no consensus on this qualitative versus quantitative distinction (García-Martínez et al., 2023). However, many converge on the viewpoint that there is insufficient evidence to support the argument that ALF is quantitatively different from classic amnesia, and they disagree that it stems specifically from acquisition/ early-consolidation deficits (Hoefeijzers et al., 2013; Mayes et al., 2019; Rodini et al., 2022). Thus, the more recent literature operates off of the proposition that ALF may originate from late-stage consolidation deficits. Nevertheless, this interpretation remains contested due to empirical research which doesn't always align with this viewpoint (Rodini et al., 2022). As such, it stands to reason, are there other memory-related processes that can explain these conflicting results? This is a point that will be returned to in subsequent sections of this review.

2.2. Do structural issues underlie ALF? and is the hippocampus central to ALF?

In the consolidation theories outlined above, although they differ in *the degree* to which they view the hippocampus and medial temporal lobes as involved in cellular and systems consolidation, they nonetheless all regard the hippocampus as a key node within memory consolidation processes. As such, if ALF stems specifically from consolidation deficits, and if consolidation processes rely on hippocampal activity, it stands to reason that structural abnormalities in the hippocampus might predict ALF. However, there has been inconsistent findings in this area.

For example, in one review of patients with epilepsy, the authors elaborate how, "while the hippocampus probably acts in both synaptic and systems consolidation, its atrophy or injury seems to be more related to immediate anterograde deficits, not long-term forgetting" (Mameniškienė et al., 2020). In this review, it was noted how hippocampal dysfunction or damage in patients with various forms of epilepsy was not sufficient, nor required, for ALF. Moreover, there is inconsistent evidence for whether ALF correlates with hippocampal volume (Mameniškienė et al., 2020). In fact, in that review there were cases where ALF persisted post-hippocampal surgery, highlighting how ALF symptoms can persist regardless of hippocampal integrity. Another study assessed patients with focal epilepsy and limbic encephalitis (considered a precursor of epilepsy in some patients), as well as healthy controls (Helmstaedter et al., 2019). While this study found that ALF over 1 week was associated with limbic encephalitis and amygdala pathology, it was less frequently related with hippocampal damage (Helmstaedter et al., 2019). Likewise, in a study of patients with temporal lobe epilepsy, no association between ALF (over 72 h) and structural medial temporal lobe abnormalities was found (Audrain and McAndrews, 2019).

Similar findings have been reported in other clinical conditions where ALF symptoms present. For example, in stroke patients, ALF over 1 week was observed in patients who had no hippocampal lesions, suggesting that rates of ALF were unrelated to hippocampal damage or volume (Lammers et al., 2022). Likewise, in mouse models of AD and preclinical AD, it has been argued that ALF may reflect impaired systems consolidation in medial temporal cortical regions rather than hippocampal pathology (García-Martínez et al., 2023; Ohno, 2023). Indeed, as Mayes and colleagues outline, the hippocampus is unlikely to be the core driver of ALF symptoms, as it is neither necessary nor sufficient for ALF to be present (Mayes et al., 2019). In fact, hippocampal damage tends to align more with classic amnesia or early/ rapid forgetting, as opposed to late-stage or long-term forgetting (Butler et al., 2009; Mayes et al., 2019). In line with this, one previously-mentioned review of epileptic patients highlights how ALF (at various delays) was associated with extra hippocampal sites (such as the amygdala or prefrontal cortex) or connectivity between these regions (Mameniškienė et al., 2020). This has led to the suggestion that ALF is a "non-lateralized fronto-limbic dysfunction rather than a lateralized hippocampal dysfunction" (Helmstaedter et al., 2019; Mameniškienė et al., 2020; Studer, G., et al., 2024). Essentially, the above studies suggest that while the hippocampus is acknowledged for its core role in memory processes, structural pathology in the hippocampus is unlikely to cause ALF symptoms in patients with various neuropsychiatric disorders.

2.3. Does overt seizure activity or subclinical epileptic activity cause ALF?

Given how ALF was first observed in patients with epilepsy, another proposed mechanistic proposition was that perhaps overt seizure activity or subclinical epileptic activity causes ALF symptoms. As Hoefeijzers and colleagues highlight, this stemmed from findings across some studies which reported that rates of ALF correlated with seizure frequency (Hoefeijzers et al., 2013). Nevertheless, as other reviews outline, the associations between rates of ALF and seizure frequency or epileptic activity is conflicting (García-Martínez et al., 2023; Geurts et al., 2015; Mameniškienė et al., 2020). Moreover, one of the obvious arguments against the idea that epileptiform activity causes ALF, is that ALF symptoms also present in non-epileptic disorders (Mameniškienė et al., 2020). Furthermore, in epileptic patients, post-surgery seizure--free patients still exhibit signs of ALF, and treating seizures with anticonvulsant medications does not prevent the occurrence of ALF (García-Martínez et al., 2023; Muhlert et al., 2011). Thus, overt seizures cannot be the sole driver of ALF across these conditions. Although, they have been suggested to contribute to its severity (García-Martínez et al., 2023; Savage et al., 2019). Similarly, subclinical activity has been proposed as a causative factor of ALF in epileptic patients (Fitzgerald et al., 2013; Hoefeijzers et al., 2013). However, for several of the above reasons and others, the evidence does not strongly support this conclusion (Mameniškienė et al., 2020).

Interestingly, in one study mentioned previously, rates of ALF (over 72 h) were not associated with seizure activity nor the site of epileptic focus (Audrain and 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 the epileptic patients were associated with reduced resting-state functional connectivity between these regions (Audrain and McAndrews, 2019). This might suggest that seizure activity disrupts other mechanisms that produce cognitive symptoms such as ALF, or that underlying mechanisms contribute to seizure activity which subsequently lead to cognitive symptoms such as ALF. For example, perhaps epileptic activity disrupts functional connectivity between memory-related brain regions such as the hippocampus, resulting in ALF in these patients. Indeed, one hypothesis proposes that ALF in temporal lobe epilepsy may stem from (overt or subclinical) epileptic activity which impairs systems-level consolidation due to disrupted hippocampal-neocortical activity, which is reflected neurophysiologically in reduced functional connectivity between these regions (Audrain and McAndrews, 2019; García-Martínez et al., 2023; Lammers et al., 2022). In line with this, interictal spikes during sleep and subclinical epileptiform activity may also disrupt hippocampal-neocortical transfer of information, resulting in ALF (Fitzgerald et al., 2013; García-Martínez et al., 2023; Muhlert et al., 2011). However, another plausible, and not wholly mutually exclusive explanation, is that rather than seizure activity disrupting memory consolidation (leading to ALF), perhaps it accelerates the processes underlying forgetting itself, impacting forgetting-specific molecular or biochemical pathways, leading to ALF. This perspective will be outlined further in the subsequent section(s).

3. An alternative unifying perspective of ALF

As is evident from the sections above, no consensus has been found as to the exact mechanism(s) underlying ALF and no clear cause has been identified.

However, if 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 and Zhong, 2017; Noyes et al., 2021), we 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, we outline how these can impact molecular and biochemical factors which may lead to the same downstream cognitive symptom, ALF. Furthermore, we will 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 Fig. 1). Before discussing how the various neuropathologies of these disorders may accelerate (or inhibit) the brain's biological forgetting processes, it is prudent to outline a potential driving factor behind these, and the molecular and biochemical pathways that are implicated in these processes.

3.1. 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 and 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 accessible state, to an inaccessible one (Ryan and 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 and 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 and 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?

3.2. 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 and Cembrowski, 2023; Ryan and 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

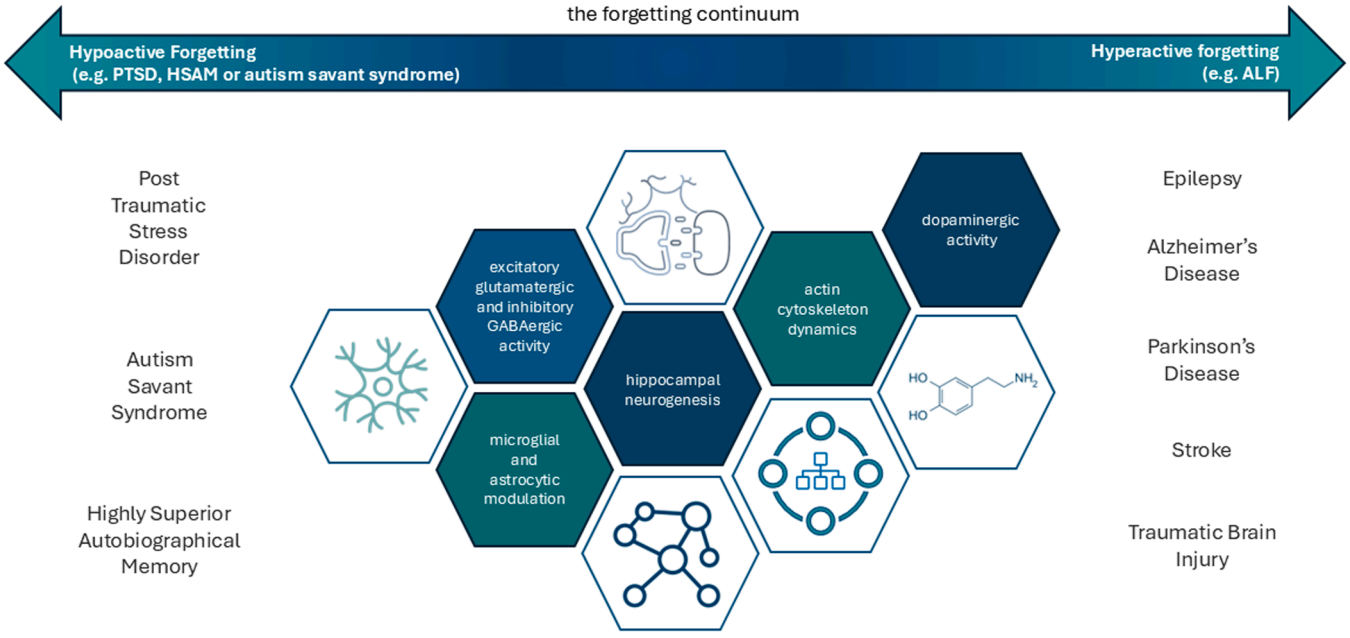

Fig. 1. Proposed Shared Neurobiological Pathways Underlying the Forgetting Continuum. The proposed shared neurobiological pathways that underlie conditions of both hypoactive and hyperactive forgetting. These conditions can be conceptualised as existing along the forgetting continuum. Abbreviations include: Post Traumatic Stress Disorder (PTSD), Highly Superior Autobiographical Memory (HSAM), Accelerated Long-term Forgetting (ALF), and gamma-aminobutyric acid (GABA).

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 these 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.

3.3. 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 and 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 Table 1 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.

3.4. Synaptic regulation and remodelling: neurotransmission and receptor functioning

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 and Cembrowski, 2023; Ryan and 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 and 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 and Frankland, 2022). Supporting this, impaired disinhibition of engram cells has been shown to result in forgetting in certain types of memories (Ryan and 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 and Hanslmayr, 2014; Anderson and 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

Table 1
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 Astrocytic Modulation	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 (AMPAR), N-methyl-D-aspartate receptor (NMDAR), dorsolateral prefrontal cortex (DLPFC), and Accelerated Long-term Forgetting (ALF).

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).

3.5. 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 and 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 and Frankland, 2022). In other words, microglia-dependent synapse elimination can both reduce engram accessibility and increase forgetting (Guskjolen and Cembrowski, 2023). Thus, these mechanisms have been shown to underlie natural forgetting in rodents (Ryan and 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 and 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 and 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 and 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 and Frankland, 2022). Another mechanism that impacts synaptic reorganisation over similar timeframes is hippocampal neurogenesis-mediated forgetting.

3.6. 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 and 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 and 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 and Cembrowski, 2023; Ryan and Frankland, 2022).

3.7. Synaptic regulation and remodelling: actin cytoskeleton dynamics

Most cellular activities rely on the dynamic remoulding of the actin cytoskeleton (Lee and 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 and 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 and 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 and 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 and Frankland, 2022). Indeed, dopaminergic signalling has been outlined as one such factor that influences Rac1 activity and likely engram accessibility (Ryan and Frankland, 2022).

3.8. 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 and 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 (over 1 week) 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 and Frankland, 2022). This suggests that dopamine bioavailability may contribute to whether ALF presents in older adults (Ryan and 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 (over 1 week) in these individuals, there was an association between this and greater sleep fragmentation i.e. more intra-sleep wakenings (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 wakenings 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 and 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 and 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.

Thus 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 and Frankland, 2022). Essentially, dopamine which is known to mediate prediction errors, may trigger both forgetting and de-forgetting processes (Ryan and Frankland, 2022).

3.9. 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 Table 2.

3.10. ALF in Alzheimer's disease (AD) and Parkinson's Disease (PD)

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 and 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 Aβ 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 another study by that same group and additional research, ALF was likewise identified in asymptomatic individuals at high risk of developing AD (i.e. APOE ε4 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 Aβ 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, Aβ expression activates Rac1, with Rac1 levels elevated alongside accelerated forgetting in mouse models of AD and in AD patients (Ohno, 2023; Ryan and Frankland, 2022). Conversely, while heightened Rac1 activity may contribute to accelerated long-term forgetting 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 and Frankland, 2022; Wang et al., 2023). However, of relevance for ALF, in both fly and mouse models of AD, inhibiting Rac1 reduces forgetting (Ryan and Frankland, 2022; Wu et al., 2019).

In the previous section of this review, 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 Aβ pathology may impact forgetting mechanisms is through disrupted sleep patterns. For example, disruptions in the sleep-wake cycle were shown to influence Aβ 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 Aβ pathology (Kaldun et al., 2021).

ALF in AD may also stem from disrupted neurotransmission and receptor functioning. For example, increased Aβ 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 and Frankland, 2022). Moreover, microglial-dependent synaptic elimination contributes to synapse loss in early stages of AD (Ryan and 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).

Table 2
Summary of Abnormal Synaptic Regulation and Remodelling Pathways That May Contribute to Engram Accessibility Across the Forgetting Continuum.

	Excitatory Glutamatergic Activity and Inhibitory GABAergic Activity	Microglial and Astrocytic Modulation	Hippocampal Neurogenesis	Actin Cytoskeleton Dynamics	Dopaminergic Activity
Hyperactive Forgetting e.g. Accelerated Long-term Forgetting (ALF)					
Alzheimer's disease (AD) and Parkinson's disease (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 symptomology.
Stroke/ Traumatic Brain Injury (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 (incl. during sleep) • ↓ 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
Hypoactive Forgetting (e.g. PTSD, HSAM or autism savant syndrome)					
Post Traumatic Stress Disorder (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 (e.g. ketamine/ memantine) exert beneficial effects through hippocampal neurogenesis • Hippocampal neurogenesis-targeting 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 in autism spectrum disorder
Highly Superior Autobiographical Memory (HSAM)	Abnormal activity in inhibitory control and memory networks (that rely on pyramidal glutamatergic neurons & GABAergic) which incl.: • Abnormal hippocampal rs-connectivity				

(*continued on next page*)

Table 2 (*continued*)

	Excitatory Glutamatergic Activity and Inhibitory GABAergic Activity	Microglial and Astrocytic Modulation	Hippocampal Neurogenesis	Actin Cytoskeleton Dynamics	Dopaminergic Activity
	• - activation of precuneus during retrieval • ↓ functional connectivity between anterior cingulate cortex & PFC & hippocampus				

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 (AMPAR), amyloid precursor protein (APP), traumatic brain injury (TBI), gamma-aminobutyric acid (GABA), Post Traumatic Stress Disorder (PTSD), Highly Superior Autobiographical Memory (HSAM), and N-methyl-D-aspartate (NMDA).

ALF (at various delays) 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.

3.11. ALF post-stroke or acquired brain injury

ALF symptoms (at various delays from 1 to 4 weeks) have also been observed in transient ischemic attack (TIA), 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 and Frankland, 2022).

In addition to ALF in patients with acquired brain injury due to stroke, ALF (over 1 week) 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 (over 1 week) 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 Aβ 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.

3.12. 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 microdeleted (i.e. missing) (Lackey and 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 and Muzio, 2023; Zinkstok et al., 2019). Moreover, ALF (at various delays from 1 day to 1 month) 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).

3.13. ALF in epilepsy

As outlined earlier in this review, 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 and 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 and 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 and 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. A novel perspective: the forgetting continuum

Building on the above logic – one viewpoint that remains to be explored in this context is whether ALF exists 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 post-traumatic stress disorder (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.

4.1. 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 2 conditions consists of case reports and small-scale studies. Thus, we 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. Notably, general episodic memory impairments have been outlined in PTSD. However, it is unclear whether or how these relate to ALF symptoms. For example, in a recent meta-analysis, which reported general episodic memory impairments in PTSD, whether or not ALF was related to these memory processes was not investigated (Petzold and Bunzeck, 2022). In fact, this meta-analysis included only studies which test memory within a 10-minute delay. Given that ALF symptoms are typically assessed after delays of ~30 min (Elliott et al., 2014), this means that whether ALF contributes to episodic memory deficits (or vice versa) in the PTSD literature has not been directly tested. Thus, it is plausible that deficits in these processes or others (Brown et al., 2018; Zlomuzica et al., 2018) may indeed contribute to PTSD symptomology alongside maladaptive forgetting processes. Another possibility is that some of the mechanisms which we propose may underly ALF symptoms, may also contribute to general memory impairments in PTSD. For example, as discussed earlier in this review, synaptic downscaling which occurs during sleep may contribute to both consolidation and forgetting processes (Berry et al., 2024; Ryan and Frankland, 2022). Given that sleep disruptions are a common clinical indication in PTSD, it could be that these aberrant mechanistic pathways during disrupted sleep influence more than just forgetting processes, contributing to ALF or other PTSD symptomology. Indeed, it has been suggested that sleep may contribute to impaired episodic memory in PTSD (Petzold and Bunzeck, 2022). 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 such 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. In healthy individuals, there is an abundance of research into active forgetting mechanisms that have implicated dorsolateral prefrontal cortical (DLPFC) regions in inhibitory control processes (Anderson and 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 and Hanslmayr, 2014; Anderson and 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 post-mortem 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 and Vanneste, 2025; O'Leary et al., 2023; Ryan and 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 authors comment that 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 review)(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 review, 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 (MRS) 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 are involved in the pathogenesis of autism spectrum disorder (Gzielo and 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 and 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 highly superior autobiographical memory (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 and 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 review, 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.

Nevertheless, a recent study reported equivalent forgetting rates on a directed forgetting task between individuals with HSAM and controls (Santangelo et al., 2025). In this study, although there were no differences in forgetting rates between the groups, those with HSAM exhibited increased neural activity during learning as well as during active forgetting. The authors conclude how superior memory in these individuals may stem from heightened stimuli processing, with those with HSAM subsequently requiring more neural resources to support active forgetting processes (Santangelo et al., 2025). This is an intriguing study that may suggest that hypoactive forgetting is not in fact a core driver of memory persistence in cases of HSAM. However, this is the first study of its kind in individuals with HSAM, and it only consisted of 12 individuals with HSAM (compared to 21 controls). Thus, future research in this area would be of critical interest to either validate or challenge the results of that study and the proposition put forth in this present perspective.

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 cross-talk 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.

5. Conclusion

Accelerated long-term forgetting (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 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, we 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, traumatic brain injury, and 22q11.2 deletion syndrome.

By reframing ALF as potentially resulting from hyperactive forgetting—rather than purely impaired consolidation—this review introduces a 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 highly superior autobiographical memory 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.

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