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Pathological forgetting from a predictive processing perspective

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ABSTRACT

Recent research suggests that natural forgetting is beneficial, allowing the brain to prioritize relevant information and disregard the irrelevant, thus aiding decision-making and mental health. Conversely, pathological conditions may arise from disruptions in these memory control processes. Without adequate memory control capacities, individuals can suffer from conditions like PTSD or addiction (where unwanted or addiction-related memories persist) on one end of the scale, to conditions such as dementia, Parkinson's disease or traumatic brain injury, which are characterised by heightened rates of forgetting on the other side. This review will explore the concept of predictive processing as a potential mechanism underlying pathological forgetting. It will summarise the neurobiological basis of predictive processing and how it influences what we remember or forget. As evident in the emerging literature, this has distinct implications for understanding pathological forgetting in psychological disorders. Finally, this review will highlight therapeutic interventions that have recently targeted predictive processes and consequently improved symptoms related to forgetting, suggesting translational applications for treatment approaches in these conditions.

1. Introduction

To *remember* something is the ability to retain information over time. The opposite to that, *forgetting*, refers to the temporary or permanent loss of, or inability to access, previously stored information. Forgetting can stem from natural causes, for example from not paying enough attention at the time of encoding; through interference; through emotional arousal at the time of consolidation; from decay of the memory trace (or engram); or by intentional suppression to the point that the memory can only be retrieved with great difficulty (Anderson and Green, 2001; Craik et al., 1996; Ebbinghaus, 2013; McIntyre et al., 2012; Robertson, 2012). However, as we age, not only do we fear our memory capacities deteriorating but so too are we concerned with forgetting information at an accelerated rate (as in the case of Alzheimer's disease). With increasing rates of dementia globally (WHO, 2023), these concerns of pathological forgetting are especially prevalent for individuals today. However, we often don't consider how on the other side of the scale, an ability to forget unwanted information can prove equally as detrimental (as in the case of Post Traumatic Stress Disorder (PTSD)). When considering pathological conditions such as PTSD, it becomes apparent that forgetting can serve an adaptive function.

Indeed, in the last decade, there has been increasing evidence in the literature that natural forgetting is a functional, adaptive process (Guskjolen and Cembrowski, 2023; O'Leary et al., 2023; Ryan and Frankland, 2022). At the cellular level, memories are stored across and between connections of cell ensembles (often referred to as engrams) (O'Leary et al., 2023; Ortega-de San Luis and Ryan, 2022). It has been proposed how memory processes such as storing, retrieving or even forgetting information, may exist along a "continuum of engram accessibility"(Autore et al., 2023; Josselyn and Tonegawa, 2020; O'Leary et al., 2023). In other words, forgetting can be viewed as an active form of *unlearning*, which is facilitated or hindered depending on engram activation. Put differently, our ability to remember *or* forget information can be viewed as active processes requiring appropriate activation of a memory trace (i.e. engrams).

Under this viewpoint, forgetting enables the brain to retain what is relevant and disregard irrelevant information. This not only facilitates decision-making day-to-day, but also supports mental health by enabling the forgetting of undesirable or unpleasant memories (Guskjolen and Cembrowski, 2023). Consequently, rather than *forgetting*

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being a pure passive consequence of a *lack of remembering*, an alternative hypothesis to consider is that *forgetting* or *remembering* both rest on one's memory control capacities, with both serving adaptive purposes. In other words, adequately functioning memory control capacities enable us to forget the irrelevant details in our day-to-day lives such as the faces of people who walk by us on the street, or the feeling of putting our socks and shoes on this morning, while retaining the information that's more important, like the name of our colleagues at work or the route for our daily commute. In line with this, pathological conditions that are characterized by *accelerated forgetting* or an *inability to forget* may also develop from aberrations in these memory control processes. Following this logic, what might be the mechanism underlying these forms of forgetting? Recent parallel rodent and human evidence are merging on the proposition that these memory control capacities, might rest on predictive processes.

As such, the aim with this review is to demonstrate how different conditions of pathological forgetting might each rest on aberrant predictive processes, and how leveraging neurophysiological markers of predictive processing has potential clinical utility in conditions characterized by pathological forgetting. To do so, this review will briefly discuss the predictive processing perspective, and how it offers an intuitive explanation for why some memories are forgotten or retained. In particular, by reviewing its neurobiological basis in the brain and giving specific attention to neurophysiological markers of predictive processes, this review then aims to outline recent research investigating predictive processing deviations in cases of pathological forgetting using examples of specific psychological disorders. Leveraging this information, it becomes apparent that viewing pathological forgetting from this viewpoint has translational applicability for potential therapeutic approaches. Thus, this paper will present recent preliminary evidence of therapeutic interventions that can target predictive processes with the potential of ameliorating forgetting symptomology in cases of pathological forgetting. Finally, it will conclude by offering high and medium priority areas for future research to focus on, as well as highlighting outstanding areas that warrant further investigation with respect to potential therapeutic applications.

2. Predictive processing

The terms 'predictive coding' and 'predictive processing' are often used interchangeably, and yet at times to describe different concepts (Sprevak and Smith, 2023). However, in line with prior work, we acknowledge predictive processing as a broad umbrella term that stems from earlier, more narrow, predictive coding accounts (Clark, 2013; Kube et al., 2020). According to predictive coding theory, the brain is a 'prediction machine' (Clark, 2013). It is constantly trying to make sense of the world around us, by generating hypotheses that are continuously updated and refined using a weighted combination of actual sensory input (both interceptive and exteroceptive); the brain's predictions about what it expects to encounter; and the difference between the two (Clark, 2013; Kube et al., 2020). In other words, our brain forms a prediction about the likelihood of a future event happening, based on past experiences, which is then compared to incoming sensory information.

The mismatch between these predictions (also called beliefs or expectations) and the actual sensory information is termed the prediction error. This mismatch can be positive or negative, depending on whether the bottom-up sensory input is more or less than predicted (Keller and Mrsic-Flogel, 2018). The more confident the model is about the sensory information or prediction, the more *precision* in that input the model is said to have. As such, the confidence (i.e. precision) given to the sensory information or predictions, subsequently determines the precision of the prediction error. Under normal conditions, prediction errors that are sufficiently large are used as a feedback mechanism that update the brain's predictions (Clark, 2013; Kube et al., 2020). From an evolutionary standpoint, these processes serve functional, adaptive purposes. With predictions about our environment or future being based on our memories, the brain needs mechanisms to flexibly update its model for the future. It needs to be able to extract the most timely or relevant information from our environments or prior experiences, to guide our behaviour in the future. Thus, accurate predictions (built by combining memories with incoming environmental information) are essential for any decision-making organism, including humans (Kraemer and Golding, 1997; Richards and Frankland, 2017; Ryan and Frankland, 2022).

Stemming from early predictive coding theories, later broader predictive processing accounts such as active inference began to theorise how these predictive processes influence not just perception, but also action (Friston, 2010; Friston et al., 2016; Kube et al., 2020). According to active inference, sensory information is viewed through the lens of prior predictions and their a-priori probability (Barron et al., 2020). In this view, predictions of high precision can in fact bias the predictive coding system such that the model is updated based on the priors rather than the prediction error (Kube et al., 2020). Moreover, this approach argues that the brain also seeks to gather evidence that supports prior predictions (Friston, 2010; Friston et al., 2016; Kube et al., 2020). To do so, one means through which an individual is argued to minimize a prediction error is through acting on their environment in a manner that results in "their priors becoming reality" (Berg et al., 2022).

Adding to this, the brain is always trying to make its model more efficient, typically by refining its predictions to minimise its prediction errors (i.e. a smaller mismatch between prediction and outcome suggests greater model accuracy (Kube et al., 2020)). Thus, building on predictive coding, and relating to the Bayesian brain hypothesis, active inference (a predictive processing approach) argues that both perceptual and decision-making processes function to "reduce uncertainty by minimizing prediction errors" (Berg et al., 2022). As such, it is important at this point to clarify that when we employ the term *predictive processing* herein, we are referring to a model that understands both cognition and action to be prediction error driven.

One factor becomes prominent when considering this view of the brain's perceptual and decision-making processes: that our memories are inextricably linked with predictions. Essentially, our brain relies in part on our memory for what has happened in the past, to form appropriate predictions about what might happen in the future. As such, the predictive processing system can be biased to be updated by hyper-precise (i.e. weighted memory-informed) predictions rather than the prediction error (the mismatch between the prediction and actual outcome). Notably, the brain's hippocampus has been acknowledged for its role in both memories and predictions, which is unsurprising with memories being recognised as a substrate of predictions (Barron et al., 2020). Not only this, but emerging evidence is suggesting how our memory control capacities (our ability to remember or forget information) can also be understood from a predictive processing perspective.

2.1. Predictive processing perspective: why memories are forgotten or retained

In recent years, there is an amalgamation of research that is highlighting how memory control capacities in both natural and pathological forgetting are driven by predictive processing mechanisms. For example, in a recent rodent study demonstrating that natural forgetting is a form of adaptive engram plasticity, the authors notably highlight how this forgetting plasticity operates as a function of an error-driven learning model, where prediction errors determine whether an engram is strengthened or weakened (O'Leary et al., 2023). Put differently, in this rodent study, the signal from prediction errors determined whether a memory was forgotten or retained. Likewise in humans, when investigating whether a fear memory was retained or forgotten, another study innovatively demonstrated how reconsolidation requires the occurrence of a prediction error (Sevenster et al., 2013). For more details on the role of prediction errors in reconsolidation, the reader is directed to a review by (Exton-McGuinness et al., 2015). However, these studies provide

novel evidence in both rodents and humans that, whether we remember or forget information relies on prediction error signals. As such, a logical question subsequently arises as to whether impairments in predictive processes underlie symptoms of pathological forgetting.

If this were the case, then pathological forgetting may vary as a function of predictive processes, with impaired predictive processing associated with memory-related symptoms ranging from an inability to forget information on one end of the scale, to heightened cases of forgetting, on the other (see Fig. 1 for a graphical representation of this proposed model of pathological forgetting). Following this logic, in individuals with disorders such as post-traumatic stress disorder, addiction, traumatic brain injury, Alzheimer's disease, dementia, or Parkinson's disease (that can be characterized by varying degrees of forgetting), one would expect to see aberrations in neurophysiological or molecular markers of predictive processing. Before elaborating on potential neurophysiological markers of predictive processing it is relevant to discuss the neurobiological basis of the predictive processing system within the brain.

2.2. *Predictive processing: its neurobiological basis within the brain and its neurophysiological markers*

In terms of neuronal systems, the predictive coding system has been proposed to operate at the level of cerebral hierarchies (Bastos et al., 2012; Kube et al., 2020). Accordingly, top-down predictions descend from higher cortical levels, to meet ascending sensory input at lower levels of the cortical hierarchy (i.e. at superficial pyramidal neurons) whereby these are weighted and compared to produce a prediction error (at deep pyramidal neurons) (Sedley et al., 2016). This prediction error then ascends up the hierarchy to inform the prior prediction, each of which are precision-weighted (Kube et al., 2020). A recent memory-related predictive coding account summarises evidence suggesting that the hippocampus serves not only as an index of neocortical memories, but also operates at the highest level of this cortical hierarchy (Barron et al., 2020).

Relevantly, both memory and forgetting processes, and aspects of these predictive processes, are modulated by synaptic plasticity mechanisms, with neurotransmitters and NMDA receptors implicated in particular. For example reducing noradrenaline levels was shown to result in greater precision of prior beliefs under times of uncertainty, stemming from reduced learning rates (i.e. slower updating of beliefs in response to new information) (Lawson et al., 2021). Conversely, acetylcholine has been linked with sensory precision (Hodson et al., 2024; Sedley et al., 2016). In particular, acetylcholine was shown to upregulate bottom-up signals by boosting sensory precision of predictable stimuli (Moran et al., 2013). Dopamine is also associated with learning, and positive and negative prediction errors (O'Leary et al., 2023; Ryan and Frankland, 2022; Yasoda-Mohan and Vanneste, 2024), and NMDA receptors with precision control (Barron et al., 2020). However, it is unlikely that these neurotransmitters and others operate in isolation. For example, dopamine has been argued to regulate both memory and forgetting, however its modulation by glutamate, GABA, acetylcholine or serotonin has likewise been discussed (Castillo Díaz et al., 2021). Moreover, as outlined in a recent review by Hodson and colleagues (Hodson et al., 2024), there is often a dynamic interplay between neuromodulators, with their cortical projections differentially impacting precision-weighted prediction errors in distinct brain regions, and at different levels of the hierarchy.

Furthermore, specific electrophysiological response potentials (ERPs) have been linked with these synaptic mechanisms as well as with predictive processes. ERPs provide a relatively low-cost, non-invasive means of measuring brain activity in relation to cognition and behaviour. Importantly, the mismatch negativity (MMN) ERP and P300 (including the P3a and P3b) ERP are both increasingly being acknowledged as potential markers of predictive coding processes (Karanasiou et al., 2010; Lao-Rodríguez et al., 2023; Ruzzoli et al., 2016; Yasoda-Mohan and Vanneste, 2024).

The MMN ERP signal (a fronto-central ERP response occurring 100–200ms post-stimulus) has been distinguished from being a purely attentional response in both human and rodent studies (Auksztulewicz and Friston, 2015; Lao-Rodríguez et al., 2023). The MMN reflects the mismatch between expectations and outcome, and can be elicited in experiments via the presentation of a novel stimulus that deviates from expectations that are set through presentation of a frequent standard stimulus (Näätänen, 1995). This deviation could be with respect to stimulus features, or through its omission. In line with this, it has been suggested that reduced MMN amplitude reflects deficient prediction errors and increased amplitude indicates hypersensitive stimulus

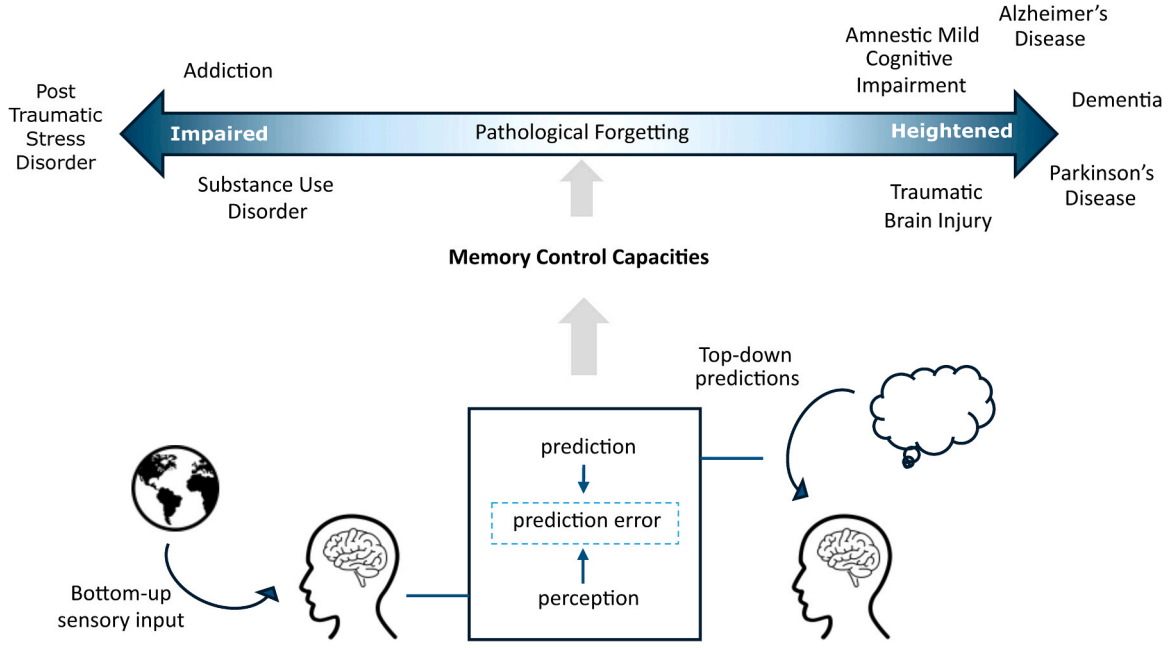

Fig. 1. Proposed View of Pathological Forgetting. Examplar representation of how predictive coding processes are proposed to influence conditions of pathological forgetting, where symptoms can range from heightened forgetting on one end of the scale, to impaired forgetting on the other.

discrimination abilities (i.e. hyper-precise sensory predictions) (Bangel et al., 2017). In other words, MMN amplitude is proposed to index the precision-weighted prediction error that is generated when there is a mismatch between top-down predictions, and bottom-up information (Harms et al., 2021; Hodson et al., 2024; Schmidt et al., 2013).

In fact, the MMN as a marker for prediction error is supported by findings which demonstrate that the MMN response reduces with learning, reflecting the updating of the prediction error (Yasoda-Mohan and Vanneste, 2024). In adults, the P300 ERP (consisting of a P3a and P3b component depending on the task) is likewise increasingly being acknowledged as a marker of prediction errors (Nieuwenhuis et al., 2005; Yasoda-Mohan and Vanneste, 2024). The P300 ERP response is expressed as a positive deflection in amplitude over centro-parietal brain regions, with its peak typically occurring around 300 ms post-stimulus (Kenemans and Kähkönen, 2011). See Fig. 2 for a schematic drawing of the MMN and P300 ERPs illustrating alterations in

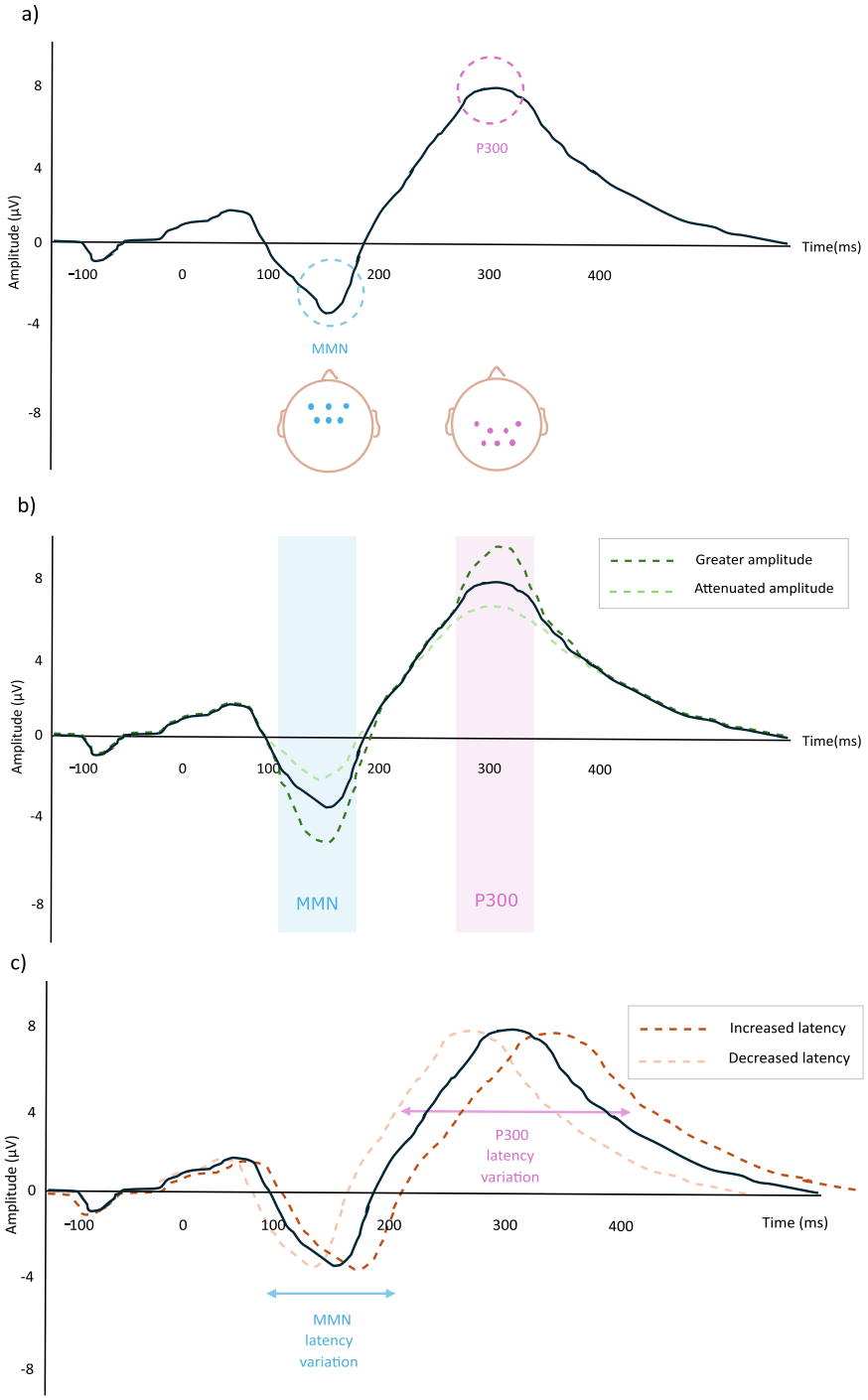

Fig. 2. Schematic drawings of the mismatch negativity (MMN) and P300 event-related potentials (ERPs). a) Schematic drawing of the MMN ERP and P300 ERP responses. The MMN ERP response is a negative deflection in amplitude that is observed in fronto-central brain regions. The peak of the MMN ERP response typically occurs around 100–250 ms after the deviant stimulus is presented. The P300 ERP response is expressed as a positive deflection in amplitude over centro-parietal brain regions, with its peak typically occurring around 300 ms post-stimulus. b) Schematic drawing of the MMN and P300 responses based on varying amplitude. The dark green dashed line illustrates greater amplitude for these ERPs. The light green dashed line reflects attenuated amplitude. c) Schematic drawing of the MMN and P300 responses based on varying latency. The dark red dashed line illustrates increased latency for these ERPs. The light red dashed line reflects decreased latency.

amplitude or latency. The P300, like the MMN response, can be elicited when expectations don't match outcomes (i.e. when novel or omitted stimuli occur throughout a sequence of expected standard stimuli) (Nieuwenhuis et al., 2005). Interestingly, it has been discussed how P300 amplitude can also be impacted by factors such as the subjective probability and motivational significance of the eliciting cues (Nieuwenhuis et al., 2005).

In terms of the associations between these ERPs and synaptic plasticity mechanisms, several neurotransmitters have been implicated in the MMN and P300 ERPs. Importantly, as outlined earlier, these neurotransmitters have also been argued to play roles in predictive processes. Specifically, the role of glutamate transmission (with respect to NMDA receptors in particular) has widely been acknowledged for its role in the generation of the MMN (Garrido et al., 2009; Harms et al., 2021; Kenemans and Kähkönen, 2011). Likewise, there is some support for GABA's role in the MMN response (Garrido et al., 2009; Kenemans and Kähkönen, 2011). However, it has been suggested that the effect of other neurotransmitters (such as serotonin and acetylcholine) on the MMN are more likely to stem from indirect modulation (Harms et al., 2021; Kenemans and Kähkönen, 2011). Thus both the MMN and predictive processes each rest on "NMDA-dependent synaptic plasticity and [their] regulation by neuromodulatory transmitters" (Garrido et al., 2009).

In terms of the neurotransmitters that are associated with the P300, there is strong evidence from both animal and human studies highlighting the role of the locus coeruleus-noradrenaline pathway (Murphy et al., 2011; Nieuwenhuis et al., 2005). Additionally, the P3a and P3b components of the P300 have been associated with dopaminergic and noradrenergic activity respectively (Yasoda-Mohan and Vanneste, 2024). However, as is often the case, other neurotransmitters have also been implicated in the generation of the P300. For example, as discussed by Nieuwenhuis and colleagues (Nieuwenhuis et al., 2005), pharmacologic and lesion studies demonstrate how glutamatergic, GABA-ergic and cholinergic activity each impact P300 generation. This is likely due to their overlapping projections, however noradrenaline can also enhance the effects of glutamatergic and GABA-ergic transmission on cortical neurons and neurons in other brain regions (Nieuwenhuis et al., 2005). Thus, the locus coeruleus-p300 hypothesis proposes that the P300 is "an electrophysiological correlate of the LC phasic response" (Nieuwenhuis et al., 2005). Under this viewpoint, the P300 and LC phasic activity concomitantly increase in response to prediction errors that are generated due to mismatches between top-down predictions and bottom-up sensory information with regards to the subjective probability and motivational significance of eliciting stimuli (Nieuwenhuis et al., 2005). As such, these ERPs have been proposed as potential markers for predictive processes.

Moreover, there is initial evidence of deviations in predictive processes (as measured via changes in P300 or MMN amplitude or latency) across several psychological disorders, where *forgetting* factors into their symptomology. Notably, abnormal forgetting in these psychological disorders can range from heightened forgetting on one end of the scale, to impaired forgetting abilities on the other. Despite this, no paper to date has discussed these together in a unified review. Thus, pathological forgetting from a predictive processing perspective will subsequently be reviewed here. Firstly, this review will explore MMN responses at these two ends of the forgetting spectrum using studies of specific psychological disorders, and secondly it will similarly do the same for P300 responses in psychological disorders at these two ends of the forgetting spectrum.

3. Aberrant predictive processes in pathological forgetting

3.1. MMN response in cases of heightened forgetting

3.1.1. Alzheimer's disease, Parkinson's disease and dementia

In studies of those with various stages of Alzheimer's disease (AD), at longer interstimulus intervals, reduced MMN amplitude or no MMN responses at all were found (Laptinskaya et al., 2018; Pekkonen, 2000; Ruzzoli et al., 2016). Adding to this, additional studies reported reduced amplitude and longer latencies as cognitive impairment progressed from prodromal stages such as subjective cognitive decline, to mild cognitive impairment (MCI) and AD (Cheng et al., 2021; Jiang et al., 2017; Papadaniil et al., 2016; Tsolaki et al., 2017). One exception to this was one study which specifically included vascular dementia, and found shorter latency for vascular dementia patients compared to healthy controls (Jiang et al., 2017). However, different pathophysiological mechanisms underlying vascular dementia could contribute to this result (O'Brien et al., 2003). Although there are only a few studies looking at the MMN response in those with AD, they largely report similar findings, and importantly several studies link these MMN responses in AD patients with memory and forgetting outcomes. Specifically, either reduced MMN amplitude or increased MMN latency was found to be associated with greater rates of forgetting (Cheng et al., 2021; Gao et al., 2018; Laptinskaya et al., 2018; Tsolaki et al., 2017). In line with this, it has been suggested that this mismatch negativity could be used as an "index of cognitive decline for the early detection of Alzheimer's disease" (Ruzzoli et al., 2016).

However, one aspect of this research that is less consistent is the exact location of these MMN responses. In one study, patients with prodromal AD exhibited reduced MMN amplitude at fronto-central sites compared to healthy controls (Jiang et al., 2017). Whereas in another study, the reduced MMN amplitude for subjective cognitive decline patients was observed at right inferior parietal lobule and right inferior frontal gyrus in comparison to healthy controls (Cheng et al., 2021). Conversely, in another study, at later stages of the condition, patients with AD were found to have reduced amplitude at parietal sites in comparison to healthy controls (Papadaniil et al., 2016). Whereas, in another study MMN locations depended on interstimulus interval lengths. In this study, at shorter interstimulus intervals, amnestic mild cognitive impairment (aMCI) patients had reduced MMN amplitude at temporal locations and AD patients at frontal locations (Ruzzoli et al., 2016), while healthy elderly participants had MMN responses at both locations. However, at longer interstimulus intervals, neither aMCI nor AD patients exhibited any MMN response at any location in comparison to healthy controls which presented an MMN response at the temporal location (Ruzzoli et al., 2016).

In auditory oddball paradigms, it has been suggested that the MMN response at short interstimulus intervals reflects the mismatch between expected and actual tone, while the MMN response at longer interstimulus intervals reflects the memory trace for the standard tone (Laptinskaya et al., 2018). Thus, the authors interpret their finding of no MMN response at longer interstimulus intervals in aMCI and AD patients compared to healthy controls, as evidence that their memory capacity is exceeded at this longer time frame (Ruzzoli et al., 2016).

With respect to the locations of the MMN response in that study, interestingly, a predictive coding perspective may also account for why these differ (Garrido et al., 2009). For example, the MMN response at frontal regions may reflect predictions from higher cortical areas that are compared against data from lower cortical areas (i.e. temporal regions) through backward connections (Garrido et al., 2009; Ruzzoli et al., 2016). At the same time, lower cortical structures (i.e. temporal regions) try to update the predictions by sending prediction error signals via forward connections (Garrido et al., 2009; Ruzzoli et al., 2016). This cycle continues until the outcome matches the predictions, and there is no prediction error. Consequently, Ruzzoli and colleagues (Ruzzoli et al., 2016) propose that the locations of the MMN response in their clinical groups reflect impairments in aspects of predictive processes. Where at a short interstimulus interval, the aMCI patients may rely more heavily on low level sensory processing (i.e. the temporal MMN) but not on higher level predictions (i.e. frontal MMN)(Ruzzoli et al., 2016). Conversely, as the disease progresses, the AD patients' frontal MMN response reflected reliance perhaps on predictions, rather than sensory

stimuli processing (which was reflected via the absence of an MMN response at temporal locations)(Ruzzoli et al., 2016). Notably there is also initial evidence linking altered prediction error processing and Alzheimer's disease pathology. In a study of dementia, aMCI and Alzheimer's patients, reduced MMN amplitude was found, with this reduction associated with increased Tau burden in patients – suggesting links between altered predictive processing and the pathological disease progression of dementia (Gjini et al., 2022).

Although the data of MMN responses in Parkinson's disease are more limited, there is initial evidence of reduced MMN amplitudes in Parkinson's disease patients. One early study reported reduced MMN amplitude in Parkinson's disease patients versus healthy controls (Pekkonen et al., 1995). Adding to this, a more recent study examined the MMN response in patients with different forms of Parkinson's disease or dementia. In that study, Parkinson's disease patients (with dementia) in comparison to those with dementia Lewy body; Parkinson's disease patients with no dementia; patients with AD; or with healthy controls; were found to have reduced MMN amplitude which correlated with task performance (Brønnick et al., 2010).

3.1.2. Traumatic brain injury

Heightened forgetting in cases of traumatic brain injury has been shown to relate to hippocampal atrophy (Bigler et al., 1996). Given the hippocampus' role in predictions, one might expect impairments in these predictive processes, measured via an altered MMN response. However, one study assessed the predictive processes of traumatic brain injury patients compared to those with schizophrenia and healthy controls (Wynn and Green, 2024). Interestingly, there were no differences between traumatic brain injury patients and healthy controls (Wynn and Green, 2024). Despite no altered sensory prediction errors in traumatic brain injury patients in this study, the authors speculate that predictive processes may deteriorate in more severe cases of traumatic brain injury (Wynn and Green, 2024). In line with this, traumatic brain injury and particularly, repeated traumatic brain injury, are risk-factors for later development of different types of dementia including AD (Graham and Sharp, 2019). Thus, potentially the predictive impairments only become apparent later in an individual's life, when they're exhibiting signs of prodromal mild cognitive impairment. Given only one study to date (to the best of our knowledge) has assessed traumatic brain injury and the MMN response, more research is needed in this area to clarify this.

While the above psychological disorders are characterised by heightened rates of forgetting, on the other end of the spectrum are conditions where an inability to forget information factors into their symptomology (for example in addiction, substance use disorder or post-traumatic stress disorder).

3.2. MMN response in cases of impaired forgetting

3.2.1. Addiction or substance use disorder

In addiction or substance use disorder, learning and memory processes are impacted. For those with substance use disorder, seeing a drug-related cue can trigger an intense memory, leading to drug-seeking behaviour and potential relapse. In other words, these individuals are plagued by an inability to forget these strong drug-associated memories. If pathological forgetting is a symptom of impaired predictive processes, one might also expect impaired MMN features in those with substance use disorder. Although only a few recent studies have investigated this in humans, reduced MMN amplitude has been observed in response to acute and chronic alcohol use (Ramlakhan et al., 2018), those with internet-addiction (He et al., 2018) and those addicted to heroin (Motlagh et al., 2018). Additionally, in the study with heroin dependents, increased MMN latency was also reported in comparison to healthy controls (Motlagh et al., 2018). In the above cases, reduced MMN amplitude may signal deficient prediction error signals, which impact an individual's ability to appropriately forget information by predictions being afforded greater precision/confidence. Under this interpretation, the individual's brain may struggle to update the model that the drug information fed from sensory pathways is no longer relevant, because the experience-dependent prior outweighs the precision of the prediction error.

3.2.2. Post-traumatic Stress Disorder (PTSD)

PTSD is a condition that can often first come to mind when we think of memories that an individual cannot forget. A recent perspective elegantly accounts for PTSD symptoms from the predictive processing perspective, suggesting that PTSD symptoms develop from an imbalance between priors and sensory input (Kube et al., 2020). The authors argue that in response to a life-threatening event, the brain's internal model gives high precision to a prediction (e.g. "this environment is unsafe") that will likely bias future decisions even if it doesn't match sensory input (Kube et al., 2020). In parallel, incoming sensory input is down-weighted, reducing its precision. Additionally, flashbacks are suggested to be triggered by interoceptive inference. For example, when experiencing an emotional reaction, the "brain infers (i.e. "reasons") that there must be a source of threat that explains the interoceptive state (i.e., "I'm scared, therefore there must be something threatening"), which is accepted as further model-supporting evidence (Kube et al., 2020). Very few studies have specifically tested predictive processing markers such as the MMN in PTSD individuals, however, the existing findings are conflicting. For example, in an early study, increased MMN amplitude in PTSD individuals was found in comparison to healthy controls, and MMN amplitude correlated with the severity of self-reported PTSD symptoms (Morgan and Grillon, 1999). In another study of 27 survivors of the Wenchuan earthquake, 13 of which had PTSD, enhanced MMN was also observed in the PTSD group (Ge et al., 2011). Similarly, in a controlled clinical trial, increased MMN amplitude in PTSD patients in comparison to trauma-exposed controls was also reported (Bangel et al., 2017).

Conversely, a separate study found that only the duration and location of the MMN response (and not the acoustic features) differed for PTSD patients in comparison to controls (Löw et al., 2019). In another study, the MMN amplitude was significantly reduced in PTSD patients in comparison to healthy controls, with the MMN response correlating with PTSD scores (Menning et al., 2008). While a reduced MMN amplitude can be interpreted as deficient prediction error capacities, increased MMN amplitude has been interpreted as hyper-precise sensory predictions (Bangel et al., 2017). Thus, perhaps the conflicting predictive processing findings in PTSD do indeed reflect an imbalance between priors and sensory information, where some individuals cannot forget traumatic memories due to hyper-precise predictions, and others because of deficient prediction error abilities.

Interestingly, in line with this, in a study examining memory suppression capacities (an intentional form of forgetting) in individuals with PTSD versus individuals without PTSD or trauma-exposed but resilient individuals; memory control processes were argued to be the result of an "imbalance between predictive and error-driven control" (Leone et al., 2022). Specifically, in cases of PTSD, both heightened emphasis of predictions or prior expectations and reduced salience given to prediction errors were found to contribute to memory control capacities, and these patients' ability to intentionally forget information (Leone et al., 2022). Another speculative hypothesis suggests these discrepancies in MMN responses in PTSD individuals may reflect the heterogeneity of the disorder, although this too remains to be confirmed (Bangel et al., 2017). Although these findings appear conflicting, the fact that significant differences in predictive processes have been found between those with PTSD versus controls, suggests impaired predictive processes that warrant further investigation.

3.3. P300 (P3a/ P3b) response in cases of heightened forgetting

3.3.1. Alzheimer's disease, Parkinson's disease and dementia

There is large support for longer P300 latencies as a distinguishing

predictive processing marker in those with various stages of Alzheimer's disease, as well as some evidence for those with dementia or Parkinson's disease. In fact, an earlier meta-analysis of studies from 1970 to 2013 examining P300 latencies in those with prodromal stages of Alzheimer's such as aMCI compared to later-stage AD or healthy controls importantly highlighted the clinical utility of the P300 latency as a preclinical diagnosis tool for these patient groups (Howe et al., 2014). Specifically, the meta-analysis reported that aMCI individuals had longer latencies than healthy controls, and AD had longer latencies than aMCI. Adding to this, the increased degradation of predictive processes as the disease progressed was underscored by the finding that strong effect sizes (.80) were found when comparing P300 latencies for AD to healthy controls, while only a low-to-moderate effect (.5) was observed for aMCI compared to healthy controls (Howe et al., 2014). Moreover, while a large effect was found between P300 latencies in those with AD and aMCI this effect was not statistically significant (Howe et al., 2014).

Subsequently, more recent studies have further validated these findings and likewise reported increased P300 latencies in aMCI and AD compared to healthy controls (Papadaniil et al., 2016; Tsolaki et al., 2017). In one of these studies, which compared individuals with aMCI or AD to healthy controls, alongside increased P300 latencies, reduced P300 amplitude was also observed in patients vs healthy controls, with these differences becoming more exaggerated as cognitive impairment advanced (Papadaniil et al., 2016). Moreover, the P300 response was located in the frontal lobe of healthy subjects but in AD it had shifted to the temporal lobe. Another study compared those with AD, Parkinson's Disease with Dementia or Vascular Dementia to healthy age- and sex-matched controls. The authors found longer P300 latency in those with AD or Parkinson's disease with Dementia than Vascular Dementia, and in comparison to healthy controls (Khedr et al., 2020). Also, while the P300 correlated with cognitive impairment, this effect was greatest for those with AD (Khedr et al., 2020). These findings suggest perhaps that pathological forgetting in vascular dementia may not stem from the same predictive processing impairments as in those with AD or Parkinson's disease.

Supporting these findings of altered P300 responses in Parkinson's disease patients, a recent meta-analysis examined P300 responses in Parkinson's patients with dementia, and those with no dementia or healthy controls. In this meta-analysis, increased P300 latency was found in the midline central region (i.e. Cz site) for Parkinson's patients with dementia compared to healthy controls (Xu et al., 2022). Conversely, increased P300 amplitude was reported at the frontal site (i.e. Fz electrode) for Parkinson's disease patients with no dementia compared to healthy controls. Given how P300 latency in particular was significantly longer in Parkinson's disease patients with dementia but not in those without dementia or healthy controls, the authors highlight how this increased P300 latency may indeed be an indicator of progressive memory impairments as one's Parkinson's disease develops (Xu et al., 2022). This was further supported by a more recent study which specifically looked at early-stage drug naïve Parkinson's disease patients compared to healthy controls (Zhang et al., 2022). In this study, these early-stage Parkinson's disease patients had lower memory performance, reduced P300 amplitude and increased P300 latency than healthy controls (Zhang et al., 2022).

3.3.2. Traumatic brain injury

Only one study (to the best of our knowledge) has examined the P300 response in traumatic brain injury patients. In this study, reduced parietal P300/p3b amplitude was observed in response to target detection in those with traumatic brain injury in comparison to controls (Gilmore et al., 2018).

Taken together, while one study demonstrates reduced P300 amplitude in the case of traumatic brain injury, in cases of heightened forgetting such as dementia from Alzheimer's disease or Parkinson's disease (but not vascular dementia), there is substantial evidence of increased P300 latency, and some initial evidence of reduced P300 amplitude. Additionally, these aberrant predictive processing markers were associated with disease progression, with the P300 differences becoming more exaggerated as cognitive impairment advanced.

3.4. P300 (P3a/ P3b) response in cases of impaired forgetting

3.4.1. Addiction or substance use disorder

It is known that P300 amplitude can be impacted by factors such as the subjective probability and motivational significance of the eliciting cues (Nieuwenhuis et al., 2005), With respect to P300 features in those with addiction or substance-use disorders, altered predictive processing in response to sensory stimuli has been reported, with differential patterns depending on if these stimuli were neutral or drug-related. Specifically, not only has altered P300 amplitude been observed in these individuals, but the amplitude has been found to correlate with or predict subsequent relapse risk or abstinence. For example, in one study, increased P300 amplitude in response to alcohol-related stimuli was observed in those who relapsed versus abstained, and their difference in P300 amplitude for alcohol or non-alcohol stimuli was the greatest predicter of relapse vulnerability (Petit et al., 2015). Similarly, in another study, reduced P300 amplitude in response to neutral stimuli was found in smokers and predicted relapse risk (Luijten et al., 2016).

The results of the addiction studies seem to suggest that in those with substance use disorder, increased P300 amplitude in response to addiction-related stimuli and reduced P300 amplitude in response to neutral stimuli are associated with addiction and may potentially confer relapse risk. This may suggest that addiction-related stimuli are afforded greater precision by the brain in those with substance use disorder, which is associated with increased P300 amplitude, whereas neutral stimuli are down-weighted, associated with decreased amplitude. Accordingly, approaches that rectify these imbalances and reduce P300 amplitude responses to addiction-related stimuli whilst increasing P300 responses to neutral stimuli may have potential therapeutic value by modulating the predictive processes in the brain and its impacts on forgetting capacities.

3.4.2. Post-traumatic Stress Disorder (PTSD)

Notably, of the studies that have looked at P300 amplitude in PTSD patients, the results are largely consistent thus far. In several studies, reduced P300 amplitude was found in PTSD patients compared to healthy controls (Araki et al., 2005; Bae et al., 2011; Charles et al., 2008; Felmingham et al., 2002; Galletly et al., 2001; Shim et al., 2019). However, the P300 latency findings were less consistent in studies of individuals with PTSD compared to healthy controls. For example, while some found prolonged P300 latency in PTSD individuals (Felmingham et al., 2002; Shim et al., 2019), others found no latency differences (Bae et al., 2011; Charles et al., 2008; Galletly et al., 2001). While it might appear that P300 latency might not be a robust indicator of predictive processing impairments, in fact, one study that used a machine learning algorithm could classify PTSD patients compared to healthy controls or those with major depressive disorder based on their P300 features (incl. amplitude and latency)(Shim et al., 2019). Another meta-analysis similarly confirmed that different P300 components (incl. P3a and P3b) each have value in accurately classifying patients with PTSD from control groups (Johnson et al., 2013). Specifically, the meta-analysis further notes how for those with PTSD, P3a amplitude was increased in response to trauma-related distractors and for trauma-related stimuli, while P3b amplitude was decreased in response to neutral stimuli. Similar to the studies of substance use disorder, this may suggest that trauma-related stimuli are afforded greater precision by the brain in those with PTSD, which is associated with increased P3a amplitude, whereas non-trauma related stimuli are down-weighted, associated with decreased P3b amplitude.

To summarise the findings on neurophysiological markers of predictive processes in pathological forgetting, heightened forgetting seems to be associated with reduced MMN amplitude and increased MMN

latency, whereas in cases of impaired forgetting the findings while significant, are more conflicting. In those with addiction or substance use disorder, reduced MMN amplitude was observed, and in those with PTSD either reduced or increased MMN amplitude was reported. It is interesting that while dementia (which is characterised by accelerated forgetting) might seem at the opposite end of the spectrum to conditions such as substance use disorder, patients with either condition tend to display reduced MMN amplitude, suggesting increased likelihood of a shared mechanism behind the two. As mentioned earlier, reduced MMN amplitude can be interpreted as deficient prediction error capacities (Bangel et al., 2017). Thus, from these studies, deficient prediction error abilities can be seen to manifest as either greater or diminished rates of forgetting. Adding to this, with increased MMN amplitude interpreted as hyper-precise sensory predictions (Bangel et al., 2017), given both the increased and reduced MMN amplitude in those with PTSD, this may suggest an imbalance between priors and sensory information, where some individuals cannot forget traumatic memories due to hyper-precise predictions, and others because of deficient prediction error abilities.

In terms of the P300 response, for cases of accelerated forgetting, increased P300 latency, and some initial evidence of reduced P300 amplitude was reported in those with various stages of Alzheimer's disease and Parkinson's Disease. Additionally, these aberrant predictive processing markers were associated with disease progression, with the P300 differences becoming more exaggerated as cognitive impairment advanced. On the other hand, in cases of diminished forgetting, differential P300, P3a or P3b amplitude responses were found depending on stimuli characteristics. Specifically, in those with substance use disorder or PTSD, increased P300 or P3a amplitude was observed in response to trauma- or drug-related stimuli respectively, whereas decreased P300 or P3b amplitude was reported in response to non-drug or -trauma stimuli respectively. Given the association between P300 amplitude and precision, this may suggest that addiction- or trauma-related stimuli are afforded greater precision by the brain in those with PTSD, which is associated with increased amplitude, whereas non-trauma related stimuli are down-weighted, associated with decreased amplitude.

4. Applications

It is one thing to review cases of pathological forgetting from a predictive processing viewpoint, however, an important consideration is whether this approach has translational applicability. This is especially relevant with regards to potential therapeutic avenues for those suffering with psychological disorders where pathological forgetting is a symptom. Notably, there are several studies examining the effectiveness of different promising techniques at modulating predictive processing outcomes in those with forgetting-related disorders. These include using approaches such as Eye Movement Desensitization and Reprocessing Therapy (EMDR), neurostimulation approaches or neurofeedback, either as stand-alone techniques or in conjunction with other therapeutic approaches.

4.1. Eye Movement Desensitization and Reprocessing Therapy (EMDR)

Based on the viewpoint that PTSD develops from dysfunctionally stored memories, EMDR was developed as a potential therapeutic approach with the intention of targeting information processing of these maladaptively stored memories (Chamberlin, 2019). EMDR is often an effective first-line treatment for PTSD (Lewis et al., 2020). Despite its clinical success (Bisson et al., 2013), there remains debate as to the exact mechanism(s) underlying its therapeutic effects (Landin-Romero et al., 2018). However, it has recently been proposed that predictive processes underlie EMDR effects on PTSD (Chamberlin, 2019). This is based on the view that persistent memories in PTSD may stem from aberrant predictive processes, whereby the brain's internal model is updated largely by predictions. Under this view, low precision is afforded to sensory stimuli as the brain deems its predictions as more relevant for survival. Because of this low sensory precision, no prediction error is generated, and the model receives no new input to challenge its predictions. Thus, the model cannot be updated. This cycle continues to perpetuate, resulting in persistent traumatic memories.

The exception to this, as seen in the P300 literature, is that in PTSD patients, trauma-relevant stimuli are afforded greater precision compared to neutral stimuli (Johnson et al., 2013). This further underscores how persistent memories can continue to be strengthened selectively by trauma-relevant stimuli whilst neutral stimuli that may challenge its predictions are down-weighted by the brain. Considering EMDR from the predictive processing perspective however, outlines how it may enable the individual to break this cycle. Under the EMDR protocol, the individual brings the traumatic memory to mind, to actively re-experience it while the therapist produces sets of guided eye movements (Chamberlin, 2019). These eye movements are argued to enable the individual to challenge the bias against down-weighting of sensory precision, by enabling sensory experiencing of the 'safe' present (Chamberlin, 2019). In doing so, a prediction error is generated, as the experiencing of the traumatic memory in a safe context differs to the brain's prediction. Over sessions and time, more 'evidence' accumulates that challenges the brain's prediction, and the model can be updated appropriately – resulting in the updating of the traumatic memory, making it less persistent.

Indeed in tinnitus, a sensory perceptual disorder that is suggested to stem from aberrant predictive processes (Hullfish et al., 2019; Sedley et al., 2016), bimodal EMDR and tinnitus retraining therapy was found to be as effective as Cognitive Behavioural therapy (CBT) and tinnitus retraining therapy (Luyten et al., 2020). As such, EMDR might be a potential therapeutic avenue for those with pathological forgetting that likewise rests on predictive processing abnormalities. As mentioned above, while EMDR is known to be an effective treatment for PTSD, very few studies are specifically examining if its therapeutic effects are associated with positive changes in predictive processes. However early evidence supporting this can be seen in one study where 10 PTSD patients underwent EMDR, whilst another 10 received a sham technique (Lamprecht et al., 2004). In the group that received EMDR, P3a amplitude was modulated in response to novel stimuli, and marked symptom improvement was observed in comparison to the sham group. Given that increased P3a amplitude to trauma-stimuli (conferring hyper-precision) is typically observed in those with PTSD and is associated with symptomology, these findings are promising, however this is the only study to date have focused on predictive processing markers when examining the effects of EMDR on PTSD symptoms. Thus, more research is needed in this area to further test the predictive processing account of EMDR's effects.

4.2. Neurostimulation approaches

4.2.1. Transcranial Magnetic Stimulation (TMS)

Repetitive TMS (rTMS) is a non-invasive neurostimulation approach that is approved by the FDA in the treatment of treatment-resistant depression and Obsessive Compulsive Disorder (NIH, 2023). However, it has not yet received approval for the treatment of PTSD despite the accumulating evidence in favour of its effects on PTSD symptomology (Harris and Reece, 2021; Kan et al., 2020; NIH, 2023). Importantly however, as well as showing the potential therapeutic effects of rTMS, recent research is demonstrating a predictive processing mechanism behind these results. Specifically, in those with PTSD, rTMS has been shown to have therapeutic value by modulating P3a amplitude and latency. In an early case study, rTMS was shown to reduce the P3a response to trauma stimuli (Tillman et al., 2011). These findings were further validated in a more recent randomized controlled trial . In that randomized controlled trial, rTMS was administered in conjunction with cognitive processing therapy (Tillman et al., 2023). Critically the results highlighted how this approach reduced P3a amplitude and latency in response to trauma stimuli, and that this was associated with decreased

PTSD symptoms (Tillman et al., 2023). To the best of our knowledge, no other studies have examined these predictive processing impacts of therapeutic rTMS for PTSD patients. Thus, this is a relatively nascent research area that is promising and warrants future research to further validate these findings.

4.2.2. Transcranial Direct Current Stimulation (tDCS)

tDCS has been applied with the intention of modulating memory and cognitive functions across various psychological disorders (Begemann et al., 2020; Hyde et al., 2022; Majdi et al., 2022; Sabé et al., 2024). Again however, there is a paucity of research investigating the mechanisms of these from a predictive processing viewpoint. However, several studies over the last few years are showing promising results. For example, one recent meta-analysis reported that anodal tDCS to the left dorsolateral prefrontal cortex and right inferior frontal gyrus can significantly increase parietal P300 amplitude (Mendes et al., 2022). However, the authors caution that a limitation to their findings is the low number of studies that are investigating this topic.

In terms of applying tDCS to modulate predictive processes in psychological conditions where pathological forgetting is a symptom, a recent study investigated the effects of tDCS on substance use disorder. There were 3 groups in the study: abstinent drug users were divided into two groups (that received either active or sham tDCS over the dorsolateral prefrontal cortex for 5 consecutive days), and there was a control group that received no stimulation (Chen et al., 2023). Notably the study demonstrated that tDCS successfully modulated P300 amplitude for abstinent drug users (Chen et al., 2023). Specifically increased amplitude in response to neutral stimuli was observed in the abstinent drug user group that received active stimulation (Chen et al., 2023). Moreover, the authors note that post-stimulation, the P300 amplitude represented more similarities to the responses of the control non-drug user group (Chen et al., 2023).

These findings offer tentative evidence that tDCS can rectify predictive processing imbalances by increasing P300 responses to neutral stimuli, which may have potential therapeutic value by modulating the predictive processes in the brain and its impacts on forgetting capacities. However, neither this study nor the meta-analysis mentioned before examined whether tDCS-induced changes in these P300 responses are specifically associated with forgetting outcomes or clinical improvement. That being said, studies of individuals with other psychological disorders are demonstrating not only tDCS' ability to modulate P300 responses, but the associated changes in memory performance or clinical outcomes that result from this.

In the case of traumatic brain injury, one pilot study examined the effects of tDCS on memory and electrophysiological measures including the P300 response for traumatic brain injury patients compared to control subjects (O'Neil-Pirozzi et al., 2017). Participants received either active tDCS (to the left or right dorsolateral prefrontal cortex) or sham tDCS. In this study, after 20 minutes of active tDCS to the left dorsolateral prefrontal cortex, both the traumatic brain injury and control group demonstrated enhanced auditory memory performance, while only the traumatic brain injury group had increased P300 amplitude compared to the sham group (O'Neil-Pirozzi et al., 2017).

In the case of Alzheimer's disease, one recent study of individuals with MCI aimed to investigate not only the efficacy of tDCS on episodic memory, but also its neural mechanism (Gu et al., 2022). In this study, 20 patients received active tDCS and 20 received sham tDCS for 20 minutes on 5 consecutive days (Gu et al., 2022). Post-stimulation and 4 weeks later, episodic memory was tested and P300 responses recorded. Notably, at both of these time points, several measures of episodic memory performance were greater for the active group compared to the sham group (Gu et al., 2022). In addition, P300 amplitude increased and P300 latency decreased for the active group compared to the sham group, with these neurophysiological changes correlating with memory scores (Gu et al., 2022). Thus, not only was tDCS a viable approach for modulating long-term memory outcomes, but this was directly related to changes in predictive processes.

In contrast to the above findings, one pilot study investigated the effects of tDCS on working memory and P300 responses in healthy elderly and Alzheimer's disease patients (Cespón et al., 2019). Interestingly, while tDCS applied once to the left dorsolateral prefrontal cortex increased P300 amplitude in the healthy elderly group, and this correlated with enhanced working memory, there were no changes to the P300 response in the AD patients (Cespón et al., 2019). There could be several potential explanations for these results. One reason is that perhaps one session of tDCS was not sufficient to exert an effect on those with AD. Another reason could be that the disease pathology was too progressed in the AD group, meaning perhaps they had passed an optimal window of opportunity where tDCS' beneficial effects on predictive processes and memory outcomes could be leveraged.

4.3. Neurofeedback

Neurofeedback most often utilises electroencephalography (EEG) biofeedback to help an individual self-regulate their own brain activity, and modulate neural mechanisms of cognition and behaviour (Enriquez-Geppert et al., 2017). Using operant conditioning, the individual is typically given real-time feedback about brain activity patterns in an oscillatory frequency range of interest that are linked with a target behaviour (Jackson et al., 2023). In the memory domain, a recent systematic review and meta-analysis reported that neurofeedback had a significant positive effect on episodic memory performance in both healthy and clinical participants (Jackson et al., 2023). Likewise another recent review in those with Alzheimer's disease or early-stage mild cognitive impairment, found that neurofeedback had positive impacts on memory and other cognitive domains no matter which training protocol or electrode placement were used, or frequency bands were targeted (Tazaki, 2024).

As mentioned above, EEG neurofeedback is typically implemented by guiding individuals to modulate a target oscillatory frequency activity. However, can EEG neurofeedback target MMN or P300 responses with the intention of regulating forgetting symptoms by targeting these predictive processing markers in those with relevant psychological disorders? To date, although few studies have looked at this specifically, there are promising initial findings. In one study of individuals with subjective memory decline, MMN neurofeedback training (which involved five 60-minute sessions over 2 weeks) was shown to significantly enhance parietal MMN amplitude and increase working memory performance (Pei et al., 2020). However, an important consideration to note is that there was no sham condition included in this study meaning placebo effects may have influenced the results. Nevertheless, other sham controlled studies have demonstrated neurofeedback's potential at modulating predictive processing markers, alongside memory and clinical outcomes.

For example, a separate sham-controlled pilot study highlighted how P300 neurofeedback in conjunction with trauma counselling was more effective than trauma counselling alone, for adult refugees with PTSD (Askovic et al., 2020). In this study, the sham group received trauma counselling for 1 hour once a week, while the neurofeedback group received one to two 1-hour trauma counselling sessions per week which included 20 minutes of neurofeedback (Askovic et al., 2020). This meant the neurofeedback group received on average 27 treatment sessions, while the sham group received 17 sessions on average. Post-treatment, the neurofeedback group had significantly reduced symptoms compared to the trauma alone group, with 12 of the 13 participants in the neurofeedback group reducing their PTSD symptoms below the clinical cut-off, compared to only 1 of the trauma alone group (Askovic et al., 2020). These effects held when controlling for the number of sessions per treatment arm. Moreover, the neurofeedback group exhibited increased P300 amplitude (to neutral stimuli) post-treatment (Askovic et al., 2020), suggesting normalisation of aberrant predictive processes in these PTSD patients. This pilot study critically highlights

how neurofeedback may be an effective adjunct to therapy for individuals with PTSD, one which can not only modulate predictive processes but also has clinically meaningful impacts on symptomology.

Additionally, another more rigorous study successfully demonstrated the benefits of P300 neurofeedback training for those with nicotine addiction. In this double-blind, randomized placebo-controlled trial, 60 nicotine-dependent individuals received two 1-hour neurofeedback sessions (separated by 1–2 days)(Bu et al., 2019). The placebo group also received two 1-hour sessions however instead of 'real' neurofeedback, they received 'sham' feedback which was neural activity of a matched participant. Cigarette craving and craving-related P300 responses were recorded pre- and post-neurofeedback, and the number of cigarettes smoked per day were recorded at baseline, 1 week, 1 month and 4 months post-neurofeedback (Bu et al., 2019). Critically, the real neurofeedback group exhibited significantly decreased cigarette cravings and craving-related P300 amplitude compared to the sham group (Bu et al., 2019). Moreover, while there were no differences between the groups in the number of cigarettes smoked per day at baseline, there was a significant improvement for the real neurofeedback group, with a long-term reduction in smoking observed at the 4 month follow up (Bu et al., 2019). Although interestingly, the peak improvement and most significant effect occurred at the 1 month follow up, suggesting that several sessions over a longer time period may be more effective at reducing addiction behaviours more permanently.

Importantly, this preliminary research highlights how neurofeedback (either alone or in conjunction with therapy) may be an effective tool for modulating predictive processes and ameliorating pathological forgetting in psychological disorders such as PTSD, substance use disorder or prodromal stages of AD. However, as evidenced above there are only a handful of studies that have examined this mechanism behind neurofeedback in conjunction with behavioural effects, and to the best of our knowledge there are none so far that have looked into this for those with traumatic brain injury, Parkinson's disease or other types of dementia. Thus, continued research is needed in this area to validate and expand the existing findings. In order to support with this, Table 1 summarises several recommendations for future studies to further validate the potential therapeutic benefit of approaches reviewed here (neurostimulation/ neurofeedback/ EMDR).

Table 1
Modulating Predictive Processing in Clinical Groups: Focus Areas for Future Research.

Application	Clinical Group(s)	Future Directions and Recommendations
EMDR		
	• Alzheimer's disease • Parkinson's disease • Traumatic brain injury • Addiction-related disorders	Examine the effectiveness of EMDR at modulating predictive processing markers (MMN or P300 ERPs) and clinical/ behavioural outcomes.
	• PTSD	Further validate the effectiveness of EMDR (either alone or in conjunction with therapy) at modulating predictive processing markers (MMN or P300 ERPs) and clinical/ behavioural outcomes.
rTMS		
	• Alzheimer's disease • Parkinson's disease, • Traumatic brain injury • Addiction-related disorders	Examine the effectiveness of rTMS at modulating predictive processing markers (MMN or P300 ERPs) and clinical/ behavioural outcomes.
	• PTSD	Further validate the effectiveness of rTMS at modulating predictive processing markers (MMN or P300 ERPs) and clinical/ behavioural outcomes.
tDCS		
	• Addiction-related disorders • Early-stage Alzheimer's disease	Further validate the effectiveness of tDCS at modulating predictive processing markers (MMN or P300 ERPs) and clinical/ behavioural outcomes.
	• Parkinson's disease • Traumatic brain injury • PTSD	Examine the effectiveness of tDCS at modulating predictive processing markers (MMN or P300 ERPs) and clinical/ behavioural outcomes.
Neuro-feedback		
	• Alzheimer's disease • Addiction related disorders • PTSD	Further validate the effectiveness of neurofeedback at modulating predictive processing markers (MMN or P300 ERPs) and clinical/ behavioural outcomes.
	• Traumatic brain injury • Parkinson's disease • Other forms of dementia besides Alzheimer's disease.	Examine the effectiveness of neurofeedback at modulating predictive processing markers (MMN or P300 ERPs) and clinical/ behavioural outcomes.

Abbreviations include: Eye movement desensitisation reprocessing (EMDR), repetitive transcranial magnetic stimulation (rTMS), transcaranial direct current stimulation (tDCS), mismatch negativity (MMN), event related potential (ERP), post-traumatic stress disorder (PTSD).

5. Future directions and recommendations for research

In the previous sections, this review has discussed clinical conditions where symptoms can be characterised by pathological forgetting (i.e. either accelerated or impaired rates of forgetting). It has proposed how these conditions of pathological forgetting may be better understood from a predictive processing perspective. Additionally, it has presented evidence demonstrating how markers of predictive processes (such as the MMN and P300 ERPs) are aberrant in these various clinical groups, with these aberrations often correlating with either memory performance or disease progression. Finally, it has outlined recent emerging evidence demonstrating how therapeutic approaches that target predictive processes (such as neurostimulation, neurofeedback or EMDR) may have clinically meaningful benefits for these patients.

Nevertheless, it is important to highlight that this is still a very nascent research area. While there several studies looking at MMN responses in Alzheimer's disease, or P300 responses in Alzheimer's, Parkinson's or PTSD, for other conditions such as traumatic brain injury or addiction-related disorders, there are only 1 or 2 studies that have investigated MMN or P300 responses. Furthermore, in some studies, they only report differences in ERP amplitude, but not whether there were variations in location and/or latency. Adding to this, in some cases, how these ERPs relate to forgetting or clinical outcomes have also not yet been investigated. Thus, these present prime opportunities for the design of future studies that are looking to investigate pathological forgetting in these conditions from a predictive processing perspective.

As such, Table 2 organises the existing MMN and P300 research by the respective clinical groups, as well as grouping them based on which ERP features (i.e. amplitude, latency or location) were investigated and whether behavioural or clinical associations were reported. In doing so, we have identified high, medium or low priority opportunities for future research, by highlighting where there are currently only minimal (0−4), moderate (5−10) or several (>10) studies. Expanding on Table 2, suggestions for how the high and medium priority areas could be empirically tested will subsequently be outlined to aid future research in further validating this understanding of pathological forgetting.

5.1. High priority research areas to further validate the predictive processing account of pathological forgetting

- Investigate the MMN response (amplitude/latency/location) in Parkinson's disease patients compared to healthy controls, and how these are associated with forgetting or clinical outcomes.

Table 2
Summary of Existing MMN and ERP Research for Conditions of Pathological Forgetting, and Priority Areas for Future Research.

	Alzheimer's disease (incl. early stages such as SMD or aMCI)	Parkinson's Disease	TBI / rTBI	Addiction/ Substance Use Disorders	Post-traumatic Stress Disorder
MMN ERP					
Future Research: Priority Level	Low	High	High	Medium	Medium
Existing Research					
Amplitude	– Laptinskaya et al. (2018) – *Pekkonen (2000) – Ruzzoli et al. (2016)	– Brønnick et al. (2010) – Pekkonen et al. (1995)	– Wynn and Green (2024)	– He et al. (2018) – Motlagh et al. (2018) – *Ramlakhan et al. (2018)	– Bangel et al. (2017) – Ge et al. (2011) – Menning et al. (2008) – Morgan and Grillon (1999)
Latency	– Cheng et al. (2021) – Gao et al. (2018) – Jiang et al. (2017) – Laptinskaya et al. (2018) – Papadaniil et al. (2016) – Tsolaki et al. (2017)			– Motlagh et al. (2018)	
Location	– Cheng et al. (2021) – Jiang et al. (2017) – Papadaniil et al. (2016) – Ruzzoli et al. (2016)				– Löw et al. (2019)
Behavioural or Clinical Associations	– Gjini et al. (2022) – Jiang et al. (2017)	– Brønnick et al. (2010)			– Menning et al. (2008) – Morgan and Grillon (1999)
P300 ERP					
Future Research: Priority Level	Low	Low	High	High	Low
Existing Research					
Amplitude		– **Xu et al. (2022) – Zhang et al. (2022)	– Gilmore et al. (2018)	– Luijten et al. (2016) – Petit et al. (2015)	– Araki et al. (2005) – Bae et al. (2011) – Charles et al. (2008) – Felmingham et al. (2002) – Galletly et al. (2001) – **Johnson et al. (2013) – Shim et al. (2019)
Latency	– **Howe et al. (2014) – Khedr et al. (2020) – Papadaniil et al. (2016) – Tsolaki et al. (2017)	– **Xu et al. (2022) – Zhang et al. (2022)			– Bae et al. (2011) – Charles et al. (2008) – Felmingham et al. (2002) – Galletly et al. (2001) – **Johnson et al. (2013) – Shim et al. (2019)
Location	– Papadaniil et al. (2016)	– **Xu et al. (2022)			
Behavioural or Clinical Associations	– Khedr et al. (2020)	– Zhang et al. (2022)		– Luijten et al. (2016) – Petit et al. (2015)	– **Johnson et al. (2013) – Shim et al. (2019)

Notes. *= Review,** = Meta-analysis.
Features of MMN and P300 ERPs are associated with predictive processing and may underlie pathological forgetting symptoms in the clinical groups mentioned. However, future research is needed to further validate this understanding of pathological forgetting. This table presents high, medium or low priority opportunities for future research to target, by highlighting where there are currently only minimal (0−4), moderate (5−10) or several (>10) studies. Reviews or meta-analyses reporting additional studies are included and indicated via * or ** respectively. The existing research on MMN and P300 ERPs are grouped based on which ERP features (i.e. amplitude, latency or location) were investigated and whether behavioural or clinical associations were reported. Abbreviations include: MMN (mismatch negativity), ERP (event related potential), Subjective Memory Decline (SMD), amnestic Mild Cognitive Impairment (aMCI), Alzheimer's disease (AD), traumatic brain injury (TBI) and repeated traumatic brain injury (rTBI).

- Investigate the MMN response (amplitude/latency/location) in patients with traumatic brain injury (or repetitive traumatic brain injury) compared to healthy controls, and how these are associated with forgetting or clinical outcomes.

- Investigate how the P300 response in those with traumatic brain injury (or repetitive traumatic brain injury) may vary depending on the nature of the stimuli, and whether this is associated with forgetting or clinical outcomes.

- Investigate how the P300 response in those with addiction-related disorders may vary depending on the nature of the stimuli, and whether this is associated with forgetting or clinical outcomes.

5.2. Medium priority research areas to further validate the predictive processing account of pathological forgetting

- Investigate how the MMN response varies in those suffering with addiction or substance-use disorders compared to healthy controls, with particular focus on whether there are variations in latency and/or location. Additionally, assess whether changes in the MMN response are associated with forgetting or clinical outcomes.
- Further investigate the MMN response in patients with PTSD compared to healthy controls, with particular focus on whether there are variations in latency and/or location. Additionally, assess whether these are associated with forgetting or clinical outcomes.

6. Conclusion

To summarise, our memories allow us to make predictions about our current environment. However, prediction error signals and other predictive processes also critically influence whether we retain or forget information. With predictive processing providing an intuitive account of natural forgetting, from reviewing the literature, there is also recent evidence that predictive processes contribute to pathological forgetting symptoms across a range of psychological disorders. Moreover, ERPs such as the MMN or P300 which offer an accessible means of measuring these predictive processes in the brain are aberrant in individuals with these psychological disorders. Specifically, alterations in amplitude and/or latency of the MMN and P300 are evident in cases of accelerated forgetting (such as traumatic brain injury, AD, Parkinson's disease or dementia) or impaired forgetting capacities (such as addiction, substance use disorder or PTSD). Finally, there is preliminary evidence that targeting these mechanisms via therapeutic approaches such as EMDR, neurostimulation or neurofeedback can not only ameliorate forgetting symptoms but may also have clinically meaningful benefits. However, applying these interventions to target predictive processes in relation to memory outcomes are still relatively nascent research areas, thus continued research is needed to further validate their findings.

Data availability

No data was used for the research described in the article.

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