Speed of Forgetting: A Computational Biomarker and Early Indicator for Memory Impairment

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Abstract

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In our increasingly digital world, medicine and healthcare must advance accordingly. This work validates a model-based tool for quantifying forgetting and capturing general biological processes behind abnormal memory impairment. We introduce an online assessment tool for early detection of memory impairments. By using the computational biomarker 'Speed of Forgetting', our system transforms memory assessment with an easily interpretable and repeatable model. It detects impairments in just 8 minutes of online interaction, far surpassing traditional methods that require up to 3 hours in a clinical setting. This metric advances proactive memory care, enabling broad and affordable cognitive health monitoring across diverse populations.

Preface

In this investigative dissertation, I dive into the concept of the *Speed of Forgetting* (*SoF*) as a computational biomarker for memory impairment.

When examining the landscape of Alzheimer's disease (AD) research and treatment, one encounters what has been commonly termed the "Alzheimer's Conundrum." That is, despite extensive research and investment, the effectiveness of drugs targeting the hallmark beta-amyloid plaques of AD has been largely disappointing. A notable example is Aduhelm, the first monoclonal antibody approved by the FDA to target amyloid plaques, which failed to conclusively demonstrate effectiveness in slowing cognitive decline across major clinical trials. This discrepancy has sparked significant debate within the medical community regarding the validity of the amyloid hypothesis.

The diagnostic process for AD heavily relies on PET imaging to detect beta-amyloid deposits, a method known for its expense, resource-intensiveness, and invasiveness, requiring the injection of radioactive tracers. While alternatives like the Lumipulse® beta-amyloid test have emerged, enabling the identification of amyloid pathology from cerebrospinal fluid, they remain invasive and discomforting. There exists a pressing need for minimally invasive, reliable diagnostic tools facilitating early detection and disease monitoring.

The urgency to address the growing prevalence of AD has put considerable pressure on translational research. There has been a rush to move drugs into clinical trials, possibly before their underlying scientific bases were fully understood or solidified. This has raised concerns about the robustness of the underlying scientific theories that underpin these fast-tracked therapeutic agents.

The challenges facing AD research and treatment are significant, but they are not insurmountable. Computational biomarkers like the *SoF* offer a non-invasive, computationally driven method to assess memory impairments. Diagnostic metrics that are both cost-effective and accessible could revolutionize the early detection of AD and other memory impairments, allowing for timely and targeted interventions.

1. General Introduction

Key Abbreviations: Speed of Forgetting (*SoF*); Mild cognitive impairment (MCI); Alzheimer's disease (AD); Adaptive fact learning system (AFLS); Multiple Trace Theory (MTT)

Understanding the mechanisms and implications of forgetting remains a significant challenge in cognitive neuroscience. One of the core difficulties in quantifying forgetting stems from the considerable individual differences observed across subjects. These differences prompt several critical questions: Which components of the memory trace, or engram, are most susceptible to forgetting? Is the vulnerability localized to specific regions involved in encoding, consolidation, or retrieval networks? Mechanistically, does forgetting primarily result from the decay of synaptic strength over time, or is it due to interference from other cognitive processes? The answers to these questions remain elusive, largely because the tools and methodologies currently available for measuring forgetting are inadequate.

A classical study by Loftus (1978) illustrates the complexity of measuring forgetting. Loftus challenged the simplicity of contrasting remembered versus forgotten items, arguing that such measures do not capture the nuanced nature of memory and forgetting. This point is critical; if our understanding of memory formation and the models used to represent memory are incomplete or inaccurate, then interpreting behavioral data related to forgetting becomes fraught with misinterpretations. The result is often a disconnect between brain activity and observed behaviors, such as response times and accuracy, which are commonly used but poor proxies for understanding the neural correlates of forgetting.

Marek et al. further complicate the picture by demonstrating that while increasing the sample size (N) in studies can stabilize measures of forgetting, the effect size observed becomes minuscule (2022). This finding suggests a disconnect between brain activity and the behavioral data typically used to infer cognitive processes, encapsulated in the critique "garbage in, garbage out." The implication is that relying on poor behavioral data can lead to misleading conclusions about the neural basis of forgetting.

A promising solution to these challenges is the replacement of purely behavioral measures with parameters derived from computational models. If the process of memory formation and forgetting can be accurately captured with a series of equations, then individual differences among subjects can be represented as variations in parameter distributions. This approach combines mathematical theory with physiology grounded in neuroscience, offering a more robust model for understanding forgetting. Such models are not only easier to parameterize but also provide measures that are both more interpretable and reliable.

Xu & Stocco (2021) advocate for this computational approach, suggesting that using model parameters to explain individual behavior offers a pathway to more accurately quantify and understand forgetting. By grounding these models in physiological evidence and aligning them with established neuroscience theory, we can create a more coherent and comprehensive framework for studying memory and forgetting.

In summary, the challenge of quantifying forgetting underscores the need for innovative approaches that bridge behavioral data with neuroscientific understanding. By embracing computational models and grounding them in the physiology of memory processes, we can overcome the current limitations and move closer to unraveling the complex dynamics of forgetting.

1.1 Toward A Computational Framework

A Brief on our Novel Computational Approach

In tackling the intricate phenomena of memory and its decline, this dissertation introduces a computational model for diagnosing and understanding memory impairments, innovating traditional methods with the Adaptive Fact Learning System (AFLS) and the ACT-R cognitive framework (John R. Anderson 2007) to represent memory activation. The AFLS, a dynamic and model-based system, significantly accelerates the detection of memory impairments through online data collection, a process that once took hours in clinical settings. This innovation leverages ACT-R's focus on the declarative memory module, crucial for encoding, storage, and retrieval of knowledge, tailoring assessments to individual memory profiles with unprecedented precision. More information on this model is detailed below in Chapter 3.5 Understanding the Computational Model of Memory.

At the core of this model is the Speed of Forgetting (*SoF*), a novel metric that quantifies the rate at which memory traces decay, providing a personalized assessment of memory function. This approach, grounded in the Multiple Trace Theory and refined through extensive research, marks a significant leap in memory assessment. By applying the AFLS in both educational and clinical settings, including longitudinal studies on MCI, the model not only offers insights into memory decline but also facilitates early detection and intervention. This integration of computational models with cognitive science represents a major advancement in personalized, efficient, and accessible diagnostics for memory disorders, setting a new standard in cognitive health assessment and intervention.

1.2 Longitudinal Clinical Study | A summary in four questions

The core of this dissertation is centered on a longitudinal observational clinical study designed to explore the dynamics of memory function and its decline, specifically focusing on the model parameter termed the "*Speed of Forgetting*" (*SoF*). This study comprises four key inquiries: *SoF* reliability, group differences, clinical relevance, and temporal stability.

1) Is the *Speed of Forgetting* reliable?
The first segment undertakes a rigorous examination of the *SoF*'s reliability across diverse cognitive materials and participant interactions. Utilizing a model-based system for online assessment, the study demonstrated the consistent reproducibility of the *SoF* measurements across time, reaffirming its potential as a reliable metric for evaluating memory function. Participants, comprising individuals with MCI and age-matched controls, engaged in weekly assessments that consistently calibrated the *SoF* parameter, affirming the parameter's reliability for longitudinal memory function monitoring.

2) Are there group differences in the *Speed of Forgetting*?
The second inquiry delves into the comparative analysis between MCI patients and healthy controls, revealing pronounced disparities in *SoF* values. MCI patients exhibited significantly higher *SoF* values, indicating a more rapid memory decay compared to their healthy counterparts. This segment underscores the capacity of the *SoF* to differentiate between normative and pathological memory decline, highlighting its diagnostic potential in distinguishing various stages of cognitive impairment.

3) Does the *Speed of Forgetting* have clinical validity?
In this critical segment, the study pivots towards validating the *SoF* as a clinically relevant measure with the examination of its diagnostic accuracy. The study meticulously evaluated the *SoF*'s effectiveness in discriminating between individuals with MCI and healthy controls, leveraging data from a series of memory assessments conducted through the adaptive fact-learning system (AFLS). Remarkably, the trial revealed that a single-session *SoF* could distinguish healthy control from impairment with an 85% accuracy rate, which notably increased to 94% when averaging *SoF* values across multiple sessions. This impressive level of precision can also be achieved with as few as four assessments, highlighting the *SoF*'s efficiency and reliability in identifying cognitive impairments with high fidelity.

These findings are particularly groundbreaking, as they demonstrate the *SoF*'s capability to not only match but potentially surpass the diagnostic performance of existing neuropsychological assessments in a fraction of the time and with greater convenience for patients and clinicians. The high diagnostic accuracy of the *SoF*, supported by rigorous statistical analysis and validated against traditional cognitive assessments, underscores its potential as a transformative tool in clinical settings.

4) Can the *Speed of Forgetting* track changes over time?
The final part of this study focuses on the temporal dynamics of *SoF*, tracking its fluctuations over 6 months to 2 years. This longitudinal analysis provided unique insights into the progression of memory decline, revealing a complex, nonlinear trajectory of cognitive deterioration in MCI patients. Such temporal monitoring is crucial for the early detection of neurodegenerative conditions and offers a valuable framework for assessing the effectiveness of therapeutic interventions aimed at mitigating memory decline.

Conclusion
The findings from this study illuminate the nature of memory decline and establish the Speed of Forgetting as a novel, reliable, and clinically valid metric for assessing cognitive impairment. By harnessing a computational

approach, this research pioneers a shift towards more personalized, precise, and scalable diagnostic tools. The integration of *SoF* into clinical practice holds the promise of transforming the landscape of cognitive health assessment, enabling more proactive and effective interventions in the battle against memory decline.

1.3 Expansions | Lifespan and Optimization

The concluding section of this dissertation, titled "Expansions," delves into two additional areas concerning the *Speed of Forgetting*: its progression throughout the human lifespan, and strategies for enhancing the accuracy of *SoF* predictions.

Lifespan Development of Memory Function
The journey of memory function across the human lifespan presents a complex narrative marked by developmental and degenerative milestones. Drawing from quantitative assessments spanning ages 5 to 85, a model-based analysis offers a uniform metric for memory function that transcends the limitations of disparate testing methodologies traditionally employed across different age groups. The emergence of a robust U-shaped function in memory capability underscores a striking parallel between the memory function of young children and that of cognitively impaired elderly individuals. This finding not only illuminates the trajectory of memory development and decline but also sets the groundwork for a unified approach to studying memory across life stages, offering fresh perspectives on age-related changes in memory function.

Optimization of Speed of Forgetting Prediction
Advancements in computational modeling have underscored the idiographic nature of memory decay, highlighting stable individual differences in the rate of forgetting. However, the integration of prior knowledge emerges as a confounding factor in model-based assessments of memory function. By employing Maximum Likelihood Estimations, this research delineates the impact of pre-existing knowledge on *SoF* measurements, revealing a discernible reduction in *SoF* for familiar facts. Despite this, the method achieved a noteworthy 81% accuracy in identifying known facts through base-level activation estimations. This novel approach advocates for the refinement of model-based assessments to accommodate prior knowledge, enhancing the precision and interpretability of *SoF* as a metric for individualized memory performance.

1.4 Conclusion

The intricate workings of memory within the human brain not only shape our individual narratives but also determine our capacity to engage meaningfully with the world. Memory, a cornerstone of cognition, enables us to store, retrieve, and process experiences, thus defining our very essence. Yet, comprehending and quantifying this process, particularly in the face of decline, presents a formidable challenge in the realm of cognitive science. This challenge extends far beyond mere academic pursuit; it carries profound implications for diagnosing and addressing memory-related disorders, devising effective educational methodologies, and advancing technologies aimed at bolstering cognitive function.

In response to this challenge, this dissertation has laid the groundwork for a transformative approach to memory assessment using computational models. Here, I will demonstrate how our system can detect memory impairments in just 8 minutes—a stark contrast to traditional assessments that take up to three hours in clinical settings. Our weekly measurements offer substantial benefits by providing a more granular view of memory changes over time, enabling earlier detection of cognitive decline and more timely interventions. This frequent monitoring enhances the model's ability to predict future memory impairments accurately, which is a crucial test of any predictive model's validity. The work presented in this dissertation excels in its predictive capabilities, showcasing how a well-designed computational approach can foresee memory decline, thus allowing for proactive management.

As we move to the next chapters, we will examine the practical applications of this system in both clinical and non-clinical settings, highlighting its potential to transform how memory impairments are managed and understood across various contexts. This transition marks a pivotal moment in leveraging computational psychiatry to foster more personalized, precise, and cost-effective healthcare solutions, thus revolutionizing the field of cognitive health assessment and intervention.

2. Understanding Memory Impairments

2.1 Significance

Dementia has been officially declared one of the biggest public health challenges of the century (M. J. Prince et al. 2016). Alzheimer's disease, a major form of dementia, was officially listed as the sixth-leading cause of death for Americans in 2019, and the fifth-leading cause for those over 65 years old (2022 Alzheimer's Association 2022). It's on track to double in prevalence every 20 years, with numbers expected to hit 65.7 million by 2030 and 115.4 million by 2050, with low to middle-income countries being the most affected (Martin Prince et al. 2013). This surge is not solely due to the demographic shift of an aging population, though that remains a significant driver. Enhanced diagnostic capabilities mean we are now identifying more cases earlier and more accurately. Lifestyle changes, such as increases in obesity, diabetes, and hypertension, contribute further, as these conditions are risk factors for dementia. Additionally, societal factors like pollution exposure, shifts in education levels, and social isolation also play a role. Recent studies also highlight a possible increase in these memory impairments following the COVID-19 pandemic, adding another layer to the escalating burden (Søraas et al. 2021). This complex interplay of factors means the increase in dementia cases far outpaces general population growth, impacting personal lives (Samanez-Larkin and Knutson 2015), healthcare, economies, and society at large (M. Prince, Bryce, and Ferri 2018). In this section, we'll delve deeper into the landscape of memory impairments, exploring their underlying mechanisms, diagnostic challenges, and the crucial role of early intervention.

2.2 Definition and Types

Memory impairments are characterized by the reduced ability to remember past events, learn new information, or both. This dissertation focuses on memory impairments falling under the umbrella of progressive neurodegenerative disorders, ranging from mild cognitive impairment, often a precursor to Alzheimer's disease, to more advanced forms like various types of dementia (Fig. 2.2.1).

Mild cognitive impairment (MCI): A condition that represents a slight but noticeable and measurable decline in cognitive abilities, including memory and thinking skills, but not severe enough to interfere with daily life or independent function (Petersen et al., 1999; Winblad et al., 2004). MCI can be a general term for cognitive impairment, and does not always indicate Alzheimer's disease.
Alzheimer's disease (AD): Characterized by the degradation of cognitive function and memory, linked to the accumulation of beta-amyloid plaques and tau tangles in the brain (Alzheimer's Association, 2021).
Vascular Dementia: Caused by impaired blood flow to the brain, leading to progressive memory loss (O'Brien and Thomas, 2015).

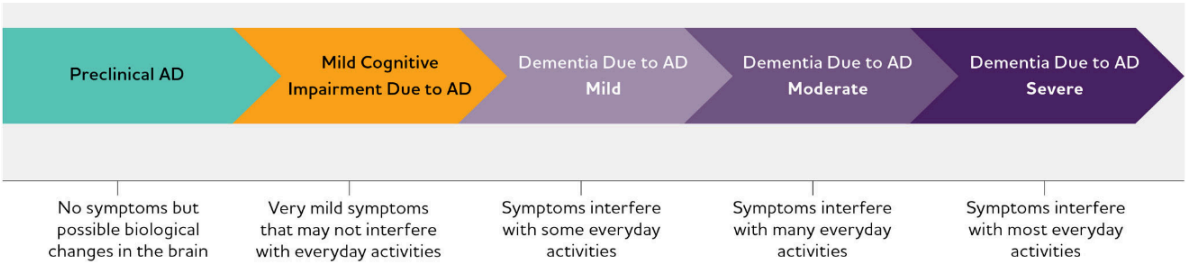

Figure 2.2.1. From 2022 Alzheimer's Association Report, a timeline of the progressive stages of memory impairments on the Alzheimer's Disease continuum. This continuum includes preclinical stages, MCI, and dementia due to AD.

Mild Cognitive Impairment (MCI)
MCI is central to this discussion, recognized as a cognitive decline that is more significant than what would be expected for an individual's age and educational level—typically 1−1.5 standard deviations below normative expectations—but that does not markedly interfere with daily activities (R. C. Petersen et al. 1999; Winblad et al. 2004). It is often described as an intermediate stage between the normal cognitive aging process and dementia (Albert et al. 2011). Epidemiological studies suggest that while some individuals with MCI remain

stable or revert to normal cognitive functioning, more than half may progress to dementia within five years. Individuals with MCI are at a notably increased risk of evolving into Alzheimer's disease—about 12% per year compared to 1% to 2% for age-matched controls with normal cognitive function (R. C. Petersen et al. 1999). MCI is thus considered a risk state for dementia, and its early identification could potentially lead to the secondary prevention of dementia by managing risk factors such as systolic hypertension (Ritchie and Touchon 2000).

Not all cases of MCI are characterized by memory loss. The next figure outlines the two main subtypes of MCI: amnestic MCI (aMCI), which is highly likely to progress to AD and might represent a prodromal stage of the disease, and non-amnestic MCI (naMCI), where memory remains intact (Fig. 2.2.2). Additionally, MCI can also affect other cognitive domains such as executive function, language, or visual reasoning (Ronald C. Petersen 2003).

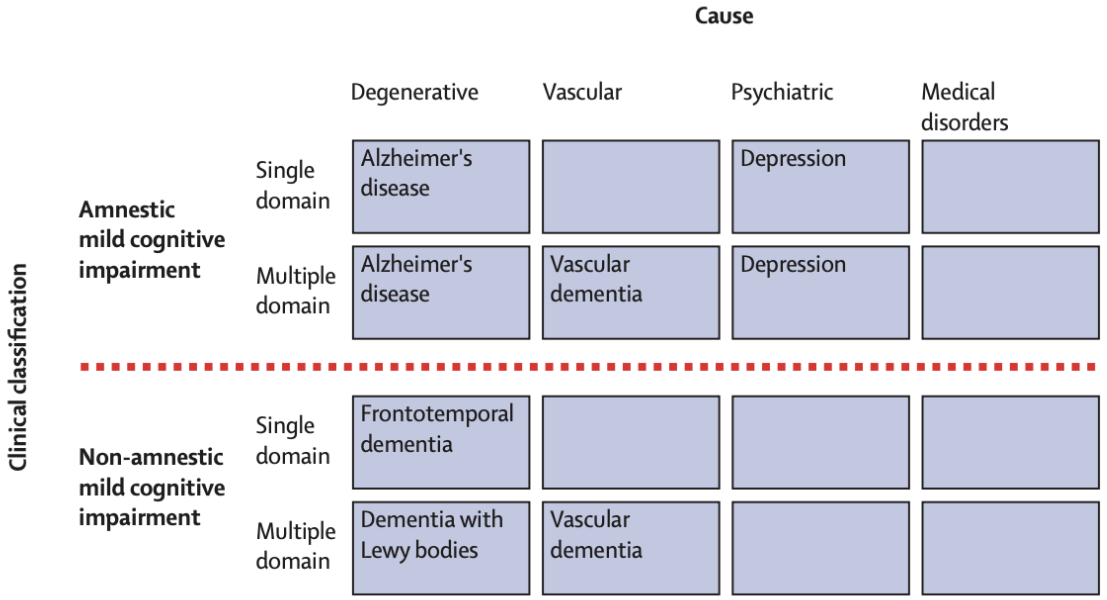

Figure 2.2.2. From (Gauthier et al. 2006), outline of mild cognitive impairment classifications and causes.

Causes

The exact causes of these memory impairments are not yet clear, but studies show that they can arise from a myriad of factors, spanning biological, environmental, and psychological realms. Biological causes encompass neurodegenerative processes, traumatic brain injuries, and genetic predispositions, each contributing to alterations in cognitive function. Environmental factors, including exposure to toxins or inadequate nutrition, can also exert profound effects on memory. Additionally, psychological factors such as stress, and in particular, depression and anxiety, have been shown to impair memory formation and retrieval (Gauthier et al. 2006).

2.3 Diagnostic Challenges

In the field of cognitive assessment, clinicians and researchers utilize a range of tools to identify memory impairments and other cognitive deficits. MCI is diagnosed through a combination of clinical evaluation, cognitive testing, and medical history. Cognitive assessments typically involve a battery of neuropsychological tests that measure various domains such as memory, attention, and executive function. Patients are usually classified as having MCI if their Clinical Dementia Rating Scale is 0.5 or lower. Among the most utilized tools are brief cognitive assessments, which provide a quick snapshot of an individual's cognitive function and are widely used in both clinical and research settings. Here are some commonly used tools:

Box | Current Diagnostic Tools

Montreal Cognitive Assessment (MoCA): Widely utilized for assessing various cognitive domains, including memory, attention, and executive function, the MoCA has been shown to have good sensitivity in detecting MCI and AD (Nasreddine et al. 2005).

Mini-Mental State Examination (MMSE): A classic screening tool for cognitive impairment, the MMSE assesses orientation, memory, attention, language, and visuospatial skills. While it is not as sensitive to MCI as the MoCA, it remains widely used due to its brevity and simplicity (Folstein, Folstein, and McHugh 1975).

Addenbrooke's Cognitive Examination (ACE): Similar to the MoCA, ACE assesses multiple cognitive domains, including memory, attention, language, and visuospatial skills. It has versions for both brief screening and comprehensive assessment (Mathuranath et al. 2000).

Mini-Cog: A brief screening tool consisting of a three-item recall task for memory and a clock drawing task. It has been shown to be effective in detecting dementia and MCI (Borson et al. 2000).

Rowland Universal Dementia Assessment Scale (RUDAS): Designed to be culturally fair, the RUDAS assesses multiple cognitive domains, including memory, and is particularly useful in multicultural settings (Storey et al. 2004).

General Practitioner Assessment of Cognition (GPCOG): Developed specifically for primary care settings, the GPCOG is a brief tool for detecting dementia and MCI. It includes a four-item memory task (Brodaty et al. 2002).

Wechsler Adult Intelligence Scale-Revised (WAIS-R): A comprehensive assessment tool used to measure intelligence and cognitive abilities in adults, covering various domains such as verbal comprehension, perceptual organization, working memory, and processing speed (Wechsler 1981).

These tools vary in their sensitivity and specificity for detecting memory impairments, as well as their suitability for different populations and settings. Clinicians often select the most appropriate tool based on the patient's demographics, the suspected cause of cognitive impairment, and available resources.

Challenges of Current Diagnostics

Despite their widespread use and efficacy, the current diagnostic tools for memory impairments face several limitations including cultural bias, subclinical presentation, variability in tests and individuals, and most notably, practice effects.

Cultural and Language Barriers

Identifying, assessing, and diagnosing cognitive impairment or dementia in elderly populations with diverse linguistic and cultural backgrounds presents significant challenges for health professionals. Common issues include misattributing symptoms to normal aging processes, language barriers, and a lack of familiarity with appropriate diagnostic tools (Sagbakken, Spilker, and Nielsen 2018). For instance, scores on the MMSE are influenced by factors such as age, education, ethnicity, and the language of the interview (Escobar et al. 1986). Many words cannot be easily translated, and several concepts are not relevant to people from different cultural backgrounds. When items that might be culturally biased were excluded, ethnic differences in the rates of "severe" cognitive impairment disappeared. Escobar et al. concluded that the MMSE should be revised to reduce social and educational biases through item selection and weighting. Additionally, the MMSE often fails to detect cognitive impairment that primarily involves the frontal lobes (Royall and Mahurin 1994). The MOCA, while available in multiple languages, may still yield unreliable results unless administered by someone proficient in the patient's first language. In the context of the Mini-Cog, while the three-item recall task was found to be a more effective component, the accuracy of the clock drawing task may be modest at best in multicultural samples (Storey et al. 2002).

Subjective Cognitive Decline

Additionally, the concept of subjective cognitive decline (SCD) is pertinent in this context. SCD refers to individuals who experience complaints of memory loss but exhibit normal performance on cognitive screens. These individuals are at greater risk compared to the general population for developing cognitive disorders. Identifying SCD is crucial as it highlights a population that might benefit from early interventions and monitoring, potentially delaying the progression to more severe cognitive impairments.

Subclinical Presentation and Variability in Tests and Individuals
Relying solely on single diagnostic tests carries inherent risks of overdiagnosis and underdiagnosis (Brodaty et al. 2017; Ranson et al. 2019). Additionally, there is considerable variability in how individuals experience memory decline during aging (Rapp and Amaral 1992). This variability, coupled with the limited feasibility of repeated measurements—most screening tools are susceptible to practice effects and are restricted to annual assessments—contributes significantly to the underdiagnosis of conditions like MCI. For instance, one study estimated that only 8% of expected MCI cases are diagnosed in the United States (Liu et al. 2024), with similar studies confirming low detection rates (11-15%; (Savva and Arthur 2015; White et al. 2022)), often due to clinicians' limited skills and time constraints.

Addressing Diagnostic Challenges

This gap in our healthcare system's capacity to identify and manage cognitive decline early underscores the need for improved diagnostic tools. Key strategies to address these challenges include:

1. **Resistant to Practice Effects:** There's a pressing need for diagnostic tools resistant to practice effects, providing unique advantages in tracking cognitive fluctuations, including "lucid days," often missed in isolated assessments.
2. **Tracking Cognitive Fluctuations Over Time:** Tools that can monitor cognitive fluctuations over time would offer valuable insights into the progression of cognitive disorders and support early detection and management.
3. **Comprehensive Monitoring and Early Intervention:** A comprehensive diagnostic approach that integrates longitudinal monitoring could significantly improve the early detection and intervention of cognitive decline.

2.4 Early Detection and Intervention

In the realm of memory impairments, the adage "forewarned is forearmed" truly resonates. There are significant advantages to early detection and intervention. In fact, many causes of MCI can be reversible. Effective intervention strategies for memory impairments include:

- **Lifestyle Modifications**: This includes *sleep*, diet, exercise, and cognitive activities.
- **Pharmacological Treatments**: These encompass medications such as cholinesterase inhibitors for AD, which have been instrumental in managing symptoms.
- **Neuromodulation Techniques**: Methods like transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial magnetic stimulation (TMS) have shown promise in improving cognitive function.

Reversion from MCI to Normal Cognition
A pivotal study exploring the reversion of MCI to normal cognition found that upon a second evaluation, 39% of individuals returned to normal cognition, while 59% remained in a state of MCI, and a marginal 2% progressed to Alzheimer’s disease dementia (Chung et al. 2019). Importantly, many memory impairments caused by factors such as vitamin deficiencies or depression are reversible if detected early (Ngandu et al. 2015), and such early intervention can significantly improve the quality of life and functional independence (Smith et al., 2020; Sperling et al., 2011). This underscores the critical window for intervention.

Chung et al., aimed to identify the characteristics that were facilitating the transition from MCI back to normal cognition. In their study, they pinpointed *cognitive control* ability as a key factor in cognitive restoration (Chung et al. 2019). Cognitive control, defined as the ability to orchestrate goal-oriented actions through the flexible deployment of mental faculties, primarily relies on integrative attention. It is a nuanced subset of executive function, distinguished by its focus on the integration of attention and the proactive management of objectives

and strategies (Badre 2008; Mackie, Van Dam, and Fan 2013); (Nigg 2017). This delineation of cognitive control highlights its potential role in mitigating cognitive impairment and enhancing patient care strategies. These findings not only illuminate the pathophysiological bases of memory impairments in the elderly but also may provide a high-level understanding of the potential neural mechanisms underpinning the effectiveness of neuromodulation treatments.

Recent Advances in Pharmacological Treatments

While advances in pharmacological treatments for MCI and AD are highly contentious and widely debated within the medical community, it is noteworthy to mention some of these developments. The approval of aducanumab, an amyloid beta-targeting monoclonal antibody, has been shown to modestly slow cognitive decline in patients with early AD by reducing amyloid plaques in the brain (Alexander, Emerson, and Kesselheim 2021), although its efficacy and approval process has sparked considerable debate (Mullard 2021). Additionally, drugs like donanemab (Mintun et al. 2021) and lecanemab (Swanson et al. 2022; van Dyck et al. 2023) which also target amyloid pathology, have demonstrated potential in improving cognitive outcomes for patients with early-stage AD. These advances represent significant strides toward disease-modifying strategies, yet their long-term efficacy and accessibility continue to be critical areas of active investigation and discussion (Perlmutter 2021).

Recent Advances in Neuromodulation

In a landmark study, Grover et al. (2022) explore the efficacy of non-invasive neuromodulation techniques like tACS to selectively enhance memory functions by targeting specific neural rhythms associated with cognitive processes in older adults. The research specifically investigated the role of rhythmic neural activities—particularly theta and gamma frequencies—in memory retention and retrieval processes. The study employed transcranial alternating current stimulation (tACS) to modulate these frequencies selectively in the dorsolateral prefrontal cortex (DLPFC) and the inferior parietal lobule (IPL). The findings revealed that application of targeted neuromodulation could effectively harness the brain's residual plasticity, offering a proactive approach to cognitive maintenance and a potential reduction in the incidence of dementia-related pathologies.

Interventions Adjunct with Repeated Measures Memory Assessment

While these interventions have been shown to improve memory, their effectiveness could be better evaluated with continuous, repeated measures of memory. This closer monitoring of individual fluctuations could then provide valuable insights into how to improve the effectiveness and timing of the interventions. To truly address these challenges and propel cognitive assessment into a new era of precision, a tool with remarkable repeatability and stability is imperative. Such a tool not only enhances diagnostic accuracy but also holds immense potential in evaluating the effectiveness of interventions. By leveraging the power of repeated measures, clinicians and researchers can unravel the fluctuations inherent in cognitive function with unprecedented granularity, paving the way for transformative advancements in cognitive healthcare.

Conclusion

The rising prevalence of memory impairments, notably in neurodegenerative disorders like AD and MCI, presents a significant public health challenge. This chapter has explored the complex nature of these impairments, detailing their underlying mechanisms, diagnostic complexities, and the crucial role of early intervention. To address these challenges, a comprehensive approach is essential, leveraging recent advances in pharmacological treatments, neuromodulation techniques, and interventions alongside repeated measures memory assessment. By developing precision diagnostic tools that resist practice effects and enable continuous monitoring, we can advance cognitive healthcare toward early detection and effective management, ultimately optimizing cognitive health for all.

3. A Computational Approach to Memory Assessment

3.1 Understanding Memory

Memory is the faculty by which the brain encodes, stores, and retrieves information. It is a fundamental aspect of human cognition, essential for learning, reasoning, and behavior (Larry R. Squire and Kandel 1999). While seemingly straightforward, the concept of memory encompasses a variety of complex processes and systems, each contributing uniquely to the overarching function of cognitive recall and recognition.

Classification of Memory Systems
One of the fundamental distinctions in the study of memory within cognitive neuroscience is the categorization of memory into different systems (Fig. 3.1.1). A widely accepted taxonomy, introduced by Larry Squire and Stuart Zola in the 1990s, differentiates between *explicit* (or declarative) and *implicit* (or non-declarative) memory systems (1996). Explicit memory includes semantic memory, which involves facts and knowledge, and episodic memory, which consists of personally experienced events. Implicit memory, on the other hand, encompasses procedural memory related to skills and tasks, conditioning, and priming. This classification primarily addresses long-term memory, distinguishing it from short-term and working memory systems, which are central to cognitive psychology.

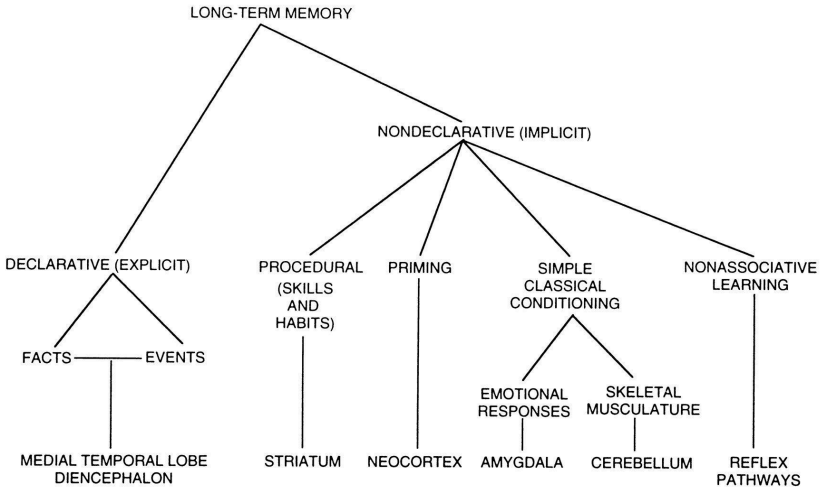

Figure 3.1.1. From (L. R. Squire and Zola 1996), a taxonomy of long-term memory systems with their accompanying anatomical brain correlates. *Facts = semantic memory; Events = episodic memory.

Neuroanatomy of Memory Systems
The anatomical regions associated with explicit memory notably include the medial temporal lobe. This area comprises the perirhinal cortex, parahippocampal cortex, entorhinal cortex, and hippocampus, all critical for explicit memory processing. These areas have strong connections with the medial prefrontal cortex (Barbas et al. 1999). Specifically, semantic content is processed in the perirhinal cortex and connected to the orbitofrontal cortex. Episodic content is managed in the parahippocampal area and linked to the anterior cingulate cortex, with further connections from the hippocampus to the ventromedial cortex. Additionally, the perirhinal and parahippocampal areas also connect with the dorsal lateral and ventral lateral prefrontal cortex, enabling explicit memory to support executive goal processing. But, before going any further, it is important to at least touch on the different stages a memory goes through.

3.2 Lifecycle of A Memory

Understanding memory extends beyond merely identifying its types and theoretical underpinnings; it necessitates an examination of its lifecycle. Similar to life itself, memory progresses through distinct developmental stages: encoding, maintenance, and retrieval. Each stage is characterized by unique processes and phenomena (Fig. 3.2.1).

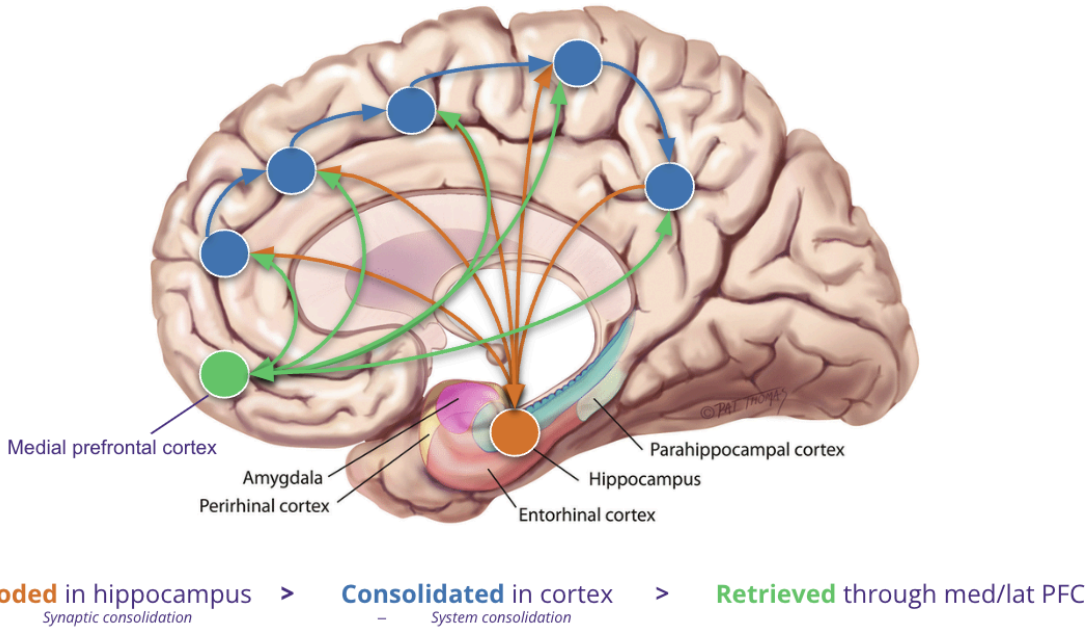

Figure 3.2.1. Diagram illustrating the memory process with bidirectional pathways in the brain.

Encoding
The initial stage involves the conversion of a memory trace into neural tissue representation. Studies involving patients with brain injuries and lesions have identified the hippocampus as playing a pivotal role in this process (Scoville and Milner 1957; Penfield and Milner 1958). The hippocampus is believed to integrate information from independent cortical modules representing various aspects of an experience and rapidly merge these features into a coherent memory trace (Eichenbaum 2004; Milner, Squire, and Kandel 1998).

Maintenance
Contrary to being a passive storage phase, maintenance involves active processes. Memories undergo a gradual transformation from a labile state to a more resistant or "stabilized" state through consolidation. Coined by Müller and Pilzecker, consolidation describes the post-experience processes of memory stabilization and maintenance (Lechner, Squire, and Byrne 1999; Müller and Pilzecker 1900), occurring in two forms: synaptic and system.

Synaptic consolidation possesses rapid kinetic properties and is completed within hours of learning, stabilizing changes in synaptic connectivity within localized hippocampal circuits (J. E. LeDoux 2002). These molecular foundations for memory are highly conserved across species and memory systems (Larry R. Squire and Kandel 1999).

System consolidation, on the other hand, is a lengthier process involving the gradual transfer of memory traces from the hippocampus to widespread cortical networks (Dudai 2004). Consequently, as memories integrate across different cortical regions, their reliance on the hippocampus diminishes (Bontempi et al. 1999). The extent of this transition will be discussed further in the subsequent section.

Retrieval
The retrieval of consolidated memories is a multifaceted process orchestrated by the prefrontal cortex. In declarative memory cases, retrieval entails the conscious re-experiencing of the event and, at the neural level, the reactivation of the original patterns of sensory information in the cortex (Danker and Anderson 2010). Initially, recent memories are retrieved through hippocampal–cortical networks. However, as memories mature and age over time, connections between different cortical modules strengthen, allowing memory function independent of the hippocampus (Miyashita 2004). At this stage, the prefrontal cortex assumes an integrative role, facilitated by reciprocal connections with sensory, motor, and limbic cortices (Miller 1996). This transition is supported by studies indicating that lesions or pharmacological inactivation of the prefrontal cortex disrupt the recall of earlier memories while leaving recent memories unaffected (Maviel et al. 2004; Takehara, Kawahara, and Kirino 2003; Frankland et al. 2004). Conversely, lesions or inactivation of the hippocampus produce the opposite pattern of results. The precise involvement of the prefrontal cortex in the storage or retrieval of remote memories, including effortful recall, remains an area of ongoing investigation.

Forgetting
Memories undergo continuous processing and reprocessing, fortifying them but occasionally leading to ***forgetting***—a natural aspect of the memory lifecycle that, if not appropriately managed, could contribute to memory impairments. Forgetting is a natural phase within the memory process where once vivid and easily accessible memories begin to fade and slip beyond our conscious reach. This phenomenon can occur at any point along the memory continuum. Nonetheless, this intricate interplay within the brain's architecture underscores the dynamic and distributed nature of memory.

3.3 Theoretical Frameworks in Declarative Memory

Various theories delve into the nature of memories post-consolidation, a key focus within the realm of declarative memory, which constitutes the primary subject of this dissertation. Two prominent theories, the *Standard Model of Memory Consolidation* (L. R. Squire and Alvarez 1995) and the *Multiple Trace Theory* (Nadel et al. 2000; Nadel and Moscovitch 1997), offer significant insights into the processes of memory consolidation and maintenance in the brain.

Standard Model of Memory Consolidation
The Standard Model suggests memories are encoded initially in the hippocampus before transitioning to the neocortex for long-term storage. Over time, reliance on the hippocampus diminishes, with the neocortex becoming the primary site for retrieving older, consolidated memories.

Multiple Trace Theory
In contrast, the Multiple Trace Theory posits that each recall of an episodic memory generates a new hippocampal trace, alongside traces in the neocortex. It asserts that the hippocampus stores multiple traces of each memory, retaining detailed, context-rich information over time. Unlike the Standard Model, the MTT emphasizes the ongoing significance of the hippocampus in retrieving episodic memories, regardless of their age.

Application of Multiple Trace Theory
The model used in this dissertation employs the MTT to elucidate memory consolidation and maintenance dynamics. The MTT was chosen over the Standard Model due to evidence suggesting the persistence of episodic memory traces within the hippocampus. Neuroimaging studies consistently demonstrate heightened hippocampal activity during episodic memory retrieval, affirming the enduring connection between such memories and this brain structure (Cabeza et al. 1997; Moscovitch et al. 2005). By integrating the MTT into the theoretical framework, this model acknowledges the continual role of the hippocampus in episodic memory retrieval, underscoring the intricate interplay among different brain regions in storing and recalling declarative memories.

3.4 Multimodal Integration

Returning to the neuroanatomy of explicit memory, it is widely recognized that semantic memories are not solely stored within the medial temporal lobe (Fig. 3.4.1). As briefly alluded to in Chapter 3.1, complex conceptual and semantic memories are also housed in multimodal convergence zones across neocortical temporal and parietal lobes, including the parietal temporal junction, superior temporal cortex, and temporal pole. The temporal pole, in particular, functions as a neocortical semantic/conceptual hub, integrating diverse unimodal and multimodal inputs to generate abstract concepts and schemas. It discerns similarities and differences among items, enabling generalized inferences and recognition based on multiple sensory inputs. **Notably, the temporal pole is one of the initial areas impacted by Alzheimer's disease, contributing to early memory issues observed in this disorder.**

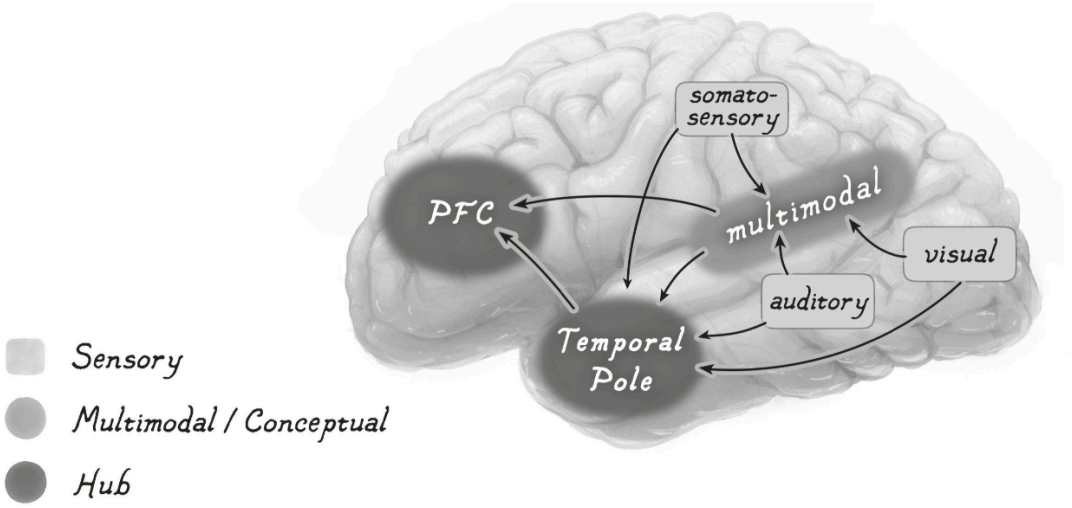

Figure 3.4.1. From (J. LeDoux 2020), the temporal pole as a semantic/conceptual hub.

Additionally, the complex networks of semantic/conceptual memory extend to several areas of the prefrontal cortex, including the lateral (dorsal and ventral), and frontal pole regions, which are known for their advanced capability to form complex conceptual representations. Connections also include the medial prefrontal cortical areas like the orbital, ventral medial, and anterior cingulate cortex. These diverse connections allow the prefrontal cortex to utilize semantic and episodic memories in the top-down control of information processing and behavior.

Semanticization of Episodic Memories

Episodic memories often undergo a process of "semanticization" especially when based on recurrent experiences or when an episodic memory is frequently retrieved (Tulving 1985). Such memories transition from being highly detailed and unique, depending crucially on the medial temporal lobe, to becoming more generalized and neocortically based (Binder et al. 2016). This transition is particularly noticeable in older memories of recurring situations. Returning to the theoretical frameworks, Randy O'Reilly, Jay McClelland, and Bruce McNaughton proposed that this is due to the hippocampus's capacity for rapid learning, which is vital for encoding unique facts or episodes, whereas neocortical areas accumulate and integrate information over time, enhancing conceptual memory (O'Reilly and McClelland 1994). Conversely, Morris Moscovitch and Lynn Nadel suggest that while the hippocampus continues to engage with old memories, duplicates of these memories are also stored in nonhippocampal sites, supporting memory retrieval even when the hippocampus is compromised. This further underscores the intricate and distributed nature of memory storage and retrieval, highlighting the significant role of both hippocampal and neocortical networks in the enduring architecture of human memory.

Conclusion

The complex mechanisms underlying memory encoding, maintenance, and retrieval emphasize the pivotal roles of both hippocampal and neocortical structures. The application of the Multiple Trace Theory within this dissertation highlights the enduring significance of the hippocampus in episodic memory retrieval. Moreover, the exploration of multimodal integration sheds light on the broader neocortical networks involved in semantic and conceptual memory, illustrating the interconnectedness of memory systems. This tapestry of memory dynamics not only advances our theoretical knowledge but also informs the development of future models and practical applications in cognitive science, neuropsychology, and beyond.

3.5 Understanding the Computational Model of Memory

This section introduces a computational model designed to quantify memory processes with precision, addressing the challenge of capturing memory's dynamic nature and translating it into practical applications in educational and clinical settings. The model leverages mathematical theories to accurately predict individual behavior regarding memory recall and decay.

Why this model?

Model Overview
Central to our study is a computational memory model that extends the foundational work of Anderson & Schooler (1991). This model integrates principles from the Multiple Trace Theory (Nadel et al. 2000), and connects them to specific neural circuits, offering a biological interpretation of memory functions. It is also a key component of the ACT-R cognitive architecture (John Robert Anderson 1983; John R. Anderson 1990), a framework highly regarded in psychology and neuroscience for its contributions to understanding cognitive processes. Supported by extensive empirical evidence, including studies by Pavlik and Anderson (2005, 2008) and van Rijn (2009), this model stands as both an independent model and a crucial part of a broader cognitive framework, making it a valuable tool for exploring the complexities of memory.

Foundational Principles
The model employs Anderson's "rational analysis," a Bayesian approach that suggests memory adapts to the statistical structure of the environment to optimally estimate the likelihood of needing a memory trace (John R. Anderson 1990). Anderson & Schooler (1991) expanded on this concept by demonstrating how factors like recency predict the probability of re-encountering an item, thereby influencing memory performance. This approach underlines the adaptability of memory in response to environmental cues, enhancing its predictive accuracy.

Modeling Techniques and Mathematical Foundations
Further modeling efforts have refined the application of these principles by incorporating estimates of non-retrieval processes (e.g., reading a word, deciding to respond, etc.) on overall performance, thus aligning theoretical predictions more closely with observed data (Schooler and Anderson 1997). The model utilizes mathematical expressions to convert memory activation values into probabilities of recall and predicted response times, illustrated by the following equations (John R. Anderson 2007):

- Probability of Recall: $P = \frac{1}{1 + e^{-A}}$
- Predicted Response Time: $RT = e^{-A} + t_o$

A corresponds to the memory's activation, and t_o is the additional time cost for encoding the stimulus and performing the motor response. This structured approach not only elucidates the mechanisms behind memory retrieval and decay but also enhances the model's utility in practical settings by providing a clear and measurable framework for assessing memory function.

3.6 The *Speed of Forgetting* (*SoF*): Core Concept and Measurement

The *Speed of Forgetting* is a key metric derived from our computational model of memory. This model parameter functions as a decay intercept that can eventually quantitatively assess how rapidly individual memories fade or are forgotten over time. When aggregated, *SoF* values offer a measure of a learner's overall memory ability (Florian Sense, Meijer, and van Rijn 2018; Zhou et al. 2021). Notably, *SoF* has proven more predictive of an individual's memory ability than other common behavioral metrics such as Working Memory Capacity (WMC) and General Cognitive Ability (GCA). Using multiple linear regression models, Sense (2018) found that the Speed of Forgetting was the most influential predictor of delayed recall, surpassing both WMC and GCA. Moreover, *SoF* explained significantly more variance in delayed recall than either WMC or GCA individually. Further detail on the *SoF* will be defined below.

3.7 Adaptive Memory Assessment

The *SoF* can be estimated through the Adaptive Fact Learning System (AFLS). The AFLS leverages a computational model to tailor fact learning experiences to individual memory performance, optimizing the spacing of factual recall. This system is based on ACT-R's model of memory, which tracks activation levels of information over time, enabling adaptive learning based on an individual's performance.

Core Components

The AFLS incorporates several key components in its operations (Fig. 3.7.1).

1) **Fact Selection:** The system selects facts for review based on their current activation levels, estimated from the learner's previous interactions. This ensures that facts nearing the threshold of forgetfulness are prioritized for reinforcement.
2) **Retrieval Practice:** Learners are prompted to recall facts, reinforcing their memory. The system adjusts its predictions of how well a learner remembers each fact based on their performance.
3) **Model Updating:** Based on the learner's responses, the AFLS updates its estimates of the *SoF* for each fact, refining the model to better predict future performance.

The AFLS dynamically adjusts the difficulty and timing of fact presentation based on a computational model that predicts when a fact will be forgotten, termed the *Speed of Forgetting*.

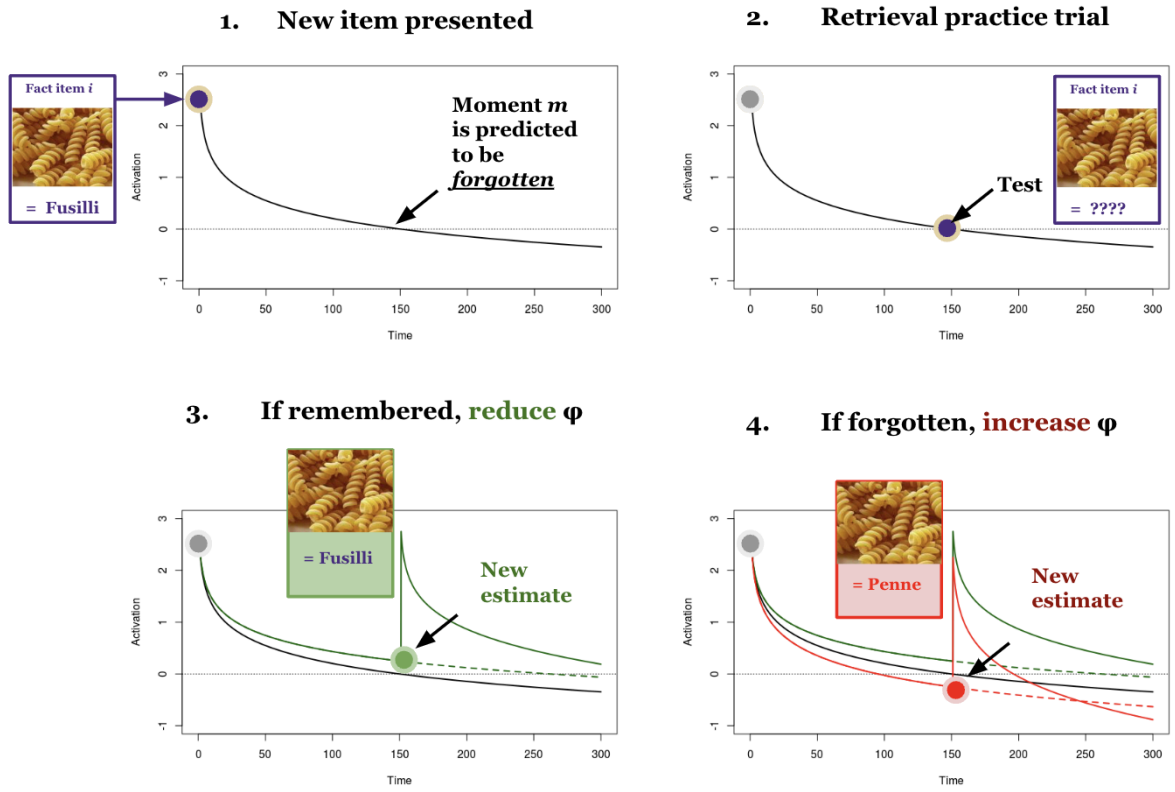

Figure 3.7.1. Visual summary of how the Speed of Forgetting is measured.

Estimating the *Speed of Forgetting* in the Adaptive Fact Learning System
The *SoF*, denoted as φ, is a key metric within the AFLS, influencing how the system schedules fact repetition. It reflects the individual-specific speed at which information is lost over time if not revisited. The AFLS estimates this rate using a combination of Bayesian prediction and updates from ongoing learner performance. As the learner interacts with the system, their performance data (accuracy and response times) are used to refine the rate of forgetting estimates. If a learner recalls a fact quicker than expected, the system adjusts the rate of forgetting downward, indicating that the fact is remembered more robustly than anticipated. The measurement of *SoF* is dynamically adjusted through a binary search process, aiming to minimize discrepancies between expected and observed response times, thereby fine-tuning the rate of forgetting to provide a more accurate assessment of memory abilities. This continuous refinement process evolves the system into a 'cognitive twin' of the user, providing personalized insights into latent memory capabilities (Somers, Oltramari, and Lebiere 2020).

Understanding the Equations
The AFLS operates within a theoretical framework developed to trace the temporal dynamics of declarative memory processes, as established by Anderson et al. (1998). According to this framework, each memory is represented in long-term memory not by duplicate entries, but through a cumulative list of timestamps documenting each occasion the memory was encoded. Thus, the creation of a memory trace results in adding a

new timestamp to this list, capturing the exact moments when the memory was reinforced. This approach acknowledges that identical memories do not exist independently; instead, they are represented through the accumulation of their instances of recall or reinforcement. It is based on the Multiple Trace Theory (Nadel et al. 2000), which argues that each encounter with a piece of information generates a distinct memory trace. These traces then decay according to a power law of forgetting. This law posits that the probability of retrieving a memory trace diminishes logarithmically over time, influenced by the aggregate activation of all associated traces.

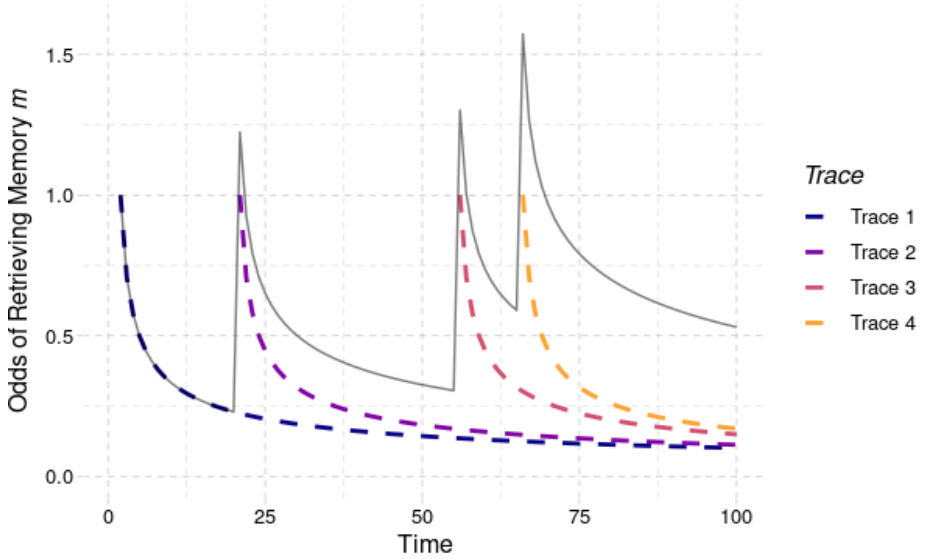

Figure 3.7.2. Hypothetical time course of the activation of a memory made of four different traces (colored dashed lines) encoded at four different times. Gray line is the sum of the traces. The Y-axis represents the log-odds or "probability" of retrieving a memory.

Primary Mathematical Model: Memory Activation

The primary equation with the AFLS quantifies the odds of memory retrieval (Figure 3.7.2). Specifically, it models the activation of a memory as a logarithmic function of the sum of individual memory traces. This equation indicates that memory activation A for a memory m at a specific time t is influenced by the times at which the item was previously encountered $t(i)$ (where i is the index for an encounter with the item). Each trace has its decay rate $d(i)$, which dynamically changes based on several factors including the time elapsed since the memory was last activated.

Secondary Equation: Decay Rate

The secondary equation relates a trace's decay rate to its activation level at the time of encoding, modified by a decay intercept φ (Pavlik and Anderson 2005; Florian Sense et al. 2016)**.**

Odds of memory retrieval

$$A(m,t) = log\sum_i (t - t(i))^{-d(i)} \quad (1)$$

$$d(i) = e^{A(m,\, t=t(i))} + \varphi \quad (2)$$

- The first equation tells us how the activation of a memory is equivalent to the log odds of retrieving any of the memory traces (i) at a specific time.
    - $A(m,t)$: this is the activation (A) level of a memory (m) at time (t). It represents how "active" or accessible this memory is in the subject's brain at that moment. The higher the activation, the easier it is to recall the memory.

- $log\sum_i(t - t(i))^{-d(i)}$: this sums up the influences of all the times a memory was activated or reinforced. Each time you recall or reinforce a memory, it gets a boost. The formula takes into account how long ago each boost occurred.
- $t - t(i)$: this is the time elapsed since the *i*th reinforcement of the memory.
- $-d(i)$: this is the rate at which the memory fades after each reinforcement. Memories fade over time, and this part calculates how much influence each past reinforcement still has on the memory's current activation.

- The second equation tells us how quickly the memory fades.
  - $e^{A(m, t=t(i))}$: this is the activation level of the memory at the time of the *i*th reinforcement. The initial strength of the memory at each reinforcement affects how quickly it fades.
  - φ : this is the *Speed of Forgetting* (*SoF*; phi) defined as the decay intercept that is used as the decay value for the first trace, and then dynamically adjusted using external values like response times and accuracy.

In essence, this equation looks at each time a memory was reinforced, considers how strong it was at those times, and calculates the overall likelihood of the subject being able to recall that memory at any given moment based on how long ago those reinforcements occurred and how memories naturally fade over time.

Spacing effect
In this model, $d(i)$ is dependent on the memory's activation level at the time it was encoded. This elucidates the spacing effect (Cepeda et al. 2008), wherein memory traces formed in close temporal proximity may decay faster due to the initially higher activation level. The decay intercept φ serves as a crucial parameter that adjusts the base decay rate, accommodating differences in individual memory strength and retention capabilities.

Power Law
The equation assumes that memory decays as a function of a power law. This is a relationship where the influence of each memory trace on total activation decreases as a function of the time elapsed since encoding or last rehearsal, raised to the power $-d(i)$, (Newell and Rosenbloom 1990). Thus, this relationship would suggest that larger intervals since encoding result in significantly reduced memory activation.

Interrelationship and Dynamics
The equations provided for the mathematical model of memory retrieval and decay do indeed depend on one another, but they are not circularly defined in the conventional sense that would render them unusable. Instead, they form a dynamic system where the current state of one variable influences the other over time, which is typical in models of complex biological processes like memory. The interplay between these two equations forms a feedback loop.

- The *decay rates* calculated in Equation (2) depend on the activation levels at previous times which were influenced by earlier experiences and reinforcements of the memory.
- The *overall activation level* at any given time as computed in Equation (1), is affected by these decay rates.

Each reinforcement of the memory updates the activation level, which in turn adjusts the decay rates for future computations. This dynamic system allows the model to adapt over time, reflecting changes in memory strength due to new encounters or reinforcements and natural fading. This kind of modeling is particularly useful in simulating how memories evolve and how easily they can be retrieved based on their history of activations and the inherent decay of memory traces. This model, therefore, provides a realistic and dynamic representation of memory processes, where the past states influence future states in a continuous feedback loop, rather than a simple circular dependency.

Visualization

In practice, these equations are visualized within the AFLS as curves representing memory activation over time for different values of φ. As φ increases, indicating faster forgetting, memory items require more frequent repetition to maintain above a critical activation threshold, ensuring they remain within the realm of recallability (Fig. 3.7.3).

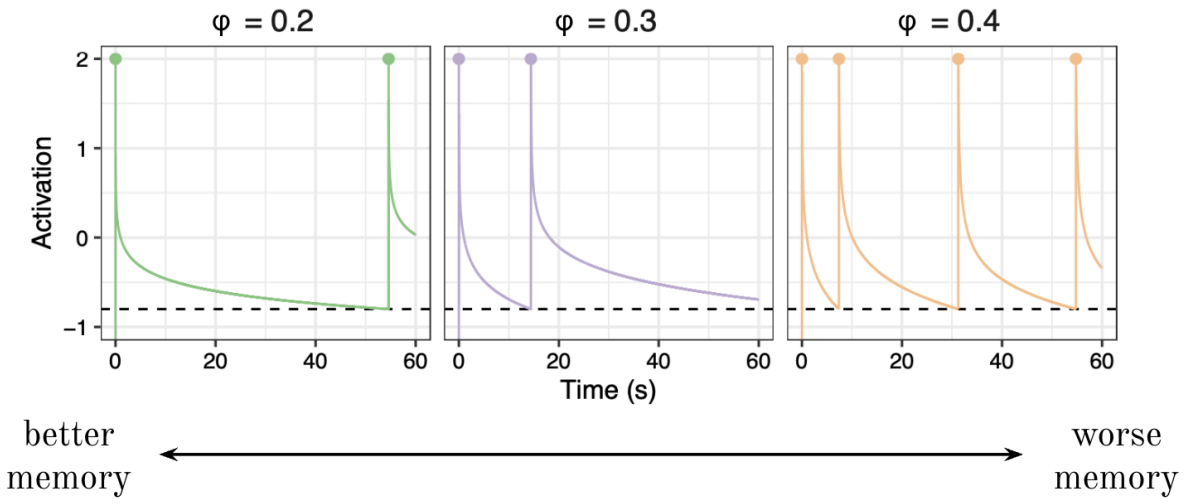

Figure 3.7.3. Adapted from (van der Velde 2023). Activation over time at three different *SoFs* (φ). In the adaptive learning system, an item is presented for restudy when its activation reaches the forgetting threshold (dotted line). As φ increases, an item requires more frequent repetition to stay above the threshold.

Overall, the model captures the idea that memories decay over time, with the activation level determining the retrievability of a memory at a given moment. This activation level is influenced by how much time has passed since the memory was last rehearsed or encoded, modulated by a decay function that can change exponentially with the activation level at encoding.

Biological Interpretation

Biologically, the *Speed of Forgetting* could be understood as a computational term that encapsulates various biological processes involved in the phenomenon of *passive* forgetting (Stocco et al. 2024). According to Davis and Zhong (2017), passive forgetting includes the type of memory loss that occurs outside of active forgetting mechanisms like retrieval-directed forgetting or motivated forgetting. It involves the gradual fading of information due to synaptic decay, cell death, and interference among neural pathways.

The biological interpretation of the *SoF*'s relation to passive forgetting suggests that it serves as a computational proxy for resting-state neural activity. Resting state activity refers to the brain's patterns of neuronal activity while a person is not focused on the outside world and not engaged in any specific mental task. This state is characterized by spontaneous fluctuations in brain activity, and can be measured using techniques like functional magnetic resonance imaging (fMRI) or electroencephalography (EEG), where it is observed in the form of neural oscillations or networks of synchronous activity across different brain regions (Fox and Raichle 2007). This notion is supported by studies linking *SoF* to variations in neural dynamics. For instance, Zhou et al. (2021) assessed the *SoF* parameter in fifty healthy participants and analyzed how individual differences in this parameter correlated with variations in the resting state EEG power spectrum, a measure known to reflect stable individual differences in neural activity. The results supported the hypothesis that the decay rate of memory, as quantified by the *SoF*, is not confined to specific locations but is rather distributed across multiple scalp locations and frequency bands. This suggests that the rate at which individuals forget information is linked to the spontaneous activity of cortical circuits.

Clinical Potential

A significant advantage of the AFLS is its capacity to maximize the retention of information. By optimizing the frequency and timing of retrieval practices, the system ensures that users are consistently engaging with the material at the most effective intervals to prevent forgetting. This strategic engagement not only enhances learning outcomes but also maintains motivation among users. The repetitive nature of retrieval practice, which could potentially be tedious, is made more bearable by the system's design. This is particularly crucial in clinical settings, where patients might engage in these tasks repeatedly as part of their diagnosis or treatment.

While the AFLS has seen widespread adoption in educational technology settings by revolutionizing how factual knowledge is acquired (Van Rijn, van Maanen, and van Woudenberg 2009; Wilschut et al. 2021), its potential in clinical contexts remains largely untapped. The study described in this dissertation pioneers the application of the AFLS in such settings by focusing on the *SoF* to derive individualized 'computational biomarkers' of memory. This marks a shift from merely enhancing learning to employing the system as a diagnostic tool that could swiftly identify memory impairments through the methodical analysis of retrieval patterns.

Conclusion

In summary, this adaptive system not only facilitates the acquisition of factual knowledge but also serves as a powerful diagnostic tool for assessing memory function. The *Speed of Forgetting,* central to our computational model, offers a novel and effective measure of how memory fades over time, allowing for personalized and dynamic memory function assessments.

4. Longitudinal Clinical Study

Parts of this chapter have been submitted as a conference paper to the 2023 Cognitive Science Society, and as preprint on MedRxiv.

Computational Phenotyping for the Detection and Continuous Assessment of Early Memory Impairment

Abstract
With the rising prevalence of age-related memory impairments, the question of how to effectively and efficiently detect and monitor these declines becomes increasingly urgent. This study introduces a first-of-its-kind, model-based system for the online assessment of clinical memory impairments, marking a significant advancement in the field. The system fits a computational model of memory to real-time data from repeated memory probes and infers memory function from the model's parameters. Utilizing just 8 minutes of online data, the model can accurately identify memory impairments and supports weekly assessments for up to a year without diminishing power assessment. The results of this study highlight the system's potential for cost-effective, wide-scale monitoring of memory functions, offering a promising tool for early detection and long-term observation of memory impairments.

Age-related memory impairments, such as those caused by dementia, pose a significant public health challenge. The early detection of such conditions is crucial, as many MCI causes are reversible, and newly developed therapies are effective at halting cognitive decline (Ngandu et al. 2015). Early detection, however, hinges on the availability and repeatability of adequate assessment tools. Unfortunately, diagnostic assessment of memory impairments is not straightforward: tests are time-consuming, culturally biased, require specialized administration, and are vulnerable to practice effects, leading to an underestimation of conditions such as mild cognitive impairment (MCI; (Liu et al. 2024; White et al. 2022; Savva and Arthur 2015)) and mounting health disparities between urban and richer areas– where qualified diagnostic services are more readily available, and rural and poorer areas– where they are not.

In the present study, we pioneer and test an innovative approach to solve the assessment bottleneck. Our approach capitalizes on wireless, and mobile technology as well as cognitive and neuroscientific insights based on long-term memory. Specifically, we combined a well-established episodic memory model (John R. Anderson and Schooler 1991) and an online adaptive fact-learning system (AFLS) to create a patient-centric, unsupervised, repeatable, portable assessment system. The AFLS tailors stimulus presentation rates to individual users, and the computational model, iteratively calibrated through AFLS response data, evolves into a "'cognitive twin" of the user. This twin's internal parameters offer a quantified measure of the patient's latent memory capacity (Somers, Oltramari, and Lebiere 2020).

The computational model is based on the principles that (1) the encoding of information leaves episodic "traces" in the brain; (2) memories are created by the accumulation of traces (MTT theory, (Nadel et al. 2000); (3) forgetting results in these traces progressively fading over time according to a power law; and (4) while different traces might fade at different rates (Fig. 4.1.1A), these rates depend on a single underlying parameter, the *Speed of Forgetting* (SoF), which is characteristic to every individual and reflects a combination of biological processes, some of which are affected by aging and compromised in dementia (Stocco et al. 2024).

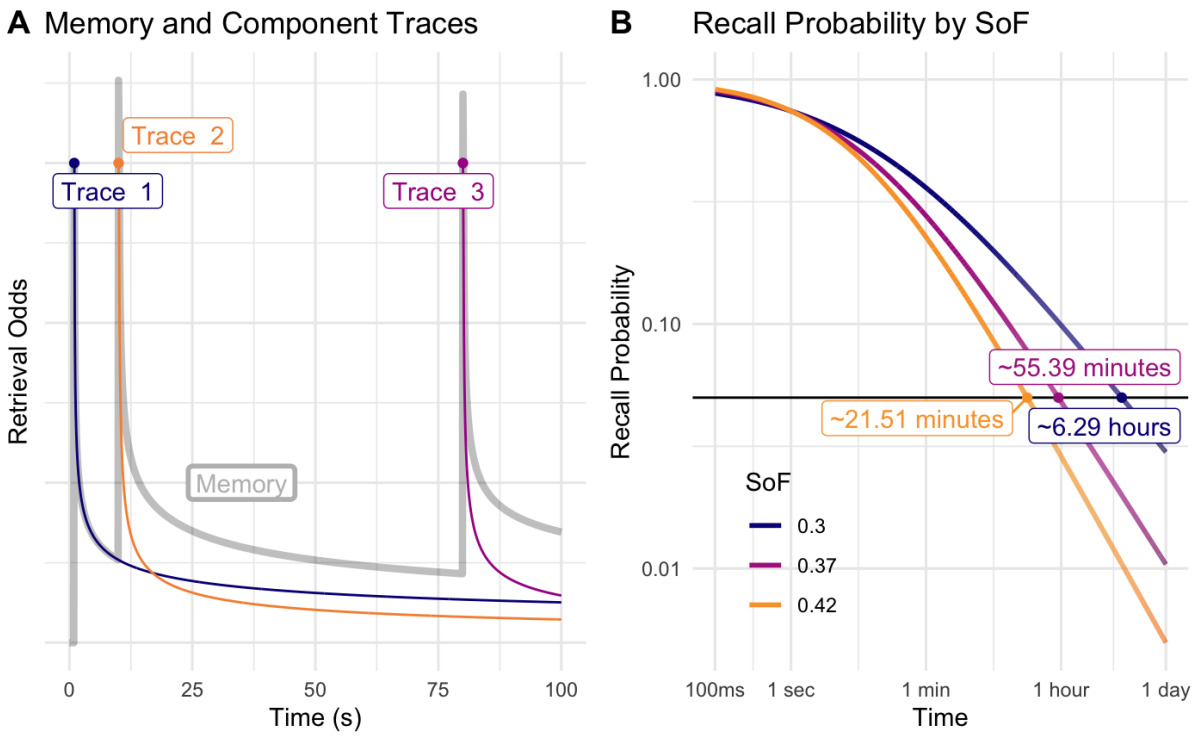

Figure 4.1.1. The Computational Model. (**A**) Memory Activation. Hypothetical time course of the activation of a memory (gray line) made of three different traces (colored lines) encoded at three different times (0, 10, and 80 seconds) and with individual decay rates; (**B**) An individual's *Speed of Forgetting* (SoF) value can be interpreted as the speed at which the probability of retrieving a memory decays over time. Points and labels refer to the time at which the probability of a memory being retrieved falls below 5% for three example individuals with characteristic SoF values of 0.3, 0.37, and 0.42.

The SoF quantifies the initial rate of episodic trace decay without rehearsal (Fig. 4.1.1B), setting the initial forgetting trajectory of a memory, and determining how much it could benefit from subsequent re-encodings and retrievals (John R. Anderson and Schooler 1991; Pavlik and Anderson 2005; Van Rijn, van Maanen, and van Woudenberg 2009). Here, the SoF parameter is used to quantify an individual's memory function. This aspect of our approach is a first in the field, enabling fast assessment of memory performance with unprecedented accuracy. Furthermore, by calibrating the SoF parameter using AFLS data, our method offers an individualized and continuously evolving assessment for each individual. This represents a significant advancement beyond the static, one-size-fits-all approach of traditional diagnostic tools.

Importantly, the SoF parameter's interpretation is transparent and straightforward, making it accessible for both clinicians and researchers. Its independence from standardization norms further enhances its utility, as it does not rely on conventional benchmarks that may not apply universally across diverse populations. This independence is crucial in ensuring that a diagnostic tool is broadly applicable and adaptable to various individual contexts. Thus, our model is not only aligned with the ideal criteria for diagnostic tools but also pushing forward the frontiers of understanding and assessing memory impairments.

To test this new approach, we conducted a longitudinal study of healthy elderly adults and elderly individuals with mild cognitive impairment (MCI). We chose individuals with MCI, rather than dementia, to both ensure participants had sufficient cognitive abilities to perform the task and to test the model's ability to detect earlier, more subtle differences in memory function as it is often a precursor to AD and other forms of dementia (R. C. Petersen et al. 1999). This cohort of individuals was followed for 6+ months, during which they performed weekly online model-based assessments to characterize their SoF.

Experimental Hypotheses

1. **Reliability:** SoF values would be reliable across repeated assessments.
2. **Group Differences:** Individuals with MCI would exhibit higher SoF values than healthy controls, with accelerated forgetting observed over time.
3. **Clinical Validity:** SoF values would have clinical validity, allowing for the identification of abnormal memory function.
4. **Longitudinal Trajectory:** SoF will reveal a complex, nonlinear progression of memory decline in MCI patients, useful for early detection and therapeutic assessment.

4.2 Methods

Participants

Fifty-one participants were recruited on a rolling basis from the University of Washington Alzheimer's Disease Research Center (Fig. 4.2.1). The inclusion criteria for the study were as follows: 1) age between 55 and 85 years, 2) fluency in English, and 3) no major medical or psychiatric conditions that would affect cognitive performance. Participants were classified into two groups: healthy cognition (N = 27; 19 female aged 58-84, 8 male aged 60-84) and those with mild cognitive impairment (MCI; N = 24; 5 female aged 64-77, 19 male aged 68-83). All participants provided informed consent and were compensated for their participation in the online memory game portion of the study. All recruitment and testing procedures were approved by the University's Institutional Review Board.

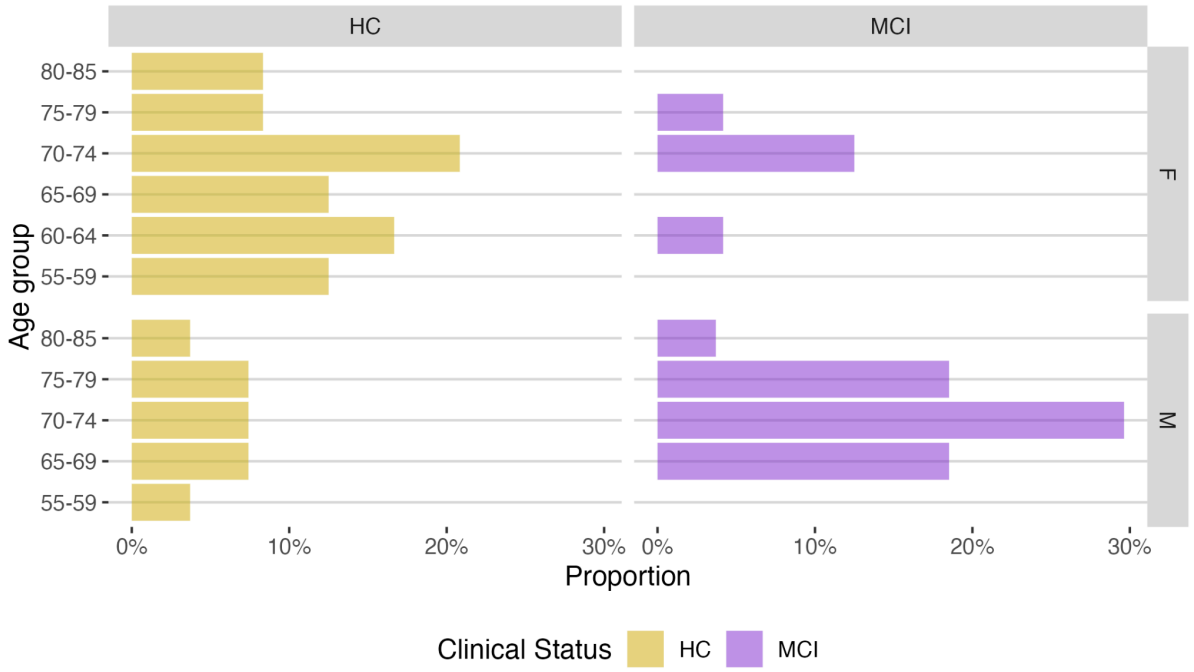

Figure 4.2.1. Distribution of Participant Age and Sex by Clinical Status. Bar charts displaying the percentage of participants within specific age groups for healthy controls (HC) and those with mild cognitive impairment (MCI), separated by sex (male and female).

Patient Selection and Diagnosis

Mild cognitive impairment (MCI) has commonly been used to describe the intermediary stage between normal cognitive aging and dementia (Albert et al. 2011). It can be defined as a decline in cognitive abilities that is greater than what is typical for a person's age and educational background (1−1.5 standard deviations below normative expectations) but does not meet the criteria for a diagnosis of dementia (Winblad et al. 2004). MCI was diagnosed using a combination of methods including clinical evaluation, cognitive testing, and medical history. The clinical evaluation was conducted by a geriatric psychiatrist or a neurologist, who assessed the participant's cognitive and functional abilities using standardized tools. Cognitive testing was performed using a battery of neuropsychological tests that measured various cognitive domains such as memory, attention, and executive function. Medical history was obtained through a structured interview and review of medical records. Participants were classified as having MCI if they had a Clinical Dementia Rating scale <= 0.5. Additionally, individuals with subjective reports of decline by self and/or informant in conjunction with objective cognitive deficits were also included in the MCI group. Healthy controls were screened for cognitive impairment using the same methods as MCI participants. They were classified as healthy controls if they scored within normal limits on cognitive tests and had no history of cognitive decline or functional impairment.

All participants with memory impairment were classified as having amnestic mild cognitive impairment (aMCI) at the moment of enrollment. During the study, two participants were reclassified as a non-amnestic MCI (naMCI), one was diagnosed with Alzheimer's disease (AD) upon re-assessment, and one was diagnosed as having Autism Spectrum Disorder (ASD) in addition to memory impairments. Of the 21 individuals who were classified as aMCI, 10 exhibited deficits only in the memory domain (aMCI Single), and 11 exhibited deficits in multiple domains (aMCI Multiple), such as executive function, language, or visual reasoning (Ronald C. Petersen 2003).

Adaptive Memory Assessment

Weekly at-home assessments were completed with the online adaptive fact-learning system (AFLS) described in Sense et al. (2016). This system continuously estimates the individualized *Speed of Forgetting* values in real-time as the participant works through the lesson. The software was designed so that participants could perform the task from home using any mobile device (Fig. 4.2.2). The AFLS works by presenting new study pairs (e.g., "Image of Fettuccine" / Fettuccine) and scheduling repeated tests (e.g., "Image of Fettuccine / ?") at strategic points based on the online estimates of a user's *SoF*.

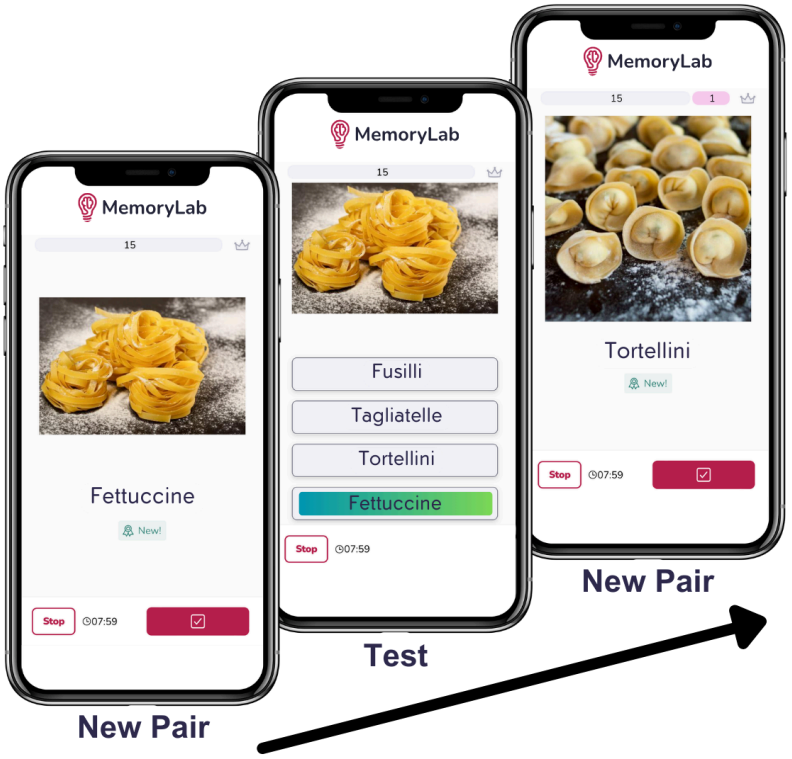

Figure 4.2.2. Interface of the MemoryLab recognition task. Test probes included only the cue of a pair; participants responded by selecting one of four options on a screen.

Study Materials

Fifty-three lessons were prepared in advance, spanning different topics (such as European capitals, Swahili words, Asian flags, bird species, types of pasta, and flower species (Fig. 4.2.3). The materials were vetted before the experiment to make sure they were comparable in terms of familiarity and difficulty with pilot beta testing. For each lesson, 15 different pairs were created, each of which associated an object with an English noun. In half of the pairs, the object was presented as an image, and in the other half, the object was a word. The number of pairs studied in each lesson depended on the response times and errors of the individual.

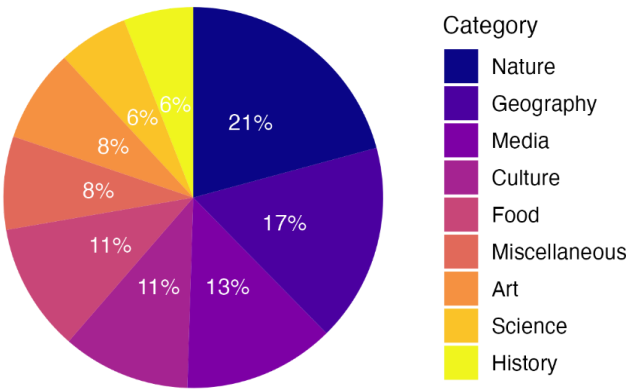

Figure 4.2.3. Pie chart shows the distribution of lessons into nine categories.

Data Processing

The repetition, activation, and *SoF* values for each fact item were calculated using functions from the AFLS. The average *SoF* values for each lesson and the individual were calculated by using the terminal φ value of each pair at the very last repetition of that term. The data was then filtered to only contain the first full session of a topic (>6 min). This was needed to eliminate any superfluous sessions (some participants desired to complete the task more than once). The data was also organized by the week the lesson was completed to view temporal trends. Behavioral data were assessed for outliers defined as being outside of 2.5×SD of the mean and were

subsequently excluded from analysis. Further statistical analysis was performed in R (v4.2.2) using the R Studio GUI (version 2022.7.2.576).

4.3 Results

In our study, 24 individuals diagnosed with mild cognitive impairment (MCI; 5 female) and 27 age-matched controls (19 female) participated in weekly assessments. These assessments were conducted through the AFLS website, allowing participants to engage remotely with a computer, tablet, or smartphone (Fig. 4.2.2). The assessments, termed "lessons" or "memory games", covered an array of topics such as Nature, History, Science, Art, Geography, Media, Food, and Culture, providing a diverse range of facts for memorization (Fig. 4.2.3). The content was presented as cue-response pair associates, with responses provided through multiple-choice options or verbal recall. Throughout the study, participants completed up to 49 multiple-choice recognition sessions and four quarterly verbal recall sessions. The verbal recall sessions were conducted online using a video conferencing platform, with vocal responses automatically translated through Google's speech-to-text software, and subsequently checked by trained assistants.

4.3.1 Reliability of the *Speed of Forgetting*

***Speed of Forgetting* Shows Reliable Patterns Across Different Cognitive Materials**

Our findings demonstrated that the *Speed of Forgetting* (SoF) remained consistent over time, corroborating earlier observations by Sense et al. (2016). Among the 51 subjects who completed >35 lessons, the SoF metrics showed a range from the lowest individual score of 0.23 to the highest individual score of 0.54 (Fig. 4.3.1A). This range, reflecting the full spread of SoF values across all participants and lessons, aligned with a normal distribution pattern. The lesson means for SoF ranged from 0.36-0.41 with a mean of 0.39 (SD = 0.0129). Although lesson averages showed limited variation from their respective means, there were slight differences in the SoF across various cognitive materials. This variability was more pronounced in some participants than others, implying that specific materials might be less memorable for certain individuals. Nevertheless, the reliability of the SoF parameter was confirmed by its test-retest reliability. Across all pairs of lessons, the SoF exhibited a mean Pearson correlation coefficient of $r = 0.70$, indicating consistent inter-lesson correlations (Fig. 4.3.1B, C). The reliability across different materials not only validates the SoF measure but also highlights its potential for repeated assessments in future studies.

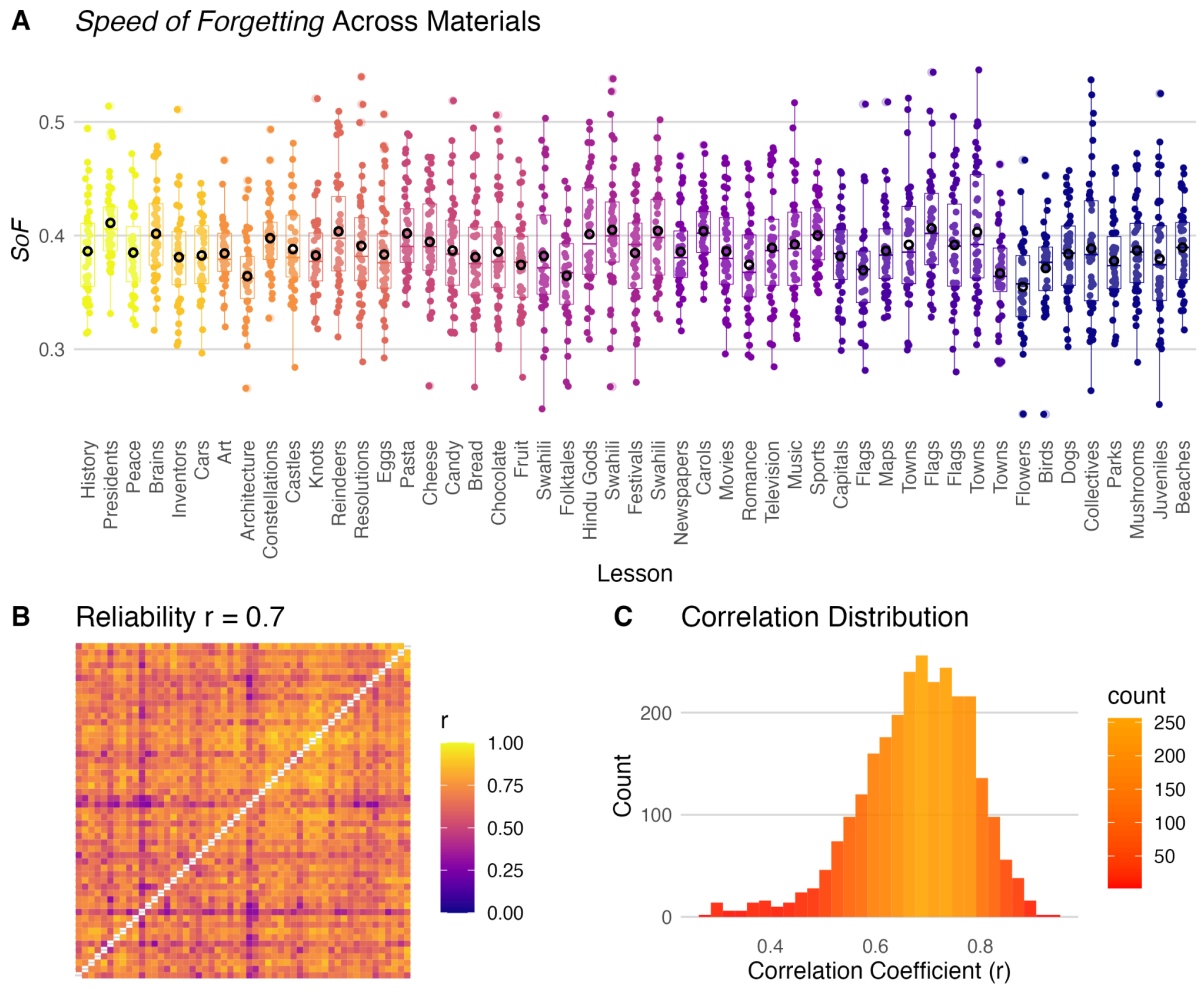

Figure 4.3.1. Analysis of *Speed of Forgetting* Across Diverse Categories. (A) Materials. Scatterplot with the horizontal axis representing individual participant *Speeds of Forgetting* (SoF) and data points colored by category. **(B)** Reliability of SoF. The heatmap represents the Pearson correlations between the individual SoF values of different lessons. The mean correlation coefficient (r) is 0.7. **(C)** Correlation Distribution. Histogram displaying the distribution of correlation coefficients from heatmap in B.

4.3.2 Group Differences in the *Speed of Forgetting*

Speed of Forgetting Reveals Clear Differences in Cognitive Performance Between MCI and Healthy Individuals

Next, we examined whether patients diagnosed with mild cognitive impairment (MCI) would exhibit significantly higher SoF values than age-matched healthy controls. On average, MCI patients exhibited markedly higher SoF values than healthy controls, with healthy controls demonstrating a mean SoF of 0.37 +/- 0.02, notably lower than MCI patients' mean SoF of 0.42 +/- 0.02 (Welch's $t = 47.65$, $p < 0.0001$) (Fig. 4.3.2A-C).

Further analysis using a mixed linear model, which explained 56% of the variance, showed a significant main effect of diagnosis, with the MCI group displaying consistently higher SoF values ($\beta = 0.34$, $p < 0.001$). The time course of the study was examined by including both linear and quadratic terms for time in the model. While the linear progression of weeks did not significantly impact SoF ($\beta = -0.03$, 95% CI [-0.15, 0.08], $p = 0.588$), the quadratic term approached significance ($\beta = 0.08$, 95% CI [-0.02, 0.17], $p = 0.107$), indicating a potential nonlinear effect of time on SoF. Notably, the interaction between MCI diagnosis and the quadratic time term was significant ($\beta = -0.14$, 95% CI [-0.26, -0.03], $p = 0.015$), suggesting a stronger nonlinear pattern of memory decline over time in MCI patients (Fig. 4.3.2D).

In addition to the main effects, age (β = 0.0016, $p < 0.005$) and sex (β = 0.020, $p = 0.02$) were significant factors influencing SoF, with older age and male sex linked to an increased rate of forgetting. The interaction between MCI status and age was also significant (β = -0.004580, 95% CI [-0.00519, -0.00397], $p < 0.001$), indicating that age modifies the relationship between MCI and SoF, albeit with a minimal effect size.

Finally, to explore our approach's ability to parse out the nuances in cognitive deficits, we categorized the MCI participants into distinct MCI subtypes based on their initial diagnosis: amnestic, with deficits in a single domain (aMCI S), amnestic with deficits in multiple cognitive domains (aMCI M), and non-amnestic with deficits in a single domain (naMCI S). Both amnestic subtypes exhibit impairments in memory, whereas the naMCI subtype demonstrates intact memory functionality (Ronald C. Petersen 2003). A Kruskal-Wallis rank sum test revealed significant SoF discrepancies between subtypes ($\chi^2(4) = 480$, $p < 0.001$), with pairwise comparisons indicating lower SoFs in healthy controls versus all MCI subtypes and distinctive SoF values among MCI subtypes (Fig. 4.3.2E). These findings elucidate that naMCI S individuals demonstrate cognitive abilities that lie between those of healthy controls and MCI patients, consistent with a diagnosis of MCI but largely preserved memory functions.

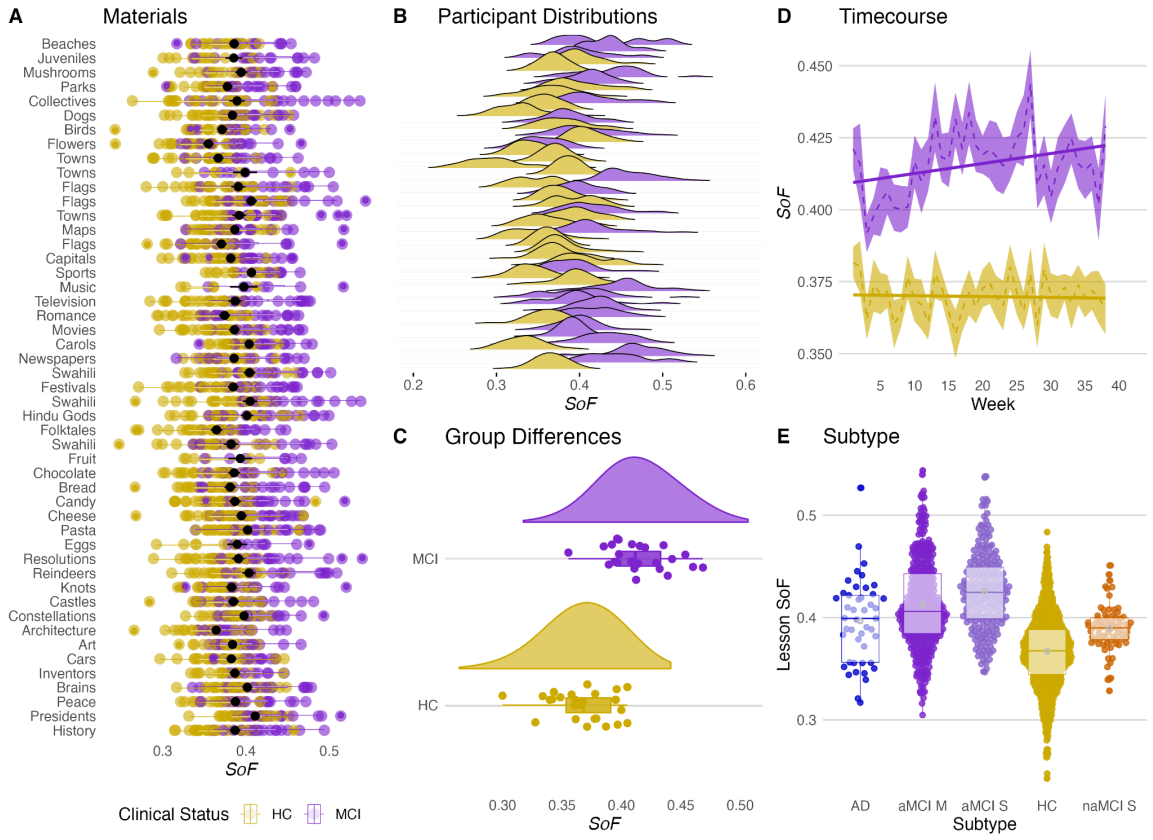

Figure 4.3.2. *Speed of Forgetting* Reveals Clear Differences in Cognitive Performance Between MCI and Healthy Individuals. (**A**) Materials. Scatterplot with the horizontal axis representing *Speed of Forgetting* (SoF), color-coded by clinical status: Healthy Control (HC) and Mild Cognitive Impairment (MCI). (**B**) Participant Distributions. Ridge plots illustrate the distribution of SoF among participants for all recognition lessons they completed. (**C**) Group Differences. Rain plots showing group differences in SoF between HC and MCI, indicating distinct memory retention capabilities between the groups. (**D**) Timecourse. Line graph displaying the time course of SoF over 40 weeks, with shaded areas representing 95% confidence intervals, for both HC (yellow) and MCI (purple) groups. (**E**) Subtype. Beeswarm plots for AD (dark blue; n = 1), aMCI M (dark purple; n = 11), aMCI S (light purple; n = 10), HC (yellow; n = 27), and naMCI (orange; n = 2), with each point reflecting an individual lesson. Median and quartiles are summarized by boxplots, and data density by violin plots.

4.3.3 Clinical Validity of the *Speed of Forgetting*

***Speed of Forgetting* as a High-Validity Diagnostic Tool for Cognitive Impairment**

To evaluate SoF as a diagnostic tool for cognitive impairment, we first compared it to the Montreal Cognitive Assessment (MoCA), the most commonly used screening questionnaire for MCI diagnosis (Nasreddine et al. 2005). As expected, we found a pronounced negative correlation ($r = -0.71$, $p < 0.0001$) between MoCA scores and SoF, confirming the predictive validity of SoF as a clinically applicable cognitive performance metric (Fig. 4.3.3.1A).

Next, we quantified the probability of MCI diagnosis given a participant's SoF values by binning results from individual sessions, using bins ranging from 0.25 to 0.55 in increments of 0.025. For each bin, we computed the proportion of scores coming from MCI individuals. Our analysis revealed that the probability of an MCI diagnosis grows as a logistic function of SoF, with an inflection point at 0.40 (Fig. 4.3.3.1B, red dotted line). A logistic model fitted to the data accounted for 42% of the variance in diagnosis probability.

We further scrutinized the diagnostic precision of SoF by employing it as a binary classifier between healthy controls (HC) and MCI cases. Receiver Operating Characteristic (ROC) analysis incorporating SoF measurements from approximately 2000 individual sessions revealed that a single-session SoF can achieve a classification accuracy of 85% (Fig. 4.3.3.1C). In a related study, automated telephone cognitive self-tests demonstrated an ROC classification accuracy of 75-78% for distinguishing between MCI and dementia from subjective cognitive decline, underlining the potential of remote screening methods in early diagnostic processes (Van Mierlo et al. 2017).

Comparatively, SoF outperformed isolated behavioral metrics derived from the AFLS, including accuracy and response time, emphasizing the added value of a model-based interpretation of data. It is important to mention that comparing SoF with accuracy and response time in this paradigm can pose challenges due to their common origin in the AFLS. This can lead to inflated accuracies and response times that could skew comparative analyses. Despite this, however, the superior performance of SoF underscores its utility as a dependable measure for detecting cognitive impairment.

Finally, we explored the impact of multiple assessments on classification accuracy. While participants' total mean SoF across all 49 recognition sessions indicated a higher diagnostic accuracy of 94% (Fig. 4.3.3.1D), ROC curves generated by starting with the first session and progressively averaging more sessions (up to 10) revealed peak predictive accuracy at four assessments (Fig. 4.3.3.1E). This key finding suggests that only four assessments are needed to achieve the same level of classification accuracy as all 49 recognition assessments.

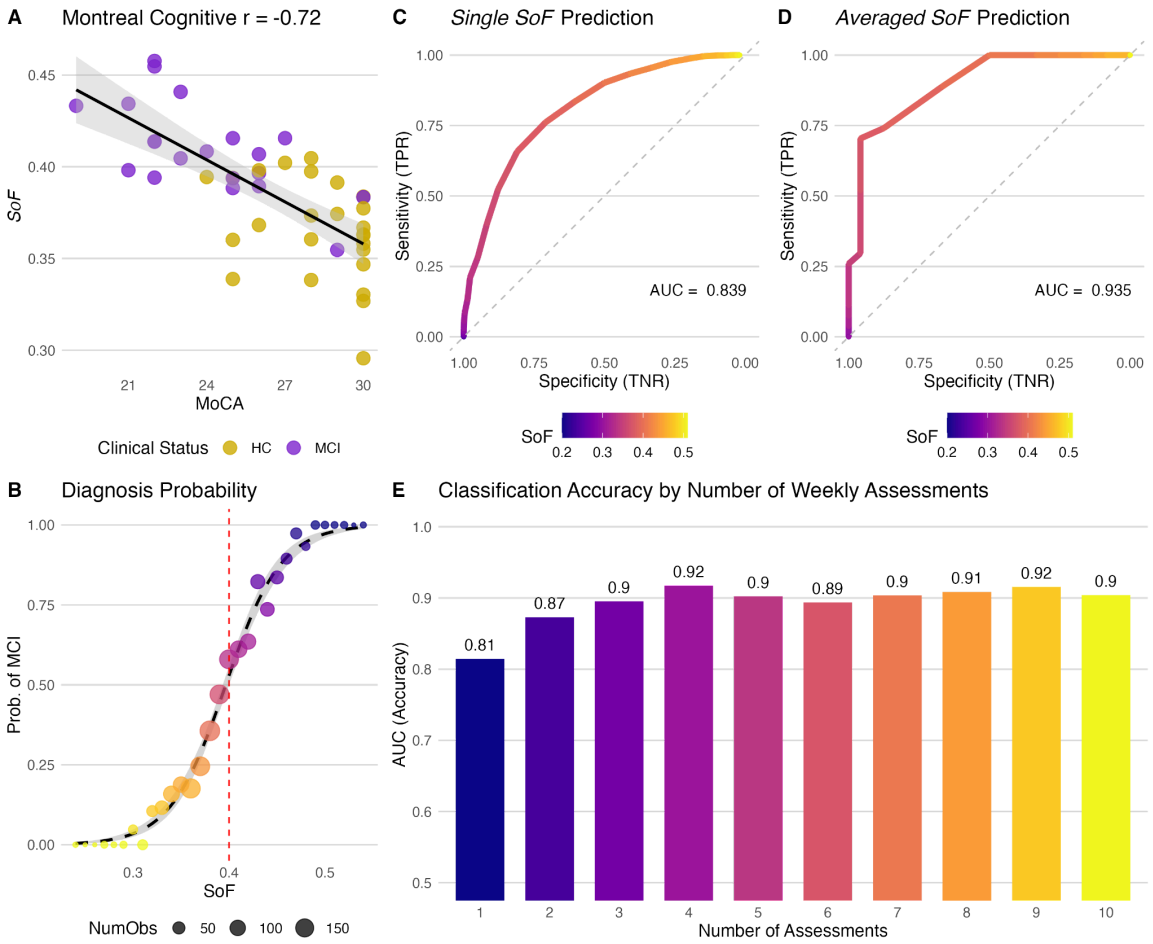

Figure 4.3.3.1 *Speed of Forgetting* as a High-Validity Diagnostic Tool for Cognitive Impairment. (**A**) Gold Standard. Scatter plot correlating *Speed of Forgetting* (SoF) with Montreal Cognitive Assessment (MoCA) scores, showing a significant negative correlation (r = -0.71). (**B**) Diagnosis Probability. Sigmoid curve correlating SoF scores with the likelihood of MCI diagnosis, where point size indicates the number of observations contributing to each data point. The red dashed line indicates the threshold at which the probability of MCI exceeds 50% (SoF = 0.388). (**C**) ROC curve for predicting cognitive status using a single SoF recognition measurement, with the area under the curve (AUC) demonstrating the model's accuracy, and individual points representing varying SoF thresholds. (**D**) Improved prediction model using the average SoF, as shown by higher AUC values, suggesting better performance with aggregated SoF data. (**E**) Multiple ROC curve AUC values represent the accuracy of predictions based on the number of recognition assessments, illustrating the incremental benefit of repeated measurements.

Recall Tests Confirm *Speed of Forgetting* Captures Consolidation Rather than Retrieval Processes

In an additional analysis, we examined the recall sessions in contrast with the recognition sessions to ascertain the underlying memory processes (Fig. 4.3.3.2 & 4.3.3.3). The rationale behind this comparison is that recall paradigms are typically harder for participants and pose additional executive function demands to control the retrieval process. Thus, if SoF values were tracking the retrieval rather than the consolidation process, we would expect higher SoF values in the recall sessions. Instead, we observed significantly *lower* SoF values in recall compared to recognition (paired $t(45) = -10.90$, $p < 0.0001$), aligning with the notion that, while free verbal recall may be more difficult, recall tests facilitate better encoding through deeper information processing (Moscovitch and Craik 1976).

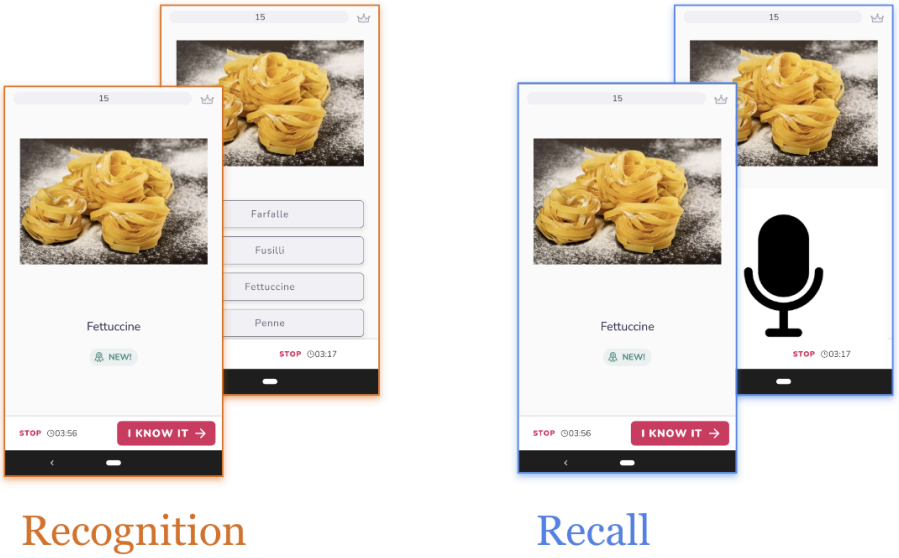

Figure 4.3.3.2. Recognition format included 4 multiple-choice options. Recall format recorded vocal responses translated through Google's speech-to-text software.

Using a random slope mixed linear model, incorporating clinical diagnosis and test type as factors, we noted a significant interaction between test type and diagnosis ($p < 0.001$). Specifically, individuals with MCI showed diminished benefits from recalling items compared to healthy controls. Despite theoretical distinctions between recall and recognition memory (Ranganath and Paller 2000), SoF values exhibited a strong correlation across all participants for both test types (Pearson $r(44) = 0.86$, $t = 11.34$, $p < 0.0001$), suggesting a common mechanism of memory consolidation processing, rather than retrieval mode specificity.

Further analysis of SoF′s diagnostic ability for recall sessions revealed comparable classification accuracy to recognition SoF, as indicated by ROC AUC values of 88-93% (Fig. 4.3.3.3D-F). The slightly higher AUCs in recall sessions likely stem from increased separation between MCI and healthy controls. This consistency between recall and recognition assessments underscores the robustness of SoF in capturing memory consolidation processes and its consistent diagnostic utility across different memory retrieval modes.

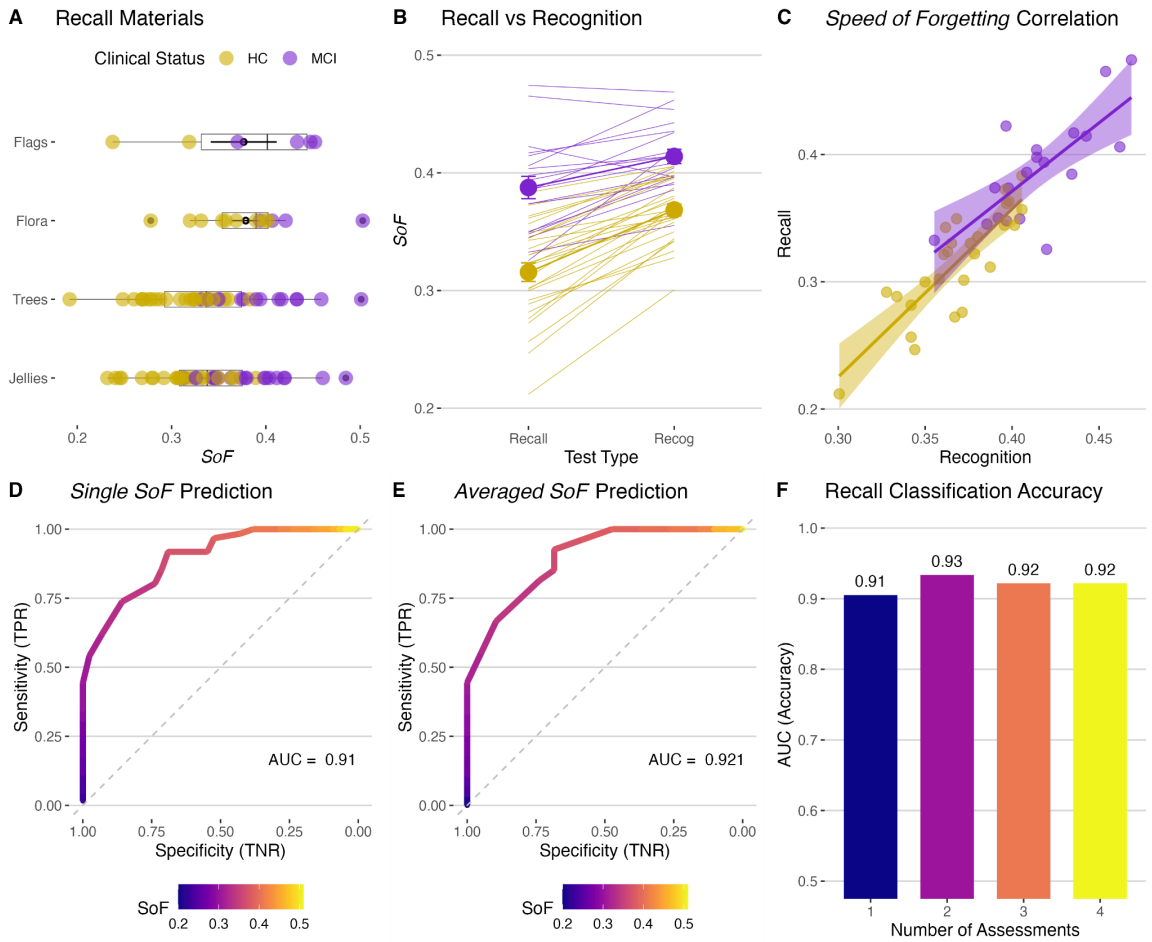

Figure 4.3.3.3. Comparative Analysis of Recall and Recognition Memory Performance. (**A**) Recall Materials. Boxplots contrasting individual performance on memory tasks, stratified by lesson topic and clinical status (MCI in purple, HC in yellow), horizontal axis represents *Speed of Forgetting* (SoF). (**B**) Recall vs Recognition. Lines connect participant mean recall SoF versus mean recognition SoF. (**C**) Correlation. Scatter plot depicting the relationship between recognition and recall performance, stratified by clinical status, shaded area represents 95% confidence interval. (**D**, **E**) ROC curves assessing the single- and average-measurement diagnostic accuracy of SoF for cognitive status, with the area under the curve (AUC) reflecting model precision. (**F**) Bar graphs depicting AUC values for multiple ROC curves, demonstrating the predictive accuracy based on the number of SoF assessments.

4.3.4 Longitudinal Trajectory in the *Speed of Forgetting*

The *SoF* as a marker for cognitive decline was longitudinally tracked across the varied clinical diagnoses (Fig. 4.3.4). Weekly measurements were fitted to both linear (Fig. 4.3.4A) and nonlinear (Fig. 4.3.4B-C) statistical models, capturing individual and group-level timecourse trends. HC individuals exhibited a relatively stable *SoF*, implying a uniformity in memory retention throughout the observed period. Conversely, those with MCI and AD showed more marked increments in *SoF,* indicative of a hastened cognitive decline. Nonlinear modeling, using a polynomial regression for fitting, revealed considerable inter-individual variability in *SoF* trajectories. The single participant with AD exhibited the highest variability in *SoF*, followed by the aMCI S and M subtypes (Fig. 4.3.4C). The HCs showed the least variability, suggesting a more uniform retention of memory over time.

The time-dependent evolution of the *SoF* was elucidated by incorporating both linear and quadratic terms in our mixed-effects modeling to capture the trajectory over the study's duration. The linear component of time did not yield a significant influence on *SoF*, with the coefficient estimate showing a negligible decrease per week (β = -0.03, 95% Confidence Interval [CI]: [-0.15, 0.08], p = 0.588). This lack of linear trend suggests that changes in SoF are not consistent over time but may vary in a more complex manner.

In contrast, the quadratic term for time provided evidence of a nonlinear relationship with *SoF*. The interaction between the diagnosis of MCI and the quadratic term for time was significant (β = -0.14, 95% CI: [-0.26, -0.03], p = 0.015). This interaction signifies that the rate of change in *SoF* for MCI patients is not uniform; rather, it varies quadratically over time, suggesting that the speed of cognitive decline in MCI patients may increase or decrease at a different rate as time progresses. Specifically, the negative value of the interaction term implies that the initial rate of forgetting may be slower in MCI patients compared to healthy controls, but over time, this rate increases more rapidly for those with MCI.

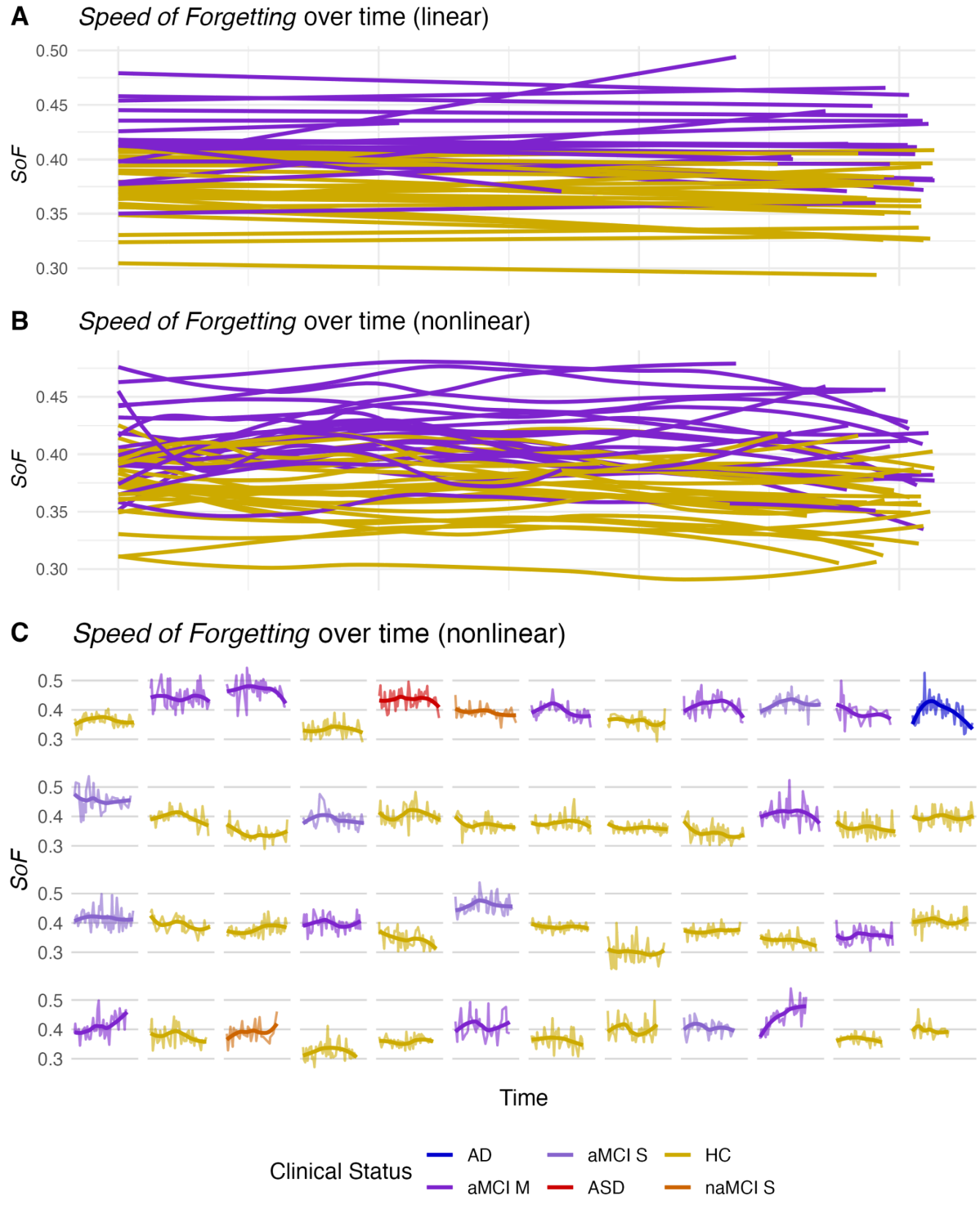

Figure 4.3.4. Longitudinal Analysis of the *Speed of Forgetting* Across Different Clinical Groups. (A) Linear Modeling of SoF Trajectories. Weekly *Speed of Forgetting* (SoF) fitted to a linear model over time. Time for

every plot corresponds to a full year. Subjects are color-coded by clinical status (MCI in light and dark purple, HC in yellow). **(B)** Nonlinear Modeling of SoF Trajectories. Each line represents a fitted nonlinear trend for individual participants' SoF over time, highlighting variability in forgetting rates. Lines are derived using a smoothing algorithm automatically selected based on data structure and count, optimizing fit without predefined assumptions about the data's underlying pattern. **(C)** Nonlinear Modeling of Individual Trajectories. Subplots colored by clinical status, highlighting variability within and across conditions among Alzheimer's disease (AD), amnestic MCI single domain (aMCI S), Healthy Control (HC), amnestic MCI multiple domain (aMCI M), Autism Spectrum Disorder (ASD), and non-amnestic MCI single domain (naMCI S).

4.4 Discussion

This study introduces a model-based, online assessment as a novel approach for diagnosing and monitoring memory impairments, such as mild cognitive impairment (MCI). By implementing a computational model that dynamically adjusts to individual forgetting patterns—captured through the novel metric, the *Speed of Forgetting* (SoF)—we have developed a more personalized solution for early memory impairment detection. Our methodology not only addresses various limitations of traditional neuropsychological assessments but also offers enhanced efficiency and scalability, particularly in handling large-scale data collection, making it a versatile tool for seamless widespread implementation.

Speed of Forgetting as a Novel Memory Metric

The SoF, central to our findings, emerges as a robust metric for memory decline, validated across a variety of cognitive materials and memory assessments. Its high test-retest reliability substantiates its role as a reliable measure of memory function, while its clarity and interpretability render it a valuable asset for both clinical and research applications.

The study design, spanning weekly assessments over a six-to-twelve-month period, provided unique insights into the trajectory of cognitive decline in MCI, crucial for identifying and intervening in early-stage neurodegenerative conditions. The well-established understanding that ‘forgetting’ follows a non-linear process, as emphasized by Newell and Rosenbloom (1990), adds a layer of complexity to the interpretation of these scores. The statistical analysis of MCI interaction with time illustrated a complex, nonlinear relationship (β = -0.14, p = 0.015), suggesting a decline in memory with patterns that change over time. A nuanced examination of time as a variable revealed that SoF did not strictly adhere to a linear progression, instead exhibiting significant nonlinear patterns. The interaction terms further highlighted the differential impact of time on SoF across clinical conditions. The substantial variability in individual participant trajectories, especially within clinical groups, underscores the relevance of the quadratic term. This term captures the essence of the nonlinear progression in cognitive decline, which is not immediately apparent from the linear analysis alone. The overall patterns suggest a more rapid and complex progression of memory decline in clinical groups compared to healthy individuals. These findings emphasize the importance of long-term monitoring to understand the dynamic nature of cognitive decline, which may exhibit phases of relative stability interspersed with periods of rapid deterioration, particularly in pathological conditions like MCI and AD.

Our study also offers a granular look at MCI subtypes. The differential cognitive profiles within MCI subgroups, especially highlighted in non-amnestic MCI individuals with memory processing intact, suggest a more intricate understanding of MCI. Such specificity in diagnosis is particularly relevant given the heterogeneity of neurodegenerative diseases like AD and the need for assessments that transcend traditional reliance on verbal memory metrics.

The *SoF*'s diagnostic accuracy—85% for single sessions and 94% for multiple sessions—strongly advocates for its adoption into clinical practice. Moreover, SoF's design for remote administration is timely, paralleling the rise of telehealth solutions and meeting the demand for accessible cognitive assessment tools in the global pivot towards digital health services for patient care and monitoring.

Comparison to Other Cognitive Assessments

When comparing our SoF-based method with the Montreal Cognitive Assessment (MoCA; (Nasreddine et al. 2005)), SoF not only matches the accuracy of MoCA but also advances the field in terms of test administration and frequency. This is particularly notable due to the potential risks associated with using brief cognitive screening tools, such as overdiagnosis and underdiagnosis, especially when relying solely on a single diagnostic test (Brodaty et al. 2017; Ranson et al. 2019). Moreover, repeated measuring using SoF offers a unique advantage, particularly in tracking cognitive fluctuations, such as "lucid days," which may not be effectively

captured by single assessments. These fluctuations provide valuable insights into the dynamic nature of cognitive functioning and aid clinicians and researchers in understanding the progression of cognitive disorders over time. Additionally, while brief assessments like the MoCA excel in identifying substantial cognitive impairments, they may overlook early or subtle deficits and struggle to determine their underlying causes. Furthermore, comprehensive neuropsychological evaluations, although considered the gold standard, are often unavailable in community-based or primary care settings.

Underlying Memory Processes

A crucial evaluation of our model revolved around whether the *SoF* parameter could form similar predictions for both recognition and recall memory. In one scenario, we would anticipate a higher *SoF* for the recall condition (due to increased error rates), while in the other, we would expect it to be lower (attributable to enhanced encoding). To validate this prediction, we included a recall version of the assessment where recognition options were omitted, and responses were recorded via a voice-activated microphone.

In our investigation into recall versus recognition memory processes, we observed lower *SoF*s in recall conditions, reinforcing the idea that recall tasks, while more challenging, enhance memory encoding and retention (Moscovitch and Craik 1976). These findings are consistent with established literature and affirm the memory processes in our model, as evidenced by the substantial correlation between *SoF* values from recall and recognition trials (Pearson $r = 0.85$, $p < 0.001$). The fact that recognition is equally effective as recall in diagnosing MCI is beneficial because the recall versions are more difficult to administer remotely.

Limitations and Considerations

While the study demonstrates the effectiveness of the adaptive fact-learning system in detecting memory impairments, it also reveals certain limitations. First, the *Speed of Forgetting,* in essence, measures what we believe to be the speed of "passive" forgetting. Passive forgetting, i.e. the loss of information over time due to the passage of time rather than a deliberate attempt to forget, could be due to loss of context clues, retrieval interference from other similar memories, and "natural" biological decay (Davis and Zhong 2017). Critically, some of these processes are accelerated in aging (Shuai et al. 2010) and abnormally elevated in amnestic dementias, such as AD. More research is needed to determine which of these passive mechanisms is most closely linked to this parameter.

However, it is important to note that a similar criticism can be made of other existing assessments. They all operate at the level of observable performance, so compared to them, our study takes a step further in the direction of mechanistic explanations of performance. By focusing on the 'forgetting' process, we delve into the underlying mechanisms contributing to memory decline, which provide valuable insights beyond mere performance metrics and could thus be used to examine existing debates in the field regarding the contributions of various biological processes.

Second, while the *SoF* model parameter is theoretically independent of the assessments used in this study and can be adapted to data from other memory assessment tools, it remains tethered to a specific model of episodic memory. This underlying computational model is derived from a Bayesian analysis of memory (John R. Anderson 1990) combined with the Multiple Trace Theory (Nadel et al. 2000) and is just one conceptual framework for understanding memory, not the sole model.

Third, while our model shows promise in assessing early memory impairment, it has not been tested on participants with dementia. This is a significant limitation, as dementia presents unique challenges in cognitive functioning that may not be adequately captured by the model's current capabilities. Additionally, like any test, there are limits to the applicability of our model across diverse patient populations. Patients must still be able to perform certain basic tasks for the model to effectively assess memory impairment. Factors such as motor skills, language comprehension, and attention span may impact the utility of the model in accurately assessing cognitive decline. However, it is worth mentioning that in the analysis of language-impaired non-amnestic MCI patients, *SoF* emerged as a more precise measure of memory impairment, suggesting it can still provide valuable insights for certain subsets of conditions.

Overall, further refinement and validation of the model in diverse populations is crucial for enhancing its clinical utility and reliability.

Future Directions and Applications

Despite these limitations, the *Speed of Forgetting* emerges as a reliable and highly valid metric for diagnosing cognitive impairment, surpassing traditional assessment tools in utility due to its online, unsupervised nature and

adaptability for frequent use. These findings hold promising implications for the field of computational psychiatry and for the broader community. This paradigm can facilitate the collection of reliable data from populations that are often underrepresented in research and lack easy access to professional clinical assessment, including ethnic, racial, and linguistic minorities, as well as individuals residing in rural, low-income, or remote regions.

The remarkable repeatability and stability of the SoF model parameter position it as an exceptional tool for evaluating the effectiveness of interventions such as newly FDA-approved immunotherapies ("Lecanemab Approved for Treatment of Early Alzheimer's Disease," n.d.), and other neuromodulation tools and cognitive enhancers. Furthermore, by integrating the *SoF* model with neuroimaging data, it is possible to uncover the underlying neural mechanisms responsible for memory decline in aging and disease. Recent studies by Zhou et al. (2021) and Xu et al. (2021) have demonstrated this approach utilizing previous iterations of the SoF task to analyze differences in functional connectivity networks and pinpoint specific brain regions correlated with forgetting.

Lastly, the *SoF*'s ability to track memory changes over time is particularly valuable for the early detection of MCI, crucial in delaying the onset of Alzheimer's Disease and related conditions. These combined attributes establish the SoF memory metric as a potent tool in both research and clinical practice.

5. Expansions

5.1 Lifespan of *Speed of Forgetting*

Parts of this section on lifespan have been submitted as a paper to the 2024 Cognitive Science Society conference.

Model-Based Characterization of Forgetting in Children and Across The Lifespan

Abstract

To fully understand human memory, it is necessary to understand its lifespan development. However, memory assessments often rely on significantly different methodologies for different age groups, and their results are typically not directly comparable. In this section, we present a quantitative assessment of memory function spanning an age range of five to 85 years that is based on the model-based memory assessment. This approach yields a uniform metric that is directly interpretable and can be compared across different tasks and materials that are appropriate for different age groups. The results show a robust U-shape function, with long-term memory function at age 5 being comparable to that of cognitively impaired elderly individuals. These results and the method utilized could provide a new foundation for future studies on memory development across life stages.

5.1.1 Introduction

Understanding how memory evolves throughout the lifespan is essential for a comprehensive grasp of human memory. Despite numerous studies, a detailed quantitative analysis that traces memory function from early childhood through senior adulthood has yet to be conducted. As discussed in Chapter 2 Understanding Memory Impairments, traditional memory assessments typically depend on tools like the Mini-Mental State Evaluation and the WAIS-R. These instruments measure accuracy scores from tests administered after specific intervals, which may not fully capture the nonlinear nature of forgetting—a complexity noted by researchers such as Sherman and Hrabok (2023) and Loftus (1978).

In this study, we employ the Speed of Forgetting (SoF) values, calculated through a model-based assessment, as a robust indicator of memory function across different age groups. This measure, with its clear mathematical interpretation, overcomes the limitations of traditional tests, enabling direct comparisons of memory performance across diverse demographic cohorts. Although over 30 million study trials have been conducted using the AFLS (memorylab.nl), this has predominantly been completed in college students. This dissertation expands these methodologies to examine SoF scores across a wider age range, marking a first in such extensive coverage.

Furthermore, our data collection across the lifespan allowed us to delve into memory development during childhood—a crucial period for cognitive growth. Previous research suggests that preschoolers can develop rudimentary episodic memories as early as 3 years old (Hayne and Imuta 2011), with notable advancements between three to five years (Saragosa-Harris et al. 2021). However, these studies did not utilize model-based techniques, raising questions about the potential influence of concurrent cognitive function development. In response, we adapted our model-based assessments to include non-verbal stimuli specifically designed for young children, aiming for a more precise evaluation of episodic memory in this age group.

Experimental Hypotheses

1. **Children (Aged 5):** We expect higher SoF values, indicative of the rapid development and relative inefficiency of their cognitive processes.
2. **Early Adults (Aged 18-29):** This group is anticipated to show lower SoF values, reflecting stable memory retention due to mature cognitive systems and advanced memory strategies.
3. **Middle to Senior Adults (Aged 30+):** We predict an increase in SoF values with age, especially among those with cognitive impairments, underscoring the impact of both normal and pathological aging on memory decay.

5.1.2 Methods

Our sample includes ***Early Childhood,*** represented by children aged 5, examining the nascent stages of cognitive development; ***Early Adulthood,*** represented by young adults aged 18-29, typically seen as the peak of cognitive maturity; ***Middle and Mature Adulthood*****,** represented by adults aged 30-64, providing insight into memory retention during working and late adult life; ***Senior Adulthood*** **and** ***Senior Adulthood (Impaired)*** represented by individuals aged 65 and above, both with and without cognitive impairments, to investigate the impact of aging and early cognitive decline on memory function.

Participants

This study incorporated data from 210 participants, aggregated from six distinct research projects executed within our laboratory during the previous year. For inclusion in the study, control participants had to meet the following criteria: (1) age in the range of 18 to 85 years, (2) proficiency in English, and (3) the absence of major medical or psychiatric conditions that could potentially interfere with cognitive performance. For our memory impairment group, they had to meet the following criteria: (1) age in the range of 55 to 85 years, (2) proficiency in English, (3) have a diagnosis of MCI, and (4) be recruited from the Alzheimer's Disease Research Center (ADRC). All individuals involved in the study participated in a minimum of four sessions, with the senior participants engaging in 30 to 52 sessions each. Additionally, 19 five year olds were recruited from the local community. All participants exhibited typical development, with no diagnosed disabilities or language delays, and had regular exposure to, or fluency in, English. Of the 19 children recruited, four did not complete the task.

Adaptive Memory Assessment

An in-lab assessment was conducted using the adaptive fact learning system (AFLS), as detailed in Sense et al. (2016) and accessible at https://www.memorylab.nl/en/. This system dynamically estimates the *SoF* for each individual in real-time, adapting as the participant progresses through the learning module. The AFLS operates by initially presenting new image-image study pairs (for example, "Dinosaur / Environment") and then strategically scheduling repeated tests (such as "Environment" / Animal?") based on the real-time *SoF* estimates of the user. An illustration of the software interface is provided in Figure 5.1.2.

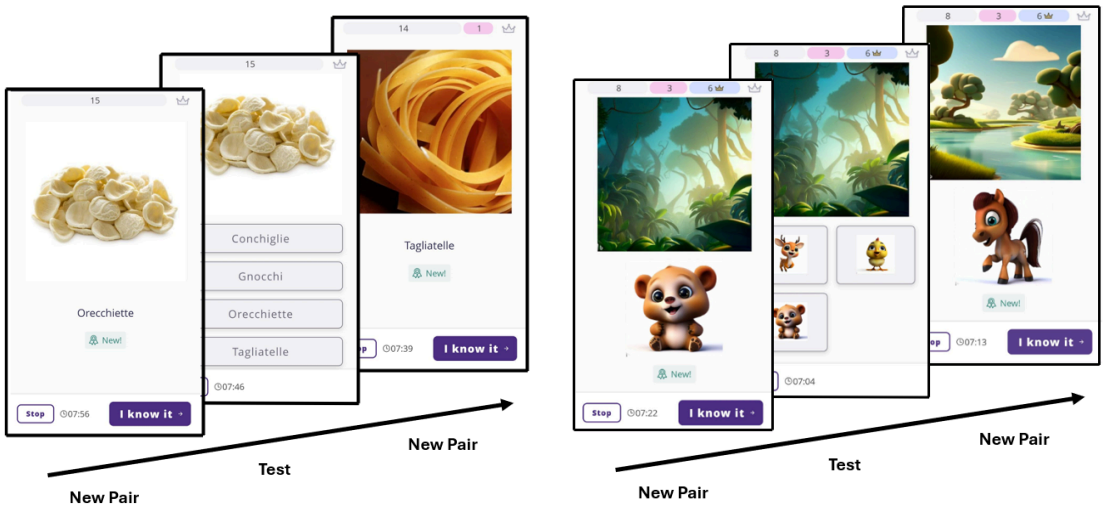

Figure 5.1.2. Left: Interface of the adaptive memory assessment for adults. **Right:** *Adapted* adaptive memory assessment.

Study Materials

The study materials were created with the goal of ensuring a balance between familiarity and difficulty. Utilizing AI-generated images from DALL·E, two tasks were developed: (1) an Introduction task, and (2) the Main Memory task. The images were generated using terms such as "3D render" and "in the style of Pixar movies". Figure 1 provides an illustration of the user interface and two example pairs. To engage the children, a narrative was introduced: *A meteorite has scattered animals worldwide and your task is to reunite them with their homes*. This setup involved pairing 17 unique animals with corresponding habitats. The selection of animals and environments varied to maintain interest (i.e. unicorns, dinosaurs, birds, underwater creatures, reptiles, horses, etc.).

Participants were shown the environment and associated animal, and then just the environment with three animal options as a test probe, as illustrated in Figure 1. To maintain engagement and tailor the task's difficulty, two of the animals were more logically associated with the given environment (e.g., "dolphin"/ "underwater" and "fish"/ "underwater"), while one was clearly incongruent (e.g., "unicorn"/ "underwater"). This design aimed to ensure the task was engaging but not overly challenging.

Participants were asked to play the game for eight minutes, requiring a minimum of six minutes of data collection to be able to assess *SoF*. The number of new pairs shown or old pairs rehearsed for each participant varied depending on the accuracy and reaction time collected from previous stimuli. This personalized approach was uniformly applied across all age groups, facilitating direct lifespan comparisons.

Data Processing

The introduction task, designed to familiarize children with the game, was excluded from the final analysis. In the main memory task, repetition, activation, and *SoF* values for each fact item were calculated using specific functions from the AFLS software package. The average *SoF* for each lesson and participant was determined from the final φ value of each pair at its last repetition. Data analysis was restricted to sessions lasting a minimum of six minutes, filtering out instances where children were unable to focus or complete the task for the required duration.

5.1.3 Results

Our analysis encompassed the age spectrum from early childhood to advanced age (Fig. 5.1.3.1). Stratifying the data into distinct age categories revealed clear trends. Children aged five exhibited mean SoF rates of φ = 0.42, akin to those observed in our senior participants diagnosed with MCI (φ = 0.41). A noticeable trend toward slower forgetting speeds was found among young adults aged 18-29, with a mean φ = 0.30. The data then revealed a gradual increment in SoF rates in the later years of life.

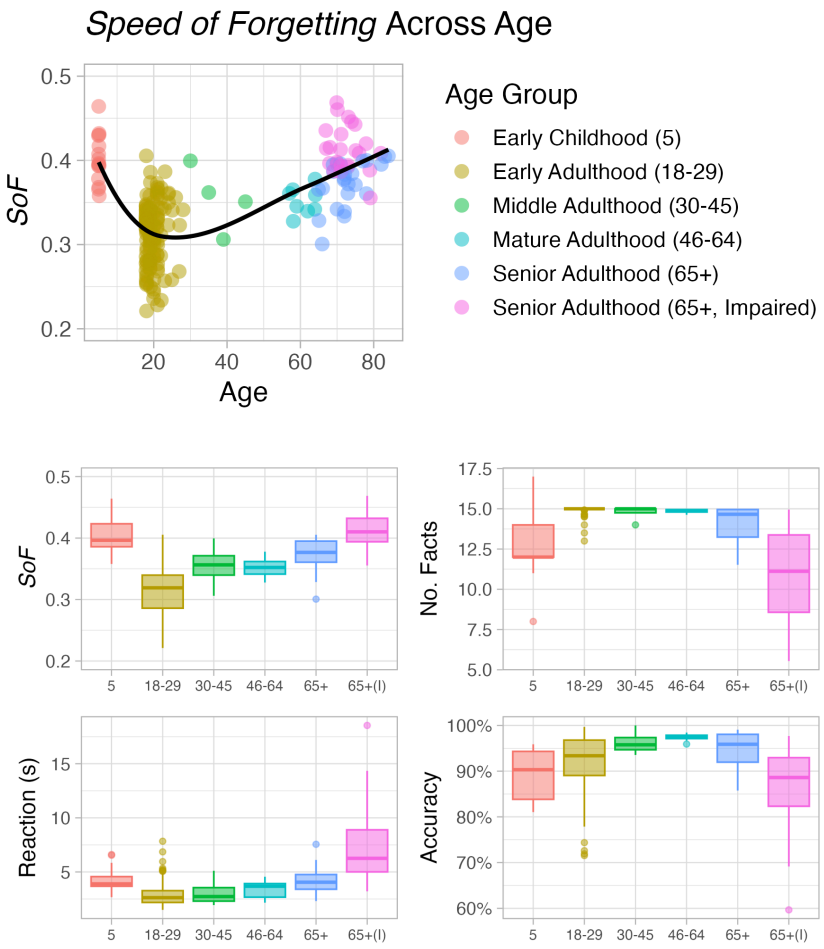

Figure 5.1.3.1. Comparative analysis of *Speed of Forgetting* (SoF) across age groups. Scatter plot depicting individual SoF values, revealing a U-shaped trend. Boxplots showing mean values across age groups for SoF, number of facts learned, reaction time (seconds), and accuracy (%). Note that our Mature Adulthood sample does not include ages 46 to 54.

This U-shaped trend was confirmed by fitting the data with a quadratic model of the form:

$$SoF \sim \beta_0 + \beta_1 Age + \beta_2 Age^2$$

The results of this model are represented in Table 1. The analysis uncovered both a significant linear (β = 0.0009, $p < 0.0001$) and a significant quadratic effect of age on SoF (β = 0.398, $p < 0.0001$). Together, the effects of age accounted for 39.8% of the variance in our data.

Table 1: Linear and Quadratic Effects of Age on *SoF*

Predictor	**β estimate**	***SE***	***t***	***p***
Intercept	0.311 ***	0.005	61.05	< 2e-16
Age (1st degree)	0.0009 ***	0.000	7.37	4.1e-12
Age (2nd degree)	0.398 ***	0.044	9.09	< 2e-16

$*p < 0.05$ $**p < 0.01$ $***p < 0.001$

The effect of age remained robust even when the age groups were used as categorical predictors. A one-way ANOVA showed a significant main effect of group on *SoF* ($F(5,204) = 51.8$, $p < 0.0001$).

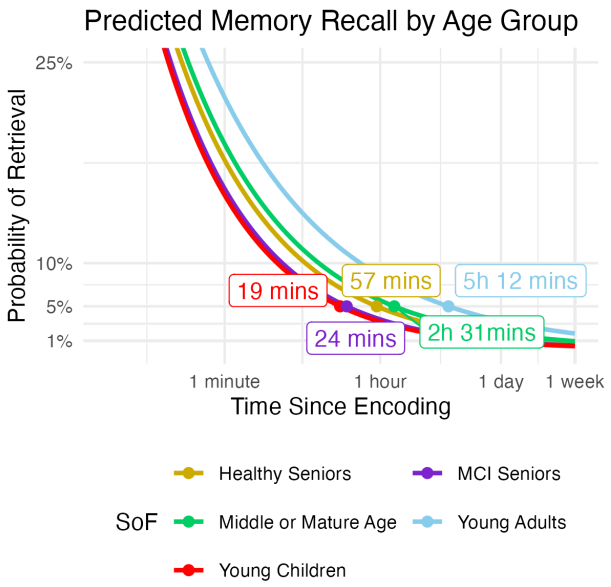

Figure 5.1.3.2. Probability of retrieval across different age groups' Speed of Forgetting (SoF) values. Points and labels refer to the time at which the probability of a memory being retrieved falls below 5%.

As noted in the introduction, the use of a model-based metric like the SoF allows for a clearer interpretation and comparison of memory function between the six groups. As an example, Figure 5.1.3.2 plots the predicted memory trajectories for the mean SoF values of the six age groups in Figure 5.1.3.1. For reference, the points and labels in this figure refer to the time at which the probability of successfully recalling a memory drops below 5%—an arbitrary but convenient threshold. Children and seniors with MCI, for example, cross that threshold at, respectively, 19 and 24 minutes after initial encoding; this fast forgetting would make it challenging to even follow a simple TV show because its average duration of 45 minutes exceeds their long-term memory ability.

5.1.4 Discussion

This paper has provided a normative trajectory of memory function over the lifetime, based on data collected from 210 individuals aged 5 to 85. Consistent with previous studies, our findings show that memory function improves rapidly between childhood and young adulthood. After that, memory function slowly decays over time, and such decay is accelerated when aging is accompanied by cognitive impairment (Schneider and Pressley 1997; Kausler 1994; Singer et al. 2003).

Our study not only reinforces those previous findings but is noteworthy for several reasons. First, it employs data from 210 individuals and over 4,000 individual testing sessions, yielding accurate individual measurements across a range of ages. But more importantly, it uses a model-based approach to quantifying memory, which

yields directly interpretable and comparable values with only 8 minutes of testing. Additionally, the *Speed of Forgetting* values computed for each child could be directly incorporated in an educational AFLS to present study materials at an individualized pace, thus bridging the gap between memory assessment and personalized education for children.

Despite these achievements, a number of limitations should be acknowledged. Firstly, the data collected comes from different experiments, and different age groups were tested under slightly different conditions and for a different number of times. Second, while the same adaptive assessment framework was uniformly used for all individuals, the specific *stimuli* used differed across studies and age groups. Specifically, children were tested on pairs of novel visual stimuli, while adults were tested with a variety of materials that included both verbal and visual stimuli, and often included relatively unfamiliar but not entirely novel materials (i.e., pairs of country names and associated flags). While Sense et al. (2016) and Hake et al. (2023) reported that *SoF* values were not significantly affected by the specific material used, the heterogeneity of stimuli employed here made it impossible for us to systematically assess this.

An additional limitation is that the children's group only tests five-year-olds and we are missing other developmental landmark ages such as middle childhood and adolescence. Furthermore, while we were able to collect data for age groups between 30 - 64 years old, this age range is relatively undersampled compared to the young adult or senior adulthood groups. Sparse sampling may affect our ability to differentiate between different functions that define *SoF* changes across the lifespan.

These limitations notwithstanding, we believe that our results provide a new foundation for understanding the nature and development of memory over the lifespan, offering new opportunities for investigating its cognitive and neural bases.

Conclusion

In conclusion, this study provides compelling evidence of the utility of the model-based *SoF* measure in characterizing memory function across the lifespan. By employing this approach, we observed a clear U-shaped trajectory of memory function, with children aged five exhibiting similar *SoF* rates as elderly individuals with MCI. Memory function improves rapidly from childhood to young adulthood and then gradually declines, with accelerated decay in older adults with MCI.

The findings underscore the value of *SoF* as a robust indicator of memory retention and forgetting. Additionally, integrating this AFLS model-based measure allows for personalized learning experiences based on each individual's memory profile. Despite the study's limitations, these results offer a new foundation for understanding the nature and development of memory over the lifespan, providing valuable insights into the factors influencing memory function and revealing opportunities for further exploration of its cognitive and neural bases.

5.2 Optimization of *Speed of Forgetting*

This section on model optimization has been submitted as a conference paper to the 2024 International Conference on Cognitive Modeling.

"I Knew It!" Model-Based Dissociation of Prior Knowledge Confounds in Memory Assessments

Abstract

The model-based assessments discussed in this paper rely on estimating an individual's rate of memory decay– a stable and idiographic parameter that can be captured by the model. However, this paper aims to demonstrate prior knowledge as a confounding factor in these model-based assessments and seeks to parse out the error using Maximum Likelihood Estimations. The metric of individualized memory performance, termed *Speed of Forgetting,* was significantly lower for facts known beforehand. Still, these facts were identified with 81% accuracy by recovered base-level activation estimations blind to the ground-truth data. A proposal for future model-based assessments to account for prior knowledge is discussed.

5.2.1 Introduction

Reliable assessment of memory function is essential to conducting research on memory processes, understanding memory-related disorders, and developing new therapeutic interventions. Memory function is typically assessed through performance in response to memory probes. However, these responses not only reflect the underlying accessibility of memory but also other confounding factors.

Among these confounds, prior knowledge–i.e., the possibility that the participant might already know the answer–is perhaps the most significant. Researchers have attempted to address the issue of prior knowledge by employing novel artificial or abstract stimuli. However, these stimuli are often challenging to encode initially, leading to an underestimation of memory function and rendering them unsuitable for clinical use (Brady et al. 2008). Alternatively, memory researchers have used paired-associates to examine how novel associations between familiar items (e.g. “fireman” and “slug”) are learned (John Robert Anderson 1974). Nonetheless, random associations are susceptible to semantic congruency effects if the stimuli are not meticulously chosen. For example, “fish” - ”sea” would have higher congruence than “zebra” - “sea” (van Kesteren et al. 2012). Analyses from Sense and van Rijn (F. Sense and van Rijn, n.d.) confirm that prior knowledge should not be neglected and subject-specific grades can be used as a proxy to control for prior knowledge. Overall, it can be useful for researchers to identify and mitigate the effects of prior knowledge rather than continually designing new stimuli or resorting to artificial/ abstract stimuli. But, how can this be accomplished if a proxy is not available?

In this section, I demonstrate the feasibility of such an approach. This method relies on model-based assessments of memory function, in which a participant’s long-term memory function is delineated as a parameter of a model fitted to their data. We illustrate that the impact of prior knowledge can be conceptualized as an additional item-level parameter in the model. Moreover, we establish that through maximum likelihood parameter recovery procedures, it is possible to accurately discern the extent to which a specific memory item was previously known.

Experimental Hypotheses

1. **Prior Knowledge Estimation:** Prior knowledge of an item would be inaccurately estimated with a lower *SoF* due to an assumption of a base-level constant (BLC) activation being set to 0 for all facts, leading to the model erroneously inferring quick and easy learning for previously known facts, thus underestimating SoF.
2. **Correlation Between Known and Unknown Facts:** A weak correlation would exist between SoF values for previously known and previously unknown facts across participants, influenced by the participants' SoF which still affects the benefit gained from multiple probes, even when a fact is already known.
3. **MLE-Based Parameter Recovery:** A Maximum Likelihood Estimation (MLE)-based parameter recovery procedure would be capable of correctly identifying previously known items as having large BLC values.
4. **Prior Knowledge Detection:** An automatic prior knowledge detector, utilizing a simple threshold model, could achieve greater than chance accuracy in identifying these facts.

5.2.2 Methods

Participants

Undergraduates enrolled at the local university ($N = 70$, 46 female, aged 18-21) were recruited on a rolling basis over a quarter to complete the study virtually. The recruitment criteria were as follows: (1) ages ranging from 18 to 29, (2) fluency in English, and (3) absence of significant medical or psychiatric conditions that could influence cognitive abilities. Participants who completed the prior knowledge survey and both fact-learning tasks were provided with course credit as compensation.

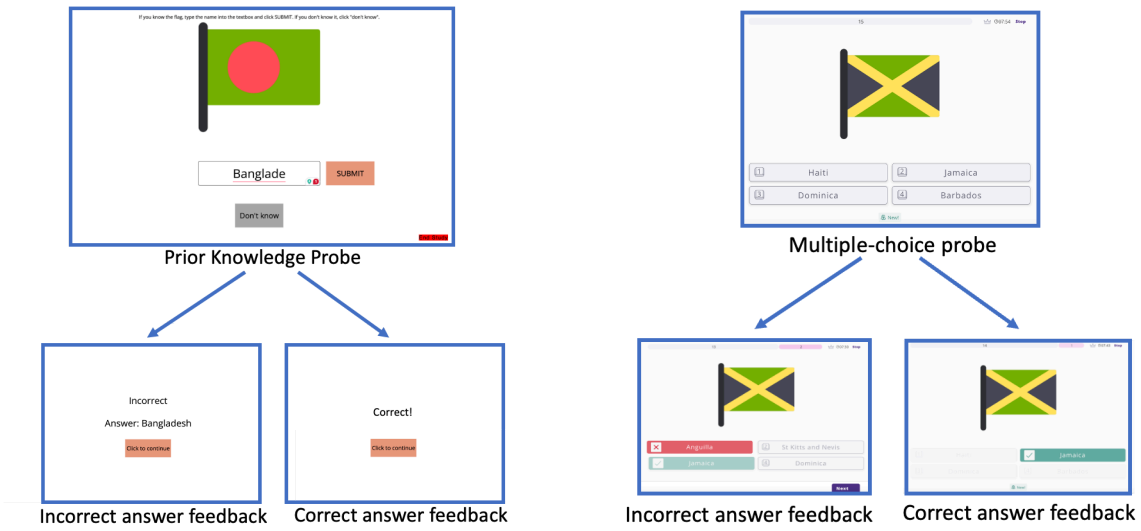

Figure 5.2.2.1. Left: Prior knowledge survey interface. Test screen followed by feedback screen that indicated typed answers as correct or incorrect. **Right:** Interface of MemoryLab adaptive fact-learning software. Presentation of multiple-choice questions, correct answer feedback, and incorrect answer feedback, shown respectively.

Prior Knowledge Survey

A PsychoPy task was designed to collect ground-truth data for participants' prior knowledge. Thirty national flags were used, pulled from the Caribbean Flags and Asian Flags learning lessons from a prior study. These flags provided an adequate range of potential prior knowledge, with flags that were more likely to be known beforehand, such as Japan, mixed with countries less likely to be known, like Montserrat. Participants were instructed to type the country name of the flag prompt if they were familiar with it. If they did not know it, participants selected the "Don't Know" button. The reaction time for country name guesses and "Don't Know" button presses was recorded. Facts that were typed correctly in the survey, with tolerance for spelling, were marked as having "prior knowledge". Participants were provided feedback on the accuracy of their answers and provided with the correct answer in the case of an incorrect response. As such, this prior knowledge survey served a dual purpose to gauge ground truth data for the facts known beforehand and also to function effectively as the first trace of the fact.

Adaptive Fact-Learning System

Next, each participant completed two learning lessons, Asian Flags and Caribbean Flags, that were administered using the MemoryLab interactive interface. This system dynamically estimates participants' *SoF* in real-time as they learn each stimulus-response pair (i.e., flag and country name). For each trial, participants answered a multiple-choice question and were shown the accuracy of their responses. Each lesson was eight minutes and consisted of 15 facts. Participants were not given a "study trial" as in prior studies due to the feedback given during the prior knowledge survey. This adaptive fact-learning assessment is described further in Sense et al. (2016) and can be accessed at https://www.memorylab.nl/en/.

Representing Prior Knowledge

The model provides an intuitive way to represent prior knowledge computationally. Generally, the activation of a previously known item results from the combined contribution of n experimentally observed traces and m unobserved previous traces, which are inherently inaccessible. To simplify computational representation, we make a key assumption.

In most cases, prior knowledge has been acquired well before the experiment begins. This means that the effect of temporal decay is negligible within the context of a single experimental session. This is illustrated over the course of 12 months in Figure 5.2.2.2, which plots the activations of three hypothetical memories that have accumulated 1, 10, or 100 traces over the first month. While the number of associated traces has a sizable effect on their residual activation, the effect of forgetting becomes negligible over time. Thus, we can assume that the effect of prior knowledge is an essential constant over time in the course of our experiment. For this reason, we will simply write that the "true" activation $A'(m)$ of a memory m is the sum of the contribution of the traces accumulated over an experimental session plus a memory-specific constant K_m:

$$A(m,t) = log\sum_i (t - t(i))^{-d(i)} + K_m$$

$A(m,t)$ = the activation (A) of a memory (m) is equivalent to the log odds of retrieving any of the memory traces (i) at a specific time (t)

In ACT-R terms, the parameter K_m represents a memory-specific *base-level constant* (BLC) that summarizes the previous history of a memory before an experiment takes place. While typically ignored, the presence of such a constant dramatically affects the estimates of other model parameters from experimental data. However, as the remainder of this paper will show, because the distortions introduced by BLC can be modeled as well, their contributions can be automatically estimated and corrected.

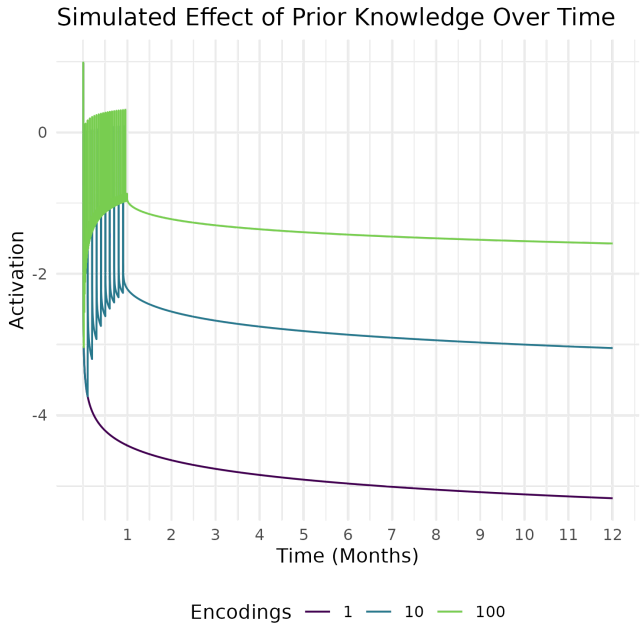

Figure 5.2.2.2. Simulated activation of three memories as a function of time following different numbers of encodings (1, 10, or 100) in the first month.

Maximum Likelihood Recovery of Prior Knowledge

To recover the amount of prior knowledge associated with each fact learned by an individual, Maximum Likelihood Estimation (MLE) was used. The model was retrospectively fitted to each individual's data by choosing the set of parameters $\boldsymbol{\theta}$ that maximized the model's likelihood. These parameters represent both individual participants' characteristics and the "unknown" pre-testing activation of each fact that was presented to the participant during the experiment. Formally, the likelihood of a set of parameters given a vector of data $\mathbf{x}$, $L(\boldsymbol{\theta}|\mathbf{x})$, is the probability of observing the data $\mathbf{x}$, given the model: $L(\theta|\mathbf{x}) = P(\mathbf{x}|\theta)$. Because our data consists of multiple independent responses $x_1, x_2, \ldots, x_N$, the likelihood can be expressed as the product of the probabilities associated with each response:

$$L(M|\mathbf{x}) = P(x_1|M) \cdot P(x_2|M) \cdot \ldots \cdot P(x_N|M) = \prod_i P(x_i|M)$$

Because the product of probabilities becomes vanishingly small, it is common to use *log*-likelihood:

$$\log L(M|\mathbf{x}) = \log \prod_i P(x_i|M) = \sum_i \log P(x_i|M)$$

In our case, each model was simultaneously fitted to two behavioral measures for each response: accuracy and its corresponding response time. Trial-by-trial probabilities for responses and response times were calculated using the following method. Given that a memory's activation reflects its log odds of retrieval, the probability $P_t(m)$ that a memory m would be retrieved at time t is given by:

$$P_t(m) = 1 / (1 + e^{-A(m,\,t)\,/\,s})$$

where s is a noise parameter that follows a logistic distribution with a standard deviation of $\sqrt{3}/\pi s$. Thus, given the state of the model, it is possible to compute the probability associated with each response. The probability of a correct response is $P_t(m)$, and the probability of an incorrect response is $1 - P_t(m)$.

When considering response times, the calculations become more complicated. In ACT-R, the response time RT associated with the retrieval time of a memory m is an inverse exponential function of the memory's activation:

$$RT = T_{ER} + F \cdot e^{-A(m,\,t)}$$

where T_{ER} is the non-retrieval time (e.g., the time needed for perceptual and motor responses) and F is an idiographic-free parameter. Note that this expression is deterministic; to transform it into a probability distribution, we must consider the distribution of noise around the activation. As noted above, noise s follows a logistic distribution. Therefore, the resulting probability distribution for response times is a shifted log-logistic distribution with parameters $\alpha = e^{-A(m)}$ and $\beta = \sqrt{3}/\pi s$:

$$P(RT) = (\beta / F\alpha)((t - T_{ER})/\alpha)^{\beta-1} / (1 + (t - T_{ER})/(F\alpha)^{\beta})^2$$

With these equations in place, it is possible to run a MLE procedure to recover the most likely BLC values for every study item in a memory experiment. The full model has one parameter (K) for each fact, and four parameters for each individual: φ, F, s, and T_{ER}. However, the adaptive fact learning system maintains F, s, and T_{ER} to constant defaults (F = 1, s = 0.25, and T_{ER} = 300ms). We will adhere to the same principle. Because no known closed-form formula exists to estimate the maximum likelihood solutions for this model, we used a derivative-free numerical minimization procedure, the simplex method (Nelder and Mead 1965), as implemented in the Python SciPy package. To address the potential difference between the first "study trial" and the beginning of the learning trial, the offset time was calculated using computer timestamps and integrated to account for potential decay in activation.

5.2.3 Results

Effect of Prior Knowledge on *Speed of Forgetting*

We found a significant impact of prior knowledge on the estimates of *SoF*. Notably, items identified by participants as previously known were consistently estimated to have a lower *SoF* compared to unknown items. This trend was evident across all participants (Fig. 5.2.3.1). Utilizing a random slope linear mixed-effects model, we further analyzed this effect and discovered that items designated as previously known were associated with a significantly lower *SoF* (β = -0.09, 95% CI [-0.10, -0.09], $p < 0.001$).

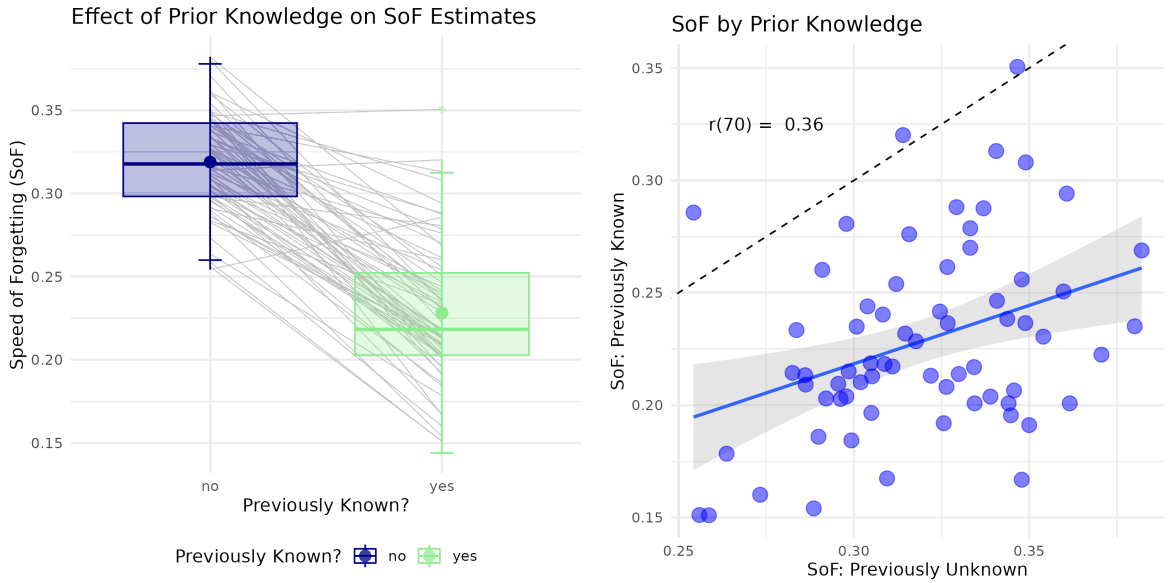

Figure 5.2.3.1. Left: Effect of Prior Knowledge across participants. Facts known beforehand (green) had consistently lower *SoF* than facts not known beforehand (blue). Gray lines represent individual participants; colored boxes represent Tukey's boxplots; colored dots represent mean values. **Right:** Correlation between the average *SoF* estimates for facts known beforehand vs. not known beforehand within each participant. Each point represents a participant in the study; the dashed line is the identity line.

Correlation Between Known and Unknown Facts

Our second hypothesis centered on investigating the relationship between *SoF* values for previously known and previously unknown facts across participants. We anticipated a weak correlation between these values, suggesting that the *SoF* of known facts would still influence subsequent assessments, even after initial familiarity. Indeed, our analysis revealed a small yet statistically significant correlation ($r(70) = .36$, $p = 0.002$; (Fig. 5.2.3.1)), supporting our hypothesis and indicating the persistence of *SoF* effects even with prior knowledge.

Recovered Base-Level Constants

To test our third and final prediction, we conducted the MLE procedure on the dataset for each participant, recovering the most likely BLC value corresponding with each fact. While the model itself is blind to whether a fact was previously known or not, it correctly estimated that, on average, the BLC values for previously known facts were much higher than those for unknown facts (paired $T(69) = -17.00$, $p < 0.0001$; (Fig. 5.2.3.2)). Importantly, the mean BLC values were higher for previously known facts across *all* participants, and were correctly estimated as close to zero for most previously unknown facts.

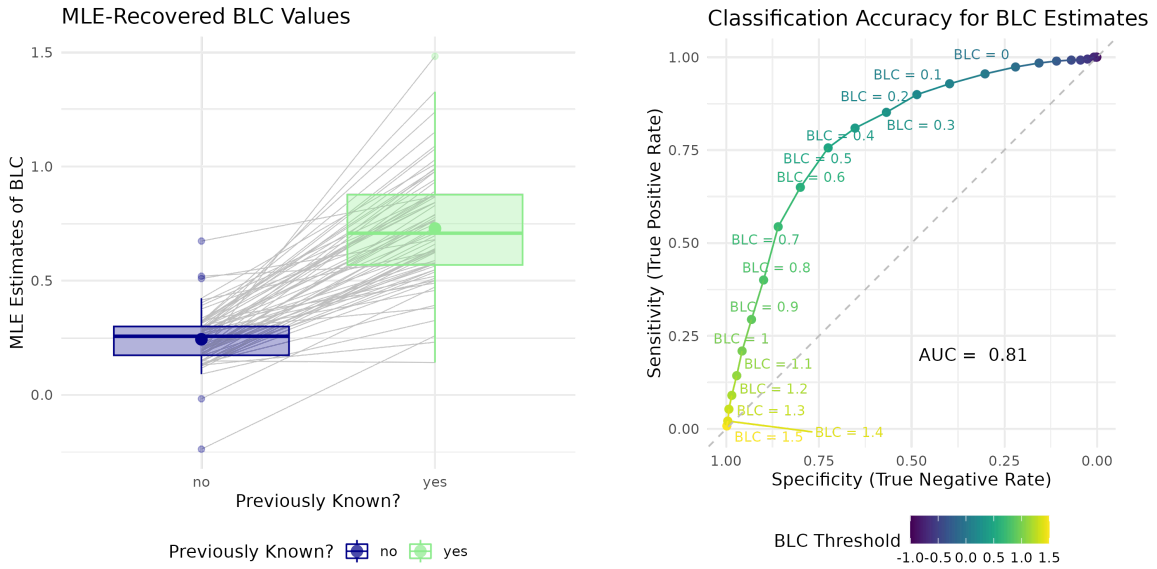

Figure 5.2.3.2. Left: Recovered Base Level Activation values for facts with true prior knowledge (green) vs. without true prior knowledge (blue). Gray lines represent values for individual participants; colored lines represent Tukey's boxplots; colored points represent means. **Right:** ROC-curve for inferring prior knowledge given the recovered base-level activation from MLE.

We show that an automatic procedure can correctly identify previously known items, but this does not provide a quantitative measure of its efficacy. To obtain this estimate, we transformed the continuous estimates of BLC values into binary predictions by applying a moving threshold: items whose recovered BLC value was greater than the threshold were classified as "previously known". For each level of the threshold, it is possible to compare the classification accuracy against the ground truth and estimate the proportion of true positives (hits) and true negatives (correct rejections) made.

These threshold-dependent proportions can be plotted to obtain the Receiver Operating Characteristic (ROC) curve (Fig. 5.2.3.2). The area under the curve (AUC) of such a curve represents the classification accuracy of the method. In this case, the AUC is 0.81, implying that the naive binary classification based on MLE-recovered BLC values alone could achieve 81% accuracy in identifying previously known items. Simply put, the *SoF* error from prior knowledge could be identified automatically and with above-chance accuracy *without* knowing which facts participants knew beforehand.

5.2.4 Discussion

The current study introduces a novel approach to disentangling prior fact knowledge in memory assessments from previously collected data. Our results confirmed the hypothesis predictions, demonstrating a significant decrease in the estimations of *Speed of Forgetting* (SoF) for items with prior knowledge. Furthermore, we observed a weak correlation between *SoF* values for facts with and without prior knowledge. Notably, we developed a simple threshold model that accurately predicted prior knowledge using Maximum Likelihood Estimation (MLE) and response times with 81% accuracy. This model-based approach effectively identified and dissociated the confounding influence of prior knowledge, representing a significant advancement in memory assessment methodology.

Identifying prior knowledge as a source of error in model-based assessments is a novel and important finding with implications across multiple levels of analysis. When it is unfeasible to account for prior knowledge initially, such as in previously collected data, it is possible to parse out individual facts that likely have prior knowledge. However, with 81% accuracy, this approach may not guarantee an improvement in model accuracy for the intention of classifying memory ability. The second level of analysis would be to include a model parameter K_m as discussed previously. Prior knowledge of a fact would alter base-level activations accordingly. The third level would be to actively collect prior knowledge data. During the fact-learning task, participants would have the option to click "I already knew that" in study trials. When this happens, the base-level activation for that would be adjusted. With these model improvements, we predict that the memory classification accuracy will improve.

To address some limitations, the sampled population likely has extensive experience taking multiple-choice examinations and could have developed alternative cognitive strategies for picking the correct answer other than successful retrieval, such as process of elimination. The multiple-choice format of the task was chosen due to previous use in the literature displaying more consistent *SoF* values (Sense et al., 2016). Finally, as memory is certainly related to age, the sample in this study does not reflect the elderly population that the task would be used for in clinical settings. A geriatric population could have more or less error resulting from prior knowledge, the results must be carefully considered before extrapolating to other age ranges.

Implications and Future Directions

Memory impairments are a common and debilitating aspect of aging, particularly in neurodegenerative conditions. The ability to quantify individual differences in memory is crucial, as early detection of memory impairment is essential for effective treatment. Moreover, the brief and user-friendly online format makes the administration of assessments remarkably convenient.

In light of our study's findings, it is imperative to minimize error in memory assessments. Our identification of error stemming from prior knowledge significantly affecting estimated *SoF*s highlights the potential for misclassification of individuals, particularly elderly participants with prior knowledge, as healthy controls rather than memory-impaired individuals. Addressing this source of error reduces the risk of Type II (false-negative) errors in memory assessment tasks, thereby enhancing the accuracy of diagnostic outcomes.

To further enhance the accuracy of our model-based assessment, we are undertaking another study aimed at better understanding the model parameter T_{ER} by integrating eye-tracking data. Analysis of scan paths extracted from eye-tracking data will enable a comprehensive examination of the components contributing to this parameter, ultimately leading to improvements in the model's accuracy. With these combined improvements, we aim to rival the classification accuracy of clinical-standard assessments, thereby facilitating timely intervention and leading to improved patient outcomes.

6. General Discussion

This dissertation presents the validation of a computational approach for memory assessment using the Adaptive Fact Learning System (AFLS). Below, I synthesize the findings from the longitudinal clinical study addressing four key questions and elaborate on subsequent expansions that examine the lifespan of memory functions and optimization techniques.

6.1 Summary of Findings and Contributions

Longitudinal Clinical Findings

1) Is the Speed of Forgetting Reliable?
Answer: Yes!
The longitudinal clinical study verified the reliability of the Speed of Forgetting as a consistent metric across different cognitive materials and participant interactions. The results demonstrated that SoF could reliably measure memory impairment across varying contexts and times, thus establishing it as a robust tool for longitudinal memory function monitoring. This finding is crucial for the utility of SoF in clinical settings where monitoring the progression of cognitive impairments like mild cognitive impairment (MCI) is necessary.

2) Are there group differences in the *Speed of Forgetting*?
Answer: Yes!
Analysis from the longitudinal clinical study revealed significant differences in SoF values between groups, specifically between patients with MCI and healthy controls. Patients with MCI exhibited higher SoF values, indicating faster rates of forgetting. This suggests that SoF is effective in differentiating between normative and pathological memory declines, making it a valuable diagnostic tool for identifying early stages of cognitive impairment.

3) Does the *Speed of Forgetting* have clinical validity?
Answer: Yes!
The longitudinal clinical study also tested the clinical validity of SoF, finding it to be a predictive marker of MCI. The model demonstrated high diagnostic accuracy, distinguishing MCI from healthy aging with notable precision. This supports the potential of SoF as a standalone diagnostic measure that could streamline the detection of memory impairments in clinical practice.

4) Can the *Speed of Forgetting* track changes over time?
Answer: Yes!
Lastly, the longitudinal analysis of SoF provided insights into the trajectory of memory decline in MCI patients over time. The study demonstrated that cognitive decline does not follow a uniform path but is characterized by variable patterns of change. This was evident in the more pronounced and accelerated SoF increases among individuals with MCI and AD compared to the relative stability observed in healthy controls. These patterns, captured through the integration of linear and nonlinear statistical models, illuminate the complex nature of memory decline and underscore the importance of long-term monitoring to inform diagnosis and intervention strategies.

Findings from Expansion Studies

Lifespan of Speed of Forgetting
The expansions into the lifespan aspects of SoF revealed that memory performance metrics vary significantly with age. The studies employed a model-based approach to track memory function across the human lifespan, demonstrating a nuanced understanding of memory development and decline. This lifespan perspective is essential for designing age-appropriate cognitive interventions and understanding age-related memory decline.

Optimization of Speed of Forgetting Prediction
Further studies focused on optimizing the prediction accuracy of SoF. By incorporating machine learning techniques and advanced statistical modeling, the research refined the predictive capabilities of SoF, enhancing its precision and reliability. This optimization is critical for tailoring interventions to individual memory profiles and improving the overall effectiveness of memory assessments.

Our research presents the *Speed of Forgetting* as a transformative metric for the assessment and monitoring of memory impairments, with substantial implications for cognitive science and clinical practice. This longitudinal study's nuanced findings on SoF progression offer a comprehensive understanding of cognitive decline trajectories across various clinical groups. Our innovative approach introduces a model-based, online assessment that dynamically captures individual forgetting patterns, transcending traditional neuropsychological assessments' limitations by offering scalability, efficiency, and personalization.

Longitudinal Findings
Our longitudinal investigation into the SoF revealed a nuanced trajectory of cognitive decline across clinical groups, which was particularly pronounced in individuals with MCI and AD. Unlike healthy controls who exhibited relative stability, these groups displayed a complex and accelerated progression in their SoF, reinforcing the notion that cognitive decline does not follow a uniform path but is instead marked by phases of variability and rapid deterioration.

The introduction of both linear and nonlinear components in our statistical analysis has been crucial. While a linear approach offered an initial glance at SoF's trajectory, it was the quadratic term that unveiled the intricate nonlinear patterns of cognitive decline. This term's significance is not just statistical but also clinical, as it highlights the variable nature of memory decline over time, which is critical for tailoring individualized treatment plans.

The complex interplay between the SoF and time elucidates the intricate dynamics of memory processes, which can significantly inform the diagnosis and intervention strategies for early-stage neurodegenerative conditions. The nonlinear relationship observed, particularly among those diagnosed with MCI, suggests changing patterns of memory decline over time, which could be pivotal for developing individualized interventions.

Furthermore, the granularity offered by the SoF in distinguishing among MCI subtypes aligns with the contemporary understanding that neurodegenerative diseases are heterogeneous. Such diagnostic specificity is essential for a nuanced approach to treatment and understanding the progression of diseases like Alzheimer's beyond traditional verbal memory assessments.

Model Simplicity and Assumptions
A general problem in mathematical models to always be aware of is: at what point have you overextended that simple abstraction and applied it in a way that is inadmissible? The foundational memory model of our adaptive fact-learning system is designed with a balance between simplicity and complexity, enabling the extraction of memory strength inferences from response data. Although the model is currently rooted in episodic memory and relies on several assumptions, its practical applicability is evident in its ability to accommodate large-scale data collection and frequent assessments.

Another significant limitation noted in the longitudinal clinical study is the "cold start" problem, which arises because both the learners' abilities and the materials' difficulty levels are initially unknown. The AFLS starts with a standard initial estimate for the rate of forgetting across all facts, which is then adjusted over time based on the responses from learners. However, at the outset, the system does not have the capability to customize repetitions to suit individual differences in ability or the varying difficulties of the material. As a result, this initial uniform approach to estimating the rate of forgetting may hinder the system's effectiveness in optimizing learning schedules during the early stages of learner interaction.

However, now that initial data for all the lessons has been collected, we can mitigate the cold-start problem and reduce the non-memory-related variability. Van der Velde (2021) and again (2023) showed that using the SoF starting estimates derived from prior learning data, the AFLS was better able to prioritize difficult items over easy ones from the outset. These results demonstrated that, especially when variance among learners and items is high, adding “warm-star”’ estimates to specific words or learners can boost the system’s assessment ability.

Assumptions About Memory Retrieval and Decay
Our methodology rests on the simplification that each fact learned is represented by an independent memory unit. While this assumption facilitates the functionality of AFLS, it contrasts with the interconnected network view of declarative memory (Eichenbaum 2004). Our understanding of the decay rate within the adaptive fact learning system hinges on basic assumptions about "passive" forgetting, as described by Davis & Zhong (2017). This type of forgetting arises from a combination of factors including biological decay (Hardt, Nader, and Nadel

2013) and interference from new memory formation (Wixted 2004; John R. Anderson and Reder, n.d.). While we do not commit to a specific mechanism underlying the decay rate, both concepts are recognized as contributing factors to memory decay. This perspective aligns with broader theories in cognitive science, which often treat memory not as isolated units but as part of a dynamic system where decay is an inevitable outcome of complex cognitive processes (Lemaire and Portrat 2018).

Semanticization in the Computational Model
While our computational model is agnostic to "semantic" vs "episodic" memory, we could consider each memory trace as episodic, and the summed memory as semantic. Over time, as these episodic traces are repeatedly activated, they undergo semanticization, where the detailed, context-rich episodic memories are abstracted into more generalized semantic forms. This transformation is particularly relevant in settings where recurring experiences or frequent retrievals of similar memories occur, effectively transitioning from unique episodic details to a broader semantic understanding. In the context of our model, the accumulated activation of these episodic traces can be conceptualized as forming a composite memory that parallels the semantic form of memory. This notion aligns with the semanticization process described in Chapter 3.4 Multimodal Integration.

The model integrates this concept by treating the collective influence of all episodic traces as a singular, dynamic memory representation. This composite memory not only retains the essence of the individual episodic memories but also evolves to embody the generalized, semantic form. Here, each episodic trace contributes to the overall memory schema, and their sum represents a memory's semantic state, mirroring the cognitive shift from specific episodic details to generalized semantic knowledge.

By employing this framework, our model captures the dual nature of memory traces—both as discrete episodic instances and as components of a broader semantic understanding. This approach allows for a nuanced assessment of memory dynamics, reflecting the natural progression of memory from episodic specificity to semantic generalization, which is crucial for long-term memory retention and retrieval.

Diagnostic and Therapeutic Enhancements
SoF's high diagnostic accuracy positions it favorably alongside established cognitive assessments like the Montreal Cognitive Assessment (MoCA). Its ability to measure cognitive fluctuations over time addresses the risks associated with one-time assessments, providing a dynamic picture of cognitive health. Furthermore, the SoF's adaptability for remote administration positions it well within the telehealth paradigm, meeting the growing need for accessible cognitive assessments. Thus, its high diagnostic accuracy, coupled with the model's ability to accommodate frequent and large-scale data collection, supports its integration into clinical practice.

6.3 Conclusion

This dissertation confirms the SoF metric's robustness, reliability, and clinical utility within the AFLS. By integrating initial longitudinal clinical study findings with expansion studies, we have enriched our understanding of memory processes and bolstered diagnostic and therapeutic approaches to memory impairments.

Looking forward, SoF's reliability positions it as an exceptional tool for evaluating interventions like FDA-approved therapies for Alzheimer's Disease. Its potential for integration with neuroimaging promises to uncover the neural mechanisms underlying memory decline. The capacity of SoF to longitudinally track memory changes is invaluable for early detection of MCI, potentially delaying the onset of Alzheimer's Disease and enhancing life quality for those affected.

In summary, our findings endorse the SoF as a formidable tool in research and clinical settings, with its unparalleled utility highlighted by its adaptability for remote, frequent use—an imperative asset in our increasingly digital healthcare environment. It stands as a testament to the potential of computational methods in enriching our approach to cognitive science and clinical practice, ensuring that ***wherever there are memory differences to be discerned, Speed of Forgetting can play a significant role.***

List of publications

1. **Hake, H. S.**, van der Velde, M., Grabowski, T., van Rijn, H., Leonard, B., & Stocco, A. (2024). Large-scale assessment and monitoring of declining memory function through individualized modeling of episodic memory. *medRxiv*. https://doi.org/10.1101/2024.03.15.24304345
2. **Hake, H. S.**, Leonard, B., Ulibarri, S., Grabowski, T., van Rijn, H., & Stocco, A. (2023). Breaking new ground in computational psychiatry: Model-based characterization of forgetting in healthy aging and mild cognitive impairment. *medRxiv.* https://doi.org/10.1101/2023.05.13.23289941
3. Williams, A., **Hake, H. S.**, & Stocco, A. (2024). "I knew it!" Model-based dissociation of prior knowledge confounds in memory assessments. In *Proceedings of the 22nd Annual International Conference on Cognitive Modeling*.
4. Leonard, B., **Hake, H. S.**, & Stocco, A. (2024). Beyond mediator retrievals: Charting the path by which errors lead to better memory consolidation. In *Proceedings of the 46th Annual Conference of the Cognitive Science Society*.
5. Capik, A., **Hake, H. S.**, & Stocco, A. (2024). Model-based characterization of forgetting in children and across the lifespan. Conference paper. In *Proceedings of the 46th Annual Conference of the Cognitive Science Society*.

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