Cognitive Neural Mechanisms of Memory Discriminability Affected by Aging and Its Applications

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Abstract

Memory discrimination is the ability to accurately discriminate between similar memory experiences, which relies on a neural computation mechanism known as pattern separation. In human subjects, it is typically measured and studied using the memory similarity task. During the aging process, memory discrimination in older adults exhibits a very significant decline, which is closely related to structural and functional deterioration of medial temporal lobe structures such as the hippocampus and entorhinal cortex, as well as aging of other neocortical structures and functions. Since memory discrimination highly depends on the structural and functional integrity of the medial temporal lobe, it can reflect abnormal brain structural and functional changes in the early stages of cognitive impairment development, endowing the memory similarity task with great potential for application in early identification of cognitive impairment. Future research needs to employ more refined imaging techniques to independently investigate the role of hippocampal dentate gyrus and CA3 subregions in memory discrimination and the effects of aging thereon, pay more attention to the neural mechanisms by which aging of neocortical structures such as the prefrontal cortex affects memory discrimination, and also establish large-sample prospective cohorts to validate the effectiveness of the memory similarity task in early identification of cognitive impairment.

Full Text

Preamble

The Cognitive Neural Mechanisms of Age-Related Decline in Mnemonic Discrimination and Its Application

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Abstract: Mnemonic discrimination refers to the ability to accurately distinguish similar memory experiences, which relies on a neural computing mechanism known as pattern separation. Currently, mnemonic similarity task (MST) is commonly employed to measure and study mnemonic discrimination. The elderly tend to exhibit a noticeable decline in mnemonic discrimination. This decline is proved to be associated with damage to the structural and functional integrity of the medial temporal lobe, which occurs during the aging process. Some researchers have also suggested that the aging of the neocortex can influence mnemonic discrimination. Given its reliance on the medial temporal lobe, mnemonic discrimination can reflect abnormal brain structural damage and functional decline in the early stages of cognitive impairment. Thus, MST has significant potential in early identification of cognitive impairment. To further explore the causes of the decline in mnemonic discrimination, future studies should employ more advanced imaging techniques to separately investigate the effects of aging in the dentate gyrus and CA3 subregion on mnemonic discrimination. It is also critical to explore the neural mechanisms underlying age-related changes in mnemonic discrimination, with a particular focus on neocortical regions like the prefrontal cortex. Large-scale prospective cohorts should also be established to validate the effectiveness of MST in early identification of cognitive impairment.

Keywords: mnemonic discrimination, pattern separation, aging, cognitive neural mechanism, cognitive impairment

1 Introduction

Episodic memory refers to long-term memory for personally experienced events that occur at specific times or places, representing a crucial cognitive function for daily life (Tulving, 2002). In everyday life, people constantly encounter highly similar events—for instance, older adults often need to recall whether they have already taken their medication today before doing so. Accurately distinguishing similar memory experiences is thus essential for normal functioning. This ability to differentiate similar memory traces is termed mnemonic discrimination, which critically depends on a neural computation mechanism called pattern separation (Marr, 1971; McClelland et al., 1995; Norman & O' Reilly, 2003; Yassa & Stark, 2011). Pattern separation refers to the transformation of highly overlapping memory inputs into two independent, fully separated neural signal outputs.

Based on the fundamental principles of pattern separation, Stark and colleagues developed the Mnemonic Similarity Task (MST) to measure and investigate mnemonic discrimination (Kirwan & Stark, 2007; Stark et al., 2013; Yassa et al., 2010a, 2011a). The task requires participants to identify old items, new items,

and lure items (similar to previously studied images) [Figure 1: see original paper]. The ability to accurately discriminate lures (by judging them as "similar") serves as an index of mnemonic discrimination (Sinha et al., 2018; Stark et al., 2019; Stark et al., 2013; Yassa et al., 2010a). In recent years, researchers have created numerous variants based on the original object version of MST, including spatial versions (Granger et al., 2022; Reagh & Yassa, 2014), scene versions (Berron et al., 2018; Güsten et al., 2021; Maass et al., 2019), face versions (Chang et al., 2015; Stiernströmer et al., 2018), emotional material versions (Leal et al., 2019; Pagen et al., 2022; Szollosi et al., 2022), and word versions (Ly et al., 2013). Despite these variations, all tasks share the core requirement of accurately discriminating similar stimuli.

The medial temporal lobe (MTL) is a key structure supporting episodic memory functions, including mnemonic discrimination. Anatomically, the MTL comprises the hippocampus, entorhinal cortex (EC), perirhinal cortex (PRC), and parahippocampal cortex (PHC). The hippocampus can be further subdivided into the dentate gyrus (DG), cornu ammonis regions 1-4 (CA1-4), and the subiculum. Since the proposal of neural computational models, extensive research has focused on the contribution of the hippocampus, particularly the DG, to pattern separation and mnemonic discrimination. However, accumulating neuroimaging evidence has revealed that mnemonic discrimination also requires support from a complete information processing circuit composed of the hippocampus and other MTL structures, as well as top-down regulation from neocortical structures such as the frontal, parietal, and occipital lobes (Amer & Davachi, 2023).

With advancing age, numerous cognitive functions decline to varying degrees (Park & Bischof, 2013; Park et al., 2002), and mnemonic discrimination is no exception. Studies using MST to measure mnemonic discrimination across different age groups have found a significant negative correlation between age and mnemonic discrimination performance, indicating that this ability deteriorates with age (Riphagen et al., 2020; Stark et al., 2013). Furthermore, when older adults develop neurodegenerative conditions that progress to mild cognitive impairment (MCI) or Alzheimer' s disease (AD), their mnemonic discrimination abilities decline even further (Bakker et al., 2015; Corona-Long et al., 2020; Lalani et al., 2022; Stark et al., 2013; Yassa et al., 2010a).

Researchers have extensively investigated the cognitive neural mechanisms underlying age-related decline in mnemonic discrimination, discovering in the process that MST holds promise for identifying subtle cognitive impairments in the early stages of cognitive disorders. This article systematically reviews and synthesizes research on the cognitive neural mechanisms of age-related decline in mnemonic discrimination, introduces applications of MST in early identification of cognitive impairment in older adults, discusses current limitations, and outlines future research directions.

2.1 Core Mechanism of Mnemonic Discrimination: Hippocampus-Centered Pattern Separation in the Medial Temporal Lobe

The medial temporal lobe serves as the hub for episodic memory processing. Following initial processing in the neocortex, object-related information enters the PRC for more complex processing before being transmitted to the lateral entorhinal cortex (LEC). In contrast, spatial or location-related information enters the PHC and is then passed to the medial entorhinal cortex (MEC). Ultimately, the hippocampus integrates information from both LEC and MEC to form complete episodic memories (Danieli et al., 2023). As a critical component of episodic memory processing, pattern separation also depends on this intact MTL processing pathway.

Classic theory posits that because the number of granule cells in the hippocampal DG vastly exceeds the number of projecting EC cells, DG granule cells can perform sparse coding of EC inputs (Chawla et al., 2005; Deng et al., 2013)—encoding input information through activation of only a small number of granule cells. Consequently, similar events are represented by different populations of DG granule cells, achieving separate representations of information. The critical role of DG in pattern separation has been confirmed by early animal studies. For example, Leutgeb et al. (2007) found that DG granule cell populations are highly sensitive to minimal environmental changes: when environments changed only slightly, CA3 pyramidal cell populations showed similar firing patterns across conditions, whereas DG granule cell populations exhibited dramatically altered firing patterns (with multiple firing fields changing incoherently). This finding, replicated by Neunuebel and Knierim (2014), demonstrates that similar environments are represented by partially distinct DG granule cells. In addition to DG, early animal research also revealed that the hippocampal CA3 subregion can execute pattern separation (Lee et al., 2004; Leutgeb et al., 2004; Vazdarjanova & Guzowski, 2004), though CA3 responses to minimal environmental changes are far less pronounced than those of DG. Only when environmental changes are substantial does CA3 exhibit pattern separation processing patterns (Knierim & Neunuebel, 2016; Neunuebel & Knierim, 2014). Recent monkey studies have also provided evidence supporting the involvement of DG/CA3 hybrid region neurons in pattern separation (Sakon & Suzuki, 2019). Thus, both DG and CA3 subregions contribute to pattern separation, but DG is more sensitive to subtle feature changes and primarily responsible for separating representations of similar stimuli.

Human studies have provided converging evidence. Research using MST to test mnemonic discrimination in patients with hippocampal damage has revealed severe impairments (Baker et al., 2016; Hanert et al., 2019; Kirwan et al., 2012), confirming the hippocampus' s contribution to human pattern separation. Additionally, high-resolution functional magnetic resonance imaging (fMRI) studies have illuminated the critical role of DG/CA3 subregions in pattern separation. For instance, Bakker et al. (2008) found in an MST study that DG/CA3 activ-

ity was significantly lower during recognition of old objects compared to new objects, but when lures appeared, DG/CA3 activity levels were comparable to those during new object presentation—a pattern not observed in other hippocampal subregions. This suggests that DG/CA3 responds to lures as if they were novel objects. Other researchers have manipulated lure similarity levels and found that DG/CA3 can transform small differences in input information into substantially different signal outputs (Lacy et al., 2011; Reagh et al., 2018), consistent with neural computational models (Norman & O' Reilly, 2003) and further confirming the key role of DG/CA3 in pattern separation.

Beyond DG/CA3, other MTL structures have garnered research attention. Studies show that PHC can categorize spatial scenes based on scene features (Dilks et al., 2022) and represent spatial dimension information such as distance (Baumann & Mattingley, 2021), while MEC can differentiate object locations and facilitate hippocampal spatial information organization (Keene et al., 2016). PRC and LEC are essential for perceiving objects with overlapping features, particularly in finely representing subjectively perceived object similarity (Ferko et al., 2022). Thus, PHC, PRC, and EC play roles in maintaining perceptual accuracy and resolving interference from similar information, suggesting that pattern separation begins as soon as highly overlapping memory information enters the MTL.

This view has received empirical support. Studies have found that successful lure discrimination is associated with higher activation levels in PRC-LEC during object MST, showing activity patterns similar to DG/CA3 (Reagh & Yassa, 2014; Stevenson et al., 2020). Similarly, PHC-MEC exhibits activity patterns comparable to DG/CA3 during spatial MST (Reagh & Yassa, 2014). However, when lures were divided into three similarity levels, PRC-LEC and PHC-MEC activity patterns did not completely align with those of DG/CA3 (Reagh et al., 2018). Researchers have interpreted this as indicating that EC, PRC, and PHC have weaker capacity than DG/CA3 for discriminating highly similar lures (Reagh et al., 2018), meaning these regions can participate in pattern separation to some extent but produce more ambiguous representations that do not achieve complete separation (Reagh & Yassa, 2014).

In summary, pattern separation is dominated by the MTL. Highly overlapping information undergoes initial selection before entering the hippocampus: object information enters the PRC-LEC pathway for fine-grained representation and preliminary separation, while spatial or scene information enters the PHC-MEC pathway for initial separation. This pre-processed information then reaches the hippocampal DG/CA3 subregions, where it is transformed into non-overlapping memory representations (Amer & Davachi, 2023; Reagh & Yassa, 2014). From this complete processing pathway perspective, the preliminary selection and separation of similar stimuli by other MTL structures constitute a foundation that enables the hippocampus to efficiently execute pattern separation.

2.2 Initial Processing Stage of Mnemonic Discrimination: Perceptual Representation Separation

Mnemonic discrimination is built upon perceptual discrimination. While the MTL is crucial for forming neural representations that distinguish similar stimuli (Kent et al., 2016), the role of occipital sensory regions in perceptual representation separation cannot be overlooked. Bowman et al. (2019) found that visual representations in ventral visual areas are sufficiently detailed to discriminate targets from highly similar lures based on activity signals alone. MST studies have also revealed significant differences in occipital activation between correct lure discrimination and correct recognition of old items (Klippenstein et al., 2020), with occipital sensory areas even exhibiting neural activity patterns similar to hippocampal pattern separation (Pidgeon & Morcom, 2016). These results demonstrate that occipital sensory regions can detect feature changes in previously presented stimuli and achieve perceptual separation representations.

Notably, although current research has not found significant correlations between occipital activation levels and mnemonic discrimination performance (Klippenstein et al., 2020), occipital regions can influence the predictive relationship between hippocampal activity and behavioral performance. For example, Koolschijn et al. (2019) found that when transcranial direct current stimulation was applied to the lateral occipital cortex during pattern separation, hippocampal neural activity no longer predicted behavioral performance. This suggests that perceptual representation separation in sensory regions is a prerequisite for successful pattern separation in the MTL.

These findings indicate that occipital sensory regions are sensitive to feature differences between similar stimuli and can generate perceptual separation representations that partially resolve interference from similar information. As the initial information processing "workshop" for mnemonic discrimination, occipital sensory regions cannot independently achieve separation of memory traces, but their fine-grained perceptual representations facilitate pattern separation dominated by the MTL.

2.3 Monitoring and Cognitive Control in Mnemonic Discrimination

Memory monitoring represents another crucial aspect of memory function, involving evaluation of encoding quality or the accuracy and relevance of retrieved information (Chua et al., 2009; Orth et al., 2023). Consequently, memory monitoring is essential for evaluating and judging memory content and distinguishing similar memory experiences. Research has confirmed that memory monitoring relies on the prefrontal cortex (Chua & Ahmed, 2016; Imperio & Chua, 2023; Shao et al., 2022). Therefore, subtle changes in stimulus features during mnemonic discrimination should also be reflected in prefrontal activity patterns. This hypothesis has received empirical support: MST studies have revealed prefrontal activity patterns consistent with hippocampal pattern separation (Nash

et al., 2021). Importantly, the input-output function curve obtained by manipulating lure similarity levels in prefrontal cortex matches the input-output function curve of hippocampal DG/CA3 reported by Lacy et al. (2011) (Pidgeon & Morcom, 2016). These findings indicate that while the prefrontal cortex may not generate separate representations of information, it can monitor differences between similar stimuli and respond to them differentially.

Beyond monitoring, another critical prefrontal function in episodic memory is cognitive control. Studies have shown that during encoding or retrieval, the prefrontal cortex can top-down modulate hippocampal activity patterns through cognitive control (Aly & Turk-Browne, 2016; Anderson & Hulbert, 2021; Malik et al., 2022; Zheng et al., 2021). Similar evidence has emerged in mnemonic discrimination research. For instance, Frank et al. (2020) found that when prefrontal-driven expectations were violated, the degree of pattern separation for highly similar objects in hippocampal DG/CA3 increased further. Lohnas et al. (2018) used intracranial electrodes to record cortical EEG and found that when participants were instructed to judge lures as "old," the hippocampus did not show pattern separation electrophysiological signals; only when required to distinguish lures from old objects did the hippocampus execute pattern separation. These findings demonstrate that the prefrontal cortex can send instructions to the hippocampus to execute pattern separation and modulate its activity according to task demands.

Critically, Lohnas et al. also found that regardless of whether participants were required to distinguish lures from old objects, the dorsolateral prefrontal cortex consistently showed significant differences in response to lures versus old objects. This indicates that the prefrontal cortex continuously monitors differences between similar objects, and upon detecting these differences, can promote separation of overlapping information through top-down regulation, thereby achieving mnemonic discrimination.

In summary, mnemonic discrimination relies on coordinated activity across large-scale brain networks: similar stimuli are first processed by occipital sensory regions, which detect feature differences and generate preliminary perceptual separation representations. After the prefrontal cortex monitors differences in neural activity patterns, it initiates and regulates pattern separation in downstream brain regions according to task requirements. Under prefrontal monitoring and modulation, information from occipital sensory regions enters the MTL via different processing pathways, undergoes preliminary pattern separation in PHC, PRC, and EC, and finally reaches the hippocampus, where DG/CA3 subregions achieve complete separation representations, ultimately transforming highly overlapping perceptual inputs into non-overlapping neural signal outputs.

3.1 Cognitive Neural Mechanisms of Hippocampal Aging Effects on Mnemonic Discrimination

Hippocampal atrophy is common in aging (Kantarci et al., 2008; Raz et al., 2005) and is considered an important cause of memory decline in older adults. However, current research has found only weak correlations between total hippocampal volume and mnemonic discrimination in healthy older adults. Some studies combining younger and older adult samples have reported significant positive correlations between total hippocampal volume and mnemonic discrimination (Stark & Stark, 2017), while Doxey and Kirwan (2015) found no association in healthy older adults alone. Other research has shown that healthy older adults exhibit significant positive correlations with total hippocampal volume only when discriminating the most similar objects (Rizzolo et al., 2021). In contrast, studies examining the relationship between DG/CA3 subregion volume and mnemonic discrimination in older adults have yielded more consistent results: Doxey and Kirwan (2015) found significant positive correlations between DG/CA3 volume and mnemonic discrimination in healthy older adults, with smaller DG/CA3 volumes associated with poorer discrimination. Similar results have been reported in studies analyzing DG volume separately (Dillon et al., 2017; Riphagen et al., 2020). These findings suggest that DG/CA3 atrophy has a more significant impact on age-related mnemonic discrimination decline than overall hippocampal atrophy, possibly because different hippocampal subregions show different rates of atrophy during aging (Bussy et al., 2021; Pereira et al., 2014), and since DG/CA3 subregions constitute only a small portion of total hippocampal volume, their atrophy may not be reflected in overall volume changes. In summary, DG/CA3 volume is closely related to mnemonic discrimination, and age-related DG/CA3 atrophy may be an important contributor to decline in this ability.

Hippocampal volume atrophy is a continuous process, and researchers believe that microscopic structural damage occurs before measurable volume loss. Hippocampal microstructural integrity may be more predictive of mnemonic discrimination in healthy older adults than hippocampal volume (Leal & Yassa, 2018). A recent study found that DG microstructural damage (reduced cell density) measured by ultra-high resolution diffusion-weighted imaging was significantly associated with poorer mnemonic discrimination, with DG microstructural damage predicting discrimination performance even better than DG volume (Granger et al., 2022). Yassa et al. (2011b) also found that reduced dendritic integrity in DG/CA3 was related to mnemonic discrimination decline in healthy older adults. These findings suggest that age-related mnemonic discrimination decline begins with hippocampal microstructural damage and worsens as hippocampal structural integrity decreases, indicating that disruption of microneural circuits for pattern separation also contributes to this decline.

Beyond structural integrity loss, hippocampal functional activity also becomes abnormal in older adults. Numerous studies have shown that balanced excitatory and inhibitory activity (E/I balance) is a hallmark of healthy brain function

(Contreras & Wilent, 2005; Lopatina et al., 2019; Yizhar et al., 2011). Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system (McCormick, 1989) that plays a vital role in maintaining E/I balance (Bi et al., 2020). During aging or cognitive impairment progression, hippocampal GABAergic interneurons and GABA receptors decrease in number (Levenga et al., 2013; Martín-Belmonte et al., 2020), leading to weakened GABA signaling and insufficient inhibitory activity. A common functional change in older adults is increased hippocampal neuronal excitability or hyperactivation resulting from GABAergic system dysfunction (Jiménez-Balado & Eich, 2021; Tang et al., 2023). In mnemonic discrimination, researchers have observed hippocampal hyperactivation: healthy older adults show higher DG/CA3 activation when correctly discriminating lures compared to younger adults (Reagh et al., 2018; Yassa et al., 2011a), healthy older adults carrying the AD risk gene APOE 4 show higher DG/CA3 activation than non-carriers (Sinha et al., 2018), and when older adults develop MCI, their DG/CA3 activation levels increase further compared to healthy older adults (Corona-Long et al., 2020; Tran et al., 2017; Yassa et al., 2010a).

Hippocampal hyperactivation in older adults who have not yet developed AD has been established as a marker of neural damage and reduced neural efficiency. Studies of healthy older adults have demonstrated significant negative correlations between hippocampal hyperactivation and mnemonic discrimination, with higher hippocampal activation associated with poorer discrimination performance (Berron et al., 2019; Reagh et al., 2018; Yassa et al., 2011a). In MCI populations, researchers using low-dose antiepileptic drugs to treat patients found that DG/CA3 activation decreased significantly while mnemonic discrimination improved (Bakker et al., 2015; Bakker et al., 2012). Additionally, AD pathological research has found that biomarkers tau protein and amyloid β-protein (Aβ) are associated not only with mnemonic discrimination in older adults (Berron et al., 2019; Maass et al., 2019; Papp et al., 2021a) but also positively correlated with hippocampal activation during correct lure discrimination (Berron et al., 2019), with higher pathological biomarker levels associated with greater hippocampal activation. Thus, before developing AD, another important factor contributing to age-related mnemonic discrimination decline is hippocampal dysfunction, primarily manifested as hyperactivation due to reduced neural efficiency.

Research has also highlighted the importance of functional connectivity between the hippocampus and other brain regions for mnemonic discrimination. Animal studies have found that EC-to-DG functional projections can affect spatial discrimination performance (Yun et al., 2023), and human intervention studies have shown that increased functional connectivity between DG/CA3 and PHC can enhance mnemonic discrimination (Suwabe et al., 2018). Given that other MTL structures play a role in preliminary separation processing, it can be inferred that information exchange between the MTL and hippocampus facilitates representational sharing between the hippocampus and upstream brain regions. Therefore, age-related disruptions in information exchange between

the hippocampus and other brain regions would affect the precision of information entering the hippocampus, leading to mnemonic discrimination decline. This hypothesis is supported by recent findings: in cognitively normal older adults, those with relatively poor object mnemonic discrimination showed significantly increased resting-state functional connectivity between anterior LEC and hippocampal DG/CA3 compared to those with better discrimination, a change associated with Aβ pathology and neurodegeneration (Adams et al., 2022). Stark et al. (2021) found that during mnemonic discrimination, older adults showed significantly reduced functional connectivity between anterior hippocampus and PHC compared to younger adults, with this weaker connectivity related to poorer discrimination performance. Thus, beyond hippocampal structure and function, age-related changes in functional connectivity between the hippocampus and other brain regions also contribute to mnemonic discrimination decline.

In conclusion, in mnemonic discrimination, the hippocampus serves both as the core hub for pattern separation, achieving complete representational separation, and as a convergence zone integrating information from multiple brain regions. Age-related DG/CA3 volume atrophy and microstructural damage, reduced hippocampal neural efficiency, and impaired information exchange with other brain regions all contribute to mnemonic discrimination impairment. Brain aging centered on the hippocampus represents a key cause of age-related decline in mnemonic discrimination.

3.2 Cognitive Neural Mechanisms of Other Brain Region Aging Effects on Mnemonic Discrimination

Among MTL structures beyond the hippocampus, EC aging has been most extensively studied. Although numerous studies report significant EC volume atrophy in older adults (Devanand et al., 2008; Gellersen et al., 2023; Tran et al., 2022; Tran et al., 2017), no significant correlations have been found between EC volume and mnemonic discrimination (Tran et al., 2022). In contrast, the relationship between EC function and pattern separation is more clearly established. Research indicates that during aging or cognitive impairment progression, EC functional changes during correct lure discrimination are opposite to hippocampal changes: healthy older adults show significantly lower EC activity than younger adults when correctly discriminating lures (Reagh et al., 2018), and when MCI develops, patients show even lower EC activity than healthy older adults (Yassa et al., 2010a). Moreover, EC activity during correct lure discrimination is significantly positively correlated with mnemonic discrimination in older adults, with lower EC activation associated with poorer discrimination (Reagh et al., 2018). A clinical trial using very low-dose antiepileptic drug levetiracetam to treat MCI patients found that after treatment, mnemonic discrimination performance improved significantly while hippocampal activity remained unchanged, but EC activity increased to levels comparable to healthy older adults (Bakker et al., 2015). These results indicate that excessively low

EC activity also contributes to age-related mnemonic discrimination decline, reflecting reduced capacity for preliminary separation of similar information.

The impact of perforant path aging should not be overlooked. The perforant path is a crucial channel for information transmission from EC to DG and CA3 subregions. Animal studies have found that perforant path fiber loss is an independent factor causing mnemonic discrimination decline (Burke et al., 2018). In human research, Bennett and Stark (2016) used ultra-high resolution diffusion tensor imaging and found that after controlling for whole-brain white matter effects of aging, perforant path integrity significantly predicted mnemonic discrimination in older adults, with greater integrity associated with better performance—a result consistent with previous research (Yassa et al., 2010b). Notably, in cognitively normal older adults, perforant path integrity does not predict other memory performance (Bennett & Stark, 2016). Although the EC-to-hippocampus transmission channel is prerequisite for all hippocampal functions, minor damage to the perforant path does not significantly affect memory functions other than mnemonic discrimination, likely because the perforant path projects directly to DG, allowing even minor damage to directly impact mnemonic discrimination. This suggests that perforant path fiber loss is also an important cause of age-related mnemonic discrimination impairment.

In recent years, researchers have begun examining how age-related decline in prefrontal monitoring and cognitive control functions affects mnemonic discrimination. Behavioral studies have found significant positive correlations between executive functions (dominated by the prefrontal cortex) and MST-measured mnemonic discrimination in older adults (Gellersen et al., 2021; Jensen et al., 2023; Pishdadian et al., 2020). Although few studies have specifically examined the neural mechanisms of human prefrontal aging effects on mnemonic discrimination, neuroimaging research indicates that prefrontal volume atrophy and dysfunction negatively affect episodic memory in older adults (Ankudowich et al., 2019; Brehmer et al., 2020; Maillet & Rajah, 2013; Shao et al., 2022), and that disrupted prefrontal regulation of the hippocampus is closely related to cognitive impairment progression (Nyberg et al., 2019). Animal and human studies have also found that inhibiting prefrontal activity leads to significant mnemonic discrimination decline (Johnson et al., 2021; Wais et al., 2018). Combined, these findings suggest that reduced prefrontal structural and functional integrity, along with impaired information transmission and regulatory functions with the MTL and other brain regions, can severely impair mnemonic discrimination, though the specific cognitive neural mechanisms require further investigation.

Additionally, research teams have found that mnemonic discrimination also depends on the default mode network (DMN). Within the DMN, reduced resting-state functional connectivity between prefrontal and temporal regions in older adults compared to younger adults is associated with mnemonic discrimination decline (Wahlheim et al., 2022). In a recent study, Cui et al. (2023) found that increased resting-state functional connectivity between anterior and posterior

DMN in older adults was significantly correlated with improved mnemonic discrimination. Although DMN' s role in episodic memory is typically considered to be dominated by functional connectivity between the hippocampus or MTL and adjacent brain regions, other brain regions also undergo various changes due to aging. Therefore, future research should further explore the role of specific neocortical structures in mnemonic discrimination and the extent to which their aging affects this ability.

In conclusion, existing evidence demonstrates that mnemonic discrimination is supported by coordinated activity across large-scale brain networks, with aging effects in various brain regions contributing to varying degrees of decline. Aging of MTL structures beyond the hippocampus primarily affects preliminary separation processing and information transmission to the hippocampus, compromising the integrity of information entering the hippocampus and preventing accurate representation formation. Aging of brain regions in control networks such as the prefrontal cortex primarily affects information monitoring and top-down regulation of MTL structures like the hippocampus.

4 Applications of MST in Aging Research

Although no cure for cognitive impairment currently exists (Grabowska et al., 2023), numerous studies have confirmed that early intervention can delay AD progression (Gaugler et al., 2019; Rosenberg et al., 2018). Therefore, early identification of cognitive impairment is crucial for disease management and reducing AD incidence and progression. Traditional neuropsychological tests play an important role in cognitive impairment assessment, with researchers often using results from multiple cognitive domain tests to classify at-risk populations in clinical and community settings (Edmonds et al., 2019; Langbaum et al., 2020). However, completing comprehensive neuropsychological test batteries requires substantial time, and their administration and scoring depend on clinicians or experienced examiners, making independent testing difficult for older adults. Consequently, simple, easily administered electronic cognitive assessment paradigms that do not require professional examiners represent an important development direction for early identification of cognitive impairment.

MST holds substantial potential for early identification of cognitive impairment. Episodic memory impairment is a primary characteristic of AD, and baseline episodic memory performance has been identified as an important predictor of cognitive decline (Johnson et al., 2009; Schaeverbeke et al., 2021), with episodic memory scores showing significant negative correlations with AD pathology progression (Albert, 2011; Bennett et al., 2006; Moscoso et al., 2019). Therefore, most researchers use episodic memory paradigms for early identification, with recognition tests being the most common format. However, studies have confirmed that simple recognition ability cannot identify individuals with subtle memory impairment or those carrying the AD risk gene APOE 4 (Sinha et al., 2018; Stark et al., 2013). Although MST uses a recognition format, its effectiveness is superior to simple recognition tasks, with MST-measured mnemonic

discrimination effectively reflecting subtle memory impairments resulting from early cognitive impairment development. For example, research has shown that among healthy older adults, those with impaired recall function (measured by auditory verbal learning test) exhibit significantly reduced mnemonic discrimination compared to those with normal recall (Stark et al., 2013). Older adults with subjective memory decline show lower mnemonic discrimination than healthy older adults (De Simone et al., 2022), and carriers of the AD risk gene APOE 4 perform worse on MST than non-carriers (Sinha et al., 2018). Additionally, MST-measured mnemonic discrimination has demonstrated high accuracy in distinguishing between normal older adults and MCI patients, as well as between older adults with subjective cognitive decline and MCI patients (Belliart-Guérin & Planche, 2023; Kim et al., 2023). These findings indicate that MST is highly sensitive to cognitive decline and can effectively reveal subtle memory impairments that begin in the early stages of neurodegenerative diseases like AD, making it a promising tool for community-based cognitive impairment risk warning and clinical early screening.

Although researchers have developed multiple MST versions based on pattern separation principles, object and spatial/scene versions remain most widely used in aging research. The object version appears more suitable for early identification of cognitive impairment. Studies have found that older adults' ability to discriminate objects declines faster and earlier than their ability to discriminate spatial/scene information (Güsten et al., 2021; Reagh et al., 2016), with cross-species research yielding similar results (Johnson et al., 2017). This difference arises because object and spatial/scene pattern separation rely on different processing pathways. As previously discussed, spatial/scene pattern separation depends more on the PHC-MEC pathway, while object pattern separation depends more on the PRC-LEC pathway. The PRC-LEC pathway is more vulnerable to age-related functional decline (Burke et al., 2014), and LEC dysfunction is more prominent in preclinical AD stages (Khan et al., 2014). This may explain why the object version of MST can reflect earlier AD pathophysiological changes and offers advantages in early identification of cognitive impairment. Based on this, research teams are increasingly attempting to apply the object version of MST to portable electronic devices such as smartphones and tablets for unsupervised cognitive assessment (Papp et al., 2021a, 2021b), while continuously optimizing MST (Stark et al., 2023; Villarreal et al., 2022) through adaptive design and other methods to shorten assessment time and improve user experience, thereby promoting its widespread application in community and clinical settings.

5 Problems and Outlook

In recent years, researchers have used MST to deeply explore the cognitive neural mechanisms of mnemonic discrimination, revealing patterns and causes of age-related decline, and gradually promoting MST in community and clinical research for cognitive impairment risk warning and early identification. While current research has yielded many important findings, several pressing issues

remain.

First, when using fMRI to examine functional activity in different hippocampal subregions during pattern separation, most studies cannot completely separate DG and CA3 due to resolution limitations, only broadly investigating the contribution of DG/CA3 activity to pattern separation. However, animal studies have long indicated that DG and CA3 make different contributions to pattern separation (Knierim & Neunuebel, 2016; Neunuebel & Knierim, 2014). Therefore, precisely examining functional activity in DG and CA3 and their functional connectivity with other brain structures in human studies is essential. The development of 7T ultra-high field fMRI provides opportunities to address this issue. With this fine imaging technology, researchers have found that DG is the only hippocampal structure capable of forming completely different neural representations for similar scenes (Berron et al., 2016), and that young adults with different APOE genotypes show functional activity differences in DG and CA3, as well as differences in functional connectivity between DG and CA3, during pattern separation of similar spatial information (Lee et al., 2020). Thus, separately examining DG and CA3 in human participants can provide more information for mechanism research and important insights into cognitive impairment development. Future studies should more frequently attempt to independently investigate functional activity in DG and CA3 during pattern separation and their interactions with different brain regions in older adult populations.

Second, although current research emphasizes the role of the MTL, particularly the hippocampus, prefrontal aging effects on mnemonic discrimination may be no less significant than MTL aging. Studies have found that functional connectivity between bilateral inferior frontal gyrus and MTL increases significantly during correct lure discrimination compared to false alarms (Wais et al., 2017), suggesting that stronger regulation of the MTL is required during mnemonic discrimination. Therefore, prefrontal aging-induced decline in regulatory function may contribute to hippocampal hyperactivation, indirectly affecting older adults' mnemonic discrimination. This view is supported by evidence: a recent animal study indicated that the prefrontal cortex can inhibit hippocampal activity through long-range GABAergic projections (Malik et al., 2022), a working memory study in young adults found that reduced prefrontal regulation was associated with hippocampal hyperactivation (Xiong et al., 2021), and another study found that altered prefrontal activation during episodic memory encoding contributed to hippocampal hyperactivation in older adults (Nyberg et al., 2019). Future research should pay greater attention to prefrontal-hippocampal interactions in mnemonic discrimination, exploring age-related decline mechanisms from multiple perspectives and holistically to enable effective early interventions for maintaining cognitive health in aging.

Finally, current research on mnemonic discrimination in older adults remains dominated by small-sample cross-sectional studies, lacking large-sample and prospective cohort studies. Although MST shows good potential for cognitive impairment risk warning and early identification, establishing it as an effective

tool for clinical diagnosis assistance and risk assessment requires prospective cohorts to determine conversion rates to MCI or AD among older adults with different mnemonic discrimination levels, thereby classifying risk levels, as well as large-sample studies to establish normative data for different older adult populations. Therefore, future research should focus on applying MST in large-sample studies and establishing prospective cohorts.

6 Summary

Extensive research has deeply explored mnemonic discrimination function, revealing cognitive neural mechanisms underlying age-related decline from both structural and functional perspectives. Current studies have confirmed that reduced structural integrity and functional abnormalities in MTL structures such as the hippocampus, along with altered structural and functional connectivity between the hippocampus and other MTL regions, are key causes of mnemonic discrimination decline. Additionally, aging in widely distributed neocortical regions significantly affects mnemonic discrimination. Future research should combine more advanced neuroimaging techniques to independently examine the roles of hippocampal DG and CA3 subregions in mnemonic discrimination and aging effects, while paying greater attention to neural mechanisms by which neocortical structure aging, such as in the prefrontal cortex, affects mnemonic discrimination.

On the other hand, mnemonic discrimination measured by MST can effectively reflect early aging and abnormal aging effects on brain structure and function, giving MST tremendous potential for early screening and risk warning of cognitive impairment in older adults. However, large-sample and prospective cohort studies are still needed to further validate its effectiveness in early identification of cognitive impairment, while MST should be improved to become an electronic assessment tool that meets older adults' needs for active cognitive health monitoring.

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