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Mnemonic Similarity Task: A Tool for Assessing Hippocampal Integrity

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Abstract

The hippocampus is critical for learning and memory, relying in part on pattern separation processes supported by the dentate gyrus to prevent interference from overlapping memory representations. In 2007, we designed the Mnemonic Similarity Task (MST), a modified object recognition memory task, to be highly sensitive to hippocampal function by placing strong demands on pattern separation. The MST is now a widely used behavioral task, repeatedly shown to be sensitive to age-related memory decline, hippocampal connectivity, and hippocampal function, with specificity to the dentate gyrus. Here, we review the utility of the MST, its relationship to hippocampal function, its utility in detecting hippocampal-based memory alterations across the lifespan, and impairments associated with clinical pathology from a variety of disorders.

Keywords

hippocampus; pattern separation; discrimination; mnemonic similarity

Mnemonic Similarity Task

The hippocampus, a critical structure for learning and memory, is vulnerable to change associated with healthy aging [1,2], Alzheimer's disease [3,4], depression [5], schizophrenia [6], and other neurological diseases [7–9]. To assess the behavioral impact of hippocampal dysfunction, we designed the **Mnemonic Similarity Task (MST)** (see Glossary), a modified object recognition memory task, to be highly sensitive to hippocampal function [10,11] by placing strong demands on **pattern separation** [12] (see Box 1). Over the past decade, the MST has become an increasingly popular measure in memory research, having now been used in over 100 publications to assess memory in a wide range of populations. While there are multiple variants of the task and multiple dependent measures that can be derived, the nature of the similarity of the lures remains the key aspect of the MST that makes it a robust

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and reliable measure of hippocampal function. Further, the lack of test-retest effects [13–15] makes the MST an ideal task for assessing change associated with a variety of interventions. Here, we will cover a) the different variants of the task and how they may or may not affect the validity of the measures; b) the different outcome measures and what they are measuring; c) how the MST has been used to assess hippocampal function in different populations; and d) why the MST provides reliable and robust estimate of hippocampal function, making it an ideal clinical tool.

MST: Design and Measures

The traditional version of the MST (Figure 1) consists of two phases. In the first phase, participants engage in an incidental encoding task, making indoor/outdoor judgments for pictures of everyday objects. Immediately following this encoding task, participants are given instructions regarding a surprise recognition memory test in which they must identify each item as “Old”, “Similar”, or “New” (Figure 2A–C). One-third of the images in the test phase are exact repetitions of images presented in the study phase (targets); one-third of the images are new images not previously seen (foils); and one-third of the images are perceptually similar to those seen during the study phase, but not identical (lures). We are particularly interested in the responses to these lure trials and the rates at which participants correctly identify these as “Similar”, avoiding the propensity to identify them as “Old”. Discriminating these lure trials from the similar studied item requires a distinct representation of the objects – a hallmark of avoiding interference and having the detailed, or “high fidelity” memory that successful pattern separation would support (see Box 2). Additionally, the similar lures used in the MST vary in their degree of mnemonic similarity from very high similarity (L1) to very low similarity (L5). Typically, we assess lure discrimination performance by calculating the difference between the probability of giving a “Similar” response to the lure items minus the probability of giving a “Similar” response to the foils to account for any bias the participant may have in using the “Similar” response overall. We term this the **Lure Discrimination Index (LDI),** and it tracks the ability to remember the rich details of the encoding event needed to reject these similar lures rather than endorse them as “Old” (e.g., knowing not only that a leftward-facing seahorse was shown, but that it had a thinner body than the one currently shown). In addition to the LDI metric for evaluating lure discrimination performance, sometimes “Similar” responses to lures are compared to “Old” responses to lures [16,17]. This alternative measure of lure discrimination performance is fairly comparable to the LDI but does not account for a potential response bias in favor of “Old” or “New” responses to targets or foils.

To assess recognition memory for repeated items, we calculate a traditional “corrected recognition memory” (REC) score as the difference between the rate of “Old” responses given to the target items minus the corresponding rate of “Old” responses given to the foils (aka hits minus false alarms). These two metrics provide a valuable contrast because simple object recognition memory is not heavily impacted by hippocampal function, while we argue that LDI performance is critically dependent on hippocampal integrity. For example, patients with hippocampal damage are seemingly unimpaired relative to matched controls for REC while displaying strong impairments in LDI [18]. Further, REC remains reliably constant across age, while LDI declines substantially (Figure 2D/E) [11]. We have made this

version of the MST publicly available (https://github.com/celstark/MST), with 6 independent sets of curated lure items, designed to be balanced for lure similarity performance across sets.

Variants of the MST: Test format and responses

In addition to the study-test MST, a continuous recognition memory format involves making "Old", "Similar", and "New" responses for each item without a separate study phase. Using this variant, the number of intervening items between the first presentation and the lure item (i.e., the lag) can be controlled over a wide range and, as one might expect, "Similar" responses to lures decrease with lag [13]. Yet, a long delay between study and test is not required to assess lure discrimination impairments associated with aging or hippocampal sensitivity to lure discrimination.

Regardless of using separate study/test or continuous designs, the MST can be run using either the traditional three response choices ("Old", "Similar", "New") or using a simpler two-choice ("Old" vs. "New") format (see also Box 2). The three-choice response has the disadvantage that standard signal detection theory [19] cannot be used to assess performance as it is clear that these three responses do not lie along a simple unidimensional axis on which one might place thresholds [20]. The two-choice version can be modeled with signal detection and we can calculate the discriminability d' between not only the targets and unrelated foils (paralleling the traditional REC measure in the three-choice version) but also between either the targets and similar lures or between the similar lures and foils (paralleling the LDI measure) [13,21]. In addition, confidence ratings can be added to the two-choice version of the task for computing a receiver operating characteristic (ROC) curve, a popular measure of recognition memory performance [22]. Finally, a forced-choice format requires participants to discriminate between a target and a similar lure, which has been useful in examining the role of encoding variability on discrimination performance [23,24].

Variants of the MST: Stimulus domains and forms of similarity

In the standard objects-based version of the MST, the lures can vary based on a variety of features, such as color, rotation, detail elements. The strength of this design is that no single feature can be used for mnemonic discrimination, resulting in a task that is robust to strategic devices and practice effects [13–15]. If a variety of features can change to create a similar lure, strategies that reduce the information load by discarding useless information will be ineffective. For example, if the stimulus is a red rubber duck and we only ever change the color, all participants need to remember is "red-duck" in order to pass the test and reject a yellow duck when shown at test as a similar lure. They can engage in a lossy compression of the information, discarding a vast amount of data about the appearance of the duck, and still perform perfectly. However, when any object features can change, no such lossy compression scheme can be utilized.

In allowing any change, "similarity", must be derived empirically, by testing a large number of individuals and determining the false alarm rates (probability of responding "Old") for each lure pair [20]. For convenience, this *mnemonic similarity* is typically binned (i.e., items in Lure Bin 1 are highly similar and elicit false alarms quite often while those in Lure Bin 5

are far more dissimilar and have very few false alarms). While initially onerous to derive, mnemonic similarity is based on our end target – memory ability – and not on *perceptual similarity.* We should note that while we find similar behavioral findings when controlling the degree of lure similarity by parametrically rotating objects from 15° to 55°, showing greater lure discrimination with greater rotation [25], this need not always be the case and such systematic forms of variation may be more prone to strategy use (e.g., “rubber-duckie, 45 degrees”).

The MST was originally developed to parallel tasks used to assess pattern separation tasks in rodents, which typically probed memory for similar spatial locations using a cheeseboard maze [26,27]. Since the initial development of the MST, animal models have been extended to more closely model this human task in rodents, using either a touch-screen version of trial-unique delayed nonmatching-to-location task [28,29] or a rodent-based task using pairs of 3D LEGO® objects that vary in the similarity of their construction [30]. In humans, the core concept of the MST – using lure items of varying similarity to their studied counterpart – has been extensively explored in recent years. Thus, while the traditional MST utilizes variations on everyday objects, similar results have been reported using scenes [31–34], faces [10,35], perceptual and conceptual words [36], spatial displays [37–39], temporal designs [40,41], and emotional stimuli [42–44] (see Box 3). These alternative designs address specific issues and some use different dependent measures, but they all share the feature that as lure similarity increases, accurate discrimination decreases, as a universal phenomenon. These findings are consistent with the hypothesis that lure discrimination performance results from pattern separation processes largely dependent on the dentate gyrus of the hippocampus, which can be considered, at least to a first approximation, to be a “universal” pattern separator. Regardless of stimulus type or minor variations in study design, the integrity of the dentate gyrus is critical for accurate discrimination of similar lures, emphasizing the utility of the MST for assessing hippocampal integrity.

The Role of the Hippocampus in the MST

Hippocampal lesions in humans

We designed the MST to measure lure discrimination performance based on pattern separation computations executed by the hippocampus. Indeed, lure discrimination performance is impaired in amnesic patients with damage limited to the hippocampus, while recognition performance is intact [18]. Consistent with the role of the dentate gyrus for pattern separation processes, a rare patient with damage limited to the dentate gyrus showed selective impairments on discrimination of similar lures, while his recognition performance was normal [45]. Similar results have been reported for patients with CA1 specific lesions, a critical output structure of the dentate gyrus [46]

fMRI activity in the MST

Functional MRI (fMRI) has been used to investigate the role of the hippocampus in pattern separation and MST performance in healthy individuals, showing that activity in the hippocampus can distinguish between whether the lure was correctly discriminated or mistakenly identified as old [47,48], which can be further localized to some degree to the

DG/CA3 [10]. While the resolution of fMRI imposes limits on subfield specificity, the task design may also have an impact. For example, in our earliest investigation, we used the continuous version of the MST with Old", "Similar", or "New" responses made to each item [10]. In this study, while there was some evidence for subfield specificity, there was a large degree of overlap in the pattern of activity across hippocampal subfields. One potential source lies in the explicit nature of the task that may encourage participants to engage in a "recall-to-reject" strategy, in which to correctly reject a similar lure item, original target memory must be recalled for comparison. Extra sources of activity associated with this retrieval would then be superimposed upon activity more directly tied to pattern separation.

To address this confound and more cleanly parallel the incidental exploration paradigms used to identify pattern separation in place-cell recordings in the rodent [49,50], we employed a purely incidental version of the MST, making "indoor" or "outdoor" judgments for each item, regardless of repeat, lure, or foil status [20,51,52]. We leveraged the repetition suppression effect, the reduced blood oxygen-level dependent (BOLD) activity for repeated stimuli [53], to investigate BOLD activity to the lures. We hypothesized that, if a given subregion was engaged in or reflecting the processes of pattern separation, activity for lure would more like a new stimulus than a repetition. In contrast, regions exhibiting either **pattern completion,** or tracking the degree of match between the current item and one in memory, would exhibit lure activity that was similar to a repetition. Using this approach, we demonstrated activity consistent with pattern separation in the DG/CA3 of the hippocampus, where even highly similar lures were treated exactly like novel items. In contrast, we observed a markedly different pattern in the CA1, where lure activity was overall more consistent with repeated items and tracked the degree-of-match (mnemonic similarity) smoothly.

These findings have now been replicated at higher MRI field strengths (which can more readily isolate subfields) [33], when spatial and temporal demands were included [40,54,55], when pattern separation demands are high [56], when emotional modulation was included [57], and irrespective of the task-relevant expectations [58]. Thus, much like the rodent, we have evidence from the human that while CA1 responds to reinstatement of the same image [59] with graded activity for different exemplars, the dentate gyrus acts as a universal pattern separator [54], sensitive to even minor changes.

Diffusion imaging

While most of the work linking the MST to hippocampal connectivity using diffusion-weighted (DWI) imaging has been in the domain of aging (see Hippocampal Decline with Ag), one of the central conclusions of that work has been that aging provides a means to amplify individual differences. For example, we observed a relationship between integrity of the perforant path assessed with DWI and lure discrimination performance in older (but not younger) participants [60]. While not reliable in younger individuals, their scores fell along the same regression line, albeit with restricted ranges. In a larger sample, we found that both fornix integrity [61] and perforant path integrity [62] correlated with lure discrimination performance regardless of "brain age" (assessed by global diffusion metrics), suggesting that

the strength of hippocampal connectivity can drive performance on the MST outside of aging *per se*.

The Sensitivity of the MST to Brain Age

Hippocampal Development in Childhood

The hippocampus and its related circuitry show protracted development [63] that coincides with the steady improvement in declarative memory during development in childhood. The MST's LDI metric has been able to track hippocampal maturity, demonstrating a gradual increase in performance in 5-6 year-olds, 8-9 year-olds, 11-12 year-olds, and into to young adulthood, while recognition of repeated targets is relatively stable across groups [64–66]. In children ages 4-8 years old, there was a linear correlation with age and lure discrimination performance that was moderated by the volumes of the DG/CA3 over the course of development [67]. Thus, differences in the development of hippocampal circuitry contribute to the improvement of pattern separation processes throughout childhood into adulthood.

Hippocampal Decline with Aging

Following the gains in lure discrimination ability in childhood to young adulthood, the trajectory of lure discrimination performance steadily declines, while recognition of repeated targets remains stable [11] (Figure 2). Wilson et al. [68] proposed a model of age-related neurobiological changes to account for this memory decline that focuses on the hippocampal circuit and its surrounding projections. Most notably, aging leads to reduced input to the DG via the perforant path [69] that is coupled with a decrease in cholinergic input [70], reducing its ability to perform pattern separation. In addition, there is a reduction of inhibitory activity in the CA3's recurrent auto-associative fibers, which results in both **hyperactivity** and a bias towards pattern completion that is only compounded by the dysfunctional DG and its own reduced perforant path input. This neurobiological framework explains why aging would be associated with a shift away from memory driven by pattern separation (e.g., being able to rapidly encode events with high fidelity and keep them separate in memory from other, potentially similar events) and towards memory driven more by pattern completion (e.g., endorsing a similar memory probe is the same as a prior experience).

Behaviorally, there is plenty of evidence to support this hypothesis, with age-related declines in lure discrimination on the MST, while recognition memory remains intact [11,13,16,17,23,34,71]. These findings are consistent for the object-based MST, but also for spatial [39,55,72,73], temporal [41], and emotional variants [44]. There is some evidence that the object version is more sensitive to age-related decline compared to a spatial variant [37] or one that employed the use of scenes [32,34]. Further, lure discrimination performance is sensitive to individual variability in age-related decline, such that individuals who score within the range of younger adults on a word recall task (aged unimpaired) exhibit lure discrimination scores that are significantly higher than those who score within the normal range for their age (aged impaired) [11,37,38] (Figure 2F). These findings parallel those in rodents that are classified as aged impaired and unimpaired based on water maze performance and show a myriad of neurobiological changes with age that correspond to their impaired status [2,74].

These behavioral deficits in lure discrimination have also been tied to age-related alterations in hippocampal activity, particularly an increase in DG/CA3 activity using fMRI in older adults [75,76]. In contrast to the age-related changes in DG/CA3, neuroimaging of the CA1 subfield of the hippocampus appears unaffected and is consistent with robust pattern completion performance [75,77]. Similarly, the volumetric decrease of the DG is predictive of lure discrimination decline in older adults [34,71,78], while CA3 volume may predict object recognition performance [78]. Outside of the hippocampus, the ratio of activity in anterolateral entorhinal cortex (alEC) and DG/CA3 was predictive of lure discrimination performance in older adults, such that hypoactivity in alEC and hyperactivity in DG/CA3 resulted in greater pattern separation impairments [75]. Consistent with this finding, the integrity of the perforant path, connecting the EC to the hippocampus, deteriorates with age [79], which also correlates with lure discrimination declines in older adults [60,62]. A similar relationship has been observed with the fornix [61], which is major white matter tract connecting the hippocampus to other cortical and subcortical regions. These neuroimaging data support the predictions based on age-related dysfunction in the hippocampal circuit and its input: namely, a bias away from pattern separation processes, supported by the DG, and a bias towards pattern completion, supported by the recurrent collateral fibers in the CA3.

Modulations of Age-Related Deficits in Lure Discrimination

The age-related reduction in lure discrimination performance is remarkably consistent across studies but raises the question of whether other factors might contribute to performance on this task, aside from hippocampal dysfunction. Typically, the MST is administered with an incidental encoding task, which may result in older adults not attending to the item details. However, providing overt instructions during encoding by instructing participants that they would be tested with similar lures and showing samples of the test did not rescue lure discrimination performance in older adults [13]. Similarly, self-paced responses without time-pressure and Old/New instructions in place of the typical Old/Similar/New instructions also did nothing to alleviate the age-related decline in lure discrimination performance [13,80]. The only things that did alleviate performance deficits in older individuals was either the use of “gist” based instructions in which “Old” was the correct response for both targets and similar lures [13] or the use of a simple zero-lag delayed-matching version that relied purely on simple working memory maintenance [77]. Together, these indicate that it is the ability to remember the specific details in the face of interference that describes the age-related performance on the MST.

Hippocampal Pathology and Lure Discrimination

Mild Cognitive Impairment and Alzheimer’s Disease

The hippocampus is a site of some of the earliest pathological changes in Alzheimer’s disease (AD) [4], with **mild cognitive impairment (MCI)** representing a likely preclinical phase of AD [81]. As noted earlier, hippocampal hyperactivity has been observed using fMRI in individuals at greater risk for Alzheimer’s disease, including those with MCI [82] and those with the apolipoprotein E-ε4 (APOE4) allele [83–85]. Using the MST, individuals with MCI and AD have demonstrated deficits in lure discrimination performance beyond those simply associated with age [11,76,86–88], with additional impairments in repeated

target recognition in MCI [11,89] and AD [86], with increasingly greater deficits as AD symptom severity increased [90]. Impairments in lure discrimination have also been reported for carriers of the APOE4 allele [91–93], which has been linked to increased risk for AD [94,95]. Using fMRI, hyperactivity in DG/CA3 has again been linked to lure discrimination performance in MCI [76,92,93] and cerebral spinal fluid amyloid-β42 levels [96], which are also associated with AD pathology [97]. Thus, lure discrimination and recognition performance are both related to hippocampal dysfunction associated with both MCI and AD, leading to the MST's use in a number of clinical trials (see Box 4).

Depression, Anxiety, and Sleep

Memory impairments have been identified in patients suffering from depression [98], accompanied by a decline in hippocampal volume [5] that may be remitted by antidepressant use [99]. Indeed, the severity of depressive symptoms negatively predicts lure discrimination performance [100–103] and has been associated with worry that accompanies anxiety [104]. Additionally, the basolateral amygdala interacts with the DG/CA3 in mediating lure discrimination in older individuals with depressive symptoms, identifying a key pathway for memory loss associated with depression [105]. There are, of course, a number of potential covariates in this relationship. High levels of stress contribute to the pathogenesis of major depression [106], which may be contributing to the deficits in pattern separation processing. Sleep disturbances are well-known in depression and anxiety and post-encoding sleep improves lure discrimination more than wakefulness [107]. Conversely, sleep deprivation results in reduced lure discrimination performance, which is rescued with sleep recovery [108]. In addition, individual differences in DG/CA3 structure accounted for individual differences in lure discrimination deficits following sleep deprivation [108].

Other Diseases with Hippocampal Pathology

Schizophrenia has also been associated with memory deficits, which are a strong predictor of illness outcome [109] and tied to hippocampal dysfunction [6]. Individuals with schizophrenia show a deficit in lure discrimination on the MST compared to healthy controls [110], indicating a role for the dentate gyrus through reduced glutamate signaling [111] and reductions in neurogenesis [112]. Martinelli & Shergill [113] found additional deficits in recognition memory performance in individuals with schizophrenia, possibly reflecting more global hippocampal dysfunction, greater severity of symptoms, or visual discrimination deficits. Likewise, lure discrimination performance is reduced in patients with multiple sclerosis [7,9], temporal lobe epilepsy [8], patients with cerebellar tumors [114], and in first-episode psychosis patients [115]. In contrast, young adults with growth hormone receptor deficiency showed improved lure discrimination performance, consistent with brain structure and function of young adults [116]. Finally, individuals diagnosed with Autism Spectrum Disorder showed deficits in lure discrimination that were correlated with measures of negative emotionality, revealing a role for emotional regulation of hippocampal function in this disorder [117]. Thus, lure discrimination performance on the MST has proven to be a sensitive marker for hippocampal dysfunction across a broad range of diseases and disorders, providing a simple and reliable measure that can be completed by most individuals, even those with severe impairments.

Concluding Remarks

The MST was designed to assess pattern separation computations specific to the dentate gyrus subfield of the hippocampus. It has proven to be a robust and versatile paradigm, with multiple variations for both humans and animals. Importantly, these variants include similar lures that vary in their degree of similarity and repeated items to assess recognition to previously viewed target items. The results have proven to be stable when assessing lure discrimination decline in aging, MCI, depression, and other diseases. While we acknowledge that no behavioral task can provide the direct link to pattern separation processes, the neuroimaging and lesion data suggest that accurate performance on lures is highly dependent on the dentate gyrus. Thus, the sensitivity and reliability of the MST make it an extremely valuable tool for tracking progression of disease or decline and critical for determining the effectiveness of treatments, both pharmaceutical and behavioral (see Box 4 and Outstanding Questions).

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GLOSSARY:

Hyperactivity
greater firing rate in the hippocampus associated with aging and early dementia

Lure Discrimination Index (LDI)
the probability of “Similar” responses to lure items minus the probability of “Similar” responses given to the foils

Mild Cognitive Impairment (MCI)
older adults with memory impairments beyond that expected for their age and education, but are not yet demented

Mnemonic Similarity Task (MST)
a modified recognition memory task that includes both repeated items and similar lures

Pattern separation
neural computation whereby similar representations are transformed into distinct, non-overlapping representations

Pattern completion
neural computation whereby incomplete or degraded representations are transformed into previously stored representations by filling in the missing information

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BOX 1.

Pattern separation, the hippocampus, and the MST

Computational models have proposed pattern separation and pattern completion as primary functions of the hippocampus [118,119]. Pattern separation refers to the process whereby similar representations are transformed into distinct, non-overlapping representations. Pattern completion refers to transforming incomplete or degraded representations into previously stored representations by filling in the missing information. Both mechanisms are critical in associative memory, storing memories independently of each other, retrieving memories from partial cues, and flexibly applying stored memories to novel situations [12].

Activity in the dentate gyrus is markedly sparse, with very few neurons firing at any given time [120], leading to a strong reduction in potential overlap between patterns, making the dentate gyrus optimal for coding unique representations and sensitive to small changes in input, critical for pattern separation computations [121]. The CA3 contains an extensive recurrent collateral network of neurons, postulated to act as an auto-associative pattern completion network [118,122]. These recurrent collaterals may be involved in matching the input from the dentate gyrus with any stored representations [123]. The winner of the competition between the information sent from the dentate gyrus and the stored representation from the CA3 is then fed onto the CA1, which may play a role in matching sensory input with an existing memory trace, while the CA3 and dentate gyrus are involved in the detection of a mismatch with a stored representation [124,125].

In an effort to evaluate the output of these pattern separation computations, we designed the MST to assess recognition memory performance for highly similar lure items. Testing memory precision using similar lure items has been employed for decades in human memory research [126–129], often with the goal of investigating detail versus gist memory. We argue that these concepts, along with discrimination and generalization, all reflect the same underlying computations based on the balance of pattern separation and completion in dictating the behavioral output on these tasks. While any direct, absolute link to the computational notion of pattern separation is impossible, there is incredible value in approximating an indirect link. Thus, we are not arguing that the MST is direct measure of the pattern separation, but instead that behavior on this task is consistent with the predictions of these computations and there is clear evidence for the role of the hippocampus in supporting this behavior.

BOX 2.

Contributions to lure responses

There are several factors that may contribute to the discrimination of similar lures, including encoding variability, pre-existing memory traces, and visual acuity. Eye-tracking studies have revealed that lures that are later identified at “old” are associated with fewer fixations [130], suggesting that these false alarms might be due to impoverished encoding. Using a simple computational model, we showed that encoding variability can account for the pattern of data in a forced-choice format, suggesting that the number of details encoded can significantly impact lure discrimination success [23]. Indeed, the number of fixations during encoding was predictive of lure discrimination performance in the forced-choice version of the MST, reflecting the effect of superior encoding on subsequent discrimination [24].

The flip side to encoding quality is the match/mismatch of the incoming lure item to an existing memory trace, impacting successful lure discrimination. Increasing the repetitions of target items at encoding from 1 to 3 resulted in improved target recognition, but impaired rejection of similar lures [21,131]. If encoding variability emphasizes different features upon each encoding episode, it may result in a memory trace that enhances overlapping central features or gist of the repeated item, while reducing the contextual details that would contribute to successful discrimination of a similar lure item. Similarly, the memory trace can be broadened by presented multiple exemplars from a single category (e.g., bicycle), resulting in poor lure discrimination performance [132]. Detail vs gist representations can be captured by recollection (details) and familiarity (gist) processes, often assessed through Remember/Know (R/K) paradigms [133]. Using an R/K procedure, “remember” responses increase with lure similarity for lures that are successfully discriminated [134], which may be mediated by recollection processes [135,136] or greater memory strength [137]. Finally, performance on the prior trial (“Old” vs “New” response) may bias discrimination of the similar lure, resulting from a competition between encoding and retrieval or pattern separation and pattern completion processes [124]. Thus, both encoding quality and memory trace fidelity are factors contributing to lure discrimination performance.

Of course, perceptual ability itself could affect lure performance and this may be particularly problematic in studies of aging. With corrected vision, older subjects perform a simple working memory version of the MST at levels indistinguishable from young adults, indicating their impaired memory for lures is not the result of perceptual issues [77]. Without such correction and with age-related impaired vision, lure discrimination is decreased [138].

BOX 3.

Emotional valence and emotional modulation in the MST

To explore the effects of emotional modulation on mnemonic discrimination, an emotional variant of the MST has been developed [43,44,57]. Here, stimuli containing a positive, negative, or neutral emotional valence have been cultivated, along with lures that contain high or low similarity to the previously encoded item. Using this task, Leal et al. [43] found that young adults showed greater lure discrimination performance on the neutral items than either of the emotional valence conditions. In contrast, older adults demonstrated the reverse, with greater mnemonic discrimination of highly-similar positively-valanced lure items [44], consistent with a positivity bias observed in older adults [139]. Performance on emotionally-valanced lure discrimination engaged both the DG/CA3 and the amygdala, which was reduced in adults with depressive symptoms [57,105] and may rely on the alpha band to synchronize hippocampal-amygdala coupling [140]. Thus, the emotional MST has proven to be a useful tool in exploring the emotional modulation of pattern separation processes in the hippocampus and its interactions with age and depression.

Emotional arousal at encoding has been shown to improve memory performance, the extent of which is positively correlated with endogenous norepinephrine (NE) in animals and humans [141,142]. The hippocampus, and the dentate gyrus in particular, contains a high concentration of NE receptors and receives NE input via projections from the perforant path [143]. Manipulating emotional arousal prior to encoding of the MST revealed a positive relationship between NE levels and lure discrimination performance, revealing a role for the modulation of pattern separation processing by NE [144], which may be further enhanced for negative stimuli [145]. Similarly, undergoing a stressor immediately following the encoding portion of the MST later enhanced mnemonic discrimination of similar lures [146]. In addition to acute modulation of emotion, individual variability in fear generalization can also result in diminished lure discrimination performance [147,148]. These findings are consistent with the post-encoding enhancement of lure discrimination following acute caffeine administration [149], emphasizing the importance of encoding strength for later lure discrimination accuracy.

BOX 4.

Use in Interventions and Clinical Trials

Interventions aimed at improving hippocampal function have utilized the MST to demonstrate improved lure discrimination alongside a backdrop of stable measures of traditional recognition memory. For example, environmental enrichment has been shown to improve hippocampal function in rodents [150], particularly following the exploration of a large, novel environment [151]. As a proxy in humans, we have shown that 2-weeks of playing an immersive 3D video game resulted in improved LDI [14], replicating these findings in older adults [152] and following 4-weeks of a real-world navigation task [153]. The novelty and richness of individual experience appear to be the driving factor. For example, when separately controlling spatial exploration and learning new complex skills within a game, we found that the degree of engagement in both correlated with LDI improvement [15]. Importantly, when these components were substantially reduced, no improvement in LDI was observed across test sessions. Acute exercise has also been associated with increased lure discrimination performance on the MST [154], particularly in those with no or mild depression, but not with moderate or severe depressive symptoms [104]. Likewise, young adults who engaged in a longer (6-weeks) exercise intervention [101,155] and young and older adults with higher aerobic fitness levels [156,157] also demonstrated greater mnemonic discrimination of similar lure items.

In addition to behavioral interventions, performance on the MST has been used as an outcome measure following pharmaceutical interventions to improve hippocampal function, particularly in individuals with mild cognitive impairment (MCI). Using a low-dose of the antiepileptic drug, levetiracetam, MCI patients showed a reduction in hippocampal hyperactivity, specifically the DG/CA3, that also corresponded to improved lure discrimination performance on the MST [87,88]. Separately, older adults who took an oral supplement of spermidine, which has been shown to have numerous health benefits [158], exhibited improved lure discrimination behavior on the MST following a 3-month intervention period [159]. It has also been included in several large-scale clinical trials on aging and dementia, including A4 and HOPE4MCI, as an outcome measure for hippocampal function, in part due to the LDI's sensitivity to hippocampal function and its robustness to test-retest or practice effects [13–15]. For example, recent work in the A4 trial has shown that the MST, along with one-card learning and a one-back task, were the only reliable predictors of Aβ− vs. Aβ+ status in cognitively normal adults [160].

OUTSTANDING QUESTIONS:

- Could the MST be adapted to be a simple and reliable tool for use by clinicians for routine, repeated assessment of older adults to track memory decline associated with dementia?
- Could the MST be useful in identifying hippocampal dysfunction associated with other clinical pathologies and behavioral diagnoses, such as post-traumatic stress disorder or the effects of radiation or chemotherapy?
- Could the use of antidepressants alter hippocampal function and thus improve performance on the MST?

HIGHLIGHTS:

- The Mnemonic Similarity Task (MST), a modified object recognition memory task, is highly sensitive to hippocampal function, placing strong demands on pattern separation processes.
- A variety of MST versions have been developed to address specific issues, but they all share the feature that as lure similarity increases, accurate discrimination decreases.
- The MST has been used to identify hippocampal dysfunction associated with healthy aging, dementia, Schizophrenia, depression and other clinical disorders.
- The sensitivity and reliability of the MST make it an extremely valuable tool for tracking progression of disease or decline and critical for determining the effectiveness of treatments, both pharmaceutical and behavioral.

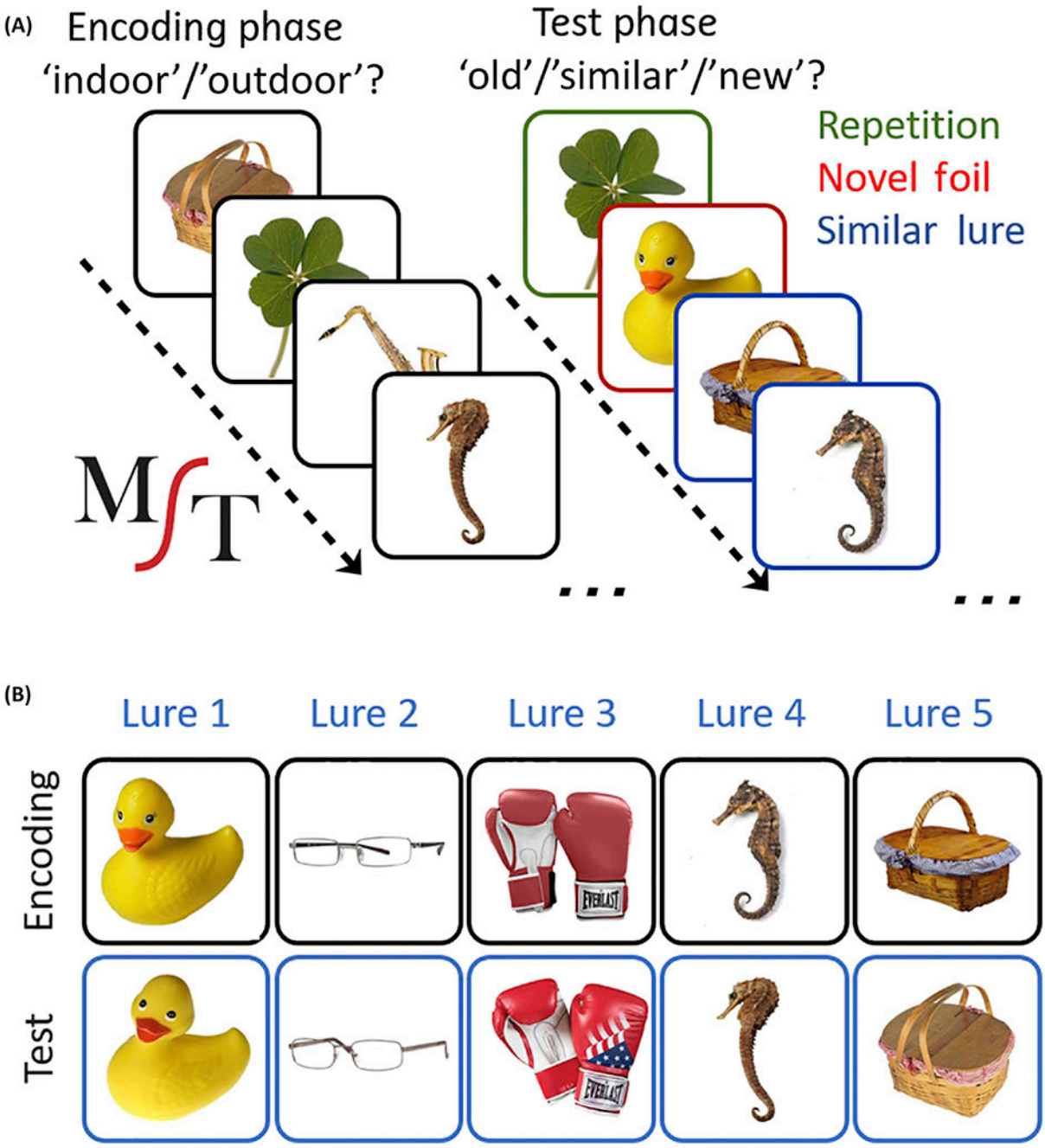

Figure 1. Mnemonic Similarity Task.

A) Examples of stimuli during the incidental encoding and subsequent Old/Similar/New recognition task. Colored boxes are to illustrate conditions, but not used during the actual task administration. B) Examples of images for each of the lure bins, ranging from most similar (lure bin 1) to least similar (lure bin 5).

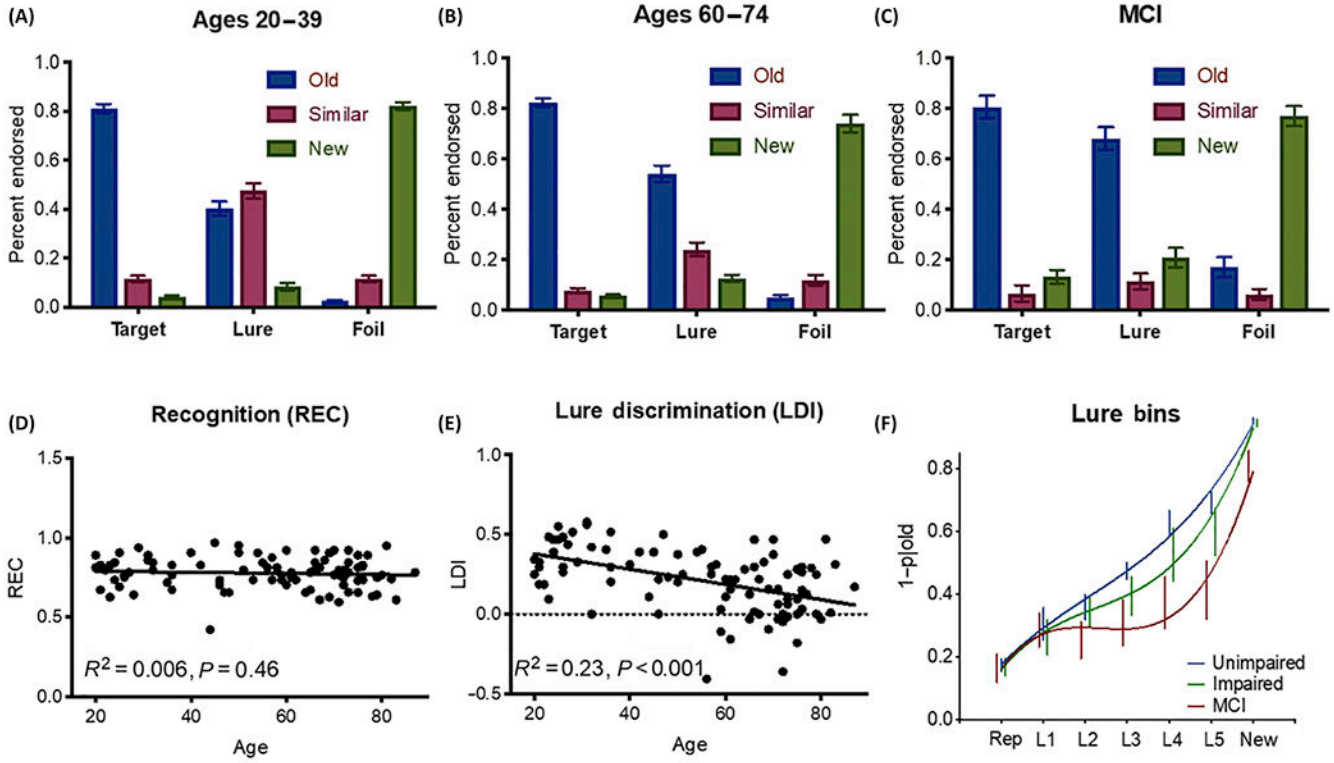

Figure 2. Old, Similar, and New responses for Targets, Lures, and New Foil items.

In young (A; 20-39), older (B; 60-74) and MCI (C) participants, LDI declines with age and MCI (D), while REC remains stable in healthy aging (E). Older adults who are impaired relative to young adults and those with MCI show different trajectories in discriminating lures across similarity bins (F).