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Review

Mnemonic Similarity Task: A Tool for Assessing Hippocampal Integrity

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The hippocampus is critical for learning and memory, relying in part on pattern separation processes supported by the dentate gyrus (DG) 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 DG. 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.

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 (AD) [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] (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 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: (i) the different variants of the task and how they may or may not affect the validity of the measures; (ii) the different outcome measures and what they are measuring; (iii) how the MST has been used to assess hippocampal function in different populations; and (iv) 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 (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'

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.

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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, nonoverlapping 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 DG 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 DG 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 DG with any stored representations [123]. The winner of the competition between the information sent from the DG 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 DG 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 a 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.

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, that are not yet demented.
Mnemonic Similarity Task (MST): a modified recognition memory task that includes both repeated items and similar lures.
Pattern completion: neural computation whereby incomplete or degraded representations are transformed into previously stored representations by filling in the missing information.
Pattern separation: neural computation whereby similar representations are transformed into distinct, nonoverlapping representations.

(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 with ‘old’ responses to lures [16,17]. This alternative measure of lure discrimination performance is fairly comparable with 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 (a.k.a. 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 six 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.