

Investigation of the relationship between visual feature binding in short- and long-term memory in healthy aging

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Binding visual features into coherent object representations is essential both in short- and long-term memory. However, the relationship between feature binding processes at different memory delays remains unexplored. Here, we addressed this question by using the Mnemonic Similarity Task and a delayed-estimation working memory task on a large sample of older adults. The results revealed that higher propensity to misbind object features in working memory is associated with lower lure discrimination performance in the mnemonic similarity task, suggesting that shared feature binding processes underlie the formation of coherent short- and long-term visual object memory representations.

An episodic memory system must represent potentially overlapping memories in such a way as to be able to discriminate between similar memory representations at retrieval without interference (McCloskey and Cohen 1989). Computational models of the medial temporal lobe suggest that pattern separation is one means by which memory systems form distinct, nonoverlapping memory representations (McClelland et al. 1995; Norman and O'Reilly 2003). Lesion studies with rodents (Hunsaker and Kesner 2013), neuropsychological studies with amnesic patients (Kirwan et al. 2012), and neuroimaging studies with young adults (e.g., Bakker et al. 2008) and healthy older adults (Yassa et al. 2011) all provide evidence for pattern separation processing in the hippocampus.

In humans, the mnemonic similarity task (MST) is a behavioral paradigm that has been used extensively to examine pattern separation processing by placing heavy demands on mnemonic discrimination (Stark et al. 2019). In the MST, participants must encode a series of objects for a later recognition memory test. At test, participants must discriminate between novel objects, repeated objects, and lure objects that are semantically and perceptually similar to studied items. Mnemonic discrimination performance is taken as the ability to correctly identify lure stimuli as similar to, but not identical with studied items. Accordingly, successful lure discrimination requires participants to form distinct memory representations of various perceptual details or object features that may be altered in the similar lure stimuli.

It has been proposed that the hippocampus serves to bind features within a representation with high resolution regardless of the duration of the memory delay (Pertsov et al. 2013; Yonelinas 2013). In support of this, recent research has demonstrated that object features are processed separately within visual working memory (WM) and that successful WM requires storage of both the object features and the bindings between features (Bays et al. 2011). Gorgoraptis et al. (2011) examined interference in WM representa-

tions using a dynamic updating paradigm in which visual stimuli were presented sequentially in rapid succession. Using stochastic modeling, these authors demonstrated that recall errors occurred due to misbinding of different object features in WM rather than temporal decay of information, supporting the importance of feature binding in successful memory performance at very short delays. While some authors have suggested that age-related WM declines may be due in part to deficits in object-feature binding (Cowan et al. 2006; Peich et al. 2013; but see, e.g., Read et al. 2016), others suggest that WM binding deficits are particularly diagnostic of hippocampal pathology, for example as in prodromal Alzheimer's disease (AD) (Pertsov et al. 2015; Brown et al. 2017). Indeed, AD patients (Della Sala et al. 2012) and otherwise healthy adults at risk for familial AD (Parra et al. 2010) demonstrate binding deficits in WM tasks.

Studies of mnemonic discrimination have shown that MST performance is largely independent of WM capacity. Bennet and Stark (2016) demonstrated in a factor analysis that digit span scores and MST lure discrimination loaded on separate factors. Older adults perform a WM version of the MST as well as younger adults but have impaired lure discrimination in the standard, long-term version (Lacy et al. 2011; Yassa et al. 2011). However, none of these studies have examined the relationship between pattern separation processes in long-term memory and its relationship with feature binding in WM, which may be a more sensitive measure than “quantal” measures of WM capacity such as digit span (Zokaei and Husain 2019).

In the current study we aimed at filling this gap by investigating the relationship between performance measured on two experimental tasks administered to a large cohort of older adults. Specifically, we examined the relationship between the MST

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assessing long-term retention and a visual WM task using a delayed-estimation technique reflecting the quality of WM representations. In our study, we demonstrate first that discrimination of long-term memories and the successful binding of object dimensions are related processes.

In order to assess the quality of visual WM representations, we applied a modified version of a delayed-estimation task of Gorgoraptis et al. (2011), where we tested the participants' memory for orientations—for a detailed description of the task, experimental procedure, and data analysis please see our previous work (Manga et al. 2020). In one trial of the WM task, three bars with different colors and orientations appeared consecutively on the screen, followed by a short retention interval and a probe bar. The orientation of the probe bar was adjustable using the keyboard of the computer, and its color was identical to one of the three bars previously shown in the current trial (target bar). Participants were instructed to memorize the color and orientation of all three bars in the stimulus sequence, and then report the orientation of the target bar as accurately as possible by rotating the probe bar. Thus, for successful memory performance, subjects had to retain both color and orientation information of the stimuli. Participants completed twelve runs of the visual WM task, with 36 trials per run. Position of the target bar in the stimulus sequence was randomized and equalized across runs, resulting in three experimental conditions (recall first, recall second, and recall third bar), with 144 trials per condition. We applied a probabilistic model (Bays et al. 2009; Suchow et al. 2013) on the data, which suggests that one possible reason behind committing an error on this task is the insufficient binding of different features of a memory item (in this case, color and orientation of a bar), also known as misbinding. Using the Swap Model, we estimated the probability of misbinding in the case of each subject, first over each trial of the experiment (overall misbinding) and then separately for the three conditions (misbinding for first, second, and third target positions), with higher probabilities of misbinding indicating poorer memory performance.

To examine long-term mnemonic discrimination, subjects completed the Mnemonic Similarity Task (MST) (Stark et al. 2019). The task started with an incidental encoding phase, where participants were instructed to make indoor/outdoor classification judgements of everyday objects presented on the computer screen. Thereafter, in a surprise memory task a portion of the images presented during the encoding phase (target images) were shown to the participants, intermixed with photographs depicting visually and semantically similar objects (lure images) and with new objects previously not presented (foil images). The subjects' task was to make old/similar/new judgements of the stimuli, where the correct answer for target, lure, and foil images was old, similar, and new, respectively. We calculated the discrimination score (reflecting pattern separation) as the proportion of lure items correctly labeled as similar minus the proportion of foil items labeled incorrectly as similar, with higher discrimination scores indicating better memory performance.

In our previous work (Manga et al. 2020) we presented the visual WM data of 71 healthy older adults, who also completed the MST (the data obtained in the latter task was not previously published). The MST data files of two older adults were not saved, and data from three older adults were unusable due to technical failure. Furthermore, six older adults did not choose the "similar" and one older adult did not choose the "new" option during the course of the task, thus were not complying with the task instructions (Stark et al. 2015; Stark and Stark 2017) and were excluded from the analysis. The remaining sample involved 59 older adults (37 female, mean age: 67.186 yr, standard deviation [SD]: 4.925 yr, age range: 60–89 yr). Each participant reached the criterion score of intact general cognition on Mini-Mental State Examination

(MMSE) (Folstein et al. 1975), with a mean MMSE score of 28.966 (SD: 0.765, range: 28–30). Participants reported normal or corrected-to-normal vision, intact color-vision, and no history of psychiatric or neurological diseases. Data collection took place in the Brain Imaging Centre at Research Centre for Natural Sciences in Budapest, Hungary, all subjects were remunerated for their participation and gave their informed consent prior to starting the experiment. The research protocol applied was designed and conducted in accordance with the Hungarian regulations and laws, and was approved by the National Institute of Pharmacy and Nutrition (file no. OGYÉI/70184/2017).

The discrimination scores (mean [M]=0.153, standard error of the mean [SEM]=0.021) were comparable to those observed in the study of Stark and colleagues investigating the effect of aging on pattern separation (Stark et al. 2013). Furthermore, the exclusion of 12 participants from the larger sample of 71 older adults published in Manga et al. (2020) did not appear to alter the average probability of misbinding (M=0.073, SEM=0.007 in the group of 59 older adults). Since previous studies showed that the recall performance is affected by the serial position of the target in the stimulus sequence (Gorgoraptis et al. 2011; Brown et al. 2017; Hitch et al. 2020), we also tested whether the position of the target bar affects the probability of misbinding using repeated measures analyses of variance (ANOVA) with position as a within-subject factor (Fig. 1). We found a significant main effect of position on misbinding ($F_{(2,116)}=23.290$, $P=3.139 \times 10^{-9}$), with post hoc comparisons (Bonferroni method) revealing significantly higher probability of misbinding when the first ($P=7.315 \times 10^{-5}$) and the second ($P=2.643 \times 10^{-7}$) bar was tested compared to the third bar, and a tendency of higher misbinding scores when the second bar was tested compared to the first bar ($P=0.068$).

The main objective in the current study was to investigate the presence of a connection between pattern separation and binding of object features. Proceeding from the position-related alterations of the misbinding probabilities, we inspected this relationship not

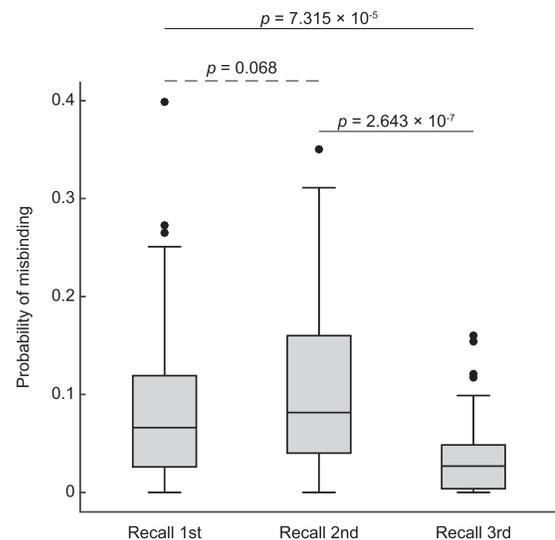


Figure 1. The box plot illustrates the probability of reporting the orientation of a nontarget item by mistake (feature misbinding) in the WM task, separately for the three possible position of the target bar in the stimulus sequence with recall first (M=0.082, SEM=0.010), recall second (M=0.104, SEM=0.011), and recall third (M=0.034, SEM=0.005) conditions. Higher values of misbinding indicate poorer recall performance. On each box, the central line indicates the median, the box limits indicate the lower and upper quartiles, and the whiskers indicate the extreme values not considered outliers (outliers are depicted as black dots).

only for overall misbinding scores, but also for misbinding scores estimated separately for the three possible target positions. We assessed the relationship between discrimination scores and the probability of misbinding (overall misbinding, and misbinding in the three target positions) using skipped Spearman's correlations computed with the robust correlation toolbox (Pernet et al. 2013). Bivariate outliers were detected (applying the Carling's modification of the box plot rule) and removed from the sample prior to the calculation of the correlation values. The number of tested correlations (NC) was four. Bootstrap confidence intervals (CIs) were determined based on 1000 samples, and were adjusted using Bonferroni correction to the NC, likewise the significance levels (corrected significance value [P_c] < 0.05, 98.75% bootstrap CI).

The investigation of the relationship between discrimination scores and probabilities of overall misbinding (misbinding data not split by positions) revealed a significant negative correlation between the two variables ($r_{s57} = -0.342$, $P_c < 0.05$, 98.75% CI = [-0.590, -0.012], number of bivariate outliers [NO] = 0) (Fig. 2A). Discrimination did not show significant correlation with the probability of misbinding when the first stimulus in the sequence was tested ($r_{s53} = -0.236$, $P_c > 0.05$, 98.75% CI = [-0.557, 0.079], NO = 4) (Fig. 2B). Furthermore, we found no evidence of significant relationship between discrimination and misbinding for the third stimulus ($r_{s56} = 0.038$, $P_c > 0.05$, 98.75% CI = [-0.329, 0.358], NO = 1) (Fig. 2D). However, in the condition when the second stimulus was the target bar, discrimination and the probability of misbind-

ing prove to correlate significantly, in a negative direction ($r_{s55} = -0.420$, $P_c < 0.05$, 98.75% CI = [-0.672, -0.114], NO = 2) (Fig. 2C). To summarize, mnemonic discrimination scores are related to the probability of misbinding when investigated across the conditions (overall misbinding score), moreover the probability of misbinding in the second target position plays a crucial role in the observed relationship.

In order to rule out the possibility that the observed relationship of discrimination and misbinding scores emerged as a result of a more general connection between the tasks, we ran an additional correlation analysis between the discrimination scores and the remaining two model parameters provided by the swap model estimated in the overall condition; i.e., the variability in the memory for the target orientation and the probability of random guessing (NC = 2, $P_c < 0.05$, 97.5% bootstrap CI). Neither variability ($r_{s55} = -0.239$, $P_c > 0.05$, 97.5% CI = [-0.484, 0.064], NO = 2) nor the probability of guessing ($r_{s50} = -0.150$, $P_c > 0.05$, 97.5% CI = [-0.441, 0.145], NO = 7) showed significant correlation with the discrimination scores of the MST.

In our study we present evidence of a correlation between feature misbinding and decreased lure discrimination performance in old age. One potential mechanism by which this might occur is domain-general decline of cognitive functions in aging. A recent study suggests that age-related impairments in mnemonic discrimination (Toner et al. 2009; Doxey and Kirwan 2015; Stark et al. 2015; Stark and Stark 2017) are, in part, due to domain-general cognitive impairments in dynamic updating of WM contents (Foster and Giovanello 2020). However, the evidence for this assertion is weak as the reported group differences between young and older adults were "marginally" or "trend(ing)" significant (Foster and Giovanello 2020).

Rather, the present results suggest that interference between memoranda occurs in WM just as in the case of long-term retention challenging successful cognitive performance, and the susceptibility to this interference measured on both the WM delayed-estimation and MST tasks may have common neural mechanisms. Yonelinas (2013) proposed a model of hippocampal function wherein the hippocampus serves to create high-resolution bindings that link together different aspects of events, thus accounting for deficits following hippocampal damage in perceptual and WM tasks with high interference loads. Numerous studies have demonstrated impairments in WM binding in AD (Parra et al. 2009, 2011, 2015; Della Sala et al. 2012; van Geldorp et al. 2015; Cecchini et al. 2017) and mild cognitive impairment (Das et al. 2016; Pietto et al. 2016). Parra et al. (2010) demonstrated that both patients with familial AD caused by the E280A single *presenilin-1* mutation and carriers of the mutation who did not meet diagnostic criteria for AD were also impaired at feature binding in a WM task compared to controls, indicating that WM feature binding may be a sensitive test of hippocampal-dependent high-resolution binding. Further evidence comes from temporal lobectomy patients

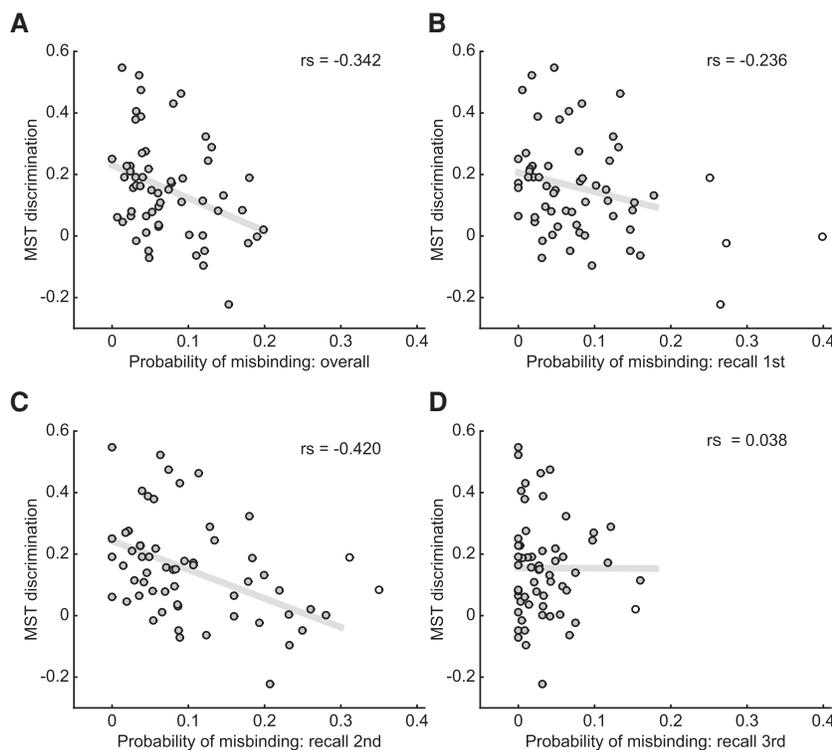


Figure 2. The scatter plots illustrate the relationship between discrimination scores obtained in the MST task, and the probability of reporting the orientation of a nontarget item by mistake (feature misbinding). While A illustrates misbinding scores estimated over each trial of the experiment, regardless of serial position, B–D depict misbinding scores estimated separately in the three conditions, with B illustrating misbinding scores when the first, C when the second, and D when the third bar of the sequence was tested. On each scatter plot, higher discrimination scores and lower misbinding probabilities indicate better long-term memory and working memory performance, respectively. Each circle represents one participant, subjects detected as bivariate outliers are marked with unfilled circles. Gray lines indicate the best linear fit to the remaining data points (not including bivariate outliers).

who show selective impairments for WM binding but not for single features such as object identity or location (Zokaei et al. 2019). Finally, while some studies suggest a relationship between hippocampal volume and WM binding performance (Parra et al. 2019) others have failed to detect this relationship (Valdés Hernández et al. 2020). The role of hippocampus is crucial not only in WM but also in long-term memory, supporting the discrimination of similar episodic memory representations (for a review, see Yassa and Stark 2011). In a current review (Zokaei and Husain 2019) the authors argue that the hippocampus is involved in the retention of binding information irrespective of how long the binding information is maintained. Future studies will be needed to confirm whether the WM misbinding effects observed here have a hippocampal basis and whether they may be related to functional markers of pattern separation processes known to be involved in long-term mnemonic discrimination.

Here, we show that a higher propensity to misbind features to objects in WM is related to lower lure discrimination performance in long-term memory. The observed association is likely to be driven by the probability of misbinding when the second item of the stimulus sequence was tested, which is in line with previous studies suggesting that the middle of three items in a WM paradigm has the highest susceptibility to interference, particularly for older adults (Brown et al. 2017). While the first item of the sequence is less prone to interference reflecting the primacy effect, a larger recency effect emerges in the case of the final memorandum (Oberauer 2003) that involves the binding of object features as well: Participants retain bound features as well as individual features when the last item is tested from sequentially presented stimuli (Baddeley et al. 2011). Taken together, we suggest that the relationship between mnemonic discrimination and feature binding in WM may reflect a potential mechanism for increased interference between representations in both working and long-term memory, possibly with a hippocampal basis.

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