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Research Report

Aging Neuromodulation Impairs Associative Binding

A Neurocomputational Account

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ABSTRACT—Relative to young adults, older adults are particularly impaired in episodic memory tasks requiring associative binding of separate components into compound episodes, such as tasks requiring item-context and item-item binding. This associative-binding deficit has been attributed to senescent changes in frontal-hippocampal circuitry but has not been formally linked to impaired neuromodulation involving this circuitry. Previous neurocomputational work showed that impaired neuromodulation could result in less distinct neurocognitive representations. Here we extend this computational principle to simulate aging-related deficits in associative binding. As expected, networks with simulated deficiency in neuromodulation resulted in less distinct internal representations than did networks simulating the processing and performance of young adults, and were also more impaired under task conditions that required associative binding. The findings suggest that senescent changes in neuromodulatory mechanisms may play a basic role in aging-related impairment in associative binding by reducing the efficacy of distributed conjunctive coding.

Central to memory and perception are mechanisms that afford dynamic, versatile integration of information (Johnson, 1992; Treisman, 1999). Memory of daily events often involves various components, such as the content of a conversation, the persons involved, and the time and place at which the conversation took place. Aging compromises mechanisms for binding together multiple aspects of a memory episode (e.g., Chalfonte & John-

son, 1996; Light, 1991). Older adults show deficits in remembering contextual details, such as whether an event was seen or heard and whether it happened at one or another possible location (Spencer & Raz, 1995). Older adults also recall less well than younger adults when different features of a memory item (e.g., shape and color) need to be combined (e.g., Chalfonte & Johnson, 1996). Memory for relations between items is affected by age as well; an aging-related deficit in paired-associate memory is evident (e.g., Kliegl & Lindenberger, 1993). Together, these various forms of memory decline have been taken to indicate that older adults have a deficit in associative binding, whether it involves associating content and context, concatenating features into a compound memory item, or generating relations between different items (Naveh-Benjamin, 2000).

Aging-related deficits in memory binding have been attributed to declines in frontal-hippocampal circuitry (e.g., Mitchell, Johnson, Raye, & D'Esposito, 2000). These deficits, however, have not been formally linked to impaired neuromodulation within this circuitry. Extant evidence suggests that aging-related declines in various neurotransmitter systems (e.g., acetylcholine and catecholamine) contribute to aging-related memory deficits (Arnsten & Goldman-Rakic, 1985; Bäckman et al., 2000; Braver et al., 2001). Extending a neurocomputational theory relating cognitive aging to senescent changes in neuromodulation (Li, Lindenberger, & Sikström, 2001), we present a simulation that explores the relation between impaired neuromodulation of conjunctive coding and older adults' deficit in memory binding.

THE SIMULATION

Theories of associative networks suggest that efficient conjunctive coding requires a neural network's processing units to be selectively sensitive to subsets of features, rather than to all features (e.g., Graham & Willshaw, 1995). Equation 1 shows the

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sigmoidal activation function of a neural network, with i and t indexing the network's units and processing steps, respectively.

$$\text{Activation}(G_i, \text{input}_{i_t}) = \frac{1}{1 + e^{-(G_i \cdot \text{input}_{i_t} + \text{bias})}} \quad (1)$$

It was previously shown that simulating aging-related decline in neuromodulation by stochastically reducing the gain parameter (G) of network units' activation function at each processing step led to less distinctive internal stimulus representations, which then resulted in deficits similar to those seen in cognitive aging (Li et al., 2001). Less distinctive internal representation is the flip side of efficient conjunctive coding because more processing units are required to code feature combinations of different stimuli. Less distinctive representation can lead to erroneous conjunctions, which are deleterious in distributed and context-dependent coding (Singer, 1998), undermining memory binding and spreading memory errors (e.g., Roediger & McDermott, 2000). In the present study, we applied this principle to model aging-related deficits in associative binding.

Older adults' associative-binding deficit has been systematically investigated in recent experiments (e.g., Naveh-Benjamin, 2000, Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003). One experiment specifically demonstrated that aging affected associative more than item memory in a joint memory paradigm requiring recognition of items and associations (Naveh-Benjamin, 2000, Experiment 2). The participants were presented with pairs of unrelated words (e.g., *chair-mail*) during study and were instructed to study each pair either as two single words (the "words" instruction) or as a pair (the "pairs" introduction). Later, recognition tests were given, without time constraints, to assess both associative and item memory. The associative test required distinguishing studied (target) pairs from pairs (lures) formed by recombining words in studied pairs; the item test

required distinguishing studied (target) from nonstudied (lure) words. Older adults performed more poorly than young adults on both the item and the associative tests; however, older adults showed a greater memory deficit for the associative test than for the item test. Moreover, when the associations between word pairs were memorized intentionally (i.e., under the pairs instruction), older adults' deficit relative to younger adults was particularly large.

We constructed a dual-path feature-association conjunctive-binding model to simulate the aging-related associative-binding deficit. The model (see Fig. 1) had parallel processing paths for intra-item features and interitem associative binding. Features of each item in a given pair were distributedly processed within the corresponding feature-binding path, whereas the associative-binding path processed interitem associations.

Network Architecture

We used networks with 18 input, 12 hidden, and 18 output units separately connected by feed-forward connections between layers of the intra-item feature-binding paths and interitem associative-binding path. The first 9 input and output units coded features of the first item of a given pair (i.e., item A of A-B), whereas the remaining 9 input and output units coded features of the second item (i.e., item B). To keep the model parsimonious, we made no assumptions of differential computational requirements for feature and associative binding; thus, the number of representation units was identical for the feature- and associative-binding pathways. The first and last 4 units at the representation layer were assigned for the distributed coding of the features of items A and B, respectively, whereas the middle 4 units were designated for distributed conjunctive representation of interitem associations.

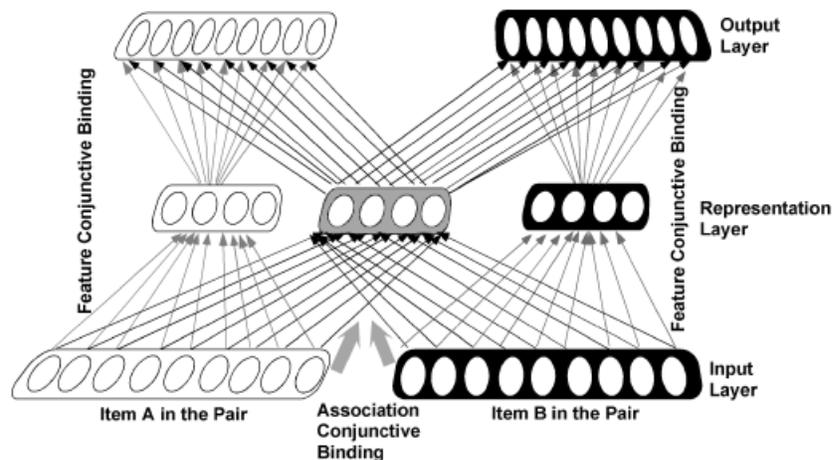


Fig. 1. Schematic diagram of the dual-path feature-association conjunctive-binding model. Within each of the processing pathways, the connections between layers are fully connected. The complexity of the diagram has been reduced by showing representative connections only.

Parameter Settings

Learning rate, momentum, and bias were fixed to conventional values of these parameters: 0.1, 0.8, and -4.0 , respectively. The networks' initial weights were randomly drawn from the range of $[-1,1]$. One group of 10 young networks and one group of 10 old networks were generated to simulate young and old performance, using a set of 10 random seeds to define the initial weights; the young and old networks can therefore be considered the yoked control groups for each other. "Young" and "old" networks were, hence, identical in all respects aside from the means of their G parameters. The mean G was 0.9 (range = 0.7–1.1) for the old networks and 1.2 (range = 1.0–1.4) for the young networks. The range of the uniform distributions from which the values of G were sampled was fixed at 0.4. Accounts of cognitive aging deficits modeled by reducing mean G hold for a wide range of means and variances of the G distributions (Li et al., 2001; Li & Sikström, 2002).

Training and Testing

Binary (1 or 0) vectors coded letters or letter pairs. On average, the ratio of "on" to "off" features was 3.9 for A items and 3.0 for B items. Before the networks studied the stimulus pairs, they were trained with a sample of single items for 500 trials and reached an identical level of initial item knowledge. Connection weights were trained with back-propagation learning. Naveh-Benjamin's (2000) manipulation of study instructions was implemented by training the networks either with the item pairs (with a list length of six) for 10 repeated trials (the pairs instruction) or with the item pairs plus the two single items of each pair for 10 repeated trials (the words instruction).

The networks were tested under two conditions. In the item and associative tests, the networks were, respectively, presented with single target items and lures and with target pairs and lure pairs. A standard indicator of match between the expected output and the network's actual output (i.e., cosine between target and actual outputs) was computed. If a test pair (or item) was a target and the cosine was greater than a fixed threshold, a hit was scored; if a test pair (or item) was a lure and the cosine was greater than the threshold, a false alarm was scored. In light of evidence showing that the response criterion in memory search tasks is higher in conditions requiring effortful processing than in conditions of automatic processing (Strayer & Kramer, 1994), we assumed a more stringent response criterion for intentional than for incidental encoding. Thus, in our model, the response thresholds were fixed, respectively, at cosine of .99 for the intentional, pairs instruction and .975 for the incidental, words instructions.¹ Furthermore, given findings that response criteria for young and older adults are equal when recognition memory tasks emphasize accuracy rather than speed (Ratcliff,

Thapar, & McKoon, 2004), we kept the response threshold constant for young and old networks.

RESULTS

Only one additional assumption—that the response criterion was slightly more stringent in the intentional than in the incidental condition—was needed for the stochastic manipulation of gain implemented in our model to be able to capture the aging-related effects observed in Naveh-Benjamin's (2000) four experimental conditions (Fig. 2). The simulation accounted for differential effects of aging on item and associative memory, and particularly for the aging-related deficit in associative binding.

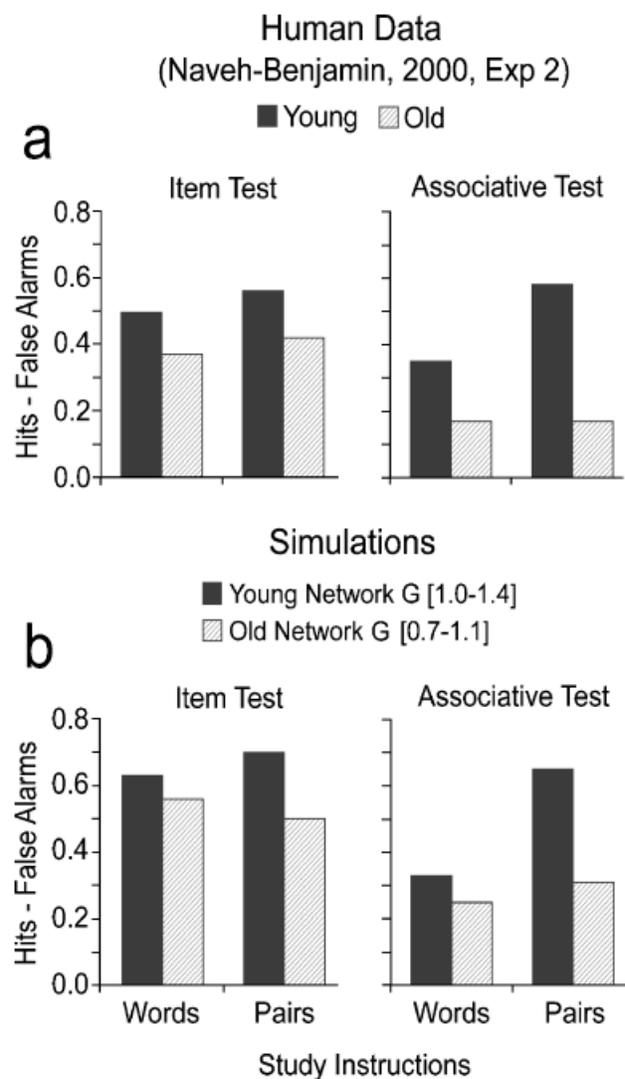


Fig. 2. Memory performance (hits minus false alarms) on item and associative tests as a function of study instructions. The graphs present empirical data (a) for young and older adults (replotted from Naveh-Benjamin, 2000, with permission) and simulation results (b) for "young" and "old" networks.

¹Constraining response thresholds in the two conditions to be identical (i.e., .975) raised overall associative memory performance, but did not affect the three-way interaction found in the results.

Performance Level

Old networks' performance was relatively spared in the item test and more impaired in the associative test. In particular, the simulation results (Fig. 2b) capture the empirical three-way interaction of age, instruction, and test type (Fig. 2a), indicating that aging-related deficits were most pronounced in associative binding when associations were learned intentionally under the pairs instruction.

Representation Level

Examining the conjunctive representations of items and inter-item associations at the representation layer revealed that the old networks' disproportionately poor associative binding was related to less efficient conjunctive coding of associative information. Figure 3 shows summary activation maps of one young and one old network. As shown, reducing mean G had relatively little effect on internal representations of the item feature-binding pathways (activations across the left-most and the right-most four units), but a clearer effect on the associative binding pathway (activations across the middle four units). This result is consistent with the evidence showing that item memory is less

affected by aging than associative memory (see Naveh-Benjamin, 2000, for review). The distributed conjunctive coding of associative binding was less distinctive in the old than in the young network, with more highly activated units responding to different stimulus pairs (i.e., larger patches of the brightest white, coding high activation, across the middle four units).

Factor analyzing activation patterns across the associative-binding units showed that in most matched old-young comparisons, the first principal component accounted for more variance in old networks than in young networks (on average 3% more, ranging from 1% to 11%), $t(8) = 2.28, p < .03$, one-tailed test. This pattern of results indicates that the internal representations of different stimulus pairs were less differentiated in old than in young networks.

DISCUSSION AND CONCLUSIONS

The simulation we have reported traced out a sequence of effects: Deficient G modulation results in less efficient distributed conjunctive coding of stimulus pairs, which, in turn, leads to behavioral manifestations of associative-binding deficit in old age. This cross-level theoretical conjecture still needs to be

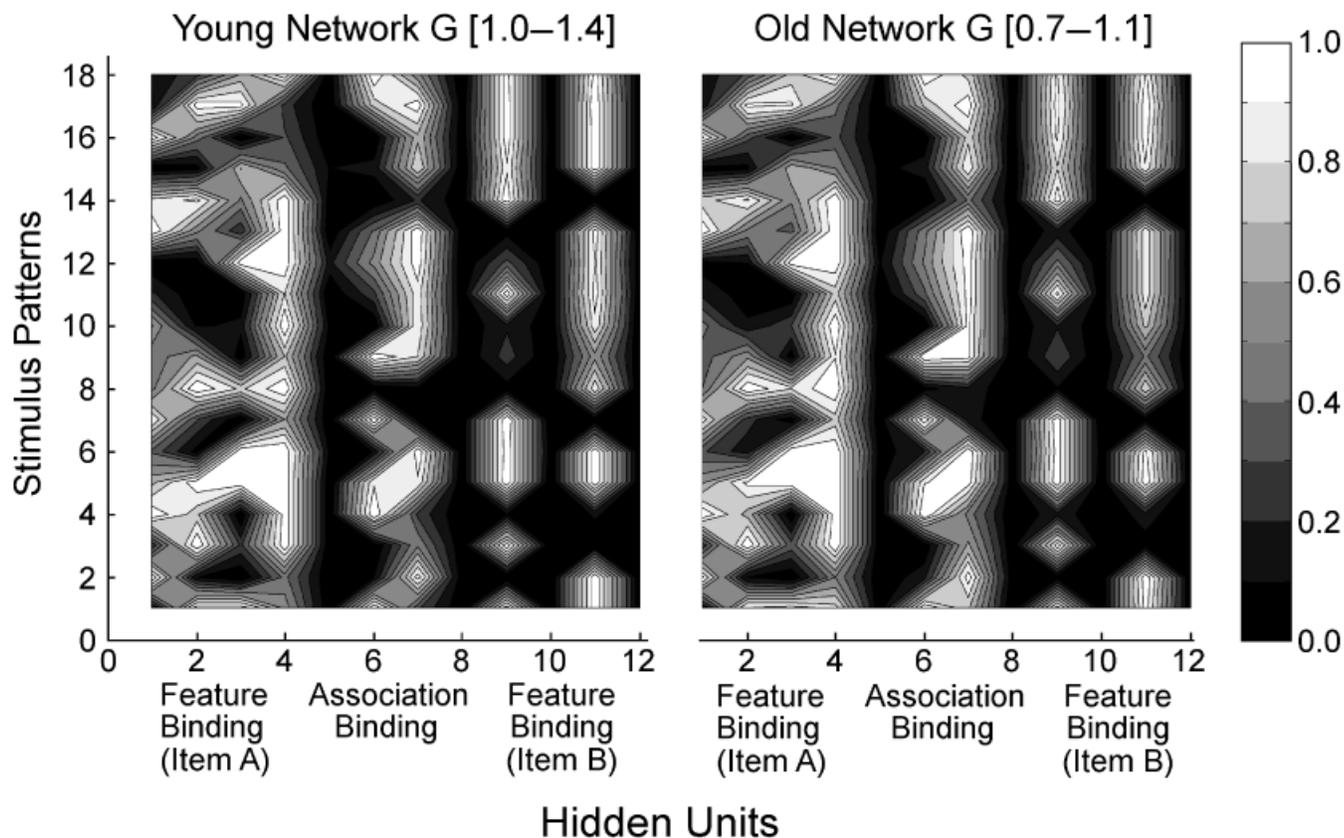


Fig. 3. Summary hidden-unit activation maps illustrating the effects of reducing mean G on the distinctiveness of distributed coding of associative information (see the text for details). Results for a “young” network and an “old” network are shown on the left and right, respectively. The y-axis indicates different stimulus pairs presented during the associative test. On the x-axis, the left-most four units and the right-most four units correspond to the feature-conjunctive representation of A and B items, respectively. The middle four units correspond to the associative-conjunctive representation of the A-B pair associations. Because of the smaller ratio of “on” to “off” features for B than for A items in the training corpus, units of the feature-binding pathway were less activated for B items than for A items.

corroborated by empirical evidence of functional relations between behavioral and neuronal levels.

Aging and Functional Connectivity

Recently, it has been proposed that the neocortex and the hippocampus may engage in two types of conjunctive learning. The neocortex uses distributed overlapping representations for intentional, effortful conjunctive learning, whereas the hippocampus uses relatively sparse coding for relatively more automatic, incidental conjunction (O'Reilly & Rudy, 2001; Zimmer, Mecklinger, & Lindenberger, in press). Recent evidence points to aging-related differences in functional connectivity between the prefrontal cortex and hippocampus. In older adults, weaker connectivity between dorsolateral prefrontal cortical regions and the hippocampus is associated with poorer memory performance (Grady, McIntosh, & Craik, 2003). Similarly, other researchers (e.g., Mitchell et al., 2000) have suggested that the dynamics of frontal-hippocampal circuitry may be implicated in aging-related memory binding deficits. Although our simulation did not explicitly model different anatomical regions (e.g., Gluck & Myers, 1993), our results show a greater effect of representational distinctiveness on effortful intentional learning of associative binding assumed to be supported by the neocortex than on associative binding under the condition of incidental encoding. Given empirical findings on the involvement of neocortex in effortful, intentional conjunctive learning (e.g., O'Reilly & Rudy, 2001) and on aging-related decline in frontal-hippocampal connectivity (Grady et al., 2003), our results suggest that deficient dopaminergic modulation of representational distinctiveness in prefrontal cortex may alter the functional dynamics of frontal-hippocampal circuitry in old age. If the patterns of neural activities in prefrontal cortex elicited by different stimuli are less separable from each other because of suboptimal neuromodulation, processes requiring dynamic interactions between these representations and brain activities in other regions, such as the hippocampus, are likely to be affected (cf. Miller & Cohen, 2001).

Relations of the Feature-Association Conjunctive-Binding Model to Other Theories

Our model provides a platform for considering binding mechanisms proposed so far. It has been suggested that the brain uses two general principles to represent relations: One involves coarse population codes of percepts that are bound together through conjunction units (e.g., Barlow, 1972), whereas the other involves dynamic, context-dependent temporal binding of cell assembly codes (e.g., von der Malsburg, 1995). Obviously, these two principles differ: The first achieves binding by conjunctive coding, and the second achieves binding through temporal synchrony. However, it is important to realize that both principles operate on distributed patterns of neuronal activities. Therefore, mechanisms affecting the representational distinctiveness

of distributed activation patterns that code stimulus- and response-related neuronal activities, such as neuromodulation simulated in our model, have implications for both binding mechanisms.

Thus far, some computational models suggest that neuromodulation affects temporal binding by influencing either the intrinsic complexity of single-cell dynamics or the effective structure of networks. For instance, increasing a parameter indicating available transmitter receptors decreases the coupling strength required to achieve stable synchronization (Breakspear, Terry, & Friston, 2003). Put differently, with deficient neuromodulation, the aging brain may require greater coupling strength between cortical columns to achieve synchronization-based binding. The details of how neuromodulation of representation distinctiveness may affect the coupling strength between local networks and the overall stability of synchronization remain to be determined in future studies.

Our model is conceptually similar to global memory models that assume (a) combination of multiple memory cues, (b) distributed storage, and (c) separate representations of item and associative information (e.g., Murdock's, 1997, TODAM2 model). Not all classical memory models can account for the distinctions between item and associative memory (see Clark & Gronlund, 1996, for a review). As we have shown, our model accounts for the finding that item memory is less sensitive to the manipulation of instructions (intentional vs. incidental) than associative memory is (Hockley & Cristi, 1996). Furthermore, our model accounts for the differential aging of item and associative memory. Our model does not, however, directly address the time course of retrieval, although it could do so if augmented with an attractor network involving recurrent connections between the representation and output layers. Nevertheless, assuming that processing times are monotonically related to lack of match between target and actual outputs (e.g., Seidenberger & McClelland, 1989), the performance advantage in the item test over the associative test in our current implementation suggests that the retrieval time course is faster for item than for associative information. Moreover, given that, in comparison with young networks, old networks performed disproportionately worse on the associative than on the item test, our simulations also suggest that the difference in the time course of retrieving item and associative information is larger in old than in young networks. The model's ability to simultaneously account for the effects of stimulus repetition and response deadline on memory in old age (Jacoby, 1999; Light, Patterson, Chung, & Healy, in press), however, needs to be investigated with future modifications of the model that directly incorporate temporal dynamics.

To conclude, our simulation suggests that neuromodulatory processes play a basic role in binding by affecting the efficiency of distributed conjunctive coding. When neuromodulatory processes function suboptimally, patterns of neural activities become less distinct. Consequently, the neurocognitive system's

task of appropriately binding together representations of experienced memory events becomes harder. This chain of effects provides a viable explanation for associative memory deficits in old age.

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