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Younger and Older Adults' Associative Memory for Medication Interactions of Varying Severity

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Abstract

While older adults face various deficits in binding items in memory, they are often able to remember information that is deemed important. In Experiment 1, we examined how younger and older adults remember medication interactions of varying severity. There were no age differences in overall memory accuracy, but older adults' performance depended on the severity of the interactions (such that the interactions associated with the most severe health outcomes were remembered most accurately) while younger adults' did not. In Experiment 2, a similar task was designed to create interference in memory. Even with this more difficult task there were no age differences in recall accuracy, and both age groups remembered the interactions with the severe outcomes most accurately. These findings suggest that, under certain circumstances, older adults do not face deficits in associative recognition accuracy of information that varies in importance.

Keywords

memory; cognitive aging; learning

When individuals try to adhere to a medication regimen, important information can be overlooked, often due to interference and limited memory capacity. More than half of older adults take five or more medications and/or supplements on a regular basis (Qato et al., 2008), while many younger adults take medications for both medical and non-medical reasons (as a stimulant, White, Becker-Blease, & Grace-Bishop, 2006), and often without considering how other medications, foods, or drinks may interact with those substances. Thus, remembering information about which substances are safe or dangerous to consume together could have important implications for overall health. Remembering medical information often requires making an association between two or more items; e.g., what medication(s) should not be taken concurrently with another medication. The associative deficit hypothesis suggests that the association of items in memory is detrimentally affected in older age (Naveh-Benjamin, 2000). This deficit is pervasive and present in various memory recall tasks, including remembering word-nonword pairs (Naveh-Benjamin, 2000), pairs of pictures (Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003), and name-face pairs (Naveh-Benjamin, Guez, Kilb, & Reedy, 2004; though this can be affected by the value of the information and reduced with repeated testing, see Hargis & Castel, 2017).

However, there are instances in which age-related differences in memory are not present, including tasks examining value-directed remembering, or the strategic focus on important items in light of memory capacity limitations (Castel, 2008). Previous studies examining how value affects memory have utilized words paired with random point values (e.g., Castel, Benjamin, Craik, & Watkins, 2002; Castel, Murayama, Friedman, McGillivray, & Link, 2013). These studies provide evidence that while older adults' overall memory performance is less accurate than younger adults', older adults are still able to remember what is valuable, especially with task experience. However, value does not always eliminate age-related recall differences in associated information, as an age-related memory deficit has been shown for recall of high-value word pairs (Ariel, Price, & Hertzog, 2015). Younger and older adults recognized that high value pairs are important (as shown by their preference to study high-value over low-value items), but older adults did not recall the pairs as accurately as younger adults did. The interplay between aging, memory selectivity, and associative memory is examined in the current study using an associative recognition paradigm and novel medication stimuli.

A value-based mechanism such as health risk could provide a structure in which older adults can overcome associative memory deficits, at least for the most important information. Middlebrooks, McGillivray, Murayama, and Castel (2016) presented younger and older participants with a list of allergens (e.g., peanut) that varied in severity. Younger participants recalled more allergens initially, but age differences in recall of the most severe items were no longer apparent after participants gained some experience with the task. Similarly, older adults have been shown to accurately remember important medication side effects if the effects are framed in terms of detecting dangerous outcomes (Friedman, McGillivray, Murayama, & Castel, 2015). Participants studied and rated the unpleasantness of a group of side effects (each of which had been previously classified as mild, moderate, or severe), and were then asked to recall as many side effects as they could in a free recall paradigm. There were no differences in younger and older adults' recall of these items, but the groups were affected by the level of severity differently, such that older adults remembered more severe side effects (e.g., stroke) than mild side effects (e.g., itching). While these studies (Friedman et al., 2015; Middlebrooks et al., 2016) suggest that older adults can prioritize valuable medical information for item recall, this has not been investigated with the added task demands of associating multiple items in memory.

The use of prior knowledge through schematic support can also benefit older adults in memory tasks (e.g., Castel, 2005); however, this benefit is not present in all domains (Morrow, Menard, Stine-Morrow, Teller, & Bryant, 2001). Older adults' memory for medication side effects, for example, is thought to benefit from schematic support (Friedman et al., 2015), as many older adults have experienced taking medications throughout their lives (Qato et al., 2008). Additionally, being able to refer a to-be-remembered item to oneself benefits older adults' recall (Gutchess, Kensinger, Yoon, & Schacter, 2007), which may occur in healthcare situations if one intentionally connects information found online or provided by a physician to one's own life or experiences. While personal connections to the information and schematic support may lead to older adults' improved memory accuracy in some situations (see Umanath & Marsh, 2014), memory for medication information that is familiar but not factually correct could in fact impair memory if it contradicts older adults'

schemas and beliefs (e.g., Rice & Okun, 1994), suggesting that schematic support is not universally beneficial.

When given multiple study-test trials, participants often learn from their prior task experience and performance improves as the task goes on. This "testing effect" is well-established among younger adult participants (e.g., Allen, Mahler, & Estes, 1969; Carrier & Pashler, 1992). However, the literature examining older adults' memory for associative information across several study-test trials is mixed. For example, Overman and Becker (2009) found that re-studying face-word pairs did not improve older adults' recall of those pairs, while findings by Kilb and Naveh-Benjamin (2011) suggest that older adults can benefit from repeated studying (as can younger adults) when given pairs of pictures to remember. There is also evidence that older adults benefit differently from prior task success than do younger adults (Geraci & Miller, 2013; Geraci, Hughes, Miller, & De Forrest, 2016). The current study utilizes multiple study-test cycles to assess how associative memory performance changes with task experience, both when binding items (Experiment 1) and when binding under conditions that may create memory interference (Experiment 2).

Due to their associative nature, medication interactions may be difficult for older adults to remember. This could have serious implications for health if one forgets that grapefruit, for example, should not be eaten while taking medication for high cholesterol. The current study examines how younger and older adults remember associative medication information of varying levels of severity across several study-test trials. If older adults engage in selective strategies during encoding, they are likely to remember the high-value (important) items as accurately as younger adults, especially with task experience, but their overall performance may be less accurate due to deficits in associating information in memory.

Experiment 1

Experiment 1 was conducted to examine how younger and older adults' associative recognition of medication interactions are influenced by the importance (in terms of health outcomes) of those associated items. Younger and older participants viewed a series of interactions that were assigned to one of three outcomes (severe, mild, or no interaction) and were tested via associative recognition for a total of three study-test cycles.

Method

Participants.—Younger adults (n = 26) were undergraduate students at University of California, Los Angeles and were recruited through the Psychology Department subject pool ($M_{\rm age} = 20.81$, SD = 1.94), 18 were female and one did not report gender. Older adults (n = 26) were recruited from the Los Angeles community ($M_{\rm age} = 68.72$, SD = 5.50), 15 were female. Most older adults had obtained undergraduate (42%) or graduate (42%) degrees. This research was approved by the UCLA Institutional Review Board.

Materials and Procedure.—Participants were asked to imagine that their doctor was describing a series of interactions between medications. They began by reading a short explanation of what medication interactions are, and that they can result in health outcomes that vary in severity. Three levels of severity were outlined to the participant: no interaction

(no effect on health), mild interaction (slight health effects), and severe interaction (lifethreatening health effects). Participants were then presented with 15 unique pairs of stimuli (five in each severity category) in randomized order. There were three pairs of each of the following combinations: real medication - real medication, fictitious medication - fictitious medication, real medication - consumable substance (e.g., bananas, licorice), and fictitious medication - consumable substance. The average length of the medications was 7.90 letters (SD = 1.45), while the average length of the food words was 9.00 letters (SD = 2.68).

Each medication was displayed on a computer screen as the label on an orange prescription bottle, and each substance was displayed as a photograph with the name of the item under (see Figure 1 for example study and test trials). The fictitious medications were chosen to resemble actual medications without being highly familiar to the participants (e.g., Dypraxa, Clavosec), thus reducing the possibility of using schematic support to recall the fictitious items. If there was a mild or severe outcome that would occur when consuming the two substances, it was presented with an example, e.g., "Severe (stroke)". Participants were given 7s to study each pair, with the instruction that they were to remember as much as they could about each interaction. The items in each pair were randomly assigned to each other, as were the outcomes to each pair, and these were held constant throughout the study-test trials for each participant. At test, participants were presented with each pair of medications and asked to choose the severity of the outcome that would occur if they were to be taken together. Participants were given the answer choices "severe," "mild," or "no interaction" and asked to choose one. This study-test procedure was completed for two additional cycles with the same information on each in newly randomized orders.

Results

The memory accuracy of both age groups across the task is presented in Figure 2. To determine whether age and severity affected recognition accuracy of medication interactions, a 2(Age group: younger or older) X 3(Severity: no interaction, mild interaction, severe interaction) X 3(Test) mixed-factorial analysis of variance (ANOVA) was conducted. There was no main effect of age on recall, F < 1, p = .80, $\eta^2 < .01$. There was a significant main effect of severity, F(2,100) = 7.23, p < .01, $\eta^2 = .12$. Follow up t-tests using Bonferroni corrections indicated that recognition accuracy of severe interactions (M = 0.78, SD = 0.16) was more accurate than recognition accuracy of mild interactions (M = 0.69, SD = 0.15), t(51) = 3.76, p < .001, and no interactions (M = 0.69, SD = 0.17), t(51) = 3.87, p < .001, but there was no difference between recognition accuracy of no interactions and mild interactions, t(51) = .21, p = 1.00. A marginally significant two-way interaction between age and severity was also revealed, F(2, 100) = 3.09, p = .05, $\eta^2 = .05$. Though this interaction was not significant at an alpha-level of .05, we conducted follow-up tests to further examine potentially interesting patterns. These ANOVAs revealed that younger adults' recognition accuracy was not significantly affected by severity, F(2,50) = 2.02, p = .14, $\eta^2 = .08$. Older adults' recognition accuracy, however, was affected by severity, R(2,50) = 6.88, p < .01, η^2 = .22, such that interactions associated with the lowest level of severity (M = 0.69, SD = 0.20) were remembered less accurately than those associated with the highest level of severity (M = 0.80, SD = 0.14), t(25) = 3.42, p < .01. Interactions associated with a

moderate level of severity (M = 0.66, SD = 0.15) were also remembered less accurately than those with the highest level of severity, t(25) = 4.61, p < .001. There was no difference in recognition accuracy of mild interaction and no interaction pairs, t(25) = 0.81, p = 1.00.

There was a main effect of test, F(2,100) = 72.03, p < .001, $\eta^2 = .59$, such that overall performance on Test 2 (M = 0.75, SD = 0.15) was more accurate than Test 1 (M = 0.58, SD = 0.17), t(51) = 4.77, p < .001, and performance on Test 3 (M = 0.83, SD = 0.13) was more accurate than on Test 2, t(51) = 2.93, p = .01. No other effects were significant, p > .45.

Additional tests were conducted to determine whether the presence of a food or drink item in an interaction led to more accurate recall of that interaction. A 2(Age group) X 2(Consumable substances or only medications) revealed that items containing food or drink (M=0.87, SD=0.10) were recognized more accurately than those that contained only medications, (M=0.62, SD=0.16), R(50)=161.24, P<0.001, R(50)=1.60. This did not interact with age, R(1,50)=1.63, R(50)=1.63, R(50)=

Both age groups recognized the "severe" outcome with relatively high accuracy. We sought to determine whether there was a bias in either age group's responses toward choosing "severe" more often than other options, perhaps as a guess if they were unsure of the outcome. Throughout the task, a total of 15 "severe" pairs were shown. Therefore, we compared the total number of times a participant chose "severe" in all three tests to 15. Neither age group deviated significantly from this number: younger adults chose "severe" an average of 14.69 times (SD = 1.78), and older adults chose "severe" an average of 15.35 times (SD = 2.71). There were no differences between the amount of "severe" responses given by younger and older adults, t(50) = 1.03, p = .31.

Discussion

Given a series of medication interactions that varied in the severity of their outcomes on health, only older adults' recognition accuracy was affected by that severity. Younger adults, who are often more accurate than older adults in remembering associative information overall (e.g., Naveh-Benjamin, 2000; Naveh-Benjamin, et al., 2003), were not sensitive to information importance (i.e., the severity of the health outcome). This is perhaps because performance was already quite accurate, so the use of a value-based selectivity strategy was not necessary. Older adults, however, remembered severe health outcomes more accurately than the outcomes that were not deemed life-threatening, but there was no evidence of a bias towards "severe" in their responses. Older and younger adults remembered high-value associations with equivalent accuracy (cf. Ariel et al., 2015), and there were no age-related differences in overall performance, in contrast with previous literature showing an age-related associative deficit in memory (Naveh-Benjamin, 2000).

Pairs of items that included a food or drink item (e.g., grapefruit) in addition to a medication were remembered more accurately, possibly due to the distinctiveness of these items (Hunt & Worthen, 2006) as compared to medication-medication pairs. Fictitious but realistic

medications were remembered as accurately as real medications. Perhaps participants did not recognize the real medications and therefore did not remember them any differently than fictitious medications. On the other hand, even if they did recognize real medications, perhaps participants did not have the time, inclination, or familiarity to use schematic support or prior experience to remember real items more accurately than items they would never have encountered before.

Overall, participants in Experiment 1 performed well on the task. It is possible that participants could have performed well by only remembering that one medication was associated with a certain outcome (e.g., knowing that the drug Namenda is associated with a mild interaction) and the pair of medication items did not therefore need to be encoded concurrently with its outcome to answer correctly on the final test. Also, it is not always the case that one medication interacts with only one other substance; in fact, one medication can interact in varying ways with a set of other medications. These types of associations in which one item is associated with several other items can cause more interference in memory, a process known as the fan effect (Anderson, 1974; Anderson & Reder, 1999). The fan effect paradigm has been used to examine how younger and older adults remember a series of items associated to another particular item (Gerard, Zacks, Hasher, & Radvansky, 1991). The larger the "fan," or the more items that are associated with that item, the more difficult the task usually is, especially for older adults. If one item is associated with several others, older adults are often less accurate than younger adults in remembering those items.

Experiment 2

In Experiment 1, younger and older adults recognized the severity associated with a pair of medications with equivalent accuracy. Experiment 2 was conducted to examine the role of interference in memory for medication information among younger and older adults. Participants viewed a set of medication interactions in which each medication interacted with five other medications. Memory was assessed with multiple study-test trials. If the connections between medications interfere with each other in memory, older adults are expected to be differentially affected by this. While they still may engage in value-directed remembering, the level of interference caused by binding one item to five other items (in addition to the task requirements of associating multiple items) may lead to age-related differences in overall performance.

Method

Participants.—Younger adults (n = 26) were undergraduate students at University of California, Los Angeles and were recruited through the Psychology Department subject pool, $M_{\rm age} = 20.19$, SD = 1.06, 15 were female. Older adults (n = 26) were recruited from the Los Angeles community, $M_{\rm age} = 68.42$, SD = 6.91, 15 were female. Most older adults had obtained undergraduate (50%) or graduate (34%) degrees. This research was approved by the UCLA Institutional Review Board.

Materials and Procedure.—Instructions given to participants were identical to Experiment 1. Unlike in Experiment 1, participants in Experiment 2 were presented with only six unique medications (no food or drinks), which each appeared in five different

interactions for a total of 15 items. For example, Dypraxa: Cordarone could lead to a mild interaction, Dypraxa: Doloxan to a severe interaction, and Cordarone: Doloxan to no interaction. The assignment of severity to each interaction was randomized for each participant. As in Experiment 1, the medications were presented on a computer screen as orange prescription bottles with only the name of the medication on the label. Participants were given 7s to study each pair, and were asked to choose the severity of the interaction that would occur given the choices "severe," "mild," or "no interaction" at test. This study-test procedure was completed for two additional cycles with the same information on each study and test in newly randomized order.

Results

The memory accuracy of both age groups across the task is presented in Figure 2. To determine whether age and severity affected associative recognition of medication interactions, a 2(Age group: younger or older) X 3(Severity: no interaction, mild interaction, severe interaction) X 3(Test) mixed-factorial analysis of variance (ANOVA) was conducted. There was no main effect of age on accuracy, F(1,50) = 1.66, p = .20, $\eta^2 = .03$. There was a significant main effect of severity, R(2,100) = 4.27, p = .02, $\eta^2 = .08$. Follow up t-tests using Bonferroni corrections indicated that associative recognition of severe interactions (M=0.53, SD = 0.17) was more accurate than that of mild interactions (M = 0.46, SD = 0.15), t(51) = 3.56, p = .03, and no interactions (M = 0.44, SD = 0.17), t(51) = 3.14, p < .01, but there were no differences between recognition of no interactions and mild interactions, t(51) = .65, p = 1.00. Unlike in Experiment 1, there was no significant interaction between age and severity, R(2, 100) = 2.30, p = .11, $\eta^2 = .04$. There was a significant main effect of test, F(2, 100) = 12.83, p < .001, $\eta^2 = .20$. Follow up t-tests using Bonferroni corrections indicated that performance on Test 2 (M = 0.49, SD = 0.13) was more accurate than performance on Test 1, (M = 0.41, SD = 0.14), t(51) = 4.05, p < .001 and Test 3 (M = 0.52, p < .001)SD = 0.17), was more accurate than Test 1, t(51) = 4.74, p < .001, but there were no differences on Tests 2 and 3, t(51) = 1.28, p = .61. No other effects were significant, ps > .22. As in Experiment 1, a 2 × 2 ANOVA revealed no differences in recognition accuracy for real and fictitious medications, F(1, 50) = 0.20, p = .66, $\eta^2 < .01$, this did not interact with age, F(1, 50) = 3.19, p = .08, $\eta^2 = .06$.

As in Experiment 1, we sought to rule out the explanation that older adults were biased toward choosing "severe." We again compared the amount of "severe" responses by each age group to 15, as there were 15 total "severe" interactions presented throughout the task. In Experiment 2, younger adults chose "severe" an average of 15.62 times (SD = 3.07), and older adults chose "severe" an average of 16.85 times (SD = 4.45). A one-sample *t*-test revealed that older adults chose "severe" marginally more than 15 times in Experiment 2, t(25) = 2.12, p = .045. There were no differences in the amount of severe responses given by younger and older adults, t(50) = 1.16, p = .25.

Discussion

Experiment 2 utilized a task that required multiple items to be bound together, depending on the interaction presented. If older adults had been detrimentally harmed by the size of the "fan" (i.e., the fact that one medication was linked with five others in different ways), this

might have led to age-related differences, at least for the associative recognition accuracy of lower-value information, as older adults are often still able to remember information that is important. Older adults can be detrimentally affected by interference to a greater extent than younger adults, but interestingly, findings from the current study suggest that there are instances in which older adults are not significantly less accurate in remembering interfering medication information. The "fan" of interfering items does not differentially affect older adults in this case. When medication interactions are presented consecutively in a simplified format (that is, with only the name of the medication on the bottle) as they are in the current study, both age groups remember them equivalently well.

Unlike in Experiment 1, both age groups were similarly affected by severity, such that both remembered items associated with a severe health outcome more accurately than those associated with a mild health outcome or no significant health outcome. Though Figure 2 suggests that older adults differentially remembered severe outcomes more accurately than other outcomes, there was no interaction between age and severity, and the power to detect such differences was adequate (if using an effect size of 0.35, which is between moderate and high, the power to detect an effect given this design and sample size is 0.86). It is possible that the task in Experiment 2 was more difficult than in Experiment 1, causing even younger adults to struggle to encode and match every outcome with relatively high accuracy; that is, the introduction of the fan design made a value-based strategy more viable, rather than attempting to remember every item. Older adults chose "severe" slightly more often than it was presented, perhaps related to the difficulty of the task: if one cannot remember everything, it is perhaps beneficial to be cautious and assume that more items are dangerous. The lack of difference between memory for mild and no interaction items is interesting: perhaps severe items, because they are life-threatening, are considered important, whereas the other two categories are grouped together into a category deemed "less important." This pattern of results is similar to that of older adults in Experiment 1, providing further evidence for a possible division of stimuli into two categories by the participants when the task is considered challenging.

General Discussion

The current study examined how younger and older adults remember information about medication pairs that varied with respect to the level of danger associated with their interaction — severe, mild, or no interaction. In Experiment 1, each pair of items was unique and memory for the interaction between the two was tested. Though it was possible that participants remembered one item of the pair and the result (e.g., "Namenda is associated with a mild interaction"), this was still a test of the association between at least those two items. Younger and older adults performed equally well in Experiment 1, and only older adults' memory accuracy was affected by severity, suggesting sensitivity to the value-based structure in this study (or perhaps that the severe interactions were most distinct to the older adults, thereby leading to their more accurate recall).

In both experiments, the associative recognition accuracy of both groups increased given task experience. This is similar to prior work suggesting that older adults benefit from prior successful task performance (Geraci & Miller, 2013; Hargis & Castel, 2017; Kilb & Naveh-

Benjamin, 2011), and suggests that repeated study and retrieval of associative information regarding medication interactions can benefit overall recall of important pairs of items, even when there are interfering connections among medications. Additionally, the information was tested via associative recognition in which there were three answer choices. If the study had been conducted such that the individual medications were tested, older adults may have performed less accurately than in the current study, but in the present task remembering that a certain pair of medications is dangerous to take together may be an effective value-based strategy. Experiment 2 employed a paradigm that was thought to lead to stronger effects of interference on remembering medication interactions, in light of previous work investigating the fan effect. The task was considered to be more difficult in that it was no longer possible to bind only one item of the pair to its outcome, as each medication appeared multiple times; indeed, Figure 2 suggests that both age groups were less accurate overall in Experiment 2. In this study, testing effects (Meyer & Logan, 2013) and value-based encoding processes (Castel, Farb, & Craik, 2007) may have helped both younger and older adults to remember important medication interactions.

Neither younger nor older adults' amount of "severe" responses differed between experiment (older adults t(50) = 1.47, p = .15; younger adults t(50) = 1.33, p = .19), but the numerical shift seen toward choosing "severe" slightly more often in Experiment 2 may be related to the possible increase in task difficulty, as noted above. Perhaps when a task requires more cognitive effort or causes interference in memory, participants may be slightly more likely to be cautious and choose "severe" when in doubt of the answer or view the example outcomes (e.g., "dizziness") as severe, though the differences were not statistically significant.

It is worth noting, however, that the associative paradigm used here may allow for a type of gist-based encoding of the health outcome that would occur if two substances were consumed together. That is, participants may rely on the general gist of the outcome (e.g., "very dangerous" versus "not so bad") rather than the exact information presented during encoding. In aging, the ability to remember verbatim information can decline, but gist-based processing is often retained (e.g., Schacter, Koutstaal, Johnson, Gross & Angell, 1997; Titcomb & Reyna, 1995; Tun, Wingfield, Rosen & Blanchard, 1998). Previous work has suggested that memory for gist-based associative information can be as accurate in older as in younger adults, even if there are age-related deficits for verbatim associative information (Castel, 2005; Flores, Hargis, McGillivray, Friedman, & Castel, 2017). Further, since the test used in this paradigm is one of associative recognition, it is perhaps the case that some associative recognition tasks do not yield age-related associative deficits, while other value-based associative memory tasks using cued recall do indeed yield such differences (Ariel et al., 2015).

The present work suggests that the associative deficit often seen in older adulthood is not ubiquitous. While older adults typically suffer from impairments when interference is present (e.g., Jacoby, Debner, & Hay, 2001), there were no age differences in this study. This may have been because the test was simple (with three answer choices for each item), or perhaps older adults are actually able to overcome these deficits in interference when the tobe-learned information is valuable or meaningful (as opposed to a long list of word pairs).

Future work may examine how this type of information is remembered in a more applied context, as the information in this study was presented on a computer screen (rather than as actual medication bottles, which may lead to more accurate recall), and may also directly assess the amount of experience participants have with taking multiple medications, further examining the impact of health on memory (Hess, 2005). It may also be of interest to pursue an explicit self-referencing manipulation (Gutchess et al., 2007), such that participants are asked to imagine that they are taking (or are actually prescribed) a subset of the medications they are asked to study. In summary, the present work shows that older adults may overcome deficits in binding to remember important medication interactions via value-based memory processes.

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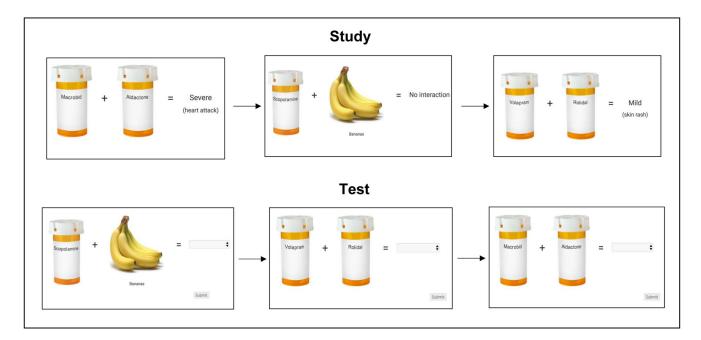


Figure 1. Three example study trials from Experiment 1. Participants were given 7s to study each of 15 pairs and were later tested on the outcome.

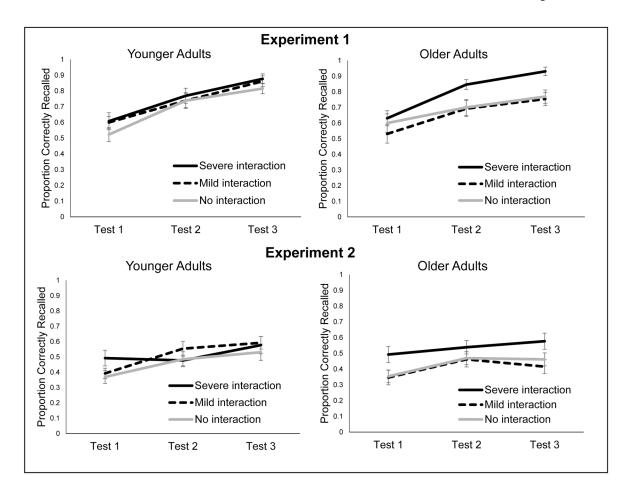


Figure 2.Performance on a series of three cued-recall tests in Experiment 1 (top) and Experiment 2 (bottom) by younger adults and older adults. Error bars represent standard error of the mean.