



Brief report

Variations in working memory capacity predict individual differences in general learning abilities among genetically diverse mice

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Abstract

Up to 50% of an individual's performance across a wide variety of distinct cognitive tests can be accounted for by a single factor (i.e., "general intelligence"). Despite its ubiquity, the processes or mechanisms regulating this factor are a matter of considerable debate. Although it has been hypothesized that working memory may impact cognitive performance across various domains, tests have been inconclusive due to the difficulty in isolating working memory from its overlapping operations, such as verbal ability. We address this problem using genetically diverse mice, which exhibit a trait analogous to general intelligence. The general cognitive abilities of CD-1 mice were found to covary with individuals' working memory capacity, but not with variations in long-term retention. These results provide evidence that independent of verbal abilities, variations in working memory are associated with general cognitive abilities, and further, suggest a conservation across species of mechanisms and/or processes that regulate cognitive abilities.
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An individual's performance on most tests of cognitive ability reflects both task-specific abilities as well as a "general" influence on cognitive function. This general influence, commonly referred to as "general intelligence," has been estimated to account for 30–50% of the performance variance across the seemingly disparate subtests that comprise common intelligence batteries (Jensen, 1998; Mackintosh, 1998; Plomin, 1999; Plomin & Spinath, 2002; Sternberg & Kaufman, 1998).

The underlying basis of general intelligence is the subject of much debate, but one theory that has gained popularity holds that individual differences in working memory capacity underlie differences in general intelligence. Working memory is thought to temporally maintain goal-relevant information under conditions of

competing demands. Thus, it is believed to be used to guide goal-directed behavior within a task (Baddeley, 2003; Conway & Engle, 1995). It is this characteristic of working memory that has led to the proposal that it is engaged by all tests of cognitive ability (Baddeley, 2003; Conway & Engle, 1996). Human studies suggest that variations in general cognitive abilities covary with individuals' working memory capacity (Conway & Engle, 1995; Engle, Tuholski, Laughlin, & Conway, 1999; Kyllonen & Christal, 1990; Süß, Oberauer, Wittmann, Wilhelm, & Schulze, 2002). Furthermore, recent imaging studies have confirmed that IQ test performance is predicted by activity in brain areas engaged by working memory tasks (Conway, Kane, & Engle, 2003). Nevertheless it is difficult in humans to isolate working memory from its related operations, such as mathematical and verbal abilities (Copeland & Radvansky, 2001; Conway & Engle, 1996). Since these complications mitigate

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any broad consensus, it is important to demonstrate this relationship in nonverbal animals where these confounds can be minimized.

We have addressed this issue by using outbred mice to assess the degree to which working memory capacity is related to individuals' abilities across a diverse battery of learning tasks that impinge on different sensory, motor, and motivational systems. We also investigated the relationship of variations in long-term retention to general learning ability. In doing so, it has been possible to determine the degree to which variations in long-term retention and the capacity of working memory covary with general learning abilities.

Individual differences in learning among mice were quantified using a variant of the procedures previously reported (Matzel et al., 2003). Adult male CD-1 mice ($n = 21$, weight = 25–35 g) were tested in five independent learning tasks (Lashley III maze, passive avoidance, spatial water maze, odor discrimination, and fear conditioning) that place unique sensory, motor, motivational, and information processing demands on the animals. Briefly, performance in the Lashley III maze depends on animals' use of fixed motor patterns (egocentric navigation) motivated by a search for food. Passive avoidance is an operant conditioning paradigm in which the animals must learn to be passive to avoid aversive light and noise stimulation. The spatial water maze encourages the animals to integrate spatial information to efficiently locate a hidden platform to escape from a pool of water. Odor discrimination is a task in which animals must discriminate and use a target odor to guide their search for food. Finally, associative fear conditioning (assessed by behavioral freezing) is a conditioning test in which the animals learn to associate a tone with a shock. As we have found that general learning abilities covary with certain patterns of exploratory behavior, unlearned behavioral patterns were also assessed in an open field.

With one exception, training and testing in the apparatuses that make up the learning battery proceeded, as specified in our original paper describing the battery (Matzel et al., 2003). In the spatial water maze, we now used black water soluble paint and different patterns of lights as the visual cues. These changes resulted in substantially more stable learning in this task.

In all of the learning tasks, animals' performance was measured during acquisition, such that an individual's learning performance could be ranked relative to other animals in the sample. The animals' average rank across the five learning tasks as the one measure of open field exploration served as well as the index of individuals' general learning ability. Exploration in the open field was included in the rankings since it has been found to be such a powerful predictor of animals' learning abilities (Matzel et al., 2003). In the tasks in which there was only one testing trial (fear conditioning and passive avoidance) we used training parameters that we previ-

ously shown to result in subasymptotic responding during testing (Matzel et al., 2003). The resulting distribution of ranks was approximately normal, with a median rank of 11. The lowest and highest average ranks in this sample of 21 were 4.2 and 18.5 (respectively), where a rank of "1.0" would indicate that an animal had outperformed its peers on all learning tasks. In contrast to the observed range of 4.2–18.5, if individuals' performance across tasks were independent, average ranks would aggregate close to an unbiased mean of 11. The existence of a common factor underlying the performance of the mice is reflected in the positive correlations of their performances across all combinations of learning tasks (Table 1A). In addition as previously reported increased exploration in the open field correlated with faster learning. Although a sample size of 21 is generally considered small for factor analytic analyses, for confirmative purposes these data were nevertheless subjected to an unrotated principal component factor analysis. A single factor accounted for approximately 40% of the variance in the performance of individuals across all learning tasks as well as the one measure of open field exploration, a degree of explanatory variance comparable to our previous studies with larger sample sizes (Matzel et al., 2003). These results are consistent with reports from our laboratory as well as others of the existence of a general learning ability in mice (Galsworthy, Paya-Cano, Monleon, & Plomin, 2002; Locurto, Fortin, & Sullivan, 2003; Matzel et al., 2003).

As well as providing a measure of learning acquisition, performance in the Lashley III maze was used to estimate animals' capacity for long-term retention. This maze is well suited for this because (1) most animals reach comparable levels of asymptotic performance during training; (2) performance is measured in errors, and as such, is inherently unambiguous; (3) performance is broadly graded across trials, typically ranging from about 20 errors on early trials to fewer than three errors on later trials. For these reasons, this task is highly sensitive to degradation in animals' performance across retention intervals.

To estimate animals' capacity for long-term retention, training in the Lashley III maze was continued beyond the point at which all animals exhibited comparable levels of performance (i.e., 10 trials). Then, following a 30-day retention interval all of the animals were again run in the maze. Long-term retention ability was said to be the difference between the number of errors on the first trial following the retention interval and the average number of errors made at asymptote.

To assess differences between animals in the efficacy of working memory, the animals were trained to asymptotic levels of performance on two distinct eight-arm radial mazes ("primary" and "secondary"). The two mazes were located in the same testing room, and thus shared an overlapping set of extramaze visual cues. The

Table 1

(A) A correlation matrix of all of the tasks in the battery (OF, open field; LM, Lashely maze; PA, passive avoidance; WM, spatial water maze; FC, fear conditioning) shows that they correlate consistently with the working memory manipulations—that is to say there is a positive manifold (INTER, radial arm maze interference manipulation; DUR, radial arm maze duration manipulation—values are equal to average errors in test/errors at asymptotic performance) $*p < .05$, $**p < .01$; (B) an unrotated principal component factor analysis extracted from this correlation matrix reveals that both manipulations load positively in the same factor as the tasks in the battery

| | OF | LM | PA | OD | WM | FC | INTER | DUR |
|------------------------------|----------|----------|--------|-------|-------|-------|--------|--------|
| <i>(A)</i> | | | | | | | | |
| OF | | −0.35 | −0.41 | −0.26 | −0.27 | −0.20 | −0.49* | −0.34 |
| LM | −0.35 | | 0.54* | 0.25 | 0.28 | 0.11 | 0.47* | 0.54* |
| PA | −0.41 | 0.54* | | 0.02 | 0.40 | 0.17 | 0.31 | 0.60** |
| OD | −0.26 | 0.25 | 0.02 | | 0.49* | 0.30 | 0.46 | 0.07 |
| WM | −0.27 | 0.28 | 0.40 | 0.49* | | 0.11 | 0.46 | 0.24 |
| FC | −0.20 | 0.11 | 0.17 | 0.30 | 0.11 | | 0.38 | 0.38 |
| INTER | −0.49* | 0.47* | 0.31 | 0.46* | 0.46* | 0.38 | | 0.62** |
| DUR | −0.34 | 0.54* | 0.60** | 0.07 | 0.24 | 0.38 | 0.62** | |
| | Factor 1 | Factor 2 | | | | | | |
| <i>(B)</i> | | | | | | | | |
| Open field | −0.64 | 0.02 | | | | | | |
| Lashely maze | 0.70 | −0.29 | | | | | | |
| Passive avoidance | 0.68 | −0.50 | | | | | | |
| Odor discrimination | 0.50 | 0.76 | | | | | | |
| Water maze | 0.61 | 0.36 | | | | | | |
| Fear conditioning | 0.46 | 0.23 | | | | | | |
| Interference | 0.82 | 0.19 | | | | | | |
| Duration | 0.76 | −0.40 | | | | | | |
| Eigenvalue | 3.45 | 1.28 | | | | | | |
| Proportion of total variance | 0.43 | 0.16 | | | | | | |

primary maze was constructed of black Plexiglas and contained a closed central hub with experimenter-operated doors that could confine animals between successive arm choices. The secondary maze had no doors on the center hub and was composed of gray Plexiglas. On the days in which the mice were trained on both mazes, they were returned to their cages for 2 h after completing the primary maze before starting a trial in the secondary maze.

It is noted that all animals were trained to comparable levels in the mazes *prior* to the introduction of manipulations intended to tax working memory, consequently, variations in the expression of spatial abilities were minimized. This fact was confirmed by the observation that there was no correlation between the animals' asymptotic level of performance in the radial arm maze and their general learning ability.

Animals received 12 trials on the primary maze, at which time all animals had performed at least four trials in which they made four or fewer errors in locating the last two baited arms. Subsequently, two manipulations were introduced to assess the efficiency of animals' working memory. In the first manipulation (simple memory span), mice were allowed to make four correct choices in the primary maze before being confined to the center compartment for a fixed amount of time (Test 1: 60 s; Test 2: 90 s), released, and then allowed to collect the final four food pellets. In the second manipulation

(working memory capacity), animals were required to perform simultaneously in both the primary and secondary mazes. After three choices in the primary maze, each animal was confined to the center compartment, removed, and placed in the secondary maze where it was allowed to make three additional choices (in no instance did an animal commit an error on either of these sets of three choices). Following this the animal was returned to the primary maze where it was again allowed to make three correct choices, followed by removal and placement in the secondary maze where it was allowed to make three correct choices. This cycle was repeated a final time, although only two correct choices remained available in each maze. On the day following each test trial, all animals received a standard training trial in the primary maze to insure stable performance and to provide a behavioral baseline.

In both the delay and the interference manipulations, working memory was assessed by comparing the number of errors each animal made in locating the last two available rewards on each trial relative to the number of errors it committed to locate the last two rewards on baseline trials (defined as the average number of errors on Trial 12 of training and the two standard trials that intervened working memory tests). The majority of animals' errors were committed during these last two choices, therefore this criterion was chosen because it was sensitive to the greatest differences between animals.

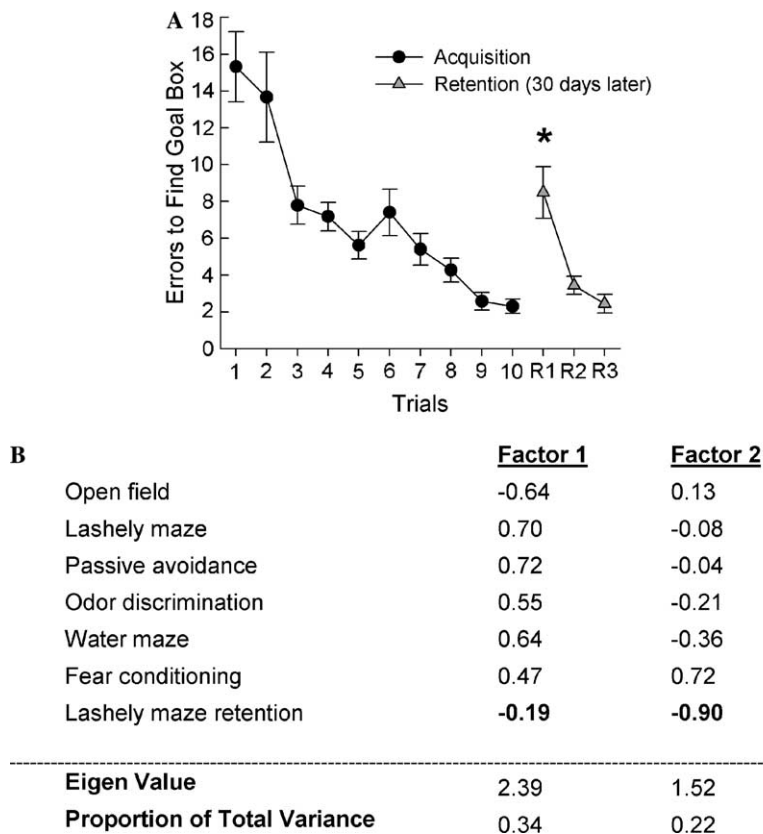


Fig. 1. Long-term retention and general learning ability. (A) Acquisition curve for 21 animals in the Lashley maze followed by performance on three retention trials 30 days later. Error bars represent standard error (* $p < .01$, repeated measures t test between last trial of training and first retention trial, $t = 4.01$). (B) Unrotated principal component factor analysis showing that the battery of tests measuring general cognitive function do not load on the same factor as the animals' performance on the first Lashley maze retention trial.

While a significant degradation in Lashley maze performance was observed when the animals were tested 30 days after training ($t = 4.1$, $p < .001$; Fig. 1A), no correlation was found between the individuals' long-term retention scores and their overall ranks in the learning battery ($r = .08$, ns). This result is in marked contrast to the strong positive correlation between the animals' overall rank on the learning battery and their performance (errors relative to baseline) following the introduction of a competing demand on working memory as measured in the radial arm maze ($r = .60$, $p < .01$; see Fig. 2A). While qualitatively similar, a weaker, and nonsignificant correlation was observed between animals' learning ranks and their performance following the introduction of a simple delay in the radial arm maze ($r = .37$, $p < .10$, ns).

Despite our limited test sample, factor analysis of animals' performance in the learning battery was consistent with our prior analysis of larger samples. Thus, to aid interpretation of the relationship of working memory capacity to general learning abilities, we asked how variations in performance following working memory manipulations loaded with performance on the battery of learning tasks. This analysis revealed that both aspects of working memory (simple delay and competi-

tion) and performance on all of the learning tasks loaded consistently on a primary factor (Table 1B). By comparison, the performance decrement associated with long-term retention loaded weakly (and in an opposite direction) on this factor, although retention performance did load heavily on a secondary factor (Fig. 1B).

The correlation between working memory capacity and general learning abilities was primarily accounted for by animals in the lower half of the distribution of overall learning ranks (Fig. 2B). The 10 (of 21) animals that had performed worst (based on overall ranks) on the learning battery made significantly more errors relative to baseline following the introduction of either demand on working memory, while no such differences were found for those 10 animals that had performed best in the learning battery. The differential sensitivity of good and bad learners to demands on working memory is not likely attributable to differences between them in their mastery of the radial arm maze, as each sample of animals reached similar asymptotic levels of baseline performance in the maze ($t = 1.3$, ns; comparison on Trial 12 of two sub-samples) and were over-trained prior to the introduction of working memory manipulations.

Given that our tests of working memory were conducted in a radial arm maze (a task which in many cir-

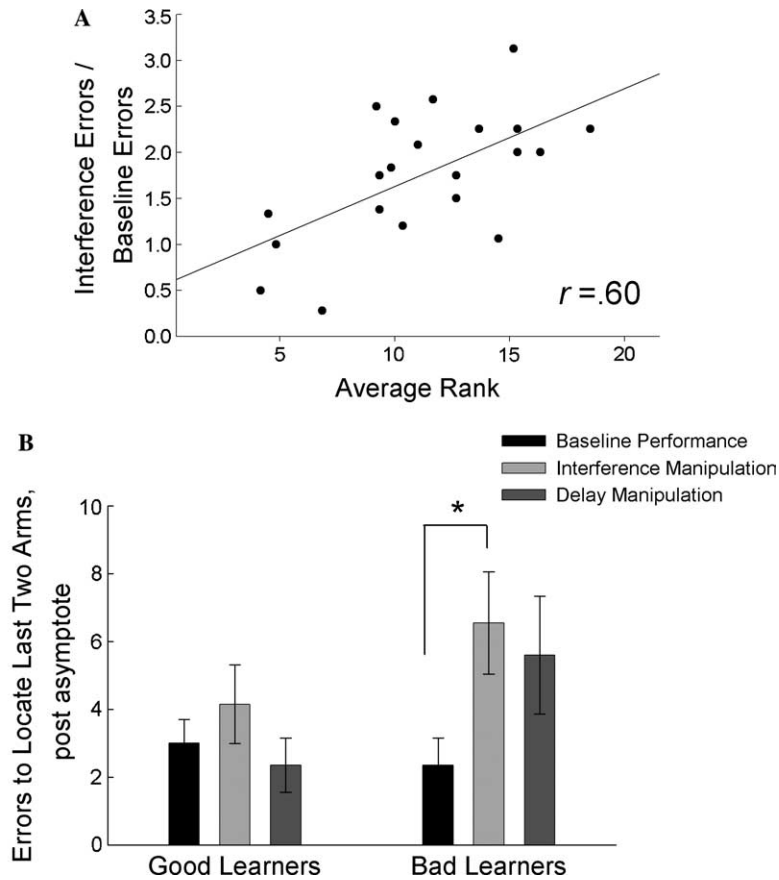


Fig. 2. Working memory and general learning ability. (A) Correlation between the animals' performance in radial arm interference trials and their average ranks across the cognitive battery. Roughly 36% of the variance of their performance on this battery can be explained by their ability to accommodate working memory interference. (B) Animals that performed poorly in the learning battery (average rank = 14) performed much worse in both the interference and delay manipulations relative to their asymptotic performance than good learners (average rank = 7) $*p < .01$ planned comparisons between baseline and manipulations.

cumstances is strongly dependent on the hippocampus), one might ask whether we have isolated a “general hippocampal factor” rather than a relationship between working memory and general learning abilities. This is a viable possibility to the extent that the hippocampus is critical to all of the nominally different tasks represented in our learning battery. This common dependence on the hippocampus cannot be entirely disregarded, as depending on task parameter, any task can to some degree impinge on hippocampal processes (Talk, Gandhi, & Matzel, 2002; Vanderwolf & Cain, 1994). However, it seems rather unlikely that tasks such as passive avoidance and the Lashley maze (tasks which load comparably and most heavily on the general learning factor) are equally dependent on the hippocampus. Even more telling, there is no reason to expect that conditioned fear, using our procedures, would have any particular dependence on the hippocampus (Schafe & LeDoux, 2000).

The present results suggest that working memory capacity (but most likely not long-term retention) covaries with the general learning abilities of genetically diverse outbred mice. This conclusion is consistent with psychometric and neurophysiological results obtained

with human test samples (Gray, Chabris, & Braver, 2004; Haier, Buchsbaum, Abel, Tang, & Siegel, 2004), although in the present case, the relationship between these variables is not attributable to processes that overlay the expression of working memory in humans, such as mathematical and verbal abilities, or educational history.

The present work also provides further support for the functional homology across distant species of a factor which regulates general cognitive abilities (Conway, Cowan, Bunting, Theriault, & Scott, 2002; Galsworthy et al., 2002; Locurto et al., 2003; Locurto & Scanlon, 1998; Matzel et al., 2003), and furthermore, suggests a conservation of relevant antecedent processes.

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