

Mical-related redox enzyme *p*-hydroxybenzoate hydroxylase, do not bind actin. Thus, a direct, actin-destabilizing, physical link between the semaphorin receptor, plexin, and the actin cytoskeleton has been established.

Hung *et al.* [2] observed profound bristle abnormalities in the course of carrying out mutational analysis of Mical's role in neuronal pathfinding. These observations included 100% of wild-type bristles becoming branched when one additional copy of wild-type Mical or Mical<sup>redoxCH</sup> is expressed; the branching occurs with no change in the number or position of bristles. Normally there is no branching, and the transgene and bristle-specific drivers alone leave the bristles unbranched. Subsequently, they wisely embarked on a comprehensive study of this bristle phenomenon. The bristle contains cross-linked parallel arrays of short actin filaments (1–5 μm long) projecting in a single gentle curve from the cell [10]. Small changes in actin nucleation, elongation, treadmilling, and depolymerization are manifested in an easily detectable modification of bristle structure, making them an ideal system for characterizing Mical activity. They also saw that the expression of constitutively active or wild-type Mical generates striking changes in neuronal growth cone morphology: proliferation of filopodia, increased shape complexity, and a four-fold increase in area (Figure 1B). Assays with purified proteins, combined with electron microscopy of filaments and bristle cells, support the author's proposal that Mical's NADPH-dependent redox activity is responsible for the multifaceted abnormal bristle and growth cone morphologies observed and is thus capable of mediating semaphorin-dependent pathfinding (Figure 1C provides a summary of their results and interpretations).

The redox modulation of other actin-binding proteins has also been shown to have significant effects on their regulation of actin dynamics. For instance, cofilin is a protein that promotes assembly and disassembly of actin depending upon the cellular conditions [11]. Oxidation of cofilin negates its depolymerizing and severing activity and can even shift its targeting from the cytoskeleton to mitochondria. However, unlike Mical's interaction with actin, the interaction of

cofilin with actin is not controlled by 'specific redox signaling'. In contrast to Mical, cofilin is oxidized by reactive oxygen species (ROS), and its oxidation is not dependent upon a particular ligand–receptor signaling pathway. For several reasons it is perhaps interesting to note that Mical can reduce molecular oxygen to H<sub>2</sub>O<sub>2</sub>: such ROS have signaling potential of their own, and their abundance would reduce NADPH levels, opening the possibility that cofilin and Mical could act synergistically in an oxidative environment to promote F-actin polymerization.

Hung *et al.* [2] reasonably argue that the branching, thickening, thinning, and other effects on bristle structure are secondary to the filament destabilization observed *in vitro*. Still left open is the question of Mical's substrate, the particular amino acids modified, and the nature of the actin destabilization seen — severing and/or depolymerization. However, these findings definitely enhance our understanding of this key signaling pathway regulating semaphorin-induced changes in cell morphology.

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## Cognitive Ability: Does Working Memory Training Enhance Intelligence?

Recent experiments in both humans and mice suggest that working memory training improves general cognitive ability. While the prospect of enhancing human and animal intelligence is enticing, several questions remain.

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Recent human and animal research has converged on the claim that extensive working memory training enhances general cognitive ability. For instance, in humans, a group of subjects that underwent multiple sessions of

working memory training subsequently performed better on a test of general fluid intelligence than a control group that had not undergone working memory training [1]. Similarly, a study reported in this issue of *Current Biology* [2] found that, in mice, an experimental group that learned to navigate two radial arm mazes with overlapping

cues, a manipulation thought to mimic processes required for human working memory, performed better on a battery of learning tasks than a control group of mice that trained on a simpler version of the radial arm maze. The prospect of enhancing intelligence in humans and learning abilities in mice through behavioral training is enticing, but serious questions remain with respect to both of these lines of research, not least of which is whether they bear upon the same underlying mechanism.

Working memory is a construct developed by cognitive psychologists to explain the role of short-term memory in complex cognition [3]. It is required for the active maintenance and manipulation of information in the face of concurrent processing and/or distraction. For example, performing an internet search to find the email address of a colleague requires mentally maintaining the name, institution and department of the colleague while performing the search and ignoring irrelevant information, such as pop-up advertisements. Working memory is a central construct in psychology because it is required for many complex cognitive tasks, such as reasoning, reading, problem-solving, decision-making and planning [4]. Moreover, healthy adults vary in their performance of working memory tasks and working memory is strongly correlated with standardized tests of aptitude and intelligence [5–7].

A possible implication of the correlation between working memory and intelligence is that working memory *constrains* intelligent behavior. According to this perspective, if working memory could be improved then perhaps intelligence could be enhanced. As mentioned, a recent study [1] on human adults has indeed demonstrated this. Subjects in the study underwent either 8, 12, 17 or 19 days of training on a working memory task called the *n*-back. In an *n*-back task, subjects are presented with a continuous stream of stimuli, typically one every two seconds, and are required to determine whether the current stimulus matches the one *n*-back in the stream. Obviously, as *n* increases so does the working memory demand and difficulty. In the training study, the value of *n* increased or decreased from block to block as performance improved or worsened. Thus, the task was titrated to individual

performance and was consistently demanding.

Subjects were also pre- and post-tested on Raven's Advanced Progressive Matrices (RAPM), a measure of fluid intelligence and abstract reasoning [8]. RAPM is a pen and paper test in which subjects identify the best-fitting missing element of a larger pattern, usually in the form of a 3 x 3 matrix. A control group did not undergo any training but also completed the pre- and post-test measures.

The working memory training groups (relative to the control group) showed improvements on RAPM and the magnitude of the improvement increased with more training. Thus, transfer of training to fluid intelligence was dosage dependent — gains in fluid intelligence were a function of the amount of training. If reliable, this is a breakthrough finding, because *n*-back and RAPM are widely considered to be valid measures of working memory and fluid intelligence, respectively, and conventional wisdom has been that working memory capacity and fluid intelligence are relatively fixed in adults.

Skeptics may take pause and wonder what *n*-back and RAPM have in common. According to the executive attention theory of working memory [9,10], tests of working memory and tests of more complex cognitive behavior, such as RAPM, require top-down cognitive control mechanisms, such as selective attention, and greater cognitive control results in greater performance on tests of working memory and tests of reasoning. Support for this view comes from experiments demonstrating that increasing the demand for cognitive control in a working memory task increases the correlation between working memory and fluid intelligence [11–13]. For example, in the *n*-back task, some stimuli, called lures, demand more cognitive control than others. A lure is a stimulus that matches a recent stimulus in the stream but not the one *n*-back. For example, a lure may match the stimulus presented *n*-1 back or *n*+1 back. Lures are more difficult to reject than non-lures and lure performance is a stronger predictor of fluid intelligence than non-lure or target performance [11,12].

Based on this view of working memory and intelligence in humans, Louis Matzel and colleagues [2]

recently trained 'working memory' in mice and demonstrated that mice which underwent working memory training performed better on a battery of learning tasks than a control group that underwent training with less of a working memory demand. While a cognitive psychologist may question whether working memory in mice is analogous to working memory in humans, the experimental manipulation used to distinguish the training group from the control group is based on executive attention theory from the human literature [14], suggesting a possible link. Specifically, mice in the working memory training group learned to navigate two radial arm mazes with overlapping cues, while mice in the control group learned to navigate the same two radial arm mazes but the mazes were separated by an opaque floor-to-ceiling curtain with distinct cues on each side. According to Matzel *et al.* [2], this manipulation targets the same type of cognitive control mechanisms implicated in executive attention theory because "animals were required to maintain a memory of two sets of choices that were guided by a common, overlapping set of visual cues, thus taxing both the animals' ability to maintain information while simultaneously segregating that information according to the task (maze) it was specific to".

Both the working memory training and control groups underwent 12 days of training and were then compared on a battery of tasks, including a water maze, Lashley maze, fear conditioning, odor discrimination and passive avoidance. The training group performed better than the control group on all of the tasks, although the difference between groups did not always reach statistical significance (particularly for fear conditioning where there seemed to be no effect). When aggregate performance across tasks was considered, by conducting a factor analysis and obtaining factor scores, the training effect was significant and strong.

Concerns can be raised about the measurement of constructs in both the human [1] and animal [2] work. In the human study [1], the RAPM was administered in a timed fashion, which is not standard. And, in some groups, a variant of the RAPM was used, and was also administered in a timed fashion, which calls into question

whether working memory training caused a gain in reasoning ability or simply processing speed [15]. In the animal study [2], the biggest difference between the training and control group was observed on factor scores, which were derived from a factor analysis of scores on several different tasks. Matzel and colleagues [2] assume the factor scores reflect 'general cognitive ability' or *g*; however, it has never been clear from the human literature on intelligence what *g* reflects. One thing is clear: it is not necessary to assume that there is a unitary cause of variance in *g* [16]. It is therefore ambiguous as to what Matzel and colleagues [2] are really measuring.

The above concerns about measurement raise further questions about mechanism. That is, what cognitive and neural mechanism(s) are being trained and result in transfer? Both the human [1] and animal [2] studies discussed here are frustratingly vague on this point. It seems that a better approach to cognitive training is to more precisely define a mechanism and tailor measurements and training regimens specifically for that mechanism [17]. The constructs working memory, fluid intelligence, and *g* are simply too complex and/or vague to derive any specific conclusions from this work about mechanism.

Neither the work in humans [1] nor the work in mice [2] has demonstrated whether gains in fluid intelligence or learning abilities are durable. That is,

subjects have not been tested again, days, weeks, or months after training. This raises the question as to whether the gains observed will be maintained or if they are just transient practice effects.

In conclusion, working memory training experiments [1,2] have recently caused excitement in psychology and neuroscience and the potential link between the human and animal literature is fascinating. However, concerns about the measurement of constructs, the underlying cognitive and neural mechanisms involved, and the maintenance of the observed gains should temper the enthusiasm for now.

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## Spindle Assembly: More Than Just Microtubules

**Do actin dynamics play an active role in mitotic spindle assembly? A new study demonstrates that cortical actin polymerization assists with the earliest phase of spindle pole migration.**

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During mitosis, cells assemble a complex protein machine known as the mitotic spindle that uses microtubules and motors to faithfully segregate sister chromatids and cell-fate determinants, as well as to establish the position of the cleavage plane [1]. These events depend upon the accurate positioning of centrosomes,

tiny organelles that nucleate microtubule growth and organize the spindle poles [2]. Normally, the two centrosomes of a mitotic cell display a series of three movements that drives their separation and eventually deposits them (and their attached chromosome complements) into separate daughter cells. These distinct centrosome movements occur during interphase/prophase ('centrosome

migration'), metaphase ('maintenance'), and anaphase ('elongation') [3]. Scores of scientists over a span of decades have striven to identify the precise molecular force generators responsible for these critical centrosome positioning events.

Because spindle assembly was viewed as solely a microtubule-dependent process, achieved by a combination of microtubule dynamics and a host of associated motors [4], the research spotlight has long focused on the microtubule cytoskeleton. Indeed, this has been best demonstrated using cell-free meiotic *Xenopus* egg extracts. In this *in vitro* system, spindles can assemble and function even in the absence of actin filaments [5]. But the work of