systems. Many other approaches are also being developed, including the use of low-resolution models in which collections of atoms making up chemical groups, or even entire molecules, are modelled as single entities [12], and the incorporation of experimental data into the calculations to restrict the extent of conformational space that need be explored in a simulation to those regions that are of interest for a particular problem [13]. The latter approach is of particular interest in the context of mechanistic studies, for example of protein folding or enzymatic action, as it enables the accurate determination of the structures of species present at low populations, such as intermediate states, or even just fleetingly, such as transition states [14].

The ability to carry out simulations for longer lengths of time, and of systems of increasing size, coupled with an ever-growing accuracy in the force fields used to describe the molecular interactions [15], will progressively enable some of the key problems in biology at the molecular level to be addressed. We find particularly exciting the possibility of generating accurate descriptions of the conformational ensembles corresponding to natively unfolded proteins and to unfolded or partially folded states of globular proteins; such descriptions are crucial for understanding the molecular processes that give rise to many of the highly debilitating neurodegenerative disorders that are proliferating with frightening rapidity in the modern world [16]. In addition, the ability to define the details of the interactions between small molecules and proteins promises unprecedented advances in the exploration of rational therapeutic strategies for other very common conditions, for example to combat infectious diseases and cancer. On a more fundamental level, the opportunity to probe large macromolecular systems offers exciting opportunities for exploring such issues as the nature of complex protein–protein interactions, and the mechanisms of trafficking of molecules to different regions of a cell, a process involving transport through membranes and diffusion over significant distances in the cytoplasm.

The progress illustrated by the recent report [5] of a millisecond simulation of a protein will steadily enhance our ability to use molecular dynamics simulations as a powerful strategy for proposing possible mechanisms for complex biological processes. This strategy will enable experiments to be devised in a rational manner to test and extend such mechanisms, and in addition will enable experimental data to be translated into descriptions of the astonishing intricacies of biological systems. Indeed, the application of Moore's law to molecular biology reveals just how much our understanding of the fundamental processes that characterise living systems is likely to develop in the next few decades.

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Motor Memory: A Declaration of Non-Independence

A new study shows that the 'fast' component of motor adaptation is distinct from its 'slow' counterpart and shares critical resources with declarative memory.

Lee A. Baugh* and J. Randall Flanagan

Despite having to perform under a wide range of conditions that alter the relationship between motor commands and their consequences, humans have a dexterity that even the most sophisticated robotic devices are unable to match. For example, we can manipulate a variety of objects, even though grasping an object can dramatically alter the mapping between arm motor commands and arm motion. This ability is, in large part, the result of adaptive systems that are able to monitor and learn from sensory prediction errors [1,2]. Numerous studies have assessed human motor learning by applying novel and unusual loads to the hand via a vertical handle attached to a robotic interface during horizontal plane reaching movements (Figure 1A). Many of these studies have

used a velocity-dependent rotary load, or viscous curl field, where the force acting on the hand scales with hand speed and acts at right angles to the direction of hand movement. This load initially perturbs hand motion resulting in curved hand paths, but after a number of reaches participants adapt such that they generate approximately straight-line movement trajectories (Figure 1B).

Previous research has demonstrated that motor adaptation can be separated into two components with differing timescales: a fast component, in which task performance improves rapidly but results in a quickly decaying motor memory; and a slow component, in which both improvement and decay take longer [3,4]. This dichotomy is well supported in the literature, providing an explanation for many patterns of data typically observed in motor adaptation tasks, such as interference between competing motor memories [5], and specific retention properties of the newly learned motor memory [6,7]. Recognizing similarities between this fast component of motor learning and memories for facts, a new study by Keisler and Shadmehr [8] provides evidence that the fast component of motor memory shares resources with declarative memory.

The similarity between motor memory and traditional cognitive tasks has not gone unnoticed in the field. The early stage of motor learning has been described as 'cognitively demanding', in contrast to well-learned performance which, since the late 1960s, has been envisaged as part of an automatic system [9]. Further, evidence for the explicit cognitive nature of the fast motor system can be seen in studies examining the transference of learned motor skills across various experimental conditions. One would hypothesize that, if the fast component of motor learning shares features with explicit cognitive tasks, patterns of generalization would be a function of the subject's explicit awareness of the introduction of novel loads that change the relationship between motor commands and consequences. Recent research has verified this prediction, demonstrating that transference is not observed across limbs when loads are introduced gradually without the subjects' awareness, but is visible when the perturbation is large enough to be explicitly identified by the subject [10].

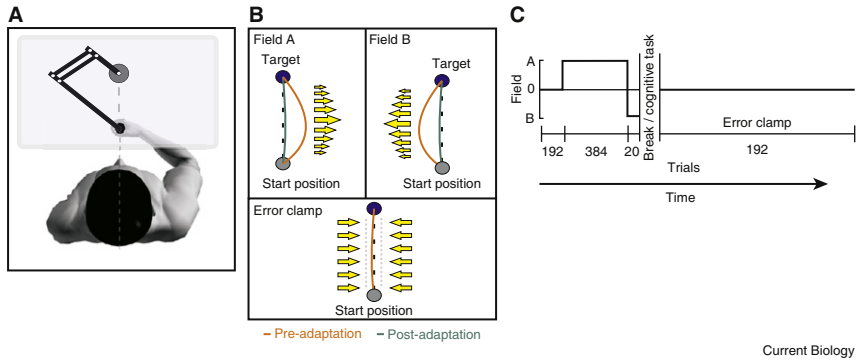

Figure 1. Experiments for investigating human motor learning.

(A) Robotic manipulandum: subjects completed a single-target task in which the participant's hand held the handle of a robotic device and made point-to-point reaching movements. Both the handle and subject's hand were obscured by a horizontal screen which was used to display cursor and target locations. (B) Example forces and movement trajectories for two opposing viscous curl fields and error clamp trials. (C) Experimental protocol used in Experiment 1 of Keisler and Shadmehr [8]. Participants first trained in a null block, followed by 384 trials of field A, resulting in 'slow' adaptation. Subjects were then exposed to 20 trials of field B, resulting in 'fast' adaptation. Following a three minute break or cognitive task, subjects performed 192 error clamp trials.

More recently, research has demonstrated that performing a secondary task during visuomotor adaptation leads to a subject's divided attention, in turn preventing the accurate encoding of errors during adaptation [11], a hallmark of cognitively demanding processes. Along similar lines, research has also shown that performing a secondary task requiring spatial resources (such as a visuomotor transformation), interfered with the early component of motor learning, yet had a diminished impact once the task was well learned [12]. Finally, a new stream of research has begun to show that the neurological correlates of early and fast motor adaptation are much more in line with higher level, cognitively demanding tasks, such as correlates implicating areas known to be recruited by a spatial working memory task (right dorsolateral prefrontal cortex and bilateral inferior parietal lobes) [13].

Although the answer has been previously hinted at, an important question in motor learning was whether the neural basis of the fast and slow processes are truly distinct, or are a by-product of the multiple timescales observed in studies examining the synaptic plasticity of single neurons. In an attempt to answer this question, Keisler and Shadmehr [8] had subjects perform a declarative memory task immediately after adapting their reaching movements to opposing novel force fields, which pushed that hand in opposite directions (Figure 1B). Subjects first adapted to field A over many trials and then briefly experienced the opposite field B (Figure 1C). At this point, the slow-learning component remained partially adapted to field A, whereas the fast-learning component was adapted to field B, with these two components cancelling each other out. If the fast component of motor learning and declarative memory share a common neuronal network, distinct from the slow component, performance immediately following the declarative memory task should show selective impairment in fast adaptation processes. Error clamp trials were used to assess the level of adaptation displayed. In these trials, the robot created an artificial channel in a straight path between the start position and target position (Figure 1B). By measuring the forces applied by the subject to the sides of the channel, the subject's current adaptation state could be measured. After training on both fields, the fast adaptation corresponding to field B initially blocked the effects of slow adaptation resulting from field A exposure. As fast adaptation effects decayed during the error clamp trials, the longer-lasting effects of slow adaptation (to the initial force field) re-emerged. However, if subjects performed a declarative memory task between the force field training and the error clamp trials, the effects of fast adaptation were

reduced. When combined with previous studies, there is increasing evidence that the fast component of motor learning is a result of a process involving a cerebello-prefrontal network, which is both neuronally distinct from the slow process that generates longer lasting motor memories, and shares some level of functional architecture with the declarative memory system.

The work of Keisler and Shadmehr [8] is both timely and informative. There has been a growing body of research suggesting a strong link between fast and slow learning mechanisms and explicit and implicit adaptation mechanisms. This demonstration that the fast system is reliant upon, and shares resources with, declarative memory helps solidify these emerging ideas. As declarative memory is responsible for memory of facts and events, it would seem the logical system to handle explicit, effortful, remembering of particular sensorimotor perturbations. Similarly, one could reasonably hypothesize that the slower component of motor learning would have substantial dependence on procedural memory. This hypothesis is supported by work with patient HM, a famous anterograde amnesic. When exposed to a novel force field task, HM demonstrated adequate retention of the novel motor memory, but displayed an abnormally slow learning rate throughout acquisition [14]: HM's marked impairments in his declarative memory system may have had a significant impact in the fast motor learning processes, leaving the slow learning processes relatively intact.

Our motor system's natural ability to identify and control for errors in movement has been well established. Identifying the specific neurological systems that are responsible for this uncanny ability will provide invaluable knowledge that could have wide ranging impact on understanding typical and atypical human motor performance, robotic control systems, rehabilitation regimens, and tele-operations. Future research aimed at quantifying both the cognitive and non-cognitive resources involved in both types of motor learning are now required to fully explore what is likely to be a diverse recruitment of neurological systems to foster successful motor adaptation across time.

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Pyroptosis: Macrophage Suicide Exposes Hidden Invaders

Caspase-1 plays a key role in host defense through its dual function in inducing a pro-inflammatory cell death termed pyroptosis and in promoting the secretion of pro-inflammatory cytokines. A new study now highlights the specific importance of pyroptosis in resistance to intracellular pathogens.

Igor E. Brodsky[1] and Ruslan Medzhitov[1,2]

Immune defense against microbial pathogens requires the recruitment of phagocytes and antigen-presenting cells to the infection site and production of pro-inflammatory cytokines that tailor immune responses to the specific nature of the infection. Macrophages and neutrophils are critical for innate immunity because they phagocytose and eliminate bacterial pathogens by targeting them to phagosomes for degradation. Many bacterial pathogens also induce activation of caspase-1 via recruitment of pro-caspase-1 into multiprotein complexes termed inflammasomes. The assembly of inflammasomes under different conditions requires a member of the Nod-like receptor (NLR) protein family, thought to act as a sensor of various stresses, including bacterial infection, and in certain cases also requires an adaptor protein called ASC [1]. Inflammasome activation in macrophages results in both a form of cell death termed 'pyroptosis' [2] and the cleavage and secretion of biologically active forms of the inflammatory cytokines interleukin-1β (IL-1β) and IL-18 [3,4].

Caspase-1 deficiency results in increased susceptibility to a variety of infections, including infection by the enteric intracellular pathogen *Salmonella* [5,6], but precisely how caspase-1 controls bacterial infection has remained somewhat unclear.