

Consolidation of motor memory

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An issue of great recent interest is whether motor memory consolidates in a manner analogous to declarative memory – that is, with the formation of a memory that progresses over time from a fragile state, which is susceptible to interference by a lesion or a conflicting motor task, to a stabilized state, which is resistant to such interference. Here, we first review studies that examine the anatomical basis for motor consolidation. Evidence implicates cerebellar circuitry in two types of associative motor learning – eyelid conditioning and vestibulo-ocular reflex adaptation – and implicates primary motor cortex in skilled finger movements. We also review evidence for and against a consolidation process for adaptation of arm movements. We propose that contradictions have arisen because consolidation can be masked by inhibition of memory retrieval.

Introduction

It is clear from experience that the nervous system can form multiple long-term (>24 h) motor memories; for example, we apparently never forget how to swim, to ride a bicycle or to drive a car. However, despite the ubiquity of long-term motor memory in everyday life, experimental demonstration of how such memories are formed and retained has proven controversial. This review will focus on the specific issue of consolidation of motor memory, with consolidation defined as a set of processes whereby a long-term memory becomes more stable with the passage of time [1]. This definition implies that consolidation is proven if the memory is susceptible to disruption by a competing memory or a focal lesion during a limited time-window.

Motor memory differs from declarative memory in that it is demonstrated through savings in performance over several trials, rather than through recall of a single item (single-trial memory). ‘Savings’ refers to a more rapid rate of relearning compared with the rate of original learning. Thus, a motor memory has consolidated when there is a limited time-window within which savings can be disrupted. Here, we first describe studies of simple associative motor learning for two well-characterized reflexes, where there is good evidence for consolidation and insight into its underlying neural circuitry. We then address consolidation of skilled sequential finger

movements. Finally, we examine adaptation of arm movements to novel dynamics and to new visuospatial mappings, two types of motor learning for which evidence of consolidation is more elusive.

Consolidation of associative motor learning

Experimental investigation of Pavlovian eyelid conditioning (EC) adaptation and vestibulo-ocular reflex (VOR) adaptation in several species has provided valuable insights into the neural circuitry, specifically in the cerebellum, involved in savings [2] and consolidation of motor memory [3–5]. EC and VOR adaptation are similar in that they both involve associative learning in a reflex circuit [6], in which a conditioned stimulus (CS; e.g. tone or head motion) is paired with an unconditioned stimulus (US; e.g. air puff or retinal slip).

In EC, the CS is often a tone, which is followed after 100–1500 ms by a puff of air, the US. After 100–200 trials, the CS elicits precisely timed eyelid closure that precedes the US [7]. This defensive conditioned response (CR) can persist for long periods in the absence of exposure to the CS, but can be extinguished by relatively few trials of the CS without the US [8,9]. Extinction does not erase the motor memory, however, because relearning of the CR shows savings [2,10]. The degree of savings on reacquisition of the CR after extinction is strongly correlated with the amount of residual plasticity in the deep cerebellar nuclei. This is detected by eliciting fixed short-latency responses to the CS, after disconnection of the cerebellar cortex by injection of a GABA receptor antagonist into the cerebellar nucleus. Importantly, disconnection of the cerebellar cortex from the interpositus nucleus prevents extinction of EC [11]. This suggests a ‘cascade’ model of adaptation, where the CS and the error signals initially produce rapid plasticity in the cerebellar cortex, resulting in a change in the discharge of the Purkinje cells. Subsequently, the altered output of the Purkinje cells, in combination with the CS signals, produces gradual plasticity in the interpositus neurons [2,3,12]. Therefore, the learned behavior in EC might be due to a system that adapts quickly (the cerebellar cortex) and then subsequently produces plasticity in another system (the cerebellar nuclei).

Passage of time affects the way that the cerebellar cortex contributes to retention of EC. Animals that receive muscimol infusion to the cerebellar cortex at 5 min or 45 min after acquisition of the CR show no savings of EC [4,5]. By contrast, control animals and animals that

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receive muscimol after 90 min resume in a second acquisition phase where they left off in the first acquisition phase. This suggests that soon after completion of training, adapted behavior strongly depends on the plasticity in the cerebellar cortex. However, passage of time reduces or eliminates this dependence.

Work on retention of VOR adaptation is also compatible with the cascade model. Lesioning of the flocculus prevents adaptation of the horizontal VOR [13] and reversible inactivation of the flocculus abolishes retention of a VOR gain acquired over 1–3 h [14–16]. By contrast, flocculus inactivation fails to abolish a VOR gain acquired over days [16–19]. It seems plausible that learned behavior initially depends on the modified synapses in the cerebellar cortex, but that with time the location of the memory shifts.

Eventually, specific adapted behaviors can exist entirely independently of the cerebellum. For example, in fear conditioning, the ability of a rat to recall the importance of an acoustic cue depends on the integrity of the interpositus for ~96 h after initial training [20]. After that interval, disruption of the interpositus has no effect on recall. Is there evidence for this time-dependent role of the cerebellum in humans? A recent study examined individuals with cerebellar cortex lesions in two different types of EC task: one task that was novel (associating tone with an eye blink) and one task that the subjects had learned before their cerebellar cortex injury (a kinesthetic threat eye-blink response, or KTER) [21]. The individuals could not learn the new conditioning task, which confirmed the idea that acquisition of the new eye-blink task depended on the cerebellar cortex. Surprisingly, they maintained the response for the old task. This suggested that in humans, the cerebellum is required for acquisition of a new conditioned response but not for its long-term retention. Overall, these results suggest that simple motor memories undergo changes in their anatomical storage site as they stabilize, with progression over time from the cerebellar cortex to cerebellar nuclei, and then perhaps to locations outside the cerebellum [21,22].

There are reasons to suppose that the cerebellar mechanisms elucidated for consolidation of EC and VOR adaptation are relevant to motor consolidation in general. First, the regularity of synaptic organization throughout the cerebellum suggests that it performs a similar computation for many types of motor learning. Second, current evidence suggests that both saccadic and reach adaptation, which are voluntary movements rather than simple reflexes, depend on the cerebellum [23–26]. For example, damage to the cerebellum, but not damage to the basal ganglia, can profoundly impair adaptation of reaching when novel forces act on the hand [27]. Third, human studies [24–27], animal data [28], functional imaging studies [29–32] and recent computational models [33–35] suggest a role for the cerebellum in storage of internal models for reaching movements.

Consolidation of skilled finger movements

Repetitive 1 Hz transcranial magnetic stimulation (rTMS) has been used to investigate the role of primary motor cortex (M1) in retention of a simple finger opposition task

[36]. Subjects performed a metronome-paced (0.5 Hz) ballistic pinch between the index finger and thumb of the non-dominant left hand. The performance measure was acceleration of the pinching movement, which was assessed across two practice sessions. Control subjects showed increases in peak pinch acceleration within a first practice session and subsequent savings in a second practice session 15 min later. Savings in the second session were eliminated if subjects received rTMS for the 15 min between the two practice sessions. The rTMS was applied over an area of right M1 selected for its capacity to elicit motor evoked potentials in the left flexor pollicis brevis, and known to be associated with practice-induced changes in excitability [37]. By contrast, when the 15 min of rTMS over M1 was given 6 h after the first practice session, it had little or no effect on savings. The authors of this study proposed that, although acquisition of this skill depended on M1, its eventual retention depended on a different neural system. This is consistent with the recent observation that induction of long-term potentiation (LTP)-like plasticity in human M1 is much more difficult immediately after training than 6 h after completion of training [38]. Another group subsequently confirmed this result [39].

Further evidence of a consolidation window for skill learning was obtained from a study in which subjects performed a finger-tapping task in a four-digit sequence [40]. Performance was measured in two ways: speed (number of complete sequences achieved) and accuracy (number of errors made compared with the number of correct sequences). Subjects showed savings for the same sequence 24 h later. However, if subjects learned a second sequence immediately after the first, then there were no savings (of the first sequence) at 24 h. By contrast, subjects showed savings for both sequences if the second sequence was learned 6 h after the first. These studies indicate that retention of some forms of skill in humans might be initially susceptible to disruption, but this susceptibility might be reduced with time. Although all these studies used a finger task, there is an important distinction to be made between studies that emphasize simple tapping or pinching skills, assessed by measuring acceleration and force, versus studies that show an increase in accuracy and reaction time as a whole sequence is learned (Box 1). It is possible or even likely that consolidation of these two aspects of motor learning will have different anatomical substrates.

Consolidation of internal models for reaching

In the past 20 years, a computational framework has been developed to characterize the behavioral and neural basis for planning and execution of reaching (reviewed extensively in [41]). It appears that the CNS plans reaching movements in extrinsic space [42–44], with target and hand location initially coded as vectors with respect to fixation that are then subtracted to produce an intended movement vector in a hand-centered coordinate system. The transformation of this vector into motor commands depends on maps or internal models. The computation that enables the CNS to predict the sensory consequences of motor commands (in both visual and proprioceptive

Box 1. The difference between skill learning and sequence learning

It is useful to distinguish between skill and sequence learning because these two types of learning are often confused in the literature. In a recent review on consolidation of 'procedural memory', it was stated that 'the evidence for sequence learning tasks requiring stabilization is mixed' [53]. This statement is based on the finger-tapping study by Walker *et al.* [40] (mentioned in the main text under 'Consolidation of skilled finger movements') and on a recent serial reaction time (SRT) study that found no evidence for consolidation of sequence learning [51]. However, the statement is debatable for two reasons. First, it compares skill learning with sequence learning. Second, the SRT study of consolidation is open to question. We will briefly deal with these issues in turn.

Finger tasks in which the sequence is short are best considered skill tasks because the performance measures of interest relate to speed of execution of the sequence, not the rate of acquisition of the sequence order *per se*. By contrast, finger tasks in which the sequence is long and embedded (e.g. a 12-element sequence with only four buttons) are based on the much-studied SRT, and the measure of interest, the reaction time (RT), captures learning of the embedded sequence order itself [65]. These two aspects to sequence learning are almost certainly cognitively distinct, because one is effector-specific and the other is effector-independent [66,67]. The interplay of these two forms of skill learning is apparent in the SRT study that purported to show no evidence of consolidation for sequence learning [51]. All subjects

learned sequence A and then returned 48 h later to be retested on this sequence. Unlike the control group, four other groups learned a second interfering sequence B, 5 min, 1 h, 5 h or 24 h after sequence A. The learning measure was the difference between the RT at the end of sequence learning and the RT for a random sequence. Savings were quantified by subtraction of the learning measure for sequence A from the learning measure for retest of sequence A. This measure was positive for the control group only and negative for the other four groups. Unfortunately, this apparent persistence of interference could be an artifact caused by increased skill in the random sequence, attributable perhaps to more practice overall because of additional training with sequence B. This is suggested by the fact that for the four interference groups, the RT for a random sequence at the beginning of the second session was actually lower than the RT for sequence A at the end of the first session. This indicates that savings for nonspecific skill component of the task led to a greater reduction in RT than did learning of the sequence order itself. The presence of an interference effect might therefore have been due to the choice of learning measure, which could be affected equally by savings in nonspecific skill learning or by interference with the specific sequence. A stronger claim could have been made if subjects, with extra training on sequence A, could have lowered their RT below that shown for the four interference groups (i.e. no RT floor effect). Without showing this, the results remain ambiguous.

coordinates) is termed a 'forward model'. For example, when one tries to reach while looking at the hand through a mirror, one observes a mismatch between the visually observed consequences of the motor command and its proprioceptive feedback. This error can produce adaptation in a forward model of the arm. The term 'inverse model' labels the computation that enables the CNS to plan motor commands to achieve a goal that is defined in sensory coordinates. For example, lifting up an apparently full cup of liquid relies on an inverse model that predicts the motor commands necessary to accelerate the cup upwards. Finding out that the cup is actually empty results in an error that modifies the internal model associated with that action. Motor learning probably involves adaptation of both kinds of map [45], although in principle it is difficult to tease apart contribution of forward and inverse models to adapted behavior [46]. Here, we use the term 'internal models' to refer to both types of computation.

Many studies have shown that after an internal model is learned, it can be recalled at a later date. This is apparent as 'savings': relearning is more rapid and complete than original learning. The first experiment to show consolidation of motor learning examined the formation of two competing inverse models using a well-characterized force-field adaptation paradigm. Subjects who adapted to a clockwise force field (B1) during reaching showed savings when they were re-exposed to the same field after an interval of hours or days. However, savings on relearning were prevented if, after learning the first field, subjects adapted to a counter-clockwise field (B2). Crucially, B2 no longer interfered with savings for B1 if the time interval between training with the two force fields was greater than ~4–6 h [47,48]. These results demonstrated for the first time that motor learning showed a retrograde gradient of susceptibility to an interfering task consistent with a consolidation process.

Interestingly, the ability to learn B2 became progressively better as the interval from learning B1 lengthened. Indeed, there was no significant difference between learning of B2 6 h after B1 and initial learning of B1. The time course of this improvement was attributable to fading of after-effects from B1. The similarity in the time courses of susceptibility of B2 to anterograde interference by B1 and susceptibility of B1 to retrograde interference by B2 suggested a possible obligatory relationship between anterograde and retrograde effects. This was addressed with an experiment in which subjects were trained with B1 on day one and then returned the next day to train again on B1 followed by B2. The degree of anterograde interference of B1 on B2 was not significantly different from the initial experiment. However, when B1 was retested on day three, retrograde interference was not seen. This supports, but is not conclusive evidence for, the idea that retrograde and anterograde interference are independent non-reciprocal processes. It is not fully conclusive because if learning on day three had been compared with a control group who learned B1 over three days without B2 on day two, then an interference effect might have been apparent.

Since the publication of the aforementioned study and its initial evidence for consolidation, attempts to replicate the result [49] or reproduce it [49–51] have, with one exception [52], failed. Instead, visuomotor adaptation experiments have consistently shown a flat gradient of interference: task B prevented savings in task A regardless of the interval between A and B. The first experiment to show a flat gradient employed a joystick-tracking task, in which the screen cursor was inverted either up–down or left–right [50]. Subjects showed savings when they repeated either task but the tasks interfered with each other even with a one-month interval between them. Similarly, interference between opposite lateral-displacing prisms, used in a ball-throwing task, persisted with

intervals of 5 min, 1 h, 5 h and 24 h [51]. If anything, interference increased as the interval increased – the opposite of what would be expected for a consolidation process. The presence of a flat gradient has led some investigators to conclude that consolidation might not occur for visuomotor learning [49,53]. However, this conclusion is likely to be incorrect. As stated by Dudai [1], ‘monotonous effectiveness of a blocking agent over time suggests that this agent impairs maintenance, retrieval or expression of memory, not its consolidation’.

A recent study addressed this issue by hypothesizing that anterograde effects prevented retrieval and thus masked consolidation [52]. The prediction was that ‘washout’ of anterograde effects by returning subjects to baseline performance would unmask a consolidation process. The motor adaptation task was a 30° rotation of the usual relationship between cursor and hand movements during reaching – a visuomotor perturbation that shows robust savings and interference [54,55]. In the first experiment, a 30° rotation followed by a 30° counter-rotation prevented savings even when the two training intervals were separated by 24 h. This result was consistent with the flat gradient of susceptibility shown in previous studies [49–51]. In the second experiment, however, introduction of baseline blocks (washout) between rotations led to interference by a counter-rotation at 5 min but not at 24 h, consistent with a consolidation process. In a third experiment, when the amount of rotation training was doubled, the counter-rotation did not interfere even at 5 min. Thus, consolidation occurred for visuomotor adaptation both through a graded effect of time interval and with increased initial training. The key factor appeared to be the washout trials. In the absence of washout, the counter-rotation prevented retrieval of the internal model for the initial rotation. A similar inhibition of retrieval effect is described in the declarative memory literature for paired-associates word learning [56].

A final point about the washout experiment is that it provides evidence that visuomotor adaptation tasks can undergo another form of consolidation called off-line learning. Off-line learning represents improvements in motor skill without practice – that is, between training sessions. Although this review is about consolidation as memory stabilization rather than as off-line learning, the issue is raised here for two reasons. First, to make readers aware that there are two distinct definitions of motor consolidation in the literature, and second, as a response to a recent statement that off-line improvement has not been convincingly demonstrated for visuomotor, or kinematic, adaptation tasks [53]. The reason for this statement is that better performance at relearning cannot be taken as evidence for off-line improvement because the improvement might result simply from practice (i.e. resuming on the learning curve from the point reached on the previous day). However, in the washout study already described [52], subjects started at the same point on the curve in the relearning session as they did at initial learning but still learned at a faster rate. This is convincing evidence for off-line learning. Thus, visuomotor adaptation tasks can undergo both types of consolidation.

Experiments have not yet directly addressed anatomical sites of consolidation for reach adaptation. However, an important clue with regard to storage and retention of internal models has been provided by single-unit recording experiments in M1 [57]. Activity in M1 neurons was averaged from just before movement onset to movement end, while monkeys adapted and then de-adapted through washout in force fields. One group of neurons rotated their preferred direction in the direction of the field during adaptation and then rotated back during washout. This is similar to the behavior of muscles [58] and might merely indicate that motor commands are changing in response to the movement errors. However, two other groups of neurons showed a much more interesting response: one group showed a change in preferred direction during field training and maintained this change despite an extended period of washout trials. Another group did not change its preferred direction during field training but rotated in a direction opposite to the field during washout. Therefore, if one measures the change in motor output as the sum of changes in preferred direction, then during washout this sum was zero even though the individual components were not at baseline. It can be conjectured that the presence of a population of neurons that do not return to baseline might form the basis for savings because they can be recruited when subjects return to the force-field condition.

Consolidation of internal models in bimanual skills

In bimanual movements, one hand often serves a supportive role by holding an object that is manipulated by the other hand. For example, if one hand holds an electronic notepad and the other hand writes on the device, the supporting hand shows compensatory adjustments to counteract the anticipated forces arising from the writing hand. A similar situation occurs when one hand holds a book while the other hand lifts it: the postural hand reduces the upward forces precisely at the moment when the lift starts. In this way, the postural hand shows little displacement as the object is lifted. By contrast, if another person were to lift the object, the postural hand would show large upward displacements [59,60].

Such adjustments demonstrate that when we perform an action with one arm, the brain anticipates its consequences on other body parts (an example of a forward model). For lifting an object, the skill is acquired in late childhood [61]. A recent study examined acquisition and retention of this skill in individuals with cerebellar damage [22]. They used a robot to simulate the load held by the postural hand. Surprisingly, these individuals showed normal anticipatory adjustments by the postural hand as the object was lifted by the other hand. In addition, long-term retention of the skill appeared intact. To measure acquisition of a new response, a novel condition was considered, which introduced catch trials where the normal behavior of the load was unexpectedly altered. In healthy individuals, the resulting error in the catch trial produced a robust change in the behavior of the postural hand in the subsequent trial. This trial-to-trial compensation was absent in the individuals with cerebellar damage. These results challenge the idea

Box 2. Outstanding issues and future directions

- In a recent study, Caithness *et al.* were unable to find evidence for consolidation of force-field learning with or without a washout paradigm. This result reinforces the fact that anterograde interference effects, which lead to flat gradients, are a robust phenomenon in motor learning and might not always be effectively removed by washout blocks. Further work is needed to characterize the factors that influence retrieval of motor memories.
- Experiments suggest that consolidation of motor memories takes place over hours, a time course compatible with synaptic consolidation. As yet, there is no evidence for a process that takes places over weeks or months, as is seen with declarative memory. Further investigation is required to determine whether this represents a fundamental distinction between these two types of memory.
- In addition to the passage of time and amount of initial learning, it has been suggested that sleep has a role in consolidation of motor memories. However, most studies to date have focused on finger-tapping skill, and consolidation has been defined as off-line learning [68,69] rather than resistance to interference. The importance of distinguishing between these two definitions of consolidation is suggested by dissociation in their dependency on sleep. For example, in one study, passage of time was sufficient to render the tapping skill for a particular sequence resistant to interference by another sequence, but sleep was required for off-line learning [40]. In a study of force-field learning, no effect of sleep deprivation on savings was observed [70], suggesting that the necessity of sleep even for off-line learning might vary for different types of motor learning. There is not yet any evidence that sleep is specifically involved in motor memory stabilization (i.e. consolidation as defined in this review).
- Numerous functional imaging studies have shown transitions in brain areas activated over short (minutes or hours) [29,71–73] and long (days or weeks) [74,75] time courses of motor learning. However, change in the location of activation over time is not itself indicative of consolidation because it could also represent multiple other processes, for example, change in performance with practice. Future studies will need to correlate behavioral measures of savings and interference with activation changes to identify brain regions associated with motor consolidation. Functional imaging studies will need to be corroborated by virtual lesions using TMS in humans or real lesions in animal models.

that the cerebellum could be the site of long-term storage of internal models that compensate for the consequence of our own actions. Rather, they suggest that although the cerebellum is crucial for acquisition of these internal models, long-term retention might be independent of this structure.

Concluding remarks

There is evidence for motor consolidation in several experimental systems – that is, the behavioral correlates of the memory suggest that under some conditions the neural substrate becomes resistant to disruption within hours or days. In specific tasks, the cerebellar cortex appears to be crucial in the initial storage of the memory but, with time, the memory can be represented elsewhere. Because motor learning comprises several distinct processes (planning of sequences of action, adaptation of internal models, and so on), motor memories might consolidate over different time periods and at different anatomical locations. There is a precedent for this with declarative memory: semantic memories become

hippocampus-independent, whereas episodic memories do not [62].

Important challenges remain (Box 2). First, computational models of motor control have focused mainly on adaptation, with little or no attempt to consider time-dependent memory processes. Key experiments that show savings after washout remain largely unexplained [52,63]. Second, motor learning is about associating knowledge with specific contextual cues. Yet attempts to learn cue-dependent internal models in the laboratory have suffered from large interference between opposing motor tasks despite explicit contextual cues. A recent report suggests that the missing element in previous work might be the presence of rest intervals between changes in contextual state [64]. It is also possible that unidentified implicit contextual cues facilitate or inhibit recall of consolidated memories. Identification of those cues that prevent retrieval of consolidated memories and those that enable switching between consolidated memories is crucial to understanding how animals can form long-term context-specific motor memories.

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