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In search of the engram, 2017

Eva Berlot, Nicola J Popp and Jörn Diedrichsen

Based on evidence from lesion and imaging studies, some authors have suggested that the 'motor engram' — a representation underlying skillful behavior — becomes more localized with learning. We critically review the evidence in favor of this view pointing out several caveats with the interpretation, most of which have been raised in Karl Lashley's classical paper from 1950. We argue that motor skills are likely not stored in a single area, but are instead encoded across multiple representations in both cortical and subcortical areas. To better understand these distributed neural changes with learning, we need a richer description of skilled performance and testable process models of skill acquisition.

Address
The Brain and Mind Institute, University of Western Ontario,
1151 Richmond St., London, ON N6A 5B7, Canada

Corresponding authors: Berlot, Eva (eberlot@uwo.ca), Diedrichsen, Jörn (jdiedric@uwo.ca)

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Introduction

Motor learning is the remarkable process by which the brain can improve performance of movements through practice. While we can readily observe the resulting behavioral changes, it remains unclear what neural processes underlie learning, and where in the brain the newly acquired skills are represented. Searching for the location of the 'motor engram' has been the central agenda of many neuroscientists from the very beginnings of our discipline. Many of the fundamental issues with this quest were already eloquently exposed in Karl Lashley's seminal paper from 1950 [1••], and despite dramatic improvements in our ability to record and manipulate neural circuits, these questions have largely remained the same in 2017. Reviewing modern evidence from neuroimaging, lesion, and electrophysiological studies, we reiterate here Lashley's argument that the search for a motor engram will in most cases not have a simple, localized answer. We discuss the conceptual advances in the analysis of neural and neuroimaging data that are needed to understand how movement skills are represented across different brain areas. We also argue that we need behavioral theories that characterize motor learning not as a monolith, but as an emergent property of parallel, interacting processes. We focus our discussion on acquisition of complex motor skills, using sequence learning as one paradigmatic example of skill development.

There is no single motor engram

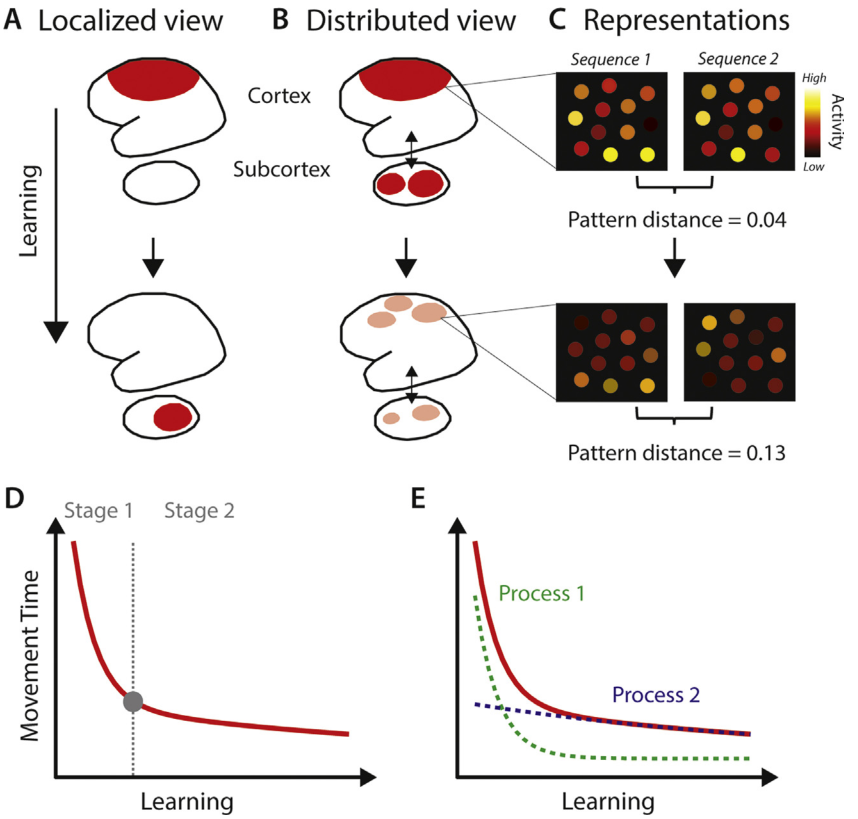
A widely-held view is that early in motor learning, skills are controlled by a wide network of cortical areas, but with time and practice the representation is transferred to a more narrow set of subcortical structures [2–4] (Figure 1a). The simplicity of this account is attractive because it follows our intuition of the roles of the cortex and the subcortex. However, the intuition can easily lead to false inferences about the representation of highly trained skills. Lashley summarized this argument as follows:

> 'Consciousness is a function of the cerebral cortex; long-practiced habits become automatic and are performed without conscious control; therefore they are no longer mediated by the cerebral cortex. Both premises of this syllogism are probably false, and the conclusion would not follow if they were true [1••].'

Of course, the view of increasing subcortical control with learning is based on more than an ill-conceived argument about flexibility, attention or conscious control. In the following section, we will review some of the main empirical results in favor of a localized subcortical storage of acquired motor memories, and point out the main problems in their interpretation. Ultimately, we will argue that there is no firm evidence for the exclusive storage of a motor engram in subcortical structures.

Numerous functional magnetic resonance imaging (fMRI) studies have attempted to study motor learning by correlating improvements in performance with changes in the overall activity in different brain areas with learning (see [5] for a review). One common observation is that early in learning, the production of motor sequences evokes extended activity in a network of cortical motor, pre-motor and association regions. This activity commonly decreases with time in the majority of cortical regions, while focal activation increases have been observed in sensorimotor regions of the cerebellum [6], basal ganglia [7] and the spinal cord [3]. This has been

Figure 1



(a,b) Localized versus distributed view of neuronal changes with learning. (a) The localized view proposes that motor skills transfer from widespread recruitment of cortical areas to a circumscribed subcortical locus with learning. (b) The distributed view suggests that both cortical and subcortical regions are involved at all stages of learning, with overall decreasing activation levels and more efficient encoding. **(c)** Changes in representational structure with learning. Neuronal population in a given area might respond very similarly during two finger tapping sequences at the beginning of learning (indicated by similar pattern of activation of activation units and a low pattern distance). With training, units become less active, but also differentially recruited for each of the two sequences. Thus, early in learning a downstream-connected area would receive identical input for production of either sequence, but later on it receive a unique input for each of them, further leading to recruitment of specific motor pools for each action. **(d,e)** Stage versus process models of behavioral changes with learning. (d) The stage model divides motor learning into distinct stages — an initial fast learning stage (often within-session), and a late slow learning stage with more incremental improvements until performance asymptotes. Translating the stage model into a neural mechanism, this would require a switching mechanism regulating the transition between stages (the 'switch' is indicated by the gray dot). (e) The same behavioral improvement can be explained by two continuous (and possibly independent) processes, where the process with a greater exponential improvement dominates in the early learning, while a slower process gains importance later on.

interpreted as evidence that well-learnt motor sequences are stored subcortically, with a decreasing cortical role in the skilled behavior (Figure 1a). The fundamental problem with this argument, however, is that decreases in fMRI activation do not necessarily reflect that an area is no longer involved in the task. It could be that the region still performs the same function, but does so more efficiently, which would result in lower fMRI activation [8]. Therefore, such results do not provide conclusive evidence for a disengagement of the cortex in performance of skilled movements.

Lesion studies are considered to be the gold standard for establishing causal relationships between regional activation and behavior. One possible outcome of a lesion experiment is that skilled performance remains unimpaired or recovers rapidly after the lesion [9•,10,11]. This is taken as an indication that the disrupted region is not strictly necessary for performing skilled behavior. But should we conclude that the region does not causally contribute to the skill at all? It is very well possible that there is no area that would lead to circumscribed deficits of skilled performance without impairing motor output in general. This would arise from a situation in which skill is represented in a distributed fashion across the brain, and where disruption of one region can be immediately compensated with activity coming from other areas. Such a behavior was recently observed in the mouse during a delayed response task, where temporary disruptions of one premotor cortex were immediately corrected by information provided by the premotor cortex from the other hemisphere. Only after additional callosal lesions was task performance impaired [12•]. Therefore, even if a lesion does not produce an immediate behavioral deficit, it is possible that the manipulated area is still involved in motor skill production in an unperturbed brain.

The interpretation of the other possible outcome, namely that a lesion of an area leads to behavioral deficits, can be problematic as well, as it does not provide specific insight into what the exact contribution of the area is. It could encode some aspect of the learnt skill, but it could also provide a non-specific drive to another area, which is actually involved in the learnt behavior. A recent study [13••] demonstrated that lesions to the songbird cortical area led to transient deficits in singing. However, this impairment was not due to a direct involvement of the cortical region in the production of the skill, but rather to downstream consequences within the basal ganglia which no longer received excitatory cortical input. After a few days, activity in basal ganglia recovered, and so did the singing. This demonstrates how monitoring activity in areas other than the lesioned one (both acutely and across a longer time period) allows us to evolve from asking 'whether' an area is involved in behavior to instead addressing 'how' it contributes to skilled performance. In the next two sections we will discuss two important challenges we have to address to achieve this goal: new techniques to characterize distributed neuronal representations, and better models of the behavioral elements of motor skill.

New analysis techniques for charactering distributed brain representations

Rather than a single motor engram, the neural substrates of motor skill more likely consist of multiple representations distributed both cortically and subcortically (Figure 1b), with their contribution dynamically changing over the course of learning. New techniques to measure large-scale activity patterns, such as high-resolution fMRI in humans and wide-field calcium imaging in rodents, allow us to investigate distributed coding across the brain. One of the next important challenges is how to quantify the neuronal processes underlying motor skill learning. One option is to examine the overall level of activity, averaged over a large population of neurons. While many authors have focussed on increases in activity with learning [5], decreases in signal are harder to interpret. As pointed out above, decreases could reflect less involvement as learning proceeds or more efficient coding. This also means that greater neuronal recruitment and more efficient coding could cancel each other out, resulting in no net change in activation.

To understand how neuronal activity contributes to motor skill, it is therefore necessary to look at what information neuronal populations encode, using the related methods of neuronal state-space analysis [14] and representational analysis for fMRI data [15]. Representational analysis examines the relationship between activity patterns evoked by different conditions (e.g. different finger-tapping sequences) rather than just examining overall levels of activation (Figure 1c). Inferences about representational structure in an area are made based on how similarly or distinctly different conditions are encoded. Some support for distributed encoding of motor skill comes from a study [16••] demonstrating that representations of movement sequences become sharper as learning progresses, with trained sequences represented more distinctly than untrained sequences across several cortical regions. While the existence of representation of one or more task-relevant variables is not sufficient evidence for concluding a functional role of the region, it is a necessary condition. Namely, only if the regional pattern of activity represents some important task variables (i.e. with different neuronal state for different versions/times of the task), will the region be able to influence a downstream-connected area in a task-specific fashion, and hence contribute to the improvement of the skill. Of course, whether or not a representation is observable depends on the spatial resolution achievable by methods employed and the scale at which representations reside (e.g. neuronal populations vs. single neurons).

Another aspect to be tackled is how representations in different brain areas interact. One important analysis tools that can help to elucidate this question is to inspect the temporal flow of activation across different areas [17••]. Another common approach is to examine the connectivity between different brain areas or networks as learning progresses [18,19]. Ultimately, these connectivity-based analysis techniques will need to be unified to arrive at a full description of the dynamic interplay between representations in cortex and subcortex that bring about highly skilled performance.

New process models of motor sequence learning

The second key challenge is to establish a correspondence between changes in neural coding and behavioral improvements. To bridge between these two levels, we need to develop models that are able to predict behavioral improvements, but also decompose the learning into its constituent components or processes, which then in turn can be related to the representational changes in specific areas. In the case of motor sequence learning, we are lacking such models. Current models often describe the observed behavioral changes in terms of learning 'stages', usually dividing a learning curve into an early stage, defined as fast behavioral improvement, and a late stage, denoted by slower learning until performance asymptotes [20] (Figure 1d). We would argue that such a stage model can at best serve as a descriptor of behavioral data, but not as framework under which to understand neural changes.

This is because a stage model would necessitate a switching mechanism regulating when one stage has finished and another one should be entered, which is neither parsimonious nor biologically plausible. It is more likely that the changes in behavioral improvement are caused by two or more continuous (and possibly independent) processes. These learning processes may have different time-scales and therefore may slowly shift in importance over the time-course of learning without the need to define a 'stage' or 'switch' (Figure 1e). Multi-process models have been extremely successful in explaining the dynamics and different facets of error-based learning (adaptation) [21,22••,23], and should serve as an inspiration for developing similar models of motor sequence learning.

In order to build such models, we first need a richer description of the skilled behavior, since a single behavioral index (e.g. movement time) usually does not yield insights into different underlying processes. One example here is to inspect the full speed–accuracy trade-off curve, rather than speed or accuracy in isolation [24]. Other potential indicators include the preparation time necessary for accurate performance [25•], facilitation after direct repetition of the same sequence, the influence of sensory feedback on performance, and learning transfer across effectors (e.g. left and right hands) [26]. Inspecting how different variables change with practice and time will help in formulating models that can predict how learning evolves under different training regimes. Only biologically plausible and experimentally tested models of behavioral processes stand a chance of enabling a link between skill improvements and the associated changes in brain representations.

Summary

The search for neural substrates of skilled performance is a complicated and daunting task, which is often simplified by examining the contribution of a single area to performance. Here we argue that the motor engram is likely not localized, but rather emerges from the reorganization of a network of brain areas. In order to relate changes in brain representation with behavioral improvements, we need valid process models of motor sequence learning. This challenge should be undertaken by finding multiple informative behavioral performance indicators, by developing models that can make quantifiable predictions of performance, and by testing them on a wide range of training protocols. This effort requires a culture in which both experimental data and models are openly shared between research groups. As better behavioral models are becoming established, we can go beyond the simple mapping of 'behavioral improvement' onto the brain and arrive at an understanding of how different areas contribute to various aspects of behavioral performance during motor learning.

Conflict of interest statement

Nothing declared.

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