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Current issues related to motor sequence learning in humans

J Doyon[1,2], E Gabitov[1,2], S Vahdat[1], O Lungu[1] and A Boutin[1,2]

The learning of sequential motor behaviors involves the integration of separate movements into a unified and coordinated sequence of actions through practice. Neuroimaging studies in humans strongly suggest that this form of procedural memory relies on the progressive reorganization of motor-related neural networks over the course of learning. This experience-driven reorganization of internal task representations is also subserved by consolidation processes that require time, and sometimes sleep, to become effective, hence constituting the mechanism by which long-term memory of the skill is achieved. In this review, we present the current understanding of the behavioral determinants, brain functional plasticity and neurophysiological processes related to the formation and long-term retention of motor sequence knowledge. Insights from clinical research and their practical implications, with the development of non-invasive and patient-oriented interventions, are also discussed.

Addresses
[1] Functional Neuroimaging Unit, Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, Québec, Canada
[2] Department of Psychology, University of Montreal, Montreal, Quebec, Canada

Corresponding author: Doyon, J (julien.doyon@umontreal.ca)

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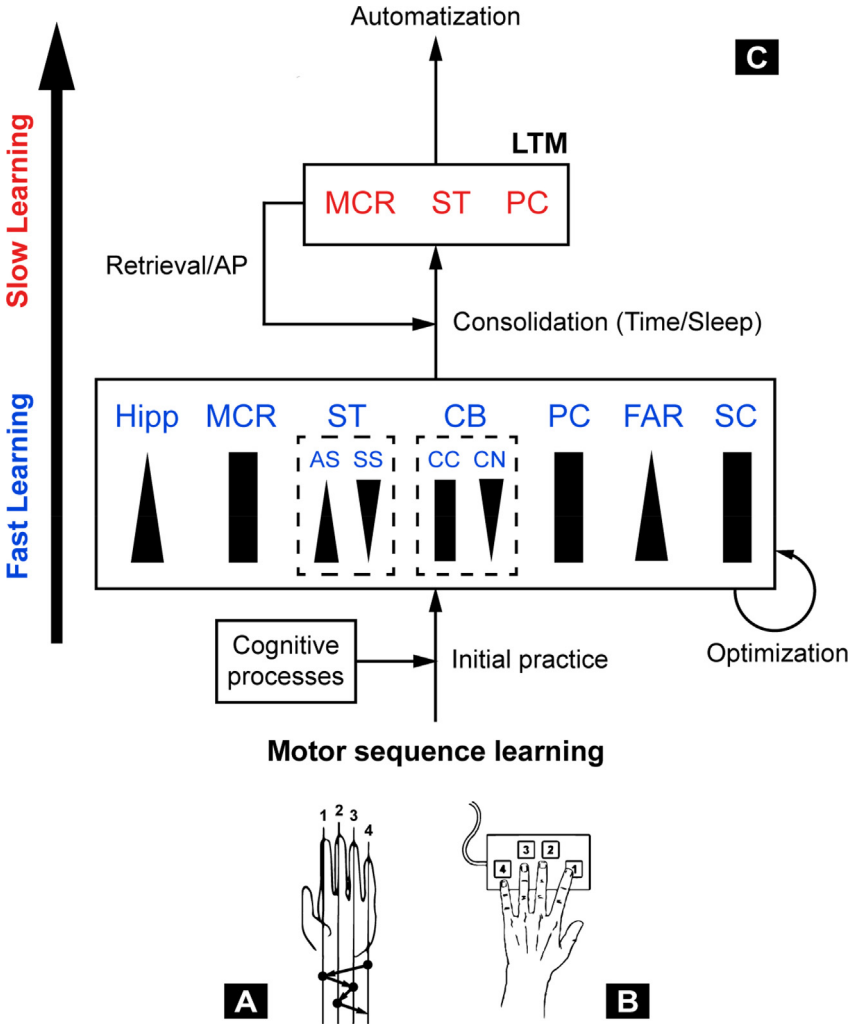
Introduction

Motor sequence learning (MSL) refers to the process by which simple, stereotyped movement elements come to be performed effortlessly as a unitary sequence through repeated practice. In recent years, our understanding of the behavioral determinants, the neurophysiological substrates, as well as the means useful to modulate the acquisition, consolidation and retention of this form of procedural memory has enhanced remarkably. Such new insights into procedural memory knowledge have been possible due mainly to methodological advances in assessing neural activity at different stages of the acquisition process, progress in neuroimaging data analyses, as well as innovative ways to use non-invasive brain stimulation techniques. In the present paper, we first briefly review the theoretical and methodological progress that has been made in the last 5 years, hence allowing us to gain a more detailed comprehension of the behavioral and neural underpinnings of MSL in humans. Next, focusing primarily on results from imaging studies, we discuss recent evidence related to the neural correlates of the acquisition, consolidation and long-term retention of motor sequence knowledge at the cortical, subcortical and spinal cord levels. The review concludes with a discussion of the clinical research that used MSL in neurological populations and tested potential patient-oriented applications.

Methodological advances in motor sequence learning research

Both implicit and explicit variations of the sequential finger motor task (see Figure 1a,b) are used as the main experimental paradigms to measure MSL, as they constitute valid substitutes to study the diverse mechanisms required for acquiring real-life motor skills (e.g. piano playing, typing, etc.), and because they are easy to implement in experimental studies, especially in restrictive conditions like neuroimaging environments. Using such paradigms, a plethora of investigations have assessed MSL through improvements in speed and accuracy performance in a wide variety of motor sequence tasks (e.g. explicit sequential finger tapping task [FTT], finger-to-thumb opposition sequence task [FOS], serial reaction time task [SRT] and discrete sequence production task [DSP]). Accumulating evidence indicates that the improvement in performance observed with practice is not only due to more efficient selection and execution of single movements, but to the binding of independent motor acts into unified sets of actions, that is, motor chunks [1–4]. This progressive development with practice from an abstract to a more effective, chunk-based representation of the sequence has inspired several neurocognitive models of MSL [5,6••,7]. Conceptualized for a wide range of sequential motor tasks, these models aimed at characterizing the cognitive (e.g. mnemonic processing strategies, nature of the sequence representation, etc.) and neural substrates mediating serial motor behaviors over the course of learning. However, one of the biggest challenges for MSL researchers is the fact that motor-sequence task demands often involve the use of different learning strategies and/or the recruitment of several non-motoric and overlapping processes (i.e. visual, spatial, attentional, cognitive control), which renders

Figure 1



(a and b) Illustrations depicting the two experimental tasks most often used to assess motor sequence learning (MSL) in human subjects. **(a)** In the finger-to-thumb opposition sequence paradigm, subjects are usually asked to execute as many times as possible an explicitly known 5-element sequence in periods of 30 s. **(b)** In the sequential finger tapping task, subjects are required to learn a new sequence of finger movements either implicitly (i.e. by responding to stimuli displayed on a computer screen that follow a sequence unbeknown to the subject) or explicitly (i.e. by repeating a motor sequence that the subject knows before practice begins). Note that in the case of implicit learning, explicit sequence knowledge can also develop during practice for some subjects, hence leading to partial-to-full explicit (structural) knowledge about the regularity of the sequential events, and possibly to a change in response strategy while subjects are training. **(c)** Neurobiological model of brain plasticity associated with motor sequence learning [Adapted from 42–44]. Here we introduce an integrative view of MSL at the cortical, subcortical and spinal cord levels during the fast (blue) and slow (red) learning phases. We propose that, depending on the nature of the cognitive processes (e.g. learning by trial and error, implicit/explicit learning, etc.) required during initial practice, the brain structures involved during MSL in the encoding fast-learning phase include the striatum, the cerebellum, the hippocampus, the spinal cord, motor cortical regions (e.g. premotor cortex, SMA, pre-SMA, anterior cingulate), as well as prefrontal and parietal cortical areas. Rectangle- (■) as well as up/down (▲/▼) triangle-shaped symbols reflect, respectively, the constant and decreased/increased engagement of a particular structure over the course of MSL. During this stage, dynamic interactions between these structures are likely to be critical for establishing the motor routines necessary to learn sequential motor behaviors and to develop an optimized representation of the sequence (e.g. chunking, neural network specialization). As learning progresses and time-dependent/sleep-dependent consolidation processes take place during the slow learning phase, however, representational memory changes are thought to occur. Hence, when a motor task is well-learned and asymptotic performance is achieved, the long-term representation of the motor sequence is believed to be distributed within a network of structures that mainly involves the cortico-striatal circuit (i.e. striatum, motor cortical regions and parietal cortices). Moreover, while retrieving or further practicing a well-learned and consolidated motor sequence, the model posits that the same cortico-striatal network is reactivated and that retrieval-induced plasticity involves the integration of new information through consolidation-like processes. After extensive (multi-session) practice and associated skill consolidation, skilled motor behaviors tend to be performed effortlessly and with little attentional resources for successful completion (i.e. automatization phase). See text for further details. *Hipp*: Hippocampus; *MCR*: Motor cortical regions; *ST*: Striatum; *CB*: Cerebellum; *PC*: Parietal cortices; *FAR*: Frontal associative regions; *SC*: Spinal cord; *AS*: Associative striatum; *SS*: Sensorimotor striatum; *CC*: Cerebellar cortices; *CN*: Cerebellar nuclei; *LTM*: Long-term memory; *AP*: Additional practice.

MSL-specific behavioral outcomes and brain activity changes difficult to interpret. Therefore, in the MSL literature, many behavioral and most neuroimaging studies have been focused on using simple experimental paradigms with short sequences (usually less than 8 elements) that are explicitly known prior to training in order to favor an (internal) plan-based and stimulus-independent mode of control, thus minimizing the involvement of such non-motoric confounds.

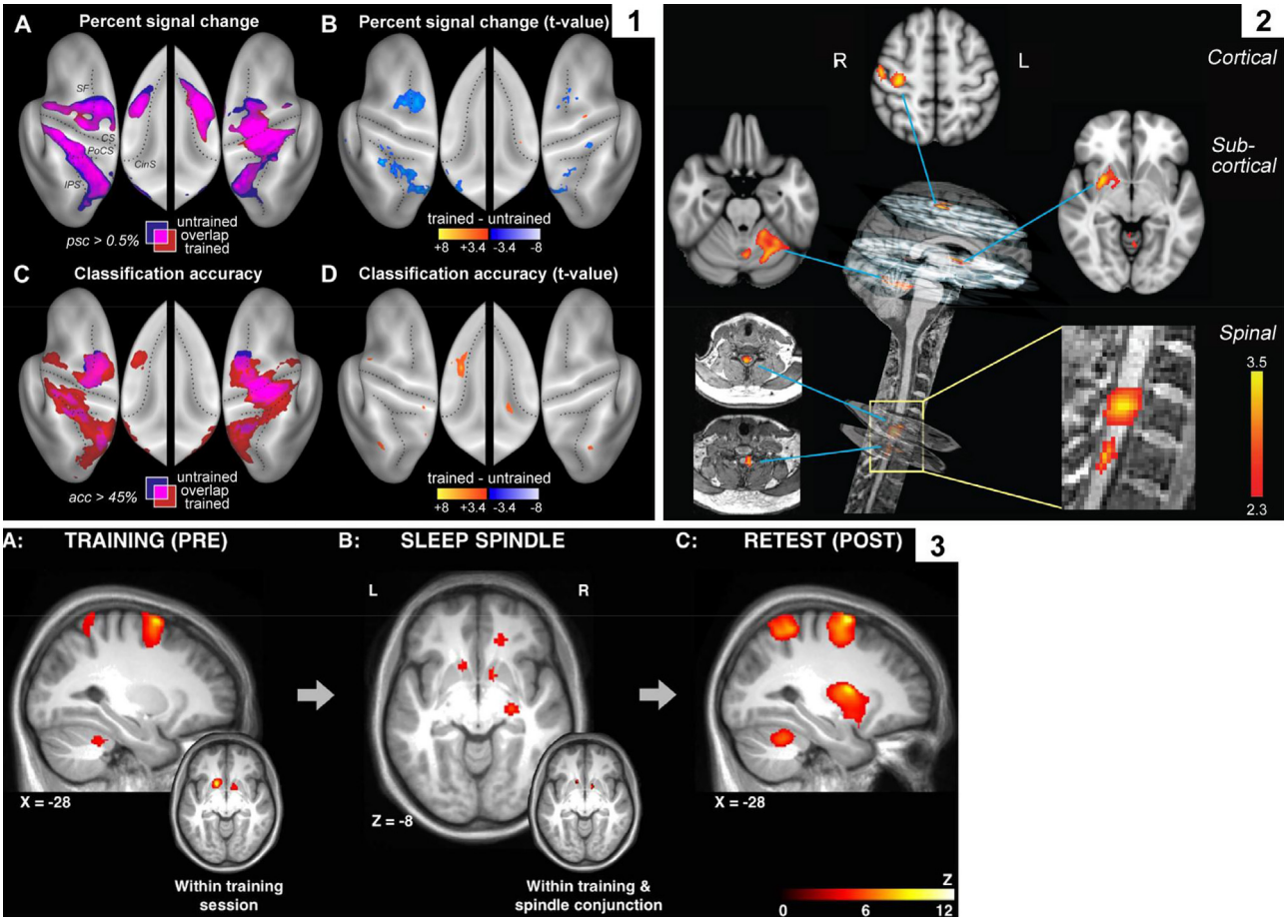
Ongoing innovations in functional and structural neuroimaging data analyses have provided a variety of tools to investigate experience-driven changes in neural representations during MSL. First, much renewed interest has been directed toward analyzing the pattern and magnitude of short-term brain activity modulations upon task repetition, rather than accessing changes in the averaged evoked signal. For example, it has been shown that, as a result of practice and memory consolidation processes, the initial pattern of decreased neural activity upon repeated performance of a new sequence (i.e. repetition suppression) may switch to a repetition-driven increase in neural signals (i.e. repetition enhancement) within the motor cortex [8,9]. These repetition-driven changes in the pattern of neural activity are sensitive to long-term, non-linear reorganization of neural representations within the motor network, hence indicating an increased functional specialization triggered by training [10]. Second, following widespread acceptance that multivariate pattern analysis (MVPA) may be a more direct measure of brain representations (see [11,12] for computational modeling of brain representations), this technique has also been successfully applied to discriminate between neural activity patterns associated with the preparation and execution of various motor sequences [13••,14,15]. These studies have shown that trained and untrained motor sequences can be discriminated (with a higher level of classification accuracy for highly practiced sequences) using activation patterns within the premotor, sensorimotor and parietal regions. These results thus further support the idea that training leads to stabilization of neural representations in a sequence-specific manner ([13••]; see Figure 2, Panel 1). However, to the best of our knowledge, evidence regarding the possibility of classifying sequence-specific neural patterns based upon activity recorded from subcortical structures using MVPA approaches is still lacking, due mainly to acquisition-related limitations (e.g. quality of signal within those structures). Thus, additional work with MRI pulse sequences allowing for higher spatial resolution and greater magnetic field strength (e.g. 7 T instead of 3 T) is needed for better application of MVPA techniques to the whole brain.

Changes in resting state connectivity before and after MSL have also been more extensively investigated as a mean to explore the neural substrates and mnemonic processes related to MSL. For instance, combining magnetic resonance spectroscopy (MRS) and resting-state fMRI (rsfMRI), recent studies have demonstrated a learning-related inverse relationship between the strength of functional connectivity within the motor network and the levels of inhibitory GABAergic activity within M1 [16,17], thus suggesting that local GABA concentration levels in M1 may play a key role in the strengthening of motor skill representations. Moreover, given that resting state allows to test for 'motor learning' without the limiting and confounding effect of having the subject physically performing the motor sequence during retest, this approach has also been successfully used to identify intrinsic functional changes in resting-state network activity related to the memory trace generated during practice [18–20]. Results from these studies have shown that the motor-network functional connectivity is increased immediately after training, and that this change in intrinsic experience-dependent activity contribute to the offline gains in behavioral motor performance. Other resting-state fMRI studies have further demonstrated that the neural circuits involved in the off-line processing of a new motor skill can be determined by the form of learning (implicit vs explicit) [18] and age [20]. Finally, resting-state fMRI and EEG recordings have successfully been applied to probe the neurophysiological correlates and reactivation mechanisms of motor skill consolidation during sleep, providing new insights into the unique contribution of this physiological state to the strengthening and reorganizations of memory traces ([21], see Figure 2, Panel 3; [22]).

Current development of diffusion-weighted imaging (DWI) and voxel-based morphometry (VBM) have also provided unique opportunity to study structural correlates of MSL. In particular, it has been shown that inter-individual differences in motor performance are associated with dissimilarities in anatomical connectivity with task performance being positively correlated with structural coherence in white matter fiber tract organization [23–26] and gray matter volumes [24,27]. Moreover, using these techniques, it has been proposed that structural brain changes with age may explain the deficit that older subjects exhibit in consolidating a newly acquired motor sequence [26,27]. Finally, an interesting work by Assaf and colleagues has revealed that visuo-motor learning produces rapid (within 1–2 h of practice) decreases in mean diffusivity, which is thought to be associated with activity dependent upon astrocyte swelling [28,29]. The latter studies, together with recent evidence that changes in skilled movements in healthy young adults are associated with an increase in myelin, as measured by MRI-derived myelin water fraction [30], suggest that MSL could also generate such structural changes. However, such hypothesis awaits further investigation.

Finally, the development of non-invasive brain stimulation techniques has shown great promise for modulating

Figure 2



Panel 1. Difference in neural representations between trained and untrained motor sequences. Maps show group-averaged signal changes compared to rest, and classification accuracy for trained and untrained motor sequences (panels A and C, respectively). Panels B and D, respectively, illustrate the statistical contrast of trained against untrained sequences for group-averaged signal change and classification accuracy maps [Figure reproduced, with permissions, from [13••]]. *Panel 2*. Neural correlates of motor sequence learning at the cortical, subcortical and spinal cord levels. Cortical, subcortical and spinal clusters that showed learning-related modulation of activity in association with behavioral improvements were found in the contralateral (to the practiced hand) sensorimotor cortex, the contralateral putamen, the ipsilateral lobule V–VI of the cerebellum and in the C7–C8 spinal-cord segments [Figure reproduced, with permissions, from [51•]]. *Panel 3*. Cortical and subcortical activation specific to motor sequence learning, as compared to a control motor task (i.e. finger movement task but without any sequence to learn), during the pre-sleep training session (panel A), time-locked to spindle activity during NREM sleep (panel B), and during the post-sleep retest session (panel C) [Figure reproduced, with permissions, from [21]].

different neural processes during MSL (for a review see [31]). These techniques are particularly interesting as they provide an innovative approach to examine causal relationship between neural processing in various brain areas and human motor behavior [32]. For example, transcranial magnetic stimulation (TMS) has been used to interfere with existing motor memories and ongoing mnemonic processes [33,34••]. Likewise, transcranial direct current stimulation (tDCS) over frontal motor areas has shown to be an effective technique to modulate MSL [35–37]. Importantly, repetitive TMS over cerebellar cortex [38] and M1 [39] has been utilized to augment MSL, providing support for a potential application of TMS to accelerate motor recovery following movement diseases [31].

Altogether, the development of new experimental paradigms and imaging-computational techniques for data acquisition and analysis has provided new insights into the cognitive processes and neural substrates underlying MSL. While traditional neuroimaging techniques (e.g. EEG, MEG, fMRI) are useful for the investigation of the brain functional networks underlying cognitive and memory processing, new non-invasive brain stimulation techniques (e.g. tDCS, TMS) allow direct assessment of the causal link between cortical brain activity and memory

function by inducing transient and/or long-lasting effects (e.g. [31,32]). Hence, the combination of the new aforementioned experimental approaches and multi-modal imaging techniques is opening a window of opportunities to investigate the neural substrates underlying the formation and long-term retention of motor skills.

Neural correlates of motor sequence learning and consolidation

Functional neuroimaging studies have demonstrated that MSL relies on the integrity and functional interaction between the cortico-striatal (CS) and cortico-cerebellar (CC) systems (in link with the hippocampus) (e.g. [40,41]). Initial experience with a new motor sequence task is usually associated with rapid within-session improvements in performance ('fast' learning phase). In line with previously proposed neurobiological models of MSL (see [42–44]), accumulative evidence suggests that this early acquisition phase encompasses a goal-based allocentric (visual-spatial) representation of the sequence (e.g. [7,43,44]), which is mainly mediated by associative cerebellar and striatal regions in conjunction with prefrontal and premotor cortical regions. As practice continues, however, asymptotic performance is gradually reached and the contribution of the sensorimotor regions of the striatum (the putamen, in particular) and motor cortical regions progressively increase [47,48], enabling a movement-based egocentric (motor) representation of the movement sequence (e.g. [45,46]). Persistence and strengthening of sequence representations depend on consolidation processes that require time to become effective, and usually result in incremental performance gains that evolve slowly over hours after the end of training ('slow' learning phase) [41]. Recent evidence suggests that during this 'slow' learning phase, changes in activity and connectivity between the striatum and cortical motor-related regions contribute to memory improvements and skillful expression of sequential behaviors [21,49••,50•]. Yet recent findings indicate that the CS and CC are not the only networks involved in MSL. Indeed, Doyon and colleagues have conducted the first fMRI study that aimed at looking at the role of the spinal cord in motor learning ([51•], see Figure 2, Panel 2). The results have shown that a significant part of learning-related modulation of activity in the C6–C8 spinal region is independent from that of related supraspinal sensorimotor structures; the latter results being consistent with the observation that implicit sequence learning is impaired following thoracic spinal cord injury [52]. Moreover, brain–spinal cord functional connectivity analyses demonstrated that the initial linear relationship between the spinal cord and sensorimotor cortex gradually fades away over the course of motor sequence learning, while the connectivity between spinal activity and cerebellum gains strength. These data suggest that the spinal cord, not only constitutes an active functional component of the human motor learning network, but that it also contributes distinctively from the brain to the learning process. Thus, based upon brain imaging findings in the MSL literature reported above, we propose an updated version of the neurobiological model of Doyon and colleagues (2009) 44 by proposing an integrative view of MSL at the cortical, subcortical and spinal cord levels during the different stages of sequence learning (see Figure 1c).

Yet practice of a new motor sequence in itself is not enough for the skill to be retained. Contemporary memory theories advocate that, after the encoding phase, new memories undergo off-line transformations over time, which allow the initially labile traces to become fixed into the physical structure of the brain; a process called 'memory consolidation' [53,54••,55]. The MSL consolidation process is thought to be dependent upon interactions between the striatum and hippocampus [45,49••]. In several cases (but not for all types of learned motor skills), overwhelming evidence also demonstrates that the consolidation of the motor memory trace is facilitated by sleep, as additional performance gains can be observed following this off-line mnemonic process ([49••,55], but see [56••,57] for an alternative view). More specifically, studies have shown that consolidation of a newly acquired and explicitly known motor sequence is mainly related to changes in non-rapid-eye-movement (NREM) stage-2 sleep (and sleep spindles in particular) as well as to recurrent reactivations of task-relevant memory networks [58–60]. Sleep spindles are transient oscillatory (~11 to 16 Hz) patterns that are thought to play a pivotal role in the strengthening and transformation of the neural representation created during initial learning through reactivation of the memory trace during subsequent sleep. In the declarative memory domain, the reactivation/reorganization of task-related neuronal activity has been associated with hippocampal, high-frequency local field potential oscillations (~100 to 300 Hz), also called 'sharp wave-ripples' (SW-Rs) that occur in conjunction with thalamo-cortical 'spindle' oscillations involved in cortical synaptic plasticity [58,59]. According to this influential model and recent work by Latchoumane *et al.* [61], the synchrony between hippocampal SW-R memory reactivation and spindle activity, phase-locked to up-state slow wave oscillations (SO), is thought to allow the formation of SO-spindle-ripple complexes that are assumed to reflect system consolidation of hippocampal memories by mediating effective hippocampal-to-neocortical exchange of information [49••,58,61]. Although still conjectural, however, animal [62] and human [21,22] work also suggest that a similar neurophysiological mechanism involving the interplay between the hippocampus and striatum might take place during the post-learning sleep episodes, hence possibly mediating the off-line memory enhancements generally observed with the consolidation of MSL in the adult brain [49••].

Interestingly, innovative methodological approaches have recently been used to gain further insights into

the role of NREM stage-2 sleep and spindles in the motor sequence consolidation process. For example, a few studies have demonstrated MSL-consolidation benefits following experimental enhancement of spindle activity using transcranial alternating current stimulation [63•], or by inducing reactivation of memory traces through olfactory/auditory stimulation using targeted memory reactivation (TMR) paradigms [60,64,65]. Yet, despite the fact that such experimental manipulations constitute promising ways to probe consolidation mechanisms, much more work is needed to identify whether the resulting gains in performance are causally related to the memory reactivation process, and to understand better the nature of the reactivated memory trace.

Following its initial consolidation, a motor memory can be retained for days to years even in the absence of additional physical practice. However, the notion that a consolidated procedural memory is immutable has been challenged in recent years. It has been suggested that reactivation of an existing (consolidated) memory through a short actual experience with the task opens a window during which the reactivated memory is again susceptible to influences. Indeed, evidence indicates that modification of a previously consolidated memory using either repetitive transcranial magnetic stimulation [34••], behavioral [66,67] or pharmacological interventions (see [68] for a review), may result in its degradation, maintenance, or strengthening through consolidation-like processes [54••,69]. In humans, this retrieval-induced plasticity of long-term memory through consolidation-like mechanisms is viewed as a crucial opportunity for updating our daily life learning habits, and to further modify the behavioral expression of context-dependent or maladaptive memories [68]. Thus, beyond the theoretical challenges, research on motor memory modification may be of major practical importance when considering its translational clinical exploitation, with the development of non-invasive clinical treatment or re-learning/rehabilitation protocols [31].

Clinical implications and interventions

In the past five years, MSL studies conducted in clinical populations aimed to: firstly, evaluate the functional impairment associated with damage to the motor system, primarily to the cortico-striatal and cortico-cerebellar circuitry, and secondly, assess the impact of clinical interventions on motor learning capacity. The clinical populations targeted by these studies have included neurological (primarily Parkinson's disease, but also amyotrophic lateral sclerosis, Huntington's disease, language impairments), neurodevelopmental (autism spectrum, developmental dyslexia) and psychiatric patients (mainly schizophrenia), as well as individuals who experienced traumatic events affecting motor-related brain regions (e.g. strokes, spinal cord injuries). Here, we chose to focus on studies conducted on individuals with Parkinson's disease (PD) and schizophrenia, given that the MSL clinical research was mainly related to these two populations (but the reader can refer to reviews by [70,71] for discussions related to normal aging effects on MSL and consolidation).

In PD, one narrative review [72•] and two systematic meta-analyses [73,74] have recently been published on the topic of implicit MSL using versions of the serial reaction time task (SRT). Even though each of these reviews employed different inclusion/exclusion criteria, the results strongly suggest that: firstly, PD patients are moderately impaired in their capacity to acquire implicitly a motor sequence, secondly, dopaminergic medication affects more the motor than the cognitive processes involved in this form of skill acquisition, and thirdly, there is a moderate to high heterogeneity between the effect sizes observed across studies. By contrast, additional research using explicit MSL paradigms in PD have revealed that, despite being slower, PD patients show normal MSL abilities as well as a capacity similar to that of older healthy-control subjects with respect to the consolidation process of a newly acquired motor sequence (e.g. [75,76]; see [70] for a review). Yet, results reveal that they are impaired in the slow learning phase of a motor sequence, that is, during automatization of that skill [76,77].

There is also ample evidence that the clinical profile of schizophrenic individuals includes soft neurological signs like deficits in sensory integration, motor coordination, and sequencing of complex motor acts [78,79]. Indeed, recent studies suggest that explicit MSL deficits are also part of the phenotype, and that they can be exacerbated by antipsychotic medication [80–82,83•]. Furthermore, studies have found marked impairments of sleep-dependent consolidation of motor sequence memory, which akin to healthy older subjects, appear to be related to the dramatic reduction of sleep spindle activity observed in these patients [80,81] as well as to the coordination between spindle and slow wave activity [83•]. Yet sleep medication (Lunesta), which is known to increase sleep spindle density, did not improve MSL consolidation capacity at the group level [81], thus suggesting that impaired sleep-dependent memory consolidation in schizophrenia may not be solely related to reduced spindle density. Although conjectural, such absence of a relationship between spindle activity and memory consolidation may be due to the fact that the latter authors did not look at the integrity of the SO-spindle-ripple oscillatory synchrony as well as the functional connectivity between subcortical and sensorimotor-related cortical regions during spindle oscillations, hence providing new promising directions for the treatment of the consolidation deficits observed in schizophrenia.

Conclusion

In this review we reported findings from behavioral and neuroimaging studies that significantly increased our

knowledge of human motor sequence memory over the last five years, both in terms of theoretical and methodological advances. Furthermore, and based on the plethora of behavioral and brain imaging studies in the MSL literature, we proposed an integrative view of human MSL at the cortical, subcortical and spinal cord levels during the different stages of sequence learning. This neurobiological model of MSL provides a comprehensive overview of the neural networks involved in the acquisition and long-term retention of a motor sequence memory, as well as their dynamics over the course of learning. In addition to the theoretical challenges, we further reviewed the advances made in non-invasive brain stimulation techniques and advocated for their clinical exploitation with the development of patient-oriented interventions in order to facilitate neuroplasticity and (re-) learning in individuals suffering from neurological diseases or memory disorders, for instance.

Several outstanding questions remain to be addressed though. There is still a need to better understand the cognitive and neural correlates of memory consolidation and reconsolidation in humans. This knowledge gap can be addressed through the development of new experimental paradigms and the use of multimodal neuroimaging techniques to assess better the causal link between brain activity and consolidation/reconsolidation-related memory processing during wake and sleep periods. More work is also necessary to provide a better understanding of the inter-individual variability in MSL and its underpinnings (e.g. genetic polymorphism, ontogenetic development) across all learning stages. Finally, future behavioral and neuroimaging studies aiming at extending our current knowledge from cross-sectional to longitudinal studies, as well as to more complex serial behaviors and clinical populations are also needed in order to gain a broader theoretical perspective and offer more relevant, optimized patient-oriented interventions.

Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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