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Does the hippocampus exhibit offline reactivation of neural activity following motor sequence learning?

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ABBREVIATIONS

BOLD	Blood-oxygen-level dependent
fMRI	Functional Magnetic Resonance Imaging
MEG	Magnetoencephalography
TMS	Transcranial magnetic stimulation

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ABSTRACT
Memory consolidation in the declarative memory domain is known to be supported by the replay or reactivation of learning-related hippocampal activity during subsequent offline epochs (i.e., during post-encoding rest). Examinations into an analogous hippocampal reactivation process following *motor* learning have, until recently, been non-existent. This gap in the literature has been fueled by the traditional – yet outdated - view that the hippocampus is not involved in motor learning. Here, we discuss recent research in the motor memory domain that provides evidence in support of hippocampal reactivation following motor sequence learning. We conclude by highlighting several areas that warrant examination in future research, including experimentally manipulating post-learning hippocampal reactivation in an effort to enhance the motor memory consolidation process.

KEYWORDS: Hippocampus | Motor learning | Memory consolidation | Reactivation | fMRI

Memory consolidation, the process by which newly encoded memories are transformed into a more robust form, is thought to be supported by the reactivation of learning-related brain regions. Indeed, seminal animal research has shown that the patterns of activity observed in hippocampal place cells during spatial learning tasks are spontaneously reactivated during the subsequent sleep episode [1,2]. Consequent research extended these groundbreaking findings and revealed that these reactivations: a) are temporally compressed; b) preserve or reverse the temporal order of firing patterns observed during the behavioral tasks; and, c) are also evident during post-task wake epochs [e.g., [3]]. These results collectively provided the foundation for the most influential memory consolidation models that posit that offline (i.e., in the absence of active task practice) brain reactivations orchestrate information transfer from the hippocampus to cortical areas for long-term memory storage [4].

The study of hippocampal replay has recently been translated to human research with the development of more sophisticated analyses of blood-oxygen-level dependent (BOLD) signals acquired with functional Magnetic Resonance Imaging (fMRI) (reviewed in [4]). Notably, Tambini and Davachi [5] used multivoxel pattern analyses of BOLD signals and demonstrated that hippocampal activity patterns during declarative learning significantly persisted into subsequent wake intervals. This persistence was thought to reflect the reactivation of encoding-related brain patterns. Importantly, the magnitude of this persistence was positively correlated with memory scores at a delayed retest, providing a link between memory retention and reactivation processes [5].

The examination of hippocampal reactivations has mainly been limited to the declarative memory domain. This is surprising given that the role of the hippocampus in motor (sequence) memory processes is now well established [6]. This leads to the following intriguing question: *Is the reactivation of learning-related hippocampal activity a mechanism that also supports memory consolidation in the motor domain?* Research released over the last two years has indeed offered evidence supporting the reinstatement of motor-task-related hippocampal activity during subsequent offline episodes [7,8]. Specifically, Buch and colleagues [7] leveraged the high temporal resolution of magnetoencephalography (MEG) and demonstrated temporally condensed reactivation of task-related hippocampal activity during the rest blocks following motor sequence task practice. Paralleling the findings from Tambini and Davachi [5] in the declarative memory domain, results from our group demonstrated that the hippocampal multivoxel patterns observed during motor sequence learning persisted into subsequent rest [8]. This research also afforded novel insights into the functional significance of hippocampal reactivation following motor learning, as it indicated that hippocampal persistence specifically reflects the allocentric (spatial) – as opposed to an egocentric (motoric) - representation of the recently acquired movement sequence.

It is our opinion that the studies highlighted above provide compelling evidence that patterns of hippocampal activity observed during motor sequence learning are spontaneously reactivated during subsequent awake rest. Although such a finding fills a critical knowledge gap in the literature, several unknowns that warrant further investigation remain. First, and in contrast to previous research in the declarative domain [4], it is unknown whether the magnitude of reactivation following motor learning is linked to subsequent long-term retention. Second, it is unclear whether post-learning hippocampal reactivation can be modulated with experimental interventions to enhance the consolidation process. Previous research from our group has shown that prefrontal transcranial magnetic stimulation (TMS) applied before motor sequence learning can alter hippocampal pattern persistence in subsequent rest epochs [9]. Investigating whether brain stimulation or other experimental interventions such as targeted memory reactivation (TMR) can enhance the consolidation process via the modulation of reactivation processes has tremendous translational potential. For example, such protocols could be used to enhance the recovery of impaired motor functions as part of rehabilitative interventions following neurological injury or disease. Third, although recent research has provided evidence for hippocampal reactivation in the wake state following motor sequence learning, evidence in support of similar reactivation during post-learning sleep is currently limited. There is evidence demonstrating hippocampal (and putaminal) activity time-locked to plasticity-related sleep features (i.e., spindles) following motor learning [10]. However, future research using multivariate analytic approaches is warranted to characterize such brain activations during sleep and to determine whether they carry motor sequence task patterns. Furthermore, it will be important to assess commonalities across - and differences between - post-motor learning hippocampal reactivation in wake and sleep states.

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