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Neural population dynamics underlying motor learning transfer

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Summary

Covert motor learning can sometimes transfer to overt behavior. We investigated the neural mechanism underlying transfer by constructing a two-context paradigm. Subjects performed cursor movements either overtly using arm movements, or covertly via a brain-machine interface that moves the cursor based on motor cortical activity (in lieu of arm movement). These tasks helped evaluate if and how cortical changes resulting from "covert rehearsal" affect overt performance. We found that covert learning indeed transfers to overt performance, and is accompanied by population-level changes in motor preparatory activity. Current models of motor cortical function ascribe motor preparation to achieving initial conditions favorable for subsequent movement-period neural dynamics. We found that covert and overt contexts share these initial conditions, and covert rehearsal manipulates them in a manner that persists across context changes thus facilitating overt motor learning. This transfer learning mechanism might provide new insights into other covert processes like mental rehearsal.

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Author Contributions

S.V., N.E.C., and S.D.S. designed the study. S.V. performed the experiments, analyses, and wrote the manuscript with input and editing by all authors. S.I.R. performed the surgical implantations. P.N. provided significant guidance on data presentation. K.V.S. supervised all aspects of this work.

Declaration of Interests

K.V.S. is a consultant to Neuralink Corp. and on the Scientific Advisory Boards of CTRL-Labs Inc., and Heal Inc. These entities did not support this work.

eTOC

Vyas et al. ask if learning “covertly,” without physical movements, can transfer to overt behavior. By using visuomotor perturbations, they show that covert and overt movements derive from a common neural substrate consisting of motor cortical preparatory activity that facilitates transfer of learning.

Introduction

Understanding motor-related covert mental processes, such as imagined or intended movements, and mental rehearsal, is tantalizing as these internal behaviors have been shown to exhibit varying degrees of motor learning transfer (Denis, 1985; Papaxanthis *et al.*, 2002). Decades of human behavioral studies have shown that mental rehearsal can improve motor skills such as throwing darts or making free throws (Feltz and Landers, 1983), and mental rehearsal has also been shown to sometimes aid in rehabilitation (Warner and McNeill, 1988; Buch *et al.*, 2008; Saposnik *et al.*, 2010; Silvoni *et al.*, 2011). Working theories posit that motor learning transfer is a result of covert learning engaging neural population activity similar to that employed during overt practice. In support of this, “mirror neurons” in ventral premotor cortex have been shown to discharge both when actions are overtly performed and when they are observed (Rizzolatti, Fogassi and Gallese, 2001). These results, however, are still debated (Hickok, 2009), and do not propose mechanistic hypotheses about why neural similarity is helpful for learning transfer.

This debate stems primarily from the fact that mental rehearsal, and covert processes in general, are difficult to define, and even more challenging to experimentally study. They are open-loop hidden processes, where experimenters cannot directly observe the internal process or the trial-by-trial progression of learning. In this study, we present a covert process that enables a direct and real-time probe into this evolution, by “closing the loop.” We use a brain-machine interface (BMI) which takes as input neural activity from dorsal premotor and primary motor cortex. This neural activity is mapped through a fixed mathematical function, i.e., “decoder,” to produce a two-dimensional cursor movement. This defines a closed-loop system by which subjects receive visual-feedback of the on-screen cursor, and the experimenters observe both the behavior and the evolving neural activity on a trial-by-trail basis. The BMI context elicits internal motor processes that share an end-goal with overt processes because subjects use the decoder (i.e., neural activity without overt movements) to make the same cursor movements as they will perform subsequently using arm movements. We constructed the decoder by associating the kinematics of automated cursor movements with neural activity recorded while subjects observed these movements (Gilja *et al.*, 2012). This was done in contrast to using neural activity measured during overt movements. Previous findings have shown that neural signals involved in watching cursor movements are engaged in mental rehearsal and involve many of the same cells as when generating movement (Cisek and Kalaska, 2004).

The BMI paradigm is a powerful tool for studying learning because the decoder establishes a causal link between behavior (i.e., cursor movements), and all the neurons directly responsible for producing that behavior. Thus, the only way to modify the behavior is to causally modify the input neurons to the decoder. Several groups have used BMIs to dissect a variety of sensorimotor and learning processes; recent germane studies include (Jarosiewicz *et al.*, 2008; Ganguly and Carmena, 2009; Ganguly *et al.*, 2011; Orsborn *et al.*, 2014; Sadtler *et al.*, 2014; Golub, Yu and Chase, 2015; Athlaye *et al.*, 2017; Prsa, Galiñanes and Huber, 2017). Here, we use BMIs to establish a "covert rehearsal" paradigm whereby subjects can "practice" or in a sense "rehearse" a motor task using directly their neural activity without movement (i.e., covertly). We can then evaluate the degree of learning transfer by having the subjects repeat the same task using overt movements.

In this non-human primate study, we cannot definitively equate covert rehearsal to imagined movements or mental rehearsal (though this may well be what the monkeys are doing). Critically, covert rehearsal differs from mental rehearsal in that it provides the monkeys with real-time visual feedback of the onscreen cursor. This design, however, is intentional as it provides a first-ever direct probe into studying the single-trial neural (and behavioral) correlates of covert learning. Thus, the goal of this study is to use the covert rehearsal paradigm to evaluate two key scientific questions underlying most covert processes: (i) Can covert processes (which covert rehearsal is a type of) facilitate overt motor learning? (ii) If so, what neural mechanism mediates this transfer? If covert processes can facilitate overt learning, we expect to observe that neural changes resulting from learning in one context would result in behavioral changes in the other. This would suggest that covert learning does transfer, and the corresponding neural activity would provide a glimpse at its mechanism. We note, however, that in this study learning is measured through the lens of motor adaptation; monkeys learn to adapt to a visuomotor rotation. Adaptation is used here, as is commonly done in the literature as one simple subset of motor learning (Jarosiewicz *et al.*, 2008; Huang *et al.*, 2011; Chase, Kass and Schwartz, 2012; Ranganathan *et al.*, 2014; Mathis, Mathis and Uchida, 2017). Thus, a conservative interpretation of our claims concerning motor learning and its transfer, including any relation to mental rehearsal, should be restricted to the transfer of adaptation. Nonetheless, recent evidence, e.g. (Churchland *et al.*, 2012), suggests that the dynamical systems based mechanism that we describe in this study could generally be at work for other more complex motor behaviors. The present experiments thus set the stage for future studies of motor learning transfer in skilled motor tasks.

In the present study, we provide key evidence that covert learning does indeed transfer to overt performance. Concomitantly, we propose a dynamical systems mechanism for motor learning transfer. In particular, our analyses will reveal that overt and covert movements derive from a common neural substrate, which consists of motor preparatory activity. Our analyses will also reveal that learning is consistent with manipulating this preparatory activity, and the common substrate enables persistence of these changes, hence facilitating learning transfer. Furthermore, we find that this substrate is also common to neural activity recorded during contexts previously shown to be engaged in mental rehearsal. While this does not prove that our covert rehearsal paradigm is the same as mental rehearsal, the neural and behavioral results suggest that our proposed neural mechanism could generally be at work in other covert processes. We will also argue that our covert rehearsal paradigm can serve as a valuable tool for motor learning (and potentially rehabilitation) in and of itself. Lastly, our results add to a growing body of evidence that suggest a dynamical systems interpretation of motor cortex (Gallego *et al.*, 2017), where in particular, we now argue for a more fundamental role of motor preparation in learning.

Results

Two monkeys were trained to move a computer cursor from the center of a virtual reality workspace to one of eight radially arranged targets. Monkeys performed this task either overtly using arm movements or covertly using a BMI (Fig. 1A; Fig. S1). The task appeared visually similar in both contexts as the virtual reality setup occluded the monkey’s view of his reaching arm. To directly test whether covert rehearsal can affect overt performance, we used the degree of transfer of motor adaptation to visuomotor rotations (VMR) as an assay to study the relationship between covert and overt movements (Krakauer *et al.*, 2000; Tanaka, Sejnowski and Krakauer, 2009; Krakauer and Mazzoni, 2011).

We first measured VMR adaptation behavior in the overt context (i.e., “overt-to-overt transfer”) and then separately in the covert context (i.e., “covert-to-covert transfer”) to confirm that our experiments replicated expected VMR adaptation. We focus on VMR after-effects because this will subsequently be a key measure of across-context learning transfer. When VMRs were applied in the overt context, monkeys learned to move their arm at an angle (45°, 60°, or 90° relative to the non-rotated condition) in order for the cursor to directly reach the target (Fig. 1B, task-flow). After adaptation, we removed the VMR and measured cursor movement errors (i.e., after-effects). We observed the well-known post-VMR adaptation after-effect: monkeys initially reached in the opposite direction of the VMR, took longer to reach the target, and had large angular errors with respect to the straight-line direction to the target (Fig. S2A–D). For VMRs introduced during the covert context, monkeys had to modulate neural activity to generate velocity commands at an angle in order to move the cursor directly towards the target. In this context, we ensured that no physical movements were made by ensuring that the correlation between any measured movement and the cursor movement (i.e., the task) was negligible, i.e., $\rho < \pm 0.1$ (Fig. S1). Results during this covert context were also consistent with VMR adaptation (Fig. S2E–H). Thus, both overt and covert VMRs exhibit well-established motor adaptation after-effects.

Motor adaptation transfers between covert and overt contexts

Next, we tested whether motor adaptation would transfer across contexts by applying a VMR in the covert context, and after adaptation, switching to the overt context without rotation (i.e., “covert-to-overt transfer”; Fig. 1B, bottom, cyan). Previous studies suggest that VMR adaptations do not typically generalize across contexts (e.g., reaching plane, direction, etc.) (Krakauer *et al.*, 2000; Taylor, Tillery and Schwartz, 2002; Tanaka, Sejnowski and Krakauer, 2009). However, we found that monkeys’ overt reaches initially erred in the opposite direction of the preceding covert context VMR (Fig. 1C). The corresponding error angles (Fig. 1D–E) were significantly larger than a control condition where arm reaches followed a no-VMR covert block (Fig. 1B, bottom, orange). This indicates that VMR adaptation during the covert context did transfer to the overt context.

While this behavioral effect was robust, its magnitude was smaller than VMR adaptation observed within the overt-only context, both in terms of the error angle, and the rate of washout (Fig. S3A–B). This suggests that while there was reliable transfer, it wasn't "complete" transfer. We found no significant relationship between the covert VMR angle and the magnitude of the subsequent transfer to the overt context as measured by initial error angle (Fig. S3C). We did find that greater adaptation during the covert context led to longer washout both for subsequent covert and overt blocks (Fig. 1F). Interestingly, this relationship was similar regardless of which context the learning occurred (covert and overt points lie along the same line). This raises the possibility that covert and overt adaptations could engage a similar neural process. Independent from degree of adaptation, we also found that decoders with higher absolute performance led to longer washouts (Fig. S3C). This suggests that decoders more similar to the "manual decoder," i.e., overt reaches, result in greater transfer of learning. Taken together, these findings suggest that covert rehearsal has strong effects on subsequent overt motor behavior (and vice versa, i.e., "overt-to-covert transfer"; Fig. S2I–L).

Learning systematically changes motor preparatory activity

Having established that transfer occurs, we investigated the neural correlates of this behavior, in hopes of discovering a potential mechanism. We were motivated to examine preparatory neural activity because of a growing body of behavioral (Johnson *et al.*, 2002; Sheahan, Franklin and Wolpert, 2016) and neural (Paz *et al.*, 2003; Stavisky *et al.*, 2017b) evidence showing a link between motor preparation and adaptation. Concretely, we asked whether adaptation transfer from the covert context was reflected in the overt context population-level motor preparatory activity.

This activity is high-dimensional, so we visualized it after dimensionality reduction (Cunningham and Yu, 2014). We found a low-dimensional state-space capturing over 80% of the co-modulation in the data (Fig. 2B). We used this state-space to visualize the delay period activity of overt trials following the switch from a VMR adaptation covert block (Fig. 1B cyan shows experimental condition, Fig. 2A shows behavior, Fig. 2C shows neural projections for one example target). A striking feature of these trials is that early after the switch, preparatory states are shifted towards the neural state corresponding to preparing to move towards the adjacent target (i.e., the 'anti-VMR' target). In other words, the monkey's motor plan is oriented in a direction that opposes the VMR from the previous block. We interpret this shift as evidence of residual adaptation reflected in the preparatory neural state. Quantifying the preparatory states without dimensionality reduction confirmed that immediately following the shift from the covert VMR block (Fig. 1 cyan condition), these states were biased in the direction of preparing reaches to the anti-VMR target (Fig. 2C). Over the course of the washout, preparatory states gradually realigned with the baseline states corresponding to reaches to the cued target (Fig. 2D–E). Consistent with these population results, we found that single neuron preferred directions (PD) rotated during learning in the direction corresponding to the VMR. During the washout epochs, PDs reoriented back to baseline (Fig. S3D).

These results demonstrate that: (i) Adaptation to the VMR systematically changes motor preparatory activity towards a pattern known to prepare movements angled away from the VMR. These changes enable the subjects to presumably adapt to the VMR, i.e., neural and behavioral changes are strongly correlated on a trial-by-trial basis (Fig. 2E). (ii) The preparatory changes persist after switching from covert to overt contexts. (iii) This neural transfer effect washes out gradually rather than exhibiting a sudden “reset” of the motor circuit, despite visual and proprioceptive feedback (Shadmehr, Smith and Krakauer, 2010) and the explicit context change of the experimenter removing the monkey’s arm restraint.

Covert and overt movements share a common neural substrate

Taken together with previous findings (Cisek and Kalaska, 2004; Sobierajewicz *et al.*, 2016), our population analyses suggest that covert rehearsal may involve “practicing” the appropriate motor system preparatory state, whereby behavioral improvements due to learning are accompanied by corresponding changes to the motor plan. This evidence dovetails with recent work arguing that motor cortical preparatory activity functions as advantageous initial conditions for subsequent peri-movement neural dynamics that generate the desired movement (Churchland, Afshar and Shenoy, 2006; Afshar *et al.*, 2011; Churchland *et al.*, 2012; Shenoy, Sahani and Churchland, 2013; Ames, Ryu and Shenoy, 2014). We therefore hypothesized that VMR adaptation transfer was due to covert and overt contexts engaging a similar dynamical system, where in particular both contexts utilized similar initial conditions.

To test this, we first projected baseline overt context preparatory activity into the baseline covert context preparatory activity neural state-space. We found that population covariance patterns explaining most of the preparatory activity was shared between the covert and overt contexts (Fig. 3A). Furthermore, the neural states corresponding to preparing either covert or overt movements to each target were well-aligned (Fig. 3B). We quantified this for full-dimensional population activity, and found that covert and overt neural states, when preparing movements to a given target, were significantly more similar to each other than to any other target (near-zero diagonal in Fig. 3C). Finally, we also found that the degree to which the covert and overt states overlapped (on a session-by-session basis) significantly predicted the magnitude of learning transfer for that session, where greater overlap led to greater transfer (Fig. 3D).

Previous findings have demonstrated that monkeys watching cursor movements elicit neural activity consistent with mental rehearsal. Since we trained our decoders using this neural activity, we compared preparatory activity during this cursor-observation period to preparatory activity recoded during covert rehearsal, and overt movements. We found that just as covert and overt movements shared preparatory states, observed movements also derive from that common subspace (Fig. 3A, ‘watch’ condition). These results suggest that at least at the preparatory level, overt behavior shares neural operation with both covert rehearsal, and putative mental rehearsal.

Together these findings suggest the following potential mechanism for VMR transfer. During covert movements in the presence of a VMR, the sensorimotor system gradually shifts the delay period initial conditions to align with the direction opposing the VMR. We suspect these changes contribute to the observed VMR adaptation. When the behavioral context switches from covert to overt, two key properties are preserved: (i) the sensorimotor system uses the same neural subspace to prepare cursor movements, and (ii) changes in which preparatory state is associated with which cued target persist across the context change. This persistence likely causes subsequent arm movements to be rotated in the direction opposing the VMR, i.e., learning transfer. As monkeys continue to make movements without any VMR, a similar adaptation process reorients the preparatory neural activity back to baseline. The corresponding arm kinematics return to normal once their preparatory initial conditions have reoriented.

This mechanism makes two testable predictions: (i) covert rehearsal should “pre-train” a motor task, and thus require fewer overt trials to learn, and (ii) covert rehearsal should achieve this in part by “pre-rotating” the preparatory states to align with the cued target. We tested these predictions by evaluating if monkeys adapted to a VMR in the overt context faster if they first covertly rehearsed the VMR (Fig. 4A, top). Compared to overtly adapting (i.e., no rehearsal), we found that covert rehearsal resulted in significantly straighter subsequent arm trajectories (Fig. 4A–B). The neural correlates of this process were also consistent with our prediction: covert rehearsal rotated the preparatory states part way to the fully adapted states, such that overt motor learning required fewer trials to approach the adaptation asymptote (Fig. 4C). We observed strong and significant trial-by-trial correlation between the post-rehearsal preparatory state and the behavioral error angle, suggesting that the magnitude of neural changes achieved by rehearsal predicts subsequent improvements in overt motor function (Fig. 4C inset).

The neural mechanism proposed here for the transfer of learning raises an important question: if the preparatory states (i.e., the initial conditions) are similar between overt and covert contexts, shouldn’t the underlying dynamical system also be similar? This would suggest a mechanism by which transfer of initial conditions results in movement behavior differences. To test this, we started by repeating the analysis from Fig. 3A for the ‘during movement’ epochs, and found that population covariance patterns explaining most of the movement period neural activity were shared between the covert and overt contexts (Fig. S4A). Next, we explicitly fit a linear dynamical system to *covert* cursor movement data, and used the initial condition from the *overt* context to predict the trial-averaged neural trajectory during subsequent reaching. We found the predicted neural trajectories to be highly similar to overt context trajectories (Fig. S4B). Finally, we found that the brief but strong oscillatory component in the neural population responses observed during overt reaches (Churchland *et al.*, 2012) were also present in the covert data, albeit predominantly the low frequency components. Together, these findings lend support for an interpretation that overt and covert movements not only are generated by a common neural substrate, but also potentially engage a similar dynamical machine.

Discussion

In this study, we investigated whether learning in a covert paradigm, where no movements are made, can transfer to overt performance. Concomitantly, we studied the neural mechanism that mediates such transfer. Our experiments revealed that learning in a BMI-guided covert context does indeed transfer to overt performance, both in terms of post-adaptation after-effects, as well as “pre-training” a motor skill in order to accelerate overt improvements. Our analyses also revealed a dynamical systems mechanism for motor learning transfer. We note that our data shows correlation, not causation, in support of this mechanism. However, we believe the significant correlation we observed on a trial-by-trail basis between the degree of preparatory state rotation and the kinematic error angle (Fig. 2E, Fig. 4C), the overlap between covert, overt, and observation-only preparatory states (Fig. 3A–C), as well as the significant correlation between the preparatory state overlap and the subsequent magnitude of transfer (Fig. 3D) point to the preparatory states likely being necessary for motor learning transfer. This causality could be evaluated in future studies by inactivating preparatory activity prior to movement onset and measuring its effect on learning transfer.

Our preparatory activity findings also touch upon a more fundamental role of motor preparation (Allen *et al.*, 2017; Chen *et al.*, 2017; Makino *et al.*, 2017). The current dynamical systems view of motor cortex ascribes motor preparation to setting the initial state from which neural activity naturally evolves (i.e., guided by lawful rules), presumably to cause movement. This interpretation argues different initial states as being used to produce different movements (Shenoy, Sahani and Churchland, 2013). Moreover, previous results found that the natural variability in the setting of the preparatory state correlates with reaction time (Afshar *et al.*, 2011). That is, a state “closer” to the desired movement results in faster movements. While the causality of these initial conditions has not yet been established, recent results show that incorrect motor preparation needs to be “corrected” before executing desired movements, albeit not by complete re-planning (Ames, Ryu and Shenoy, 2014). Taken together with our present findings, perhaps a major part of learning can be viewed as the process by which the motor system finds the optimal set of initial conditions that produces the best possible subsequent movement. The fact that we observe motor learning transfer suggests that motor cortex has the ability to perform this manipulation even in the absence of muscle activity. This view is consistent with studies arguing that motor cortex performs important work in “muscle-null” neural dimensions (Kaufman *et al.*, 2014; Stavisky *et al.*, 2017a). Furthermore, recent human results demonstrate that motor preparation, and not execution, helps separate interfering motor memories (Sheahan, Franklin and Wolpert, 2016). The neural correlates of this process could be consistent with the mechanism described in the present study, especially given recent findings that the dynamical systems features of motor cortex are conserved between humans and non-human primates (Pandarinath *et al.*, 2015).

Our study also presents evidence that a similar dynamical machine is in operation for both overt and covert movements (Fig. S4). While on one hand this could explain why preparatory activity plays a central role for learning transfer, on the other hand it raises questions about the precise role of M1 (Miri *et al.*, 2017). Why should a dynamical system for a context where no overt movements are made be largely similar to one which generates strong activity for overt movements? One explanation is that these brain regions are primarily concerned with high-level movement intentions, which are shared between the tasks (i.e., directing the cursor to the target). Certainly, the prosthetics community has benefitted from using the strong velocity-related signals present in M1 (Kao *et al.*, 2014). Future studies recording from other and/or deeper areas could reveal more pronounced differences between overt and covert movements and help contextualize the present results. Another possibility is that our undoubtedly simplified model of motor cortex as a low dimensional linear dynamical system does not capture differences between the contexts that explain a relatively low fraction of the variance but have important effects upon the true, nonlinear dynamical system.

Another contribution of this study is the use of BMIs to describe a “covert rehearsal” paradigm. While we cannot directly assert that covert rehearsal is the same as mental rehearsal, or any other covert process for that matter, we believe this paradigm is a reasonable strategy for studying motor-related internal processes. First, the fact that covert rehearsal enhances overt performance suggests that, at the very least, it engages some common subset of motor skills and their associated neural machinery, without the need for overt practice.

Second, we found that the performance of the BMI decoder strongly correlated with degree of learning transfer (Fig. S3C). This resonates with reports of mental rehearsal being more effective when performed with more vivid imagery (Ryan and Simons, 1982), and more realistic rehearsal results in better transfer (Hwang, Bailey and Andersen, 2013). In particular, we found that even in rare cases of poor decoding performance, monkeys were still able to learn the rotation, albeit with a small degree of learning transfer. Our results suggest that the reduction in the magnitude of transfer is likely a result of the poor performing decoder causing the monkeys to practice a noisier version of the true neural pattern, while still allowing adaptation; increasing the trial counts to overcome this noise could potentially boost the magnitude of transfer. This is consistent with the view that the decoder was still built in a ‘biomimetic’ fashion (Shenoy and Carmena, 2014). A non-biomimetic decoder, on the other hand, would likely result in the monkeys cognitively learning the rotation, but the rehearsed pattern would fundamentally differ between contexts, thus resulting in a small degree of transfer regardless of trial count. Future studies could readily investigate this prediction. This would also reconcile the difference between our study and those that find that learning does not generalize across certain contexts, e.g., reach direction (Krakauer *et al.*, 2000). We speculate that in those studies, the learning focused on rehearsing patterns of activity that were not common to the new context. If so, even with a predominantly biomimetic decoder, no transfer should be expected if the rehearsed physical movement differs. In contrast, in our study, the same task was presented and performed in both contexts, and our analyses revealed that generalization likely occurred due to a similar dynamical machine being engaged during both contexts.

Third, we found that not only do covert and overt movements share a large degree of preparatory activity variance, but the same holds for neural activity recorded during observation of cursor movements. Previous findings defined such observation as mental rehearsal (Cisek and Kalaska, 2004). Thus, at least at the preparatory level, covert movements, overt movements, and mental rehearsal derive from a common substrate. Finally, we constructed our decoders using neural activity from the observation epochs. The fact that monkeys could use decoders to make successful cursor movements implies that during covert rehearsal they engage neural activity similar to that during decoder training (i.e., putative mental rehearsal), albeit with visual feedback. Taken together, this evidence suggests that mental rehearsal could engage a similar dynamical systems mechanism to the one described here, even if only at the motor preparation level, for facilitating motor learning transfer. Of course, learning could just be a process of refining motor preparation (via above-mentioned argument). From this view, the covert rehearsal paradigm provides a much-needed new avenue for studying covert processes. We note however that in contrast to classical mental rehearsal, the covert rehearsal paradigm is closed-loop. Thus, subjects use visual feedback to help guide producing neural activity patterns associated with overt movements. Future studies will need to evaluate the role of such feedback (Liu and Scheidt, 2008; Shabbott and Sainburg, 2010), both in terms of its relation to mental rehearsal, and in terms of how best to take advantage of covert rehearsal to guide overt improvement.

One important caveat in this study is that we used VMR adaptation as a specific instance of motor learning because it is amenable for reductionist experiments and has a rich prior literature. It is possible that VMR adaptation is learned and potentially transferred by a different mechanism than complex skilled movements, and thus the generalization of our results to other forms of motor learning remains an open question. However, previous studies have implicated motor preparatory activity as initializing peri-movement neural dynamics in more complex arm reaching behavior, e.g., (Churchland *et al.*, 2012). Thus, we speculate that complex motor skill learning, including learning from covert rehearsal, also involves changes in preparatory activity, as seen in VMR adaptation. Future studies could compare whether motor preparatory state is the substrate for learning transfer for more complex skilled movements.

BMI tasks designed to be similar to desired overt motor skills can also be valuable tools in and of themselves with a variety of translational applications. For example, in a rehabilitation application, a patient could be instructed to imagine or attempt to make movements. The patient would receive sensory feedback about how accurately they are modulating their neural activity, perhaps by their arm being moved by external means (Ajiboye *et al.*, 2017), and could iteratively refine subsequent attempts. A second application could use covert rehearsal as a tool to accelerate motor skill learning (for example, a surgical or flight simulator) by allowing safe, targeted, and frequent practice, augmenting existing simulators that provide feedback only on the movement output, rather than the neural output associated with the motor skill. In summary, we used BMIs as a window into previously inaccessible covert mental processes to discover a common neural substrate between covert and overt movements that facilitates motor learning transfer.

STAR Methods

Key Resources Table

REAGENT or RESOURCE	**SOURCE**	**IDENTIFIER**
Experimental Models: Organisms/Strains		
Rhesus macaque (*Mucacca mulatta*)	Wisconsin and Yerkes Primate Centers	N/A
Software and Algorithms		
MATLAB	Mathworks	https://www.mathworks.com/products/matlab.html
Simulink RealTime	Mathworks	https://www.mathworks.com/products/simulink-real-time.html
Other		

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Cerebus system	Blackrock Microsystems	http://blackrockmicro.com/neuroscience-research-products/neural-data-acquisition-systems/cerebus-daq-system/
Utah microelectrode arrays	Blackrock Microsystems	http://blackrockmicro.com/neuroscience-research-products/low-noise-ephys-electrodes/blackrock-utah-array/
Polaris optical tracking system	Northern Digital	https://www.ndigital.com/medical/products/polaris-family/

Contact for Reagents and Resource Sharing

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Saurabh Vyas (smvyas@stanford.edu).

Experimental Model and Subject Details

Recordings were made from motor cortical areas of two male adult monkeys (*Macaca mulatta*), R (15 kg, 12 years old) and J (16 kg, 15 years old), while they performed an instructed delay cursor task in one of two contexts (Fig. 1A). Use of two animals is standard practice in the field. Each monkey had two chronic 96-electrode arrays (1 mm electrodes, spaced 400 μm apart, Blackrock Microsystems), one implanted in the dorsal aspect of the premotor cortex (PMd) and one implanted in the primary motor cortex (M1). The arrays were implanted 5 years and 7 years prior to these experiments for monkey R and J respectively. Voltage signals were band-pass filtered from each electrode (250 Hz – 7.5 KHz). These signals were processed to detect multi-unit "threshold crossing" spikes. We detected spikes whenever the voltage crossed below a threshold of −4.5 times the root-mean-square voltage. In this study, we do not spike sort, or assign spikes to individual neurons. In our view, this is justified due to three reasons: first, multi-unit spike trains are the standard signal used in the BMI literature; second, our scientific claims rely on the motor-cortical population activity, which includes both single- and multi-unit activity; finally, decoding both multi-unit spikes as well as well-isolated single units can potentially increase the amount of information available on chronically implanted electrode arrays (Pandarinath *et al*., 2015, 2017; Oby *et al*., 2016; Stavisky *et al*., 2017a). Animal protocols were approved by the Stanford University Institutional Animal Care and Use Committee.

Method Details

Task design—Monkeys performed instructed-delay movements in one of two contexts as described in Fig. 1A. Our standard methods have been previously described (Gilja *et al*., 2012; Shenoy, Sahani and Churchland, 2013; Ames, Ryu and Shenoy, 2014). In the 'overt' context, both monkeys performed a Radial 8 Task, where they reached using their contralateral-to-arrays arm in order to move a computer cursor in virtual reality (latency of 7 ± 4 ms). Eight targets were arranged radially in a 2D circle, along with an additional target at the center of the circle. Monkeys started by holding the cursor on the central target continuously for 500 ms. After a variable instructed delay period (sampled uniformly from 400 – 800 ms), monkeys moved the cursor within a 4 × 4 cm acceptance window of the cued target. This target also had to be held continuously for 500 ms. The target changed color to signify the hold period. If the cursor left the acceptance window, the timer was reset, but the trial was not immediately failed. Monkeys had 2 s to acquire the target. Success was accompanied with a liquid reward, along with a success tone. Failure resulted in no reward, and a failure tone. Regardless, the center target was then presented, which the monkeys had to acquire in a similar fashion as above. The period starting from the instructed delay and ending with the target acquisition (or failure) constituted a trial.

In order to train monkeys to perform the instructed-delay task, we used the following protocol. First, we jittered the cued target during the entire instructed delay period as a means to indicate the beginning and end of the period. Second, monkeys were required to limit cursor velocity to a maximum of 1 mm/s during the delay period. Violating this condition automatically resulted in a failure. During training, we increased the time between a failed trail and the beginning of the next trial to 5 s to discourage failures. By comparison, the time between a successful trail and the subsequent trial was 20 ms. In the ‘covert’ context, the same task design was used, with the exception that monkeys’ arms were restrained and they had to control the cursor velocity using a BMI by modulating their neural activity.

The key manipulation on the Radial 8 Task was to introduce a visuomotor rotation (VMR), parametrized by angle θ. This consisted of rotating the cursor position θ degrees counter-clockwise around the workspace origin. In order to acquire targets in these cases, monkeys had to move their arm (overt context) or modulate neural activity (covert context) in a fashion that would ordinarily move the cursor at an angle $-\theta$ relative to the cued target. Thus, monkeys had to apply e.g. a clockwise rotation in order to counter the effect of the counter-clockwise VMR. Monkeys received constant visual feedback, so they could correct their cursor trajectories during learning. We used four VMR angles in this study: −45°, 45°, 60°, and 90°.

In order to encourage the monkeys to “try hard” to adapt to the VMR (rather than accepting making highly curved and inefficient movements to targets), we employed the following strategy. First, we decreased the maximum reach time every 500 trials (on average) from 10 s initially to 1.5 s in the last 500 trial block. In later sessions, we started from 3 s. Second, we introduced a path efficiency check, where we automatically failed a trial if the maximum orthogonal deviation (relative to the straight-line distance to the cued target) exceeded a bound. The experimenter manipulated this bound, making it more challenging, as a function of time. This factor in particular played a critical role in eliciting precise behavior which led to the effects described in Fig. 1.

In order to perform the experiments described in Fig 1 (experimental flow in Fig 1B), we used the following protocol. For the control conditions, monkeys were arm-restrained and used a BMI (under no VMR) for 2000 ± 1000 trials of the Radial 8 task. This typically took 90 minutes. After this adaptation phase, the experimenter went into the monkey’s room and removed the restraint of the arm contralateral to the arrays. This readied the overt context (still with no VMR), in which the monkey performed the Radial 8 task for 500 trials. For the experimental conditions the same procedure as the control experiment was followed, with the one change that during BMI use, a VMR was introduced. Both control and the experimental conditions were performed within the same experiment session. We analyzed a minimum of four sessions for each analysis, with alternating order of control and experimental blocks. The experiments described in Fig. 4 followed a similar flow, with two changes. First, the control comprised of only overt arm reaches in the presence of a VMR. Second, the experiment comprised of first using the BMI (in the presence of the same VMR as the control) for 2000 ± 1000 trials of the Radial 8 task, followed by a block of overt reaches in the presence of the same VMR. The precise number of trials for all of these experiments was based in part on the monkey's degree of VMR adaptation as qualitatively assessed by the experimenter at each session. To minimize day-to-day or residual adaptation effects, monkeys started and ended each session with overt arm reaches without VMR.

BMI decoder fitting—In order to train the BMI decoder at each session, we adapted the recalibrated feedback-intention trained Kalman filter (ReFIT) procedure (Gilja *et al.*, 2012). At the start of each session, monkeys observed 200 trials of Radial 8 automated cursor movements from the center of the workspace to one of 8 radially arranged targets at a distance of 12 cm. We performed three such blocks of 200 trials, each block with cursor velocity of 8, 10, and 12 cm/s. We used the neural and kinematic data from these blocks to estimate a position and velocity Kalman filter. Since BMI performance is sensitive to velocity gain, we manipulated this gain (i.e. scaling from neural activity to cursor velocity) on a session-by-session basis so as to help the monkey balance three factors: being able to successfully hold the center during the delay period (which benefits from low gain), moving in as straight as line as possible during the movement period (which benefits from low gain), and reaching the target as quickly as possible (which benefits from high gain). This procedure was followed for all Monkey J sessions.

Monkey R has poorer signal quality, and thus on roughly 50% of the sessions, the initial decoder (estimated the same was as done for Monkey J) was used by monkey R in closed-loop to perform another 200 Radial 8 task trials. This data was used by the final Kalman Filter decoder, estimated using the ReFIT algorithm. We again manipulated the gain of the decoder to strike a balance between performance and ease of accomplishing the instructed delay period (i.e., staying below the 1 mm/s requirement during the delay period). For the other 50% of sessions for Monkey R, we built a decoder in a similar fashion as was done for Monkey J. We found no difference in the scientific findings by using the ReFIT decoder (versus the standard Kalman filter) for Monkey R. In our decoders, no distinction was made between PMd and M1; all neural data was used jointly.

Residual Movement Tracking—While monkeys performed covert movements (via the BMI), we tracked the position of various body parts using infrared video cameras at a rate of 24 frames per second. Three cameras were positioned such that the dorsal forearm, the hand, the fingers, the rhomboids and deltoids regions, the pectorales and deltoid regions, and the shoulder, biceps, and triceps regions were visible, and took up most of the field-of-view. We used an open source implementation of the Lucas-Kanade optical flow algorithm (Liu, Adviser-Freeman and Adviser-Adelson, 2009) in order to estimate a velocity for each pixel from frame-to-frame. In order to ascribe a single velocity for each frame, we averaged the horizontal and vertical components (individually) of the velocity for all pixels in the field-of-view. We used intentionally placed physical landmarks visible in the videos to convert pixel coordinates into real-world coordinates. Finally, we used the millisecond-level timestamp from each frame to associate it with each individual trial. This analysis is presented in Fig. S1.

An alternative way to perform these control experiments could be to use an EMG preparation as done in many of our prior studies, e.g., (Kaufman *et al.*, 2014). After consideration, we believe that a computer vision approach is more appropriate in this study primarily because we want to *simultaneously* monitor multiple muscles. While it is possible that the animals' muscles sometimes undergo isometric co-contractions, which would result in minimal visible movement while still producing muscle activity, this is quite unlikely for three primary reasons: (1) given the number of hours of BMI experiments the animals must do, it is quite unlikely that they sustain co-contractions for that long as it is energetically expensive (i.e., very tiring), (2) even if there are isometric co-contractions, the shape of the muscles changes slightly, which can be measured at our camera working distance, which has hundreds of pixels for each anatomy of interest, and finally (3) co-contracting would not help the animals anyway because in order to affect the cursor movement, the muscle activity would need to systematically vary as a function of target direction; such distinct patterns of co-contractions would be picked up by our cameras. Thus, we believe that our approach well assesses the degree to which correlated movements are made during the covert context, and has the key advantage over EMG of being less likely to “miss a muscle” when measuring.

Preparatory neural state analysis—All of the analyses in Fig. 2 and Fig. 3 examine motor cortical preparatory neural states using a standard application of Principal Components Analysis (PCA)[24]. In brief, neural data was arranged into a data matrix comprising of neural firing rates of every neuron for every condition for every time point. We only looked at 200 ms worth of time points at the end of the instructed delay period. We then applied PCA on this data matrix. This results in a low-dimensional representation capturing the naturally occurring co-modulation in the data. Fig. 2B is a visualization produced by applying this procedure on a block of no-VMR overt trials. For each condition, trails (averaged in a bin of size three) were projected onto the top two PCs. These are 500 baseline trials that were collected at the beginning of the experimental session.

In the behavioral data (Fig. 2A) we observed that overt no-VMR trials following a block of covert trials with a VMR initially erred in the direction corresponding to the adjacent target in the opposite direction of the VMR. In order to do a similar analysis on the neural data, we fit a line between the centroids of neural data recorded while the animal prepared reaches to pairs of targets from Fig. 2B. We then projected trial-averaged (5 trials) firing rates corresponding to overt reaches (after adapting to a VMR under the covert context), directly onto that line. These projections are shown in Fig. 2C. We established a normalized distance metric so that trials can be combined across reach conditions and sessions. Concretely, trails that were projected directly onto the centroid corresponding to the cued target are assigned a distance of 0, whereas trials projected directly onto the centroid of the target in the opposite direction of the cued target are assigned a distance of 1. Fig. 2D shows this visually for all eight conditions, and Fig. 2E shows the statistics across all reach conditions and sessions.

In Fig. 3A we use PCA in the same fashion to compute the cumulative variance captured by each individual PC. We find that 4 PCs (in Monkey R) and 6 PCs (in Monkey J) capture over

90% of the variance in the data. In order to find the amount of shared neural variance between overt and covert behaviors, we project the 4 PCs (6 in Monkey J) from the overt context onto the 4 PCs (6 in Monkey J) of the covert context, and compute the inner product, normalized by the amount of total variance captured by each PC. Vice-versa gives the shared variance between covert and overt. A similar procedure was performed (not reported here) where both sets of data were combined and a joint subspace was found. We found no significant difference between the joint analysis and the analysis presented in Fig. 3. The same procedure was followed for the pairwise comparisons for the 'watch' condition. The same procedure was followed for Fig. S4A.

Statistics—For all histograms (Fig. 1, Fig. 4, and Fig. S2), the significances of the differences in the distributions were determined with two-tailed Student's *t*-tests, assuming non-equal variances of the two samples. We confirmed that each histogram followed a normal distribution using the Kolmogorov-Smirnov test. For data that did not follow a normal distribution, we used the Wilcoxon rank-sum test (Fig. 2, Fig. 3, and Fig. S3), using the paired (i.e., signed) test where appropriate. For all linear regressions (Fig. 1, Fig. 3, Fig. 4, Fig. S1, and Fig. S3) we used the *F*-statistic to assess the significance level of the slopes being different from zero. Partial correlations were used to rule out influence from other experimental parameters. In Fig. S3, we compared the slopes using a two-tailed Student's *t*-test. In Fig. 3 we measured the statistical overlap between the populations using the Bhattacharya coefficient, normalized such that 1 indicates no statistical overlap. For all tests, we used $p = 0.05$ as the significance threshold.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Learning covertly, without physical movements, transfers to overt behavior
- Covert learning systematically changes motor cortical preparatory activity
- Covert and overt movements share preparatory neural states and facilitate transfer
- Covert and overt movements engage a similar neural dynamical system

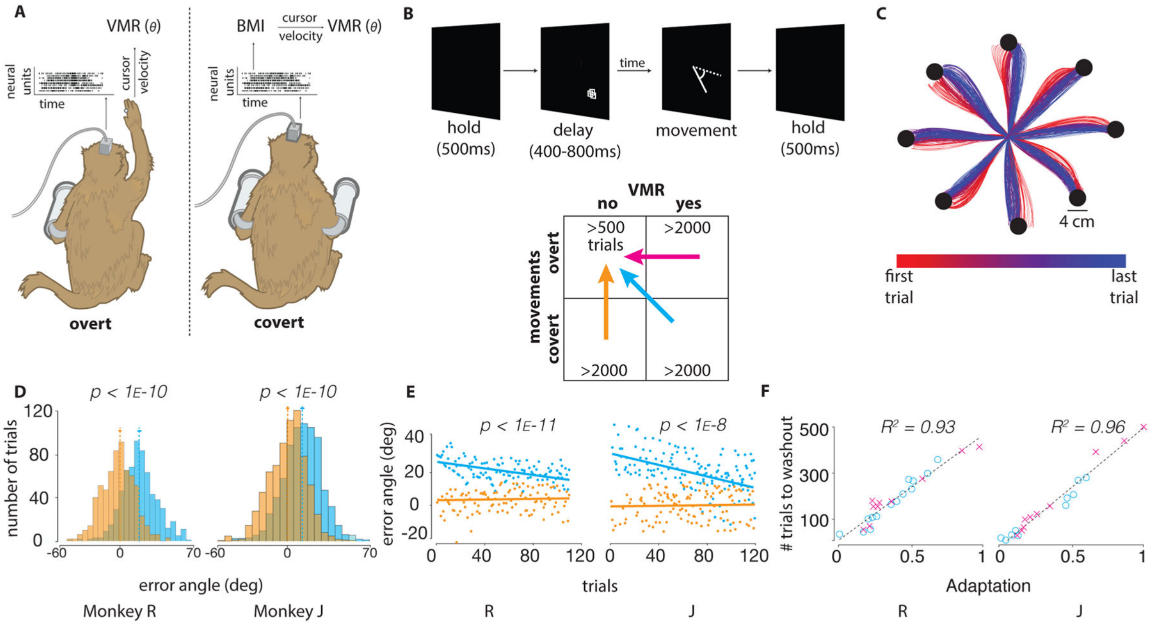

Fig. 1. Motor adaptation transfers between covert and overt movement contexts

A. Monkeys performed a cursor movement task in one of two contexts: ‘overt’ where cursor velocity tracked hand velocity, or ‘covert’, where cursor velocity was controlled by neural activity via a BMI. When a visuomotor rotation (VMR) was applied, the cursor’s movements were offset by the corresponding angle (θ).

B. (Top) Instructed delay task flow; (Bottom) Experimental flow.

C. Raw arm-controlled cursor trajectories (no VMR applied) immediately following covert VMR movements. Initial trajectories (red traces) exhibit curvature, which indicates transfer of adaptation to the VMR that was applied during the preceding covert context.

D. Histograms (first 100 trials of each session) of the error angle between the arm’s velocity (measured at the half-way radius towards the target) and the vector from workspace center to the target. Colors represent conditions from B. Vertical dashed lines show means of distributions, and horizontal solid lines mean ± s.e.m. *P* values obtained from two-tailed Student’s *t*-tests.

E. Error angle over time for the same conditions as panel D. Solid lines show mean.

F. Number of trials needed to wash out VMR adaptation (i.e., reach 90% of control) during no-VMR overt (magenta) or covert (cyan) blocks is strongly correlated with the degree of adaptation during the preceding covert block (VMR applied). Adaptation is defined as number of targets acquired per second in the 50 trials at the end of the VMR covert block (less the initial performance), normalized by the maximum performance across all blocks. Each point corresponds to one post-VMR block.

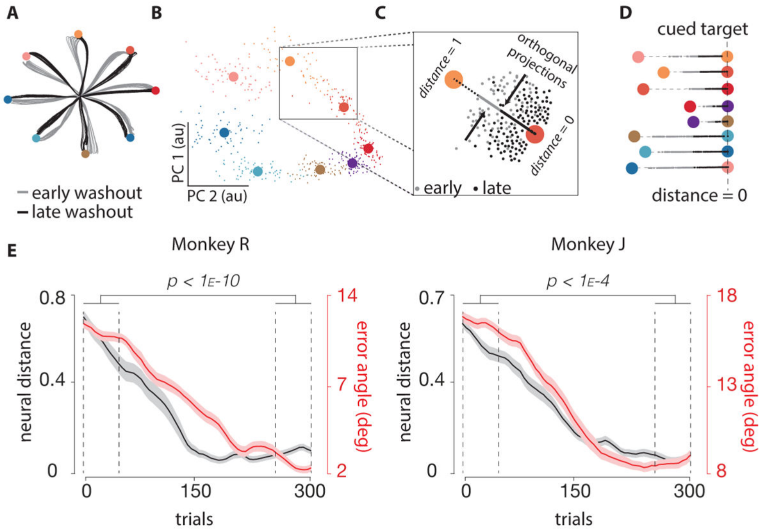

Fig. 2. Motor adaptation is reflected in population-level preparatory activity

A. Raw arm-controlled cursor trajectories following adaptation to a VMR applied during preceding covert use. Traces are divided into the first 25% (gray) and the last 25% (black) of trials.

B. 200 ms of instructed-delay period activity from a block of no-VMR overt trials projected into the top two PCs. Point clusters are three-trial-averaged overt trajectories projected into the PC state-space. Larger circles are cluster centroids. Colors denote the eight target conditions and match panel A.

C. Zoom into one overt movement condition from panel A. Preparatory activity projected into the corresponding region of the PC state-space of panel B. Gray/black points correspond to reaches from A. Neural states are orthogonally projected onto the line connecting the orange and red centroids from B. Each point is assigned a projection distance, where zero distance denotes being at the cued-target cluster centroid.

D. Example orthogonal projections for all eight conditions, aligned on the cued-target cluster centroid (from B). Early after the switch from VMR covert use, preparatory states were closer to the 'anti-VMR' target.

E. Normalized neural distances (combined across reach conditions and sessions) plotted as a function of trials since the switch from covert VMR to overt no-VMR contexts. Red shows the corresponding error angle. Inset compares the first 25% and the last 25% of trails. P values computed using the Wilcoxon rank-sum test.

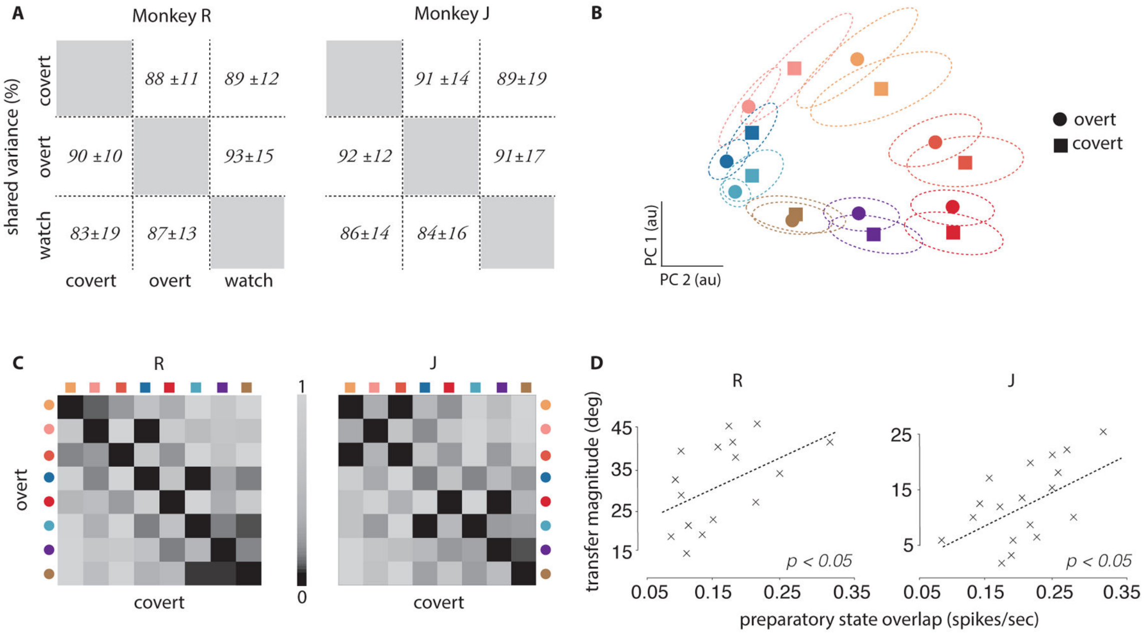

Fig. 3. Covert and overt movements share motor preparatory states

A. Percentage of shared variance between the overt context, covert context, and watch (i.e., during decoder training) context neural data. Data from each context is projected into the other contexts before the calculations are done. The subspaces were comprised of PCs (4 for Monkey R, and 6 for Monkey J), which collectively captured over 90% of the neural variance. There is no pairwise statistical significance. *P* values computed using the Wilcoxon rank-sum test.

B. Example visualization of mean overt (circle) and covert (square) preparatory states projected into a two PC state-space. Colors represent reach conditions. Dotted ellipses represent s.e.m.

C. Pairwise statistical population overlap (for the full high-dimensional distributions); zero corresponds to complete statistical overlap. Note that diagonals are close to zero.

D. The degree of overlap between covert and overt states in the full dimensional space (measured in spikes per second) is correlated with the magnitude of the transfer (error angle measured in degrees for the mean of the first five trials post-switch from covert to overt). Baseline overlap data, and subsequent transfer data were collected in the same sessions, with similar parameters (i.e., trial counts, VMR angle, etc.). *P* values computed using the Wilcoxon rank-sum test, and test the hypothesis of no correlation.

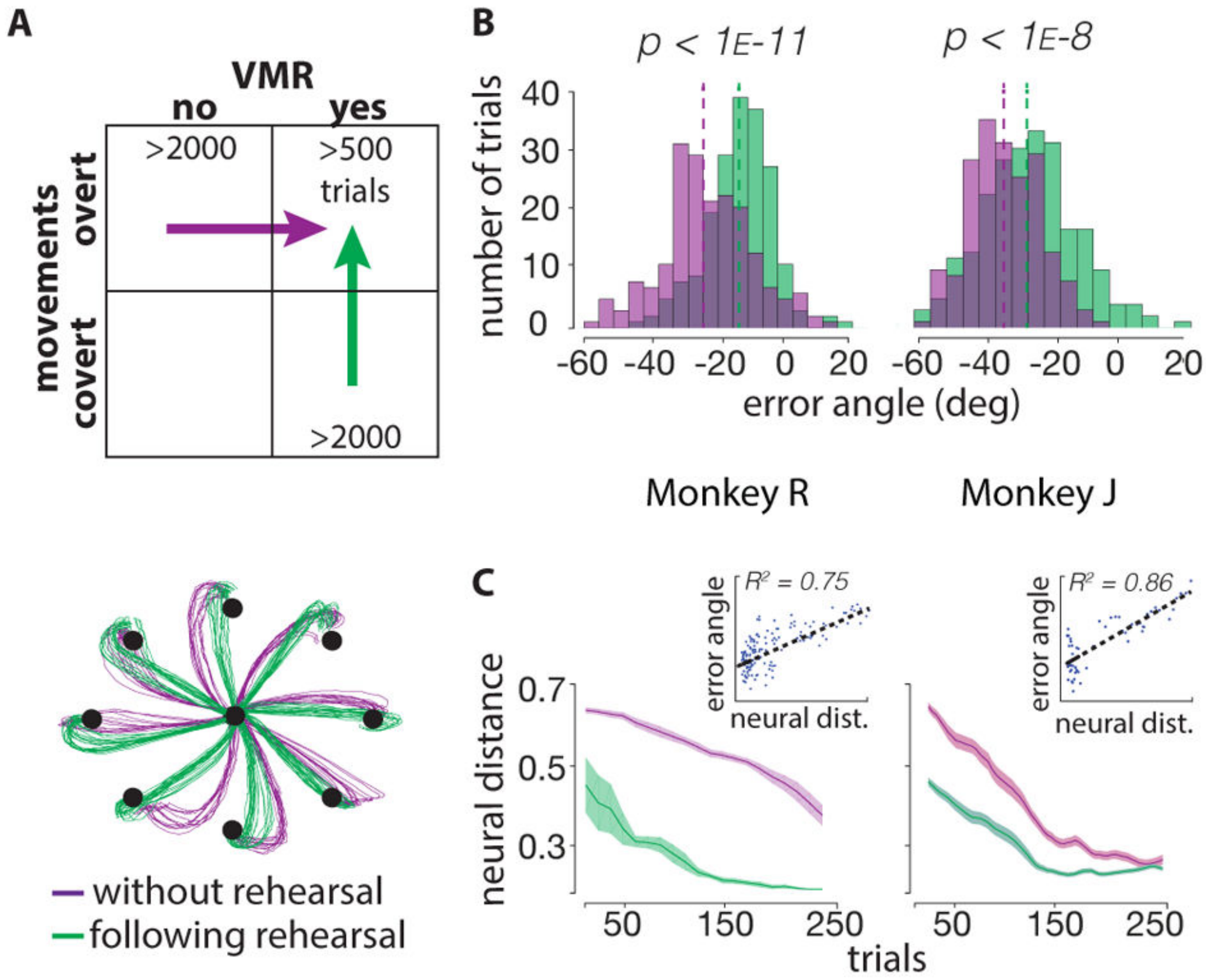

Fig. 4. Covert rehearsal can enhance overt motor learning

A. (Top) Experimental flow. (Bottom) Purple traces show overt arm trajectories with a −45° VMR applied following a no-VMR overt block. Green traces show overt −45° VMR arm trajectories following a covert −45° VMR block. The rehearsed green trajectories are more direct.

B. Histograms of error angles for the two conditions. Colors matched to A.

C. Comparison of rehearsed and non-rehearsed normalized preparatory neural state-space distance (as described in Fig. 2B–C) as a function of trial number. Preparatory states start more adapted after covert rehearsal. Data averaged across sessions and reach conditions. Insets show strong correlation between individual trials' normalized preparatory distance and subsequent error angle ($p < 0.05$). P values were obtained from two-tailed Student's t-tests.