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Cortical state dynamics as a target for stroke motor rehabilitation

Aamir Abbasi[1] **and Tanuj Gulati**[1,2,3,4,*]
[1]Center for Neural Science and Medicine, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[2]Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[3]Department of Bioengineering, Henry Samueli School of Engineering, University of California, Los Angeles, Los Angeles, CA, USA
[4]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
*Correspondence: tanuj.gulati@csmc.edu
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In this issue of *Neuron*, Choi et al.[1] demonstrate that stroke disrupts cortical state transitions underlying reach-to-grasp control. Recovery depends on restoring separability between beta bursts and execution-related co-firing, a process enhanced by low-frequency stimulation that promotes motor recovery.

Stroke often impairs arm and hand movements, yet how cortical activity reorganizes during recovery remains incompletely understood. Understanding these mechanisms is critical for designing targeted neuromodulation strategies to enhance rehabilitation. In this issue of *Neuron*, Choi et al.[1] report that, in monkeys with motor cortex lesions, stroke blurs the brain's "pre-movement" and "movement" phase signals, disrupting coordinated control. The authors show that recovery is associated with re-establishing greater separation between these neural states, and low-frequency brain stimulation delivered through a novel "ringtrode" interface enhanced this separability and improved hand function. These findings suggest that reinstating distinct cortical states before and during movement may be a key mechanism of post-stroke recovery.

Recent work posits that low-dimensional population dynamics underlie coordinated movement generation,[2,3] and movement preparatory activity and movement execution activity lie in two orthogonal neural subspaces in overlapping neuronal populations.[4,5] Choi et al. apply this framework to show that transitions between these modes are disturbed post-stroke and restored during recovery and with neurostimulation. They identify pre-movement neural mode, represented by oscillatory beta-band activity (12–30 Hz), which is movement suppressive, and a movement-permissive mode, represented by coordinated neuronal ensemble co-firing ($F1_{move}$), active during goal-directed action. Their experiments showed how stroke disrupted the transition between these modes, while recovery correlated with restored pre-movement and movement population dynamics, concomitant with improved reaction time, and reach-to-grasp (RTG) task performance.

In the study, three monkeys were trained on a cued RTG task, after which focal lesions were induced in contralateral primary motor cortex (M1). Neural spiking and local-field potentials were recorded from dorsal premotor cortex (PMd) during recovery. Behavioral metrics included reaction time (reflecting the transition from pre-movement to movement initiation) and RTG time (capturing whole movement including dexterous grasping). Beta-band amplitude and ensemble co-firing were quantified using the first latent factor ($F1_{move}$) extracted via Gaussian-process factor analysis (GPFA). The greater temporal distance (ΔT) between beta and $F1_{move}$ peaks correlated with slower reaction times and submovement durations.

Next, the authors showed that during recovery, the joint distribution of beta and $F1_{move}$ activity evolved into two distinct clusters, representing separable pre-movement and movement execution states. They used a distribution separability index (d'), which revealed that increased separation between pre-movement beta and execution-related co-firing was a key neural signature of restored RTG task performance. These results indicate that clear transitions between "movement-idle" and "movement-potent" cortical

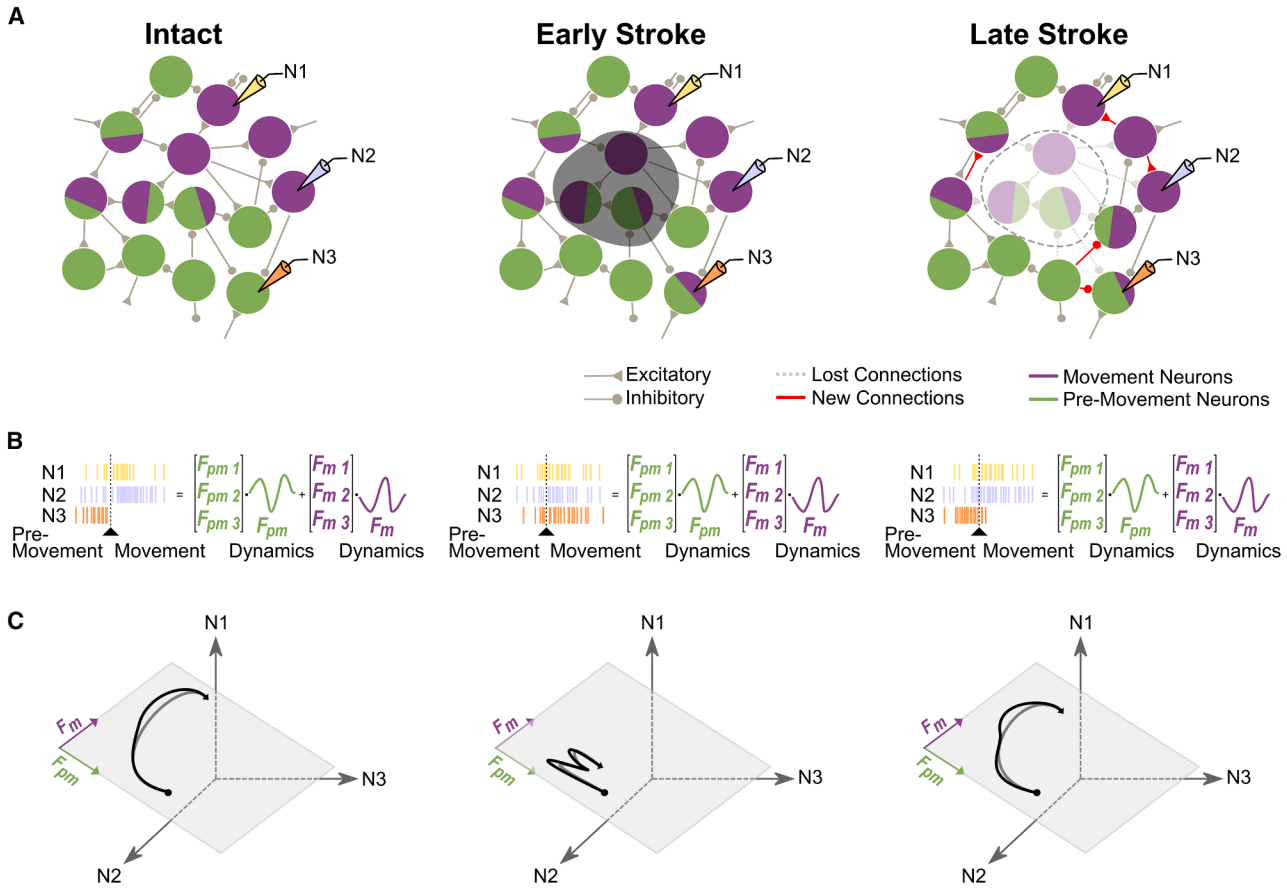

Figure 1. Neural trajectories in stroke recovery

(A) Movement generation requires transitioning from a pre-movement to a movement-execution state through coordinated activity of interconnected neurons. Population activity during these phases evolves along a low-dimensional neural manifold (*C*, adapted from Gallego et al.[3]), shaped by intrinsic connectivity. Stroke disrupts these transitions by altering connectivity (early stroke, middle), whereas recovery restores more organized trajectories through network reorganization (late stroke, right). Each neuron's contribution to pre-movement (purple) and movement (green) phases is shown, with red lines indicating post-stroke connectivity changes.

(B) Example spiking activity from three neurons expressed as linear combinations of two latent factors—pre-movement (F_{pm}) and movement (F_m)—during intact (left), early (middle), and late (right) post-stroke periods.

(C) Time-varying population trajectories in the neural space of the same neurons, shown on the manifold spanned by F_{pm} and F_m modes. Black lines depict the actual trajectory; its projection onto the linear manifold (gray plane) represents a local linear approximation of the nonlinear path.

states can be a biomarker for recovery. The RTG task used here had both "gross" reaching and "finer" grasping subcomponents, which may be associated with separate neural modes.[6] The authors suggest that $F1_{move}$ here may represent a condition-invariant latent factor whose temporal separation from beta primes the cortex for movement initiation and execution—a principle that may extend to other skilled actions. They also showed that beta suppression was linked to the dexterous grasp phase, suggesting that full suppression was necessary for clean "grasp" execution. Future work could explore how transitions from movement-null to movement-potent states occur in naturalistic, unconstrained tasks, and whether movement modes across tasks are orthogonal to preparatory modes.

The authors confirmed that the bistable regime identified was not exclusive to stroke recovery. In healthy monkeys performing a touchscreen task, beta activity dropped before movement while movement co-firing increased, forming two distinct clusters. This indicates that both intact M1 and PMd in stroke-recovering monkeys rely on a built-in "two-state switch" between holding and acting. They also built a simple mathematical model that replicated their experimental findings, producing alternating transitions between strong beta activity and movement co-firing. By adjusting a parameter κ (kappa), the model showed that lower κ, as may occur post-stroke, led to sluggish transitions with higher ΔT and lower d', supporting the idea that recovery involves restoring bistable switching dynamics. Complementary work with recurrent neural networks (RNNs) has shown that strong recurrent excitation requires fine-tuned inhibition for stability,[7] and electrophysiology studies show that post-stroke, this balance is disrupted,[8] suggesting that recovery entails relearning excitatory-inhibitory interactions to support transitions to movement generation mode (Figure 1). Future work can test the findings here with RNNs resulting in loss of neurons and subsequent reinstatement of excitatory and inhibitory regimes with re-training.

To investigate the orthogonality of pre-movement and movement states, Choi et al. extracted factors (using GPFA) representing activity during beta bursts and movement. They calculated the principal angle (θ) between these factors, showing that orthogonality correlates with independence between the states. Early post-stroke, the states were poorly separated, but they gradually re-separated during recovery. In the RTG task, neural activity likely occupied a local region of the manifold (possibly representing a condition-invariant movement-potent state), so GPFA was appropriate (Figure 1C). In the future, for more complex, less restrained behaviors, nonlinear methods may be needed to better capture high-dimensional dynamics.[3]

The authors also reconcile the role of previously reported low-frequency oscillations (LFOs) in stroke[9] with the results here. Phase-amplitude coupling between beta amplitude and $F1_{move}$ or the LFO phase was weak early after stroke but strengthened during recovery, suggesting that LFOs act as a physiological scaffold for bistable interactions between $F1_{move}$ and beta.

In the authors' final experiment, low-frequency 3 Hz alternating current stimulation (ACS) was applied using a ringtrode to modulate LFOs and improve separability between neural modes. While the electric field likely influenced both ipsilesional and contralesional hemispheres, ACS improved RTG performance. Beta oscillations became more tightly locked to the ACS phase, and $F1_{move}$ and beta peaks occurred consistently at specific ACS phases. The temporal difference (ΔT) between these signals became more regular, and the dot product between subspace vectors decreased under ACS, enhancing orthogonality. These results suggest that low-frequency ACS entrained cortical oscillations, improved timing and coupling between preparatory and execution signals, and enhanced separability, providing causal evidence that stimulation restores rapid switching between "ready" and "move" states.

Regarding clinical translation, the authors suggest that the separability phenomena between beta band and movement-potent spiking may apply to stroke survivors with partially intact descending tracts, representing mild-to-moderate impairments. Since the lesions were restricted to M1 and spared descending projections, the authors mention that mechanisms observed may support recovery of dexterity rather than abnormal synergies or spasticity, which are more common in extensive strokes. However, the low-dimensional population-factor framework has also been related to instantiation of muscle synergies,[5] and contra-lesional reticulospinal tract (RST) upregulation may underlie spasticity and abnormal synergies seen post-stroke.[10] Future work can explore how dexterity, which depends on ipsilesional corticospinal tracts, and abnormal synergies, linked to contralesional RST activity, evolve after stroke. It will also be important to examine how adjustments in contralesional and ipsilesional corticoreticular pathways relate to cortical pre-movement and movement neural modes and their transitions, along with simultaneous electromyography (EMG) recordings.

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DECLARATION OF INTERESTS

T.G. has been awarded a patent related to methods for brain stimulation to improve motor function after stroke (PCT/US19/42617).

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