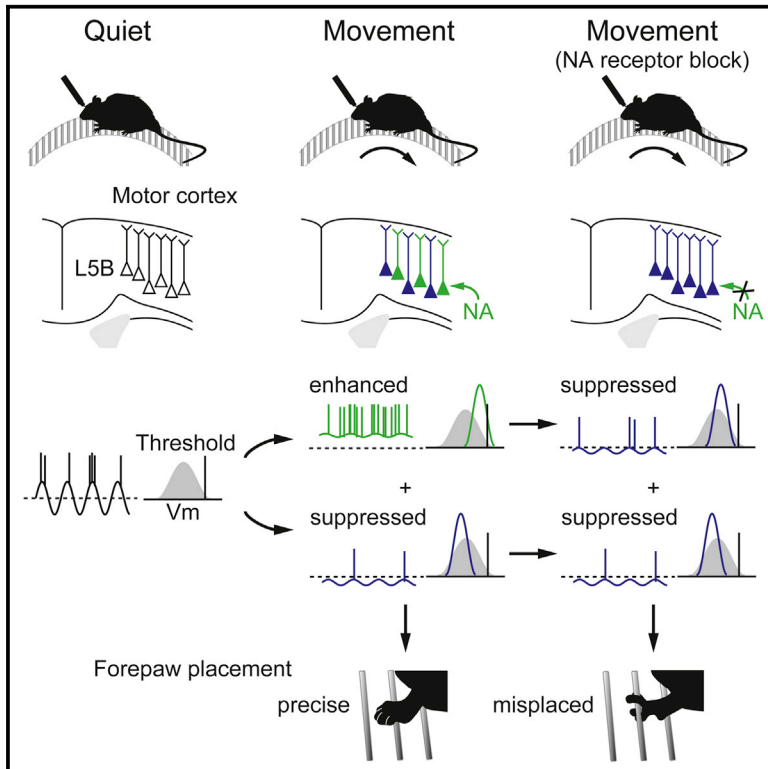


Cell Reports

Cellular Mechanisms Underlying Behavioral State-Dependent Bidirectional Modulation of Motor Cortex Output

Graphical Abstract



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In Brief

Schiemann et al. show that, in mouse motor cortex, layer 5B pyramidal neuron firing rates are suppressed or enhanced during movement due to a global reduction in membrane potential variability and coincident noradrenaline-mediated depolarization in a subpopulation of neurons, respectively. Blocking noradrenergic input to M1 impairs motor coordination.

Highlights

- During movement, reduced V_m variance lowers spike probability in L5B output neurons
- Noradrenaline mediates a tonic depolarization in L5B_{enh} neurons during movement
- Noradrenaline selectively enhances signal-to-baseline ratio of L5B_{enh} neurons
- Blocking noradrenaline receptors in M1 reduces contralateral forepaw motor coordination



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Cellular Mechanisms Underlying Behavioral State-Dependent Bidirectional Modulation of Motor Cortex Output

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SUMMARY

Neuronal activity in primary motor cortex (M1) correlates with behavioral state, but the cellular mechanisms underpinning behavioral state-dependent modulation of M1 output remain largely unresolved. Here, we performed *in vivo* patch-clamp recordings from layer 5B (L5B) pyramidal neurons in awake mice during quiet wakefulness and self-paced, voluntary movement. We show that L5B output neurons display bidirectional (i.e., enhanced or suppressed) firing rate changes during movement, mediated via two opposing subthreshold mechanisms: (1) a global decrease in membrane potential variability that reduced L5B firing rates (L5B_{suppressed} neurons), and (2) a coincident noradrenaline-mediated increase in excitatory drive to a subpopulation of L5B neurons (L5B_{enhanced} neurons) that elevated firing rates. Blocking noradrenergic receptors in forelimb M1 abolished the bidirectional modulation of M1 output during movement and selectively impaired contralateral forelimb motor coordination. Together, our results provide a mechanism for how noradrenergic neuromodulation and network-driven input changes bidirectionally modulate M1 output during motor behavior.

INTRODUCTION

Neuronal activity in layer 5 (L5) of primary motor cortex (M1) correlates with rhythmic voluntary movements (Armstrong and Drew, 1984a, 1984b). During walking or running, pyramidal neurons display changes in firing rate that reflect periods of coordinated muscle activity (Armstrong and Drew, 1984a; Beloozerova et al., 2003). Although spontaneous locomotor activity can be controlled by central pattern generators (CPGs) in the spinal

cord (Forssberg et al., 1980; Grillner, 1981; Grillner and Zangger, 1979), descending motor commands from M1 are integrated with ongoing rhythmic spinal cord signals and sensory input from the periphery to initiate, adjust, and maintain locomotor function (Armstrong and Drew, 1984a; Beloozerova et al., 2003; Orlovsky, 1972; Ueno and Yamashita, 2011). In lower mammals, such as cats, rabbits, and mice, discrete subpopulations of L5 output neurons display enhanced or suppressed (i.e., bidirectional) firing rate changes during locomotion (Armstrong and Drew, 1984a; Beloozerova et al., 2003; Costa et al., 2004). In rodents, these changes can be either abrupt, sustained changes—so-called on-off responses—or gradual frequency changes linked to the velocity of running (Costa et al., 2004). Although we are now beginning to understand how patterns of motor cortex activity relate to changes in behavioral state in rodents (i.e., quiet wakefulness to movement), the cellular mechanisms underpinning bidirectional modulation of M1 output during self-paced movement remain largely unresolved.

Several mechanisms could underlie the bidirectional modulation of M1 output, such as a change in cortical state-dependent network-driven input structure, intracortical or long-range excitatory input, and/or neuromodulation. During quiet wakefulness or slow-wave sleep, cortical networks remain in a synchronized state that consists of slow, large-amplitude oscillations in neuronal population activity (Cowan and Wilson, 1994; Steriade et al., 1993c). During active behavior, cortical networks enter an activated state characterized by a reduction in slow oscillations and, in some cases, an increase in higher frequency activity (Steriade et al., 1993b; Timofeev et al., 2001). This change profoundly alters the subthreshold V_m dynamics and spike output patterns of cortical pyramidal neurons (Castro-Alamancos, 2004; Castro-Alamancos and Oldford, 2002; Constantinople and Bruno, 2011; Crochet and Petersen, 2006). Thalamic activation promotes the cortical awake state and direct depolarization of superficial and deep-layer pyramidal neurons (Castro-Alamancos and Connors, 1996; Castro-Alamancos and Oldford, 2002; Constantinople and Bruno, 2013; Hirata and Castro-Alamancos, 2010; Poulet et al., 2012), suggesting input from the thalamus could contribute to changes in M1 output during motor

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