Short-Talk Abstracts

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The Cellular and Synaptic Architecture of the Mechanosensory Dorsal Horn

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The deep dorsal horn is a poorly characterized spinal cord region implicated in processing low-threshold mechanoreceptor (LTMR) information. We report an array of mouse genetic tools for defining neuronal components and functions of the dorsal horn LTMR-recipient zone (LTMR-RZ), a role for LTMR-RZ processing in tactile perception, and the basic logic of LTMR-RZ organization. We found an unexpectedly high degree of neuronal diversity in the LTMR-RZ – seven excitatory and four inhibitory subtypes of interneurons exhibiting unique morphological, physiological, and synaptic properties. Remarkably, LTMRs form synapses on between 4 and 11 LTMR-RZ interneuron subtypes while, conversely, each LTMR-RZ interneuron subtype samples inputs from at least one to three LTMR classes, as well as spinal cord interneurons and corticospinal neurons. Thus, the LTMR-RZ is a sensory processing region endowed with a neuronal complexity that rivals the retina and functions to pattern the activity of ascending touch pathways that underlie tactile perception.

Characterization of Zic2+ Dorsal Spinal Neurons as Potential Integrators of Sensory and Motor Circuits

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The dorsal spinal cord is the integrative center that processes and transmits a variety of somatosensory modalities such as touch, pain, temperature and itch. It is also becoming clear that the integration of spinal microcircuits, sensory feedback and supraspinal descending circuits necessary for accurate motor performance occurs in the dorsal spinal cord. Nevertheless, the molecular identity and specific function of individual interneuron classes in this circuit is largely unknown. In our previous work, we identified a population of dorsal spinal neurons marked by the co-expression of EphA4 and the transcription factor Zic2, which we suggested represents a subpopulation of postsynaptic dorsal column (PSDC) neurons (Paixão et al., Neuron, 2013). We have recently developed an inducible Zic2-CreER line to genetically target these neurons. Zic2+ excitatory neurons reside in laminae III-V in a medial position surrounding the dorsal funiculus, where they partially colocalize with the recently described markers of lamina III/IV interneurons RORα, and lamina V interneurons Tcfap2β and SatB1/2. Intraspinal cord trans-synaptic rabies virus experiments have confirmed that Zic2 neurons receive sensory input primarily from cutaneous afferents. Retrograde tracing experiments, indicate that at least a subset of Zic2 neurons send projections to the cuneate nucleus in the medulla, suggesting that Zic2 likely represents a molecular marker of PSDC neurons and could be involved in discriminative touch sensation. Furthermore, Zic2 neurons receive monosynaptic inputs from ventral spinal cord interneurons and several descending brain centers involved in motor control, like the motor cortex and numerous brainstem nuclei. In turn, Zic2 neurons seem to have synaptic outputs to spinal motorneurons raising the interesting possibility that Zic2 dorsal spinal neurons could play a role in the integration of sensory and motor spinal circuits. Ongoing efforts are aimed at investigating the *in vivo* activity of Zic2+ spinal cord neurons during somatosensory stimulation and their requirement for specific motor outputs.

RORb Interneurons Act as Spinal Filters for Refined Motor Movement

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Studies to date point to essential roles for sensory feedback in shaping the locomotor output. Proprioceptive inputs arising from muscles and tendons, as well as cutaneous input from the skin have been shown to modify stepping behaviour allowing for tuned responses to environmental cues. These effects have been attributed to spinal integration, but how this sensory information is relayed and filtered within the spinal cord, and the mechanisms that elicit the sensory-evoked refinement of the motor output have not been fully described. We have identified a subpopulation of spinal dorsal inhibitory interneurons that can be genetically targeted by the expression of the nuclear orphan receptor *RORβ*. Using a combinatorial approach involving genetic manipulation, behavioural analysis, anatomical tracing and electrophysiology, we find that RORβ interneurons selectively inhibit cutaneous and proprioceptive afferent input into the spinal cord. Deletion of *RORβ* from inhibitory interneurons in the dorsal horn results in an altered motor gait, which is driven by aberrant cutaneous and proprioceptive input. Pharmacological silencing of afferent input from the periphery is sufficient to attenuate the behavioural phenotype highlighting the important function of inhibitory RORβ interneurons in the integration of cutaneous and proprioceptive sensory input for normal locomotion. As such, these neurons provide a critical piece in the puzzle of the sensory-motor interface.

Mechanosensory Neurons Control the Timing of Spinal Microcurcuits Selection during Locomotion

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Mechanosensory feedback to spinal circuits shapes the patterns of motor neuron recruitment during active locomotion. Yet, the circuits underlying this sensory-motor integration have been identified solely at the sensory level. Here, we address this issue by combining optical methods for monitoring neuronal activity in motion, quantitative high-throughput kinematic analysis of zebrafish larvae and *in vivo* optogenetic-mediated mapping of connections. We compare intact animals to those genetically- or pharmacologically- deprived of mechanosensory feedback. First, by targeting the bioluminescent calcium sensor GFP-aequorin to motor neurons, we demonstrate that mechanosensory feedback enhances during active locomotion spinal motor neuron recruitment. Second, we show that the silencing of glutamatergic mechanosensory neurons leads to a large decrease in locomotor speed, associated with an early termination of the fast component and a corresponding prolonged slow component of the escape behavior. Finally, we demonstrate that glutamatergic mechanosensory feedback projects monosynaptically onto premotor V2a interneurons sustaining fast locomotion. Altogether, our work demonstrate that mechanosensory feedback gates the transition between fast and slow modules of locomotion by a direct excitatory drive onto premotor interneurons dedicated to fast locomotion. Furthermore, the net effect of mechanosensory feedback on speed that we investigated here in zebrafish larva from circuits to behavior provides a general explanation for the massive slowdown of locomotor rhythms observed throughout vertebrates during fictive locomotion.

The Role of the Sodium Pump in Mouse Spinal Locomotor Network Activity

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Locomotor rhythm generation must be flexible to adapt motor behaviour to prevailing demands. The Na+/K+-ATPase (or sodium pump) influences locomotor networks in Xenopus tadpoles (Zhang et al., 2015) and Drosophila larvae (Pulver and Griffith, 2010) in an activity dependent manner, but its contribution in equivalent mammalian networks is less well described. We describe a functional role for sodium pumps in murine locomotor networks. Using spinal cords isolated from neonatal mice (postnatal day (P)0-P4), we induced locomotor-related activity pharmacologically (NMDA 5 µM, 5-HT 10 µM and DA 50µM) and recorded it through glass suction electrodes attached to lumbar ventral roots (L1, L2, L5). The sodium pump inhibitor, ouabain (1-3µM), increased rhythm frequency and decreased burst amplitude, an effect that was more pronounced in the presence of 50µM DA. The sodium ionophore monensin (10µM) was used to increase intracellular sodium concentration and hence to mimic sodium pump activation. Monensin decreased locomotor burst frequency and disrupted right-left and extensor-flexor phase relationships. We next used dorsal root sensory stimulation in the absence of drugs in order to induce short episodes of more natural locomotor activity. When the interval between evoked episodes was reduced, episodes became shorter and slower. Ouabain (1-3µM) increased the frequency and duration of these episodes whilst monensin (10µM) exerted the opposite effect. These data suggest a possible role for sodium pumps in network self-regulation. Using spinal cord slices from neonatal mice (P2-P15) we performed whole-cell patch-clamp recordings from spinal motoneurons (MNs) and ventral horn interneurons (INs). We observed an ultra- slow afterhyperpolarisation (usAHP) in 40/97 MNs and 15/35 INs of ~5mV amplitude with ~60s duration following high frequency firing. In MNs, this was blocked by ouabain (1-3µM) and TTX (0.5µM), suggesting the usAHP involves a spike dependent increase in sodium pump activation. In MNs with a usAHP, monensin (10µM) caused a ~5mV hyperpolarisation. Perfusion of dopamine (10µM) increased the duration of this pump current by ~60%. Taken together, our data reveal a role for the sodium pump in mammalian spinal locomotor control circuits. Interestingly, this feature is present in some, but not all MNs and INs, suggesting that the functional role of the sodium pump may be restricted to specific neuronal subtypes, as in frog tadpoles (Zhang et al., 2015). The data also highlight the importance of the sodium pump as a spinal target for the neuromodulator DA.

Pulver & Griffith (2010) Nat. Neurosci. 13(1):53-9
Zhang, Picton, Li, & Sillar (2015) Sci. Rep. 5, 16188

Functional Diversity of Excitatory V0 Interneurons in the Adult Zebrafish

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Flexibility in the bilateral coordination of muscle contraction underpins variable locomotor movements or gates. The left-right coordination during locomotion can vary in a context-dependent manner to produce alternation through the activity of commissural interneurons connecting local interacting circuits on the two sides of the spinal cord. The V0 interneurons represent a major commissural neuronal population comprising ventral excitatory (V0v) and dorsal inhibitory (V0d) classes. The current view of V0 function derives from studies in immature motor systems (larval zebrafish and newborn mouse), but the activity patterns of V0d and V0v classes is unknown. Here we examined how the activity of the V0v interneurons varies with the speed of locomotion in adult zebrafish. Our results show that although V0v interneurons express a defined transcription factor and transmitter phenotype, their activity patterns during locomotion are heterogeneous. V0v interneurons could be segregated into two distinct types based on whether or not they display rhythmic activity during locomotion. The rhythmically active V0v interneurons could be further subdivided into three main sub- classes engaged sequentially during swimming, first at slow then intermediate and finally fast locomotor speeds. The order of recruitment of the three sub- classes of V0v interneurons is defined by a combined computation of their synaptic drive and intrinsic properties. The extent of the rhythmic excitation is the result of a scaling of the synaptic current with the input resistance of the different V0v interneurons. This study thus uncovers, for the first time in an adult vertebrate, an important organizational principle for a key class of commissural interneurons and the underlying cellular and synaptic mechanisms defining their pattern of recruitment as a function of locomotor speed.

Comparative Modeling of Different Spinal Mechanisms for Speed-dependent Gait Transitions in Quadrupeds

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As speed of locomotion is increasing, most quadrupeds demonstrate sequential gait transitions from walk to trot and to gallop and bound. Neural mechanisms underlying these transitions are poorly understood. It has been suggested that the expression of different gaits results from speed-dependent changes in the interactions between spinal circuits controlling different limbs and that interlimb coordination is mediated by different commissural interneurons (CINs) whose axons project to and affect neurons located on the contralateral side of the cord[1]. We have recently developed a computational model of the mouse spinal circuits consisting of four rhythm generators with left-right interactions mediated by genetically identified V0 CINs ($V0_D$ and $V0_V$ sub-types), providing left-right alternation, and V3 CINs, promoting left-right synchronization[2]. The locomotor speed in this model was controlled by brainstem drives to the rhythm generators and the gait transitions resulted from speed-dependent changes in the balance between the activity of V0 and V3 CINs. Our simulations led to two alternative hypotheses: (i) the sequential gait transitions from walk to bound with increasing speed results from an increasing excitatory brainstem drive to V3 CINs, promoting left-right synchronization, or (ii) these gait transitions are caused by progressively increasing inhibitory brainstem drives to V0 CINs, suppressing left-right alternation. In this study, we used two alternative models to compare these hypotheses. In the model with increasing excitatory drives to V3 CINs, only walk, trot, and bound represented stable regimes/gaits, whereas gallop occurred only as a transient state between trot and bound. In contrast, in the model with increasing inhibitory drives to V0 CINs several types of gallop represented stable regimes. Furthermore, stronger inhibitory drives to the $V0_V$ CINs of the hindlimb circuits than to those of the forelimb circuits caused the expression of half-bound gallop. Both models could reproduce changes in gait expression in mutants lacking $V0_V$ or all V0 CINs[1]. Specifically, trot was not expressed after removal of $V0_V$ CINs, and only bound was expressed after removal of all V0 CINs. Based on our simulations we proposed experimental studies allowing identification of the more realistic model and the exact spinal interactions responsible for speed-dependent gait expression: this studies should include investigations of the effect of brainstem stimulation on the activity of different genetically identified CINs.
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The Diversity of Spinal Inhibitory Interneurons Delineates Variant Motor Microcircuits

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Animals interact with the world through movement, transforming patterns of neural activity into the orderly contraction of muscles. The circuits directly responsible for movement reside in the spinal cord, where inhibitory interneurons play a crucial role in shaping patterned motor output. Yet the identity of these inhibitory interneurons and the organizational logic through which they influence motor output remain obscure. In prior studies, we showed that the cardinal class of spinal V1 inhibitory interneurons can be fractionated into highly diverse subsets on the basis of the expression of 19 transcription factors[1,2]. Many of these V1 subsets exhibit distinct physiological signatures and occupy restricted spatial domains, consistent with the idea that they correspond to distinct V1 cell types. Using a combination of anatomical and physiological approaches, we found that distinctions in interneuron position are largely predictive of patterns of input from sensory and motor neurons, suggesting that neuronal position functions in parallel with molecular recognition cues to direct inhibitory circuit organization. Our findings also revealed the existence of a variant circuit architecture for V1 interneurons that operate on motor pools controlling hip, ankle, and foot muscles, potentially to accommodate distinctions in the biomechanical features of individual muscles and different limb joints. The extensive diversity of inhibitory interneurons documented in these studies raises important questions about the need for such heterogeneity within the context of the motor system. Are flexor and extensor motor pools that drive movement around limb joints regulated by distinct V1 subsets, in an analogous manner to the spatial segregation of flexor and extensor premotor interneurons found in the dorsal spinal cord[3]? And to what extent do different descending pathways recruit specific V1 subsets? In ongoing experiments, we are using trans-synaptic viral tracing strategies to map the organization of these premotor V1 networks, which should inform the design of targeted behavioral experiments aimed at testing the functional role of V1 subsets in motor control. Given the high degree of molecular diversity exhibited by interneurons in other regions of the CNS[4], defining discrete spinal interneuron types may also inform the organizational logic and function of inhibitory microcircuits in the brain. Supported by HHMI, NINDS, NSF, ONR and ARO MURI, the Brain Research, Gatsby, Mathers, and Swartz Foundations, and Project ALS.

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Genetic-based Dissection Unveils the Inputs and Outputs of Striatal Patch and Matrix Compartments

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The striatum contains neurochemically defined compartments termed patches and matrix. Previous studies suggest patches preferentially receive limbic inputs and project to dopamine neurons in substantia nigra (SNc), whereas matrix neurons receive sensorimotor inputs and do not innervate SNc. Using BAC-Cre transgenic mice with viral tracing techniques we mapped brain-wide differences in the input-output organization of the patch/matrix. Findings reveal a displaced population of striatal patch neurons termed "exo-patch", which reside in matrix zones but have neurochemistry, connectivity, and electrophysiological characteristics resembling patch neurons. Contrary to previous studies, results show patch/exo-patch and matrix neurons receive both limbic and sensorimotor information. A novel inhibitory projection from bed nucleus of the stria terminalis to patch/exo-patch neurons was revealed. Projections to SNc were found to originate from patch/exo-patch and matrix neurons. These findings redefine patch/matrix beyond traditional neurochemical topography and reveal new principles about their input-output connectivity, providing a foundation for future functional studies.

Decoding of Midbrain Circuits Involved in Initiation of Locomotion and Context-dependent Gait Selection

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During locomotion and depending on behavioral demands, changes of speed are necessary. In quadrupeds, changes in speed are often associated with changes in limb coordination leading to expression of different gaits. The command for initiation of locomotion and the selection of gaits are assumed to originate in the midbrain and include activity in the Mesencephalic Locomotor Region (MLR). MLR has been proposed to be restricted to two areas in the midbrain: the cuneiform nucleus (CnF) and the pedunculopontine nucleus (PPN). However, their specific contribution to the initiation of locomotion and behaviorally relevant selection of gaits remain controversial. In this study we use cell specific mouse genetic and viral approaches to bi-directionally modulate the activity of glutamatergic excitatory neurons in CnF and/or PPN and to trace their afferent and efferent connections. We show that glutamatergic neurons in PPN are important for the initiation of locomotion but it controls only slow speed of locomotion phenotypical for exploratory behavior. In parallel, glutamatergic CnF neurons control all speeds of locomotion including alternating gaits (like walking and trotting) and synchronous gait (like galloping and bounding) typically used for defensive or escape locomotion. Moreover, we observe that the firing behavior of glutamatergic neurons during enforced locomotion encode different speed of locomotion in CnF and in PPN. This dual control of the locomotor activity is reflected in different afferent and efferent connectivity matrices in CnF and PPN. Our results dissolve the concept of MLR as an entity and points to the role of distinct groups of glutamatergic neurons in the PPN and CnF that may be recruited separately to control the specific aspects of the locomotor behavior expressed in different behavioral contexts. Supported by ERC grant to OK and the Swedish Research Council.

Medullary Reticular Formation Microcircuits Comprising Chx10 Neurons

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Reticulospinal neurons in many species are involved in the initiation and termination of locomotor activity. In the lamprey, reticulospinal (RS) neurons have 3 distinct firing patterns that correlate with starting, maintaining, or stopping locomotion. In the mouse, some Chx10 positive neurons of the medullary reticular formation (medRF) have been shown to be RS, and they have been implicated in initiation and cessation of locomotion. We therefore asked whether subpopulations of Chx10 neurons could be identified in this region. The purpose of this study was to characterize the electrophysiological properties and connectivity patterns of Chx10 neurons in the gigantocellular nucleus (GRN) of the medRF. This was achieved by 1) recording subthreshold and rhythmic firing properties of Chx10 neurons, and 2) using a spatial light modulator system to dissect connectivity, by photoactivating presynaptic Chx10 neurons while recording post-synaptic responses in other Chx10 neurons in transverse slices of the rostral medulla. We found two discrete Chx10 populations (termed type 1 and type 2) based on their morphology, electrophysiological properties, and connectivity patterns. Compared to type 2 neurons, type 1 neurons are larger, have greater dendritic branching, fire rhythmically as opposed to bursts, and have little to no sag potentials. Synaptic mapping revealed type 1 neurons do not receive inputs from other type 1 neurons but receive input from type 2 neurons. Type 2 neurons show high connectivity with other type 2 neurons and do not receive input from type 1 neurons. Our results demonstrate that Chx10 medRF neurons are not a homogenous population, with the presence of at least two discrete subpopulations based on their respective morphology, electrophysiological properties and connectivity patterns.

Transcription Factor Profiling of the Vestibulospinal System in Mouse and Chicken Embryos by RNA Sequencing and Immunohistofluorescence

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Vestibulospinal neurons are organized into discrete groups that project from the brainstem to either the ipsilateral or the contralateral side of the spinal cord, enabling animals ranging from agnathans to humans to maintain proper balance and posture. Our previous studies in the mouse and chicken have demonstrated that the ipsilateral lateral vestibulospinal tract (LVST) group derives from rhombomere (r) 4, the contralateral medial vestibulospinal tract (cMVST) group derives from r5 and part of r4, and the ipsilateral medial vestibulospinal tract (iMVST) group derives from r6. To characterize differential transcription factor expression in the LVST and cMVST, we performed RNAseq analysis on manually sorted retrogradely labeled LVST and cMVST neurons in embryonic day (E) 13.5 mice and embryonic day (d) 7.5 chickens. RNAseq of more medial regions of r4 and r5 was performed to exclude pan-neuronal and rhombomere-generic transcription factors. Highly differentially expressed transcription factors were further investigated by immunohistochemistry and 3D reconstruction at E13.5-15.5 in the mouse and d7.5-9 in the chicken. RNAseq analysis revealed over 100 differentially expressed transcription factors, and immunohistochemistry corroborated the same group-specific expression patterns for several of these in the two species, including patterns that defined intragroup subpopulations. In the mouse, a specific set of 3 TFs was expressed in nearly all LVST neurons, and a distinct set of 4 TFs was expressed in nearly all cMVST neurons. Concurrent immunolabeling with the three LVST-related transcription factors combined with 3D reconstruction showed overlap exclusively in the LVST, a small domain immediately rostral to the LVST, and a domain immediately caudal to the LVST. The caudal domain overlapped with the iMVST. Neither the caudal nor rostral domain were labeled by a mouse r4 lineage specific reporter line, demonstrating a transcription factor profile specific to the LVST at E13.5. These data provide new information about the transcription factors that differentially specify the three vestibulospinal neuron groups and that define distinct neuron subpopulations within them.

Neural Mechanism of Optimal Limb Coordination in Crustacean Swimming

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Effective locomotion arises from the integration of central neural circuits, muscle dynamics, mechanical interaction with the environment and proprioceptive feedback to the central neural circuit. In vertebrates and arthropods that walk and swim using limbs, the movements of different limbs must be synchronized, and the phases and forces of each limb's movements must be adapted to changes in behavioral requirements. Crayfish, krill, lobsters, and other long-tailed crustaceans swim by rhythmically moving limbs called swimmerets. Movements of adjacent swimmerets maintain an approximate quarter-period phase difference, with the more posterior limbs leading the cycle. Here, we show that this frequency-invariant stroke pattern is optimal from a fluid dynamics point of view, and explain how this optimal behavior arises from the synaptic dynamics and network topology of the crayfish swimmeret neuronal circuit.
Specficially, we first simulate numerically the fluid-limb interaction, and show that the back-to-front quarter-period delayed limb coordination is the most effective and mechanically efficient stroke pattern. We then show that the asymmetric network topology and the strong mutual inhibition in the swimemret central pattern generators combine to provide a robust neural mechanism for generating this optimal stroke pattern. Given the high metabolic cost of crustacean swimming, our results suggest that natural selection has pushed the swimmeret neuronal circuit toward a network topology that produces this optimal behavior.
Future work will be devoted to a complete neuromechanical model that includes the key neural components, a realistic musculoskeletal periphery and interactions with the fluid environment in the aim to extract general principles of neuromechanical control.

Sensorimotor Circuit Function in Orientation and Avoidance - A Common Vertebrate Plan

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Sensory-based decisions for redirecting gaze involve the interaction of subcortical and cortical circuits. The optic tectum (superior colliculus in mammals) is central for multisensory integration and motor control of gaze movements (both orienting and aversive). The interaction between multisensory afferent inputs, the basal ganglia and cortex with local tectal circuits play a determinant role in guiding gaze - the synaptic integration of which remains unknown on the cellular, synaptic and circuit level.
We have previously shown using the lamprey that the tectal GABAergic system is necessary for generating visual stimulus selection through a process of local excitation and global inhibition for the direct regulation of activity in brainstem projecting neurons[1]. We found that retinotopic recruitment of GABAergic neurons across the tectum is integrated directly by tectal output cells. Recently, we have also shown that two senses (visual and electrosensory) converge onto the same output neurons with monosynaptic excitatory connections, and that the evoked synaptic currents from the two inputs summate thus potentiating each other when they are aligned in space and time[2].
Here, by taken a systems approach, we developed an isolated preparation that maintains eyes, brain and spinal cord intact enabling us to simultaneously monitor neural responses from the optic nerve, optic tectum (and other brain areas), extraocular muscles and ventral roots, while delivering various types of visual stimuli ranging from dots, bars and looming in a computer-controlled environment.
By monitoring neural activity in the ventral roots of the same segments in the rostral spinal cord and deep layer tectal activity, we identified two distinct motor response patterns selective to the specific type of looming visual stimuli. Fictive orientation or evasion to or away from a stimulus, respectively, were characterized based on recording assymetries in the ventral root burst, i.e. ventral root bursting on the ipsilateral side to the screen would be fictive orientation and vice versa. Fast looming stimuli and vertical bars would induce fictive aversion, whereas slow looming stimuli would induce fictive orientation (n = 6). This selectivity is abolished when we removed the action of the local inhibitory system with GABAzine and/or disrupted glutamatergic synaptic transmission in the tectoreticular pathway with Kynurenic acid. We controlled this effect of tectal activation and inactivation by recording extracellular activity during the visual stimulus presentation as a measure to determine the causal role of tectum in gaze action selection.
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Behaviorally Selective Firing Dynamics Differentially Engage Motor Output Circuits

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Defining when and how the motor cortex engages downstream circuits that drive movement remains challenging. Across a broad range of behaviors, motor cortical neurons fire in patterns that correlate strongly with muscle activity[1] and electrical stimulation of motor cortex demonstrates the ability of neuronal firing to influence muscle activity[2]. Yet inactivation of motor cortex has led to a view that its functional role may be limited to movements that are novel or dexterous, or those that require sensory-guided adaptation[3]. To clarify the logic of motor cortical control of spinal output systems, we have used optogenetic perturbation and neural recording together with electromyography (EMG) in mouse to examine the influence of motor cortex on skilled forelimb movements, and in parallel on untrained treadmill walking. We developed a behavioral paradigm in which head-fixed mice are trained through an incremental shaping procedure to reach toward and grasp a joystick before pulling it a set distance – a precision pull task. Unilateral motor cortical injection of muscimol, as well as ablation of motor cortex, markedly diminished task performance, demonstrating a requirement for motor cortex in task execution. To quantify movements, we recorded the activity of forelimb muscles with chronically implanted EMG electrodes. Rapid optogenetic silencing of motor cortical output using *vGAT*-targeted activation of inhibitory interneurons during precision pull caused muscle activity time series to deviate from controls within 10 ms. Such short-latency effects were not observed during treadmill walking. Thus motor cortex operates in distinct control modes depending on behavioral context. To probe the origins of this differential influence on motor tasks, we performed population-level analysis of neural activity recorded in motor cortex during the two behaviors. Our analysis points to a mechanism based on differential coordination of firing patterns across motor cortical neurons. Motor cortical firing was correlated with muscle activity to a similar degree during the two behaviors, yet correlations between neuronal firing patterns were dramatically different. Observed changes in neuronal correlation indicate that motor cortical activity varies along different directions in a neural activity space in which each cardinal dimension represents the firing rate of an individual neuron. Such changes permit a divergent functional impact of motor cortex on downstream effector circuits. Our findings both reveal, and indicate a mechanism for, behavioral selectivity in the influence of motor cortical activity on motor output.

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