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Studying motor cortex function using the rodent vibrissal system

Challenges in understanding motor cortex function

The idea of the existence of a cortical region responsible for the control of different muscle groups was first promulgated by Hughlings Jackson in the 1870s [45], based on his observation of seizures or muscle twitches travelling across adjacent body parts in epileptic patients. These 'marching spasms' led him to postulate that the representation of these muscle groups were related to each other in the brain. Such a cortical map was indeed demonstrated by Gustav Fritsch and Eduard Hitzig [30] in their pioneering experiments involving electrical stimulation of the neocortical surface in dogs, and since then have been replicated, among others, in humans [63, 69], monkeys [6, 77], dogs [12], cats [21, 22], mice [51, 61, 62], and rats [41]. Using stimulation via intracortical microelectrodes (ICMS), it became quickly clear, however, that the muscle map demonstrated by the pioneering studies with coarse surface stimulation does not hold on the small scale. Rather, the motor cortex map appeared as a heterogeneous 'mosaic of small discrete zones', only a few hundred micrometers wide, with particular muscles receiving convergent input from a wide area of the cortical surface. In addition, from an anatomical perspective, the existence of long range horizontal connections in the motor cortex [14, 58] and the large divergence/convergence of widespread corticospinal motor cortex neurons onto motoneurons [13, 27, 28, 49, 50, 53, 64] integrate diverse inputs to diverse sets of muscles and strongly argue against the presence of a precise map of muscles in M1. Marc Schieber [68] postulated that the cortical representations on the larger scale that had been described earlier could have in fact been due to the concurrent excitation of many such scattered zones with high currents.

These findings led to the idea that movements (rather than muscles) were represented in the motor cortex. An expression of this notion was the idea, first expressed by Apostolos Georgopoulos, that variables describing the trajectories of movements, like the direction of movement, rather than patterns of muscle activity are coded by the motor cortex [31, 56, 57, 70]. The development and the remarkable success of so-called brain–machine interfaces, decoders that translate trajectory information carried by motor cortex neurons into sensible and precise movements of external actuators (e.g., robot arms), lend substantial credence to this view [19]. Graziano et al. addressed this debate in the early 2000s by demonstrating that long trains of electrical stimulation elicit complex, behaviorally relevant, multijoint movements such as feeding and defensive postures and that the sites evoking these various movements were clustered on the surface of M1. Comparing trajectory endpoints of those complex movements evoked from neighboring points on the cortical surface, they suggested that large parts of primary motor and premotor areas map trajectory endpoints in 3D space surrounding the body [1, 33, 34, 35, 36].

A troubling fact about ICMS is that it severely distorts natural local cortical activity [11], such that the cortical dynamics evoked by ICMS cannot explain the smooth and naturalistic movements observed after long ICMS. A possible solution to this problem comes from the observation that the movements described by Graziano et al. [7, 8] resemble the force fields obtained by direct spinal stimulation in frogs. Force fields are movements that end at a certain end point irrespective of the initial position of the moved limb. Importantly, different spinal sites of microstimulation reveal different endpoints of the respective evoked trajectories. These findings suggested that the spinal cord contains a detailed, varied and hardwired machinery for leg movements and a mapping for these end points, which Bizzi called 'equilibrium points'. If those circuits can be differentially activated by the rather coarse tool of microstimulation, then it is also feasible that the motor commands descending from the motor cortex can do the same. In the following, we will use the term central pattern generator (CPG) for any subcortical network that receives higher level motor commands and transforms them into low level patterns of muscle activation. In view of Graziano's experiments it appears feasible that high-level motor commands may access a subset of spinal or brainstem CPGs to drive the muscles in the intended way.

Simpler CPGs than those considered above for complex nonrhythmic limb movements have long been thought to drive rhythmic movements such as sniffing, whisking, licking, mastication, and locomotion in different mammals. For mastication and whisking, it has been
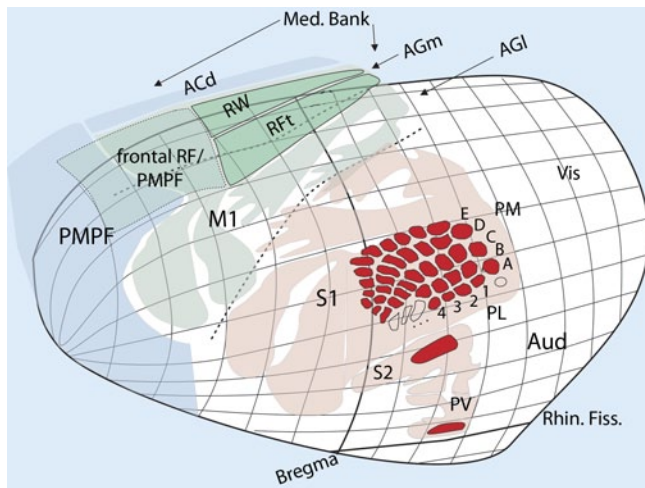
Fig. 1 ▲ A surface map of the rat sensorimotor cortex. The primary somatosensory cortex (*S1*) and tactile, partly multimodal, association areas are depicted in *light red*. Motor areas are in *light green* and premotor/prefrontal areas in *light blue*. The *strong colors* indicate whisker representations. The modularity of the primary motor cortex (*M1*) whisker representation (*VM-Cx*) is indicated. The rhythmic whisker area (*RW*) reaches the dorsal surface of the neocortex but likely extends well into the medial bank. The barrel cortex recipient zone (*RFt*) is located on the dorsal surface of the neocortex. Frontal RF and whisker representations in the premotor/prefrontal cortex (*PMPF*) are little investigated. Their delineation is unclear and within PMPF the detailed topography of limb and head representations is not consistent in the data available today. To indicate this uncertainty, these modules have been paled in color and limits are depicted by *broken lines*. *ACd* dorsal anterior cingulate cortex, *AGm* medial agranular cortex, *AGl* lateral agranular cortex. *Thick broken lines* indicate borders between AGm and AGl and between AGl and S1. *S2* secondary somatosensory cortex, AGm houses the head and whisker representations while AGl houses trunk and limb representations (*indicated by arrows*), *PV, PL, PM* posterior ventral, lateral and medial cortex, *Aud* auditory cortex, *Vis* visual cortex. *Med. Bank* medial bank of the hemisphere (the parts of the map extending into the medial bank are folded up for clarity. *Rhin. Fiss.* rhinal fissure. The coronal section line corresponding to anterior–posterior coordinate 0 is labelled *Bregma*

demonstrated that cortical microstimulation is able to drive the CPG, if the stimulation lasts at least a few hundred microseconds in order to let the movements devolve [40, 44]. The case of locomotion is more complex. It cannot be elicited by simple microstimulation in M1, but a large body of work, making use of spinalized and deafferented animals, indicates that a CPG for locomotion exists on the spinal level in mammals including cats, dogs, and monkeys. Furthermore, the performance of the spinal CPG for locomotion can be improved by electrical stimulation and pharmacological intervention [37, 38, 73]. The most complex and elaborate situation is found with nonrhythmic limb movements like the ones mentioned to exist in frogs but prominently expressed in reaching and grasping of primates. The

challenge here is that arm/hand and finger movements generate trajectories that are continuously mapped in 3D space and that a respective continuous mapping has been found in the motor cortex [33]. Thus, if CPGs for these movements exist, they would have to be organized in a continuous fashion as well: an incremental change in location within M1 would result in an incremental change in activation and/or the recruitment of a subset of a presumed reaching CPG. With respect to the quest to prove the existence of CPGs and to elucidate their properties, these are complicating factors and do not constitute favorable experimental preconditions, because incremental positional changes in M1 can always be interpreted as distinct neuronal activity in motor cortex driving the different muscle subgroups directly. For in-

stance, it has been recently demonstrated by the group of Krishna Shenoy that motor cortex population activity shows signs of quasirhythmicity expressed as rotatory components in the state–space trajectory of population firing [17, 72]. These findings clearly liken motor cortex attractor dynamics to rhythmic activity classically attributed to CPGs. For hand reaching movements in primates at least, these results, therefore, could be interpreted in favor of motor cortex participation in CPG activity (i.e., being involved in the task to transform movement ideas to concrete patterns of muscle activations), an idea fitting the unique existence of direct connections of motor cortex to motoneurons only found in primates. However, the fact that complex and naturalistic arm and hand movements can be readily evoked by ICMS in M1 [33], which, as mentioned, completely abolishes any naturalistic local neuronal dynamics, speaks against this view. Thus, whatever the reason for rotatory attractor dynamics during preparation and execution of reaching movements in the motor cortex, they do not seem to be necessary for the type of arm/hand movements observed with long ICMS in the motor cortex.

In summary, at present it is not clear which signals M1 holds—ideas and convincing underlining evidence range from abstract variables within an attractor network [72], via dynamic variables [46, 71] to kinematic variables [31]. Whatever M1 does, it becomes increasingly clear that it organizes movements on a rather abstract control level. The detailed conversion of M1 signals into detailed muscular commands is largely done by subcortical CPG networks of quite variable degrees of complexity. In primates, this statement seems to be generally true as well, despite the existence of direct connections of M1 (and S1) to motoneurons [64]. Our lack of knowledge concerning the organization of even the simplest of these CPGs may, thus, be the main reason why deciphering the M1 signals strikes us as an insurmountable problem. The general abstinence of M1 from direct muscular activation does not mean that the mentioned signals—from attractor to kinematics—are not needed on its level of organization. They all are plausible constituent parts of senso-

rimotor and cognitive processes leading to the generation of flexible and meaningful movement. However, we still do not know whether and in which form each of these signals must be fed to the varied CPGs to realize the intended movement. The consequence in the search for promising experimental strategies is that we need simple model systems in which CPGs are organized in a very simple, accessible fashion. Also we deem it advantageous if motor cortex mapping is discrete with quite different classes or types of movement mapped within the confines of motor cortex topography. This would allow us to determine whether discontinuous changes of movements evoked from neighboring cortical sites are matched by corresponding changes of subcortical connections to entirely different CPGs—greatly increasing the chances to identify and explore them. In the remainder of this article we will argue that the modularity of the rat vibrissal motor system offers great future potential that will be highly useful for the outlined experimental strategy.

Modularity of the rat vibrissal motor cortex (VMCx)

The first ICMS-based map of rat M1 [41] confirmed the location of M1 to be in the frontal and dorsomedial areas of the neocortex and a movement map that represents large body parts in a topographical fashion (◘ **Fig. 1**). The M1 agranular cortex is composed of a lateral and a medial agranular area (AGl and AGm), two areas differing in relative thickness of layers 3 and 5. Layer 3 is prominent in AGl, but thins toward AGm within a transition zone (TZ). Layer 5 shows the reverse tendency—it is relatively thick in AGl and then thins down in TZ to reach medium thickness in AGm [23, 74, 78]. An ICMS study [59] and an in vivo intracellular study [10] revealed that the border between AGm and AGl aligns with the border between the head/vibrissal and the trunk/paw representations. Matching this observation, AGm sends its major projection to the colliculus superior, while main target of the AGl is the spinal cord [59].

The representation of the vibrissae within M1 (VMCx), confined to the AGm, appears to be largely magnified, oc-

cupying around 20% of the motor cortical area. Some authors have found single vibrissae responses, but no study so far has been able to come up with a generally accepted topographic map of the vibrissal pad. Rather the number of moving whiskers was reported to depend on the type and depth of anesthesia. Evoked movements in awake animals and lightly ketamine anesthetized animals were observed to encompass many if not all whiskers while other anesthetics, and generally deep anesthesia decreases number of moving whiskers [9, 40]. Even single cell intracellular stimulation in vivo consistently yielded movement of several whiskers, supporting the hypothesis that muscle synergies rather than individual muscles are represented in VMCx [10].

Via which pathways does VMCx activity reach the vibrissal musculature? Direct connections of the VMCx to the motoneurons in facial nucleus innervating the vibrissal pad have been reported to be either absent or extremely sparse [3, 39, 42, 54], so that, in our view, direct control of motoneurons can be assumed to be of minor importance. VMCx, however, does project strongly to a number of intermediate structures in the midbrain and brainstem that project in turn to the facial nucleus and, thus, must be considered candidate projections connecting VMCx to distinct CPGs driving vibrissal movements and coordinating them with head and body movements. Specifically, candidates for an oligosynaptic connection between VMCx and the facial nucleus have been reported to be the reticular formation, superior colliculus, nucleus ambiguous, and the deep mescencephalic nucleus, the periacqueductal gray, the interstitial nucleus of the medial longitudal fascicularis, and the red nucleus [3, 42, 54, 65].

As discussed for the primate motor cortex above, there is mounting evidence that VMCx is systematically connected to different CPGs and, thus, represents different types of whisker movements in a modular fashion. At present four such candidate modules can be distinguished. There are three presumptive modules in VMCx, two of which have been identified by the different kinds of movements evoked by long ICMS in awake animals, a

Abstract

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### Studying motor cortex function using the rodent vibrissal system

Abstract

The function of the mammalian motor cortex was one of the first problems studied in neuroscience. But until today, the major principles of the workings of the motor cortex have remained conjectural. It is clear that motor cortex holds a topographic map of body parts. But does that mean that the motor cortex itself is undertaking the challenging task of converting motor plans (i.e., intended trajectories and effects of actions) into low level motor commands appropriate to drive the muscles? Work of many decades on motor function has revealed the existence of dedicated networks, the so-called central pattern generators (CPGs). Many, if not all of these CPGs, are located subcortically and are likely to be involved in the translation of motor plans into actual muscle contractions. Unfortunately the detailed circuitry and cellular elements of CPGs are only vaguely known. More recent work has elucidated continuous as well as discontinuous (discrete) mapping of the motor cortex to movement. For the quest of understanding motor cortex–CPG interactions, discontinuities are important because they allow us to dissect how neighboring motor cortex sites connect to different CPGs for different purposes—but driving the very same muscles. The rodent whisker motor system is a decidedly modular system. Neighboring cortical areas drive very distinct whisker movements used by the animals in different contexts. We argue that the modularity of the whisker system together with its great accessibility is promising to establish a model system for the interactions of the motor cortex and CPGs on the cellular and network levels and, thus, will also be of high value in understanding the more complex and continuously organized motor cortex of the arm/hand/finger system in primates.

Keywords

Head-fixed awake rodent · Whisking · Motor cortex · Central pattern generator · Animal model

smaller caudomedial one evoking rhythmic whisking (RW) and a larger frontolateral one evoking whisker retraction accompanied with other face but also body movements (RF) [40]. RF as originally de-
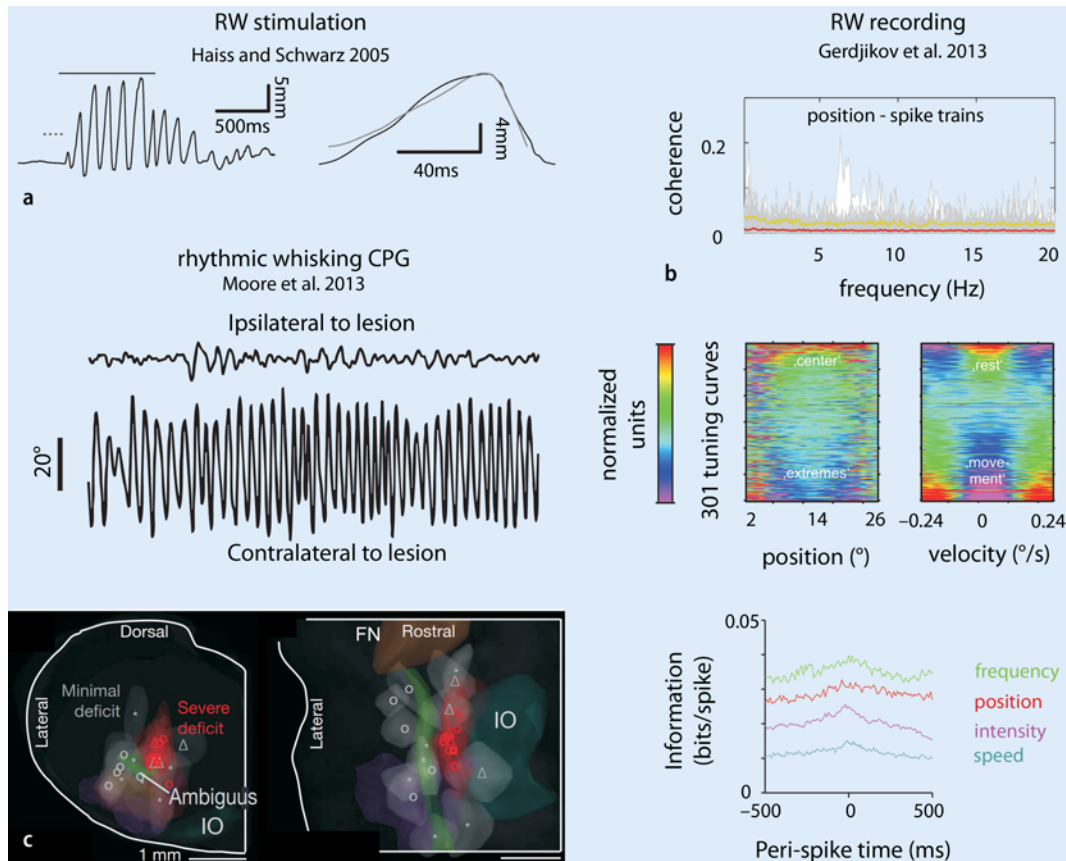
Fig. 2 ▲ Functional organization of RW and rhythmic whisking CPG. **a** Rhythmic whisking evoked by long ICMS in RW. The *line* above the whisker trace on the *left* indicates the duration of 60 Hz ICMS. *Right* Individual strokes, one evoked by ICMS (*thin line*) and another voluntarily generated by the rat (*thick line*). The close similarity between the two argues in favor of the action of a CPG as cortex activity itself is grossly distorted by ICMS. (Modified from Haiss and Schwarz [40] with permission). **b** Unitary recordings from RW in awake head-fixed animals engaged in a whisking task. *Top* Coherence between the spike train and the whisker position trace. The coherence function of all RW units is low and flat, excluding any significant stroke-by-stroke coding in RW (which would be expected to show up as significant coherence in the range of whisking frequencies (ca. 5–15 Hz) (*line colors: gray* individual single (n=301) and multi units (n=261); *red* median of distribution; *yellow* 90% percentile). *Center* Color coded tuning curves for position (*left*) and velocity (*right*) calculated from spike trains of 301 single units. The tuning strength (color code) is scaled in normalized units. Note that the units were ordered according to the coefficient of the first principle component obtained from the sample of tuning curves to reveal different types of tuning (i.e., the location of tuning curves in the two stacks does not correspond to the same cell). The types of tuning encountered in the sample are indicated as 'center position', 'extreme position' as well as 'rest cells' and 'movement cells'. Note that these types are not clearly demarcated cell classes but occur in a continuum. *Bottom* Average Shannon information carried by a single RW spike about the whisker trajectory at a certain latency. Information transferred from different whisking variables are shown. A bootstrap procedure using scrambled spike trains indicated that the majority of RW neurons convey significant information about the whisker trajectory. Importantly, information about a large interval around the spike (time 0) is present, making a pure causal role of RW for whisker movement unlikely. An interesting possibility is that RW is reciprocally connected to the rhythmic whisking CPG and, thus, also monitors internal movement signals. (Modified from Gerdjikov et al. [32] with permission). **c** The rhythmic whisking CPG. *Top* Two whisking traces ipsilateral and contralateral of the electrolytic lesion in the medulla are shown. Rhythmic whisking requires intactness of the lesioned site in the medulla. *Bottom* Effective lesion (*red symbols*) sites in the medulla as seen in the frontal (*left*) and horizontal planes (*right*). The location of the rhythmic whisking CPG is in the ventral intermediate band of the reticular formation (*vIRt*). *FN* facial nucleus, *IO* inferior olive. *Ambiguus* nucleus ambiguous. (Modified from Moore et al. [55] with permission)

fined by the study of Haiss and Schwarz [40] can be divided apart into two areas (◘ **Fig. 1**). One located around TZ that is distinguished by its prominent and reciprocal connections input from the whisker representation of somatosensory cortex (barrel cortex) [74] and a frontal one. In the following we will refer to these two distinct subareas as the 'tactile RF (RFt) and the 'frontal RF', respectively. Both give rise to retraction movements with long ICMS, but the latter differs greatly from RW and frontal RF by the reception of the strong afferent inputs from BCx. A fourth possible module is located rostral to M1 in vibrissal representation of pre-

motor and prefrontal cortex (PMPF; [60, 76], ◘ **Fig. 1**).

In the following we will focus on the two presumptive modules that were analyzed in functional terms by several studies, the RW and the RFt, and refrain from discussing the two rostral ones (frontal RF and PMPF), as further work is needed for

their proper delineation and functional characterization.

Rhythmic whisking area

Guided by the work of Graziano in the monkey, and an earlier study in the rat, describing separate whisker protraction and retraction motor regions [67], Haiss and Schwarz [40] used long pulse trains at 60–100 Hz in awake, chronically implanted rats. They found that VMCx could be subdivided into two distinct regions, which caused whisker retraction and complex face movements (RF), and another that caused naturalistic rhythmic whisking without any other movements (RW) [40]. The presence of RW and RF modules were confirmed also in the mouse VMCx [26].

The rhythmic whisking trajectories initiated by electrical stimulation in the RW region were virtually indistinguishable from self-initiated whisking and occurred at natural frequencies ([40], **Fig. 2a**). Under anesthesia, depending on the anesthetic, these rhythmic movements are either strongly reduced or absent [20, 40]. Electrophysiological recordings in RW in awake whisking rats [32] revealed that kinematics of whisker movement is coded exclusively on a long time scale (in the range of seconds) excluding any contribution of RW to the computation of whisker trajectories on a stroke-by-stroke level which typically happens in the frequency range between 7 and 12 Hz (**Fig. 2b**). Two independent variables describing whisker movements are encoded. One is the whisker position and the other is velocity, intensity, or frequency (the three latter variables appeared highly correlated within a typical whisking trace). Many neurons are active during whisker rest and decrease their firing rate during movement. These findings are not compatible with the notion of a low level motor function of RW and support the existence of a rhythmic whisking CPG. Such a CPG located in the ventral part of the intermediate band of the reticular formation (vIRt, medial to the ambiguous nucleus pars semicompacta and near the pre-Bötzinger complex) was revealed recently by the work of Deschenes et al. ([55], **Fig. 2c**). The slow positional RW

signals can be interpreted as coding for the set point (i.e., the average whisker position during a whisking bout), while slow velocity/intensity/frequency signals may set general parameters of rhythmic movements around that set point. Furthermore, RW may provide a go (movement cells) and stop signal (rest cells). These high level movement signals together with the confined location of the rhythmic whisking CPG in the brainstem are promising cornerstones for future establishment of a model system of M1-CPG interaction. The rhythmic whisking CPG contains neurons that respond phase locked to different phases of the whisker rhythm. Their inactivation abolishes rhythmic whisking ([55], **Fig. 2c**). Once the connectivity of RW and/or or other modules to the rhythmic whisking CPG is morphologically clarified, this model system has a good chance to be simple and confined enough to be amenable to decipher the functionality of local CGP circuits and their modulation by corticofugal terminals. The possibility that RW lacks significant preparatory activity and conveys information about the whisking trajectory of the past as well as the one in the future suggests that RW may causally influence as well as monitor whisking movement [32]. An interesting further lane of investigation should be the possibility that RW is interacting in reciprocal ways with the rhythmic whisking CPG.

The area RFt

Around TZ, an area responding to long ICMS with whisker retraction movements, direct tactile inputs originating from septal columns in BCx have been described using tract tracing and electrophysiology [4, 5, 15, 16, 18, 47, 48, 52, 54, 66, 74, 75]. The inactivation of the S1 barrel cortex has been shown to abolish sensory responses from M1 of anesthetized rats to peripheral whisker stimulation [5, 16, 25]. A study that, considering the reported stereotactic coordinates, most likely recorded in the area we call here RFt, initially suggested that this area of VMCx represents the rhythmicity of explorative whisker movement [2]. However, unit recordings there revealed that the modulation of unit firing rate with the whisker rhythm was weak

and infrequent [43]. Over-representing the best of these rare units in a probabilistic model enabled Hill et al. [43] to reconstruct the detailed whisker trajectory from synthesized population activity. However, whether such a biased read-out is actually realized in M1 remains an open question. Apart from these considerations, it is not clear how the suggested coding for rhythmic whisker trajectory [43] can be reconciled with the whisker retraction and other body movements observed with long ICMS form this area [40]. A closer match between ICMS-evoked movements and the neuron's movement representation was found in a study employing an orientation task [24]. Judging from the stereotactic coordinates of electrode placements, these authors presumably were also recording in the RFt. They found that individual neurons coded well for the direction of an orientation response, which typically consisted in whole body orientation movements with concomitant whisker retraction. Inactivation of the studied M1 site resulted in deficits of task-related orientation movements. Furthermore, the significant correlation of spike activity with orientation direction, present even in a memory period before execution of the movement found by Erlich et al. [40], together with the earlier results with long ICMS, argues in favor of a role of this area in the coordination of whisker, head, and body movements. The CPG intercalating these movement signals with muscles is likely to be spread out more widely involving brainstem (whiskers, face, neck) as well as spinal circuits (body). Differential analysis of brainstem connectivity of RW and RFt should help to clarify this question in the future.

Summary and outlook

We hold that the VMCx in rodents promises to be a relatively simple and useful model system to understand how the motor cortex contributes to the realization of movement. A widely accepted view is that the motor cortex acts on diverse subcortical circuits, the CPGs, which take over the task to interpret the rather abstract, high level motor commands issued by the motor cortex and

transform them to low level motor instructions driving the muscles.

It is worth pointing out that this view originates from studies in the primate motor system, which does show direct projections to motoneurons and, thus, does not require to posit the existence of neuronal structures intercalated between M1 and motoneurons. The reason for the unique presence of the direct projection in primates and its detailed function is unknown. But the naturalistic movements in primates observed with long ICMS, which disrupts local neuronal dynamics, is a clear indication that the main bulk of low level control of motoneurons/muscles is carried out by external CPGs. In monkeys the trajectories of reaching movements evoked by long ICMS are mapped in a continuous fashion on the surface of the cortex. However, there are instances, in which the mapping becomes discrete and modular because entirely different types of movements are mapped. In the primate motor system such an instance is an area in which defensive movements are mapped next to reaching movements involving the same muscles. Furthermore, discrete modules may be mapped on a scale too small to be differentiated by ICMS. Arguably, such discontinuities are most promising as these are the instances where neighboring cortical sites likely take effect on disjunctive CPGs and, thus, allow us to dissect these connections and the associated CPGs.

The VMCx offers a model system to investigate just that in great detail. Albeit the VMCx is only in the course of being established as model system, and a lot of detailed knowledge is still lacking, it seems clear that the simple whisker movement are not mapped continuously in M1 but in a modular fashion. Two modi of whisker movements, rhythmic explorative whisking (RW) and whole body orientation movements cum whisker retraction (RFt), have been outlined. The respective cortical modules coding for these different movement contexts are adjoining on the cortical surface but must be assumed to connect to widely differing CPG networks. Two other possible modules (frontal RF and one in PMPF) await detailed characteriza-

tion. The modularity and discreteness of this motor system offers great promise to make headway in the understanding of how the motor cortex interacts with CPGs to realize the intended movement. The roadmap to make use of the vibrissal motor system for this purpose is first a detailed and complete mapping of connectivity of the mentioned cortical modules to subcortical structures. Second, the simplicity of the rhythmic whisking CPG recently found [55] needs to be exploited—best combining in vivo work with an in vitro slice preparation—to determine in detail how the CPG is internally organized and how the motor cortex connects to the identified cellular elements of the CPG.

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Compliance with ethical guidelines

Conflict of interest. S. Chakrabarti and C. Schwarz state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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