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PERSPECTIVES

Channelling actions in motor cortex: how I_h gates cortical control of movement

Julian J. Ammer and Ian Duguid

Centre for Integrative Physiology and Patrick Wild Centre, University of Edinburgh, Hugh Robson Building, George Square, Edinburgh EH8 9XD, UK

Email: ian.duguid@ed.ac.uk;
julian.ammer@ed.ac.uk

Whether we run, throw a ball or play the guitar, volitional movement requires the generation of descending motor commands to coordinate appropriate sequences of muscle contractions. For centuries researchers have been fascinated by the simple but fundamentally important question of how movement representations are organised in the brain. As early as 1870, Fritsch and Hitzig demonstrated that electrical stimulation of specific cortical areas in the dog elicited discrete, reproducible motor movements (Fritsch & Hitzig, 1870; for an English translation see Carlson & Devinsky, 2009). This initial discovery prompted a wealth of human and animal electrical stimulation studies that developed the idea of a structured somatotopic map of the external musculature in primary motor cortex (M1), now commonly referred to as the 'cortical homunculus'. Since then, however, a more complex picture has evolved.

The development of high-resolution intracortical microstimulation (HR-ICMS) – a technique in which a single microelectrode is used to produce focal, layer-specific cortical stimulation – revolutionised cortical mapping experiments (Asanuma and Sakata, 1967). With the application of HR-ICMS it became increasingly apparent that describing M1 as a simple topographic map of individual muscles was an oversimplification. Instead, M1 contains representations of more complex, coordinated movements, where multiple different joint and muscle movements can be evoked from the same site depending on the strength and duration of the stimulus (Graziano, 2006). Although significant advances have been made in mapping movement representations in M1, the cellular and circuit mechanisms

that control the selection and execution of simple *versus* complex motor movements remain elusive.

In a recent issue of *The Journal of Physiology*, Boychuk *et al.* (2017) explore the importance of the hyperpolarisation-activated cation current (I_h) in regulating single and multiple movement representations in M1. They begin by using HR-ICMS to map sites in forelimb motor cortex where simple (i.e. digit, wrist, elbow or shoulder) or multi-joint (i.e. uni- or bilateral combinations of digit, wrist, elbow and shoulder) movements can be elicited. By applying the selective hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channel blocker ZD7288, they show an increase in the proportion of HR-ICMS sites that elicit multi-joint movements, without an increase in the overall area of the movement representation map. Thus, I_h appears to play a pivotal role in regulating forelimb movement complexity within localised areas of M1, rather than a more general role in controlling cortical excitability.

Boychuk *et al.* then explore whether experience can alter motor representations in M1 through changes in I_h expression levels. They show that electrically induced seizures reduce I_h currents in M1 layer 5 (L5) pyramidal neurons while increasing the proportion of sites eliciting multi-joint movements. In contrast to ZD7288 application, seizure induction also enhances the overall area of the M1 movement representation map. However, given the widespread cellular and systems level changes occurring during seizure induction, it is not clear whether this effect results from the selective modulation of I_h or other off-target effects. To address this potential caveat, the authors use a global HCN1 knock-out mouse to demonstrate that I_h is critical for regulating both the threshold and the extent of ICMS-driven multi-joint movement representations in forelimb M1.

But do changes in I_h affect behaviourally relevant movements? Boychuk *et al.* show that HCN1 knock-out mice display atypical reaching movements in a single pellet reaching task. The behavioural effects manifest as reaching component errors where digit to midline and elbow to midline movements are impaired. Since the global

deletion of HCN1 could affect long-range M1 inputs and/or activity in downstream motor areas, Boychuk *et al.* perform an elegant series of experiments using intracortical microinfusion of ZD7288 to selectively abolish I_h in forelimb M1. They show that task engagement is unaltered, i.e. rats perform a similar number of reaching attempts, but the accuracy with which the task is executed is significantly reduced. These results provide compelling evidence to suggest a critically important role for I_h in coordinating the execution of behaviourally relevant forelimb movements.

What are the implications for understanding cortical motor control? The findings clearly show that HCN channels play a previously unappreciated role in 'gating' single or multi-joint movements and that I_h -mediated regulation of motor cortical excitability is a necessary prerequisite for performing accurate, skilled forelimb reaches. Given the predominant expression of I_h in M1 corticospinal neurons (Sheets *et al.* 2011) and hierarchical intralaminar L5 connectivity patterns that limit cross-cell-class connections (Kiritani *et al.* 2012), HCN1 channel modulation could provide a cell type-specific mechanism to differentially regulate corticospinal neuron recruitment depending on changing behavioural demands. Moreover, I_h is under potent noradrenergic neuromodulatory control, profoundly altering synaptic integration and output selectively in M1 corticospinal neurons (Sheets *et al.* 2011). It therefore invites speculation that long-range noradrenergic input from the locus coeruleus and subsequent regulation of I_h in corticospinal neurons could provide a mechanism for channelling information to the spinal cord during movement selection and execution. Outstanding issues still to be addressed include which L5 cell type(s) underpin I_h -mediated changes in motor cortical output *in vivo*, whether apical and/or basal dendritic HCN channels regulate pyramidal neuron excitability during behaviour, and whether I_h shapes the precision and accuracy of other simple and complex motor behaviours.

In summary, Boychuk *et al.* demonstrate a crucial role for I_h in controlling single and multi-joint movement representation in M1, providing exciting new insights

into the possible cellular and circuit mechanisms that coordinate cortical control of movement.

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Additional information

Competing interests

None declared.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.