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Low-threshold motor units can be a pain during experimental muscle pain

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Neural control of muscle force while experiencing muscle pain is not fully understood yet. The idea of a differential modulation of the activity across the entire motor unit (MU) pool is highly attractive. However, whilst lower discharge rates of MUs during low-force contractions in the presence of pain have been previously observed, much uncertainty remains regarding alterations of the firing behaviour of higher-threshold MUs.

There has been considerable progress in the decomposition of MUs from high-density surface electromyograms (HD-sEMG), allowing the simultaneous investigation of the activity of many MUs. These methods are proving instrumental for advancing our understanding of the motor commands during low and high-force contractions. A good example of opening new perspectives is the work by Martinez-Valdes and colleagues (2020), recently published in the *Journal of Physiology*. For the first time, MU activity was concurrently analysed for both low- and high-threshold MUs during painful (intramuscular hypertonic saline injection) and non-painful contractions, providing novel mechanistic insight into the effect of muscle pain on the modulation of motor commands. Decomposition of HD-sEMG from both low- (20% of maximal voluntary contraction [MVC]) and high-force (70% MVC) isometric ankle dorsiflexion contractions allowed the authors to observe that in the presence of muscle pain, firing rates of low-threshold MUs are decreased, whereas firing rates of high-threshold MUs are increased and recruitment and derecruitment thresholds are lowered. These novel findings show that firing frequency and recruitment strategies are adjusted differently across the motor pool in response to muscle pain.

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Non-uniform distribution of afferent inhibitory inputs

The authors hypothesised that the observed differential modulation of MU behaviour can be explained by a non-uniform distribution of afferent inhibitory inputs across the motor pool, with greater inhibitory input distributed toward low-threshold MUs (Figure 1B). This is indeed a possible mechanistic scenario. Given that changes in muscle fibre contractile properties or synergistic-antagonist activity should not be expected, the inhibition of MU activity by acute noxious stimuli potentially necessitates a higher descending corticospinal drive to allow the successful performance of a ramp contraction to a target force. If the afferent inhibition is predominantly distributed to low-threshold MUs, the augmented descending drive would up-regulate the activity of higher-threshold MUs that are not as highly affected by the afferent inhibition, increasing their firing rate and recruiting them earlier.

Additionally, a greater corticospinal drive could result in the recruitment of a new population of MUs, as it has been shown with fine-wire intramuscular recordings. It is challenging, however, to clearly identify differences in the recruitment of MUs through decomposition of HD-sEMG. Although the number of decomposed MUs were not significantly different between conditions, the possibility of recruitment of additional MUs (e.g. new, higher-threshold MUs and/or new MUs with a different force direction) should not be disregarded.

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The potential role of persistent inward currents

Other mechanisms could have potentially contributed to the observed differential modulation of the behaviour between low- and high-threshold MUs. Motoneurons (MNs) are characterised by a strong intrinsic property: persistent inward currents (PICs), which are activated via voltage-dependent ion channels along and cause non-linearity of the synaptic input-output relationship. PICs amplify and prolong the effects of synaptic input by providing a sustained depolarising current to the MNs, accelerating initial MN firing and contributing to the repetitive firing required for muscle contractions. PICs are longer-lasting in low-threshold MUs (Lee & Heckman, 1988), and highly sensitive to inhibitory synaptic input. If experimental muscle pain actually induced a uniform distribution of the afferent inhibition across the entire motor pool, it can be hypothesised that lower-threshold MUs were more susceptible to the afferent inhibition. This differential modulation could have then been caused by a greater down-regulation of PICs in low-threshold MNs (Figure 1C), highly compromising the maintenance of firing. In comparison with high-threshold MNs, the low-threshold MNs are more dependent on lasting PIC activity than on excitatory synaptic inputs from corticospinal drive to maintain firing. Conversely, the maintenance of firing in high-threshold MNs has a reduced reliance on PICs but a higher dependence on excitatory synaptic input. Thus, a differential modulation of MU activity could be explained by the pain-induced increase of corticospinal drive to guarantee force maintenance, which possibly outweighs the decreased PICs in high-threshold, but not in low-threshold MNs. Alternatively, muscle pain could have a direct (i.e. spinal) excitatory effect on high-threshold MUs. This was hypothesised by Martin et al. (2008) who observed an increased amplitude of cervicomedullary motor evoked potentials after hypertonic saline injections, at rest and during constant-EMG contractions.

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Potential avenues for further analysis: estimation of PIC magnitude

The aforementioned PIC-related explanation is somewhat speculative and although *in vitro* and *in vivo* studies in both animals and humans have shown a reduction or full deactivation of PIC activity with synaptic inhibition, changes in PIC magnitude with muscle pain have not been investigated, to the best of our knowledge. Techniques to estimate PIC magnitude are available and we believe that the authors could conveniently explore whether there is a differential effect of muscle pain on PIC magnitude throughout the motor pool. Data already collected could be used to estimate PIC magnitude with the ΔF technique developed by Gorassini et al. (2002). This technique quantifies MU recruitment/derecruitment hysteresis (ΔF), using pairs of MUs decomposed during ramp contractions. The hysteresis of a higher threshold MU (test unit), with respect to a lower threshold MU (control unit), is the estimate of PIC magnitude and is quantified by the difference between the instantaneous firing frequency of the control unit at test unit recruitment and the instantaneous firing frequency of the control unit at test unit derecruitment. The authors could independently calculate the ΔF in different populations of MUs and track them across conditions: in the range of 0-20% (low-threshold MUs) from the 20% ramps and in the ranges of 0-35% (also low-threshold MUs) and 35-70% (high-threshold MUs) from the 70% ramps. Additionally, it would be interesting to estimate PIC magnitude in the low-threshold MUs that were identified in both the 20 and 70% ramps, to examine whether this population of MUs behaves similarly between tasks (i.e. low vs high-force ramps). Two other complementary analyses could be considered: the examination of rate modulation of MUs from the point after the initial acceleration of firing rates to peak MU

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firing by using a break point analysis, as well as the comparison of MU firing-rate profiles with respect to force, in the ascending phase of the ramp. An indication of lower PIC magnitude would be higher rate modulation, and firing rate profiles that are better fit by linear functions (rather than exponential functions). These outcomes are due to higher MN responsiveness to additional excitatory input and an attenuated acceleration of MN firing with lower PIC activity, respectively. We therefore hypothesise that down-regulation of PIC magnitude in the different populations of MUs, with a more accentuated decrease in low-threshold MUs, is a possible source of differential modulation between low- and high-threshold MUs in the presence of muscle pain.

We must be cautious with our suggestion to perform additional analysis due to existing limitations related to the way the experiments were conducted, as the primary aim of the authors was not to examine intrinsic MN properties. For instance, it should be noted that studies have previously utilised the ΔF technique only during lower force levels (<40% MVC); as such, validation of this technique at higher force levels might be required before such analysis can be undertaken. Further, the characteristics of the contractions may affect the estimate of PIC magnitude: the duration of the ascending phase and the existence of a 10-s hold-phase. It should be noted that the torque was increased at a rate of 10% MVC/s, reaching the 20 and 70% MVC target in 2 and 7 s, respectively. A minimum 1-s time difference between the recruitment of the control and test MU should be used to ensure that the PIC activity of the control MU is fully activated prior to the recruitment of the test unit. This criterion could potentially impair the ability to find suitable pairs in the 20% ramps due to the quick ascending phase. Regarding the existence of a hold-phase, Vanderberk & Kalmar (2014) observed that performing a hold-phase (rather than a triangular contraction) can inflate the ΔF,

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possibly due to a greater contribution of spike frequency adaptation. Thus, the contamination of other intrinsic properties should be considered in the proposed analysis.

Where does this leave us?

Great insight has been gained from the work of Martinez-Valdes and colleagues (2020) about how motor commands are altered in the presence of muscle pain. Further work is required to fully understand whether the underlying mechanisms are due to a non-uniform distribution of inhibitory synaptic inputs to the MN pool, and/or differential intrinsic MN properties and the susceptibility of these MN properties to inhibitory input across the motor pool. Elucidation of the exact underlying mechanisms will allow the development of strategies to possibly attenuate the inhibition of low-threshold MUs and the consequent increased activity of higher-threshold MUs. Although this compensatory neural strategy has a short-term benefit of ensuring force maintenance, high-threshold MUs fatigue faster and their prolonged activity can exacerbate muscle fatigue. Thus, attenuation of their prolonged activity is of high importance in conditions marked by an elevated nociceptive afferent input, such as chronic pain.

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ADDITIONAL INFORMATION

Competing interests

The authors declare no competing interests, financial or otherwise.

Author contributions

All authors have read and 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.

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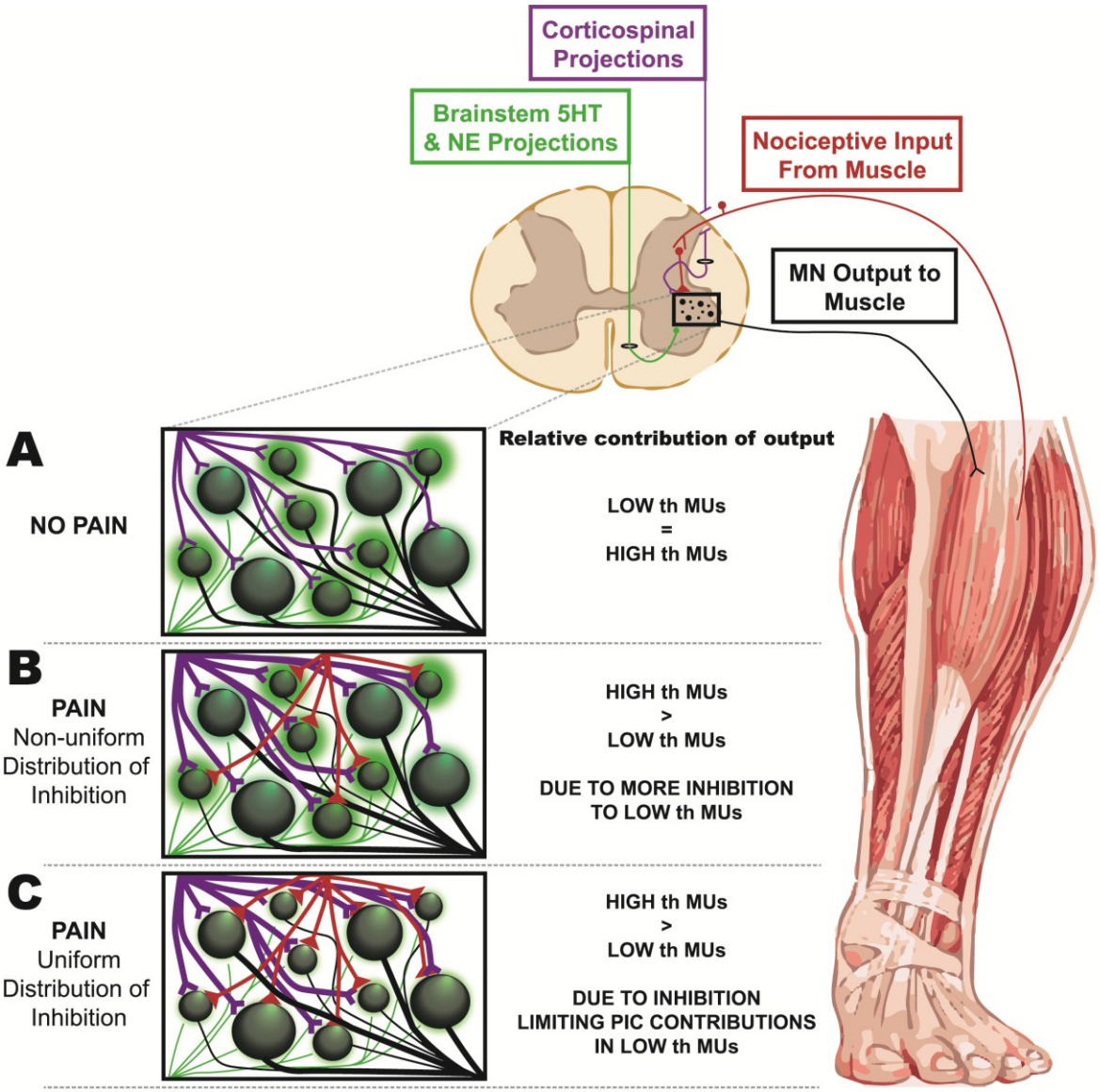

Figure 1. Hypothetical underlying mechanisms of differential changes in motor unit discharge properties during experimental muscle pain.

During muscle contractions, motoneurons receive ionotropic, corticospinal input (purple), increasing the excitability of motoneurons. This excitability is mediated by neuromodulatory input from the brainstem (green) releasing serotonin (5-HT) and norepinephrine (NE), that is particularly long-lasting in low-threshold motoneurons (the magnitude of the activity of persistent inward currents [PICs] is represented by the outer green glow surrounding each motoneuron in the panels). When no pain is present,

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there is a unifying discharge of motor units (MUs) across the motor pool (A). In the presence of pain however, there is an acute increase in nociceptive input from muscle (red), providing inhibitory synaptic input to motoneurons. This inhibitory input might be distributed non-uniformly across the motor pool, being greater in low-threshold MUs, with augmented descending drive up-regulating high-threshold MU activity to maintain force output (B). Alternatively, inhibitory input might be uniformly distributed across the motor pool, but PICs are down-regulated, disproportionally affecting low-threshold MUs that predominantly rely on them to maintain firing (C). Conversely, high-threshold MUs predominantly rely on corticospinal input, possibly outweighing decreased PIC magnitude, and resulting in maintained or increased firing on high-threshold MUs to maintain force output in the presence of pain.

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