

Spontaneous and voluntary activity in motoneurons of paraspinal musculature in symptom free and patients with acute low back pain

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and Oslo University Hospital
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To Alexandra, Tengel, Jakob & Tim

I am very comfortable with the idea that we can override biology with free will. – Richard Dawkins

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Preface

The work in this thesis has been carried out with the financial support of the Norwegian Research Council, initially in the planning and data collection phase through a fellowship position at Institute of Basic Medical Sciences at the University of Oslo, and later as a technician at Oslo University Hospital Aker and Ullevål where analysis and statistical methods were established in collaboration with a parallel project on the cervical multifidus.

This work was preceded by a pilot project that was partially funded by the Norwegian Chiropractors' Association Research Fund and made possible by the help of Jan Arve Borge, Øyvind Nilsson, Heidi Eggesbø, Tim Raven and Erling Bekkestad Rein. Thank you for taking on the challenge of exploring this field between clinical science and basic science together with me.

I wish to express sincere appreciation to my supervisor Torsten Eken for inspiring the project from inception to conclusion. He will no doubt recall receiving an email many years ago questioning whether plateau potentials and self-sustained firing could be investigated in the lumbar spine and whether they perhaps played a roll in the LBP enigma. His meticulous eye for detail, in depth knowledge of just about everything, ability to share his insights, engage me in fruitful discussions, patience, fine sense of humour and exceptionally warm heart has made this learning process both enjoyable and worthwhile. In this I would like to include Signe Søvik, who also helped us solve statistical conundrums.

I will always be in debt to Professor Terje Lømo who has made this work possible; for advice and insight when instigating the project, and for his generous support in providing room and equipment. Thanks to Professor Arild Njå for taking on the responsibility as anchoring supervisor following Professor Lømo's retirement.

A special thanks to the staff at the Department of Radiology at Oslo University Hospital - Aker, for diagnostic imaging and for performing the implantation of electrodes, particularly Heidi Eggesbø for developing and overseeing the ultrasound procedure and equally Gunnar Sandbæk for the CT implantation procedure. Likewise,

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I would like to especially recognise the research participants who gave a day of their life to take part in the experiments in hope that their contribution would add to the understanding of the low back in health and disease.

Thanks to colleagues and staff at *Klinikk for Alle* for recruiting participants and to my colleagues that have maintained my clinic in order for me to immerse myself in research. If all else fails, I still have a practice to fall back on.

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Tim, my partner in all aspects of life, including this project and the next, you being at my side makes it all worthwhile. Giving a detailed recognition of your contribution to this venture would fill the pages of this thesis from cover to cover.

Thank you!

List of papers

This thesis is based on the following papers, which will be referred to by Roman numerals (I, II and III) in the text. All papers have been submitted for publication to Journal of Neurophysiology.

- I: Lothe LR, Raven TJL and Eken T. Single-motor-unit discharge characteristics in human lumbar multifidus muscle. (Submitted).

- II: Lothe LR, Raven TJL, Sandbæk G and Eken T. Single-motor-unit discharge characteristics in lumbar multifidus muscle of acute low back pain patients. (Submitted)

- III: Lothe LR, Raven TJL, Sandbæk G and Eken T. Single-motor-unit discharge characteristics in lumbar multifidus muscle of acute low back pain patients after spinal manipulation. (Submitted)

Glossary, acronyms and abbreviations

AP	Action potential - a rapid change in the electrical membrane potential of a cell caused by a nerve impulse. Also called a spike.
ALBP	Acute low back pain.
CDC	Common Drive Coefficient – a measure of the common drive to the motoneuron pool.
EMG	Electromyography - a technique for recording and evaluating skeletal muscle activity.
HVLA-SM	High velocity, low amplitude, spinal manipulation delivered as a thrust to a joint often accompanied by a “cracking” noise.
ISI	Interspike intervals – the time between two successive spikes usually given in milliseconds (ms).
LBP	Low back pain.
LM	Lumbar Multifidus - deep muscles of the spine consisting of a number of fasciculi that works to stabilise and move the vertebrae.
Motoneuron	Neurons located in the central nervous system (CNS) that project axons outside the CNS to control muscles.
MU	Motor unit - MU is made up of a motor neuron and the skeletal muscle fibres innervated by its axon.
MUAP	Motor unit action potential - MUAPs are spikes of electrical activity in a contracting muscle recorded by EMG.
Muscle fibre	Muscle cell.
Muscle fascicle	A bundle of muscle fibres surrounded by connective tissue.
PIC	Persistent inward current – an intrinsic ionic mechanism activated as long as the membrane potential is depolarised, allowing motoneurons to respond to brief synaptic input with prolonged firing activity that persist even after cessation of the input. Self-sustained firing The motoneuron fires without modulation from other

	neurons and is dependent on plateau potentials which increase the excitability of the neuron.
SF-EMG	Single fibre EMG - electrodes recording from muscle fibres inside the muscle.
Spike Train	The temporal sequence of action potentials generated by a neuron.
Surface EMG	Muscle activity recorded by electrodes placed on the skin over the muscle.
PIC	Persistent inward current – an intrinsic ionic mechanism activated as long as the membrane potential is depolarised, allowing motoneurons to respond to brief synaptic input with prolonged firing activity that persist even after cessation of the input.
Plateau potentials	Lasting depolarisations caused by persistent inward currents (PICs) enabling the neuron to fire action potentials independent of synaptic input (self-sustained firing). Neurotransmitters such as monoamines, modulate the activity of dendritic L-type Calcium channels allowing a sustained, positive, inward current into the cell.

Summary in English

The thesis describes the electrical activity in nerve cells (motoneurons) that control the deep back muscles in humans. The experiments were conducted using thin wire electrodes that were implanted deep in the spinal muscles in nine acute low back pain patients and in nine healthy, pain free volunteers. The main focus was on the spontaneous, free activation of the postural muscles, which was also compared with voluntary activation. We studied the activity of motoneurons when subjects stood or sat quietly and during voluntary movements. The thesis describes the overall activity, firing discharge, variability in firing and the extent of common drive signals. A main finding was that activity in individual motoneurons to some extent appears to be independent of common control signals, i.e. the nerve cells maintain their activity independently (self-sustained activity). This suggests that the nervous system is able to distribute activity and rest between motoneurons over time (rotation) in the postural muscles of the spine.

We also compared the activity in healthy volunteers with the activity in acute low back pain patients before and after manipulation. The thesis describes a difference in the common drive between nerve cells on opposite sides of the spine in acute low back pain and a difference in firing variability after spinal manipulation. We also describe a different control strategy when the motoneurons fire in free activation of the postural muscles as opposed to under voluntary force production. The possible underlying neurophysiology of these findings is discussed in the thesis.

Summary in Norwegian

Avhandlingen beskriver den elektriske aktiviteten i nerveceller (motonevroner) som styrer de dype ryggmusklene hos mennesket. Forsøkene ble utført ved bruk av tynne, myke, trådelektroder som ble implantert dypt i ryggmuskulaturen hos ni akutte ryggpasienter og ni friske, smertefrie frivillige. Hovedfokus var på den spontane, frie aktivering av holdningsmuskler. Vi studerte den elektriske aktiviteten til motonevroner når personen sto eller satt stille samt under viljestyrte bevegelser. Avhandlingen beskriver totalaktivitet i muskelen rundt elektrodene, fyringsraten til motorenheter, variabilitet i fyringen og grad av påvirkning fra felles overordnede styringssignaler. Vi har funnet at aktivitet i individuelle motonevroner i noen grad ser ut til å være frikoblet fra felles styringssignaler, det vil si at nervecellene enkeltvis kan vedlikeholde sin egen aktivitet (selvbærende aktivitet). Dette medfører at nervesystemet er i stand til å fordele aktivitet og hvile for motonevronene og muskelcellene de styrer over tid (rotasjon).

Videre har vi sammenlignet aktivitet hos friske frivillige med aktivitet hos ryggpasienter samt denne aktiviteten før og etter manipulasjonsbehandling. Vi har funnet en forskjell i felles styringssignaler til motoneuronpar på hver sin side av ryggen hos akutte ryggpasienter mens hos friske er de felles styringssignalene like til par som fyrer samtidig i samme muskel som til par som er på hver sin side av ryggen når personen står. Etter manipulasjonsbehandling er det en reduksjon i fyringsvariabilitet, denne fyringsvariabiliteten kan forklares av synaptisk støy som kan være forårsaket av smerte. Avhandlingen diskuterer mulige underliggende nevrofysiologiske mekanismer og beskriver forskjeller som vil kunne være hypotesegenererende for videre forskning på friske og smertefulle rygger.

Introduction

General introduction

If you happen to be part of the species homo sapiens you are likely to experience back pain during your lifetime. If you are so unfortunate, there is a high risk of having back pain more than once. Relapses are common and 70% experience a new episode of low back pain (LBP) within a year (1). On a global level LBP is the highest ranking individual cause of years lived with disability (YLD) (2) accounting for 10.7% of total YLDs at the global level (3) If you live in Norway you share the experience of having back pain with 15-20% of the population at any time, half the population had LBP the previous year and 40% within the last month (1). The Norwegian society will let you and your fellow musculoskeletal pain sufferers rest at home with paid sick leave for the total sum of 34 billion NOK a year (1). Unfortunately, rest is not the cure. The back pain paradox is that physical activity can both be the cause and cure of the condition. If you have your back condition examined, there is an 85% chance that there are no objective findings that will give you a clear diagnosis (4) and you may fall into a different diagnostic category depending of where you seek help (5). The tissues involved in injury and causing pain can be anything from disc, nerve, muscle, tendons and joints or a combination of them. You may have worked in a bent or twisted position overloading the disc and predisposing you for disk protrusion or a prolapse. This may cause nerve inflammation and pain down your leg. You may have overextended you back causing compression injury to the joints and bony structures. If you have overexerted yourself you may experience a gradual stiffening and loss of back function. You may not have done anything at all, in fact you may have done too little and have become deconditioned and out of shape leaving you too weak to withstand the strain of daily activities. No matter the reason, you have an urge to get better. Searching public information on the Internet or in popular literature will advise you to stay active, take over-the-counter pain medication, and avoid bed rest. If this does not help, you are advised to seek professional help and you are told that receiving spinal manipulation may alleviate pain and restore function (6). Your main objective is to get rid of the pain and do whatever it takes to avoid a relapse. The normal reaction to this abnormal experience is to avoid whatever is painful. You

become afraid to move and restrict your movements. Your family and social life may suffer and your quality of life is reduced. Most of us can tolerate this for a couple of days, but there is a risk that your pain will persist and develop into a chronic condition where unrelenting pain and dysfunction is only interchanged by recurrent episodes of worse pain. If you are one of the “fortunate” back pain sufferers you may be pain free between episodes and function well between attacks.

The really alarming fact is that your back muscles will start changing their composition within days of pain onset no matter what the reason for the pain (7,8). This has been experimentally examined in young pigs where the researchers showed that pain caused by inducing injury to the disk or nerve causes changes in the back muscles within just a few days (9). The changes include fatty infiltration and breakdown of muscle cells. The undesirable change in the muscle is particularly evident in the deepest part of the muscle on the same side and same segmental level as the injury to the disc (10).

So what is the underlying cause of this apparent flaw of the human back? Is the intrinsic instability of the spine in the human upright posture predisposing the low back for injury? Is the guarding we see with back pain caused by cramping in the affected muscle, or caused by avoidance of movement because of fear of re-injury? Does the pain inhibit normal muscle activity and thereby cause atrophy? What happens to muscle activity during and after spinal manipulation? What is the neurophysiological effect of manipulation? These are the questions that led us to do the experiments that are the basis of this thesis.

First in the introduction to this thesis, some of the tissue injuries and pain theories associated with back pain are described. Second, the neurophysiology behind motor control of the spinal musculature is presented. Third, an overview of the current management of acute low back pain (ALBP) including spinal manipulation, is given. Lastly, the experiments we have conducted are explained and the results presented and discussed.

Somatic pain from nociceptive structures of the lower back

Different forms of LBP fit well into the three classifications systems currently used to describe pain (11). First, *nociceptive pain* can be part of the early-warning physiological protective system detecting and avoiding contact with tissue damaging stimuli such as acute pain from trauma. When activated, the nociceptive pain system overrules most other neural functions and aims to protect the individual from re-injury and to promote healing. Nociceptive pain arising from different spinal tissues can feel very similar and is difficult to differentiate (12). ALBP leads to increased spinal stability that is not stereotypical but involves an individual-specific response to pain (13). Secondly, LBP can also be inflammatory. Pain from a sprained facet joint, bone injury or a disc prolapse can activate the immune system and cause *inflammatory pain*. Underlying inflammatory diseases such as rheumatoid arthritis may complicate a nociceptive LBP condition caused by injury. Finally, *pathological pain*, which is maladaptive and not protective, can occur after damage to the nervous system, or in syndromes where there is substantial pain but no noxious stimulus and little to no inflammatory pathology of the spine. Psychosocial issues influence the course of LBP through the pathological pain pathway and are one of the best identified predictors for developing chronicity. In primary care, 11-28% of LBP patients have been found to belong to a high risk group for developing chronicity from psychosocial contribution (14,15).

Disc

The intervertebral disc has a gelatinous core surrounded by fibrous rings and only the disc exterior is served by the circulatory and nervous system. Injury to the anterior ligaments of the intervertebral disc can cause significant pain and has been shown to be the source of pain in 26% (16) to 39% (17) of LBP even without disc derangement. The posterior margin of the intervertebral disc is innervated by the sinuvertebral nerve branching off the ventral primary ramus and shares this innervation with other structures within the spinal canal including the posterior longitudinal ligament and the dura (18). The superficial layers of the normal lumbar disc have sensory nerve endings involving the outer lamellae and penetrating only a few millimetres into the annulus, whilst the inner annular zones are devoid of nerves (19). Nerves have been

observed to extend deeper into degenerative discs even up to the inner third in 57% of painful discs. Isolated nerve fibres are also seen in the degenerative discs but are usually accompanying blood vessels (20). Inflammatory granulation tissue present in annular tears is associated with invading nerves and blood vessels and may cause peripheral sensitisation of otherwise mechanically insensitive tissues (21,22). Modic changes are commonly seen in LBP patients (18-68%) (23), especially in patients with disc involvement (24,25), and thought to be caused by anaerobic bacteria that thrive in the injured anaerobic intervertebral disc and brought there by invading blood vessels during the healing process of an injured disc.

In addition there have been found increased numbers of mechanoreceptors in discs from chronic LBP patients (21,26). All these changes may cause sensitisation and enhance the pain experience. Further, a high proportion of nociceptive nerve fibres from the lumbar discs pass through the sympathetic trunks in a non-segmental manner and relay a form of visceral pain (27). The visceral pain concept makes spinal pain of discogenic origin unique in musculoskeletal pain and opens the door to the possibility of “central sensitisation” of descending autonomic nerves associated with a lowering of the threshold of visceral afferents (27).

Ligaments and joints

The facet joints of the spine are complicated biomechanical structures, with complex anatomy, that provide a biomechanical function of supporting loads and coupling motion affecting the mechanical performance of the spine. These are true synovial joints with hyaline cartilage surfaces, a synovial membrane and a surrounding fibrous capsule. They are oriented sagittally in the lumbar spine effectively protecting the disc from axial rotation and loading (28). The lumbar facet joints are innervated by the nociceptive fibres of the medial branch of the dorsal ramus of the spinal segmental nerves in the same way as the multifidus muscle and the interspinous ligament (18). The facet joints are located in pairs on the posterolateral aspect of each spinal motion segment and the cartilage surfaces provide a low friction interface to facilitate motion during normal conditions. Healthy joints of the lumbar spine are estimated to carry 3-25 % of the compressive load while arthritic joints carry up to half the load (29).

The facet joints have been identified as the nociceptive tissue in approximately one third of people with chronic LBP investigated using diagnostic blocks (16,30). The cause of joint pain is poorly understood, capsule tissue damage has been proposed as well as displacement or entrapment of synovial membranes and fibro-adipose meniscoids (31-33). The joints are prone to degrading due to aging, a process that can be accelerated by injury or infection. This may cause a local mechanical deficiency affecting the surrounding tissues that will either mechanically adapt or fail. Osteophyte formation, articular hypertrophy, articular thinning, formation of synovial and subchondral cysts and calcification of the joint capsule are all associated with LBP, sciatica and osteoarthritis (33). There are no radiological or clinical diagnostic tests that are reliable in identifying facet joint pain and degeneration of facet joints is never in isolation but affected by and impacts on the surrounding tissues such as disc, nerves, bone and muscles. It is therefore impossible to measure the isolated contribution of joint dysfunction in LBP.

Muscles

Muscular pain can arise from muscle sprain, muscle spasms and muscle imbalances but the neurophysiology is poorly understood. The paraspinal low back muscles consist of several layers of muscle fascicles that span from one vertebra to the next. The deepest fascicles that belong to the lumbar multifidus (LM) are short and span across two vertebrae, the more superficial the fascicles, the longer the span. LM is thought to stabilise the spine and is active in movements opposing gravity as well as in contralateral rotation of the torso (34-37). The origin of the muscle is along the spinous process and the attachment is lateral at the mammillary process or lamina of a vertebra more caudal (38). An interesting observation is that all fascicles arising from the same vertebra obtain nerve signals from the posterior branch of the nerve belonging to the same level as the origin of the muscle fascicle (18). The nerve signals from L1 is easily detected at the surface over L5/S1, whereas the nerve signals belonging to the L5 dorsal nerve is buried deep in the tissues under all the overlying fascicles origination from the vertebrae above.

Muscles have little nociceptive nerve receptors and muscular pain is believed to be inflammatory in nature arising from pain receptors around blood vessels responding to inflammation from tissue damage such as after training or overuse (39).

The cross sectional area of LM is reduced in LBP (10) and there is a characteristic fatty infiltration of the deepest part of LM in LBP patients (Figure 1).

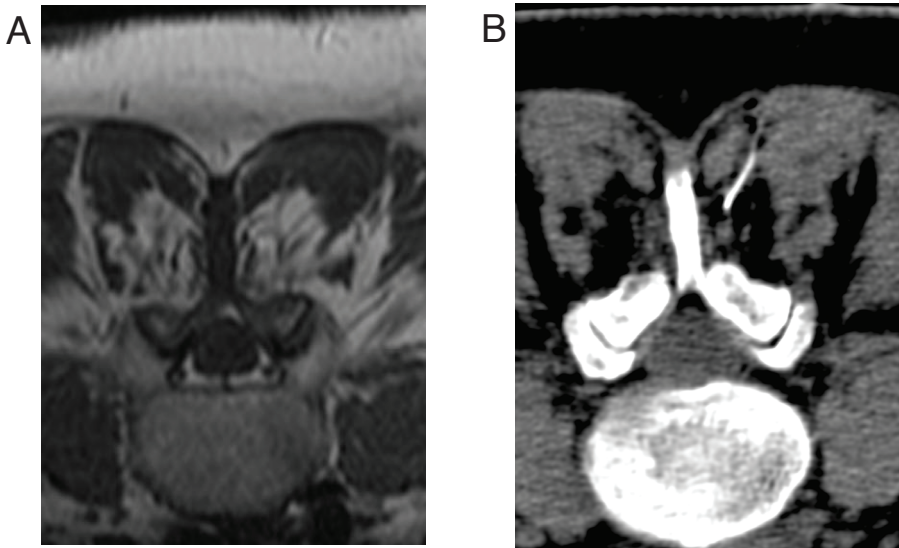


Figure 1. A) MR image showing extensive fatty infiltration of the erector spinae and lumbar multifidus bilaterally at L4. B) CT image of the same subject showing one SF-EMG electrode bundle implanted in the target muscle. There was no electrical activity, most likely due to the electrode recording from an area without electrically conductive muscle tissue.

Experiments in animal models have shown an increased EMG response from the contralateral LM after electrical stimulation of the annulus fibrosus to the lateral side of the intervertebral disc, and from the ipsilateral LM when stimulating the facet joint capsule (9,40). This indicates an interaction between injured or diseased facet joint or disc and the paraspinal musculature. It has been demonstrated in a porcine model that the cross sectional area of LM is reduced on the ipsilateral side within a week of injury to a disc at the level of disc lesion. Similarly, cross sectional area is diminished ipsilaterally two segments below the level after nerve transection of the dorsal ramus (7). Histological changes with enlargement of adipocytes and clustering of myofibres

at multiple levels have been found as well as a reduction of water and lactate levels indicating rapid disuse atrophy following reflex inhibitory mechanisms (7).

Neural structures

The mechanical and chemical consequences of pathology affecting the neural tissues in the intervertebral foramen are well established (41-47). Spinal disc herniation, degenerative disc disease, osteoarthritis as well as spinal stenosis can affect neural structures causing nociceptive pain. Pathological pain may also play a role and be associated with changes occurring in the peripheral terminals of nociceptors sensitised by inflammation. Axons may become hyperexcitable and spontaneously generate action potentials, and spinal cord synapses can undergo structural reorganisation. The neural tissues in the intervertebral foramen possess unusual anatomical properties in that they have less connective tissue support and protection than the peripheral nerve (48). This may predispose for effects of mechanical compression in the dorsal root and dorsal root ganglion, such as altered conduction velocity, disturbed axoplasmic transport and oedema of the peripheral neuron (49).

Pain modulating pathways

Nociceptive inputs from disc, joints, ligaments, bone and muscle fascia enter the spinal dorsal horn through primary afferent fibres that synapse onto transmission neurons. Ascending projections target the thalamus through the contralateral spinothalamic tract, and collateral projections target mesencephalic nuclei, and the midbrain periaqueductal grey (PAG) (Figure 2). Projections from the thalamus reach cortical sites, where cognitive and conscious perceptions of pain are integrated, as well as the amygdala where the formation and storage of memories associated with emotional events occur.

Just as there is an ascending pain pathway from the body to the brain, there is a descending pathway that allows the brain to modulate pain. The brain uses descending pathways to send command signals down to the spinal cord to modulate the pain message sent up by the pain receptors. Thus, the primary role of the descending pathways is to close the pathways in the spinal cord to ascending messages (for review see (51)).

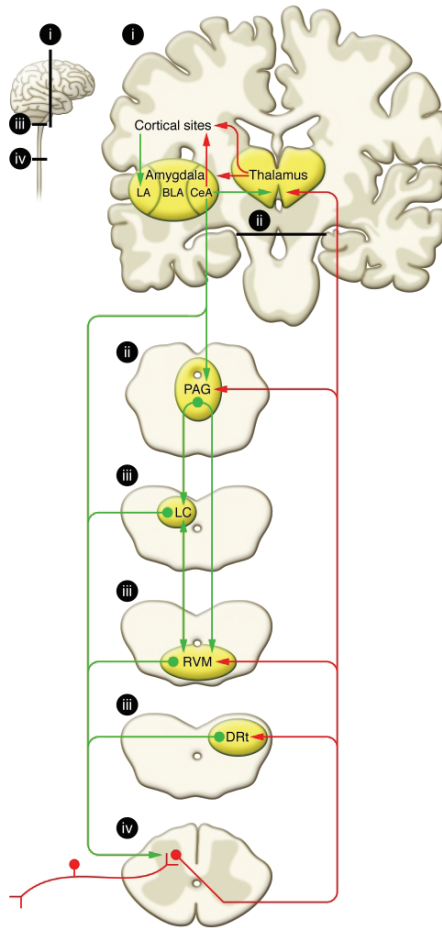


Figure 2 Schematic representation of pain modularity circuitry. Nociceptive inputs enter the spinal dorsal horn through primary afferent fibers that synapse onto transmission neurons. The projection fibers ascend through the contralateral spinothalamic tract. Ascending projections target the thalamus, and collateral projections also target mesencephalic nuclei, including the dorsal reticular nucleus (DRt), the rostral ventro medial (RVM), and the midbrain periaqueductal gray (PAG). Descending projections from the DRt are a critical component of the diffuse noxious inhibitory control pathway. Rostral projections from the thalamus target areas that include cortical sites and the amygdala. The lateral capsular part of the central nucleus of the amygdala (CeA) (“nociceptive amygdala”) receives nociceptive inputs from the brainstem and spinal cord. Inputs from the thalamus and cortex enter through the lateral (LA) and basolateral (BLA) amygdala. The CeA sends outputs to cortical sites and the thalamus, in which cognitive and conscious perceptions of pain are integrated. Descending pain modulation is mediated through projections to the PAG, which also receives inputs from other sites, including the hypothalamus (data not shown), and communicates with the RVM as well as other medullary nuclei that send descending projections to the spinal dorsal horn through the dorsolateral funiculus. The noradrenergic locus coeruleus (LC) receives inputs from the PAG, communicates with the RVM, and sends descending noradrenergic inhibitory projections to the spinal cord. Antinociceptive and pronociceptive spinopetal projections from the RVM positively and negatively modulate nociceptive inputs and provide for an endogenous pain regulatory system. Ascending (red) and descending (green) tracts are shown schematically. Areas labeled “i–iv” in the small diagram correspond with labeled details of the larger diagram. Copyright © 2010, reprinted with permission from American Society for Clinical Investigation (50)

Preventing further damage to already damaged tissue is protective and obviously important. Enhanced pain and discomfort from activation of descending facilitatory influences is a defensive mechanism to maintain secondary hyperalgesia as tissue heals to prevent further injury. The descending inhibitory modulation of pain is likewise important for the organism's ability to control pain in order to escape a predator when injured. Descending inhibitory processes have been investigated in anesthetised animals (52) where it has been found that dorsal horn neuron firing in response to noxious skin heating can be inhibited by stimulation in the PAG and the lateral reticular formation (LRF) in the midbrain. Inhibition of the spinal cord neurons can also be achieved by electrical stimulation in other regions of the brain, such as the raphe nuclei, the locus coeruleus, and various regions of the medullary reticular formation, as well as sites in the hypothalamus, septum, orbital cortex, and sensorimotor cortex (52). Application of serotonin to dorsal horn neurons inhibits noxious responses and inhibits the withdrawal reflex such as removing a hand from a hotplate (53-55).

The interpretation of the role of serotonin in pain modulation is complicated by the different descending serotonergic populations that are activated (50). The effect of spinal serotonin can be either inhibitory or facilitatory, depending on the receptor subtype activated (56-58). Systemic administration of serotonin agonists has been found to block capsaicin-induced hyperalgesia in mice, whereas serotonin antagonists have been found to elicit mechanical hypersensitivity (59). Consistent with a role in pain modulation serotonin receptors have been identified in the dorsal root ganglion and on central terminals of primary afferent fibres as well as on GABAergic interneurons in the dorsal horn of the spinal cord (60). There is a strong contribution of other monoamines such as norepinephrine in antinociception associated with descending inhibition. Although there is an apparent important role for serotonin in pain modulation, the precise spinal mechanisms involved remain unclear (50,61).

Pain theories

Travell proposed the pain-spasm-pain model postulating that pain increases muscle activity which in turn causes pain (62). This model fails to explain the atrophy and

muscle weakness that follows muscle pain which led to the pain-adaptation model where pain is thought to decrease muscle activation when muscles act as agonists and increases it when the muscle is acting as an antagonist (63). Both models have been contested, evidence suggests that the observed neurophysiological changes found in LBP are task-dependent, related to the patient's problem and highly variable between individuals (64) and are further complicated by the strong psychosocial component of LBP that may influence an individual's pain coping and modulation abilities.

Pain coping

Recent developments in functional imaging have revealed a range of brain areas activated during nociception and that pain can be influenced by attention, distraction and manipulation of mood (65). Long standing pain may affect the structure of the brain reinforcing the notion of chronic pain as a disease of the nervous system. LBP is associated with altered brain maps demonstrated by lack of discrete cortical organisation of inputs to back muscles and an increased overlap in the motor cortical representation of deep multifidus and the more superficial erector spinae in patients with recurrent LBP (66). Despite these changes, effective treatment of chronic LBP may reverse abnormal brain anatomy and function particularly in the dorsolateral prefrontal cortex which has been found to be thinner in LBP patients before successful treatment (67). Psychosocial issues such as catastrophising, passive coping, depression, and fear avoidance are some of the best predictors of chronicity in LBP patients. In a study of 565 LBP patients on sick-leave for more than 2 months, 31% had a psychiatric diagnosis based on the Mini-International Neuropsychiatric Interview, of these 18% were somatoform, 12% were diagnosed with anxiety and 4% suffered from depression (68). It is likely that there is a reciprocal link between LBP and psychosocial issues with individual adaptations to pain. Hodges has proposed a theory to explain pain adaptation with five key elements (69): "Adaptation to pain (1) involves redistribution of activity within and between muscles; (2) changes the mechanical behaviour such as modified movement and stiffness; (3) leads to protection from further pain or injury, or from threatened pain or injury; (4) is not explained by simple changes in excitability but involves changes at multiple levels of the motor system, and these changes may be complementary, additive, or competitive;

and (5) has short-term benefit but has potential long-term consequences due to factors such as increased load, decreased movement, and decreased variability.”

Motor control of the paraspinal musculature

The central nervous system regulates movement through the pyramidal and the extrapyramidal systems (55). The pyramidal tract conveys information from the motor center of the cerebral cortex to the anterior horn of the spinal cord and is responsible for motor activity. The extrapyramidal system focuses on the modulation and regulation of anterior horn cells involved in reflexes, locomotion and complex motions. The pyramidal and extrapyramidal systems have extensive feedback loops and are heavily interconnected with each other in motor control. The extrapyramidal system is comprised of the rubrospinal, vestibulospinal, tectospinal and reticulospinal tracts. The rubrospinal tract is responsible for large muscle movement as well as fine motor control and is one of the major motor control pathways in the upper body, particularly involved in flexion and mediation of voluntary movement. The vestibulospinal system conveys information important for postural control in response to proprioceptive, vestibular and visual information, and maintains head and eye coordination, upright posture and balance, and is involved in conscious realisation of spatial orientation and motion. The tectospinal tract mediates reflex postural movements of the head and neck in response to visual and auditory stimuli. The reticulospinal tracts integrate information from motor systems to coordinate automatic movements of locomotion and posture as well as modulate nociceptive impulses. The pontine reticulospinal tract is responsible for excitation of anti-gravity extensor muscles, while the medullary reticulospinal tract is responsible for inhibiting excitation to axial extensor muscles. The raphe nuclei of the reticular formation thus have vast impact upon the central nervous system and are of particular interest in our study of spontaneous postural activity in non-pain subjects and in ALBP subjects. Many of the neurons of the raphe nuclei are serotonergic and will be further reviewed.

Serotonergic neurons and tonic motor activity

The serotonergic system is found in all vertebrates from fish to primates indicating a common physiology and behaviour across species. Serotonergic cell bodies are

among the first to develop in an embryo and primarily found in the brain stem midline implying a strong involvement in basic motor processes associated with axial functions such as controlling the trunk and proximal limb muscles (70). There are two major groups of serotonergic cell bodies found in vertebrates, one that projects to the forebrain from the nucleus centralis superior and the dorsal raphe nucleus, and another that project to the spinal cord from the nucleus raphe magnus, obscurus and pallidus. The cells fire regularly at low frequency resembling an endogenous pacemaker that can be increased to 30-50% above quiet waking level and reduced by 50% and lose its regularity when drowsy or sleeping (71). During REM sleep, the activity of most serotonergic cells are almost totally suppressed and contribute to the paralysis produced by inhibition of motoneurons controlling postural muscle tone, a fundamental feature of REM sleep (70). The activities of these neurons are indifferent to a variety of stressors. However, they are activated in association with increased tonic motor activity, particularly in the repetitive or central pattern generator mode (70). It is thus likely that serotonergic neurons partake in the regulation of muscle tone in the spinal musculature in the upright position and are therefore of particular interest in this thesis.

Postural Control

The erect human is in a labile postural equilibrium with a small base and a high centre of gravity. The human body is constantly making small adjustments even when standing still to maintain upright posture. The central nervous system requires continuous information from receptors monitoring movements in the joints and body parts (55). Signals from receptors in joints, skin, eyes and vestibular apparatus are centrally integrated and adjustments are made with reference to calculations based on an “inner model” of the position of the body in space (72).

The signals from different receptors are partially integrated in the vestibular nuclei and in the reticular substance. The vestibulospinal pathways have a specific effect on postural muscles to stabilise the body, while the reticulospinal pathways are diffusely scattered without a specific localisation, and therefore not thought to contain precise information about exact movements. Many of the reticulospinal neurons that project

to the anterior horn contain serotonin also known to induce plateau potentials in animal studies (73). Small amounts of serotonin from these neurons have a general stimulating effect on their postsynaptic neurons. Those cells then react more readily to signals from other pathways disseminating more specific actions. Plateau potential membrane properties reduce the need for steady ongoing synaptic drive and have been suggested as a useful mechanism for postural control (74). Conversely, selective depletion of spinal monoamines in intact rats has shown a change in general postural activity, such as altered spinal curves and a tendency for the hindquarters to “hang”, while no change is observed in the animals’ general movement ability (75).

In addition to the effect of motor drive, some of the neurons from the raphe nuclei in the reticular formation end on spinal cord motoneurons where they influence pain transmission in the dorsal horn. The raphe neurons may thereby contribute to the drive of movements at the same time as they inhibit disturbing pain signals (50,55).

Motoneurons

Sherrington (76) was the first to describe motoneurons as “the final common pathway”. There are so many pathways converging on the motoneurons that the contribution of any single tract to the final motor act is extremely difficult to determine (77). Both descending fibres from the brain and segmental reflex paths converge onto motoneurons where the final synaptic integration takes place. The signals are converted to action potentials (AP), which in turn are sent down the axon and ultimately cause the muscle fibres to contract. A motoneuron can control several muscle fibres, but each muscle fibre is controlled by a single motoneuron. A motoneuron and the muscle fibres it controls are collectively called a motor unit (MU).

There are two main types of inputs to motoneurons, ionotropic and neuromodulatory (for review see Heckman (78)). Ionotropic inputs depolarise and hyperpolarise the MU in response to motor commands and reflexes while neuromodulatory inputs control the state of excitability of the motoneuron by modulation its response to ionotropic input. The response of a motoneuron to ionotropic input is dependent on the type and level of neuromodulatory input to the motoneuron. Ionotropic input from

sensory and descending inputs as well as via recurrent inhibition from Renshaw cells produces both excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). In their role as inhibitory interneurons, Renshaw cells receive excitatory collaterals from the motoneuron axon and send inhibitory axons to synapse with the cell body of the same motoneuron and to other motoneurons of the same motor pool. Antagonists are inhibited by a Ia inhibitory interneuron. Renshaw cells also inhibit the inhibitory interneurons, causing a disinhibition of antagonistic motoneurons. Although reciprocal inhibition from Renshaw cells has been demonstrated to modulate spike timing it has little effect on the average firing rate of motoneurons (79).

A sufficient change in the cell membrane electrical potential will enable the motoneuron to fire an AP. As an AP travels down the axon there is a change in polarity across the cell membrane. The voltage gated ion channels open and close as the membrane reaches the threshold potential. Na^+ channels open and Na^+ ions move into the cell causing a depolarization. This influx changes the electrochemical gradient, which further raises the membrane potential and cause more channels to open. The rapid influx of Na^+ causes a reversal of the membrane polarity, which in turn inactivates the ion channels. Repolarisation occurs when the K^+ channels open and K^+ moves out of the axon returning the electrochemical gradient to its resting state. The additional K^+ currents produce a transient negative shift called the after-hyperpolarisation or refractory period and prevent another AP from occurring. This change in polarity between the outside and inside of the cell causes the electrical impulse to travel down the axon to the muscle fibre synapse making the muscle cell contract. Every APs from the motoneuron will elicit an AP in all the muscle cells innervated by the motoneuron. The temporal sequence of APs generated by a neuron is called a spike train that is mirrored in the muscle and can be measured by electromyography (EMG), at the muscle fibre membrane.

An interesting phenomenon in motoneurons is when they occasionally fire two APs that are extremely close to each other called a doublet. The short interval between the two APs leads to a summation of after-hyperpolarisations causing the post-doublet interval to be particularly long (80,81). Doublets inserted early in a train of APs will

lead to faster build up of force to a maintained higher level and enhance muscle force production (82,83).

Muscle force gradation is mainly achieved either by increasing the discharge rate of motoneurons (rate-coding) or by increasing the number of contracting muscle fibres by recruiting an increasing number of motoneurons to firing (84). Henneman (84) established that MUs of small size were recruited before larger size MUs.

Motoneurons are traditionally believed to summate linearly the inputs that they receive. De Luca (85) and others have shown that the average firing rates of MUs during force-varying contractions in extremity muscles have a hierarchical “onion skin” organisation, with higher firing rates for early recruited units. At any given force level the lower-threshold MUs fire at greater rates than the higher-threshold units. This may be the response of individual MUs to a “common drive” of the motoneuron pool from supraspinal motor centres.

However attractive this hypothesis is in providing a simple scheme for the control of force output of a muscle, it is not a likely control method for postural muscles that must generate a sustained force output (86-89). This has been studied in the human trapezius muscle, which is involved in prolonged contractions during postural demands (90). It has been shown that MUs of higher recruitment threshold substitute activity in low-threshold MUs of this muscle when operating under long-term sustained contraction such as static voluntary contraction, mental concentration and typewriting. This substitute phenomenon is thought to protect the postural muscles from excessive fatigue when there is a demand for sustained low-level muscle activity (90).

Research in this field in the last decades has suggested that recruitment of plateau potentials in motoneurons may be a mechanism whereby constant muscle tone is produced, thereby reducing the need for a steady on-going synaptic drive from the central nervous systems (86,89). Some neurons have the ability to switch between two different firing states. In these conditions there is not a linear relationship between the collective synaptic influence of the neuron and its discharge rate. Specific transmitters control this transition between one condition and the other, which in itself does not

make the neuron fire, but changes how the cell reacts to other synaptic influences. The nerve cell can thereby switch between trains of action potentials and single spikes, or between high discharge rate and no activity at all as a response to synaptic influences (89).

Plateau potentials and self-sustained firing

The concept of motoneurons as purely passively driven followers in the “final common pathway” has been revised; they are now considered to be more actively involved in the expressions of normal motor behaviour (89,91,92).

Plateau potentials are long-lasting membrane depolarisations caused by a persistent inward current (PIC) that enable a nerve cell to fire trains of action potentials in the absence of continuous synaptic excitation (93) (Figure 3). Plateau potentials underlying self-sustained firing are depolarising potentials that can persist for several minutes. They are initiated by a transient depolarisation of sufficient amplitude, and they can also be turned off actively by a brief inhibition (86).

Animal studies

Motoneuronal plateau potentials found in reduced preparations of vertebrate motoneurons have provided detailed insights into the regulation of plateau potentials by neurotransmitters (94-96).

Self-sustained firing is dependent on plateau potentials that increase the excitability of the cell. Animal studies have demonstrated a triggering through the activation of voltage-sensitive, and highly persistent L-type Ca^{2+} channels in the dendrites of motoneurons that cause a persistent inward Ca^{2+} flow (97-100). Once activated, these channels tend to stay open. The PIC amplifies the synaptic current and continues to generate current on its own after the input ceases (93) (Figure 3). Self-sustained firing is observed when a plateau potential is activated and outlasts the duration of the excitation (74,100).

Hultborn et al. (101) first described bistable behaviour in MUs in the decerebrate cat as prolonged contraction by the soleus muscle evoked by a burst of volleys in Ia afferents and turned off by short-duration synaptic inhibition. Schwindt and Crill (97,102) had already described self-sustained firing and plateau potentials in cat α -

motoneurons and suggested that the PIC responsible for the plateau potentials was carried by Ca^{2+} ions. The animals had to be exposed to substantial pharmacological treatment to display plateau potential, but the phenomenon was later shown to be spontaneously present in anaemically decerebrated unanaesthetised cats (see review by 89).

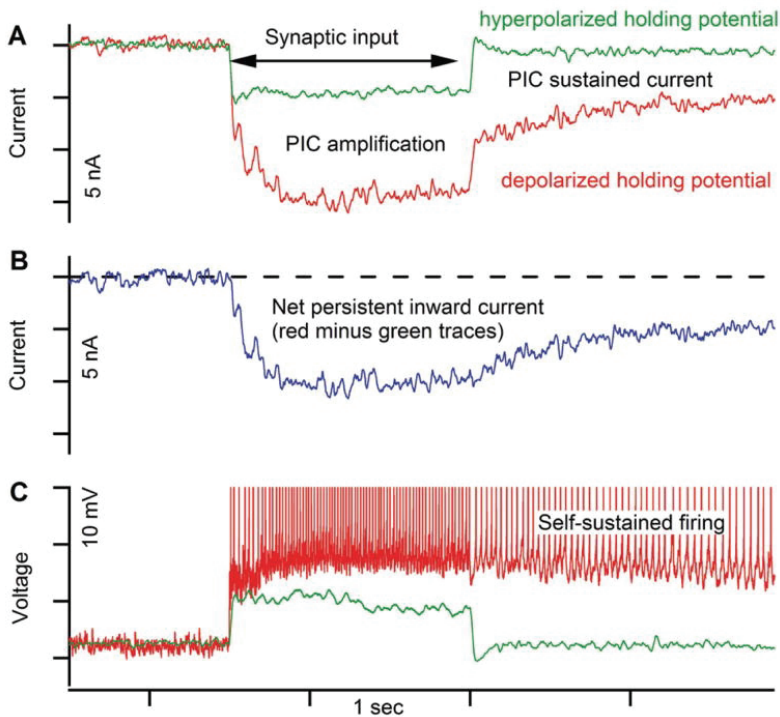


Figure 3. Membrane currents and potentials in spinal motoneuron in decerebrate cat after application of a noradrenergic agonist. During voltage clamp at hyperpolarised holding potential, excitatory synaptic input delivered through Ia afferents produces only a brief synaptic current (A green). This current is not sufficient to bring the membrane potential of the neuron to threshold for activating a persistent inward current (PIC). At a more depolarised holding potential the same excitatory input activates a PIC in the dendrites generating amplification of the synaptic input followed by a long lasting tail current (A red). Baseline holding currents were removed to allow the traces to be superimposed. The net effect of the dendritic PIC is shown in B. In unclamped conditions (C), this PIC causes intense repetitive firing during the input followed by continued, self-sustained firing at a lower level after the input ceases (C red). At hyperpolarised levels, only the excitatory postsynaptic potential is seen (C green). Copyright © 2004, reprinted with permission from Wiley Periodicals, Inc. (93).

The plateau potentials are dependent on activity in serotonergic and noradrenergic fibres, which descend from nuclei in the brainstem (103). In intact animals, these serotonergic neurones are intrinsically active and their activity are related to tonic motor output (61).

The first evidence of plateau potential in intact animals was found in rats in the late 1980's. In a study in unrestrained rats, a bistable firing pattern was discovered, probably caused by plateau potentials (86,104). Single MU and whole muscle EMG activity showed good correlation of single unit activity to whole muscle activity during locomotion while there was an apparently random recruitment to long-lasting firing of individual motoneurons during tonic activity resulting in a rotation of activity between motor units over time. During low-level tonic activity a small number of units were firing at a remarkably high and similar frequency and different units were active in different tonic segments. Such tonic activity behaviour challenges the hierarchical "onion skin" recruitment principle and corresponds well with the existence of motoneuron plateau potentials (104).

Of particular interest for the present study are the findings of postural changes seen in rats after selective depletion of monoamines. Within the first weeks the rats lost spontaneous long lasting tonic firing abilities and exhibited shorter and more frequent EMG episodes compared to controls. Total firing activity as well as mean activity was reduced and there was a tendency towards a less erect posture without any other changes in the normal movement ability of the rat (75).

The potent effects of PIC that amplify, saturate and prolong excitatory inputs are sensitive to synaptic inhibition (78). Stimulation of skin afferents has been shown to inhibit tonically active postural MU in intact rats (105). Another example of reciprocal inhibition can be demonstrated by how a slight change in the angle of the ankle joint can regulate intrinsic cellular properties set by a background of diffuse descending neuromodulation (106).

Human studies

The discovery of self-sustained firing in motoneurons has introduced a novel principle in motor control where the central nervous system is relieved from the tight feedback

control that otherwise would be necessary to produce stable tension in postural musculature (87). Animal studies have led to further investigations in humans, implicating plateau potential as an important mechanism by which the central nervous system regulates motoneuron activity during normal behaviour (86).

It appears that sustained firing in humans is different from that in animals. In humans the MUs jump from rest to a stable discharge rate referred to as the “preferred firing range” and a background level of excitability is apparently required to elicit self-sustained firing (74). This “warm-up” property has been used as criterion for the presence of a plateau potential (107). It is believed that the maintained firing is supported by the presence of a plateau potential so that the action potentials are riding on a plateau potential when the motoneurons are firing in the preferred firing range. This was proposed in a study whereby excitation of human leg motoneurons via application of vibration to the homonymous muscle tendon recruited neurons from silence to long lasting firing (74). Unlike in the rat, a true shifting between two stable frequency levels has not been demonstrated. With voluntary control of force output, neurons tend to jump directly from silence to the “preferred firing range” making it nearly impossible to maintain steady firing at lower frequencies (74).

These findings from Kiehn & Eken (74) were confirmed in another study where human subjects were instructed to maintain a constant dorsiflexion effort of the ankle until a single tibialis anterior MU was recruited (108). Vibration of the muscle tendon recruited a second “test” unit, which continued to fire after the vibration was removed, while the firing rate of the control unit remained the same or decreased. In this and a follow-up study (109) it was found that the duration of the prolonged firing often increased progressively after each vibration, similar to a “warm up” property shown for plateau potentials in animal neurons (86,108,110). Intrinsic activation of motoneurons represented a possible 40% reduction in the estimated synaptic drive needed to maintain firing of a MU compared with the estimated amount needed to initially recruit the unit (109).

Plateau potentials have also been suggested as an intrinsic mechanism for generating large forces and thereby making a substantial contribution to the control of voluntary

movement (111). Five times as much force was produced than could be accounted for by peripheral properties alone when relaxed humans received electrical stimulation of 1 ms pulses at 100 Hz over muscles active in plantar flexion of the ankle. During maximal voluntary contraction this additional force produced up to 40% of the additional force when superimposed on the direct response to motor axon stimulation. This force was abolished during anaesthesia of the tibial nerve proximal to the stimulation site. The additional force was even found in sleeping subjects and evident in subjects with thoracic spinal cord lesions and hence not attributable to inadvertent volitional descending drives to the motoneurons. The sustained contraction would outlast the stimulus and could be ended by contraction of antagonistic muscle. A request to relax completely would terminate the sustained muscle contraction if it did not end spontaneously, even though the subjects would typically state that they were relaxed.

These findings and the difference between sustained firing in humans and animals imply a difference in membrane properties and suprasegmental control between species. In turtles, where the conductance underlying plateau potentials has been most carefully studied, serotonin acts through G-protein-coupled receptors reducing after-hyperpolarisation of the motoneuron. The motoneuron is then able to build up a slight depolarisation when subjected to a series of action potentials. This depolarisation opens voltage gated Ca^{2+} channels, and the resulting calcium currents maintain plateau depolarization. Plateau potential in spinal motoneurons are facilitated by the tonic activity of descending serotonergic and noradrenergic neurons (99,112). In an attempt to assess the functional role of the descending monoaminergic fibres in modulating the tonic motor output in intact rats, monoamines were chemically depleted (75). This caused the normal tonic soleus EMG pattern to be replaced by a more phasic pattern indicating the importance of the monoaminergic descending systems in facilitation of tonic motor output as observed with plateau potentials.

The exact mechanism behind the membrane property in self-sustained firing in spinal motoneurons has not been demonstrated in humans. In a double blind, placebo controlled study (96), the effect of caffeine on self-sustained firing was examined in 7 healthy male subjects. At doses comparable to four cups of strong coffee there was a

significant increase in self-sustained firing compared with placebo. In this study caffeine was chosen because of its excitatory effect on neurotransmitter release and particularly its ability to increase electrical activity spontaneously in noradrenergic neurons, and also because caffeine increases serotonin concentration in the serotonergic neurons of the raphe nuclei (96). The raphe nuclei have excitatory projections to spinal motoneurons and are believed to play an integrative part in suprasegmental control of plateau potentials (86).

The role of plateau potentials in normal movement as well as in pathological processes is still speculative. One human study has proposed motoneuron bistability as a pathogenetic mechanism for muscle cramps in the lower limb (113). This was described in three patients suffering from chronic muscle cramps in extremity musculature. Electrical stimulation or tendon taps were applied to the dysfunctional muscles that produced a stepwise recruitment of MUs until cramp developed. The cramp or myokymia persisted after stimulation had discontinued, and was terminated by synaptic inhibition of the discharging motoneurons. The cramp consisted of rhythmic firing of MUs and involved recruitment of new MUs measured by surface EMG.

The role of intrinsic MU properties has been studied in relation to spasticity following spinal cord injury and stroke. The regular low frequency discharge of spontaneously active units found in chronically spinal cord injured subjects is suggested to be driven by PIC activation of motor units (114). Prolonged afterhyperpolarisation found in motoneurons following stroke has been associated with compromised descending monoaminergic influences (115). This is supported by recent evidence that serotonin reuptake inhibitors improve motor deficit in stroke patients independent of the presence of depression (116). Medication that activates serotonin receptors has been known to induce “Serotonin syndrome” characterised by myoclonus, tremor, hyperactivity and rigidity (117). Jacobs & Fornal (70) raises the important issue of why the manipulation of a system that is primarily associated with motor activity has such profound mood altering effects suggesting an unexplored link between mood and motor activity.

Management of the acute low back

Multimodal

There appears to be no single treatment that is best for all patients. Owing to the complexity and multidimensional nature of LBP there is often a need to combine evidence based treatment regimes in order to tailor the treatment to the patient individual need (118). Therapists have to be careful that patients' nociceptive pain is not so blunted by the therapy that its protective role is lost, for example may excessive load on an osteoarthritic facet joint conceivably accelerate joint destruction if the natural protection from pain is dulled by medication. At the same time it is important to stay active in order to avoid muscle atrophy and promote tissue healing by ensuring good vascularisation to the injured area. This is particularly important for the structures with poor vascular supply such as disc and ligaments. Clinical guidelines for nonspecific ALBP recommend early and gradual activation of patients, nonsteroidal anti-inflammatory drugs, spinal manipulation therapy, the discouragement of bed rest and provision of patient information (6,119). Exercises, behavioural therapy and short-term opioid analgesics are suggested for chronic LPB in clinical guidelines (6). Patients with neurological involvement should have a similar management with the addition of epidural steroid injections or decompression surgery if more conservative approaches are not successful. Guidelines recommend that management should emphasise early recognition of psychosocial factors that may lead to chronicity if not properly treated.

Cognitive therapy

Cortical influence that commonly increases pain perception can also reduce it. This gives the neurobiological basis for placebo as well as cognitive therapy and is the source for the success of the therapeutic alliance between patient and therapist. LBP patients who have been categorised as belonging to a group with a high risk of developing a chronic condition seem to benefit from cognitive therapy in addition to physical therapy (14). Catastrophisation, fear avoidance beliefs and low self-efficacy have been shown to be potential barriers to early improvement but that these patients show a reduction of high psychological distress scores within a few days after an initial chiropractic visit (120). The extent of improvement from physical treatment of

the mechanical LBP condition as opposed to the role of the therapists' reassurance of the patient remains to be determined. Patient advice and reassurance that they do not have a serious disease is highly recommended in clinical guidelines (119) and is important in helping the patient overcome the fear of movement that often accompanies spinal pain.

Activity

Exercise therapy is widely used as an intervention in non-specific LBP (121) and an evaluation of the literature has found exercise therapy to be effective at decreasing pain and improving function in adults with chronic LBP and that a graded activity program improves absenteeism in sub-acute LBP (122). For ALBP exercise is no better than other conservative treatments or no treatment. Exercise therapy has been shown to be equally effective in pain reduction as SM, while supervised exercise is superior to SM in improving trunk muscle strength and endurance (122). SM followed by exercise has been shown to be superior to evidence based medical "best care" for LBP patients (123) and SM alone is more cost effective than SM followed by exercise (124). Specific core stability exercises appear to have some short term benefits over general exercise for some LBP conditions (125,126).

Medication

Over the counter pain medication is recommended for ALBP and first choice is paracetamol (acetaminophen) due to the lower incidence of gastrointestinal side effects compared to nonsteroidal anti-inflammatory drugs that can be used in cases where paracetamol is insufficient (119). Pain medication is recommended administered on a time schedule rather than pain driven. There is insufficient evidence to support the use of injection therapy in LBP (127). Use of antibiotic protocol may be a promising treatment for LBP caused by bone edema (vertebral endplate signal changes on MRI, Modic type I) (128). Antidepressants, including serotonin reuptake inhibitors, have been used in the management for non-specific LBP for decades both to provide pain relief and to reduce depression but has not been found to relieve back pain or depression more effectively than placebo (129,130).

Surgery

Surgery is not indicated for non-specific LBP but is considered in acute LBP with cauda equina syndrome (131). Surgery has not been proven better than non-operative treatment for limb paresis, and preoperative duration of paresis does not seem to influence the rate of recovery of strength after surgery (132) which support the recommendation of conservative management in the acute phase even for ALBP with extremity paresis. As there is a risk of failed back surgery syndrome the aforementioned conservative treatments are recommended before surgery such as decompression, discectomy, fusion or disc prosthesis, is considered. SM is commonly used as part of conservative management for low back-related leg complaints but there is very little evidence for the use in clinical care (133).

Spinal manipulation

Spinal manipulation is used as part of management of ALBP by chiropractors, manual therapists, medical practitioners, osteopaths and others and its use is recommended in clinical guidelines (118,134,135). Most reviews indicate that spinal manipulative therapy provides some short-term benefit to patients although not superior to other treatment modalities (136-139). There is evidence for the clinical effectiveness and cost effectiveness of SM in sub-acute and chronic LBP (140,141), however this is yet to be demonstrated in ALBP. A systematic review of the literature has determined that spinal manipulation is safe and effective for the treatment of acute lumbar radiculopathy (142), but very little is known of the effect of spinal manipulation on the neural structures and whether spinal manipulation can alter neural function by mechanically changing compressional forces or reducing inflammation in the intervertebral foramen.

Proposed mechanisms for spinal manipulation

The mechanisms responsible for the relief of pain and functional restoration after SM are not well understood and the exact neurophysiological mechanisms underlying the effects of SM have yet to be determined. There are receptors contained in the facet joint capsule, muscle spindles, intervertebral disks and spinal ligaments all of which can potentially contribute to the neurophysiologic responses associated with SM. One

theory suggests that stretching of the facet joint capsule causes reflex inhibition of the facilitated motoneurons which are responsible for an increased muscle excitability thought to accompany LBP (143), but the evidence supporting this theory is lacking.

Spinal manipulation manoeuvre

Chiropractors offer a range of treatment modalities aimed at reducing pain and restoring function in the locomotor system.

A common treatment maneuver performed by chiropractors is a high-velocity, low-amplitude spinal manipulation (HVLA-SM). In the lumbar spine the patient is positioned in a lateral recumbent position with the shoulders rotated back in relation to the pelvis. The practitioner places a preload force directed towards the vertebral segment to rotate the vertebra near the limits of its range of motion followed by an impulse load that brings the joint to its physiological end range without exceeding its anatomical limits (143). The preload force is approximately 100 N and the transmitted force during the impulse ranges from 50 to 400 N with a duration of < 200 ms (144,145). The segmental displacement is small with an intervertebral translation of < 2.3 mm and < 2.2° rotation (146). A HVLA-SM is often associated with a cracking noise from joint cavitation as the articular surfaces are separated leaving a gas bubble that is slowly reabsorbed (147). The cavitation is an indicator that a gapping of the joint has occurred (148).

A number of different techniques and treatment modalities are available for clinicians to choose from but the literature has not yet demonstrated that one technique is better than others or that outcome in randomized clinical trials improves when clinicians are able to tailor the treatment modality to the patient (149). There are questions regarding the accuracy of manual contact in HVLA-SM in the lumbar spine (150). Treatment regimens such as mobilisation and the use of a high-impulse mechanical device called the Activator™ are also commonly used by chiropractors. Although these procedures have similar clinical effects, the following will focus on the cavitation producing HVLA-SM.

Theories of the effect of spinal manipulation

Theories explaining the mode of action of spinal manipulative therapy have focused on the mechanical effects of manipulative forces on the spine and the neurologic responses to manipulation (151). The postulated modes of action of SMT include disruption of adhesions in and around the joint, improvement of trunk mobility, relaxation of hypertonic muscle by sudden stretching, release of entrapped synovial folds, attenuation of alpha-motoneuron activity, enhancement of proprioception and increasing the pain threshold by the release of beta endorphins (152). One postulation suggest that SM alters sensory signals from paraspinal tissues in a manner that improves physiological function (153). Recently, a model compiling the excising mechanistic literature of SMT as a framework for research has been developed. The model suggests that a mechanical stimulus initiates a number of potential neurophysiological effects that produce the clinical outcomes associated with SMT of musculoskeletal pain (154). As HVLA-SM likely works through biomechanical and/or neurophysiological mechanisms, research should be aimed at the interactions between the specific sections of the model closing the gap between clinical effects of treatment, biomechanical parameters, spinal cord and supraspinal neurophysiological mechanisms, inflammatory mediators and psychosocial issues such as expectation, fear and catastrophising (154).

Pain sensitivity changes after spinal manipulation

Spinal manipulation seem to have a local/regional hypoalgesic effect on experimental pain from stimuli such as pressure or temperature while a systemic effect is unclear (155). There are many theories regarding the central effects of SM, some of the rationales are based on the premise of persistent alternations of sensory input from the vertebral tissues that alters the excitability of neuronal circuits in the spinal cord and that this may influence the central processing of pain. This is supported in classical studies that found that the size of painful skin area was reduced 15 s after SM of the lumbar spine compared to controls (156) and that pain tolerance levels increased over the next 10 minutes after SM (157). Furthermore, SM has been found to reduce LPS-induced production of the inflammatory cytokines TNF- α and IL-1 β but not substance P production in normal subjects (158).

The pain experience is comprised of complex interactions of both the peripheral and central nervous system. The recording of cerebral evoked potentials after magnetic stimulation of lumbar paraspinal muscles has been used to study the central effects of SM. Muscle spasm has been shown to reduce the magnitude of the paraspinal muscle–evoked cerebral potential and SM reverses these effects, reducing muscle spasm, pain and restoring the magnitude of the cerebral evoked potential (159). Transient cortical changes have been observed after SM of the cervical spine using somatosensory evoked potentials in patients with a history of cervical pain (160) but the long term central modulation, the neurological pathways involved and the clinical significance of these central effects remain to be determined.

Mechanical effects

HVLA-SM has been shown to increase joint gapping on MRI in an RCT with 112 ALBP patients, supporting the assumption that HVLA-SM breaks up adhesions and re-establishes spinal motion in facet joints that have become hypomobile from disuse, injury or other causes (161). In a study of metacarpophalangeal joints, the joint gap increased by 1.1 mm immediately after cavitation, there was still an increased 0.4 mm joint separation remaining 5 minutes after and the joint space returned to pre-cavitation values within 15 minutes (162). Stretching the lumbar facet joint by injection of 1 ml saline solution has been shown to abolish EMG activity in the multifidus that had been activated by electrically stimulation to the intervertebral disc in an animal experiment (40). The maintained joint separation that follows SM could possibly affect the sensory input from tissues surrounding the joint.

SMT has not shown an obvious effect on general mobility measured by range of motion (163), particularly not in the lumbar spine. However, it is unlikely that a change in mobility in one joint amongst many will cause a global effect on range of motion.

Muscle reflex effects

HVLA-SM is thought to stimulate proprioceptors by stretching the joint capsule as well as the muscles operating the joint (143). Muscle spindles are sensory stretch receptors in the muscle belly, which detect changes in the length of the muscle into

which they are embedded. They convey information of muscle length to the central nervous system where the information is processed to determine the position of body parts. Furthermore, they regulate muscle contraction by activating motoneurons via the stretch reflex to resist muscle stretch. In contrast, the sensory information from the Golgi tendon organ Ib afferents activates inhibitory interneurons to the motoneuron causing the muscle to relax (55).

A history of LBP has been associated with a longer response time to sudden loads, which suggests the presence of abnormal spinal and supraspinal reflexes in LBP patients (164-166). Muscle spindle input from the lumbar multifidus helps to accurately position the pelvis and lumbosacral spine, but this ability is impaired vibration is applied to the multifidus (167,168). Vibration stimulates muscle spindles and creates a sensory illusion that the muscle is lengthened and that the spine more flexed than it actually is.

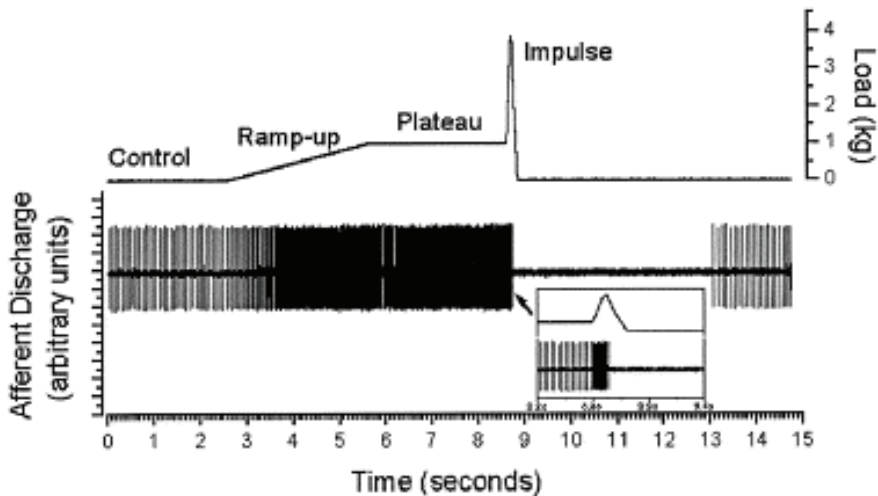


Figure 4. Original tracing of a muscle spindle's response to a spinal manipulative-like load. The single unit activity was obtained from a muscle spindle afferent in the L6 dorsal root in an anesthetised cat. The muscle spindle was located in the lumbar paraspinal muscles. Inset shows the spindle's discharge on an expanded time scale immediately before, during and shortly after a HVLA-SM like impulse. Copyright © 2001, reprinted with permission from Elsevier (158).

HVLA-SM has been shown to stimulate muscle spindles (169). Muscle spindles discharge increased more to the impulse than to the manipulative preload (200% compared with 30%), and the spindles were silenced for an average of 1.3 seconds after SM (169).

In an experimental animal model applying a SM like load to a lumbar vertebra, more activation of the Golgi tendon organ afferents has been demonstrated by an impulsive thrust than by the static preparatory load associated with SM (169) (Figure 4), with the pre-manipulation silence resuming at the end of manipulation. The literature seems to support both an increase in the excitability of the spinal cord motor pathways and the depression of the inflow of sensory information from muscle spindles associated with SM (for review see 153,170).

Peripheral effect measurements

Attempts have been made to measure peripheral neurophysiological change after spinal manipulation. The Hoffmann reflex (H-reflex) is an electrically induced involuntary and nearly instantaneous movement of muscles in response to a stimulation of Ia afferents from muscle spindles. The H-reflex is analogous to the mechanically induced spinal stretch reflex and used as a tool in assessing modulation of monosynaptic reflex activity in the spinal cord. A few published studies have shown changes in tibial nerve H-reflex after SM but with disagreeing outcomes (171,172). One of the studies showed transient reduction in H-reflex amplitude after HVLA-SM in non-patient subjects (172). In another study the H-reflex amplitude was found to be lower on the side of disc herniation before HVLA-SM in patients suffering from unilateral sciatica. Following HVLA-SM the abnormal H-reflex amplitude increased significantly on the affected side while the healthy side remained unchanged (171). Dishman et al. (173) contend that the H-reflex is a reliable index of motoneuron excitability and is reliably attenuated following spinal manipulation. However, the H-reflex is influenced by small postural variations (174) and further it has limited utility in measuring long lasting spontaneously occurring activity.

EMG as a measuring tool after spinal manipulation

The notion that a pain induces increased muscle tone has led investigators to search for reductions in EMG after HVLA-SM. Most studies examining low back EMG are utilising surface EMG, often with divergent and irreproducible results. One study measured a reduction in spontaneously occurring resting EMG activity in a recumbent position post manipulation compared to pre-manipulative recordings, suggesting a reduction in paraspinal muscle activity (175). This study used both Activator™ technique and a HVLA-SM technique.

A consistent increased surface EMG activity response to manual HVLA-SM was found in 10 asymptomatic young men with a reflex response occurring within 50100 ms after the onset of the thrust, lasting for 100400 ms (145). In this study manual HVLASM was applied to the cervical, thoracic and lumbosacral spine, while surface EMG recordings were made from 16 sites including paraspinal musculature as well as trapezius, deltoid, latissimus and gluteal musculature. In regards to the results from lumbar side-lying HVLA-SM it is imperative to call attention to the fact that the only muscle with consistent EMG response was the trapezius. It is also noted that the treatments given to the left and right lumbar spine showed the greatest asymmetry in EMG response of all unilateral treatments, this was thought by the authors to be clinician dependent.

Research opportunities

In the attempt to regulate and standardise activity when studying muscle function there has been a focus on isolated movements and voluntary action of muscles. As a result, the significance of tonic, automated function of the paraspinal musculature has been neglected. When using EMG as a measuring tool for muscle activity it seems sensible to actually perform measurement when the muscle is active in the subjects under study. However, what in fact has happened is that most SMT research has recorded spontaneously occurring EMG activity after SM in the relaxed, recumbent position where no activity is to be expected.

It is an anatomical reality that the muscles of interest lie deep beneath the skin surface, covered in part by the dorsolumbar fascia and origins of the latissimus dorsi

and gluteus maximus muscle. Subcutaneous fat, skin impedance, and electrode placement are some candidate sources for intermuscular and intersubject variability using surface EMG (176). Surface EMG of the lumbar spine does not reflect only intrinsic lumbar muscle activity since, even at rest, upper extremity or pelvic movements may provide volume-conducted EMG signals picked up by widely placed paralumbar surface electrodes (145). This makes SMT studies relying only on surface EMG less reliable. Although single fibre or needle EMG is the method of choice for studying the deep paraspinal musculature, this method has not yet been embraced for use with HVLA-SM, possibly due to the unsuitability of needle EMG as a measuring tool in a procedure that causes tissue displacement.

Although there are many hypotheses concerning the mechanisms behind the effect of spinal manipulative therapy, there are a limited number of studies describing the neurophysiological processes influenced by or instigated by spinal manipulation. Few studies have described normal function in the lumbar spine and compared this with altered neurophysiology in ALBP. Activity in individual MUs has to be studied in order to find the strategies at play; this includes the relative contribution from MU recruitment, frequency modulation and intrinsic motoneuron properties such as self-sustained firing. To our knowledge there are no published studies of long lasting normal or pathological tonic activity in motoneurons to deep paraspinal musculature and this is what we set out to explore.

Aims of the study

The primary aim of this study was to characterise activity in motoneurons to lumbar multifidus in healthy subjects and in ALBP patients and to describe potential effects of spinal manipulation on this activity. In particular, we looked for evidence of self-sustained firing and if present to determine the role of this phenomenon in pain free subjects and in subjects with ALBP:

1. *Motoneuron activity in healthy subjects* – Characterise normal activity in the motoneurons to lumbar multifidus by collecting data from non-pain subjects of both genders and look for firing patterns that could be attributed to self-sustained firing such as plateau potentials. The results from this part of the study could be used as a basis for comparison to the firing patterns in ALBP subjects.
2. *Motoneuron activity in subjects with acute low back pain* – In this part of the project we intended to study volunteers of both genders with ALBP but without other neurophysiological pathology. In particular we looked for evidence of muscle spasm or alternatively reduced firing indicative of inhibition. We also looked for self-sustained firing in the ALBP group as well as pathological activation of plateau potentials which has been linked to painful muscle cramps (113). We wanted to compare the findings from ALBP with findings from non-pain subjects.
3. *Effects of spinal manipulation on motoneuron activity* – The third stage of the project involved delivering a spinal manipulative procedure (HVLA-SM), as commonly performed by chiropractors and other manual therapists, to the ALBP subjects involved in part 2. Subsequent to the HVLA-SM we characterised the motoneuron activity and compared it to pre-manipulation findings and results from pain free subjects.

A key point of the study was to record EMG during naturally occurring muscle activity in typical postures, namely sitting and standing, so as to gain more understanding of the importance of motoneuron function in the broader context of the

intact freely moving human. Moreover, we wanted to compare spontaneous with voluntary tonic firing in order to see if the underlying control mechanisms are the same.

Normative data for spontaneous postural activity in deep lumbar musculature in humans is lacking and we hoped that our findings would provide a reference for muscular physiology both in pain and non-pain conditions and subsequently provide data for power calculations to further studies.

Methods

Subjects

Subject recruitment

Eleven clinically healthy symptom free subjects and eleven ALBP subjects who met the inclusion criteria as outlined in papers I, II and III were eligible for participation and recruited to the study. ALBP subjects were recruited from two multi disciplinary private outpatient clinics. The medical definition of acute varies from 0–3 weeks and up to 6 weeks. In order to recruit subjects in the early phase of a pain episode we chose to recruit patients from chiropractic clinics offering emergency appointments. Patients with previous episodes of LBP were included if there was more than 6 months interval since their previous episode. One requirement for inclusion of ALBP subjects was a positive palpatory finding of tenderness in order for us to localise the level for electrode placement. Subjects with contained intervertebral disc protrusion were accepted as long as they were without neurological findings on physical examination.

Subjects excluded

Two male ALBP subjects were rejected prior to final inclusion due to pathology findings on MRI. An eligible male subject was excluded due to MRI phobia and another female for not being able to lie down in the MRI machine due to the severity of her ALBP. The total number of patients invited to the study and declined to participate, is unknown.

Pain free group

One male subject accepted to the study was excluded from the analysis due to the discovery of the use of selective serotonin re-uptake inhibitor prescription medication not disclosed to the examiner prior to study inclusion. One pain free female subject was not able to complete the required tasks due to near syncope shortly after commencement of EMG recording. One female participant had electrodes implanted on only one side as the other electrode came out with the needle. This resulted in recordings from 17 electrodes in 9 subjects that provided the data for paper I.

ALBP group

In the ALBP group, data was lost in one female due to technical problems. EMG recording was unattainable in one female conceivably due to extensive fatty infiltration in the target muscle with no electrical signal at the electrode tip. Due to poor recording quality from one electrode set, data from one side in one male was excluded from analysis. One male had only one electrode successfully implanted. This resulted in recordings from 16 electrodes in 9 ALBP subjects that provided data to both paper II and paper III.

Demographic data

Subjects in both groups were asked for information including age, gender, history of LBP, handedness and coffee consumption. In addition the ALBP subjects were asked about pain duration and pain location. Answers are summarised in Table 1. Four of the nine ALBP subjects reported unilateral pain. Whether the electrode was implanted in a painful side (N = 4) or non-painful side (N = 12) was not significant in univariate analysis for firing rate and total activity (for analysis see: *statistical analysis*).

We created a variable for common drive analysis with categories depending on whether the electrode in the electrode pair was in painful or pain-free muscle:

- No pain – Unilateral recording
- No pain – Bilateral recording (category only possible for the pain free group)
- Unilateral pain – Unilateral recording on pain free side
- Unilateral pain – Unilateral recording on painful side
- Unilateral pain – Bilateral recording
- Bilateral pain – Unilateral recording

This was further recoded into a Pain in pair variable for either No-pain (three top categories) or Pain. Pre-manipulation had only one MU pair from each of 3 different patients in the No-pain category, while there were 134 recordings where at least one electrode was in in the painful side. Post-manipulation had a total of 16 No-pain MU

Table 1

Participant	Gender	Age	BMI (kg/m ²)	Duration	Numeric rating scale	Patient reported side of pain	Level of implantation	MRI findings
LBP002	M	48	27	7	3	Left	L5	L4/L5 left posterolateral prolapse affecting left L5 root L5/S1 small posterolateral prolapse affecting left S1 root
LBP004	M	35	19	1	6	Right	L4	L5/L6 posterior midline prolapse
LBP005	M	59	25	1	6	Bilateral	L5	L3/L4 broad based posterior midline protrusion w/annulus rupture L4/L5 disc degeneration L5/S1 advanced disc degeneration
LBP006	M	38	26	2	7	Bilateral	L5	No pathology
LBP007	M	26	22	14	4	Bilateral	L5	L4/L5 small left intraforaminal prolapse L5/S1 broad based left posteromedial prolapse affecting both S1 roots
LBP008	M	35	26	1	2	Right	L5	L4/L5 disc degeneration L5/S1 small left posterolateral prolapse w/annulus rupture
LBP009	F	34	19	21	3	Right	L3	L3/L4 posterior midline protrusion L4/L5 posterior midline annulus rupture
LBP010	M	41		3	6	Bilateral	L5	L4/L5 posterior midline protrusion L5/S1 posteromedial prolapse possibly affecting right S1 root
LBP011	M	39	31	6	6	Bilateral	L5	L4/L5 posterior protrusion

pairs from the four subjects with unilateral pain and 88 from recordings where at least one electrode was in the painful side. The Pain in pair variable was significant in univariate analysis, but did not make it to the final model (for analysis see: *statistical analysis*).

Single-motor-unit EMG electrodes implantation

Electrodes

Motor units can be studied using intramuscular needle electrodes or flexible wire EMG electrodes. We chose soft, flexible electrodes that give very little or no discomfort, are well tolerated by subjects and allow normal movement. The latter was important since we wanted to record EMG during a spinal manipulation procedure characterized by a short, rapid spinal rotation, in addition to recording during full range of spinal motion in all planes. Pain was an important variable in this study and we did not want the electrode to cause any added pain. The electrodes had to be sturdy enough to ensure that they could be removed without breaking. We therefore chose flexible single-fibre electromyography (SF-EMG) electrodes, which were custom made from 25 cm long, 50 μm diameter Teflon-insulated platinum/iridium wires, with a cross sectional surface area of 0.002 mm^2 (A-M Systems, Everett, WA). In comparison the fibre diameter in human lumbar multifidus is 58-66 μm (177). See the Methods section in Papers I, II and III for a detailed description on electrode construction. All the SF-EMG electrode bundles were sterilised prior to implantation.

Implantation procedure

In order to implant the electrode bundles we needed a hollow needle that was small enough to cause as little tissue damage as possible and large enough to allow the soft electrode bundle with its doubled diameter in the hooked end, to pass through. We also had to avoid the electrode to be guillotined or the insulation to be damaged by the cutting surface of the needle. We chose a single-use 18G Tuohy epidural needle (Portex Ltd, system 1 minipack, UK) where the distal opening is on the side of the needle. The needle has depth markers at 1 cm intervals that aided correct implantation in the target muscle in addition to a funnel-shaped opening to the cannula that eased insertion of the electrode into the needle. Prior to electrode implantation, the skin was

disinfected with Chlorhexidine solution and anaesthetised with a small volume of lidocaine 10 mg/ml (Xylocain®, AstraZeneca) injected subcutaneously. It was important to avoid pharmacological contamination of the target muscle by the local anaesthetic. During electrode implantation, the interventional radiologist noted a resistance as the needle perforated the fascia surrounding the paraspinal muscles, which often coincided with the subject reporting slight pain. This gave us confidence that the cutaneous anaesthesia had not affected the muscle. To ensure minimal tissue damage only one attempt at placing the needle was permitted. The SF-EMG-electrode bundle was fed all the way through the needle, and the needle was subsequently removed.

Ultrasound guidance was used to guide the needle at L4 level in the symptom free subjects while Computerized Tomography (CT) guidance was used for the ALBP subjects. The tip of the needle could be visualized and positioned in the desired target for electrode placement in both methods.

Diagnostic ultrasound gave good visualization of the spinous processes and allowed us to confidentially find L4 level, but we often lost visualization of the tip of the needle as it approached the echo shadow of the spinous process. More importantly, we were not able to confirm final electrode placement with diagnostic ultrasound after removal of the needle.

A CT guided implantation protocol was developed in collaboration with the interventional radiologist for use in the ALBP subjects (papers II and III):

1. The level of complaint was localized by palpation and marked by felt pen.
2. Anatomical level was confirmed by a low radiation overview image.
3. Needles for electrode implantation were inserted bilaterally.
4. A CT image was obtained for final guidance of needle positioning.
5. Final adjustment of needle position was performed.
6. The electrode was fed through the needle and the needle was removed.

7. The subject flexed, extended, and rotated the back to allow the electrodes to settle.
8. A final CT image confirmed electrode positioning.

The protocol limited the scan to only 20 mm and consequently a low and acceptable radiation dose.

We attempted to implant a four-wire bundle in one ALBP participant in order to differentially record from two electrode pairs. This made the electrode bundle thicker causing the electrode hook to lodge in the cannula and be removed with the needle.

EMG recordings

Differential recordings were made between the two SF-EMG electrode wires in each bundle that provided the best possible discrimination of MU activity (105). A standard ECG pad was placed on the skin in the midline somewhat apart from the muscle under study and used as ground electrode.

Spontaneous recording protocol

Recording of spontaneous EMG activity during normal unhindered standing and sitting demanded that the subject be distracted from the recording process. To facilitate distracting subjects from their surroundings, they were instructed to watch a comedy film (*Rat Race*, Paramount Pictures, 2001) on a laptop computer equipped with earphones. It is conceivable that the experimental set-up could also to some extent distract the subject from any discomfort associated with electrode implantation (178,179).

Voluntary activation protocol

Voluntary activity was recorded while the subject was standing with the spine in a slightly forward-bending position and instructed to recruit MUs with auditory feedback. An attempt was made to first recruit one unit into steady firing for at least 10 s and then increase force production to recruit one or more additional MUs for another 10 s.

Signal acquisition

The signal acquisition procedures are described in detail in the Methods sections of papers I, II and III.

Spinal manipulation procedure

The manipulative procedure utilized is described in detail in paper III. There are a number of manipulative techniques commonly used in the treatment of the lumbar spine, and the chosen technique was intended to cause the least amount of physical derangement of the paraspinal tissues by the investigator's hand on the skin. The investigator was electrically grounded during the manipulative procedure.

Experiment conditions

Each trial lasted 2–4 hours. None of the subjects reported discomfort or pain from the electrodes but some were conscious of the tape used to fasten electrodes and wires.

The electrode bundle was removed and examined visually to ensure that each electrode wire was undamaged. After removal of the tape and dressings the subjects were not aware of the electrode bundle and could not feel it as it was pulled out.

Room temperature varied from 21 to 23 degrees Celsius between the different experiment days but no variation was detected during each experiment.

Data analysis

Confirmation of electrode positioning

In order to ascertain that the SF-EMG electrode was positioned in the desired muscle, initial recordings were performed during active lumbar spine movements in flexion, extension, rotation, lateral bending, and hip extension. The LM has previously been found to be active in flexion and extension against gravity, contralateral rotation, ipsilateral hip extension, and to a lesser extent contralateral hip extension, and to be inactive in hyperextension and ipsilateral rotation (34,36). Electrodes were classified as not on target if there was no contralateral rotation and no ipsilateral hip extension.

Aiming for the deep LM fascicles innervated by motoneurons from the same segment enabled us to measure any effects from segmental pain reflexes. In order to record from a particular lumbar segment the electrodes had to be inserted deeply into a

region close to the inferior half of the spinous process (36). Comparison of needle placement and SF-EMG-electrode positioning in the ALBP group was done by measuring the dept of the electrode tip into the muscle from CT images. The desired placement was defined as the inner 1/3 of the paraspinal bulk.

Motor unit identification

All signal analyses were performed with Spike2 version 7 (Cambridge Electronic Design) software that was used to identify the MUAPs off-line. High-pass filtering distorts the shape of the potentials and therefore only raw data signals were used to identify MUs. Further detail concerning MU identification is given in paper I.

Total time and activity

A script developed in Spike2 was utilised to mark periods of different settings as seen from the concurrent video recordings. We defined three “phases”; pre manipulation, intervention and post manipulation, within pre- and post manipulation we defined periods of sitting and standing as well as when these activities were spontaneous or voluntary as described previously. We also defined the periods where the subject was asked to move the spine in flexion, extension and rotation as well as hip extension. The instant of HVLA-SM was identified from video recordings in the intervention phase. The total time for spontaneous activity was defined as the time recorded while the subject was quietly standing or sitting while watching a movie without interference.

Spike selection and storage

The time stamp of each MUAP was stored together with unique subject and MU identifiers in a custom-built relational database (FileMaker Pro 11.0v3, FileMaker Inc., Santa Clara, CA) from where interspike intervals (ISIs), instantaneous frequencies, and train lengths were calculated. FileMaker Pro enabled us to store data in different data sets and connect information on subject demographics with data from SF-EMG recordings, activity period identifiers, gross activity and common drive analysis. This enabled us to link each timestamp to the corresponding activity period. The data was exported to a text file for import to statistical analysis program JMP 11.0.0 (SAS Institute Inc., Cary, NC).

Firing train

MUAP trains were defined as consecutive MUAPs with interspike intervals <500 ms. Excluding ISI > 500 ms was implemented to avoid assignment of recruitment or derecruitment to sporadically occurring discharges (180) and has been used in a human plateau potential study (96). MUs discharging with a low firing rate may with time fire with ISI > 500 ms and some authors have accepted ISIs up to 1000 ms before a unit is considered derecruited (181-183). Different methods have been used in order to determine train length in order to avoid misclassified spikes. Mochizuki et al. (184) refer to Andreassen and Rosenfalck (185) when using 2 x mean ISI as the upper limit for ISI. Andreassen and Rosenfalck (185) set this criterion in order to use floating serial correlation coefficient (FRHO) on data that display a non-Gaussian distribution. Their reasoning is statistical rather than biologically justified. They further report that representative sections of 20 s or longer, corresponding to at least 200 ISIs, should be used as this was the shortest recording that gave a sufficiently accurate estimate of the statistical parameters of the ISIs (185).

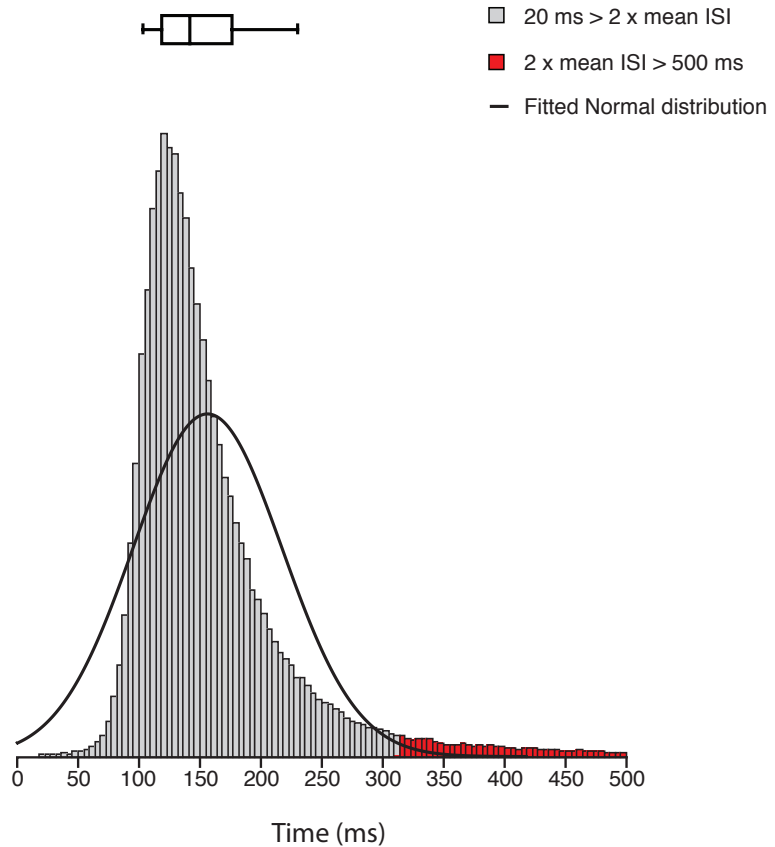
A simple measure using standard deviations of the intervals is useful when the intervals have stationary Gaussian distribution. However, when the distribution is skewed, as is seen in our data and noted by others, removing long ISIs is neither mathematically nor biologically indicated. Below is a histogram of ISIs recorded during spontaneous standing that illustrates a skewed distribution with long ISI > 2 x mean ISI. Note that the number of intervals > 2 x mean ISI represents only 3.2% of all ISI in spontaneous standing (Figure 5).

Variability

The coefficient of variation (CV) is a commonly reported measure of interspike interval variability. However, CV does not take into account that ISIs are temporally related. Regularity of firing was therefore assessed by computing the difference between successive interspike intervals (Δ ISIs), and using the inter-quartile range of the resulting distribution (Δ ISI IQR) as a measure of MU firing variability (186). For comparison CV has been reported in Table 1 of Paper I, II and III.

Figure 5

Interspike interval distribution



Distribution of interspike intervals (ISIs) (N=189 982 ISIs) from spontaneous standing from all subjects. Box plot median (140.5 ms) and quartiles (118.1–176.1), whiskers 10 and 90 percentiles. Mean 156.9 ms (95% CI 157.1 to 156.5). The superimposed fitted Normal distribution illustrates how the material is skewed. The tail (red; N = 6 098) represents 3.2 % of all ISIs. Goodness-of-Fit Test < 0.0100*. Small *P*-value ≠ normal distribution.

Paired recordings

We used one unit as a monitor of the general excitability of the motoneuron pool and looked for periods where one unit (test unit) jumped from zero to its preferred firing range while the frequency of others (reference unit(s)) remained unchanged. A situation where a test unit is recruited while the reference unit remains unchanged is

indicative of an intrinsic property of the motoneuron and not a result of an increase in the common drive onto the motoneuron pool.

Rotation between units was defined as a period where two units alternate their firing; a test unit is recruited from inactivity to its preferred firing range with an already firing reference unit and where the reference unit pauses while the test unit continues to fire with little or no change in discharge rate.

Common drive was assessed by determining the extent of cross correlation between concurrently active units (184,187). All computations were performed off line in Spike2. A continuous waveform representing smoothed instantaneous discharge rate was calculated after spike sorting by replacing each discharge event with a 600 ms wide raised cosine waveform of unit area symmetrical about the event time. A second-order high-pass Butterworth filter with cut off frequency at 0.75 Hz was then applied to remove mean frequency and low-frequency oscillations, and cross correlograms between the high-pass filtered smoothed frequency traces from the individual MU pairs were computed.

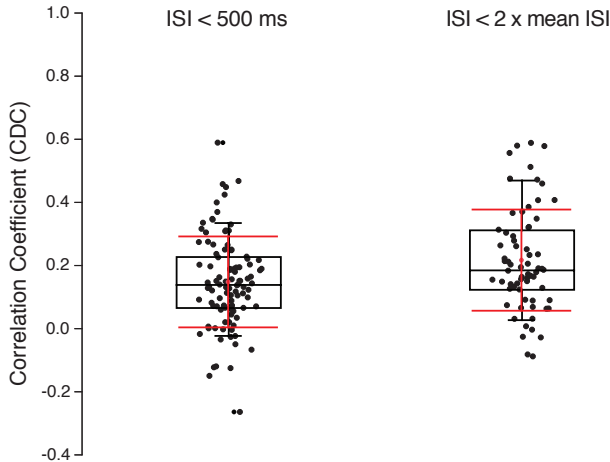
Definition of episodes for common drive analysis

Long interspike intervals will provide fewer APs available for cross-correlation analysis. It is therefore important to ensure that the longest acceptable ISI is within the mathematical range for CDC analysis and at the same time, is representative for the biological phenomenon we aim to describe. A sample of our material was therefore tested to see if there was a difference in CDC dependent on whether a discharge episode was defined as spikes with $ISI < 500$ ms or $ISI < 2 \times \text{mean ISI}$.

Two of the ALBP data sets with a large number of MU pairs were selected. Mean discharge rate was calculated for each unit and a threshold was set where $ISI \geq 2 \times \text{mean ISI}$ defined the end of a firing train. The CDC was then calculated for all spike trains where the interval before and after a spike was within $2 \times \text{mean ISI}$. $ISI < 2 \times \text{mean ISI}$ yielded fewer unit pairs and shorter episodes than $ISI < 500$ ms. The $ISI < 2 \times \text{mean ISI}$ procedure gave slightly higher CDC

but did not display a significant difference compared to $ISI < 500$ ms ($P = 0.57$) as illustrated in Figure 6. Based on this and with the support of the literature (96,180,181,188), we decided to use $ISI < 500$ ms as cut off value for episodes in our CDC analyses.

Figure 6



Combined datasets from spontaneous MU activity in two ALBP subjects ($n=88$ and 80).
 Coss correlation of motor unit pairs is similar when comparing two different methods of defining firing trains; either allowing interspike interval ($ISI < 500$ ms ($n=100$) or $ISI < 2 \times$ mean ISI ($n = 68$); $P=0.57$.

- Mean CDC (red whiskers show standard deviation)
- ☐ CDC (Boxes show medians and quartiles, whiskers denote 10 and 90 percentiles)

Epoch size for common drive correlation

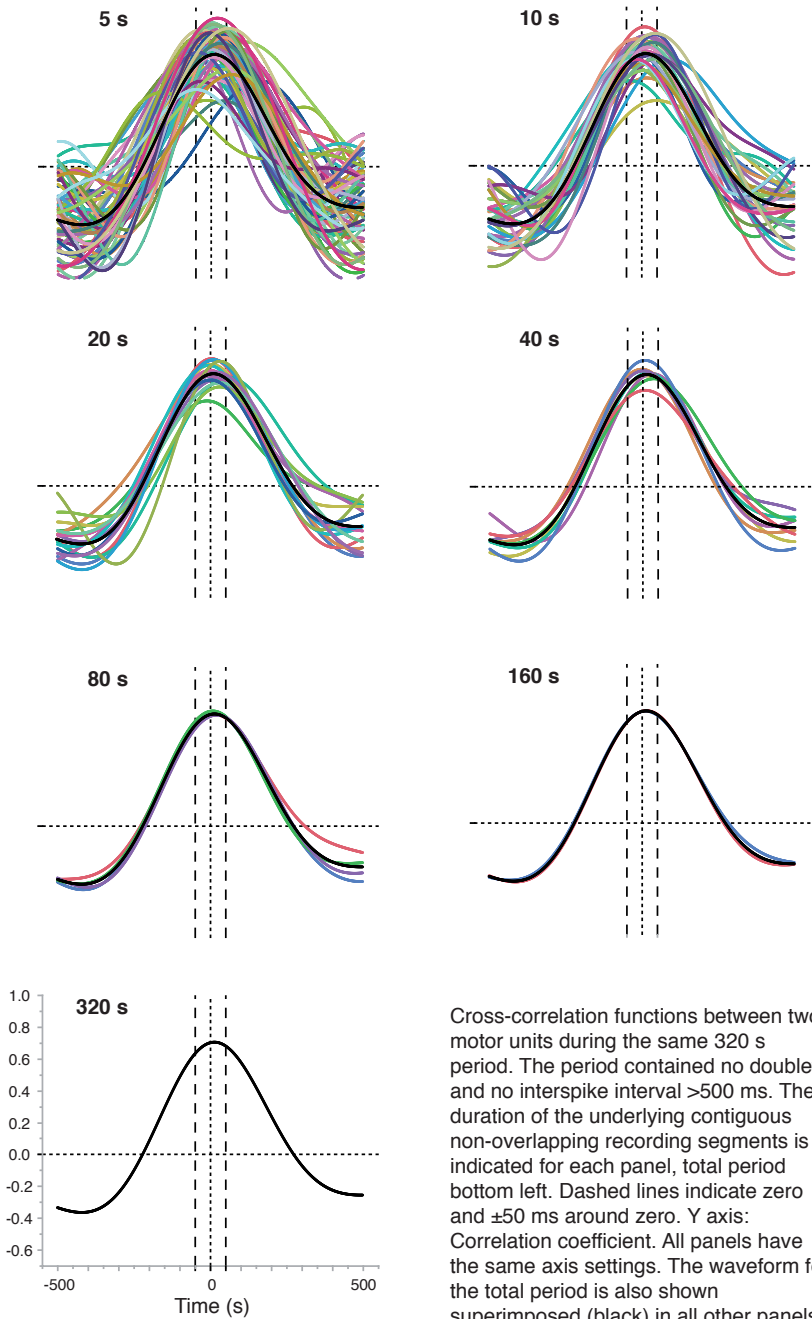
Standardizing the epoch used for calculation and averaging multiple epochs across experiment has been used in an attempt get a more robust estimate of the common drive. Mochizuki et al. (184) used 5-10 s long epochs provided that all ISIs fell between 50 ms and $2 \times$ mean ISI calculated over 20 s of data. Contrary to this, De Luca & Erim (189) state that “choosing a different interval or increasing the length of the analysis window changes the resultant cross-correlation function, but not to a significant degree” and refer to analysis windows (epoch duration) of 10-30 s where CDC ranges from 0.56 to 0.74.

Andreassen & Rosenfalck (185) used representative sections of 20 s or longer. In their material (having MUs discharging up to 20 pps) this corresponded to about 200 ISIs, and was the shortest recording that gave a sufficiently accurate

estimate of the statistical parameters for the interspike intervals. If we were to follow the recommendation of Andreassen & Rosenfalck (185) we should have used epochs of 25-40 s duration (our MU discharging 5-8 pps). This would have worked fine for our spontaneous recordings, but not for voluntary recordings as ALBP subjects had difficulty holding the required position for longer than 10-20 s. A reason for the short epochs in much of the literature on tonic firing may be due to short recording durations in some experimental designs. For example, De Luca & Erim (190) report a maximum recording time of 20 s with approximately 15 s tonic firing. We chose to follow the literature down to a minimum of 5 s and to follow the unit pair until one unit had a ISI > 500 ms. If they both continued after this and for longer than 5 s, we analysed it as a separate epoch.

The common drive coefficient is reported as the maximal cross correlogram value within the chosen time window. But how should this value be calculated for a unit pair with several cross correlograms from different epochs? Mochizuki et al.(184) chose to measure the maximal positive cross correlogram value for all individual 5–10 s long epochs and report the average of those values. However, after noting considerable differences in correlogram shapes between some of our unit pairs, we suspected that averaging a large number of individual maximal values would constitute a bias towards high values compared to reporting the maximum value of the average of the individual correlogram waveforms. We thus decided to analyse a 320 s firing episode as a whole and broken down into shorter segments: two 160 s epochs, four 80 s epochs, eight 40 s epochs, sixteen 20 s epochs, thirty-two 10 s epochs and sixty-four 5 s epochs (Figures 7 and 8). As expected, we found that using the maxima from the 5 s epochs produced a larger scatter with mean and median values that were higher than those of longer epochs, and that the measured common drive coefficient for the whole 320 s episode was representative also for the shorter periods with no significant differences between epoch durations ($P = 0.96$). We also tested the effect of epoch length on the location of the cross correlogram peaks, and found similarly reduced scatter and more robust estimates of lag from zero with longer epoch durations (Figure 9). Consequently, for our common drive analyses we decided to use

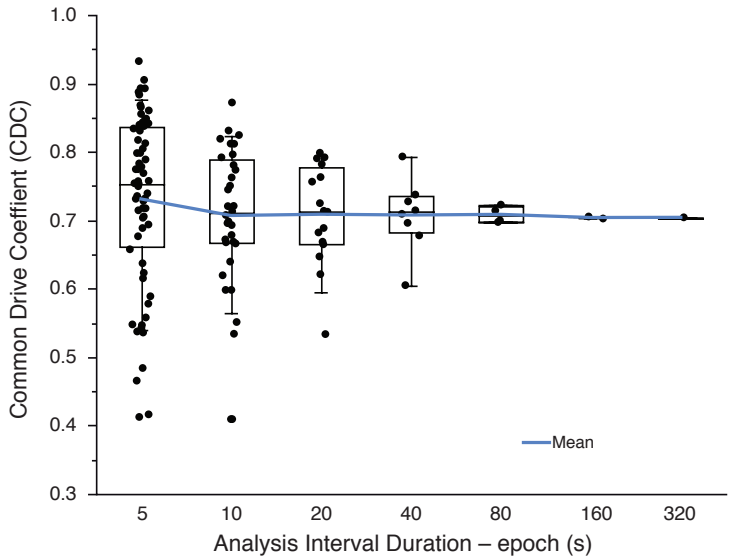
Figure 7



Cross-correlation functions between two motor units during the same 320 s period. The period contained no doublets and no interspike interval >500 ms. The duration of the underlying contiguous non-overlapping recording segments is indicated for each panel, total period bottom left. Dashed lines indicate zero and ± 50 ms around zero. Y axis: Correlation coefficient. All panels have the same axis settings. The waveform for the total period is also shown superimposed (black) in all other panels.

Figure 8

Cross correlation at different durations within same time period



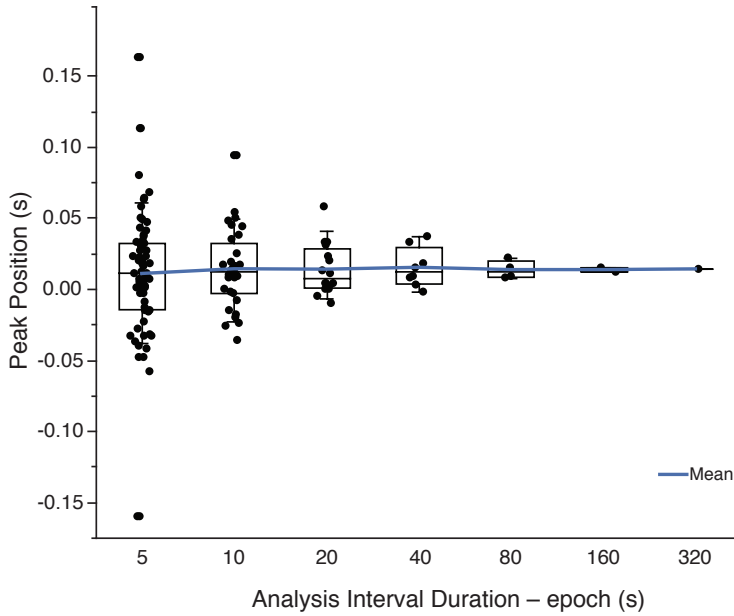
Quantiles

Epoch	Minimum	10%	25%	Median	75%	90%	Maximum
5	0.413	0.540	0.662	0.754	0.837	0.876	0.933
10	0.409	0.565	0.666	0.710	0.789	0.823	0.872
20	0.534	0.595	0.666	0.713	0.777	0.794	0.799
40	0.605	0.605	0.682	0.712	0.735	0.793	0.793
80	0.700	0.697	0.698	0.707	0.721	0.723	0.723
160	0.702	0.702	0.702	0.704	0.705	0.705	0.705
320	0.704	0.704	0.704	0.704	0.704	0.704	0.704

Means

Epoch	N	Mean	Std Error	Lower 95%	Upper 95%
5	64	0.731	0.014	0.704	0.758
10	32	0.707	0.019	0.669	0.745
20	16	0.709	0.027	0.655	0.763
40	8	0.708	0.038	0.632	0.784
80	4	0.709	0.054	0.601	0.816
160	2	0.704	0.077	0.552	0.856
320	1	0.704	0.109	0.489	0.920

Figure 9
Peak position of common drive coefficient at different epochs



Quantiles

Epoch	Minimum	10%	25%	Median	75%	90%	Maximum
5	-0.160	-0.039	-0.015	0.011	0.033	0.061	0.163
10	-0.036	-0.023	-0.003	0.012	0.033	0.049	0.094
20	-0.010	-0.007	0.002	0.008	0.029	0.041	0.058
40	-0.002	-0.002	0.004	0.012	0.029	0.037	0.037
80	0.008	0.008	0.008	0.012	0.020	0.022	0.022
160	0.012	0.012	0.012	0.014	0.015	0.015	0.015
320	0.014	0.014	0.014	0.014	0.014	0.014	0.014

Means

Epoch	N	Mean	Std Dev	Lower 95%	Upper 95%
5	64	0.011	0.044	-0.001	0.022
10	32	0.014	0.027	0.004	0.024
20	16	0.014	0.018	0.004	0.023
40	8	0.015	0.014	0.004	0.027
80	4	0.014	0.006	0.003	0.024
160	2	0.014	0.002	-0.006	0.033
320	1	0.014			

as long epochs as possible, compute weighted averages of all cross correlograms for each unit pair using epoch duration as weight, and to report the common drive coefficient as the maximum value of the resulting waveform within ± 50 ms from zero time lag.

Common drive coefficient definition

The common drive coefficient (CDC) was defined as the maximum value within 0 ± 50 ms (187) in the resultant weighted average correlogram. This 100 ms range was chosen to follow what is commonly used in the literature. I have not been able to find any publications that calculate the optimal range from which to collect the peak value. It appears that the width of this range around zero is arbitrarily chosen based on findings that this is where most of the highest cross-correlation scores are obtained (191,192). De Luca and co-workers were the first to describe the use of this narrow range for determining the CDC value (187) but they have later used larger windows to quantify signal correlation (189,190). A near zero location of the cross correlogram peak indicates that the two units modulate their firing rates simultaneously while the peak value of the cross correlogram represents the level of correlation between the firing activities of the MUs (189). If the peak value is not located at zero on the time axis there is a time lag between the units. Thus, a too narrow window will miss units that may be correlated but that have a different innervation leading to a longer time lag. We decided to use the conventional ± 50 ms window for determining peak CDC values and to report time lag from zero in the papers.

Common drive coefficient magnitude

The values of the firing rate cross-correlation function range between +1 (perfect positive correlation) and -1 (perfect negative correlation). Values near zero signify that the fluctuations in mean firing rates of MU pairs are unrelated. Recordings from two fibers belonging to the same MU would give a value close to 1. De Luca et al.(187) refer to CDC > 0.6 as “high” and > 0.4 as “relatively high”. Kamen et al.(191) chose the use of a narrow range of ± 50 ms as almost all the highest cross-correlation scores fell within this range resulting in average cross-correlation values between 0.4 and 0.6. Semler et al.(192) used the same

argument and reported that most cross-correlation histogram peaks > 0.4 lay within ± 50 ms of time zero. The literature does not provide any consensus on the significance of the magnitude of the correlation coefficient.

When constructing histograms for the resultant cross correlogram CDC values, we found that while the distribution of CDC values for bilateral unit pairs appeared to have a near normal distribution, the distribution of CDC values from unilateral pairs was clearly skewed and seemed to consist of two populations. In order to better describe the CDC distributions we fitted a single Normal curve and a mixture of two Normal curves to our data. There appears to be two approximately normal populations in our material, one with a mean CDC of 0.167 and another with a mean CDC of 0.542. This is further described in Paper II and Paper III.

Doublets

Since doublet firing in MU is caused by intrinsic membrane properties we decided that all MU pairs displaying doublet firing had to be removed from CDC analysis in order not to contaminate the common drive analysis. Most of our MU doublet firing occurred as a few doublets in the beginning of a train, and did not have influence on MU median discharge rate. MU firing episodes with repetitive doublets were also excluded from Δ ISI IQR analysis, as this would affect variability analysis. See paper I.

Statistical analysis

In all our analyses, spike trains were defined as consecutive spikes with intervals < 500 ms, i.e. analysed discharge rates were always > 2 pps. The reasons for this are outlined above. The shortest interval that we measured was 4.65 ms (intra-doublet interval). We therefore also excluded ISIs < 4 ms, i.e. firing rates > 250 pps, from our analyses as they most likely represented misclassified spikes.

Our experimental design emphasised repeated measurements 1) within the same subject, 2) on the same side, and 3) within the same MU or MU pair. It was therefore necessary to use a mixed model repeated measures design with a hierarchical data structure where side was nested within subject and MU nested within subject and side. MU pairs were only nested within subject, to allow for analyses of unilateral versus

bilateral MU pairs. All these variables were regarded as random effects in the model, and their levels were not estimated.

Details for the statistical analysis in each of the papers are found in the respective Methods sections in the papers. The results are presented as medians and quartiles as these are robust measures where outliers have only minor influence or none at all, in contrast to how they will always affect means and standard deviations.

Statistical analyses were performed using JMP 11.0.0 (SAS Institute Inc., Cary, NC). A significance level of $P < 0.05$ was assumed for all tests.

Ethics

All subjects received detailed information prior to signing consent forms. All procedures were performed in accordance with the Declaration of Helsinki and were approved by the Regional Committee for Medical Research Ethics of Southern Norway.

Summary of papers

Paper I

In the first paper we characterised the normal firing pattern in lumbar multifidus. The median discharge rate varied little and is in the 5-7 pulses per second (pps) range, and 1 pps higher in relaxed standing as opposed to when sitting. There are individual differences in activity duration when sitting and standing. The MU quickly jumps to its preferred firing range and join other active units to produce long lasting firing trains. This preferred firing range appears to be close to maximum effort for the muscle cell as the discharge rate remain the same when voluntarily activating more units by leaning forward while listening to and watching MUs on an oscilloscope.

A main finding presented in this paper is the large difference in common drive between spontaneous and voluntary activity. The common drive is not significantly different between sitting and standing, but significantly higher in spontaneous activity than in voluntary activity. We also found that the common drive was not significantly different during spontaneous standing between units belonging to multifidus muscles on opposite sides of the spine and units in the same muscle. We take this as evidence that there is synchronisation between muscles on both sides of the spine during quiet upright postures.

In spite of a common drive, MUs were able to fire seemingly independent of nearby units. We attribute this to self-sustained firing caused by intrinsic membrane properties in the motoneuron. Periods of rotation between MUs further support this.

Paper II

For the ALBP trial we developed a new procedure for implantation of fine wire electrodes. This proved to be superior to the ultrasound guided implantation procedure that we used for the non-pain subjects, particularly in visualising the final electrode position.

The main finding of this paper was the dissociation of common drive between unilateral and bilateral unit pairs with a significantly lower bilateral CDC during spontaneous standing, this is contrary to the findings from the non-pain subjects

reported in paper I where there was no significant difference between unilateral and bilateral MUs during spontaneous standing. In paper II we introduce a novel approach to CDC analysis that confirms and extends this finding, ascribing the reduced CDC in bilateral MU pairs in ALBP subjects to a reduced proportion of motor unit pairs in a specific high-CDC population. Lower bilateral common drive was apparent for both sitting and standing as well as during spontaneous and voluntary activity.

We used the normative data from paper I to look for similarities and differences between non-pain and ALBP subjects. We found the same frequency range for MUAP firing and that the individual postural strategies are just as diverse for ALBP patients as they are for non-pain subjects although we in ALBP subjects found a significant difference in gross activity between sitting and standing. The values for interspike interval variability were higher for ALBP but not statistically different from non-pain subjects.

Paper III

A HVLA-SM directed toward the painful segment was given to the same subjects as in paper II, after which we collected SF-EMG recordings during sitting and standing while the subject continued to watch the movie. We also had the subject perform a voluntary contraction of the LM in forward flexion with audiovisual feedback of intramuscular EMG activity.

The main finding was that interspike interval variability was significantly reduced after HVLA-SM and similar to non-pain values. We do not know the background for this finding but it could possibly be due to less synaptic background noise, in that case it can be caused by changes in inhibitory and excitatory segmental and suprasegmental signals.

We were not able to identify muscle spasm in the LM when the subject was in a lateral recumbent position before or after HVLA-SM. We have investigated 32 HVLA-SM procedures in 16 muscles from 9 subjects and only found MUAPs present immediately before HVLA-SM in one muscle. Thus, the effect of HVLA-SM on

interspike interval variability in our material was not dependent on the presence of muscle spasm.

Discussion

Main findings

Significant effects of sitting vs. standing were seen on median discharge rate and interspike interval variability in LM MUs. Several LM units fired repetitive doublets at low discharge rates or in the beginning of a MUAP train. The common drive is stronger in standing and in spontaneous activity. CDC is equally high bilaterally in non-pain subjects during spontaneous standing but significantly different bilaterally in ALBP. In spite of a common drive, MUs to the LM exhibit self-sustained firing properties enabling a sustained force output where rotation of activity is evident in the non-pain group and to a lesser extent also in an ALBP group during spontaneous postural activity. We have also found a reduction of the Δ ISI IQR in ALBP after spinal manipulation demonstrating a significant reduction in firing variability after HVLA-SM. Spontaneous activity display different properties compared to voluntary, this is apparent in discharge rate, ISI variability and CDC.

Lumbar multifidus activation pattern

Lumbar multifidus is active in a standing posture in flexion, in extension from flexion, in ipsilateral rotation and in ipsilateral hip extension. We did not test for lateral bending. Our findings concur with other investigators (34-36) who also found variations to this pattern. When using ultrasound guided electrode placement we used the movement patterns to verify that the electrode was positioned in the correct muscle with emphasis on the presence of contralateral activation in rotation as well as activation against gravity. Interestingly, we found that the LM is active in the full range of forward flexion in non-pain subjects unless they hang on the passive structures at full range, demonstrating the protective role of LM that is probably even more at work during ALBP.

Implantation and verification of electrode position

CT is superior to ultrasound guided implantation due to better visualisation of the placement of fine wire electrodes (Figure 10). We are not aware of other investigators that have used CT guided implantation of SF-EMG-electrodes and have presented an implantation method that can be modified for use in other regions of the spine.

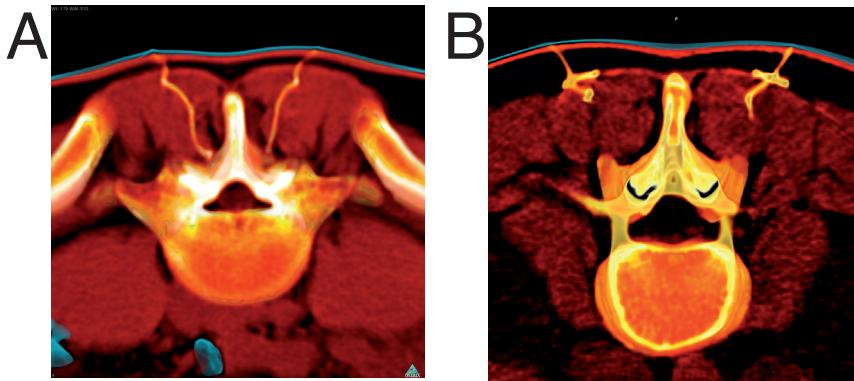


Figure 10 shows optimal electrode placement (A) in the inner third of the lumbar multifidus (LM) at L5 level and an example (B) of off-target placement at L3 level in a subject where the electrode coiled itself in the subcutaneous layer.

Total activity

In an extensive review of the literature looking at trunk muscle recruitment van Dieen et al. (64) found that LBP patients display a range of recruitment strategies for the LM that fit neither the pain-spasm-pain adaptation model nor the pain-adaptation model and that any change in muscle behaviour is task dependent and variable between subjects. Our results, based on the total activity, support this conclusion.

We found that during spontaneous activity in standing, LM is active in about 10 % (median) of the time in non-pain subjects and less active during sitting, with large individual variations. Mork and Westgaard (193) found that LM less active during sitting and postulated that this is due to the flexion relaxation phenomenon. In ALBP there is generally more activity, nearly 60% (median) of the time during standing, but due to large individual variations this is not statistically significant from sitting to standing or in non-pain subjects. Although no indication of activity duration was provided, Morris (34) noted that the lumbar multifidus was periodically active as the subject swayed slightly forward during standing at rest and (36) reported that the activity was sometimes continuous and other times intermittent and graded it to slight to moderate. This is similar to our findings indicating individual differences in firing and that activity is task dependent acting to promote spinal stability even in quiet standing.

MU discharge rate

The discharge rate of the LM is ~1pps higher during standing than while sitting, but not significantly higher during voluntary activation in non-pain and in ALBP both before and after HVLA-SM. Discharge rate was not different between our study groups. Muscle contraction strength depends on the firing rate (194). Although we did not record EMG during maximum voluntary contraction, our finding that higher force production requires recruitment of more units rather than increased firing rate, suggests that the MU fires close to its maximum discharge rate during spontaneous standing. It is important to note that our findings only relate to MUs close to the electrode and not to other motoneurons that could conceivably behave differently in the recruitment hierarchy. The possibility exists that there could be total muscle effects in ALBP that our design was unable to reveal.

The MU appears to jump to its preferred firing range and maintain steady firing until turned off indicating self-sustained firing releasing the MU from constant modification from supra-segmental control (86,195). Kiehn and Eken (86) have postulated that the presence of stable long-lasting muscle contractions resulting from sustained action potential production, plays an crucial role in the generation of stable postural activity. Such self-sustained firing is most likely from monoamine dependent PICs.

A MUAP train may be initiated by a slight movement such as a deep breath or weight shift, also noted by others (34), and continue to fire until the subject moves slightly again. It was not always possible to observe the action that derecruited the MUAP train and one possible explanation is that de-recruitment resulted from motoneuron fatigue. Motor fatigue induced by physical activity has been attributed to a “spill over” effect of serotonin at motoneuron axon initial segments (196). This central fatigue mechanism may contribute to rest and regeneration of force production of the MU and be essential for the rotation of activity between units.

Doublets

We have described MU firing with particularly short interspike intervals (doublets), typically 5-6 ms. The doublets occurred either as one or a few at the start of a MUAP

train, and repetitively when motoneurons were firing spontaneously at low frequencies. Doublets inserted early in a MUAP train can lead to faster buildup of muscle force as well as maintain a higher level of force production (82). High-frequency doublet discharges have been reported in a large number of human muscles (197). The properties of the doublets correspond to those described by Bawa and Calancie (81), who list the following criteria for identification: Intradoublet interval generally less than 10 ms; the second spike in a doublet of similar shape and amplitude always less than or equal to that of the first spike; and always followed by a longer interval than those occurring during single discharges. High-frequency doublets probably arise from delayed depolarisation during the falling phase of the action potential (81,197). We found that where a MU fired concurrently with a doublet firing unit it was apparent that the two units fired in synchrony and that the doublet firing MU fired doublets at times when the concurrent unit fired at a slightly lower frequency as opposed to when the doublet firing unit fired single MUAPs. Repetitive doublet firing has been proposed to possibly reflect the presence of plateau potentials in human motoneurons (198) but the rationale behind this proposal is allusive. Bawa (81) argue that doublets are conceivably more difficult to produce in patients as they may have more difficulty in holding a force steady. We found doublets in both the non-pain and the ALBP population during spontaneous firing but we did not quantify our findings.

Interspike interval variability

In the ALBP group we found that the firing variability represented by the Δ ISI IQR was reduced after HVLA-SM. Increased firing variability, measured by coefficient of variation, has been found by other investigators during induced muscle pain (199), in women with neck pain (200) and that variability is exacerbated with stress (201). Variability may be of benefit in the sensory system when conveying information from highly receptive sensors while variability or neuronal “noise” in the motor system will cause inconsistency in force output and is not associated with any benefits (202). Variability in motoneuron ISI may be the underlying cause of a reduction in maximum force production compared to what could have been achieved had units discharged with constant ISI as demonstrated in a model by Fuglevand (203).

Variability could thus conceivably contribute to the reduced muscle capacity associated with LBP (204,205).

The reduced interspike variability that we have found post manipulation suggests that HVLA-SM facilitates a return to a more stable motoneuron output to the lumbar multifidus. In clinical practice it is often how the patient moves and the quality of movement that is observed rather than how far they move (range of motion) (206,207). LBP patients undergoing 12 weeks of treatment with spinal manipulation have demonstrated a change to a smoother motion pattern compared to exercise groups while there was no difference in range of motion between groups (208). This could conceivably be the clinical manifestation of the MU variability changes we have observed following spinal manipulation.

The observed changes in variability could be caused by changed activity in sensory afferents or in supra-segmental descending pathways. Another possible mechanism is activation of motoneuronal PICs as an underlying factor for the reduced variability in spiking. Once activated PICs tend to limit efficacy of additional synaptic input (209). Uncoupling of spike generation from the variability in synaptic input and the shunting effects of increased input conductance could render synaptic inputs less effective (86). Renshaw cell activation has been shown to modulate ISI variability during voluntary muscle contraction of the extensor carpi radialis muscle where recurrent inhibition is operative but not in the abductor digiti minimi muscle, where it is absent (210). This raises a third possibility that it is recurrent inhibition that is involved in limiting MU discharge variability. Whether recurrent inhibition acts by locally shunting a specific component of the synaptic noise or damping the overall impact of the synaptic noise remains to be elucidated.

The results of this study demonstrate that the median ISI is strongly associated with the Δ ISI IQR. The variability is reduced in instances of high discharge rate, such as during voluntary activation. Any differences in variability are more likely to be observed during low frequency activities. Furthermore, even after the effect of median ISI was accounted for in the REML model there was still a significant difference

between spontaneous and voluntary activity. This should inform the choice of experimental set up when using interspike interval variability as an outcome measure.

Common drive

The common drive differed during spontaneous activity compared with voluntary activation in non-pain subjects. This concurs with findings from voluntary versus spontaneous soleus activation (184). During voluntary contraction the subjects had to regulate and control the force production in forward bending with visual and auditory feedback, thereby creating a variety of inputs from a range of peripheral and central inputs that may contribute to the reduction in CDC.

The LM on each side of the spine acts as antagonists during movements such as rotation of the torso, lateral bending or when walking. In upright posture the LM act as agonists to one another and a strong common drive is to be expected. The higher common drive that we found in the non-pain group during standing points to the unique role of the bilateral axial back muscles in working as a functional unit to extend and stabilise the spine while in an upright position. The anatomical substrate is probably the particularly high degree of bilateral descending projections to motoneurons to axial muscles (see Marsden et al. (211)).

Mochizuki et al. (184) found that CDC values in unilateral MU pairs to be significantly higher than bilaterally recorded MU pairs, both in the soleus muscle during spontaneous standing and during voluntary contractions while sitting and similarly Marsden et al. (211) in weak voluntary contractions in lumbar paraspinal muscles during sitting. However, the present material from deep LM did not reveal significant difference between unilateral and bilateral MU pairs during standing in pain free subjects. The LM probably has a different drive compared to the soleus. The soleus muscles have to be able to act independent of each other, while the bilateral paraspinal muscle pair, acting on the same motion unit, rarely are disconnected and have to act either as agonist or antagonist to each other. Our findings concur with Gibbs et al (212) who found evidence for common drive between pairs of muscles that share a common joint such as the paraspinal muscles, but no evidence for a common drive to co-contracting muscles that did not share a common joint. The difference in

voluntary vs. spontaneous activation that we have reported in the non-pain group may contribute to the discrepancy when comparing our finding with Marsden et al. (211).

Contrary to the non-pain group we found a significant difference in CDC between unilateral and bilateral units in the ALBP group during spontaneous standing indicating that the bilateral control signals contributing to common drive may be disrupted in subjects with ALBP. The lower bilateral CDC in the ALBP group may represent a different common drive to the painful side. This raises the question whether LBP causes an altered common drive or alternatively whether the altered common drive predisposes to LBP. Our study group was a mix of bilateral and unilateral pain conditions and subsequently the group size was too small to study effects of painful versus non-painful side.

Self-sustained firing and rotation between units

Despite strong unilateral common drive, there is a sudden recruitment and de-recruitment of individual units during spontaneous activity. Abrupt recruitment of individual units with little or no change in discharge rate of other already active units, in spite of evidence of common drive, suggests recruitment of intrinsic motoneuronal properties resulting in self-sustained firing (105). Oscillations in our material remain correlated even after removal of larger fluctuations. This is true not only during voluntary activation but even more apparent during spontaneous tonic activity shown by the significantly larger CDC.

The pain free LM group demonstrated evidence of rotation of activity between MUs further implying self-sustained firing as an underlying mechanism of tonic motor control of the LM. We have defined rotation between units as a period where two units alternate their firing; a test unit is recruited from inactivity to its preferred firing range in phase with an already firing reference unit and where the reference unit pauses while the test unit continues to fire with little or no change in discharge rate. That is, a prerequisite for rotation is that the tail end of the concurrent firing display quenching of long-lasting activity in the first unit while the second unit continues to fire. A cellular mechanism contributing to rotation could come from by serotonin spillover to inhibitory 5-HT_{1A} receptors at the axon initial segment from the raphe-

spinal pathway ending long-lasting MU activity (196). Thus serotonin, may contribute to both the activation and ending of self-sustained firing.

The benefits of rotation of MU activity are numerous. Firstly, it has been proposed as beneficial in maintaining a constant force production whilst allowing restitution of the muscle fibres of the silent MUs and recover their ability to generate force (213-215). Secondly, rotation of activity may protect postural muscles from excessive fatigue during sustained contractions (90,216). Finally, rotation of activity allows for aerobic training of the muscle fibres and is likely to be responsible for the maintenance of homogenous slow muscle-fibre properties in postural muscles (104).

Rotation has been described for a century (89,213,215) but it is still a challenge to quantify the phenomenon in spontaneous tonic muscle firing.

Strengths and weaknesses

We have used a pain free intramuscular EMG recording method that the subjects tolerated well and that permitted full mobility of the spine. We allowed the electrode to be pulled in and not out by having the subject move in all ranges of motion before the final CT image and before anchoring the electrode to the skin.

We have recordings of long durations that allow ample time for the MU to display activity, rest and fatigue. This provided a substantial number of MUAPs and MUs to analyse from. Furthermore, we chose common daily postural activities such as standing and sitting with little instruction in order to obtain recordings from spontaneous occurring activity. Recordings were made bilaterally that allowed us to use ALBP subjects with unilateral pain as their own control and we also used the same subjects before and after manipulation in a repeated measures design enabling longitudinal analysis and fewer ALBP subjects.

The non-pain and ALBP populations have different baseline characteristic; age, gender and other demographic criteria, rendering them not directly comparable. It was difficult to select subjects with ALBP of similar age to the non-pain group.

After meeting basic inclusion criteria, ALBP patients were either included or excluded primarily based on reported symptoms and examination findings. Since there are no validated clinical tests that differentiate discogenic pain and facet joint pain, we were not able to conclusively discern the pathoanatomical structure responsible for the patient's symptom. Interestingly, we found evidence of disc disease in all but one ALBP patient in spite of no overt neurological findings upon examination. Our pain population may therefore be a mix of facet joint pain, discogenic pain, and soft tissue pain. The neurophysiological response to pain and HVLA-SM could have different effects on patients with dissimilar pain producing tissues (40).

Subjects were not select based on a particular posture and as a result the study population exhibited a variety of different postural strategies. Such strategies may be dependent on gender, paraspinal muscle endurance (217), mood, personality as well as lumbar instability patterns in the ALBP group (218). Determining the involvement of different motoneuron firing characteristics in different postural strategies is not possible in such a varied group of pain-free and ALBP subjects and it may be interesting for future research to investigate the differences between such postures by examining more homogeneous groups.

In order to minimise radiation exposure to subjects we did not verify the electrode placement after the experiment was completed. The target muscle is small and ideally we should have verified visually the position of the electrode after the experiment. Although aiming for the deepest fascicle we cannot be certain that we measured from the fascicles innervated by the vertebral segment we aimed for. Likewise, we may have missed fascicles displaying motoneuron pathology underlying the rapid atrophy noticed in LBP. Optimal implantation must be confirmed by dissection and is not a viable method for research in humans. We did however measure the length of the electrode under the skin upon removal and found that all electrodes had been drawn into the tissues. All CT images of the electrode bundles were obtained after the subject had moved the spine in flexion, extension and rotation, and in all but one subject the electrode tip had not moved substantially from the target. The soft hook was intact but stretched out upon removal. This experimental method is commonly

used but to our knowledge has not been assessed for accuracy against alternative implantation guidance methods, such as CT, that provide better visualisation of the electrode.

In one subject the soft hook did not hold and the electrode had curled itself in the subcutaneous layer superficial to the muscle. This subject did not display any spontaneously occurring muscle activity, only voluntary activity. We decided to include the data from this subject since distance from target did not show any significant effect in any of the statistical models. The lack of activity in this subject may however indicate less activity in the superficial part of the paraspinal musculature during the spontaneous postures we tested.

The fine-wire-electrode to cable connection was sensitive to movement and created artefacts that sometimes made it difficult to follow units over time during periods of movement. The EMG signal that is evident during spinal manipulation may be a movement artefact. If this is indeed an artefact from electrode movement within the muscle, subsequent recordings may not be from the same MUs as at the start of the experiment. Movement artefacts were not a concern during slow, controlled movements such as during flexion, which had the greatest movement range.

Accurately determining discharge rate is dependent on appropriately sorted MUAP. Difficulty correctly determining thresholds for spike discrimination results in some spikes missing (drop outs) in periods where the amplitude of the spikes gradually fell into the background “grass”. Periods where the MUAPs were so similar that discrimination was not possible were not included in the final dataset available for analysis. This makes our data robust, but at the same time excluded a substantial part of the available material. To allow for all the recorded EMG material to be analysed we used the single fibre electrode as a gross electrode and included all available activity in a separate dataset for total activity.

Total activity determination was performed by including all periods where single spikes were present, including periods where neither Spike2 nor the investigator were able to discriminate and separate spikes, as well as periods with spikes present together with electrical noise signals. This procedure was done manually which may

introduce human error to the total activity material. We were interested in the duration of activity and not the amount of gross EMG activity. This method was chosen instead of area under the curve in order to avoid giving emphasis to signals from electrical noise. Furthermore, total activity is only a representation of the MU activity close to the electrode and may not be representative of whole muscle activity.

CDC is a measure of how well correlated two concurrent MUs are firing. The high pass filtering recommended for CDC analysis removes low-frequency oscillations including oscillations linked to respiration. CDC analysis was performed in order to give an indication of common drive and is dependent on optimally sorted MUAPs. We included all periods where at least two units were active at the same time and used long durations, up to several minutes, if possible. Others have commonly used epochs of 5 s duration and in part of the material we tested whether different epoch size gave a different average. Long durations gave a slightly lower CDC but not substantially different and we chose to keep the long durations to avoid selection bias and add robustness to the material. Unfortunately, this increased the likelihood of including periods with missing spikes. Choosing a narrow time window ± 50 ms for detection of maximum CDC may discriminate against MUs that are under a strong common drive and discharging with a time lag longer than 50 ms.

To date there has been no validation of the criteria for detecting plateau potentials in animal or human motoneurons. The research community is yet to agree on criteria for quantifying self-sustained firing. Therefore it is difficult to determine to what extent self-sustained firing exists in a given set of fine-wire EMG recordings. This is particularly the case in our study design where we are not inducing MU activity (by use of vibration, etc.), but assess spontaneously occurring activity. The expression of plateau potentials in humans and animals differs; in animal experiments plateau potentials have been observed as an abrupt change from one discharge range to another. This has not been observed in humans. In regards to human studies, the following criteria have been used (107):

1. Recruitment threshold being greater than derecruitment threshold (219).

2. Rapid acceleration in motor unit discharge upon recruitment, with concurrent measure of motor drive (74). A sudden increase in the rate of one motor-unit discharge without simultaneous changes in activity of other units indicates that the common drive to the motoneuron pool is constant, and that a change in individual units is an expression of intrinsic membrane properties such as plateau potential.

3. Decreased recruitment threshold with repetitive contractions (warm-up) (219).

Of these 3 criteria, both 1. and 3. have been brought into question by Fuglevand et al. (180) in a study where recruitment thresholds of single motor units were unchanged during repeated contractions, and where the derecruitment force was consistently greater than the recruitment force. For the purpose of this study, self-sustained firing is defined as where a MU (test unit) was recruited from inactivity to its preferred discharge range or was abruptly derecruited while the discharge rate of other units which were already active (reference units) remained unchanged.

As mentioned before there is no set standard for determining rotation between units. In our analysis rotation of units has been characterised as occurring when a MU (test unit) was recruited from inactivity to stable tonic discharge while another MU (reference unit) continued to fire with little or no change in discharge rate, and the reference unit subsequently was derecruited while the more recently recruited test unit continued to fire with little or no change in discharge rate. Instances where two units qualified according to the above criteria but discontinued firing due to a shift in posture or a deep sigh were thus not meet the criteria of rotation. We have therefore chosen not to quantify the incidence of self-sustained firing in our material, but shown that it exists both in non-pain and ALBP subjects.

Spinal manipulation has been shown to differ substantially between practitioners and was therefore performed by a single chiropractor ensuring similar procedure across all subjects. The SM-thrust time was comparable to other studies (144) but the force applied by the chiropractor was not measured.

It is assumed that spinal manipulation alleviates pain arising from facet joint dysfunction. Indahl (40) found that stretching the facet capsule by injection of saline

caused an inhibition of EMG activity induced by stimulation and that the EMG activity was different when stimulating the annulus as opposed to stimulating the joint capsule. Disk pathology was present in nearly all of our ALBP subjects. We may therefore have a group of subjects with primarily discogenic pain and not responsive to joint manipulation the same way as a group of ALBP subjects with an established facet joint pain origin.

Implications

- Both the low discharge rate range for LM and self-sustained firing properties point to the deep LM being a postural muscle capable of long lasting force production that both protects and supports the lumbar spine.
- An underlying common drive ensures bilateral control of the spine.
- LM motoneurons display different properties during spontaneous as opposed to voluntary activation. This must be taken into account both when performing and interpreting research.
- Our findings support neither the pain-spasm-pain theory nor the pain-adaptation theory.
- From our study the firing properties between deep and more superficial LM fascicles appears to demonstrate no significant differences.
- The firing properties we have explored do not provide an explanation for the underlying mechanisms of the rapid atrophy observed in the deepest fascicles of the LM. Fatty infiltration was one of the reasons why we chose to study the deep LM. If the fatty infiltration is generalised to all fascicles innervated by the same segment it will be most prominent in the in the deepest fascicle, while the fatty infiltration of the more distal and superficial fascicles will be less detectable as they hide between fascicles from other segmental levels.
- Interspike interval variability analysis may be a method to reveal the potential influence that pain may have on MU firing.
- Interspike interval variability changed significantly after HVLA-SM, which may be a result of a reduction in neuronal noise to the MU. It is possible that this then represents one of the underlying effects of spinal manipulation.

- If pain reduction alone is responsible for the reduced variability, the effect on variability should be measurable after other pain modulating therapies as well.
- There may be subgroups in the material that we were unable to detect due to small numbers. Power calculations based on our data may give rise to larger studies on particular subgroups.

Conclusions

The neural drive to the lumbar multifidus is dependent on the descending drive from supraspinal centres and the afferent excitatory and inhibitory segmental input, integrated and transmitted through the spinal motoneurons. An overall balance of the intrinsic spinal mechanisms, peripheral inputs and excitatory or inhibitory inputs from supra-segmental sources, governs the behaviour of the individual. These individual differences make it a challenge to obtain consistent data in both non-pain and in ALBP subjects in an experimental set up investigating gross activity.

Common drive is significantly different in spontaneous as opposed to voluntary activity, and there appears to be a difference in bilateral common drive to the spine during ALBP. The difference between spontaneous and voluntary activity is also true when measuring ISI variability. Care should be given to differentiate between spontaneously occurring activity as opposed to voluntary control of tonic activity when designing an experiment protocol for measuring MU activity to postural muscles. Despite being seemingly similar protocols, they can result in quite different MU output.

Lumbar multifidus appears to be governed by intrinsic motoneuron properties such as self-sustained firing enabling it to fire with a steady discharge rate with little supra-segmental modulation during quiet postural activities such as standing and sitting. This allows for periods of activity and rest shared between MUs promoting muscle endurance as well as continued support to passive structures. Our study was not able to demonstrate rotation of MU activity in ALBP subjects. Methods to quantify rotation need to be established in order to determine whether rotation is impeded during ALBP.

The reduction in ISI variability that we found after HVLA-SM suggests an influence on neuronal noise and possibly on the intrinsic motoneuron firing mechanisms thought to be important for long lasting tonic firing in postural muscles. This is the first study to use interspike interval variability as an outcome measure after HVLA-SM in ALBP and our findings need to be confirmed. Our data will hopefully add to the reference base for studying the low back in health and disease.

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