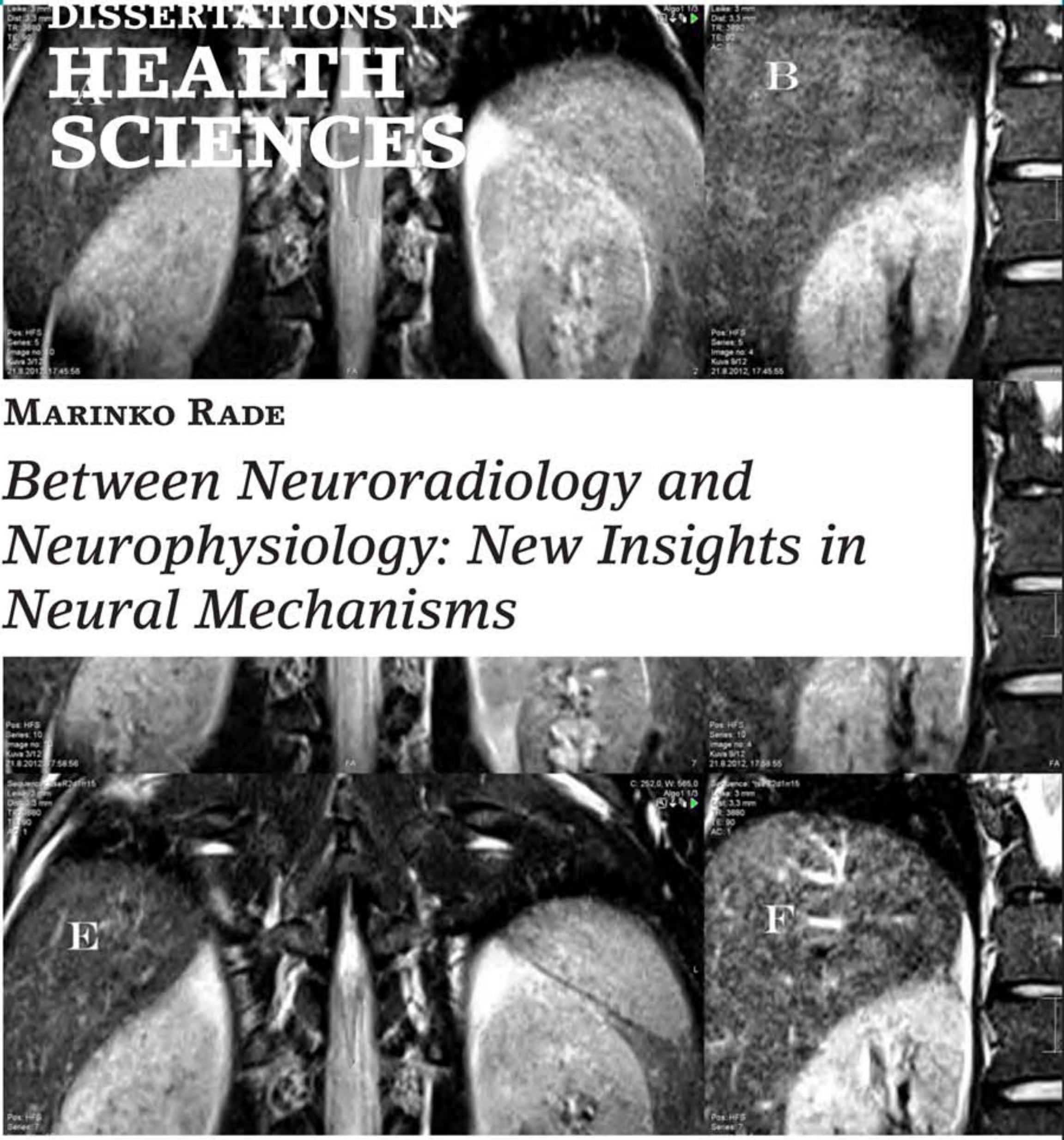
DISSERTATIONS IN
HEALTH
SCIENCES



**Marinko Rade**

# *Between Neuroradiology and Neurophysiology: New Insights in Neural Mechanisms*

Publications of the University of Eastern Finland
*Dissertations in Health Sciences*

UNIVERSITY OF
EASTERN FINLAND

AUTHOR: MARINKO RADE

# *Between Neuroradiology and Neurophysiology: New Insights in Neural Mechanisms*

To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in Kuopio on Friday, May 8th 2015, at 12 noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
Number 278

Department of Physical and Rehabilitation Medicine, Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland
Department of Radiology, Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland
Department of Applied Physics, Biosignal Analysis and Medical Imaging Group, Faculty of Science and Forestry, University of Eastern Finland

Kuopio
2015

Kopio Niini Oy
Helsinki, 2015

Distributor:
University of Eastern Finland
Kuopio Campus Library
P.O.Box 1627
FI-70211 Kuopio, Finland
http://www.uef.fi/kirjasto

ISBN (print): 978-952-61-1740-9
ISBN (pdf): 978-952-61-1741-6
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

| | |
|---|---|
| Author's address: | Department of Physical and Rehabilitation Medicine,<br>Kuopio University Hospital<br>KUOPIO<br>FINLAND |
| Supervisors: | Associate Professor Olavi Airaksinen, M.D, Ph.D.<br>Department of Physical and Rehabilitation Medicine,<br>Kuopio University Hospital<br>KUOPIO<br>FINLAND |
| | Associate Professor Markku Kankaanpää, M.D, Ph.D.<br>Department of Physical and Rehabilitation Medicine<br>Tampere University Hospital<br>TAMPERE<br>FINLAND |
| Reviewers: | Professor Jeremy Fairbank, MA, MD, FRCS.<br>Former president of the International Society for the Study of Lumbar Spine (ISSLS)<br>Professor of Spine Surgery in the Nuffield Orthopaedic Centre,<br>Oxford University Hospital<br>Oxford School of Medicine<br>University of Oxford<br>OXFORD<br>UNITED KINGDOM |
| | Professor Jaro Karppinen, M.D, Ph.D.<br>Professor of Physical and Rehabilitation Medicine,<br>Department of Physical and Rehabilitation Medicine,<br>Oulu University Hospital<br>University of Oulu<br>OULU<br>FINLAND |
| | Finnish Institute of Occupational Health<br>HELSINKI<br>FINLAND |
| Opponent: | Professor Jacob Patijn, M.D, Ph.D.<br>1st Science Director of the International Academy of Manual/MusculoskeletalMedicine (IAMMM)<br>Department of Anaesthesiology/Pain Management<br>Maastricht University Medical Centre<br>MAASTRICHT<br>THE NETHERLANDS |

Rade, Marinko
Between Neuroradiology and Neurophysiology: New Insights in Neural Mechanisms
University of Eastern Finland, Faculty of Health Sciences
Publications of the University of Eastern Finland. Doctoral Programme of Clinical Research, Dissertations in Health Sciences number 278. Year 2015. 125 p.

ISBN (print): 978-952-61-1740-9
ISBN (pdf): 978-952-61-1741-6
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

## ABSTRACT

Starting from the assumption that nerves are not simply inert tubular structures limited to the conduction of sensory and motor information, but that they do also show inherent protective mechanisms that may impact on their very function, this doctoral dissertation is going to present arguments to support the notion that i) nerves move, and that their movements can be quantified using appropriate non-invasive techniques, and ii) the human body does present some innate mechanisms to protect nerves from excessive mechanical forces.

In this thesis T2 weighted turbo spin echo fat saturation magnetic resonance sequences were used to visualize the conus medullaris displacement in response to unilateral and bilateral SLR following the notion that the magnitude of conus medullaris displacement in response to SLRs is proportional to the displacement of L5 and S1 nerve roots and dependent on the number of nerve roots involved in the movement (i.e. unilateral and bilateral SLRs), as dictated by the "principle of linear dependence" here presented for the first time.

Furthermore, surface electromyography was employed to quantify muscular responses to neural mechanical testing in in-vivo and structurally intact human subjects in order to explore whether muscles can be reflexively activated in order to protect the nerves by i) avoiding further elongation of neural bed, ii) shortening the neural pathway in order to decrease tensile stress.

The neuroradiology line results show that the conus medullaris displaces consistently in response to SLRs and that the magnitude of displacement is doubled with bilateral SLR, suggesting that a linear relationship may exist between magnitude of conus displacement and number of nerve roots involved into this movement. Moreover, the unpublished data presented in this thesis shows that this relationship is maintained at higher degrees of hip flexion.

The neurophysiology line results show that changes in myoelectric activity in the test muscles are an expression of a specific protective response related to mechanical force acting on peripheral neural tissues, and that these can be modified with positions that decrease tensile forces from the brachial plexus and peripheral nerves. The unpublished data related to this line of research shows clearly that this activity is modulated and highly specific.

With the cumulative results of these two lines of research, in which nerves are shown to move in response to body movements (neuroradiology) and muscular protective mechanisms in response to mechanical stress applied on peripheral nerves are proved to exist (neurophysiology), we hypothesize that the sliding of neural structures in anatomical tunnels and canals may be a protective effect which preserves the spinal cord, neural roots and peripheral nerves from strain and compression, and that inherent protective mechanisms are activated in case sliding effect fails. Importantly, it seems that these reactions do bear aspects of predictability.

National Library of Medicine Classification: WL 400
Medical Subject Headings: nerve; nerve root; spinal cord; sciatica; radiculopathy; low back pain; straight leg raise; muscle; electromyography; epicondylalgia; elbow;
tennis elbow syndrome; radial nerve; nociceptive flexion reflex.

Rade, Marinko
Between Neuroradiology and Neurophysiology: New Insights in Neural Mechanisms
Itä-Suomen yliopisto, terveystieteiden tiedekunta
Publications of the University of Eastern Finland. Doctoral Programme of Clinical Research, Dissertations in Health Sciences number 278. 2015. 125 s.

ISBN (print): 978-952-61-1740-9
ISBN (pdf): 978-952-61-1741-6
ISSN (print): 1798-5706
ISSN (pdf): 1798-5714
ISSN-L: 1798-5706

## TIIVISTELMÄ

Ihmisen hermot eivät ole vain yksinkertaisia putkirakenteita, joiden tehtävänä on välittää sekä tunto- että liikeinformaatiota, vaan niiden toimintaan liittyy myös yksittäisiä suojamekanismeja, jotka voivat vaikuttaa niiden toimintaan. Tämän väitöskirjatutkimuksen tarkoituksena on esittää niitä havaintoja, jotka tukevat sitä, että hermot liikkuvat ja niiden liikkeitä voidaan mitata ei-kajoavilla tekniikoilla. Lisäksi ihmisen kehossa on sisäisiä suojamekanismeja hermoihin kohdistuvia mekaanisia voimia vastaan.

Magneetti kuvauksessa T2 painotetuilla rasvasaturaatio segvensseilla voitiin havainnollistaa selkäytimen conuksen liikevasteita joko toispuoleisen tai molemmin puoleisen suoran jalan nostotestin yhteydessä. Conuksen liike kuvastaa L5 ja S1 hermojuurien liikettä ja näyttää olevan riippuvainen hermojuurien lukumäärään. Lisäksi molemmin puolinen suoran jalan nosto lineaarisesti lisää liikettä – toisin sanoen ilmiöön liittyy lineaarinen riippuvuus.

Niinikään pinta ENMG mittauksessa voitiin mitata lihasvasteita hermojen venytys testauksen yhteydessä in vivo asetelmassa rakenteellisesti terveillä koehenkilöillä. Tämän mittauksen tarkoituksena oli selvittää voidaanko lihaksia reflektoorisesti aktivoida suojaamaan hermorakenteita joko välttämään ylimääräisen venymisen hermorakenteessa tai lyhentämällä hermovastetta tarkoituksena alentaa jännityksestä johtuvaa kuormitusta hermoihin.

Neuroradiologisten tutkimusten tulokset osoittivat että conus medullaris liikkuu johdonmukaisesti suhteessa suoran jalan nostotestin tulokseen. Conuksen liike lisääntyy kaksinkertaiseksi molempien raajojen suoran jalan nostotestin yhteydessä verraten yhden raajan nostotestin tulokseen. Viime mainittu havainto viittaa siihen että conuksen liikkeen määrä saattaa olla yhteydessä hermojuurien lukumäärään. Lisäksi tässä yhteydessä esitetty vielä julkaisematon materiaali osoittaa että tämä yhteys näyttää lisääntyvän suuremman lonkan koukistus liikkeen aikana.

Neurofysiologisten tutkimusten tulokset osoittavat että muutokset lihasaktiivisuudessa mitatuissa testilihaksissa ovat spesifisiä suoja vasteita mekaaniseen kuormitukseen joka kohdistuu ääreishermoihin. Näitä suojavasteita voidaan muovata asennoilla jotka alentavat jännnitystä hartiapunoksesta ja ääreishermoista. Vielä julkaisematon materiaali suhteuttuna neurofysiologisiin tutkimuksiin osoittaa selkeästi, että tätä aktiivisuutta säädellään hyvin spesifisesti.

Yhdistämällä nämä kaksi tutkimuslinjaa, joissa todettiin siis hermojen liikevasteita kehon liikkeisiin (neuroradiologia) sekä lihasten suojamekanismeja mekaaniseen kuormitukseen perifeerisissä hermoissa (neurofysiologia) havaittiin sekä liikettä että myöskin sähköisiä vasteita. Tämän perusteella syntyy hypoteesi, että hermorakenteiden liukuminen anatomisissa kanavissa ja tunneleissa näyttäisi olevan suojamekanismi, jolla suojataan selkäydintä, hermojuuria ja ääreishermoja venytystä ja puristusta vastaan. Nämä suojamekanismit aktivoituvat niissä tapauksissa, kun liukumisvaikutus epäonnistuu. Merkittävää näyttää olevan se että näitä reaktioita voidaan ennakoida.

National Library of Medicine Classification: WL 400
Medical Subject Headings: nerve; nerve root; spinal cord; sciatica; radiculopathy; low back pain; straight leg raise; muscle; electromyography; epicondylalgia; elbow;
tennis elbow syndrome; radial nerve; nociceptive flexion reflex.

# Acknowledgements

It was nearly 4 years ago when I first heard my main doctoral supervisor and Associate professor Olavi Airaksinen. At that time I was living in Italy, and I remember a telephone call I made to my father after a 40 minutes-long telephone conversation with Prof Airaksinen, and saying to my father „dad, I heard a Finnish professor and he seems like a very nice guy to work with...I think I will move to Finland“. Of course as every parent with his only child travelling around the world, he and my mom were hoping that at some point I was going to move back to my hometown Rovinj, but he found the courage in his heart to say „son, do whatever you think it is best, and if you believe in it, we will support you“.

And here I am after four fantastic years, leading a regional hospital in my hometown with great research projects going on in Finland, and great friendships collected over the years. Of course, as in every good story, we do have a pile of good results to show that we have been working hard in Finland and not only enjoying our time.

I am and will always be grateful to my main supervisor and now also dear friend Associate professor Olavi Airaksinen for giving me such a nice opportunity, and for having showed in countless situations that he believes in me. These are things I will never forget. I am also very grateful to my second doctoral supervisor Associate professor Markku Kankaanpää; even if we didn't had the chance to meet a lot in person because our working commitments took us apart, he always found the time for very lengthy discussions via telephone. His encouragements helped me a lot over these years.

I am also very grateful to Professor Ritva Vanninen, to Medical physicist Mervi Könönen and Radiologist Jarkko Marttila for believing in my ideas, for their unconditioned support and for the long evenings spent scanning volunteers with the Radiology department when everyone else was at home with their families and the hospital was empty. Big thanks also for the Biosignal Analysis and Medical Imaging Group from the Department of Physics of University of Eastern Finland. Before designing these two lines of research I engaged in courses organized by the Department of Physics in order to fully understand the principles of the devices we was going to employ. The newly acquired knowledge allowed for several problem solving sessions, and most of all, allowed me to recognize soon enough bad research designs. It takes time and humbleness to admit our own mistakes before it is too late, but also knowledge. It is for this reasons that I am particularly grateful to this department. Of these outstanding scientists I would like to point out the Postdoctoral researcher Saara Rissanen and Professor Pasi Karjalainen. Thanks for believing in this project and investing your time in it.

Of course my gratitude goes also to Michael Shacklock, my instructor at the beginning of my career and beloved friend and irreplaceable collaborator now. You are a volcano of ideas; some of them are just crazy and some of them are just brilliant. You are

the one shooting for the stars and I am the one re-adjusting the aim and telling that we don't have enough fuel to reach the stars right now, but if we plan our steps right we will eventually get there. Every good team needs a dreamer and an engineer... I am sure we will do great things together.

Thanks Susanna Kopponen for having allowed me to assist you in all those neurosurgeries, I really learned a lot with you while still having fun! Thanks to Juha Pekka Tikkanen, you were the first one to welcome me upon my arrival in Kuopio and to help me settling up in a city far away from home. You helped a lot, believe me, and I will never forget it.

Of course the life in Kuopio was not just about work. Thanks to the person I consider one of my best friends, Ville Pekka Vuorinen, and to Henri Tuomilehto, Jussi Hyyrynen, Mika Pohjonen, Antti Lepola, Juha Seppä, Marko Kivimäki and Juhani Sneck. Without you guys life would be just boring! Thanks for my basketball friends Joona Lähdeaho and Jere Reijula, you helped really a lot with all my experiments and kept me in good physical shape. Thanks to my roommate and little brother Aleksei Torsukov, it was really nice to see you growing up and becoming a man. Keep going and don't stop until you get the white helmet you want so much, I believe in you.

And last but most important, thanks to my mum and dad Marisa and Đulijano Rade: thanks for all your support, for having taught me how to build something from nothing and how to never give up even in the most adverse situations. And thanks to my girlfriend Ana for her patience and stubbornness in dealing with a boyfriend who is always travelling and maybe also working too much. Sorry. Many thanks for accepting me the way I am.

I hope one day you will all be proud of me.

# List of the original publications

This dissertation is based on the following original publications:

I Rade M., Könönen M., Vanninen R., Marttila J., Shacklock M., Kankaanpää M., Airaksinen O. 2014 young investigator award winner: In vivo magnetic resonance imaging measurement of spinal cord displacement in the thoracolumbar region of asymptomatic subjects: Part 1: Straight leg raise test. *Spine. 39(16):1288-1293, 2014.*

II Rade M., Könönen M., Vanninen R., Marttila J., Shacklock M., Kankaanpää M., Airaksinen O. 2014 young investigator award winner: In vivo magnetic resonance imaging measurement of spinal cord displacement in the thoracolumbar region of asymptomatic subjects: Part 2: Comparison between unilateral and bilateral straight leg raise tests. *Spine. 39(16):1294-1300. 2014.*

III Rade M., Shacklock M., Peharec S., Bačić P., Candian C., Kankaanpää M., Airaksinen O. Effect of cervical spine position on upper limb myoelectric activity during pre-manipulative stretch for Mills manipulation: A new model, relations to peripheral nerve biomechanics and specificity of Mills manipulation. *Journal of Electromyography and Kinesiology. 22: 363-369, 2012.*

IV Rade M., Shacklock M., Rissanen S., Peharec S., Bačić P., Candian C., Kankaanpää M., Airaksinen O. Effect of glenohumeral forward flexion on upper limb myoelectric activity during simulated Mills manipulation: Relations to peripheral nerve biomechanics. *BMC Musculoskeletal Disorders. 15:288. 2014.*

The publications were adapted with the permission of the copyright owners.

This thesis contains unpublished data presented in the *Results* section.

# *Contents*

# Abbreviations

| | |
|---|---|
| 3D | 3-dimensional |
| A/D Board | Analogue-to-Digital Board |
| Ag/AgCl | Silver/Silver chloride electrodes |
| BMI | Body Mass Index |
| BPTT | Brachial Plexus Tension Test |
| BSAMIG | Biosignal Analysis and Medical Imaging Group |
| CEO | Common Extensor Origin |
| EMG | Electromyography |
| ETL | Echo Train Length |
| FID | Free Induction Decay |
| FLAIR | Fluid Attenuated Inversion recovery |
| FOV | Field of View |
| GΩ | Giga Ohm |
| Hz | Hertz |
| IVD | Intervertebral Disc |
| kΩ | Kilo Ohm |
| LBP | Low Back Pain |
| MAV | Mean Amplitude Value |
| MDF | Median Freqecy |
| MNF | Mean Frequency |
| MNT | Median Neurodynamic Test |
| MR | Magnetic Resonance |
| MRI | Magnetic Resonance Imaging |
| ms | Millisecond |
| MVC | Maximal Voluntary Contraction |
| NFR | Nociceptive Flexor Reflex |
| NMV | Net Magnetization Vector |
| PACS | Picture Archiving and Communication System |
| RF | Radio Frequency |
| RNT | Radial Neurodynamic Test |
| ROM | Range of Motion |
| SD | Standard Deviation |
| sEMG | Surface Electromyography |
| SLR | Straight Leg Raise |
| SMM | Standard Mills Manipulation |
| TE | Echo Time |
| TI | Time from Inversion |
| TR | Repetition Time |
| ULTT | Upper Limb Tension Test |
| UNT | Ulnar Neurodynamic Test |
| VAS | Visual Analogic Scale |
| Wi-Fi | Wireless Fidelity |

# 1 Introduction

Daily motions can be extremely various in terms of movements of peripheral nerves.

For example office workers can be writing for hours on computer keyboards, repeatedly compressing the median nerve in its pathway into the carpal tunnel but not all of them will develop carpal tunnel syndrome. Water polo and handball players are vulnerable for stretching of the median nerve around the glenohumeral joint and in front of the elbow, and for compression of the nerve between the two heads of pronator teres muscle during the preparation for a shoot, but not all of them will become symptomatic and will develop peripheral neuritis. Auto mechanics are prone for compression of the median nerve in the carpal tunnel in a similar way as keyboard workers do but not all of them will eventually become our patients. In this doctoral thesis the author will try to present data and information that will hopefully allow us to provide a proper answer to those and other closely related clinical questions in the near future.

It is generally accepted that nerves move. However, it remains to be understood whether the direction and magnitude of such movements can be predicted or not. But why should nerves move within the body in the first place? Our current hypothesis is that they move in order to avoid potentially harmful mechanical forces such as tension and compression. As already shown by Sunderland & Bradley in 1961(1-3), the viscoelastic characteristics of peripheral nerves allow them to elongate between 18 and 22% before occurrence of structural failure (4). Moreover, neural elongation produces relevant changes in neural blood flow in terms of changes in diameter of vasa nervorum. Lundborg and Rydevik (5) have shown in 1973 that 8% of elongation is enough to decrease the blood flow through intraneural veins, while Ogata and Naito (6) showed in 1986 that at 15.7% of elongation all the blood flow through the nerve, both venous and arterial, is completely blocked. From our clinical experience it is well known that if tensile and/or compressive forces are acting on a neurovascular bundle during ultrasound imaging, the vein will always be the first structure to collapse. This is due to its intrinsic low pressure. However, regardless of the fact that is it the vein or is the artery that collapses first, the important notion here is that the blood flow into the nerve does decrease, causing hypoxia into the neural tissues.

Knowing that i) some muscles as biceps brachii and rectus femori may change their length by 65% (7) without occurring in any sort of plastic modification, ii) that nerves often run parallel to muscles and can be stretched by similar movements by which muscles are, iii) that a decrease in venous blood flow in vasa nervorum can occur already at 8% of neural elongation, and that 15% of neural elongation is enough to entirely block the blood flow in vasa nervorum (5,6), iv) that structural damage is likely to occur already at 18% of elongation (4), there must be some innate mechanisms in the human body that protect the nerves from such detrimental forces acting on them during our daily activities.

Mc Lellan and Swash (8) and Wilgis and Murphy (9) introduced what is now called "neural sliding". Nerves slide longitudinally, that is, parallel to the direction of the applied force vector and down their anatomical pathway, in order to avoid tension. In the same way a kid would pull his dog by the leash, and the dog would follow the kid in order not to be choked by his roguish owner, the nerve displaces toward the place where tension is initiated, i.e. down the tension gradient, in order to avoid the onset of adverse mechanical forces into the neural tissue. It becomes only logical to think that this is the most effective way, both in terms of rapidity of action and energy consumption, to avoid the onset of tensile forces into the neural tissue. It is fast because it acts directly in response to mechanical stimuli, and, as this is a passive reaction, it is also effective in terms of energy consumption. It might therefore be said that nerves does slide longitudinally to avoid the establishment of tensile stress into the neural tissue itself.

If it is true that the nerves slide longitudinally to avoid the establishment of tensile stress into the neural tissue, there must also be a mechanism that will protect them from compression. In 1983 Gelberman and colleagues (10) investigated the pressure threshold for peripheral nerve dysfunction by artificially elevating the pressure into the carpal tunnel of asymptomatic subjects. By evaluating motor and sensory latencies and signal amplitude deterioration in the median nerve, they showed that 40 mmHg of compression was enough to induce functional loss and that a direct pressure of only 50 mmHg was enough to block completely the motor and sensory responses. The post-compression recovery phase was also shown to last longer the greater the pressure and the longer period the pressure was applied. In asymptomatic subjects, the median nerve has been shown to displace laterally 1-5 mm in response to tendon movement, effectively avoiding direct compression from underlying tendons (11-14). In other words, nerves seem to avoid compression from the interfacing structures by displacing away from them.

It might be therefore said that longitudinal and transverse sliding are inherent protective mechanisms that protects nerves from excessive mechanical forces. However, in less than ideal situations, things might be different. It has consistently been shown that external adhesions or direct compression on peripheral nerves from interfacing structures have the potential to alter neural mechanics (15-17) and that local inflammation can lead to fibrotization of the perineural connective tissue resulting in loss of gliding ability, with subsinovial connective tissue fibrotization being a consistent finding in carpal tunnel syndrome patients (18-23). In pathological situations, it is common to detect that nerves have lost their sliding capabilities (21,24). While it is not the aim of this thesis to discuss in depth whether decreased neural excursion may be a consequence of hypoxia and micro damage caused by direct tensile or compressive forces acting on the neural tissue itself, it is relevant to state that decreased neural excursion is a consistent finding in peripheral neuropathies (17).

Once we have ascertained that nerves move in order to avoid the establishment of both tensile and compressive forces into and onto the neural tissue, and that these gliding characteristics may be impaired in pathology, it is of clinical value to establish how these movements can be quantified in order to provide tools designed help the clinicians to formulate graded diagnoses. This would in turn allow for more specific treatment management and informed decision making in case surgery is suggested.

In the first part of this doctoral thesis the author is going to explore and discuss i) on the use of magnetic resonance imaging to investigate neural biomechanics into the thoraco-lumbar region of in-vivo and structurally intact asymptomatic human subjects, ii) whether a relationship exists between L5 and S1 lumbar nerve root and spinal cord movement into the vertebral canal, iii) whether these neural movements can be predicted and adopted in clinical settings.

The second part of this doctoral thesis is going to focus on methods of collecting indirect data on neural adaptation mechanisms by means of quantifying the muscular reactions in response to neural mechanical loading in-vivo in structurally intact human subjects. This line of research will be presented in the context of analysis of extraneous muscular reactions to the standard Mills manipulation pre-manipulative positioning, in which the radial nerve and its posterior interosseus branch are hypothesized to be stressed around the elbow during this pre-manipulative positioning. Change of muscular activation patterns and amplitude in response to neural unloading movements performed in proximal joints, cervical spine and shoulder girdle, will be analysed. The rationale underpinning this line of research is that the muscles may be reflexively activated in order to protect the peripheral nerves in the most logical way; by shortening their pathway and opposing the manipulation movement. The author will explore i) whether the overall changes in myoelectric activity in the test muscles are an expression of a specific protective response related to mechanical force production in the neural tissues, and not just the effect of a general increase of myoelectric activity, ii) whether the Mills manipulation specificity for the common extensor tendon origin at the elbow can be improved with the addition of a neural unloading movement to the standard Mills manipulation. Of those, point ii) is of a more practical nature, that is, exploring a matter that may have some immediate clinical application in terms of improvement in specificity of a commonly used Grade C manipulation at the elbow, but with the final aim of setting the path to investigate far more deep and complex neural mechanisms and pathways allowing for such muscular activation likely in function of neural protection.

It is now known that neural tissues move in the body. However this dissertation goes further by trying to provide an answer to the general research question of how can neural movements be quantified using non-invasive techniques. This will be achieved in a way that offers new data on the subject, particularly in aspects that have not been studied before; spinal cord movement and muscular protective effects during limb movements that produce excursion of nerve tissues. It is the author's strong belief that in order to explore the normal neural adaptation mechanisms, the principle of *no- harm* has to be respected, that is, the investigation methodologies have to be non-invasive.

# 2 *Review of the Literature*

## 2.1 RESEARCH LINE N.1: NEURORADIOLOGY

### 2.1.1 Anatomy of the lumbar spine

The anatomy of the human spine has been described in details by Bogduk and Twomey (25), Singh (26) and Hansen (27). The essential structures forming the lumbar spine are described based on those books, unless otherwise stated.

### *2.1.1.1 The vertebral column*

The *vertebral column* or *spinal column* forms the central axis of the human body and is usually composed of 33 vertebrae distributed as follows:

*Cervical spine*: 7 vertebrae, of which the first is called the atlas (C1) and second the axis (C2). *Thoracic spine:* 12 vertebrae each articulating with a pair of ribs. *Lumbar spine:* 5 vertebrae. The lumbar vertebrae are relatively large compared to the cervical and thoracic ones and this may be due to their function of bearing the weight of the trunk while being fairly mobile, but not nearly as mobile as the cervical vertebrae. *Sacral spine:* it consists of five fused vertebrae for stability in the transfer of weight from the trunk to the lower limbs. *Coccyx:* four vertebrae in total, with Co1 being often not fused, and Co2-Co4 fused. The actual number of vertebrae can vary, especially the number of coccygeal vertebrae.

### *2.1.1.2 Bony and ligamentous structures of the lumbar spine and formation of the lumbar canal*

A "typical" vertebra has the following bony features, listed in a frontal to dorsal direction:

Vertebral body: the weight-bearing portion of a vertebra that tends to increase in size as one descends the spine. Pedicles: paired portions of the vertebral arch that attach the transverse processes to the body. Transverse processes: the lateral extensions from the union of the pedicle and lamina. Laminae: paired portions of the vertebral arch that connect the transverse processes to the spinous process. Articular processes or facets: two superior and two inferior facets for articulation with adjacent vertebrae. Zygapophyseal joints: formed by the articular processes or facets of two contiguous vertebrae. Spinous process: a projection that extends posteriorly from the union of two laminae.

The lumbar vertebrae are connected by intervertebral discs (IVD) placed between the adjacent vertebral bodies. The IVD is composed of the *anulus fibrosus,* which runs obliquely from one vertebra to another, and the *nucleus pulposus,* which is a highly hydrated structure surrounded by the anulus fibrosus, which provides the strongest attachment between the adjacent vertebras while enabling large amount of reciprocal movement and transmitting and partly absorbing axial shocks.

In addition to the above listed bony features, the lumbar vertebrae include special features as attachment of muscles and ligaments, listed here in a frontal to dorsal direction:

*Anterior longitudinal ligament:* attached on the anterior upper and lower borders of the lumbar vertebral bodies. *Posterior longitudinal ligament:* attached on the posterior upper and lower borders of the lumbar vertebral bodies. *Right crus of diaphragm:* attached on the front of the upper three lumbar vertebral bodies (L1 to L3). *Left crus of diaphragm:* attached on the front of the upper two lumbar vertebral bodies (L1 to L2). *Psoas major:* with its deep part originating from the transverse processes of L1 to L5 lumbar vertebrae and the superficial part originating from the lateral surfaces of the last thoracic vertebra and of L1 to L5 lumbar vertebrae. *Ligamenta flava:* strong thick ligaments attached to the laminae of adjacent vertebrae. *Posterior layer of thoraco-lumbar fascia:* attached to the spinous processes of lumbar vertebrae. *Supraspinous and interspinous ligaments:* attached to the spinous processes of lumbar vertebrae. *Erector spinae and multifidus muscles:* attached to the spinous processes of lumbar vertebrae. *Middle layer of thoraco-lumbar fascia:* attached to the tips of transverse processes of all lumbar vertebrae. *Anterior layer of thoraco-lumbar fascia:* attached to the faint ridge on the front of transverse processes. *Multifidus and intertransverse muscles* are attached to the mammillary processes. *Iliolumbar ligaments:* attached to the tips of the transverse processes of the fifth lumbar vertebra.

Two vertebrae, the IVD in-between and zygapophyseal joints form the functional spinal unit (28). By contiguity the following structures or tunnels are formed:

*Vertebral arch*: a projection formed by paired pedicles and laminae. *Vertebral notches***:** superior and inferior semicircular features that in articulated vertebrae form an intervertebral foramen. *Intervertebral foramen* or *foramina*: the space or tunnel traversed by spinal nerve roots and associated vessels and delimited proximally and caudally by the vertebral notches, anteriorly by the posterior part of the IVD and vertebral body, posteriorly by the articular processes or facets and the zygapophyseal joints. *Vertebral foramen* or *vertebral canal*: a foramen formed anteriorly by the vertebral body and laterally and posteriorly by the vertebral arch as well as the ligament flava attached to the bony laminae of adjacent vertebrae. It contains and protects the spinal cord and its meningeal coverings.

Relevant vertebral structures are presented in figures 1 and 2.

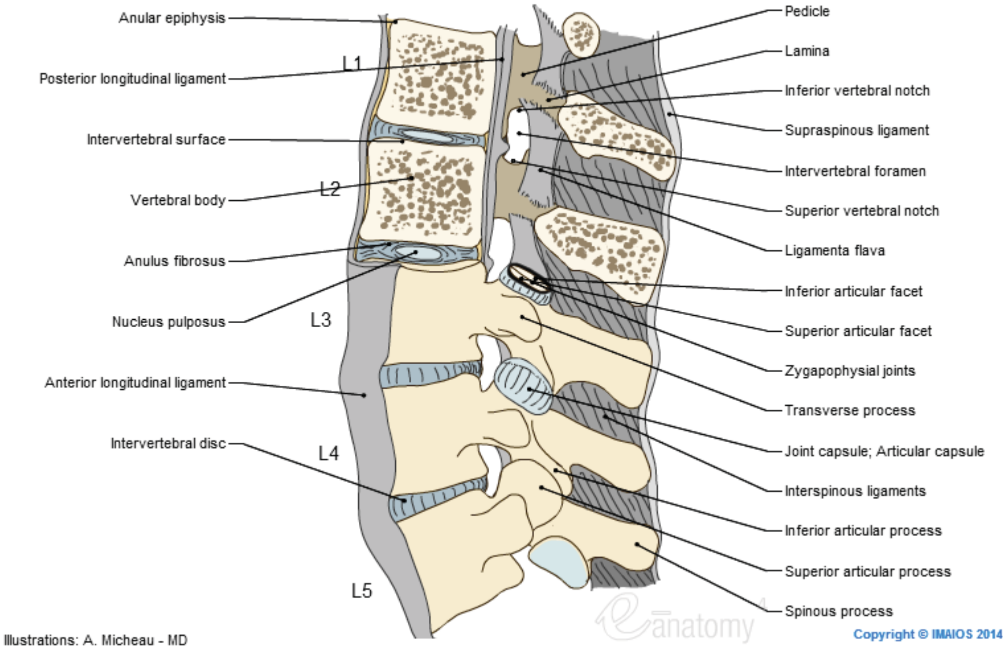


*Figure 1.* Normal anatomy of the lumbar spine, lateral view. From Imaios.com, with permission.

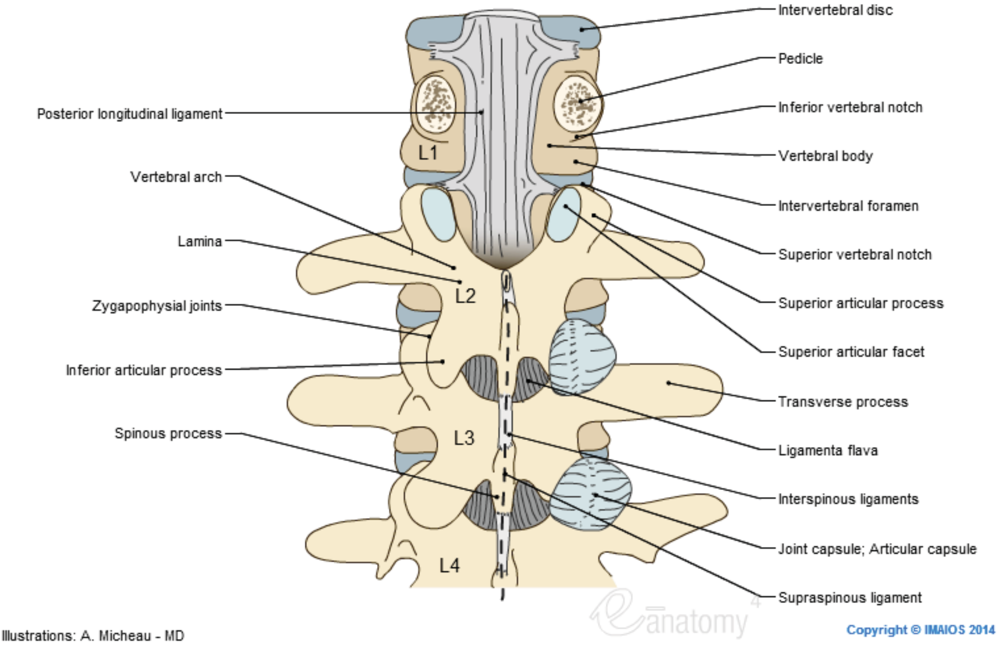


*Figure 2.* Normal anatomy of the lumbar spine, posterior view. From Imaios.com, with permission.

### 2.1.1.3 *Neural tissues into the lumbar spine*

The *spinal cord* or *medulla* is the part of the central nervous system that lies into the vertebral canal. In adults, it extends caudally from the brainstem, running from the medullary-spinal junction located at the level of the first cervical vertebra (C1) to about the level of the twelfth thoracic (T12) or first lumbar (L1) vertebrae. As it runs into the vertebral canal, it is protected by the spinal meninges: dura mater, arachnoid mater and pia mater. Between the arachnoid mater and pia mater there is the subarachnoid space, which contains the cerebrospinal fluid and blood vessels supplying the spinal cord.

Two regions of the spinal cord are enlarged to accommodate the greater number of nerve cells and connections needed to process information originating from the upper and lower limbs. These are: the *cervical enlargement* that includes the segments of C5-T1 and the *lumbar enlargement* that includes the spinal cord segments in L2-S3 (Figure 3). As the vertebral column is considerable longer than the spinal cord running into the vertebral canal, lumbar and sacral nerve roots run vertically for some distance into the vertebral canal before reaching their foramina, forming a collection of nerve roots known as the *cauda equina* (Figure 3). The *filum terminale* is a thin fibrous band that originates at the *conus medullaris* or *medullar cone,* runs distally into the subarachnoid space until S2 and inserts on the dorsum of the coccyx. The functional significance of this structure is still matter of debate.

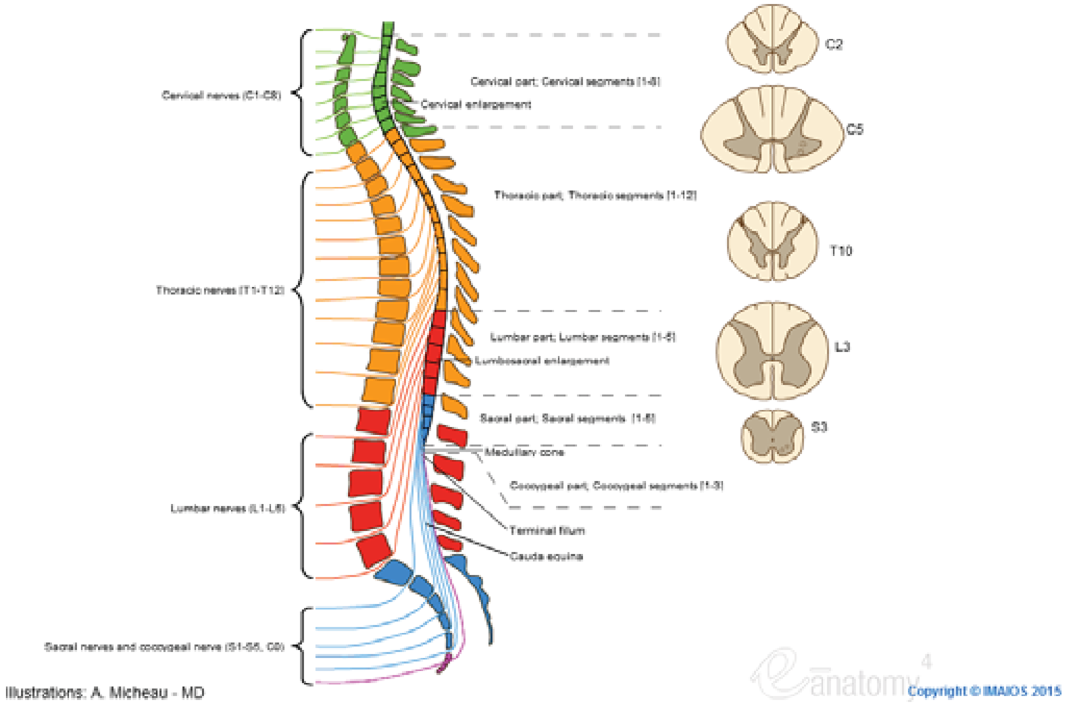


*Figure 3.* Schematic representation of different regions of the spinal cord along with cervical, thoracic, lumbar and sacral nerves and Filum terminale. Lateral view. From Imaios.com, with permission.

### *2.1.1.4 Spinal nerves*

Motor commands carried by the efferent motor axons leave the cord via the ventral roots. The cell bodies of motor neurons creating the ventral spinal roots are located in the ventral grey horn of the spinal cord.

Sensory information carried by the sensory afferent axons of the spinal nerves enters the cord via the dorsal roots. While the cell bodies of motor neurons creating the ventral spinal roots are located inside the spinal cord, the cell bodies of axons creating the dorsal spinal roots are located outside the spinal cord, in the *spinal ganglia* or *dorsal root ganglia.* The dorsal root ganglion of the dorsal, afferent, root of each spinal nerve is located into the foramina, often resting in contact with the adjacent vertebral pedicle. Just outside the vertebral foramina, and just distal to the dorsal root ganglion, the ventral and dorsal nerve roots merges and form a *spinal nerve* (Figure 4).

The peripheral nerves that innervate major part of the body arise from the spinal cord in 31 pair of spinal nerves. On each side of the midline, the spinal cord gives to eight cervical spinal nerves in the cervical (C1 to C8), twelve thoracic spinal nerves in the thoracic (T1-T12), five lumbar spinal nerves in the lumbar (L1-L5), five sacral nerves in the sacral (S1-S5), and one coccygeal nerve in the coccygeal region. The segmental spinal nerves leave the vertebral canal through the foramina that lies adjacent to the respectively numbered vertebral body.

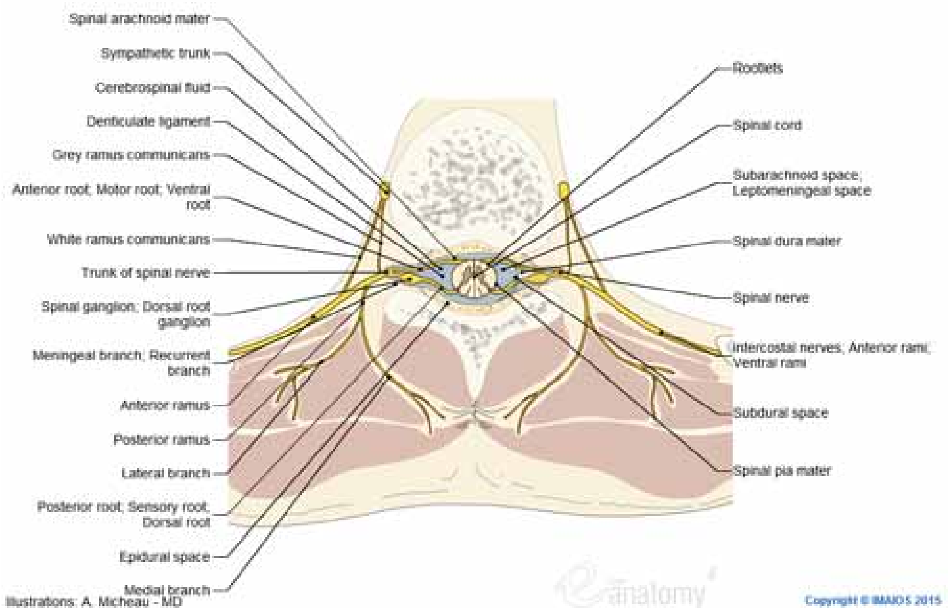


*Figure 4.* Visual representation of neural structures in the spinal canal along with meninges and spinal cord. Axial view. From Imaios.com, with permission.

### 2.1.2 **Origin and Development of the Straight Leg Raise Test**

The Straight Leg Raise test (SLR) is a widely used clinical physical test designed to test the mechanosensitivity of the sciatic nerve and its nerve roots by applying mechanical stress on it in form of tension (29).

Its codification is commonly credited to Lasègue (30), but as reported by De Beurmann (31) and noted by Sjöqvist (32) and later reported by Woodhall and Hayes (33), in Lasègue's dissertation on the subject of sciatica published in 1864, there is no mention of the description of what we nowadays call the SLR test. Its first description is currently attributed to J.J.Forst in 1881 (34). However, we were able to retrieve and translate the original publication in the Serbian Archives of Medicine from 1880 in which Laza Lazarević discusses the subject of sciatica and where we found the first description of what is now called SLR test (35). It is shown that Forst's and Lazarević's description of the test itself were extremely similar, suggesting lifting the patient's lower limb observing hip flexion while the knee was extended, and marking the test as positive when pain was produced at the sciatic notch after few degrees of hip flexion. Also, both Lazarević and Forst described knee flexion being a differentiating manoeuvre for sciatica. However, Forst and Lasègue felt that the painful response was primarily due to muscle contraction in the posterior thigh while it was Lazarević who first advocated sciatic nerve stretch, presenting his straightforward reasoning based on simple anatomical and clinical notions.

De Beurmann (31) also questioned the muscular response theory in 1884, and after an interestingly designed experiment in which elastic rubber bands inserted into post-mortem exposed sciatic nerves were observed to elongate during the SLR, advocated for sciatic nerve stretch. This was tested and confirmed many years later by Sjöqvist, in 1947 (32). Inman and Saunders (36) reported in 1942 a considerable caudal displacement of the fifth lumbar and first two sacral nerve roots quantified in 2-5 mm in cadavers, with a maximal motion recorded of 7 mm and showing a peak in neural displacement between 60° and 80° of hip flexion. In a study of 3 cadavers, Falconer and colleagues (37) supported Inman and Saunders's results, reporting that L5 and S1 moved caudally through their respective foramina by a variable amount of 2-6 mm during the SLR test and confirming the maximum movement magnitude taking place between 60° to 90° of hip flexion. In 1951 Charnley (38) reported 4-8 mm of caudal displacement of L5 and S1 neural roots in cadavers, with the maximal peak of movement being at 70°, while Goddard and Reid (39) announced 3mm of caudal displacement for L5 and 4-5mm for S1 nerve root, and Breig and Troup (40) reported 6-10mm of displacement for the sacral plexus toward the greater sciatic foramen during SLR, with similar findings shown on medial hip rotation performed in isolation. Importantly, variation in the methods of measurements used in those studies may account for the differences found in nerve root movements during the SLR.

The scientific community had to wait until the year 1993, for Smith and colleagues (29) to perform a rigorously designed study using standardized measurement methods to quantify the displacement and strain in lumbosacral nerve roots during the SLR performance in 10 unembalmed (fresh) cadavers. Following posterior unilateral laminectomies and facetectomies, they reported 1.4mm of mean linear displacement of the L4 nerve root, 2.1mm for L5 and 2.5mm for the S1 nerve root with maximal displacement taking place around 60° hip flexion, in both fused and unfused lumbar spines. Strain in the nerve roots was measured to reach 2-4%. In 2003 Kobayashi (41) quantified intraoperatively L5 neural root displacement in 3.8±0.5mm (Mean±SD) and S1 nerve root displacement to be 4.1±0.4mm at 60°hip flexion once the IVD herniation has been surgically removed in patients scheduled for microdiscectomy. More recently Kobayashi (42) and colleagues reported 2.1mm of caudal displacement of the same nerve roots at 60° of hip flexion using a similar study design.

After the first descriptions made by Trolard (43) and Hofmann (44) and later De Peretti (45), Grimes and colleagues (46) documented the existence with 4 distinct bands of foraminal ligaments extending from the nerve root sleeve with the most prominent ligament being directed posteriorly toward the facet capsule. Following this, Gilbert and colleagues (47,48) tested the hypothesis that, in a cadaver exploration, if these ligaments are to remain intact, lumbosacral nerve root motion during SLR would be less than previously reported. Using a novel nerve root marking technique, they confirmed that the nerve root caudal displacement amounted to only 0.53±0.83mm for L4, 0.48±0.55mm for L5 and 0.51±0.73mm for S1, which was significantly less than in previous studies.

A convenient summary of all the published evidence on lumbosacral nerve root displacement with unilateral SLR is presented in table 1.

**Table 1. Summary of published evidence on lumbosacral nerve root displacement with unilateral SLR**

| | | Authors | Nerve roots | Amount of displacement (mm) | Direction of displacement | Hip angle at which maximal motion occurs (in degrees) |
|---|---|---|---|---|---|---|
| Cadaver investigations | Studies with possible measurement errors estimated in 1mm | Inman and Saunders (1942) | L5<br>S1 | 2-5mm<br>(maximal recorded movement = 7mm) | Caudal | 60° to 80° |
| | | Falconer et al. (1948) | L5<br>S1 | 2-6mm | Caudal | 60° to 90° |
| | | Charnley (1951) | L5<br>S1 | 4-8mm | Caudal | 70° |
| | | Goddard and Reid (1965) | L5<br>S1 | 3mm<br>4-5mm | Caudal | 70° |
| | | Breig and Troup (1979) | Sacral plexus motion toward the greater sciatic foramen | 6- 10mm | Caudal | Not reported |
| | Studies using standardized measurement and rigorously designed measurement protocols | Smith et al. (1993) | L4<br>L5<br>S1 | 1.4mm<br>2.1mm<br>2.5mm | Caudal | 60° |
| | | Gilbert et al. (2007a, b) | L4<br>L5<br>S1 | 0.53±0.83mm<br>0.48±0.55mm<br>0.51±0.73mm | Caudal | 60° to 75° |
| In- vivo investigations | | Kobayashi et al. (2003) | L5<br>S1 | 3.8±0.5mm<br>4.1±0.5mm | Caudal | 60° |
| | | Kobayashi et al. (2010) | L5<br>S1 | 2.1±0.8<br>2.1±1.0 | Caudal | 60° |
| | | Graham et al. (1981) | L5 | Only observed, not quantified | Caudal | Not reported |

From this structured summary (Table 1), it appears that of 11 scientific articles found in the published literature, eight of them are investigations performed on cadavers (29,36-40,47,48) and in only three of them the research hypothesis is tested on in vivo human subjects (41,42,49). Of those, only two studies done by Kobayashi employs standardized measurement and rigorously designed measurement protocols (41,42). However, in Kobayashi's studies flavotomy and laminotomy were performed as part of the microdiscectomy procedure, and upon discussion with the author, it emerged that in order to allow the intraoperative measurement of L5 and S1 nerve roots in response to a SLR, the laminotomy had to be considerably extensive toward the foramina. This may have compromised the structural integrity of the foraminal ligaments described by Trolard (43), Hofmann (44), De Peretti (45) and Grimes and colleagues (46). This point was also raised by Gilbert and colleagues (47).

It appears that at the moment there are no studies that quantify neural displacement in response to SLR performed on in-vivo and structurally intact human subjects. This notion may be quite worrying, as the majority of the patients we usually see and on whom we would perform an SLR for diagnostic reasons are indeed alive and do not come with wide opened vertebral spine. It would be thus interesting to understand what happens in structurally intact human subjects during the execution of this physical test. It seems quite interesting to acknowledge that, even if the SLR test is one of the most consistent and widely used physical tests in formulating the diagnosis of sciatica, apart from the direction in which L5 and S1 lumbar nerve roots displaces in response to the execution of a SLR manoeuvre, caudal, the published evidence on neural behaviour in response to SLR seems to be far from conclusive in terms of magnitude of displacement, and that in the last decade only a few investigators have decided to look up in the basic neural mechanisms underpinning the execution of this test.

With the results presented in this line of research, the author of this doctoral thesis will try to fill this gap in the current published knowledge.

### 2.1.3 Clinical use of the Straight Leg Raise Test

Low back pain has been recognized to be a major health and socioeconomic problem in western countries (50) . In patients who report symptoms that also radiate into the lower limb, clinicians evaluate the possible causes of radiculopathy both through history and physical examination.

Physical tests for nerve root tension signs have been designed to aid the diagnosis of intervertebral disc herniation causing lumbar radiculopathy. Of those, the straight leg raise test is the most widely used, consistent and accepted (29,38,51). Its performance dictates the patient lying supine while the clinician performs a passive elevation of the symptomatic lower limb with extended knee. However, at this moment there seems not to be agreement between clinicians regarding other aspects of this test. One question is whether this test should be performed on the asymptomatic or symptomatic side first. This choice is now entirely left to the clinician, but performing the test on the symptomatic side first may bear some advantages in terms of i) not providing the patients with enough information about what the normal response to this physical test should be, ii) avoiding false responses, iii) decrease concerns in acute patients that may employ defensive mechanisms so as to avoid the painful limb being lifted far up as the asymptomatic one.

It is generally accepted that this manoeuvre does apply some tensile stress mainly to L5 and S1 nerve roots, and to a lesser extent to L4, allowing the clinician to obtain information on the mechanosensitivity of the sciatic nerve and its nerve roots by evaluating the clinical response to mechanical stress in form of tension. However, upon lifting of the symptomatic leg with extended knee some musculoskeletal structures are stressed around the hip joint along with the sciatic nerve. Point of interest is represented by the question of what would be a valuable structural differentiation manoeuvre to differentiate neural aspect to symptoms. Following the notion that the nervous system is in a structural continuum, and forces may be transmitted along the system so that ankle dorsiflexion may increase the tension into the nerve roots as subsequently shown by Gilbert and colleagues(48), Shacklock proposed that if the hip is kept stable and symptoms increase with foot dorsiflexion, there is high likelihood that a neural aspect exists, while if symptoms are not modified by this manoeuvre, this does not support the existence of such neural mechanism (17,52). While foot dorsiflexion has been shown to increase tension in the L4, L5 and S1 nerve roots (48), this is also true for hip internal rotation (53). These, together with hip adduction, are currently considered sensitizing manoeuvres for the SLR test.

*Figure 5.* Graphic reproduction of a unilateral SLR test. The likely anatomical region where reproduction of symptoms may occur is marked. From: Neurodynamic solutions, Adelaide, Australia. With permission.

Current evidence indicates poor diagnostic performance of most physical tests used in isolation to identify lumbar disc herniation (54). It would therefore be of use to understand the neural mechanisms underpinning this widely used physical test in order to support the standardization of this test and to construct diagnostic algorithms that encompasses different neural tensile tests in conjunction.

In order to fulfil this objective, the basic notion that increased knowledge of the local mechanics may lead to better diagnosis and treatment planning will be pursued.

### 2.1.4 Neural Tissues as a Continuum

As mentioned in chapter 2.1.3 and presented in figure 5, the neural tissues in the human body exhibit a structural continuum. This means that in normal and asymptomatic human subjects, the neural system begins with the brain and ends far distally at the tip of the fingers and toes without any structural interruption in its whole pathway through the brain stem, spinal cord, nerve roots, plexuses and peripheral nerves with their terminations.

Due to this structural continuum, it can be hypothesized that forces, tensile rather than compressive, can be transmitted via the nervous system. This theory has been intensively investigated in human cadavers by the Swedish neurosurgeon Alf Brieg. His findings have been carefully presented in his book "Adverse mechanical tension in the central nervous system„ published in 1978 (55), and again in the latest re-edition by Shacklock (56). The following information are based on these books, unless otherwise stated.

On flexion, the lumbar vertebral canal increases its length, particularly along its posterior wall. From full extension to full flexion, the central axis of the canal can increase his length by as much as 20 percent (56). Also lateral flexion does affect the length of the vertebral canal, accounting up to 15% of its changes in length between performance of right and left full lateral flexion movements. The same principles are applicable also to the cervical spine, although amounts of change in length of vertebral canal in response to movements may vary between lumbar and cervical spine. If in cervical flexion the length of the posterior wall of the cervical vertebral canal increases, the neural tissues contained in this canal should also adapt and accept some degree of tension, particularly on the dorsal side of the medulla. As the neural system is in a structural continuum, some degree of tension should be transmitted and distributed along the neural system in order to avoid local peaks.

Alf Brieg has consistently observed using direct visualization of neural adaptive movements in fresh and embalmed human cadavers that movement of the cervical spine does have an influence on the neural tissues in the lumbar spine by means of transmission of tensile forces. In human specimens, when the cervical spine is flexed, tensile forces in the pons-cord tissue tract and cervical spinal cord increases and are transmitted to the spinal cord in the thoracic spine, which in turn moves proximally by 3 to 4 mm in relation to a bony reference point on the intact vertebral arch. Following this, it may be hypothesized that neural tissues displace toward the zone where tension is applied in order to avoid excessive stress into the neural system. In other words, they follow the tension gradient.

In an opposite fashion, on cervical spine extension, the shortening of the vertebral canal allows for progressive relaxation of the dura mater, nerve roots and cauda equina into the lumbar canal. In the following figure (figure 6), a dorsal view of the thoraco lumbar spine is presented. The vertebral arch has been removed and dura mater opened to allow direct visualization of the neural tissues. The spinal cord is dissected approximately at T12-L2 level.

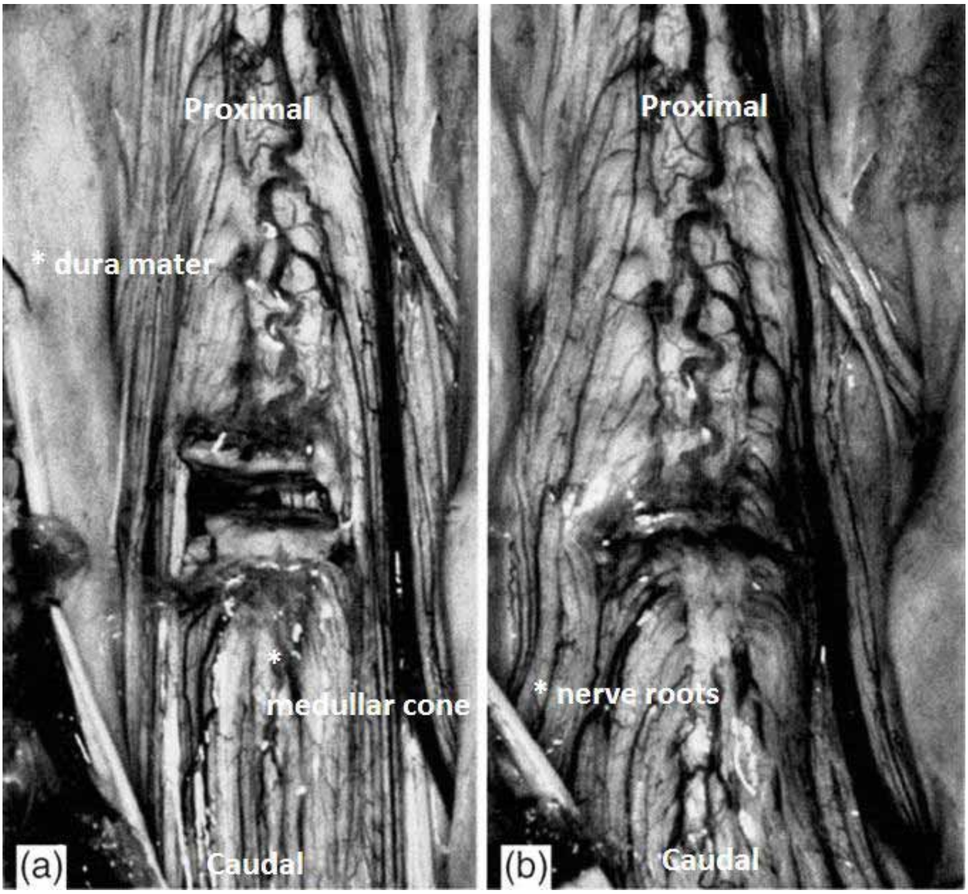


*Figure 6.* Dorsal view, T12-L2 spinal level - the bony covering has been removed and the dura mater is opened so the neural tissues can be seen. The cord is cut and the opening and closing of the neural tissue ends is seen with neck movements. This shows transmission of forces along the neural system. A) The spinal cord dissection opens showing separation of the neural tissues with cervical flexion. B) Cervical extension brings slumping of the nervous system with consequent collapsing of the gap.

From: Biomechanics of the Nervous System: Breig Revisited. Shacklock M., (2007), p. 69. Copyright Neurodynamic solutions, Adelaide, Australia. With permission.

In figure 6a, the attentive reader can notice that neck flexion produces separation of the neural tissue and an increase in the gap in the spinal cord. This is likely produced by transmission of tensile forces along the neural system in response to elongation of the spinal canal in the cervical area with cervical flexion. The opposite behaviour is shown in figure 6b where the shortening of the cervical spinal canal caused by neck extension allows for progressive relaxation of the neural tissues with consequent collapsing of the gap. This illustrates a crucial point already introduced at the beginning of this subchapter: that the nervous system is in a structural continuum and tensile forces can be transmitted throughout the system.

An important notion that emerges from this is that proximal movements can have a relevant impact on the behaviour of distal, distant, neural structures. Moreover, if mechanical tension applied proximally in the nervous system can be transmitted caudally modifying the behaviour of distal neural tissues, the opposite may be true, so that tension applied on the peripheral nerves and nerve roots may have an impact on more proximal structures as the spinal cord.

It follows logically that it is not the same thing to perform an SLR on a patient lying supine with a thick pillow under their head versus no pillow. The neural system is in a structural continuum and neural pretensioning effects have to be taken into account.

This is a key feature in research line n.1 that will be discussed again in chapter 4.1.1. “Pilot; the Basic Idea Underpinning Research Line N.1”.

### 2.1.5 **The Magnetic Resonance Imaging**

The principles of functioning of Magnetic Resonance (MR) scanners have been described in details in books by Brown and Semelka (57), Westbrook (58) and McRobbie et al. (59). The essential principles of functioning and their application are here described based on those books, unless otherwise stated. The presented figures are adopted from the site Imaios.com, with permission.

#### *2.1.5.1 Principles of functioning*

In normal circumstances the magnetic moments of MR active nuclei in a human body point in a random direction. In this situation they produce no overall magnetic effect.

When a volunteer is being inserted into a very homogeneous magnetic field, there is the tendency of this magnetic field to line up the magnetic moments of the nuclei. This is true mostly for Hydrogen which is present in all our tissues. The sum of all the magnetic moments of the Hydrogen nuclei forms the Net Magnetization Vector (NMV). The magnitude of the NMV does actually represent the balance between the Spin up and Spin down nuclei.

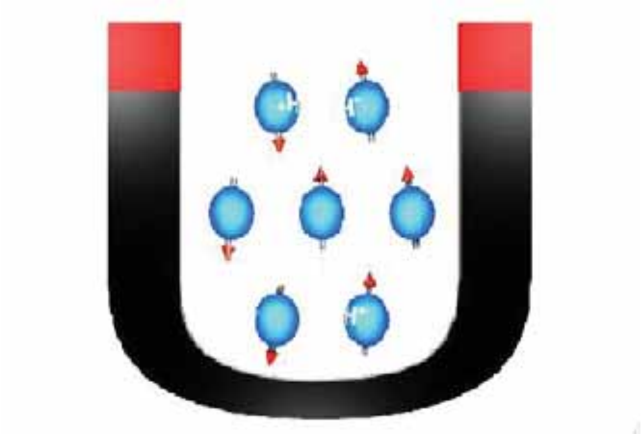


*Figure 7.* Within an external magnetic field $B_0$, nuclear spins align with the external field. Some of the spins align with the field (parallel) and some align against the field (anti-parallel). The number of nuclei in each spin state can be described by the Boltzmann distribution. From Imaios.com, with permission.

If we were now to apply a radiofrequency (RF) pulse on resonance frequency for the precessing Hydrogen nuclei, we may induce the hydrogen nuclei to resonate and thus absorb energy without any other MR active nuclei responding to this stimulus. If just the right amount of energy is applied, the number of spin up nuclei equals the number of nuclei in a spin down positon. So as the Hydrogen nuclei absorbs energy form the RF pulse, we are able to turn the direction of the NMV 90° away from the direction of the magnetic field $B_0$.

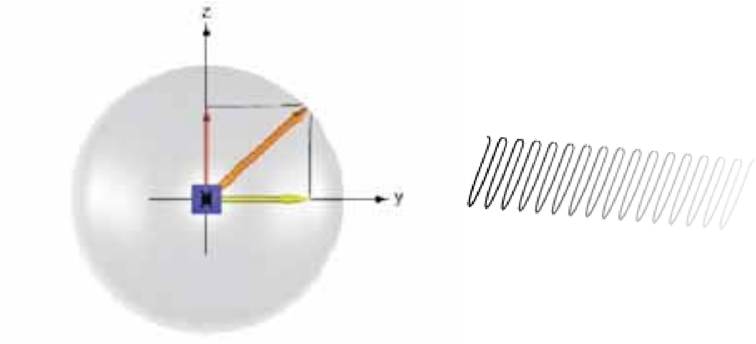


*Figure 8.* As any vector, also the Net Magnetization Vector can be broken down into a longitudinal component aligned with $B_0$ (Z axis,), and a transverse component lying on the transverse plane (X,Y). We can now apply a radiofrequency (RF) pulse on resonance frequency for the precessing Hydrogen nuclei. If the right amount of energy is applied, the Hydrogen nuclei absorb this energy form the RF pulse and we can turn the direction of the NMV on the transverse plane, so 90° away from the direction of the magnetic field $B_0$. From Imaios.com, with permission.

As the NMV rotates on the transverse plane as a result of resonance, it passes through a coil situated on this plane inducing a voltage in it. This voltage is the MR signal. So it may be said at simplest that in Magnetic Resonance Imaging (MRI) the signal is the result of the voltage induced in the receiver coil by the rotation of the Net Magnetization Vector on the transverse plane as a result of resonance.

### 2.1.5.2 *Signal contrast*

An image displays contrast if there are areas of high signal (white colour) and areas of low signal intensity (dark colour). In MRI, a tissue has high signal (white on the image) if it presents a high transverse component of magnetization. That is, if there is a large component of transverse magnetization, the amplitude of the magnetization received by the coil is large, and thus the signal in form of voltage induced in the coil is large, therefore this tissue is likely to appear white in the MR image.

Vice versa, a tissue gives low signal (black on the image) if it has a small transverse component of magnetization. By extension, an intermediate signal (grey) has a medium transverse component of magnetization.

Image contrast is controlled by extrinsic parameters such as:

- Repetition time (TR): This is the time that passes between the application of one RF pulse and the next, and is usually measured in milliseconds (ms).

- Echo time (TE): This is the time between the application of the RF pulse and the collection of the signal.

- Flip angle: angle through which the NMV is moved as a result of a RF excitation pulse.

- Turbo factor: Certain fast sequences employ a train of 180° rephrasing pulses with each one producing a Spin echo. The number of 180° rephrasing pulses and resulting echoes is called Echo train length (ETL) or Turbo factor

- Time from Inversion: Used in Inversion recovery spin echo sequences that begins with a 180° inverting pulse. When the pulse is removed and the NMV begins to relax back to $B_0$ a 90° pulse is then applied at interval TI (Time from Inversion) after the 180° inverting pulse. These versatile sequences are frequently used in the central nervous system to visualize periventricular Multiple Sclerosis plaques for example (Fluid Attenuated Inversion recovery – FLAIR).

### *2.1.5.3 Relaxation*

In Magnetic Resonance Imaging, this term describes several processes by which nuclear magnetization induced in a non-equilibrium state by the RF pulse returns to the equilibrium distribution. In other words, relaxation describes how quickly spins in the sample come to equilibrium with the surroundings. At a practical level, the time needed for this process determines how fast an experiment can be repeated.

As described before, in MRI an RF pulse is applied to achieve resonance and desired flip angle. Once the RF pulse is removed, the signal induced in the receiver coil by the coherent component of NMV in the transverse plane passing across the receiver coil begins to decrease. This is called free induction decay (FID). The NMV in the transverse plane decreases due to relaxation processes and field inhomogeneities.

The removal of the RF pulse produces several effects:

- Nuclei emit the energy previously absorbed from the RF pulse through a process called spin lattice energy transfer. In response to this phenomenon, they shift their magnetic moments from the high energy state to the low energy state and the NMV recovers and realigns to the direction of the external magnetic field $B_0$. This relaxation process is called T1 recovery.

- NMV decays in the transverse plane as nuclei lose precessional coherence and dephase in the transverse plane. The dephasing relaxation process is called T2 decay.

One of the factors that create image contrast is the rate of relaxation of each tissue. Fortunately, different tissues relax at different rates.

### *2.1.5.4 T1 decay*

T1 recovery is also called *spin lattice* energy transfer and is caused by the exchange of energy from nuclei to their surrounding environment or lattice.

The rate at which this occurs is an exponential process defined as the time it takes for 63% of the longitudinal magnetization to recover. The spin-lattice (or longitudinal) relaxation time T1 i) quantifies the rate of transfer of energy from the nuclear spin system to the neighbouring molecules (the lattice), ii) determines what recycle delay between pulses should be used. The nuclear spin system must be allowed to relax back to equilibrium before the next pulse is applied and this time period is determined by T1. The period of time during which this occurs is the time between one RF excitation pulse and the next one, and is called Repetition Time (TR).

Fortunately longitudinal relaxation and spin-lattice energy transfer rate are intrinsic parameters inherent to each tissue being imaged. By extension, T1 time is an intrinsic contrast parameter that is inherent to the tissue being imaged. This feature allows us to obtain image contrast by recording different signal intensities at a specific time point.

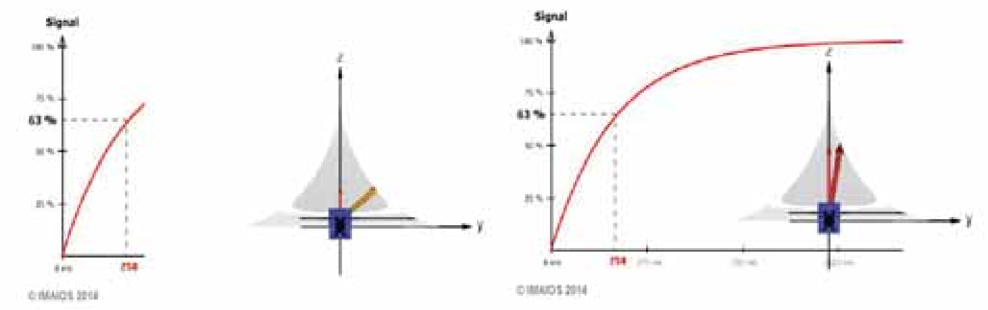


*Figure 9.* The recovery of longitudinal magnetization (spin lattice energy transfer) follows an exponential curve. The rate at which this occurs is defined as the time it takes for 63% of the overall longitudinal magnetization to recover. From Imaios.com, with permission.

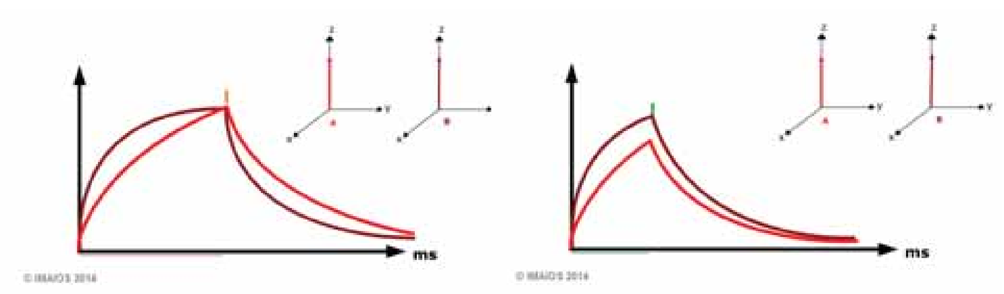


*Figure 10.* Image contrast can be tuned by changing the TR time. By setting the TR time to short values, tissue contrast will depend on differences in longitudinal magnetization recovery (T1). From Imaios.com, with permission.

### *2.1.5.5 T2 decay*

After a 90° RF pulse the nuclear spins are phase coherent and the transverse component of the NMV is maximal, but this phase coherence is gradually lost due to field inhomogeneities and direct interactions between the spins without energy transfer to the lattice. This process leads to decay of the NMV in the transverse plane and is called T2 decay.

T2 decay is an exponential process that represents the time it takes for 63% of the transverse magnetization to be lost due to dephasing. Similarly to T1 recovery time, as T2 decay occurs at different rates in different tissues, it represents an intrinsic contrast parameter inherent to the tissue being imaged. The period of time over which this occurs is the time between the RF excitation pulse and the MR signal collection or the Echo Time (TE). T2 decay, or spin–spin energy transfer, is caused by two factors: i) magnetic field inhomogeneity and (ii) spin-spin relaxation which represents the exchange of energy from one nucleus to another. It occurs as a result of the intrinsic magnetic fields of the nuclei interacting with each other.

Despite attempts to make the main magnetic field as uniform as possible, owing to the Larmor equation by which the precessional frequency of a spin is proportional to $B_0$, as spins passes through these inhomogeneities they experience magnetic field strengths that are slightly different from $B_0$. Following this also their precessional frequencies change. This change in precessional frequency results in dephasing of the NMV and thus transverse magnetization decay due to loss of phase coherence. As in T1 relaxation and in T2 decay, this decay occurs exponentially and is known as T2*. As magnetic field inhomogeneities cause the NMV to dephase before the intrinsic magnetic fields of nuclei can influence dephasing, T2* always happens before T2.

As a direct consequence of the above, in order to produce images where T2 contrast can be visualized, there must be a mechanism to rephase spins and compensate for magnetic field inhomogeneities. This is achieved by using pulse sequences.

In synthesis, we shall now repeat the essential notions: TE and TR times determine the weighting of a MRI scan;

- A short TR and short TE gives a T1-weighted scan.

- A long TR and long TE gives a T2-weighted scan.

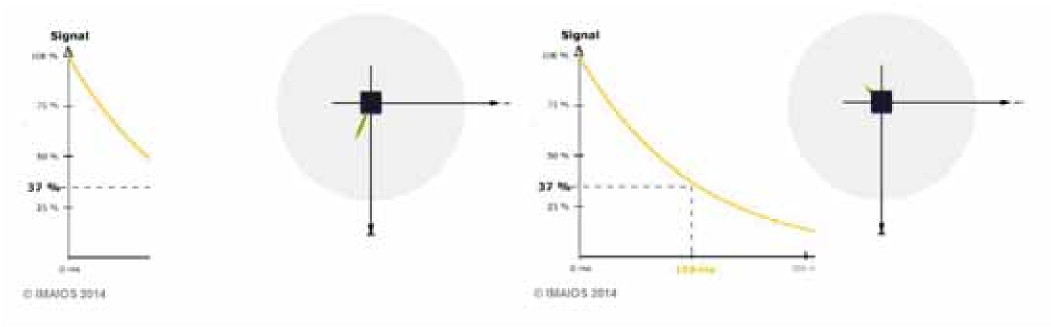


*Figure 11.* T2 decay is an exponential process that represents the time it takes for 63% of the transverse magnetization to be lost due to dephasing. Similarly to T1 recovery time, as T2 decay occurs at different rates in different tissues, it represents an intrinsic contrast parameter inherent to the tissue being imaged. From Imaios.com, with permission*.*

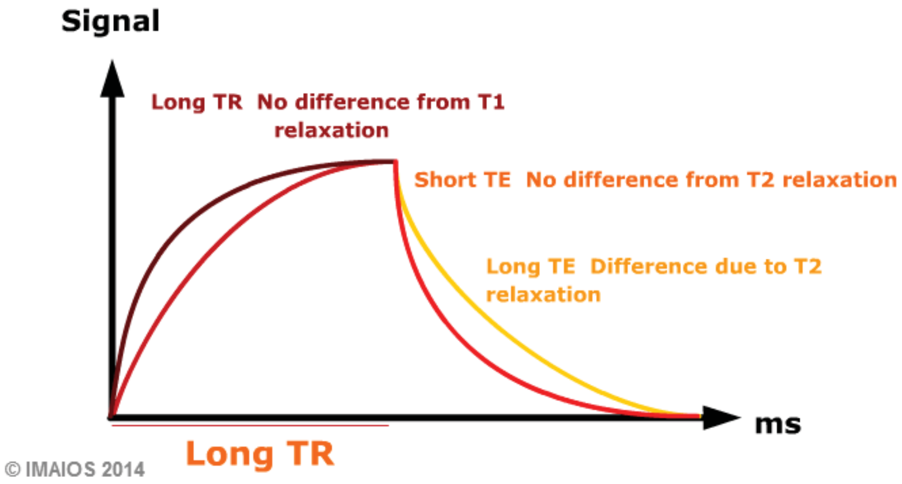


*Figure 12.* TR time determines the contrast obtained through different rates of longitudinal magnetization recovery (T1) in different tissues, while TE time determines the contrast obtained through different rates of transverse magnetization decay (T2) in different tissues. From Imaios.com, with permission.

### *2.1.5.6 Pulse sequences*

A pulse sequence is defined as a series of RF pulses, gradients applications and intervening time periods. By precisely selecting the intervening time periods in which the system applies RF pulses and gradients, image weighting is controlled.

### *2.1.5.7 Spin echo pulse sequences*

As spin phase coherence is lost almost immediately after the RF excitation pulse has been removed, without a mechanism of refocusing spins there is insufficient signal to produce an image. For this reason Pulse sequences are required for imaging purposes.

A spin echo pulse sequence is constituted by a 90° excitation pulse followed by a 180° rephasing pulse followed by an echo. As previously mentioned, after the application of the 90° RF pulse, spins lose precessional coherence because of an increase or decrease in their precessional frequency caused by the magnetic field inhomogeneities. Spins that experience an increase in precessional frequency gain phase relative to those that experience a decrease in precessional frequency. As a result, the transverse magnetization decays and the ability to generate a signal are lost.

To eliminate magnetic field inhomogenities a 180° RF pulse is used. This is achieved by flipping the dephased nuclei through 180°. As a result, the fast edge is now behind the slow edge and eventually catches the slow edge reforming the NMV. This phenomenon is called rephrasing and can be nicely visualized at the internet site: http://www.imaios.com/en/e-Courses/e-MRI/MRI-signal-contrast/180-RF-pulse

In synopsis, after the 90° RF pulse spins dephase during a time defined as TE/2, the 180° RF pulse restores phase coherence before they dephase again. The magnitude of the signal in the receiver coil is now regenerated and can be measured. This regenerated signal is called an echo and, because an RF pulse has been used to generate it, it is specifically called a spin echo. Whenever a 180° RF rephasing pulse is applied, a spin echo results. Rephasing pulses may be applied up to several times to produce several spin echoes.

Conventional spin echo pulse sequences are used to produce T1, T2 or proton density weighted images and are one of the most basic pulse sequences used in MRI.

### *2.1.5.8 T2 weighed images*

In a T2 weighted image the differences in the T2 relaxation times of tissues must be demonstrated. To achieve this, a long enough TE is selected to ensure that the NMV in both fat and water has had time to decay enough so that the contrast between the recorded signals from these two tissues can be distinguished.

A too long TE will allow a complete T2 decay to occur before the signals are collected, resulting in absence of contrast in the reconstructed image. If TE is properly selected, tissues with a short T2 decay time such as fat will appear as dark (low signal) because they will have lost most of their coherent transverse magnetization during the TE period. Concurrently, tissues with a long T2 decay time such as water will appear as bright (high signal), because they will have retained most of their transverse coherence during the TE period.

Typical parameters are TR ≥ 2000 ms and TE ≥ 70 ms.

T2 weighted images best demonstrate pathology as most pathology has increased water content which will appear as bright on T2 weighted images.

*Figure 13.* Example of a T2-weighted image. From Imaios.com, with permission.

### 2.1.6 **Use of Magnetic Resonance Device for Neuroimaging**

#### *2.1.6.1 Scanning sequences and their applications*

As already described, a pulse sequence is basically defined by a series of Radio Frequency pulses, gradient applications and intervening time periods. While gradient applications and intervening time periods application principles may be comparable to Gradient Echo sequences, Spin echo sequences are peculiar due to the existence of a 180° rephrasing RF pulse following the first 90° excitation RF pulse and applied at a time defined as half echo time (TE/2).

A single Spin Echo consists of a single 180° rephrasing RF pulse applied after a 90° excitation RF pulse, while multiple Spin Echo sequences imply that multiple 180° pulses are applied after the 90° pulse. The application of the 180° rephrasing RF pulse is supported by the theory that the NMV on the transverse plane is reformed with a flip of 180° of dephased nuclei. This eliminates the effect of field inhomogenities that leads toward increase in precessional frequency of spins immersed in zones of higher magnetic field and which as a consequence do gain phase relative to the slower spins. Up to now Spin Echo sequences are still considered the gold standard in MRI as the produced contrast is understood and predictable. A relevant disadvantage is the long scanning time that can however be controlled by modifying the number of slices or the Repetition Time (TR).

In this line of investigation in neuroradiology we used T2 weighted turbo spin echo fat saturation sequences to quantify the medullar cone displacement in response to Straight Leg Raise manoeuvres building upon the results presented by Alf Brieg from cadaver investigations. T2 sequences were used as they allow nice contrast between the cerebro-spinal fluid and the neural structures.

### 2.1.7 **Artefacts**

An image artefact is a structure not normally present but visible on the image.

Artefacts can be due to i) hardware problems as calibration issues, power stability, electromagnetic spikes, ringing, ii) software problems as programming errors, iii) physiological phenomena as blood flow or motion of the scanned anatomical area, or iv) by inherent physics as Stochastic Processes on a Lattice and Gibbs Measures, chemical shift, susceptibility, metal implants.

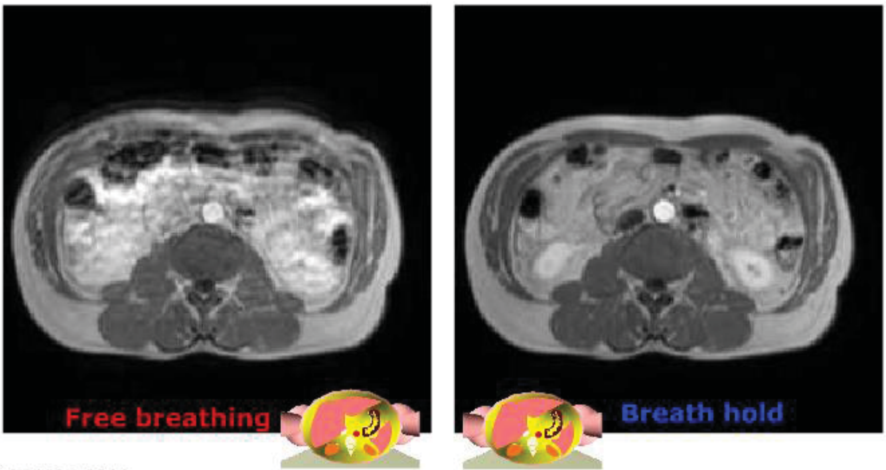
There are numerous kinds of artefacts that can occur in MRI, of those, we are going to list only the more common motion artefacts.

### *2.1.7.1 Motion artefacts*

Movement or Motion artefacts can be caused by the physiological movement of neighbouring tissues as heart, lungs, big vessels, eyes, swallowing or direct movements of our patient.

They usually appear as ghosting or blurring of the images. Noise or repeating densities are usually oriented in the phase direction. Motion artefacts do usually extend across the entire Field of View (FOV), unlike truncation artefacts that diminish quickly away from the boundary causing them.

They can be avoided by Eddy current compensation, respiratory compensation, cardiac gating, by choosing the right coils and other imaging equipment, by supporting the patient comfortably with cushions and pillows, using fat suppression sequences, assuring that the faraday cage is intact and by choosing the right imaging sequences and parameters (in this view, fast scan techniques as Gradient Echo sequences or single shot methods may be of use).



© IMAIOS 2014

*Figure 14.* Example of a thoracic MRI scan showing motion artefact and increase in the scan quality with breath hold technique. Further improvement can be achieved with respiratory triggering and respiratory compensation techniques. From Imaios.com, with permission.

As in the experiments presented in this doctoral thesis relatively slow Spin Echo sequences have been used in order to reconstruct images of better quality from the scanned anatomy, particular attention was drawn toward avoiding motion artefacts. This was achieved by careful positioning of volunteers inside the MR scanner and by investment of considerable efforts in informing each volunteer about the consequences that body movements during operational scanning sequences may have on the reconstructed images.

## 2.2 RESEARCH LINE N.2: NEUROPHYSIOLOGY

### 2.2.1 Lateral Epicondylalgia

Tennis elbow, lateral epicondylitis and lateral epicondylalgia are the terms commonly applied to a condition affecting the myotendinous common extensor origin (CEO) as it inserts into the lateral epicondyle of the humerus, leading to pain and loss of function of the affected limb.

In agreement with Gruchow and Pelletier (60), Noteboom et al. (61) have presented that 50% of competitive tennis players experience at least one episode of lateral epicondylitis, of which 75% comprise a condition diagnosable as true tennis elbow. As the condition is commonplace, painful and disabling, it is of significant interest to sports medicine practitioners. It should be recognized also that, despite the term ‘tennis elbow’, the syndrome is of course not limited to tennis players. In a recent literature review on golf injuries emerged that 85% of all possible elbow injuries occurred at the lateral aspect of the elbow (62). In Stockard (63), lateral epicondylitis appears to be by far the most common elbow injury in amateur golfers, representing approximately 27.4% of the total reported injuries and being second only to lower back injuries (34.5%), and is thought to be caused predominantly by overuse mechanisms.

Due to the high incidence of lateral epicondylitis in active golf and tennis players, and the actual increasing interest in these two sports, together with other racquet sports, with participation rates fairly spread across all age ranges, the possibility of increasing the effectiveness of non-invasive therapies for this condition is of particular interest to sports medicine practitioners.

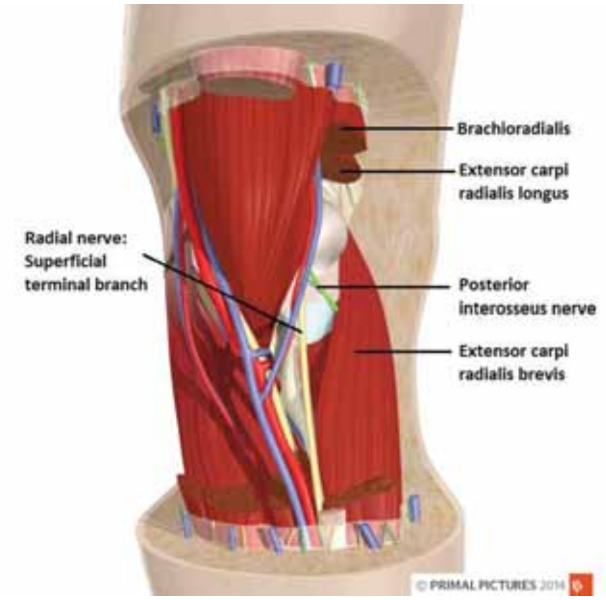


*Figure 15.* Cubital fossa, anterolateral view. Anatomic structures relevant to investigations in manuscripts III and IV are presented. Modified from Primal's 3D Atlas of Human Anatomy of the Shoulder and Arm - 2014 Edition. (3D anatomy images copyright Primal Pictures Ltd.).

### 2.2.2 Mills Manipulation

Common extensor origin stretch techniques have been performed in physical medicine and manual therapy since Mills described his eponymously named manipulation for the treatment of lateral elbow pain (often termed 'tennis elbow' or lateral epicondylalgia) when it is clinically related to the myotendinous common extensor origin into the lateral epicondyle of the humerus (64-67). The Mills manipulation was first described by the English orthopaedic surgeon Sir G.Percival Mills (64) from the initial observation that, in patients with tennis elbow, the elbow joint could not be fully extended when this movement was combined with full forearm pronation and wrist and finger flexion. Notwithstanding various theories concerning the underlying therapeutic mechanisms (65,67-69), the manoeuvre remains current in manual and musculoskeletal medicine practice for the treatment of the lateral elbow pain (66).

As described by Kesson and Atkins (67) and Atkins, Kerr and Goodlad (69), the clinician stands behind the patient and, supporting the patient's elbow, takes the patient's shoulder to approximately 90˚ abduction and allows the shoulder girdle joint to passively settle into an appropriate amount of internal rotation. The clinician then fully flexes the patient's wrist and completes forearm pronation and elbow extension. At this point, the patient's elbow reaches the position in which a high velocity-low amplitude thrust toward elbow extension should be applied, and that we define as the 'pre-manipulative stretch position for Mills manipulation' (articles III and IV).

Points of scientific and clinical importance are if, and how, muscle and nerve may be affected by the manoeuvre.

*Figure 16.* Pre-manipulative positioning for Standard Mills Manipulation. From Kesson M, Atkins E. Orthopaedic medicine, a practical approach. 2nd Edition ed. Edinburgh: Elsevier; 2005. p. 211. With permission.

### 2.2.3 **The Neural Tissues of the Upper Limb**

The peripheral nervous system of the upper limbs is varied in terms of architecture. It originates from C5 to T1 nerve roots so that C5 and C6 nerve roots fuse together to form the superior trunk of the brachial plexus, C7 nerve root continues to form the middle trunk while C8 and T1 nerve roots fuse together to form the posterior trunk of the brachial plexus.

Each of the 3 trunks then divides into anterior and posterior divisions. The anterior divisions of the superior and middle trunks will continue their distal pathway and fuse together to form the lateral cord of the brachial plexus. The anterior division of the inferior trunk will continue in its distal pathway and form the medial cord of the brachial plexus, while all the posterior divisions of superior, middle and inferior trunks will merge to form the posterior cord of the brachial plexus. The cords then divide to form the peripheral nerves as we know them.

The posterior cord gives origin to the radial nerve and axilliary nerve.

The lateral cord exhibits three branches; one side branch that gives origin to the lateral pectoral nerve, and two terminal branches that gives origin to the musculocutaneous nerve and the lateral root of the median nerve.

The medial cord has five branches. Of those the three side branches gives origin to the medial pectoral nerve, medial brachial and antebrachial cutaneous nerves, and two terminal branches gives origin to the ulnar nerve and the medial root of the median nerve.

The medial root from the medial cord joins the aforementioned lateral root from the lateral cord of the brachial plexus to form the medial nerve.

At this point we are located in the lower axilla and, making exception for anatomical variations and anomalies, the main peripheral nerves of the upper limb are now formed and engage in their own descending pathways toward the hand (figure 17).

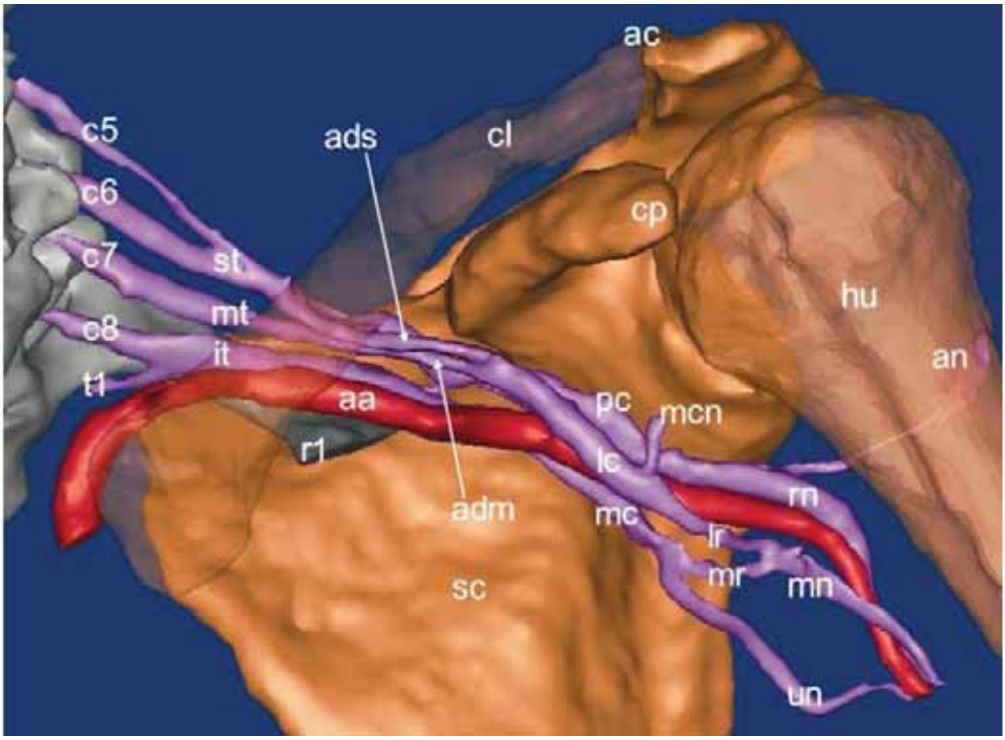


*Figure 17.* CT scan 3D reconstruction of a left brachial plexus. Abbreviations: c5–c8, roots cervical 5–8; t1, root thoracic 1; st, superior trunk; mt, middle trunk; it, inferior trunk; ads, anterior division of superior trunk; adm, anterior division of middle trunk; pds, posterior division of superior trunk; pdm, posterior division of middle trunk; pdi, posterior division of inferior trunk; pc, posterior cord; lc, lateral cord; mc, medial cord; mcn, musculocutaneous nerve; lr, lateral root of median nerve; mr, medial root of median nerve; mn, median nerve; an, axillary nerve; rn, radial nerve; un, ulnar nerve; cl, clavicle; sc, scapula; ac, acromioclavicular joint; hu, humerus; cp, coracoid process; r1, posterior part of first rib; aa, axillary artery.

From: Tom Van Hoof; Neurodynamic testing and 3D visualization of the brachial plexus (Doctoral thesis, Gent University, Faculty of Medicine and Health Sciences, Department of Anatomy, Embryology, Histology and Medical Physics) page 10. With permission.

The median nerve descends on the medial side of the humerus, turns forward before the medial epicondyle and passes in front of the elbow, next to the brachialis muscle and before entering the pronator tunnel. It then continues through the carpal tunnel to innervate the first three digits of the ipsilateral hand. The motor innervation of the median nerve includes all the muscles of the forearm ventral (anterior) compartment except for the flexor carpi ulnaris and the ulnar half of the flexor digitorum profundus. It also innervates the thenar muscles and first two lumbrical muscles of the ipsilateral hand.

The ulnar nerve descends on the medial side of the humerus close to the medial nerve and progresses on the convex side of the elbow joint to enter the cubital tunnel. It then continues its pathway following the ulna and entering the Guyon's canal before innervating the last two digits of the ipsilateral hand. The motor innervation of the ulnar nerve includes the flexor carpi ulnaris muscle and the ulnar half of the flexor digitorum profundus muscle in the ventral forearm and most of the intrinsic hand muscles as hypothenar muscles, two lumbricals, adductor pollicis, and all the interossei.

The radial nerve spirals posterolaterally around the shaft of the humerus and divides into its posterior interosseous branch and radial sensory branch approximately one centimetre above the lateral humeral epicondyle, before progressing in front of the elbow joint and engaging the supinator tunnel under the forearm supinator muscle (Posterior interosseous branch). In the forearm the radial nerve innervates the extensor muscles of the wrist and fingers and the supinator muscle (posterior/dorsal compartment forearm muscles). It also conveys sensory information from the posterior forearm and the radial side of the dorsum of the hand.

A current way to test the mechanosensitivity of peripheral nerves is to apply tensile stress using manoeuvres that elongate the neural pathway and the neural bed. In the following subheadings some of these physical tests, also called Neural Tension Tests or Neurodynamic tests, will be described. Of those, the Radial Neurodynamic Test will be relevant for this work.

### 2.2.4 Neurodynamic Tests for the Upper Quadrant

Different clinically applied physical tests have been created to aid the clinical diagnosis and treatment of disorders that affect neural structures in the body as carpal and supinator tunnel syndromes and radiculopathies. On a mechanisms level, such manoeuvres move, apply force to, and test the responsiveness of, the relevant nerve structure so the clinician can obtain an impression of its state and mechanical function.

The first descriptions of tests designed for the assessment the peripheral nervous system with a specific set of upper limb movements were suggested in 1929 by Bragard (70) and later by Lanz und Wachsmuth (71). As stated earlier in this thesis, relative mobility between nerves and the bony structures has been mentioned by Breig and Marions already in 1963 (72). From this notion, and from observations of brachial plexus nerve root mobility in cadavers, Elvey developed the Brachial Plexus Tension Test (BPTT) (73). The aim of this test was to aid the differential diagnosis of pain referring into the arm (73,74) by testing the mobility of C5-T1 nerve roots following the assumption that in pathology neural sliding could be compromised by local adhesions. The term "Upper Limb Tension Test" (ULTT) was later introduced by Keneally, Rubenach and Elvey in 1988 (75) and was meant to replace the name Brachial Plexus Tension Test.

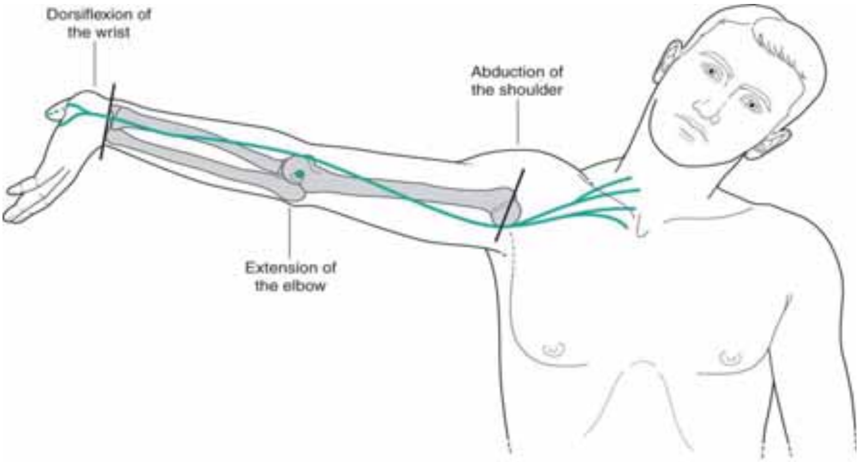
Observing the etymology of these terms, it is easy to note that the common denominator is represented by the word "tension", which indicates the presence of mechanical forces acting on the neural tissue. In 1995 Shacklock proposed that the test ought to be called a "neurodynamic test" in order to take account not just of the mechanical forces applied on the neural tissues during this clinical testing, but also of the physiological changes, predominantly in terms of blood flow, that occur within the neural tissues during such testing. It was suggested that the term neurodynamic would be more comprehensive and less limiting compared to the term "tension."

These physical tests are currently termed "neurodynamic" tests (17), of which there is a number of manoeuvres that relate to different peripheral nerves of the upper limbs, namely the median, ulnar and radial (17,71,73,74,76,77). Of those, we are going to list the most relevant tests for the upper quadrant.

### *2.2.4.1 Median Neurodynamic Test*

The Median Neurodynamic Test (MNT) is a physical test designed to manually test the mechanosensitivity of the median nerve and the brachial plexus by means of increasing the length of the nerve bedding and thus tensioning the peripheral nerve and the brachial plexus. (73,78-82).

The standard execution of a MNT involves respectively glenohumeral abduction up to 90-110° in the frontal plane, glenohumeral external rotation to available range, forearm supination and wrist and finger extension, and finally elbow extension to the point of symptom production. This test has been shown with buckle force transducers to apply a significant magnitude of tensile force to the median nerve, as well as to the medial and lateral cords of the brachial plexus (82).



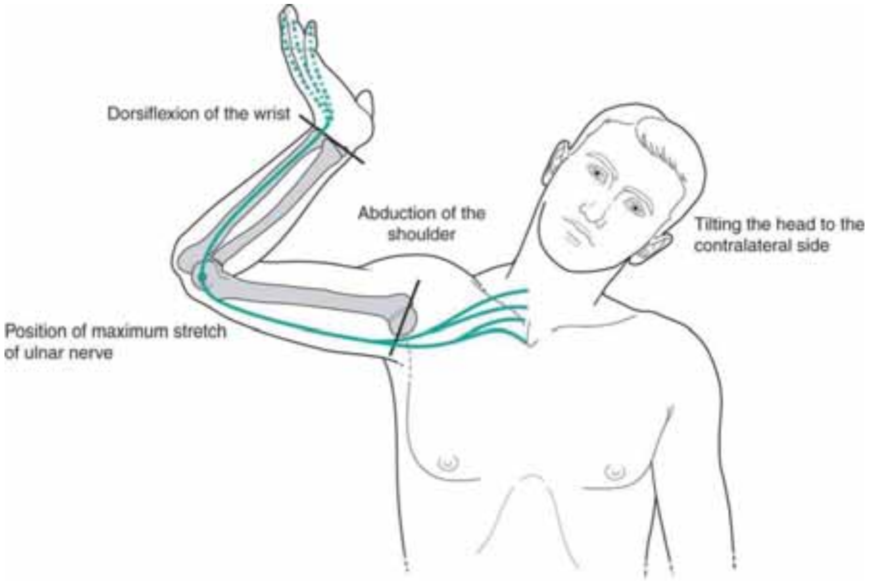
(i) Median neurodynamic test (von Lanz T and Wachsmuth W 1959 Praktische Anatomie, Springer-Verlag, Berlin, p. 38, with permission).

*Figure 18.* Schematic example of a Median Neurodynamic Test (MNT). From: Clinical Neurodynamics, Shacklock M.,(2005), preface p. 10, Copyright Elsevier, adapted from Praktische Anatomie. Ein lehr und Hilfsbuch der Anatomischen Grundlagen Ärtzlichen Handelns, Lanz and Wachsmuth (1959) p. 47. Copyright Springer- Verlag, Berlin. With permission.

### 2.2.4.2 *Ulnar Neurodynamic Test*

The Ulnar Neurodynamic test (UNT) has been designed to test the mechanosensitivity of the ulnar nerve when symptoms occur in the field of the ulnar nerve, lower trunk of the brachial plexus or the C8-T1 spinal nerve roots.

It involves shoulder depression, wrist and finger extension and forearm pronation, elbow flexion, glenohumeral external rotation, glenohumeral abduction to the point of symptom production, all performed in the mentioned order (17,71,77). As shown by Kleinrensink et al.(82) this test applies some tensile forces to the ulnar and radial nerves, with significant amount of tension applied to the medial and posterior cords of the brachial plexus.



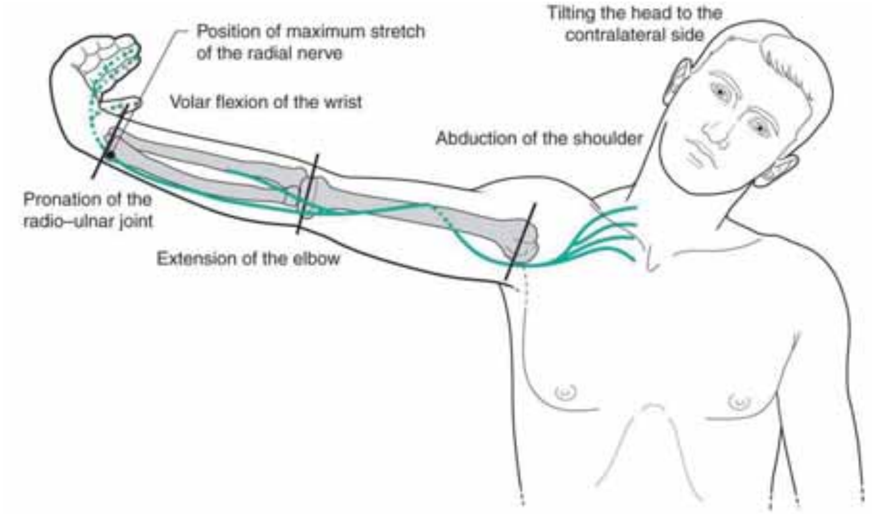
(ii) Ulnar neurodynamic test (von Lanz T and Wachsmuth W 1959 Praktische Anatomie, Springer-Verlag, Berlin, p. 41, with permission).

*Figure 19.* Schematic example of a Ulnar Neurodynamic Test (UNT). From: Clinical Neurodynamics, Shacklock M.,(2005), preface p. 10, Copyright Elsevier, adapted from Praktische Anatomie. Ein lehr und Hilfsbuch der Anatomischen Grundlagen Ärtzlichen Handelns, Lanz and Wachsmuth (1959) p. 47. Copyright Springer- Verlag, Berlin. With permission.

### *2.2.4.3 Radial Neurodynamic Test*

The radial neurodynamic test (RNT) is a physical test designed to manually test the mechanosensitivity of the radial nerve by means of increasing the length of the nerve bedding (83).

The standard execution of a RNT involves passive scapular depression, shoulder girdle abduction and internal rotation, elbow extension, forearm pronation and wrist and finger flexion to the point of symptom production (17,71,74,77) all in in the presented order.



(iii) Radial neurodynamic test (von Lanz T and Wachsmuth W 1959 Praktische Anatomie, Springer-Verlag, Berlin, p. 47, with permission).

*Figure 20.* Schematic example of a Radial Neurodynamic Test (RNT). From: Clinical Neurodynamics, Shacklock M.,(2005), preface p. 10, Copyright Elsevier, adapted from Praktische Anatomie. Ein lehr und Hilfsbuch der Anatomischen Grundlagen Ärtzlichen Handelns, Lanz and Wachsmuth (1959) p. 47. Copyright Springer- Verlag, Berlin. With permission.

The RNT has been shown with buckle force transducers to apply a significant magnitude of tensile force to the radial nerve as well as to the medial, posterior and lateral cords of the brachial plexus (82) and produce symptoms at its end range in asymptomatic subjects (84).

It is pertinent that the final position in which the upper limb is positioned during the RNT which is specifically designed to apply mechanical tension to the radial nerve and its posterior interosseous branch is extremely similar to the one in which the upper limb is positioned in the Mills manipulation, right before applying the elbow extension thrust. It is possible that during the Mills manoeuvre nerves are stressed along with muscles. This information represents part of the rationale underpinning the investigations presented in research line n.2 in which analysis of extraneous muscular reactions during Mills manipulation pre-manipulative positioning will be presented.

### 2.2.5 Electromyographic Investigation of Neural Protective Mechanisms

In order to support the hypothesis that muscles can be directly activated to protect peripheral nerves from aberrant mechanical forces, it is necessary to demonstrate the existence of nerve terminals in the connective tissues of peripheral nerves and possibility of ectopic electrogenesis at the peripheral nerve level. In 1963 Hromada (85) described the innervation of the connective tissues of peripheral nerves by nerve fibres termed "nervi nervorum", whilst in 1995 Bove and Light (86) reported neurovascular bundle nociceptors (nervi vasa nervorum) that responded to mechanical stimulation, which indicates that the observed responses to mechanical stimulation were not exclusively linked to discharge due to injury and in fact could be within the natural physiological receptive capabilities of peripheral nerve. The presence of C nociceptive and compression/stretch-responsive endings in the neural connective tissue (e.g. epineurium) supports the notion that ectopic electrogenesis can indeed be produced by mechanical forces applied to the nerve trunk.

If it is true that nerves can react to mechanical forces, both tensile and compressive, there must be an innate protective mechanisms in the human body designed to protect nerves from such forces. Apart from the longitudinal and transverse neural sliding mechanisms already described in Chapter 1, it may be that muscles does activate in response to the efferent volley triggered by excessive mechanical forces on the peripheral nerves.

These muscles may become active in order to protect the nerves by simply i) avoiding further elongation of neural bed, ii) shortening the neural pathway in order to decrease tensile stress (figure 21).

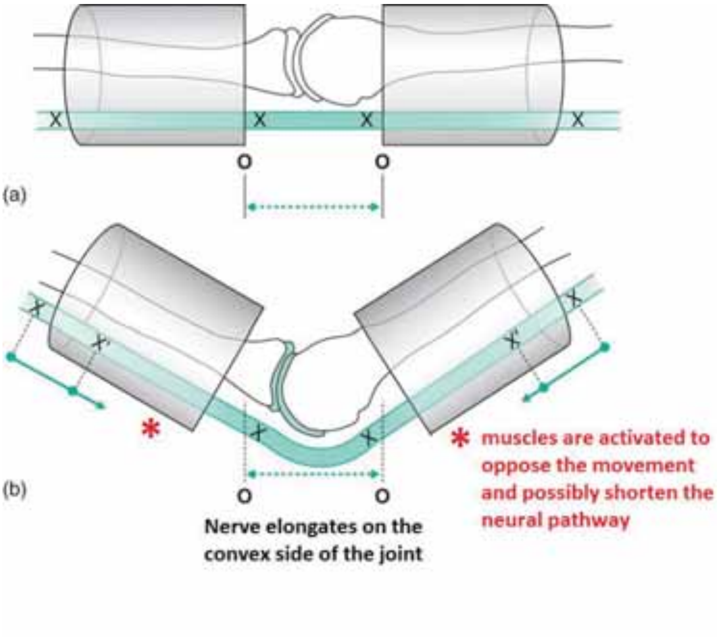


*Figure 21.* Muscles may become active in function of neural protection to avoid further elongation of neural bed and to shorten the neural pathway as to decrease tensile stress onto the neural tissues. Modified from: Neurodynamic solutions, Adelaide, Australia. With permission.

If this is true, it may be possible to record such myoelectric activity with Ag/AgCl electrodes used in surface electromyography (sEMG).

The aim of this line of research will then be to set the basis for new investigations designed to understand such mechanisms. We will start from exploring whether this activation in function of neural protection does actually exist. If such activation will be proven to occur, the authors will then try to test its specificity and make sure that it is not just a general and unspecific increase of myoelectric activity taking place within the human body. Future steps may then be the analysis of quantitative parameters of such myoelectric activation, and detect the neural pathway that may allow for such mechanism.

# 3 *Aims of the Study*

## 3.1 RESEARCH LINE N.1: NEURORADIOLOGY

### 3.1.1 General Aims

It seems quite interesting to acknowledge that, even if the SLR test is one of the most consistent and widely used physical test in formulating the diagnosis of sciatica, apart from the direction in which L5 and S1 lumbar nerve roots displaces in response to the execution of a SLR manoeuvre, caudal, the published evidence on neural behaviour in response to SLR seems to be far from conclusive in terms of magnitude of displacement.

### 3.1.2 Specific Aims

In order to visualize the sliding of a nerve relative to a particular bone, a reference point has to be specified on both structures. This can be an easy task on a bony structure, but as the nerve root is essentially a tube with no exact discernible distinctive features at a MR scan, no reliable reference points can be defined on its structure.

In order to solve this issue, the author of this doctoral thesis proposed to track the movements of the spinal cord in response to unilateral and bilateral SLRs. It was hypothesized that if any movement would be shown to happen, it may occur via sliding of, and direct transmission of forces through, the lumbosacral neural roots and dura to the spinal cord. Moreover, it was hypothesized that the lumbosacral nerve root would move by at least the same amount the spinal cord did.

The specific aims of the studies conducted as part of research line n.1 were:

- To investigate and quantify the medullar cone displacement in response to the execution of a unilateral SLR (article I).
- To investigate and quantify the medullar cone displacement in response to the execution of a bilateral SLR (article II).
- Ascertain if a difference exists in the mechanical effects on the cord between the unilateral and bilateral SLR (article II).
- Verify whether the effect on the spinal cord may be cumulative between the two (article II).
- Verify whether those neural displacements may bear aspects of predictability (article I and II).

## 3.2 RESEARCH LINE N.2: NEUROPHYSIOLOGY

### 3.2.1 General Aims

The second part of this doctoral thesis focuses on methods of collecting indirect data on neural adaptation mechanisms by quantifying the muscular reactions in response to neural stretch in in-vivo and structurally intact human subjects.

The rationale underpinning this line of research is that the muscles may be reflexively activated in order to protect the peripheral nerves in the most logical way: by shortening their pathway and opposing the manipulation movement.

The author is here exploring:

i) whether the overall changes in myoelectric activity in the test muscles are an expression of a specific protective response related to mechanical force production in the neural tissues, and not just the effect of a general increase of myoelectric activity,

ii) whether the Mills manipulation specificity for the common extensor tendon origin at the elbow can be improved with the addition of a neural unloading movement to the standard Mills manipulation.

### 3.2.2 Specific Aims

Following the notion that the RNT applies mechanical tension to the radial nerve and to the medial, posterior and lateral cords of the brachial plexus (82), as well as to its posterior interosseous branch, it is pertinent that the final position in which the upper limb is positioned before applying the elbow extension thrust in Mills manipulation is similar to the one reached during the RNT.

Following this assumption it was decided to ascertain:

- If there is any objective evidence to suggest that the pattern of muscular activation may be interpreted in relation to anatomy and biomechanics of the related muscle and nerve structures (articles III, IV).
- Whether any discernible pattern in electromyographic activity would emerge during the execution of the pre-manipulative stretch for Mills manipulation in selected muscles, possibly reflexively activated in order to protect the peripheral nerves from excessive mechanical forces by shortening their pathway (articles III, IV).
- Whether non-specific neural and muscular effects of Mills manipulation could be controlled with cervical ipsilateral lateral flexion; with “non-specific” meaning “effects that are not the direct target of the manipulation” (article III).
- Whether brachial plexus unloading with forward flexion of the shoulder girdle joint may influence the EMG activity in different muscles that anatomically and biomechanically relate to the nerves and elbow joint per se (article IV).

- An additional objective was to present a new model for investigation of muscle activation in function of neural protection, in which movements hypothesized to apply mechanical tension on peripheral nerves are executed in in-vivo and structurally intact human subjects and change in range of motion during the execution of such manoeuvres is correlated with change in myoelectric activity in selected muscles (article III).

# 4 Methods

## 4.1 RESEARCH LINE N.1: NEURORADIOLOGY, ARTICLES I-II

### 4.1.1 Pilot; the Basic Idea Underpinning Research Line N.1

In the present research line the authors intended to investigate neural biomechanics during the execution of both unilateral and bilateral SLRs in in-vivo asymptomatic subjects with the aid of magnetic resonance imaging in order to shed some light into the ambiguous question of whether the nerve roots does indeed move in response to those neural tension tests. The answer to this question will impact on the specificity of this widely used test.

Due to the diameter of the MR bore, 60 cm, and being the anatomical area of interest the lumbar spine from which the L5 and S1 nerve roots emerges, if the lumbar spine was to be placed into the centre of the MR bore, no more than 20° of hip flexion could be achieved during both unilateral and bilateral SLRs. If the experiments were to be performed in such conditions, the distinct possibility of not recording any neural movement in response to the performed SLR manoeuvres would likely manifest, possibly leading the investigators to refute the research hypothesis (research error type 2).

Knowing from the literature review that the greater amount of neural displacement is found to occur between 60° and 75° of hip flexion during an SLR, it soon became clear that a solution that would allow the resemblance of the clinical SLR had to be found.

Following the observation studies performed by Alf Brieg (56) it emerges that the neural system is indeed in a structural continuum, and that this circumstance can be used to our advantage. If it is true that the neural system originates with the brain and ends up at the tip of our hands and feet, it is also true that tensile forces may be directly transmitted from peripheral nerves via neural trunks, neural roots and adjacent dura to the central nervous system. In other words, if we pull the sciatic nerve hard enough during the execution of a SLR, the nerve roots and the spinal cord will likely follow by a certain amount. This distal movement may occur via sliding of, and transmission of forces through, the lumbosacral neural roots and dura.

Following this, we decided to place the cervical spine of the volunteers in the centre of the MR device's magnet, and knowing that the C6 and C7 cervical nerve roots holds an oblique orientation relative to the Normal (56), it was hypothesized that if the spinal cord was to displace caudally following the tension gradient originating mainly to L5 and S1 nerve roots in response to unilateral or bilateral SLRs, the angle of C6 and C7 nerve roots relative to the Normal would change. That is, if the spinal cord would displace caudally, the angle between these nerve roots and the spinal cord itself, would increase.

It is as simple as opening an umbrella; when the umbrella is opened and the central tube is sliding caudally relative to the ribs holding the fabric canopy, the angle between the central tube and the ribs increases.

#### *4.1.1.1 Methods*

An asymptomatic subject was placed supine into the MR device and coronal slices were taken of his spinal cord during the execution of unilateral and bilateral SLRs. T2 sequences were used as they allow nice contrast between the cerebro-spinal fluid and the neural structures.

The coronal slices (T2 weighted turbo spin echo fat saturation sequence, TR 3880ms, TE 90ms, 10 slices, slice thickness 3mm, gap 0.3mm, FOV 400mm$^2$, pixel size 1.3mm*0.9mm, phase encoding direction proximal to caudal) were aligned with spinal cord in order to allow for a better identification of the nerve root exit angle.

The changes in angle between C6 and C7 nerve roots and the Normal were then calculated relative to the values measured into the reference position; that is subject lying relaxed in the anatomical position.

### *4.1.1.2 Results*

The results of the first scan were very promising, showing and increase of nerve root angle relative to the orientation of the spinal cord in response to a bilateral SLR form 55.2° to 65.7° for C6 nerve root and from 45.2° to 47.7° for C7 nerve roots.

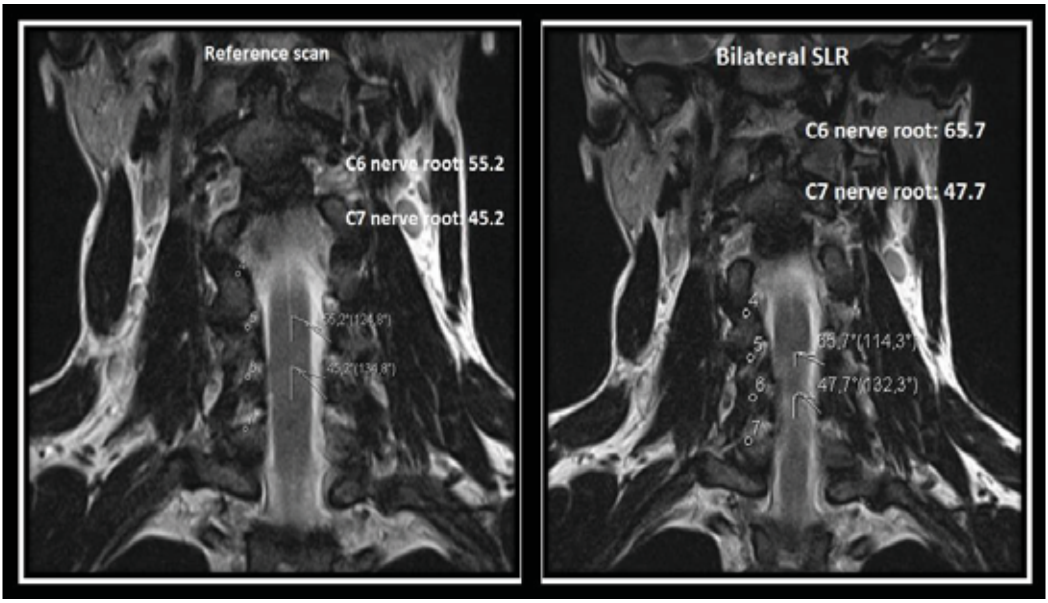


*Figure 22.* Change in C6 and C7 cervical nerve roots relative to the Normal in a coronal plane following execution of a bilateral SLR. Unfortunately those scans were very prone to motion-related artefacts. Source: own database.

However, the scans of the second volunteer were of unacceptable quality due to motion-related artefacts, which did allow for precise quantification of nerve root angles. It became clear that the research design was not strong enough. This led the author of this thesis to conclude that this measurement methodology is weak and not feasible at all.

#### *4.1.1.3 Discussion*

After the initial enthusiasm, it became clear that this measurement methodology presented several problems:

i) Due to the small amount of displacement and the objective difficulties in deciding which part of the nerve root would serve as reference point for the measurements, it was likely that the reliability testing of the measurement procedure would present very low values

ii) Due to both micro and macro movements taking place around the anatomical area of interest, as for example volunteers' micro adjustment of the cervical spine as well as swallowing, the resulting images were very prone to present movement artefacts.

iii) The individual degree of cervical lordosis of each volunteer would make it very difficult to select an appropriate slice orientation so that both C6 and C7 nerve roots can be visualized in the same slice. This would make the measurements rather difficult and the results questionable.

These data were considered weak. However, they lent relevant support to the author's hypothesis of transmission of tensile forces along the neural system and provided data that shows that something is actually going on into the vertebral canal during the execution of these neural tension tests, something that is still well worth investigating. The question remained about how to do it without compromising the structural integrity of the vertebral spine.

### 4.1.2 Quantification of Conus Medullaris Displacement in Response to Unilateral and Bilateral SLRs. (I, II)

#### *4.1.2.1 Background (I, II)*

Following the results of the pilot study, it was clear that a different method to quantify the displacement of L5 and S1 nerve roots in response to unilateral or bilateral SLRs was needed.

Knowing that it was virtually impossible to visualize directly the L5 and S1 lumbar nerve roots while performing an SLR due to issues linked to the MR device architecture explained in paragraph 4.1.1, it was decided to place the volunteers into the MR device as much as needed to allow at least 50º of hip flexion, and visualize the distal displacement of the spinal cord at T12-L2 level in response to the test manoeuvres.

This was done following the basic assumption that if the sciatic nerve would be tensioned during the execution of a unilateral or bilateral SLR, due to the neural continuum, the forces could be transmitted through the lumbosacral nerve roots and dura to the spinal cord. A key question was whether the effects of the SLR are transmitted via the nerve roots to the spinal cord and, if so, what might be the relationship between nerve root and cord movement, such that improved knowledge of the local mechanics may lead to improved clinical diagnosis.

Due to the neural structural continuum, in which the lumbosacral neural roots are directly connected via the cauda equina to the spinal cord, we hypothesized that if any caudal movement of the medullar cone would show itself in the SLRs, it may occur via sliding of, and direct transmission of forces through, the lumbosacral neural roots and dura to the spinal cord.

#### *4.1.2.2 Subjects (I, II)*

Following the results of the a pilot study and due to the dimensions of the scanner (Siemens Avanto 1.5T, Erlangen, Germany), the authors calculated that subjects taller than 182cm were needed to allow performance of the SLR in the scanner, permitting at least 50° of unrestricted hip flexion.

A total of 20 male volunteers were recruited and screened for eligibility, 16 of whom met the inclusion criteria (table 2). The age of enrolled volunteers ranged from 23 to 56 years. Their mean age was 33 (SD 10.7 years), height 187 (SD 4.2) cm, and BMI 24.9 (SD 2.2) kg/m$^2$.

Asymptomatic volunteers were chosen in order to make use of the normal situation providing normative measurements and avoid potentially confounding variables such as local impairments or neural dysfunctions that may occur in a symptomatic population. All tested subjects signed an informed consent form and the study was approved by the institutional ethics committee. The study was performed in accordance with the Declaration of Helsinki.

*Table 2.* Exclusion and inclusion criteria.

| ***Table 2. Exclusion and inclusion criteria*** |
|---|
| **Exclusion criteria** |
| • Subjects currently experiencing painful symptoms in the tested area<br>• Incomplete and/or painful knee extension<br>• Incomplete and/or painful hip range of motion<br>• History of known neurological disorders of the tested extremity<br>• History of diagnosed lumbar intervertebral disc herniation<br>• History of previous abdominal or lumbar surgeries<br>• Other joint involvement, like arthritis or already recognized metabolic bone disease<br>• Subjects with any known arthrogenic, muscular or neurogenic dysfunctions in the lumbar spine area which, on provocative physical testing, gave positive signs and/or pain into the lower limb<br>• Presence of pacemakers and ferromagnetic implants |
| **Inclusion criteria:** |
| • Subjects assessed to be asymptomatic<br>• Subjects' consent to participation by signing the consent form<br>• No present exclusion criteria at the time of testing |
| **Summary of exclusion criteria:** *All the volunteers were screened to be asymptomatic and to have a pain-free and complete range of bilateral movement in the hip, knee and ankle joints and did not match the exclusion criteria.* |

### *4.1.2.3 Magnetic resonance imaging (I, II)*

The tested subjects were lying supine into the MR scanner. The imaging area was centred approximately 3cm proximally from the xiphoid process of the sternum and the coronal images centred at the lower part of the imaging area to T12-L2 anatomic region. The volunteers were scanned using an 8-channel spine matrix coil.

The coronal slices (T2 weighted turbo spin echo fat saturation sequence, TR 3880ms, TE 90ms, 10 slices, slice thickness 3mm, gap 0.3mm, FOV $400mm^2$, pixel size 1.3mm*0.9mm, phase encoding direction proximal to caudal) were aligned with spinal cord in order to allow for a better identification of the medullar cone.

### 4.1.2.4 Medullar cone displacement measurement (I, II)

The displacement of the medullar cone relative to the upper intervertebral surface of the adjacent vertebra during the unilateral passive right and left SLRs was quantified and compared with the position of the conus in the neutral (anatomic) position. Figure 23.

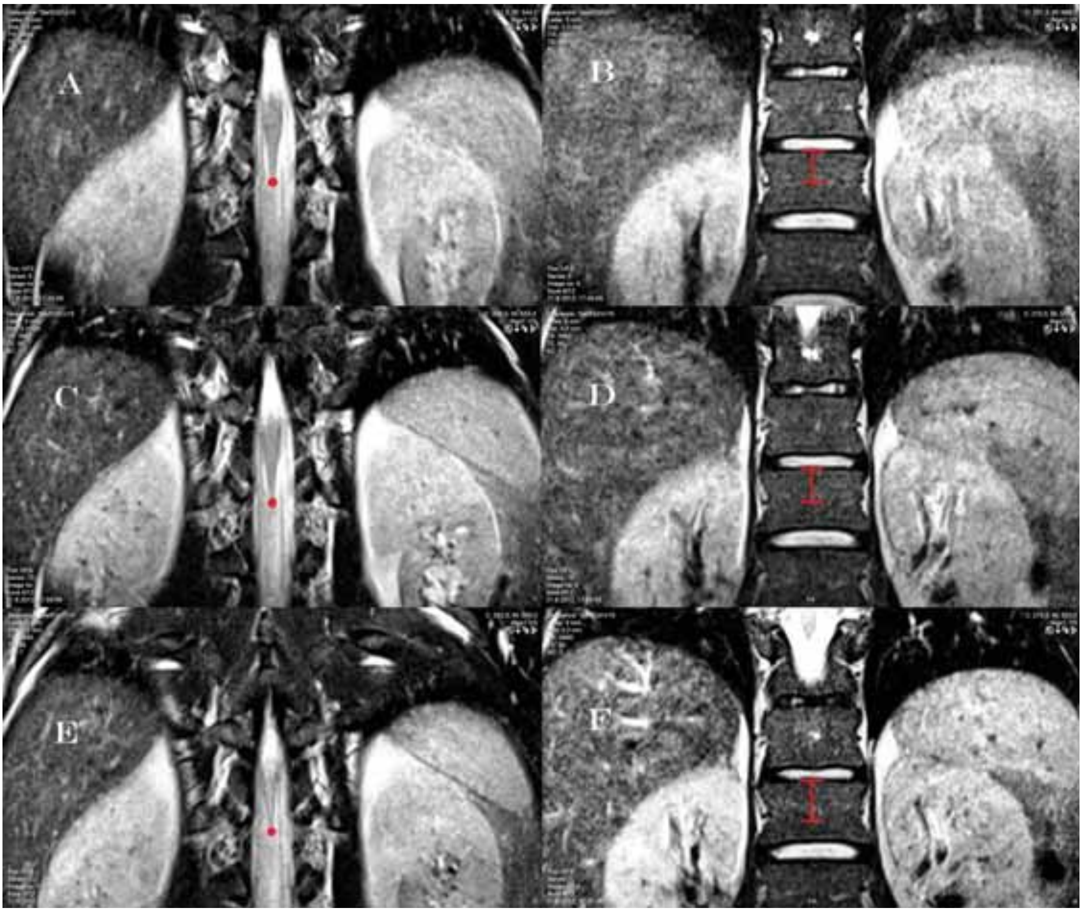


*Figure 23.* Magnetic resonance scans. Coronal slices of the thoracolumbar region of a sample subject during A. reference scan, C. unilateral SLR, E. bilateral SLR are presented. The apex of the medullar cone is marked. The vertical distances from the upper intervertebral surface of the adjacent vertebral body are marked and presented in B, D, and F. NOTE: measures and marking symbols are emphasized for readers' convenience. Scans showing original measurement lines and tools used in SECTRA PACS program are included in the original articles, appendixes I and II. Source: own database. NOTE: marking symbols are emphasized for readers' convenience.

Measurements were taken twice by the main author, with two months between each measurement, and once by co-author J.M. in order to allow for evaluation of intra- and inter-observer reproducibility testing.

The two observers independently assessed the conal displacement by first identifying the tip of the conus. Particular care was taken to identify the origin of filum terminale as to confirm the localization of the tip of the conus. The mark was then precisely projected onto the coronal slice at the centre of the adjacent vertebral body by using the crosshair and localizer tools available in Sectra PACS program where the distance between the mark on the vertebral body and the anatomical reference point represented by the upper intervertebral surface was measured. Special care was used to guarantee that the conus marking process was always performed on the same slice between different tests. This is valid also for measurements of distance between the upper intervertebral surface and conus tip mark on the vertebral body. The measurements were identically repeated at each phase of the test. The measurements were made in Sectra PACS program (Sectra Workstation IDS7, version 15.1.8.5-2013 – Sectra AB, Sweden).

#### *4.1.2.5 Subject positioning and tested movements (I,II)*

The volunteers were scanned in the following positions in a random order:

-Neutral: Subject lying supine, aligned symmetrically in anatomic position, lower limbs extended in the purest relaxed form.

- SLR on the right side: The practitioner performed a passive SLR manoeuvre on the volunteers' right lower limb at the maximum degree of hip flexion allowed by the MR scanner architecture, holding the lower limb still, with the knee extended and the ankle in a plantargrade position (0° of dorsiflexion).

- SLR on the left side: The practitioner performed a passive SLR manoeuvre on the volunteers' left lower limb in a similar fashion as to the right side.

- Passive Bilateral SLR: maximum hip flexion allowed by the MR device architecture, with the knee extended and the ankle in a plantargrade position (0° of dorsiflexion) while the scan sequence was operated. Two investigators were required for this in which subjects' legs were raised, one by one, starting from the right, left or both legs together in a random order

Due to the MR device architecture with a tube diameter of 60cm, a mean value of only 50° of hip flexion could be achieved in the tested subjects.

Hip flexion was measured with an oil-filled precision goniometer placed on the anterior surface of the distal third of the tibia. This method has been shown to have good intra-observer repeatability with the SLR (87) and was considered safe to be operated in the MR scanning room, security zone IV.

Each movement was performed twice for evaluation of reproducibility. Four practitioners performed the manoeuvres in a random sequence in order to avoid possible series effects.

Cervical flexion in the subjects was always avoided so as not to influence spinal cord position or movement.

*Figure 24.* Passive SLR with subject lying supine into the magnetic resonance device. A: Passive right SLR. B: Passive bilateral SLR.

As an outline:

- In bilateral SLR the subjects' legs were raised, one by one, starting from the right, left or both legs together in a random order.
- Four practitioners performed the manoeuvres in a random sequence in order to avoid possible series effects.
- Each movement was performed twice for evaluation of reproducibility.
- The measurements were repeated by two observers, allowing for inter and intra observer reliability testing

In summary, the authors did everything possible not to influence the outcomes of these experiments and to provide genuine results.

#### *4.1.2.6 Statistical methods (I,II)*

The purpose of the data analysis was to detect any statistically significant differences in medullar cone position between the reference position and the tested manoeuvres, right, left SLR and bilateral SLR.

All the presented metric values were truncated to the next lowest decimal integer (2.55=2.5) to provide more conservative and reliable data.

A one-tailed hypothesis that the medullar cone would displace caudally during the performance of the SLR manoeuvres versus no change was tested. Also, one-tailed hypothesis that the conus medullaris displacement in response to SLR will be larger with bilateral rather than unilateral SLR, versus no change was tested (article II).

The Spearman correlation between the two scans of the same manoeuvres performed on each subject was calculated as well as for inter- and intra-observer reliability.

Having found strong correlation between the measures from different scans of the same manoeuvres performed on each subject, as well as high correlations between different measurements performed by different observers on those scans, it was decided to average all the available measurements when presenting the mean values and their standard deviations, in order to present the results as more accurately and conservatively as possible.

Student´s t-test was used to test the significance of medullar displacement during the SLR manoeuvres in relation to the position found in the reference scans. The Alpha level was set at $p<.05$.

The Observed Power was calculated on the data using t distribution, while the minimum number of subjects needed to extract statistically significant results was calculated from the collected data.  Statistical analysis was performed using R Program (R Foundation for Statistical Computing), Version 2.15.2 (2012).

### 4.1.3 Developing Methods of in Vivo MRI Measurement of Spinal Cord Displacement in the Thoracolumbar Region of Asymptomatic Subjects with Unilateral and Bilateral Straight Leg Raise Tests

In this section the author of this doctoral thesis is going to present advancement in the methods related to the line of research in neuroradiology. This is done to provide evidence that this line of research is currently developing and new hypothesis are being formulated. Also, unpublished data will be presented in the Results section.

#### *4.1.3.1 Aims*

As in the literature, the bulk of nerve root excursion has been shown to occur between 60° and 75° of hip flexion (29,38,39,47,48) it is probable that a greater amount of caudal displacement would be reported if greater hip flexion angles were achieved.

Of particular interest is:

i) whether the magnitude of conus medullaris displacement increases with more hip flexion
ii) whether the 'principle of linear dependence', linking magnitude of conus medullaris displacement to number of nerve roots involved, would be substantiated at greater amounts of hip flexion.

Another limiting aspect our previous studies is that the sample consisted of only male volunteers. Even if, to the author's knowledge, there is no published evidence that supports the existence of gender related differences in L4, 5 and S1 nerve root and conus medullaris, it would be of interest to construct a set of normative data including also female volunteers prior to the commencement of clinical investigations.

Additionally, attempts were made to improve the measurement methodology with the aid of 3D MRI scanning, so as to investigate whether the methodology itself could be improved in terms clinical feasibility and better values with inter- and intra-rater reliability testing.

#### *4.1.3.2 Subjects*

A total of 11 volunteers were recruited and screened for eligibility, one of whom met the exclusion criteria (Table 2) and was thus excluded from the study. Ten asymptomatic volunteers (eight males, two females) ranged from 20 to 32 years (mean age 25.1±3.9 years (Mean±SD)), height 186.7± 2.9 cm, BMI 24.22±3.92 kg/m$^2$, were included in the study.

### *4.1.3.3 Magnetic resonance imaging*

As before, the tested subjects were lying supine into the 1.5T magnetic resonance scanner (Siemens Magnetom Aera, Erlangen, Germany). The imaging area was centred approximately 3cm proximally from the xiphoid process of the sternum and the coronal images centred at the lower part of the imaging area to T12-L2 anatomic region. The volunteers were scanned using a 32-channel spine matrix coil.

Differently from before (I, II), in this study separate scanning sequences for planning and for measurement were used:

1. Planning employed T2 weighted turbo spin echo sequence (TR 3530ms, TE 96ms, 17 slices, slice thickness 3mm, FOV 300mm, in plane resolution 0.8x0.8mm, flip angle 150 degrees). Sagittal slices were aligned with the spinal cord to allow better identification of the conus medullaris.
2. Measurement used T2 weighted spc 3D-sequence (TR 1800ms, TE 128ms, slice thickness 1mm, sagittal scan, FOV 300mm, phase encoding direction proximal to caudal, in plane resolution 0.6x0.6mm, flip angle 160 degrees).

Coronal, axial and sagittal slices (slice thickness 1mm, approximately 70 slices in each plane) were reconstructed from the native T2 weighted spc 3D-sequence sagittal scans using the MPR program available in Sectra PACS workstation (Sectra Workstation IDS7, version 15.1.8.5-2013 – Sectra AB, Sweden).

### *4.1.3.4 Conus medullaris displacement measurement*

The displacement of the conus medullaris relative to the upper intervertebral surface of the adjacent vertebra during the unilateral passive right, left and bilateral SLRs was quantified and compared with the position of the conus in the neutral (anatomic) position (figure 25).

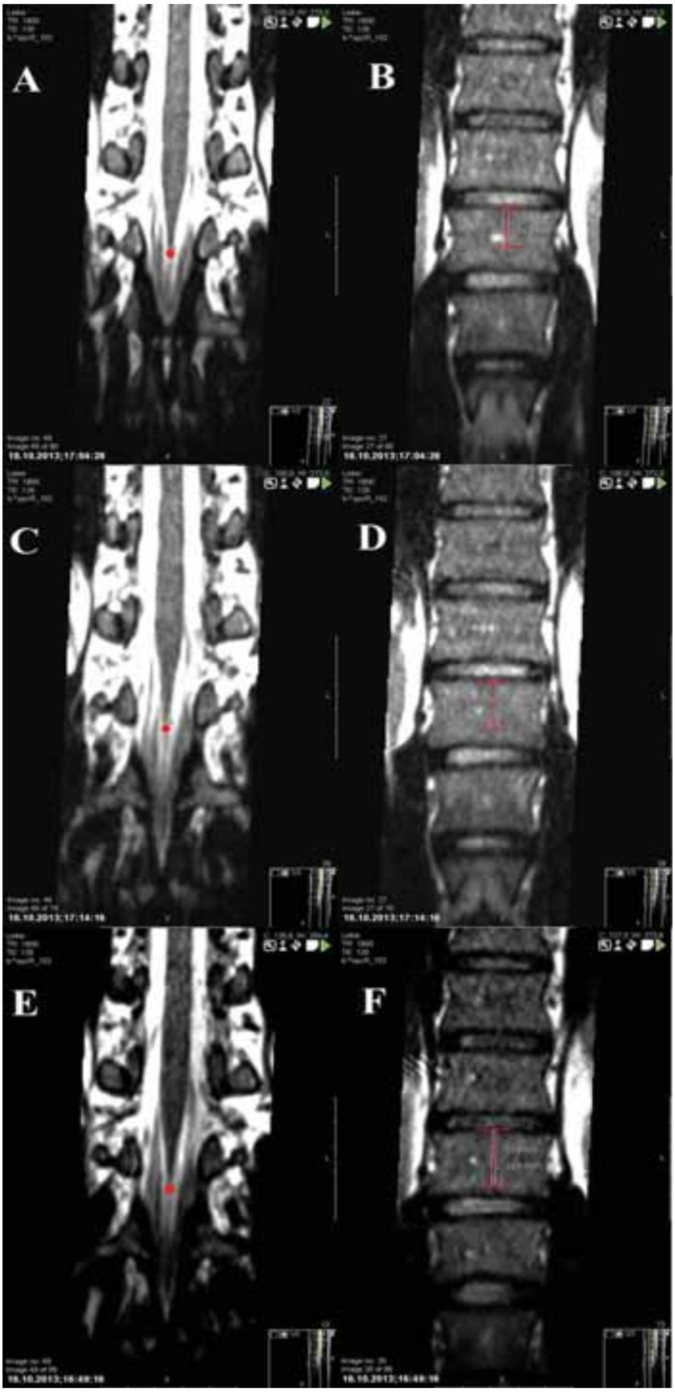


*Figure 25.* Magnetic resonance scans. Coronal slices of the thoracolumbar region of a sample subject during A. reference scan, C. unilateral SLR, E. bilateral SLR are presented. The apex of the medullar cone is marked. The vertical distances from the upper intervertebral surface of the adjacent vertebral body are marked and presented in B, D, and F. Different measurements from both observers are presented. Source: own database. NOTE: marking symbols are emphasized for readers' convenience.

As before (I, II), measurements were taken twice by the main author, with two months between each measurement, and once by co-author (JM) in order to allow for evaluation of intra- and inter-observer reproducibility.

The two observers independently assessed the conus displacement by first identifying the tip of the conus. The tip was initially identified on the coronal slices and its position concurrently verified on the axial and sagittal slices using the crosshair and localizer tools available in Sectra PACS workstation. Particular care was taken to identify the origin of filum terminale so as to confirm the localization of the tip of the conus.

The mark on tip of the conus was then precisely projected at the centre of the adjacent vertebral body by using the crosshair and localizer tools available in Sectra PACS program. As in Rade et al.(88,89) the distance between the mark on the vertebral body and the anatomical reference point represented by the upper intervertebral surface was measured on the coronal slices. The measurements were made using Sectra PACS program (Sectra Workstation IDS7, version 15.1.8.5-2013 – Sectra AB, Sweden).

#### *4.1.3.5 Subject positioning and tested movements*

The volunteers were scanned in the Neutral, Right SLR, Left SLR and bilateral SLR positions in random order as in previous investigations (I, II).

As before, hip flexion was measured with an oil-filled precision goniometer placed on the anterior surface of the distal third of the tibia. Due to the MR device architecture with a tube diameter of 70cm, 60° (Mean 59.6°) of hip flexion was achieved.

Each movement was performed twice for evaluation of reproducibility. This time, three investigators performed the manoeuvres in random order in order to avoid possible series effects.

As before, subjects' cervical spine was always placed in a neutral position so as to avoid producing any positional effects in the spinal cord.

*Figure 26.* Passive right SLR (A) and passive bilateral SLR (B) with subject lying supine into the magnetic resonance device.

#### *4.1.3.6 Statistical methods*

As in previous investigations, the purpose of the data analysis was to detect any statistically significant differences in conus medullaris position between the reference position and the tested manoeuvres, right, left and bilateral SLR.

All the presented metric values were truncated to the next lowest decimal integer (3.55=3.5) to provide more conservative and reliable data.

Differently from before, a two-tailed hypothesis that the conus would displace in response to SLR versus no change was tested.

The Pearson's correlation between the two scans of the same manoeuvres performed on each subject was calculated as well as for inter- and intra-observer reliability.

Having found strong correlations between the measures from the different scans of the same manoeuvres performed on each subject, as well as high correlations between different measurements performed by different observers on those scans, it was decided to average all the available measurements when presenting the mean values and their standard deviations, in order to present the results as more accurately and conservatively as possible.

Student´s t-test was used to test the significance of conus medullaris displacement during the SLR in relation to the position found in the reference scans. The Alpha level was set at $p<.05$.

The Observed Power was calculated on the data using t distribution, while the minimum number of subjects needed to extract statistically significant results was calculated from the collected data. Statistical analysis was performed using R Program (R Foundation for Statistical Computing), Version 2.15.2 (2012).

## 4.2 RESEARCH LINE N.2 : NEUROPHYSIOLOGY, ARTICLES III-IV

### 4.2.1 **Rationale**

#### 4.2.1.1 *Effect of Cervical Spine Position on Upper Limb Myoelectric Activity During Pre-Manipulative Stretch for Mills Manipulation: A New Model, Relations to Peripheral Nerve Biomechanics and Specificity of Mills Manipulation (III)*

In the present study, as part of a new model for investigation of the myoelectric effects that may approximate those of the Mills manipulation, a pre-manipulative stretch technique was performed during simultaneous measurement of electromyographic (EMG) activity of various muscles of the upper limb in different positions of the cervical spine.

As already mentioned in subheading 2.2.4.3, even if this technique was originally designed to stretch the CEO (64,66,67,69), it is pertinent that the final position in which the upper limb is positioned before applying the elbow extension thrust is similar to the one reached during the RNT which is specifically designed to apply mechanical tension to the radial nerve and its posterior interosseous branch.

In this investigation the test manoeuvre was performed as described by Kesson and Atkins in 2005 (67) but no thrust toward elbow extension was applied. The end range position was merely maintained strongly and for long enough to produce measureable muscle responses.

In this study, cervical position was used to alter the mechanical tension in the peripheral nerves of the limb in order to ascertain whether any consequent changes in EMG occurred with this change in nerve mechanical posturing. Various cervical and shoulder positions are known to change mechanical tension in the nerves of the shoulder and upper limb (8,80,82,90,91). Cervical contralateral lateral flexion increases tension in the brachial plexus and contiguous distal nerves (82,90) and it has been observed with high resolution ultrasound nerve imaging that ipsilateral lateral flexion decreases such tension (17).

The hypothesis underpinning the presented rationale is that if stretches similar to Mills manipulation involve such neural and/or muscular aspects, there is potential for variation of the cervical position to influence the EMG activity in different muscles that anatomically and biomechanically relate to the nerves and elbow joint per se.

#### *4.2.1.2 Effect of Glenohumeral Forward Flexion on Upper Limb Myoelectric Activity During Simulated Mills Manipulation: Relations To Peripheral Nerve Biomechanics and Specificity of Mills Manipulation (IV)*

The notion that the design of the Mills manipulation is noticeably similar to the position designed to stress the radial nerve in order to test its mechanosensitivity has already been presented in subheading 2.2.4.3.

On a mechanism level, shoulder abduction and elbow extension increase mechanical tension in the radial and contiguous nerves, these effects of which are cumulative between these two component movements (92) . Moreover, it seems that the critical factor in increasing strain in the nerves around the humerus is shoulder abduction to 90° (93).

Furthermore, even though treatment with Mills manipulation is designed to reduce pain, in practice, this movement is often described by patients as painful and uncomfortable.

Similarly to article III, here the investigators explored i) whether any discernible pattern in electromyographic activity would emerge during the execution of the pre-manipulative stretch for Mills manipulation in selected muscles, possibly reflexively activated in order to protect the peripheral nerves from excessive mechanical forces in the most logical way; by shortening their pathway and ii) whether non-specific neural and muscular effects of Mills manipulation could be controlled with forward flexion of the shoulder girdle joint; with "non-specific" meaning "effects that are not the direct target of the manipulation".

It was chosen to add the forward flexion of the shoulder girdle joint to the standard Mills positioning as a neural detensioning movement because the brachial plexus passes anterior to the shoulder joint, and posteriorly angulated shoulder movements are likely to apply tension to the plexus through a pulley effect on the plexus as it passes in front of the joint.

The corollary is that anteriorly angulated movements would do the opposite, thus decreasing tension in the plexus. More specifically, shoulder girdle forward flexion would decrease the mechanical forces applied to the brachial plexus by i) decreasing the distance between the lower cervical region and the axilla, ii) increasing the area of the thoracic outlet tunnel as the clavicle moves anteriorly away from the first and second ribs, while not modifying any other component of the Mills manipulation manoeuvre.

### 4.2.2 Subjects (III, IV)

Eleven healthy university student volunteers were recruited (see Table 3 for inclusion and exclusion criteria). Three subjects (2 males and 1 female) satisfied the exclusion criteria and were eliminated. Eight remaining volunteers (7 male, 1 female), aged from 26 to 33 years (mean age 28.62±2.28 years), BMI (mean value 24.68±3.16), all right-handed, were tested bilaterally, providing 16 recordings. All tested subjects signed an informed consent form and the study was approved by the Middlesex University, School of Health and Social Sciences Ethics Sub-committee (London, United Kingdom). The study was performed in accordance to the Declaration of Helsinki.

*Table 3.* Exclusion and inclusion criteria

**Table 3. Exclusion and inclusion criteria**

**Exclusion Criteria:**

- Subjects currently experiencing pain or symptoms on the tested side
- Subjects who did not have pain-free-full range of movement of the cervical spine or shoulder, elbow, wrist and hand joints bilaterally
- Previous history of lateral elbow symptoms
- History of known neurological disorders of the tested extremity
- Other joint involvement, like arthritis or already recognized metabolic bone disease
- Associated wrist disorders or previous trauma of the cervical spine, shoulders, elbows or wrist, bilaterally.
- Subjects with any known arthrogenic, muscular or neurogenic dysfunctions in the cervical spine area which, on provocative physical testing, gave positive signs and/or pain into the arm.
- Previous surgery on tested side, including the cervical spine, shoulder, elbow, wrist and hand
- Any known structural abnormality of the upper limb
- Associated diagnosed neck disorders, lesions including those of the cervical spine and brachial plexus
- More than 3 corticosteroid injections in the last 3 months
- Associated shoulder disorders, previous trauma with fracture
- Subjects older than 55 years to reduce likelihood of significant degenerative changes.

**Summary of exclusion criteria:** *All the volunteers were screened to be fully asymptomatic and to have a pain-free and complete range of bilateral movement in the cervical spine, shoulders, elbows and wrist and did not match the exclusion criteria.*

**Inclusion Criteria:**

- Subjects assessed to be asymptomatic
- Subjects' consent to participation by signing the consent form
- No present exclusion criteria at the time of testing

### 4.2.3 **Subject Positioning (III, IV)**

Subjects were seated and, as with other investigations into neurodynamic tests, overall consistency in posture was achieved by means of a custom-made device designed to prevent scapular elevation and cervical movements (94-96).

Support bracing was also applied at the wrist for consistency in joint posture. The wrist was therefore maintained at an angle of 70° flexion, in accordance with Kleinrensink et al. (82).

### 4.2.4 **Electromyographic Recordings (III, IV)**

#### *4.2.4.1 Devices (III, IV)*

Electromyographic signals were recorded with a 16 channel pocket EMG patient unit (POCKETEMG, BTS spa, Garbagnate Milanese, Milano, Italy). Data were collected at a rate of 1000 Hz using a 16-bit A/D board. Electromyographic signals were band passed with a Butterworth filter at 10-499 Hz with a common mode rejection ratio of >100 dB at 65 Hz, an input impedance of >10 GΩ, and transmitted via Wi-Fi to a computer so that the data could be processed off-line using the BTS smart analyser program.

#### *4.2.4.2 Signal Preprocessing (III, IV)*

The EMG signals were smoothed with a root mean square function with a 50 ms sliding window and the area under the processed signals was integrated within five seconds, during which the pre-manipulative stretch was maintained in order to provide quantitative measures of the amount of muscular activation. A 50 ms sliding window was selected following the rationale that the authors were investigating gradual muscular reactions to slow passive movements, rather than performing on-off analysis. The results of the analysis were then exported to a Microsoft Excel program so that the data could be statistically analysed and displayed graphically.

#### *4.2.4.3 Poweline noise check (III, IV)*

The power spectrum of each individual signal was checked for 50 Hz peaks using the Discrete Fourier Transformation function included in the analysis tool provided by the manufacturer before accepting the signals for further analysis.

In article number IV, the records were also double-checked by an independent laboratory (Biosignal Analysis and Medical Imaging Laboratory at University of Eastern Finland, Kuopio, Finland) by calculating the Fourier-based spectrum with the Welch's averaged periodogram method (length of overlapping epochs was 1000 ms and overlap was 75 %). No peaks were observed in the spectra in the 50 Hz frequency bin, allowing the investigators to reject the existence of power line interference in the recorded signals.

### 4.2.5 **Electrodes (III, IV)**

Disposable disc surface foam Ag/AgCl electrodes for EMG recording (Ambu®, Ballerup, Denmark, model N-00-S Blue sensor) were secured over the selected muscles.

#### *4.2.5.1 Electrode application (III, IV)*

Electrode application and skin preparation followed the recommendation of the European Society of Surface Electromyography (97).

The skin was shaved and lightly abraded until the appearance of a light red colour and cleaned with distilled water prior to electrode placement. Skin impendence was measured at every electrode placing site with a dedicated device (EMG electrode impedance tester–Noraxon inc, USA) and was verified to be less than 5 kOhm (kΩ) in all electrode sites. Each electrode pair was positioned in bipolar configuration and was placed near the centre of the muscle bellies, parallel to the direction of muscle fibres with a fix inter-electrode distance measured between the centres of the electrodes of 30mm in order to gather information from a sufficient number of motor units, as in Hashimoto et al. (98), Rissanen et al. (99) and Rissanen et al. (100). The common ground electrode was placed over the spinous process of the C7 vertebrae.

### 4.2.6 **Data normalization (III, IV)**

Maximal voluntary contraction (MVC) data normalization was avoided for three reasons. First, a maximal voluntary contraction of the tested muscles would not be suitable for the normalization of the EMG activity recorded during a passive movement. Second, it was possible that the electrical response of muscle during passive nerve stretch could be influenced by muscular fatigue due to the prior contraction. Third, it was decided that the EMG data should be presented as absolute rather than normalized values because authors were comparing changes in EMG activity between the two positions (Standard and Varied).

Compared values were the integral of the EMG signal within a 5 second time period in which the pre-manipulative stretch was maintained. This procedure is consistent with those reported in Jaberzadeh et al. (101).

### 4.2.7 **Kinematics (III, IV)**

The kinematic data were collected with an optoelectronic motion capture system (Smart-D, BTS, Garbagnate Milanese, Milano, Italy) with a 3 charge-coupled device (CCD) cameras adjustable system (sampling frequency of 50 Hz). This was done to correlate joint passive movements with changes in EMG activity. As shoulder abduction and wrist flexion were kept stable by external fixators (Figures 28, 29), particular interest was invested in verifying full elbow extension as this may affect the tension of the nerves passing on the anterior side of the elbow joint.

Ten millimetre reflective passive markers were applied on the skin at specific locations, in accordance with the International Society of Biomechanics recommendations on joint coordinate systems in upper limbs (102). Such locations consisted of the temporomandibular region (bilaterally), mid-frontal region, interclavicular notch, mid-clavicle (bilaterally).

In addition, two triplets of markers (each triplet forming a right angle triangle), were secured by straps over the distal insertion of the deltoid muscle on the humerus and over the distal radio-ulnar joint in order to track the torsional movements of the upper limb in 3D. This was so as to ensure that, during the off-line data analysis, the body positions used were accurate and consistent.

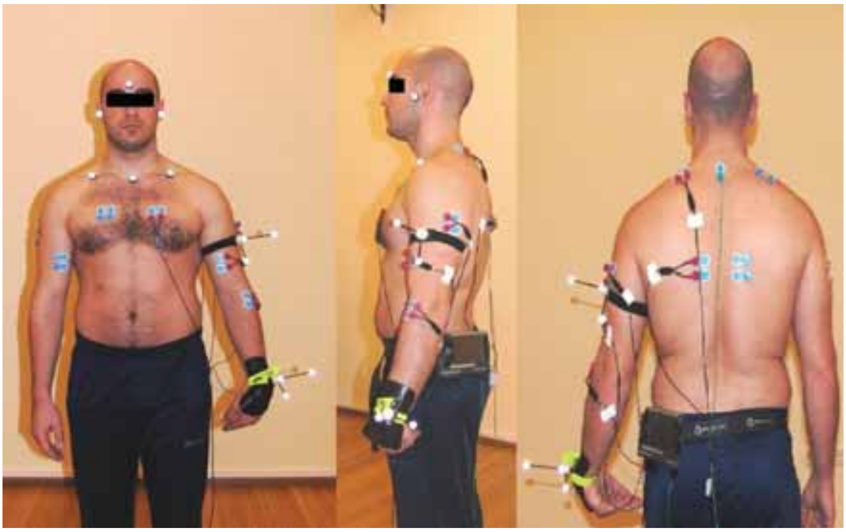


*Figure 27.* Positions of Markers and EMG electrodes for a left test side

The temporomandibular and mid-frontal region markers were inserted in order to track cervical lateral flexion movements (III, IV).

Also, the range of motion of elbow extension was measured during pre-manipulative stretch in both the Standard and the Varied (forward flexion) positions with a full-circle hand goniometer with one-degree increments following the directions of the American Academy of Orthopedic Surgeons (103) and verified off-line with the optoelectronic tracking system mentioned above.

### 4.2.8 **Tested Muscles**

The choice of test muscles was based on their capacity to produce protective effects by: i) shortening the pathway of the peripheral nerves passing on the concave (anterior) side of the elbow joint (biceps brachii and brachioradialis), ii) shortening the neural pathway in the shoulder region by shortening the distance between the axilla and the lower cervical spine (upper trapezius and pectoralis major), or because they were directly innervated by the radial nerve (brachioradialis and lateral head of the triceps brachii)(104,105) .

In contrast, the lower trapezius muscle was used as a "non-protective or control muscle" to verify that changes in EMG activity in the other muscles were not simply due to a non-specific increase in muscle activity of the tested upper limb in response to the pre-manipulative stretch. The lower trapezius is connected to the test limb by its scapular insertion, but is not directly innervated by the radial nerve and it is here thought not to participate in the protection mechanism supposedly operating by shortening the neural pathway, making his activation discordant with those of the test muscles. For these reasons it is considered to be a suitable comparative muscle.

### 4.2.9 **Test Manoeuvers**

#### *4.2.9.1 Pre-manipulative stretch for mills manipulation (III)*

The pre-manipulative stretch itself consisted of holding the elbow firmly in the end-range position for Mills manipulation in elbow extension and pronation, with wrist and finger flexion, for five seconds. In order to establish if an effect on muscle activity occurred with cervical spine positioning, the pre-manipulative stretch was performed in two different postures, A. the usual position as applied clinically (Standard)(67), and B. a position involving ipsilateral lateral flexion of the cervical spine (Variation) (Figure 28).

As opposed to performing the sudden manipulative thrust, the pre-manipulative stretch technique was chosen because; A. the rapid movement of a manipulation was likely to produce significant movement-related electromyographic artefacts that would contaminate the EMG data, B. the small amplitude high-velocity thrust was likely to amplify the myoelectric data already recorded during the pre-manipulative positioning due to an increased instantaneous tension in the affected tissues which would not add useful information and, C. the manipulative thrust would raise ethical concerns because the manoeuvre is usually painful and may produce unwanted structural changes in healthy subjects.

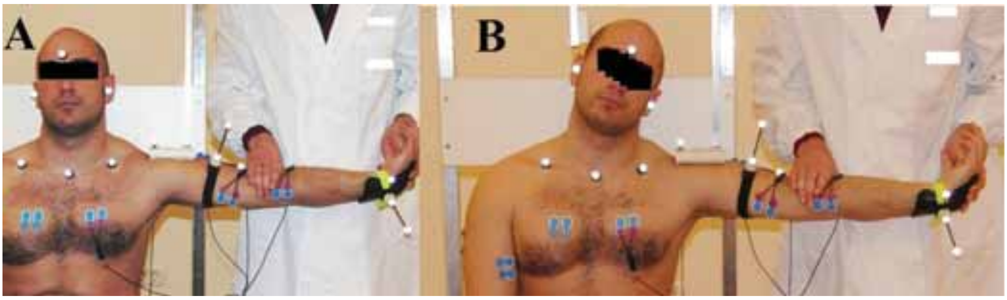


*Figure 28.* Pre-Manipulative Stretch for Mills Manipulation performed in the two tested positions. A. left, Standard position, B. right, Variation position with ipsilateral lateral flexion of the cervical spine.

### *4.2.9.2 Pre-manipulative stretch for mills manipulation (IV)*

As before, the pre-manipulative stretch itself consisted of holding the elbow firmly at the end-range position for Mills manipulation in shoulder girdle joint abduction to 90° and medial rotation, elbow extension, forearm full pronation, with wrist and finger flexion for five seconds.

In order to establish if an effect on muscle activity occurred with shoulder girdle positioning, the pre-manipulative stretch was performed in two different postures, A. Standard position, the usual position as applied clinically as in Kesson and Atkins (67) and Atkins, Kerr et al. (69), and B. Varied position involving 65° forward flexion of the shoulder while maintaining the 90° abduction in frontal plane (Figure 29).

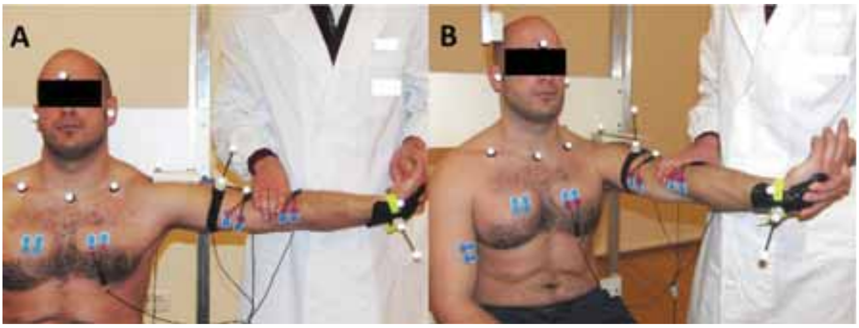


*Figure 29.* Pre-manipulative stretch for Mills manipulation performed in the two tested positions. A. left, standard position, B. right, shoulder forward flexion by 65° on the transverse plane. Positions of 10mm reflective markers and EMG electrodes for a left test side are also visible.

In both investigations (III and IV) the test manoeuvres were performed in random order on each subject in order to prevent any test bias and avoid the possibility that a recorded abnormal or anomalous electromyographic pattern could partly be a consequence of the order of performance.

Moreover, the tested subjects were fully blinded to basic differences between the manoeuvres that were performed, and no useful information could be extrapolated from the performance succession pattern.

### 4.2.10 **Subjective Data Collection (IV)**

A simple questionnaire was given to all the tested subjects immediately after testing, where it was asked which of the two manoeuvres was felt to be the more or less painful. The term 'painful manoeuvre' was associated with the position less likely to be held before a short amplitude-high velocity elbow extension thrust.

### 4.2.11 **Statistical Analysis (III,IV)**

The purpose of the data analysis was to detect any statistically significant differences in the amplitude values of electrical responses in the test muscles when the pre-manipulative stretch was performed in the different positions, Standard and Varied. The hypothesis that electrical responses in the Varied position were less than in the Standard position versus no change was tested. As the conditions for application of parametric tests were not satisfied, Wilcoxon matched-pairs signed-ranks non-parametric testing was used, since this method can be applied to small samples. The alpha level was set at $p$=.05.

### 4.2.12 **New developments: Muscles in Function of Neural Protection.**

As before (chapter 4.1.3), in this section the author of this doctoral thesis is going to present advancement in the methods related to new experiments of this line of research. Preliminary unpublished data will be presented in the Results section. This is done to provide evidence that this line of research is currently developing and new hypothesis are being formulated.

#### *4.2.12.1 Experiment n.1: Activation Patterns in Response to Opposite Sequences of Radial Nerve Neurodynamic Test Performed to Maximum Tolerable Pain*

As dictated by the Neural convergence theory (17) , the nerves move toward the joint at which tension is applied following the tension gradient. In other words during the performance of a neural tension test or neurodynamic test, nerves move toward the joint moved first. By extension, the sequence of movements influences the location of symptoms with more symptoms arising at the region that is moved first and most strongly (52,106).

Following this notion, the author of this doctoral thesis designed a new study in collaboration with Dr.Saara Rissanen from the Biosignal Analysis and Medical Imaging group (BSAMIG) from the Department of Physics of University of Eastern Finland, in which the muscular activation pattern in response to different sequences execution of the Radial neurodynamic test would be recorded and analysed. It was hypothesized that if these muscular protective mechanisms were to be specific, potentially protective muscles would activate before others around the joint at which the tension test for the radial nerve was started and around which the tension into the neural tissue was assumed to be greater in magnitude or to last for a longer period during the movement execution time-span (106) .

This was done following the notion that muscles may be activated via the common nociceptive flexion reflex (NFR) in response to painful stimuli associated with tensile or compressive loads on peripheral nerves, and it may be that muscular activation pattern differs as nerves tends to converge toward, are tensioned more strongly and for a longer period of time, around the joint that is moved first.

#### *4.2.12.2 Aims*

To investigate non-invasively the pattern of muscular activation in response to elongation stress of the radial nerve with a radial nerve neurodynamic test (RNT) performed until the onset of subjectively maximal tolerable pain in two different sequences: proximal and distal.

### *4.2.12.3 Methods*

Ten asymptomatic volunteers were selected, scanned for exclusion criteria (Table 3) and tested bilaterally (N=20).

The test movements were those of the radial neurodynamic test (RNT) performed until the onset of subjectively maximal tolerable painful symptoms in a proximal sequence (shoulder, elbow, wrist) and a reverse, distal sequence (wrist, elbow, shoulder). The manoeuvres were performed in a random sequence.

The volunteers were instructed to lie relaxed on the couch while the test manoeuvres were performed. Clear instructions were given to volunteers as to avoid any possible active muscle contraction during the test execution as to allow the recording of changes in myoelectric activity during the *passive execution* of the test manoeuvres.

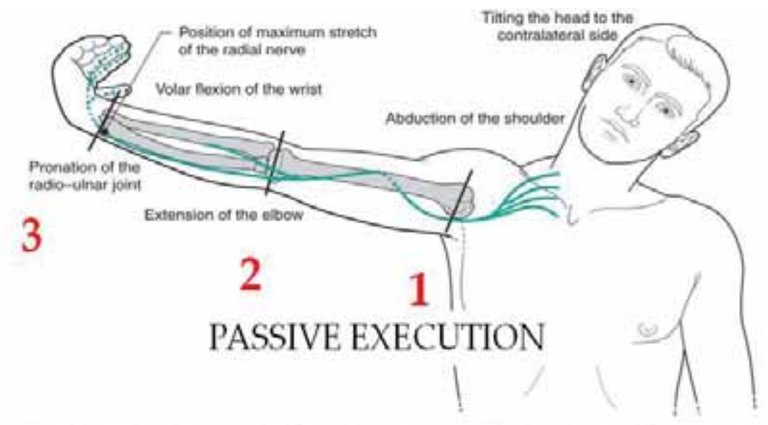
Similarly to the methodology presented in articles III and IV, surface EMG (ME6000-biosignal monitor (Mega Electronics Ltd., Kuopio, Finland) was employed to record myoelectric activity in the test muscles.

Electrogoniometer data (SG110 and SG150; Biometrics Ltd., Gwent, United Kingdom) were used to detect different phases of RNT. Onsets of muscle activation were visually detected from the measured EMG signals and placed into the EMG activation maps. Each manoeuvre was performed twice to allow for reproducibility check.

Upper Trapezius, biceps brachii, brachioraldialis and extensor carpi radialis were chosen as test muscles for their capability of decreasing the mechanical tension in the brachial plexus and radial nerve by shortening the neural pathway by means of i) elevating the shoulder girdle, ii) flexing the elbow, iii) extending the wrist.

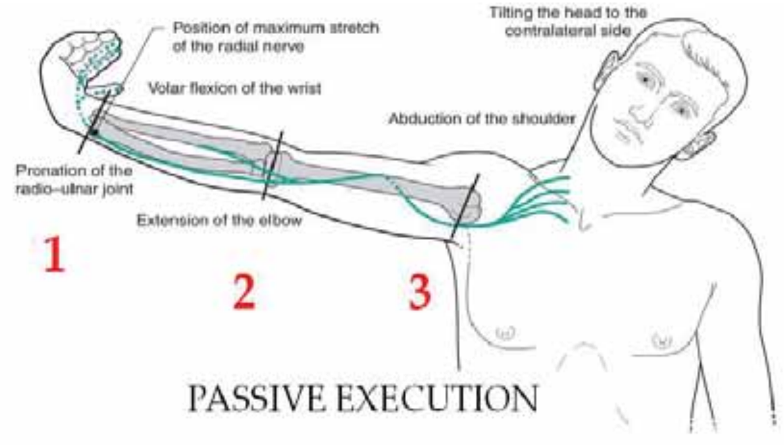
Volunteers were instructed to signalize verbally i) the first onset to of painful symptoms and ii) onset of subjectively maximal tolerable pain during the execution of the RNT manoeuvres so that time points could be marked on EMG records, iii) quantify the magnitude of this pain on a visual analogic scale (VAS) after the manoeuvre was performed.

All tested subjects signed an informed consent form and the study was approved by the institutional ethics committee.



(iii) Radial neurodynamic test (von Lanz T and Wachsmuth W 1959 Praktische Anatomie, Springer-Verlag, Berlin, p. 47, with permission).

*Figure 30.* The Radial Nerve Neurodynamic Test performed in a proximal sequence (shoulder, elbow, wrist). From: Clinical Neurodynamics, Shacklock M.,(2005), preface p. 10, Copyright Elsevier, adapted from Praktische Anatomie. Ein lehr und Hilfsbuch der Anatomischen Grundlagen Ärtzlichen Handelns, Lanz and Wachsmuth (1959) p. 47. Copyright Springer-Verlag, Berlin. With permission



(iii) Radial neurodynamic test (von Lanz T and Wachsmuth W 1959 Praktische Anatomie, Springer-Verlag, Berlin, p. 47, with permission).

*Figure 31.* The Radial Nerve Neurodynamic Test performed in a distal sequence (wrist, elbow, shoulder). From: Clinical Neurodynamics, Shacklock M.,(2005), preface p. 10, Copyright Elsevier, adapted from Praktische Anatomie. Ein lehr und Hilfsbuch der Anatomischen Grundlagen Ärtzlichen Handelns, Lanz and Wachsmuth (1959) p. 47. Copyright Springer-Verlag, Berlin. With permission.

### *4.2.12.4 Experiment n.2: Quantitative Parameters of Muscular Activation in Response to Opposite Sequences of Radial Nerve Neurodynamic Test Performed to Maximum Tolerable Pain*

Following the previous results, the author of this doctoral thesis decided to further analyse the quantitative parameters of myoelectric activation in response to opposite sequences of radial nerve neurodynamic test performed to maximum tolerable pain in order to better understand these reactions.

### *4.2.12.5 Aims*

To investigate non-invasively quantitative parameters of muscular activation in response to elongation stress of the radial nerve with a Radial neurodynamic test performed until the onset of subjectively maximal tolerable pain in two different sequences: proximal and distal. Again, this was done following the notion that muscles may be activated via the common nociceptive flexion reflex in response to painful stimuli associated with tensile or compressive loads on peripheral nerves, and that nerves tend to converge toward, and are tensioned more strongly and for a longer period of time, around the joint that is moved first.

### *4.2.12.6 Methods*

Ten asymptomatic volunteers were selected, scanned for exclusion criteria (Table 3) and tested bilaterally (N=20).

As before (4.2.12.1), electromyography signals and joint angles were recorded continuously from 10 asymptomatic volunteers, using ME6000-biosignal monitor (Mega Electronics Ltd., Kuopio, Finland). Disposable Ag/AgCl-electrodes (Neuroline 720; Ambu, Ballerup, Denmark) were used in bipolar connection for surface EMG registration. Twin-axis goniometers (SG110 and SG150; Biometrics Ltd., Gwent, United Kingdom) were used for joint angle measurement.

The test movements consisted of a common RNT performed until subjectively maximal tolerable painful symptoms in a proximal sequence (shoulder, elbow, wrist) and a reverse, distal sequence (wrist, elbow, shoulder).

The author anticipated that common criticism would focus on the possibility that the myoelectic activity is increased by simple muscular and/or fascia stretch. For this reason the myoelectric components were subsequently compared with those recorded during a 20 second relaxed position (reference), and during a strong biceps brachii muscle stretch.

EMG amplitude and median frequency (MDF) were calculated for each manoeuvre, while EMG amplitude and mean frequency (MNF) was calculated for each phase of RNT. Amplitude was calculated as mean amplitude value (MAV) and it was normalized to the reference positions. MNF was calculated from the estimated Welch's averaged periodogram.

The manoeuvres were performed in a random sequence. Each manoeuvre was performed twice to allow for reproducibility check.

Upper Trapezius, biceps brachii, brachioraldialis and extensor carpi radialis were chosen as test muscles for their capacity to decrease mechanical tension in the brachial plexus and radial nerve by shortening the neural pathway by i) elevating the shoulder girdle, ii) flexing the elbow, iii) extending the wrist.

The volunteers were instructed to lie relaxed on the couch while the test manoeuvres were performed. Clear instructions were given to volunteers as to avoid any possible active muscle contraction during the test execution as to allow the record of changes of myoelectric activity during the *passive execution* of the test manoeuvres.

Volunteers were instructed to notify about i) the first onset of pain, ii) point of maximal tolerable pain so that time points could be marked on EMG records, iii) quantify the magnitude of this pain on a visual analogic scale after the manoeuvre was performed.

The RNT was then maintained for 5 seconds in the position that evoked maximal tolerable pain in order to collect enough EMG data for analysis.

All tested subjects signed an informed consent form and the study was approved by the institutional ethics committee.

# 5 Results

## 5.1 RESEARCH LINE N.1: NEURORADIOLOGY (I,II)

### 5.1.1 In Vivo Magnetic Resonance Imaging Measurement of Spinal Cord Displacement in the Thoracolumbar Region of Asymptomatic Subjects: Part 1: Straight Leg Raise Test. (I)

It is shown that the number of subjects required to produce statistically significant results ($p<0.05$) using the presented methodology is five, both for right and left SLR.

When compared to the position in the neutral (anatomic) position, the medullar cone displaced caudally in the spinal canal by 2.31 ± 1.2mm (Mean±SD) with the right SLR ($p\leq.001$) and 2.35 ± 1.2mm with the left SLR ($p\leq.001$).

The comparison between right and left SLR did not show statistically significant difference ($p=.867$). Figure 32.

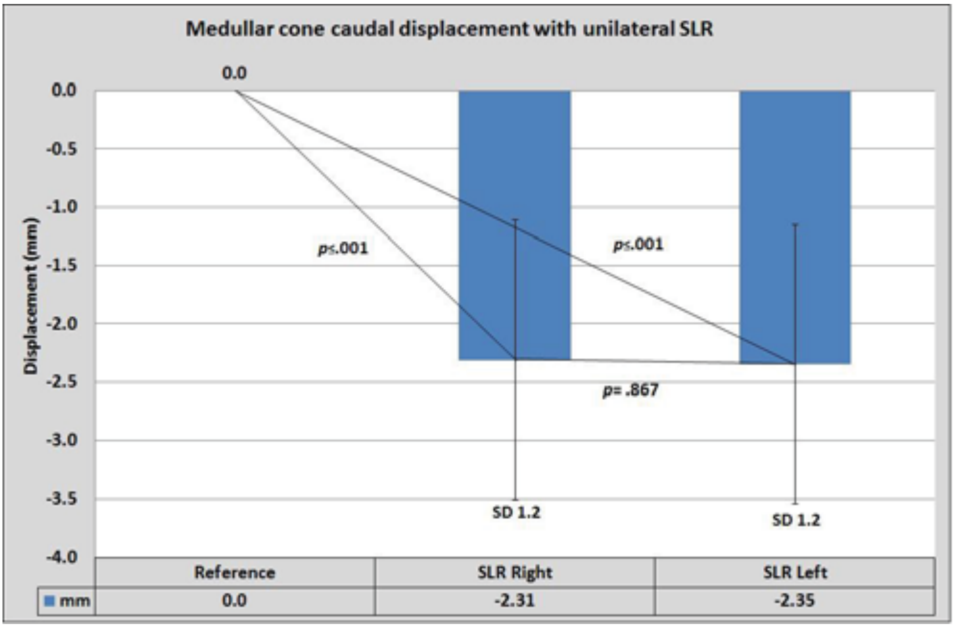


*Figure 32.* Caudal medullar cone displacement with unilateral SLR test. Mean value and standard deviations of measurements are presented. Note the lack of statistical significance between left and right SLR indicating that a similar amount of neural displacement took place on each side. Values are expressed as negative to indicate the caudal direction of the displacement.

The Spearman correlations, as well as observed ranges and results for the observed power are presented in Table 4.

*Table 4.* Reproducibility values and observed power of medullar cone displacement measurements with unilateral SLR.

**Table 4. Reproducibility values and observed power of medullar cone displacement measurements with unilateral SLR.**

| | RANGES (mm) | | SPEARMAN CORRELATIONS | | | NUMBER OF SUBJECTS TESTED | NUMBER OF SUBJECTS NEEDED FOR SIGNIFICANT RESULTS | OBSERVED POWER |
|---|---|---|---|---|---|---|---|---|
| | MIN | MAX | RESULTS REPRODUCIBILITY | INTRA OBSERVER | INTER OBSERVER | | | |
| **RIGHT SLR** | -0.2 | -5.3 | 0.993 | 0.998 | 0.997 | 16 | 4.37 | 0.99’ |
| **LEFT SLR** | -0.8 | -4.4 | 0.997 | 0.998 | 0.996 | 16 | 4.30 | 0.99’ |
| **REFERENCE SCAN** | | | 0.996 | 0.998 | 0.994 | 16 | | |

Note: negative values indicate caudal displacement.

### 5.1.2 In Vivo Magnetic Resonance Imaging Measurement of Spinal Cord Displacement in the Thoracolumbar Region of Asymptomatic Subjects: Part 2: Comparison Between Unilateral and Bilateral Straight Leg Raise Tests. (II)

The number of subjects required to get statistically significant results ($p<0.05$) compared to the reference position is four for Bilateral SLR and five for unilateral SLR.

When compared to the position in the neutral (anatomic) position, the medullar cone displaced caudally in the spinal canal by 4.58 ± 1.48 mm (Mean±SD) with bilateral SLR ($p \leq .001$). This displacement was also statistically significant when compared with the right SLR ($p \leq .001$) and left SLR ($p \leq .001$) in which the medullar cone displaced by 2.31± 1.2mm and 2.35 ± 1.2mm respectively (Mean 2.33± 1.2mm).

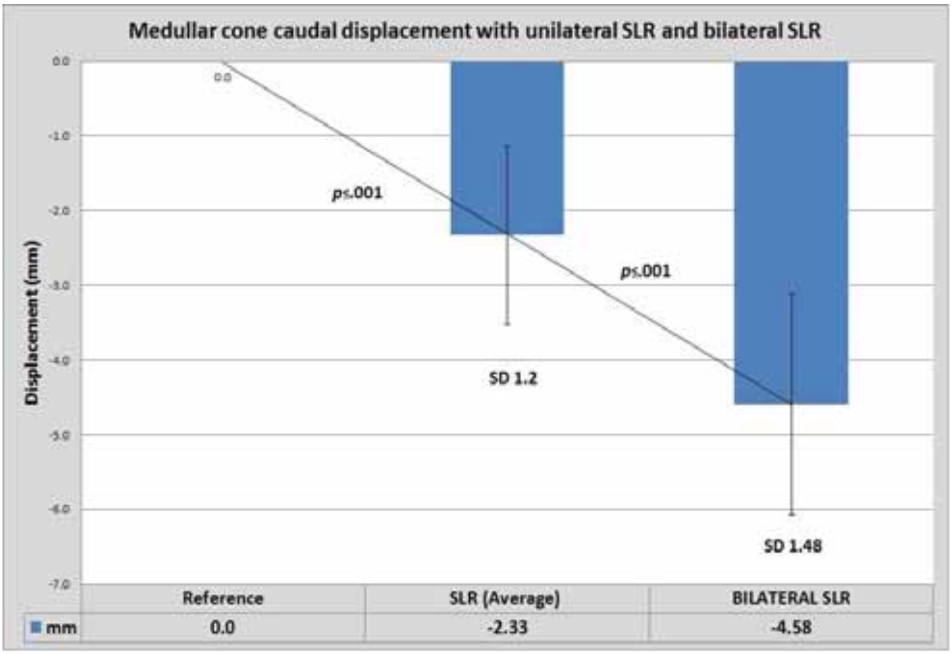


*Figure 33.* Medullar cone displacement with unilateral and bilateral SLR. Mean value and standard deviations of measurements are presented. Values expressed as negative to indicate caudal displacement. Note: Compared with the unilateral SLR, the magnitude of conus displacement was almost double with bilateral SLR, approximating a linear dependency between the conal movement and number of nerve roots involved.

The Spearman correlations, as well as observed ranges and results for the observed power are presented in Table 5.

*Table 5.* Reproducibility values and observed power of medullar cone displacement measurements with unilateral and bilateral SLR.

**Table 5. Reproducibility values and observed power of medullar cone displacement measurements with unilateral and bilateral SLR.**

| | RANGES (mm) | | SPEARMAN CORRELATIONS | | | NUMBER OF SUBJECTS TESTED | NUMBER OF SUBJECTS NEEDED FOR SIGNIFICANT RESULTS | OBSERVED POWER |
|---|---|---|---|---|---|---|---|---|
| | MIN | MAX | RESULTS REPRODUCIBILITY | INTRA OBSERVER | INTER OBSERVER | | | |
| **UNILATERAL SLR** | -0.2 | -5.3 | 0.995 | 0.998 | 0.997 | 16 | 4.34 | 0.99’ |
| **BILATERAL SLR** | -2.2 | -7.8 | 0.984 | 0.997 | 0.994 | 16 | 3.08 | 1 |
| **REFERENCE SCAN** | | | 0.996 | 0.998 | 0.994 | 16 | | |

Note: negative values indicate caudal displacement.

### 5.1.3 Unpublished results

Number of required subjects to obtain statistically significant results ($p<0.05$) compared to the reference position using the here presented improved methodology is three both for unilateral (2.71) and bilateral SLR (2.87).

When compared to the position in the neutral (anatomic) position, the conus medullaris displaced caudally in the spinal canal by 3.52 ± 0.77 mm (Mean±SD) with the right SLR ($p \leq .001$) and 3.57 ± 1.14 mm with the left SLR ($p \leq .001$), presenting an average of 3.54 ± 0.87 mm for unilateral SLR.

In response to bilateral SLR, the conus medullaris displaced by 7.42 ± 2.09 mm, showing statistical significance when compared to the reference position ($p \leq .001$), as well as with magnitudes of displacement achieved with unilateral SLR ($p \leq .001$).

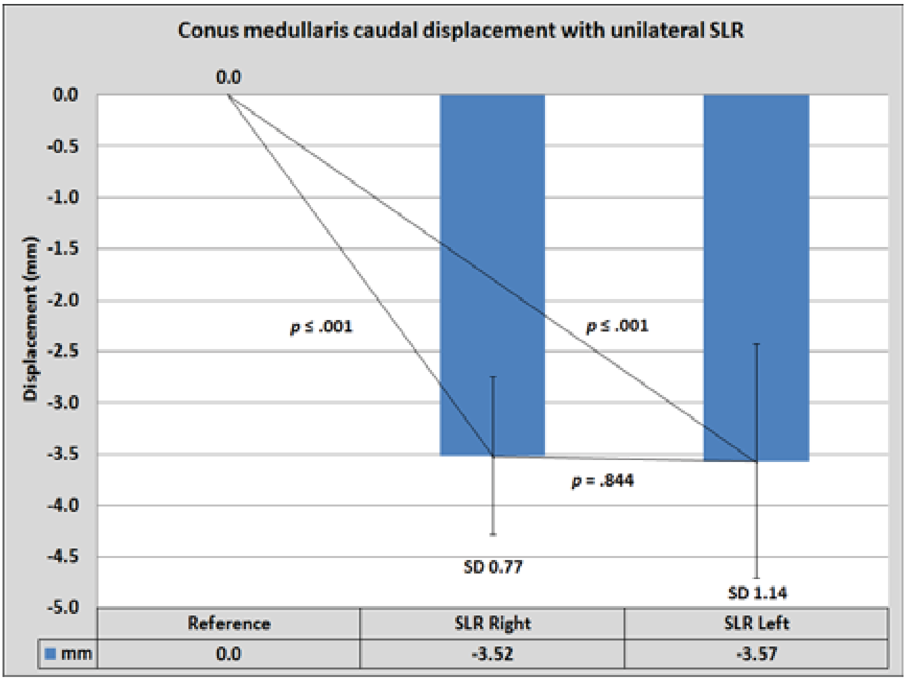


*Figure 34.* Caudal medullar cone displacement with unilateral SLR test. Mean value and standard deviations of measurements are presented. Note the lack of statistical significance between left and right SLR indicating that a similar amount of neural displacement took place on each side. Values are expressed as negative to indicate the caudal direction of the displacement.

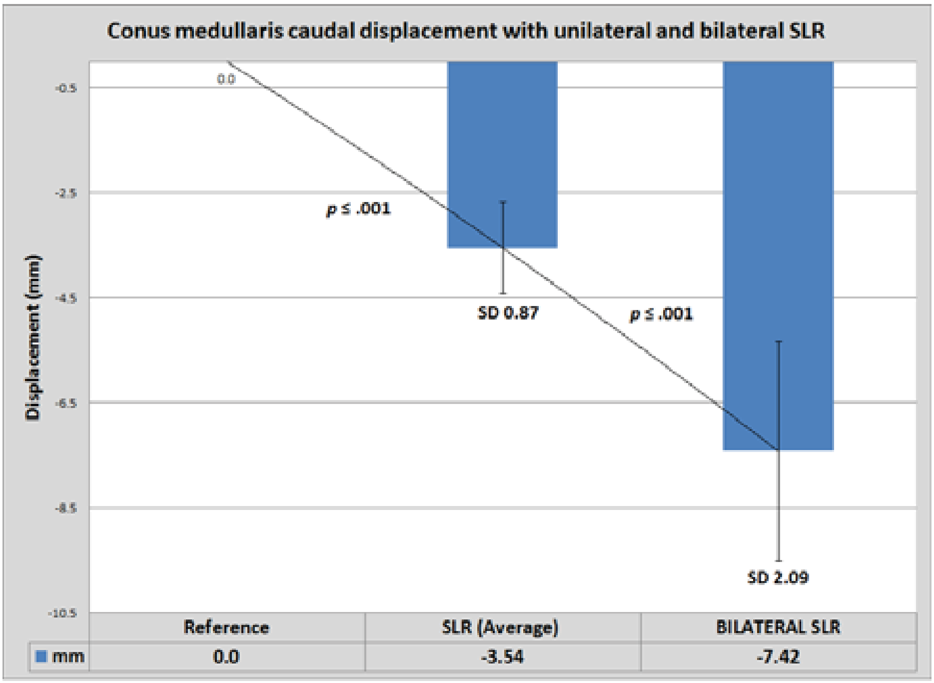


*Figure 35.* Conus medullaris displacement with unilateral and bilateral SLR. Mean value and standard deviations of measurements are presented. Values are expressed as negative to indicate caudal displacement. Note: Compared with the unilateral SLR, the magnitude of conus displacement was almost double the bilateral SLR, approximating a linear dependency between the conus movement and number of nerve roots involved.

The Pearson's correlations, as well as observed ranges and results for the Observed Power are presented in Table 6.

*Table 6. Reproducibility values and observed power of conus medullaris displacement with unilateral and bilateral SLR.*

**Table 6. Reproducibility values and observed power of conus medullaris displacement with unilateral and bilateral SLR.**

| | RANGES (mm) | | PEARSON'S CORRELATIONS | | | NUMBER OF SUBJECTS TESTED | NUMBER OF SUBJECTS NEEDED FOR SIGNIFICANT RESULTS | OBSERVED POWER |
|---|---|---|---|---|---|---|---|---|
| | MIN | MAX | RESULTS REPRODUCIBILITY | INTRA OBSERVER | INTER OBSERVER | | | |
| **RIGHT SLR** | -2.3 | -4.9 | 0.990 | 0.999 | 0.998 | 10 | 3 | 1 |
| **LEFT SLR** | -2.1 | -5.4 | 0.996 | 0.999 | 0.998 | 10 | 3 | 1 |
| **BILATERAL SLR** | -3.7 | -11 | 0.979 | 0.999 | 0.997 | 10 | 3 | 1 |
| **REFERENCE SCAN** | | | 0.994 | 0.999 | 0.998 | 10 | | |

Note: negative values indicate caudal displacement.

## 5.2 RESEARCH LINE N.2: NEUROPHYSIOLOGY (III,IV)

### 5.2.1 Effect of Cervical Spine Position on Upper Limb Myoelectric Activity During Pre-Manipulative Stretch for Mills Manipulation (III)

The mean elbow extension passive ranges of movement (ROM) during the pre-manipulative stretch were verified to be consistent at (Mean±SD) 181, 62º±1,85º for the right tested side and 183, 12º±2,1º for the left tested side during the Standard position and 182º±1,93º and 183,25º±1,83º during the Variation position execution, right and left side respectively. These are consistent with those of Günal et al.(107).

The data showed that there was a different pattern of muscle responses between the Standard and Variation positions. There was a significant reduction in activity in biceps brachii (*p*=0.018) and brachioradialis (*p*=0.000) in the Variation position whereas this did not occur in the lower trapezius (*p*=0.086), upper trapezius (*p*=0.232), pectoralis major (*p*=0.329) and triceps brachii (*p*=0.174) muscles (table 7, figure 36).

*Table 7.* Absolute myoelectric values (µV) of test and control muscles during Pre-Manipulative Stretch for Mills Manipulation.

**Table 7. Absolute myoelectric values (*µV*) of test and control muscles during Pre-Manipulative Stretch for Mills Manipulation.**

| Muscle | Mean ± Standard Deviation | Standard Mills Position | Variation Position (ipsilateral lateral flexion) | Mean percentage change in electrical activity | ***P*** value | |
|---|---|---|---|---|---|---|
| Biceps Brachii | Mean ± SD | 14.444±21.19 | 6.242±1.235 | -56,784% | **0.018** | Test muscles |
| Brachioradialis | Mean ± SD | 13.706±16.339 | 5.588±6.532 | -59,229% | **0.000** | |
| Triceps Brachii | Mean ± SD | 28.706±20.666 | 23.675±15.841 | -17,525% | 0.174 | |
| Pectoralis Major | Mean ± SD | 9.638±3 | 9.756±5.032 | +1,224% | 0.329 | |
| Upper Trapezius | Mean ± SD | 134.631±99.511 | 121.181±97.035 | -9,990% | 0.232 | |
| Lower Trapezius | Mean ± SD | 12.219±7.295 | 13.225±6.405 | +8,233% | 0.086 | Control muscle |

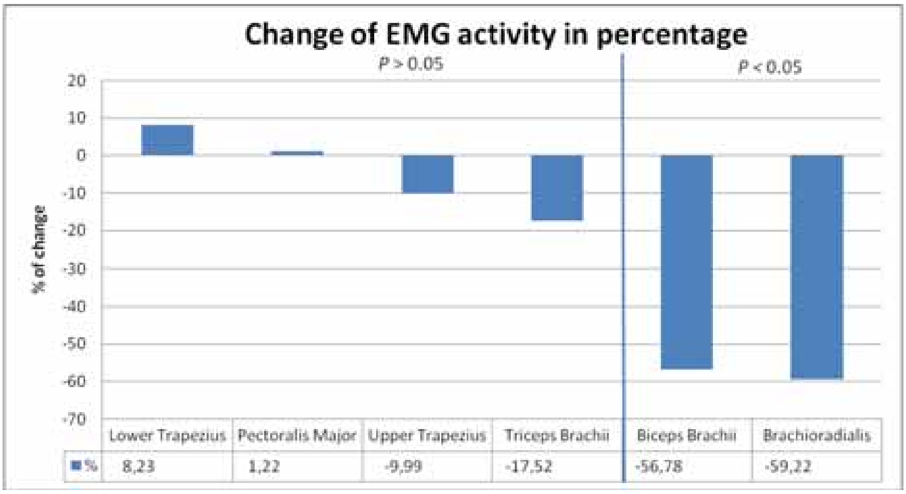


*Figure 36.* Percentage change in electromyographic activity of muscles when the Pre-Manipulative Stretch for Mills Manipulation was performed in different cervical positions, Standard and Variation (ipsilateral lateral flexion of cervical spine).

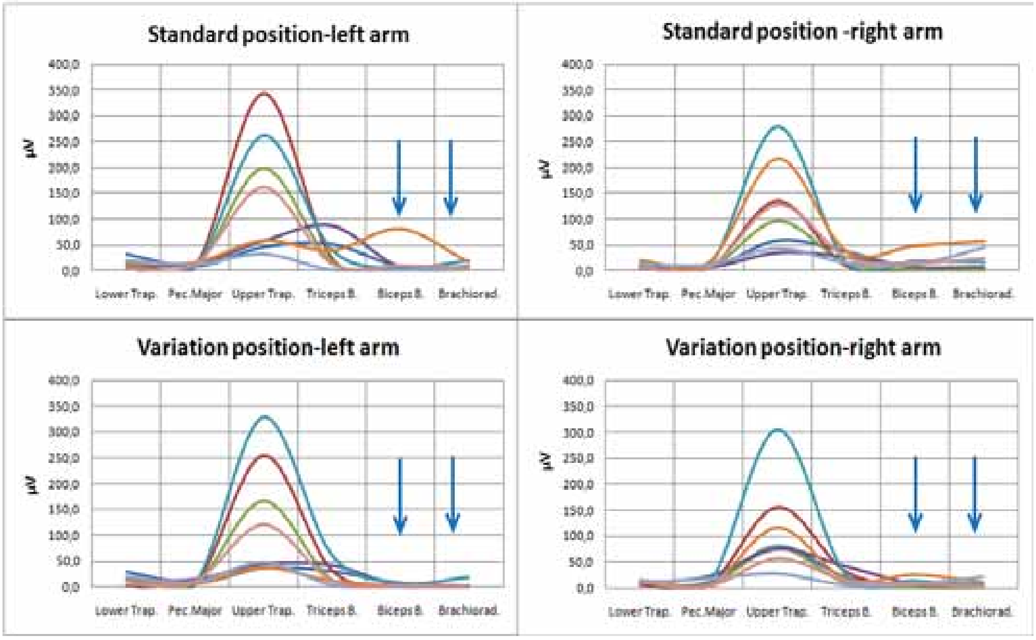


*Figure 37.* Myoelectric trends (each line representing individual subjects) during the Pre-Manipulative Stretch for Mills Manipulation, Standard and Variation positions. Note the significant decrease of myoelectric activity in Biceps Brachii and Brachioradialis muscles during the Variation position. No significant difference in myoelectric activity was found between the right and left tested side ($p>0.05$). Abbreviations: Lower Trap - Lower Trapezius, Pec.Major - Pectoralis Major, Upper Trap - Upper Trapezius, Triceps B - Triceps Brachii, Biceps B - Biceps Brachii, Brachiorad - Brachioradialis muscles.

### 5.2.2 Effect of Glenohumeral Forward Flexion on Upper Limb Myoelectric Activity During Simulated Mills Manipulation (IV)

The mean elbow extension passive ranges of movement (ROM) during the pre-manipulative stretch were verified to be consistent at mean 181.6° (SD 1.9°) for the right tested side and 183.1°(SD 2.1°) for the left tested side during the Standard position, and 182.9°(SD 2°) and 184.1°(SD 1.7°) during the Varied position, right and left side respectively. These were again consistent with those measured by Günal et al [(107)].

The data showed that, compared with the Standard positioning, there was a significantly different pattern of muscle responses to the pre-manipulative stretch for Mills manipulation between the two positions of the shoulder. In the Varied position there was a significant reduction in myoelectric activity in all the test muscles, namely brachioradialis (*p*≤.001), biceps brachii (*p*≤.001), upper trapezius (*p*≤.001), triceps brachii (*p*≤.001), pectoralis major (*p*≤.001) and a significant increase of myoelectic activity for lower trapezius (*p*≤.002), which was considered the non-protective muscle (table 8, figure 38, 39 and 40).

*Table 8.* Absolute myoelectric values expressed in micro volts (μV) for test and control muscles during Simulated Mills Manipulation.

**Table 8. Absolute m*yoelectric values expressed in micro volts (μV) for test and control muscles during Simulated Mills Manipulation.***

| | | Standard Mills Position | Varied Position | Mean percentage change in myoelectric activity | ***P*** value | Observed power | Effect size |
|---|---|---|---|---|---|---|---|
| **Test muscles** | **Brachioradialis** | Mean 13.71 (SD 16.34) | Mean 1.63 (SD 0.61) | -88.1% | **≤.001** | 0.99 | 0.73 |
| | **Biceps Brachii** | Mean 14.44 (SD 21.2) | Mean 2.26 (SD 0.80) | -84.56% | **≤.001** | 1 | 0.58 |
| | **Upper Trapezius** | Mean 134.63 (SD 99.51) | Mean 37.08 (SD 33.58) | -72.46% | **≤.001** | 1 | 1.31 |
| | **Triceps Brachii** | Mean 28.71 (SD 20.67) | Mean 8.98 (SD 6.46) | -68.73% | **≤.001** | 1 | 1.27 |
| | **Pectoralis Major** | Mean 9.64 (SD 3) | Mean 6.34 (SD 2.92) | -34.18% | **≤.001** | 0.99 | 1.14 |
| **Non-protective muscle** | **Lower Trapezius** | Mean 12.22 (SD 7.26) | Mean 24.71 (SD 21.64) | +102.25% | **≤.001** | 0.92 | 0.63 |

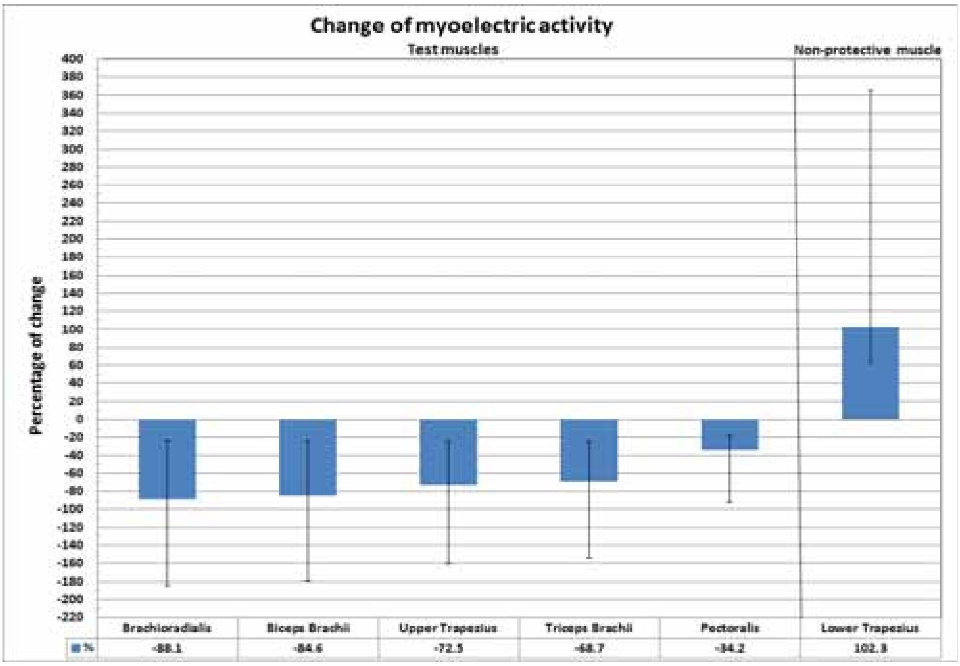
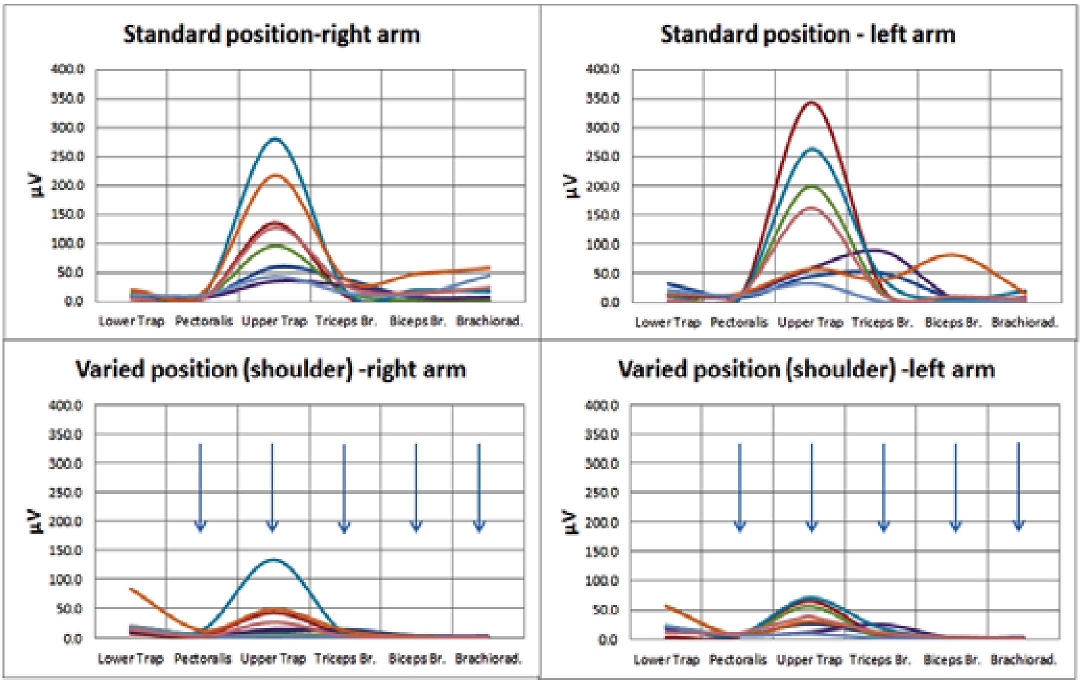


*Figure 38.* Percent change in EMG activity of upper extremity muscles when the pre-manipulative stretch for Mills manipulation was performed in different shoulder positions (Standard versus Varied).



Standard position-right arm

Standard position - left arm

Varied position (shoulder) -right arm

Varied position (shoulder) -left arm

*Figure 39.* Myoelectric trends (each line representing individual subjects) during the standard pre-manipulative stretch for Mills manipulation and the Varied positions. Note the significant decrease ($p \leq .001$) of myoelectric activity in all the test muscles in the Varied position. No significant difference in myoelectric activity was found between right and left sides ($p > .05$).

Abbreviations: SMM - Standard Mills Manipulation, Lower Trap - Lower Trapezius, Pec.Major - Pectoralis Major, Upper Trap - Upper Trapezius, Triceps B - Triceps Brachii, Biceps B - Biceps Brachii, Brachiorad - Brachioradialis muscles.

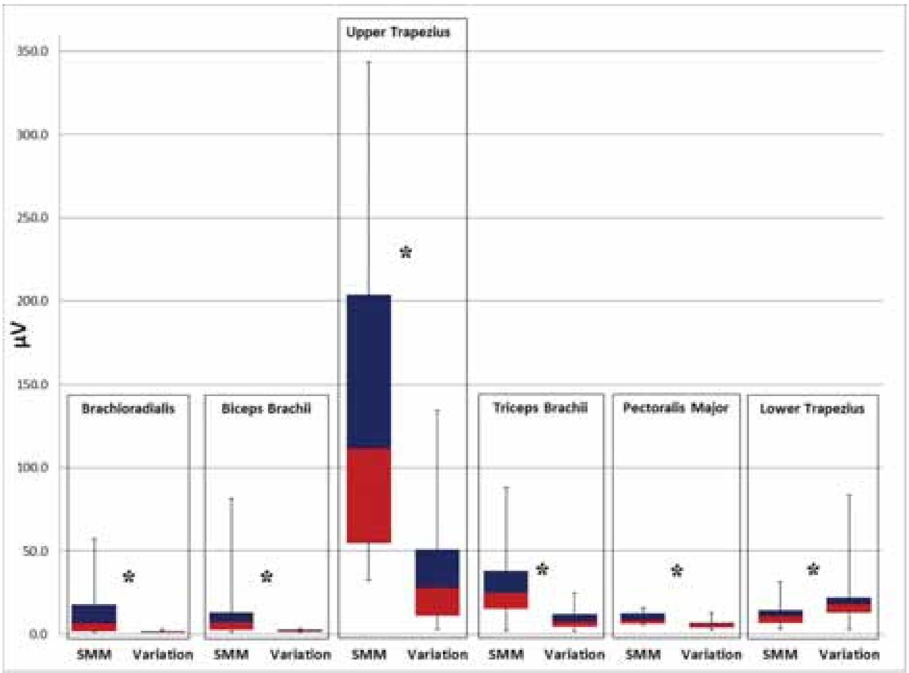


*Figure 40.* Directional change in myoelectric values during the standard pre-manipulative stretch for Mills manipulation and the Varied position. Significant changes (p<.05) are marked with an asterisk (*). Note the significant decrease of myoelectric activity and variance of the signal in all the test muscles in the Varied position. No significant difference in myoelectric activity was found between right and left sides (p>.05).

Abbreviations: SMM - Standard Mills Manipulation.

#### *5.2.2.1 Subjective Data Results (IV)*

From the subjective questionnaire it emerged that, of the two positions in which the pre-manipulative stretch was performed, Standard (0˚ forward flexion) and Varied (65˚ forward flexion), 100% (16 out of 16) of the tested subjects reported the position of 65˚ forward flexion of the shoulder to be the less painful one (figure 41).

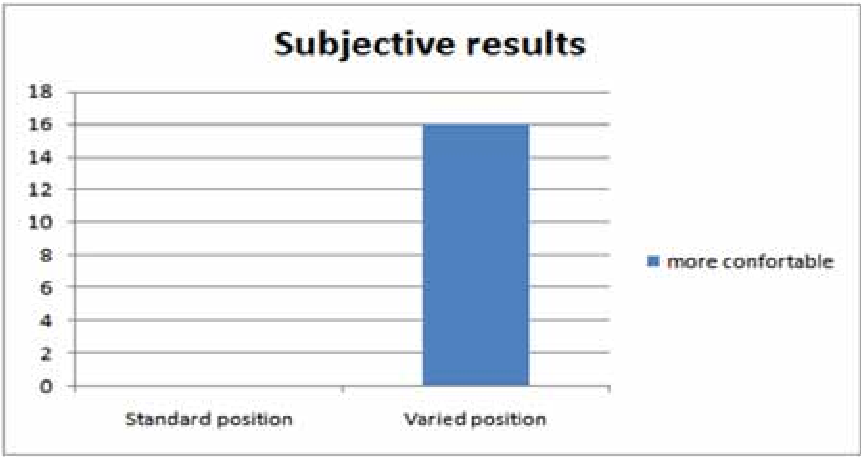


*Figure 41.* Subjective results comparing discomfort felt by the test subjects during execution of a standard Mills manipulation (Standard) and the Varied position encompassing 65° of shoulder forward flexion (Varied).

## 5.2.3 Unpublished Neurophysiological Results

### *5.2.3.1 Activation Patterns in Response to Opposite Sequences of Radial Nerve Tension Test Performed to Maximum Tolerable Pain*

Maximal tolerable pain achieved during the manoeuvres execution was 8.4 (Mean VAS).

The activation mapping showed that the upper trapezius was consistently the first muscle to be activated in the proximal (shoulder first) RNT sequence, while brachioradialis and extensor carpi radialis were consistently activated before others in a distal (wrist first) RNT sequence. The onset of muscle activation always appeared near the first onset of pain, with muscle activation starting before the first onset of painful symptoms in the great majority of cases (89%).

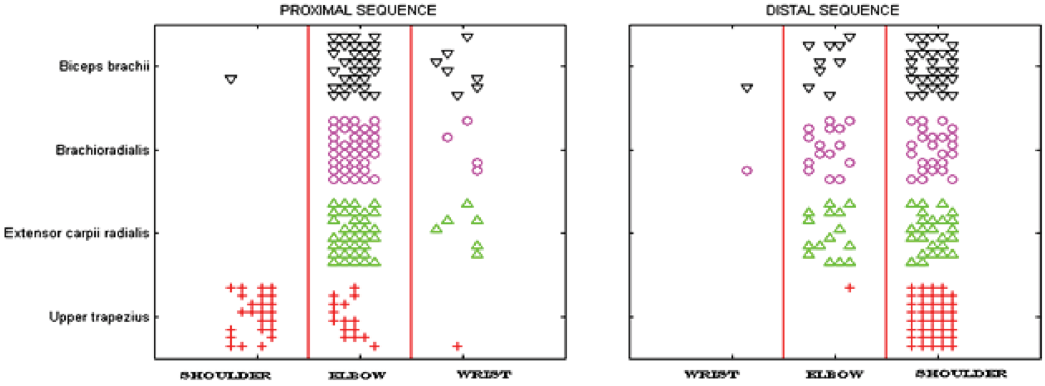


*Figure 42:* Activation maps. Results for all test movements are presented.

#### 5.2.3.2 *Quantitative Parameters of Muscular Activation in Response to Opposite Sequences of Radial Nerve Tension Test Performed to Maximum Tolerable Pain*

As before, maximal tolerable pain achieved during the manoeuvres execution was 8.4 (Mean VAS).

The myoelectric mean amplitude values (MAV) increased continuously while the myoelectric mean frequency (MNF) decreased in an opposite continuous trend during the performance of the neural tension manoeuvres, showing synchronization of motor units firing activity and mimicking pure muscular contraction. The results are statistically significant when compared to those of the relaxed reference position [$p \leq 0.03$ (MAV), $p \leq 0.004$ (MDF)] and those recorded during a strong biceps brachii muscle stretch [$p \leq 0.02$ (MAV), $p \leq 0.002$ (MDF)].

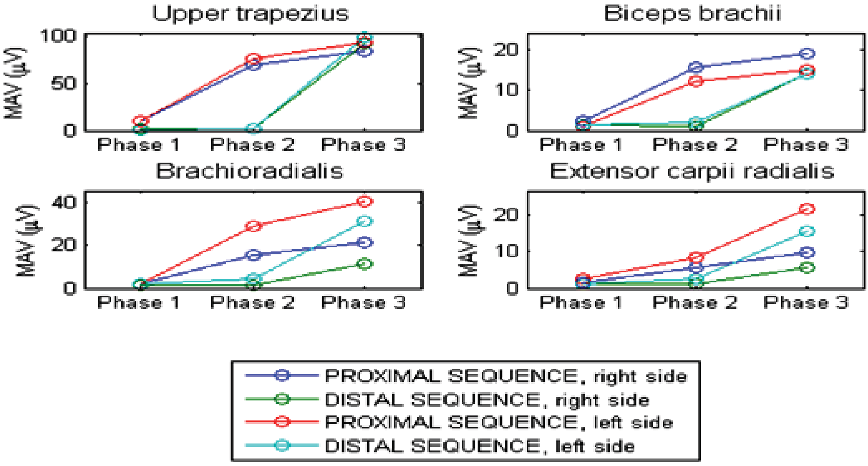


*Figure 43.* Mean amplitude values (MAV) recorded during the execution of the test manoeuvres. All results are averaged

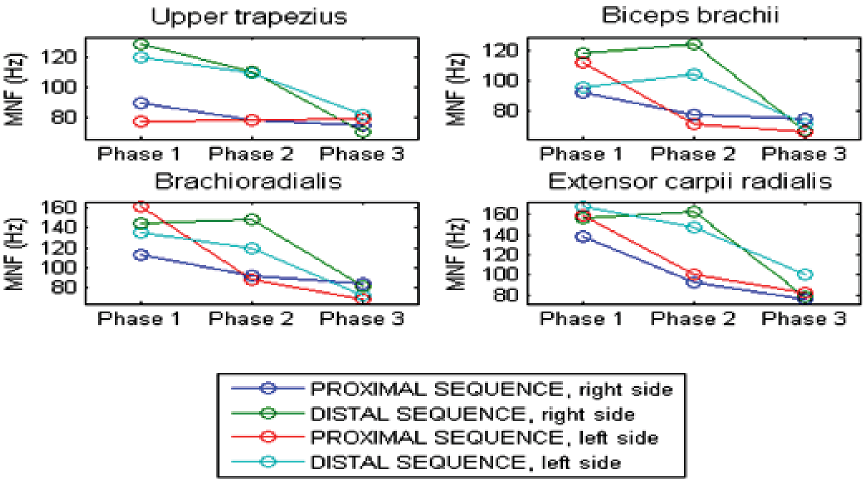


*Figure 44.* Mean frequency (MNF) recorded during the execution of the test manoeuvres. All results are averaged.

# 6 Discussion

## 6.1 RESEARCH LINE N.1: NEURORADIOLOGY (I,II)

It seems quite interesting to acknowledge that, even if the SLR test is one of the most consistent and widely used physical test in formulating the diagnosis of sciatica, apart from the direction in which L5 and S1 lumbar nerve roots displaces in response to the execution of a SLR manoeuvre, caudal, the published evidence on neural behaviour in response to SLR seems to be far from conclusive in terms of magnitude of displacement.

In order to visualize the sliding of a nerve relative to a particular bone, a reference point has to be specified on both structures. This can be an easy task on a bony structure, but as the nerve root is essentially a tube with no exact discernible distinctive features at a MR scan, no reliable reference points can be defined on its structure.

In order to solve this issue, the author of this doctoral thesis proposed to track the movements of the spinal cord in response to unilateral and bilateral SLRs. It was hypothesized that the recorded movements of the conus medullaris in response to SLRs may occur via sliding of, and direct transmission of forces through, the lumbosacral neural roots and dura to the spinal cord. Moreover, it was hypothesized that the lumbosacral nerve root moves by at least the same amount the spinal cord did.

This is now part of the principle called "*principle of linear dependence*" in which the magnitude of conus medullaris displacement is proportional to the displacement of L5 and S1 nerve roots and dependent on the number of nerve roots involved in the movement (i.e. unilateral and bilateral SLRs). This principle was presented for the first time in articles I and II.

### 6.1.1 **Key findings**

From the presented results, some basic questions can here be answered:

- Does the medullar cone displace in response to unilateral and bilateral SLRs?

  Answer: Yes it does. The spinal cord displaced caudally by an average of 2.33mm in response to the clinically applied unilateral SLR test, and by 4.58mm in response to a bilateral SLR. These spinal movements proved to be consistent and reproducible. Moreover, the presented unpublished data supports the notion that greater amount of conus displacement does occur with greater amount of hip flexion during unilateral or bilateral SLRs.

- Is there a difference in the mechanical effects on the cord between the unilateral and bilateral SLRs? For example, may these effects on the spinal cord be cumulative between the two?

  Answer: The results showed that the caudal displacement of the medullar cone was significantly greater (almost double) with the bilateral SLR compared to the unilateral. This phenomenon does show cumulative effects between unilateral and bilateral SLRs, approximating a linear dependency between the conal movement and number of nerve roots involved into the movement.

- Is there any reason to think that nerve roots move along with the medullar cone in response to a clinically applied SLR?

  Answer: Due to the neural continuum, the authors speculate that the presented medullar cone movement might be directly proportional to the sliding of the L5 and S1 neural roots in response to unilateral and bilateral SLR, and that these effects are indeed cumulative.

### 6.1.2 Comparison to Previous Literature

In the first study (I), the authors investigated in vivo medullar cone displacement in the thoracolumbar vertebral canal during the performance of the passive SLR in asymptomatic subjects. This was based on the notion that the L5 and S1 nerve roots displace caudally during the SLR and the spinal cord follows this displacement by similar magnitude and direction (principle of linear dependence).

The spinal cord displaced caudally by an average of 2.33mm in response to the clinically applied SLR test. The lack of statistical significance ($p$ =.867) in cord displacement between the SLR on the left and right sides indicates that the medullar cone displaced a similar amount and direction in response to SLR on both sides.

In the second study (II) the authors investigated in vivo spinal cord displacement in the thoracolumbar vertebral canal during the performance of the passive bilateral SLR in asymptomatic subjects in order to obtain quantitative data that will produce a better understanding of mechanical behaviour of the neural tissues of this clinically important region, and to verify whether the effect on the spinal cord may be cumulative between unilateral and bilateral SLRs.

The results showed that caudal displacement of the medullar cone was significantly greater with the bilateral compared to the unilateral SLR. The fact that the displacement was virtually double with bilateral SLR may indicate a linear dependency in movement of the cord and number of nerve roots involved into the movement. At least in the current circumstances, an explanatory mechanism may be that traction applied to more nerve roots produced proportionally more cord movement. Furthermore, due to the neural continuum the authors speculate that the conus movement might be directly proportional to the actual sliding of the L5 and S1 nerve roots in the context of the SLR.

In the literature, even though there is consensus regarding the direction in which L5 and S1 nerve roots displace with the SLR, caudal, there is significant variation in the magnitude between studies. In the first study (I) the spinal cord displaced caudally by an average of 2.33mm in response to the clinically applied unilateral SLR test. This amount of displacement is consistent with other studies on the nerve root mobility with the test (29,36,37,42) and was shown to be highly significant. Furthermore, the average caudal displacement of the medullar cone with the bilateral SLR (II) (4.58 ± 1.48 mm) seems also to be in agreement with amounts of caudal displacement of the L5 and S1 nerve roots reported by other authors (29,36-39,41,42) (table 1) and to fall within a reasonable range of motion (<10mm).

As stated by Goddard and Reid (39) and De Peretti et al. (45), the movements of the sciatic nerve might be larger in magnitude in the posterior thigh and decrease toward the spine due to the many fibrous adhesions present around the foramina, and particularly the foraminal ligaments described by Trolard (43) , Hofmann (44), De Peretti (45) and Grimes, Massie and Garfin (46) which have been hypothesized to influence nerve root mechanics (47). This, together with the data presented in this thesis (articles I,II), might support the notion that there is a difference both in terms of magnitude and direction of neural sliding between the periphery, including the peripheral joints, and the vertebral canal. This can be due to the different nature of forces acting on the neural structures (tensile or compressive) and to different type of restrains limiting adaptive movements, but it also means that the neural structures does move in those anatomical regions.

As already stated in the literature review presented in subheading 2.1.2, in a very well designed cadaver experiment done by Gilbert et al. (47) the L5 and S1 nerve root excursion during the unilateral SLR was shown to be 0.48±0.55mm for L5 and 0.51±0.73mm for S1, which is much less than presented in this doctoral thesis and in the existing literature. This stimulated the author of this thesis to explore possible reasons for such limited amount of movement. In Gilbert and colleagues' opinion, the lesser amount of neural root displacement was primarily attributed to the preservation of intact foraminal ligaments in the investigated cadavers. Gilbert and colleagues also commented on Kobayashi's amount of L5 and S1 nerve roots displacement in response to a modified SLR measured intraoperatively in in-vivo patients undergoing microdiscectomy surgery (41) , and quantified as 3.8±0.5mm for L5 and 4.1±0.4mm for S1 nerve roots. They hypothesized that the larger amount of displacement was probably attributable to the flavotomy and wide lateral laminotomy performed by the surgeons and needed to visualize the nerve roots clearly. Gilbert and colleagues' argument was that this wide structural damage may have impacted the function of foraminal ligaments, thus allowing for greater nerve root excursion.

While admitting that Gilbert and colleagues do have a valid argument regarding Kobayashi's results , the author of this dissertation feels that further reasons for such differences may lie in i) the old age of the cadavers donors (average 78.2 years) used by Gilbert and colleagues in their investigations (47,48) which can warrant for age-related degenerative changes that may have altered the normal biomechanics of the investigated region, ii) the lack of full knee extension in two of the five explored cadavers and iii) the fact that pelvic and spinal motion were limited with lag bolts screwed into the Ilium bilaterally, which did not allow to replicate the clinical SLR performance. The points i) and iii) were discussed also by Gilbert and colleagues in their paper (47).

Upon measurement of lumbar nerve roots displacement with SLR, Smith and colleagues (29) also fixed the pelvis with a metal spike driven through the anterior iliac wings and into the underlying wooden board, abolishing the pelvic motion. However, the presented results of caudal sliding of L5 and S1 nerve roots does comply with the one presented in previous works (36,37,39), possibly because the performance of posterior unilateral laminectomies and facetectomies may have impaired the function of the foraminal ligaments.

A relevant notion that emerges from the comparison between the investigations performed by Smith et al. (29) and Gilbert et al. (47) is that both foraminal ligaments integrity and natural pelvic motion should be preserved when attempting to replicate the clinical SLR performance in cadaver investigations.

Moreover, the data presented in this doctoral thesis are indeed disproving Gilbert and colleagues' conclusion that nerve roots do not move due to the limitation posed by foraminal ligaments, and seems to reconfirm the notion proposed in earlier investigations that nerves do move (29,36-39,41,53) . This is hypothesized to happen in order to avoid the instauration of tensile forces into, and compressive forces onto, the neural tissues. If this is true, the preservation of a free vertical sliding of the neural structures in the vertebral canal, along with the dura, might be the *conditio sine qua non* for maintaining an asymptomatic spine.

From the presented results it might be also said that during a clinically applied SLR manoeuvre, not only the mechanosensitivity of the L5 and S1 nerve roots to tensile forces is tested (29,47,48) but also the sliding capacity of the nerve roots. In certain cases, such sliding may be compromised, for example, by direct compression by herniated nucleus pulposus (41).

### 6.1.3 **Methodological Considerations**

A limiting aspect of these two studies (I, II) is that the sample consisted of only male volunteers. However to our knowledge there is no published evidence that supports the existence of gender related differences in L4, 5 and S1 nerve root and medullar cone excursion with the SLR. Following the results of the statistical power calculation in which five subjects were sufficient to provide statistically significant results with unilateral SLR and four with bilateral, it appears that the hypothesis presented would be supported.

Another limitation was likely provided by the limitation of hip flexion to only 50°due to the MR device architecture. In other studies, maximum nerve root excursion has been shown to occur between 60° and 75° of hip flexion (29,38,39,48). Relying on the published literature (table 1) and knowing that the displacement of the medullar cone took place consistently in the same direction, caudal, it is possible that a greater amount of caudal displacement would be reported if greater hip flexion angles were achieved.

Moreover, in those studies only coronal images were obtained to analyse the conus medullaris behaviour in response to SLR manoeuvres, so only vertical displacement could be analysed. In order to obtain information about latero-lateral and anteroposterior displacement of conus medullaris in response to SLR manoeuvres, the scanning methodology itself should be improved so that coronal, sagittal and axial slices could be reconstructed from a single scan. This would provide more information on neural adaptation mechanisms while making the scanning procedure shorter.

From the analysis of the limitations showed here, the author would like to point out that:

I) Following the assumption a greater amount of caudal displacement could be reported if greater hip flexion angles were achieved, it would be of interest to test amount of spinal cord displacement in response to both unilateral and bilateral SLRs with grater angle of hip flexion.

II) While 4.58mm of cord displacement in response to bilateral SLR may be a reasonable amount to be radiologically quantified and analysed, this cannot be said for the magnitude of medullar displacement recorded in response to a unilateral SLR (2.33mm). If the investigators want to correlate limitation of neural displacement with severity of symptoms, it would be of great utility to have considerably bigger neural displacements to work with.

III) The scanning methodology itself should be improved, so that coronal, sagittal and axial slices could be reconstructed from a single scan. This would allow the investigators to quantify the conus medullaris displacement in all three planes. Attempts to improve the methods with the aid of 3D MRI scanning should be made.

IV) It would be of interest to include female subjects in our experiments in order to obtain a full set of normative data to be used for further comparison in future clinical experiments including patients.

In order to solve these issues, and as a result of this line of reasoning, more investigations were designed by the author of this doctoral thesis and the preliminary results have been here presented.

As the manuscripts related to these new investigations are still under review, the author has presented in this doctoral thesis only the most salient points regarding the methods employed (chapter 4.1.3) and the unpublished results (chapter 5.1.3).

### 6.1.4 **Implications and Future Directions**

The results gained form the neuroradiologic investigations (I,II) showed caudal displacement of the medullar cone occurring consistently in response to unilateral and bilateral SLRs performed on asymptomatic subjects.

It was shown that the displacement was virtually doubled with bilateral SLR. At least in the current circumstances, an explanatory mechanism was that traction applied to more nerve roots produced proportionally more cord movement. Furthermore, due to the neural continuum the authors speculated that the conus movement might be directly proportional to the actual sliding of the L5 and S1 nerve roots in the context of the SLR.

This seems to support the "principle of linear dependence" in which the magnitude of conus medullaris displacement is proportional to the displacement of L5 and S1 nerve roots and dependent on the number of nerve roots involved in the movement (i.e. unilateral and bilateral SLRs).

With these results, we hypothesized that:

- The sliding of neural structures in the vertebral canal may be a protective effect which preserves the spinal cord and neural roots from strain. If this were true, the preservation of a free vertical sliding of the neural structures in the vertebral canal, along with the dura, might be the conditio sine qua non for maintaining an asymptomatic spine.
- The high correlation values presented in these studies showed that these sliding movements in response to SLRs are significant, consistent and reproducible. This indicates that they may also be predictable both in terms of magnitude and direction. Predictability is a key feature that may allow the design of new diagnostic algorithms.
- These adaptive and possibly protective movements may be impaired by a space occupying element, such as a herniated nucleus pulposus or a meningioma for example, compressing the neural component into the vertebral canal, or by epidural scar tissue limiting the displacement of the nerves.

All these options warrant further investigations.

In this doctoral thesis the author also presented unpublished data collected form new experiments designed to investigate in vivo spinal cord displacement in the thoracolumbar vertebral canal during the clinically applied unilateral SLR on each side and bilateral SLR in asymptomatic subjects in order to i) verify whether the 'principle of linear dependence' described earlier (88,89) is supported evidentially at greater angles of hip flexion, ii) verify whether previous methods of measurement could be improved with the aid of 3D MRI scanning.

The results showed that caudal displacement of the conus medullaris at a 60° SLR was definitely greater than our previously reported results for a 50° SLR (88,89). This is in agreement with the literature on cadaver investigations, in which bulk of nerve root excursion is shown to occur between 60 °and 75° of hip flexion (29,36-39,47,48).

Following the results presented in the literature, it seems probable that even greater amounts of conus medullaris displacement would occur with more hip flexion. Even though there is agreement that the L5 and S1 nerve roots displace in the caudal direction with the SLR (29,36-39,41,42,47-49,53), there is significant variation in the magnitude between studies. In this new investigation the average caudal displacement with the unilateral (3.54 ± 0.87 mm) and bilateral SLR (7.42 ± 2.09 mm) seems to be in agreement with other studies (36-39,41) and to fall within a reasonable range of excursion (<10mm). As before, the lack of statistical significance ($p$=.844) in cord displacement between left and right SLRs indicates that the conus displaced a similar amount and direction in response to each unilateral SLR. The $p$ value is equivalent to what presented earlier (88).

As previously reported (88,89), the results showed that caudal displacement of the conus medullaris was significantly greater with the bilateral compared to the unilateral SLR, suggesting that the amount of conus medullaris displacement may be cumulative between the two. The fact that the displacement was again virtually double with bilateral SLR may support the notions that i) there is a linear dependency between the magnitude of cord movement and number of nerve roots involved into the movement, and ii) that this relationship is maintained at greater angles of hip flexion.

Compared to previous methods in which coronal slices were obtained to measure the spinal cord displacement into the vertebral canal (88,89), attempts were made to improve the methods with the aid of 3D MRI scanning. Previously (88,89) 3mm thick coronal slices were used to identify the conus medullaris; this could have allowed the conus medullaris to fall between the slices thus being visually represented as a partial volume. In this investigation the use of 3D scanning allowed ad-hoc reconstruction of 1mm slices in the desired planes (coronal, axial, sagittal), offering the investigators easier identification of the tip of the conus medullaris and confirmation of its position in the other planes.

Further improvement of the previously presented methodology is represented by the circumstance in which the whole marking and measurement procedure could be verified in real time using the remaining two scanning planes, axial and sagittal. This improved the precision of the measurement while reducing the time needed to perform the analysis.

Also, the higher correlation values reported for both intra- and inter-observer reliability testing achieved in the new experiments indicate improvements that may have positive effects on the clinical feasibility of this radiological feature.

#### 6.1.4.1 *Future directions*

Shortly the authors will have constructed a complete set of normative data that will be available for comparison with data collected from pathology. We do hope that we will soon be able to start scanning patients.

As current evidence indicates poor diagnostic performance of most physical tests used in isolation to identify lumbar disc herniation (54), it would be of use to understand the neural mechanisms underpinning the SLR test in order to support the standardization of this test and to construct diagnostic algorithms that uses more neural tensile tests in conjunction. With this line of research we believe we will be able to provide i) new quantitative data that will produce a better understanding of mechanical behaviour of the neural tissues of this clinically important region ii) new data on neural tensile tests as Unilateral and Bilateral SLRs that will allow the informed codification of new diagnostic algorithms including several neural tensile tests in conjunction. This will be done following the notion that increased knowledge of the local mechanics may lead to better diagnosis and treatment planning. Also, a new radiological feature that may be used in the near future as an addition to those diagnostic algorithms has been presented.

The new research proposal has already been submitted to Prof Olavi Airaksinen, clinical director of the Department of Rehabilitation Medicine in Kuopio University Hospital-Finland, and Prof Ritva Vanninen, clinical director of Department of Radiology in Kuopio University Hospital-Finland.

This line of research has already been awarded by the 2013 Finnish Young Investigator Award awarded by the Finnish Spine Society, and the 2104 Spine Young Investigator Award awarded by the top-ranked scientific journal *Spine (phila pa 1976)*.

We do believe that we have provided proofs that this line of research is innovative and has great development potential.

## 6.2 RESEARCH LINE N.2: NEUROPHYSIOLOGY (III,IV)

This line of research focuses on electrophysiological methods of collecting indirect data on neural adaptation mechanisms by quantification of the muscular reactions in response to neural stretch in in-vivo and structurally intact human subjects.

The rationale underpinning this line of research is that the muscles may be reflexively activated in order to protect the peripheral nerves in the most logical way; by shortening their pathway and opposing the manipulation movement.

Following the notion that the Radial neurodynamic test (RNT) applies mechanical tension to the radial nerve and to the medial, posterior and lateral cords of the brachial plexus (82), as well as to its posterior interosseous branch, it is pertinent that the final position in which the upper limb is positioned before applying the elbow extension thrust in Mills manipulation is similar to the one reached during the RNT.

The author was here exploring:

i) Whether the overall changes in myoelectric activity in the test muscles are an expression of a specific protective response related to mechanical force production onto the neural tissues, and not just the effect of a general increase of myoelectric activity,

ii) Whether the Mills manipulation specificity for the common extensor tendon origin at the elbow can be improved with the addition of a neural unloading movement to the standard Mills manipulation.

### 6.2.1 **Key Findings**

From the presented results, some basic questions can here be answered:

- Do muscles activate when peripheral nerves are exposed to mechanical loads in terms of tensile and/or compressive forces in in-vivo and structurally intact human subjects?

  Answer: Yes, they do. The presented results shows that all muscles tested demonstrated some degree of activity during a Standard Mills pre-manipulative position, which was hypothesised to stress the radial nerve and its posterior interosseus branch along with the common extensor origin.

- Can those neural and muscular effects be controlled with the addition of neural unloading manoeuvres?

  Answer: Yes they can. Even if all muscles tested demonstrated some degree of activity during a Standard Mills pre-manipulative position, this could be significantly decreased with the addition of a neural unloading movement without changing any other component of the manipulation positioning itself. It is hypothesized that these muscles may become active in order to protect the nerves by simply i) avoiding further elongation of neural bed, ii) shortening the neural pathway in order to decrease tensile stress.

  Following this line of reasoning it might be said that manoeuvres that have an opposite effect on peripheral nerves and does have the potential to shorten the neural pathway of the affected peripheral nerves may be used to control such muscular reactions. Of those, cervical ipsilateral lateral flexion was employed as it has been observed with ultrasound imaging to reduce tension in the brachial plexus (17) (article III), and shoulder girdle forward flexion to 65° was employed as it has the potential to decrease the mechanical tension in the brachial plexus by i) decreasing the distance between the lower cervical region and the axilla, ii) increasing the area of the thoracic outlet tunnel as the clavicle moves anteriorly away from the first and second ribs, while not modifying any other component of the Mills manipulation manoeuvre (article IV).

- Is there any objective evidence that suggests that the pattern of muscular activation in response to mechanical loading of peripheral nerves may be interpreted in relation to anatomy and biomechanics of the related muscle and nerve structures?

  Answer: Yes, there is. In the Standard pre-manipulative stretch position for Mills manipulation, all muscles tested demonstrated some degree of activity.

However, upon addition of neural unloading movements to the Standard Mills positioning, myoelectric activity changed significantly.

Compared with the Standard position, in the Varied position encompassing cervical ipsilateral lateral flexion position, the biceps brachii and brachioradialis muscles showed significant reductions ($p \leq .01$) in their activity levels (article III). Also, the Varied position encompassing shoulder forward flexion by 65° showed significantly lower ($p \leq .001$) myoelectric activity in all the test muscles if compared with the Standard Mills position (article IV).

It seems plausible that these muscles were reflexively activated in order to protect the peripheral nerves in the most logical way; by shortening their pathway and opposing the manipulation movement. In this context, biceps brachii and brachioradialis could have been activated in order to oppose the manipulation movement (elbow extension) that would induce further tensile stress to the radial nerve and its posterior interosseous branch passing in front of the elbow joint, while the upper trapezius could have been activated in order to take tensile stress off the brachial plexus by producing a reduction in the distance between the lower cervical spine and the axilla.

From this data it emerges that this muscular activity may indeed bear aspects of functional significance, and their reaction can be interpreted in relation to anatomy and biomechanics of the related muscle and nerve structures.

- Can the presented methods be considered as a new model for investigation of neural mechanisms by means of quantification of muscular protective mechanisms?

Answer: It has been shown that muscles does activate in function of neural protection if mechanical forces are applied to peripheral nerves in in-vivo and structurally intact human subjects. Such changes in muscular activity can be easily recorded with Ag/AgCl electrodes used in surface electromyography (sEMG) and quantified using common biosignal analysis methods. As in certain positions as in neurodynamic tests, tensile forces into the peripheral nerves does increase with concomitant increase in range of motion in certain joints, it would be of interest to correlate changes in myoelectric activity in selected muscles with changes in joint range of motion. It seems that this new model of investigation of neural mechanisms is feasible and promising. This proposition is also supported by the data presented in chapter 5.2.3, Unpublished Neurophysiological Results. However, further work is needed before providing a conclusive answer to this question.

### 6.2.2 Comparison to Previous Literature

The Mills manipulation was first described by the English orthopaedic surgeon Sir G.Percival Mills (64) from the initial observation that, in patients with tennis elbow, the elbow joint could not be fully extended when this movement was combined with full forearm pronation and wrist and finger flexion. The manoeuvre is hypothesized to be effective by breaking the adhesions that may occur between bone and the body of common extensor tendon in lateral epicondylalgia (69).

It is pertinent that the final position in which the upper limb is positioned during the RNT which is specifically designed to apply mechanical tension to the radial nerve and its posterior interosseous branch is extremely similar to the one in which the upper limb is positioned in the Mills manipulation before applying the elbow extension thrust. Therefore, it may be that during this manoeuvre nerves are stressed along with muscles.

In the Standard pre-manipulative stretch position for Mills manipulation, all muscles tested demonstrated some degree of activity. However, upon addition of cervical ipsilateral lateral flexion to the Standard manoeuvre, the myoelectric activity in some muscles decreased significantly. Compared with the Standard position, in the Variation encompassing cervical ipsilateral lateral flexion position, the biceps brachii and brachioradialis muscles showed significant reductions ($p\leq.01$) in their activity levels. This suggests that the functions related to pre-manipulative stretch and possibly Mills Manipulation may not be isolated and instead may be disseminated, integrative and distinct.

As mentioned in subchapter 4.2.1.1, contralateral lateral flexion has been shown to increase mechanical tension in the brachial plexus (8,81) and this effect passes distally along the peripheral nerves of the upper limb to the elbow (82,90,91). Conversely, ipsilateral lateral flexion has been observed to reduce tension in these nerves (17).

In relation to the results, the muscles of importance are biceps brachii and brachioradialis. This is because, when contracted, they produce an elbow flexion moment that induces restraint of elbow extension. Elbow extension is the key movement in Mills manipulation and is typically painful. These two muscles may therefore produce local protective effects during the manipulation via their capacity to resist the manipulation movement. Reduction in activity only in the muscles that restrain elbow extension (protective) related directly to cervical spine ipsilateral lateral flexion. Based on this interaction, it appears that dual muscle and nerve mechanisms may operate during CEO stretch, suggesting that Mills manipulation may have collateral effects that may need controlling during the clinical procedure.

In a subsequent investigation aimed at exploring whether other neural unloading movements may bear the same effect (article IV) it was shown that EMG activity was significantly lower ($p\leq.001$) in all the tested muscles during the pre-manipulative stretch in the Varied position encompassing shoulder forward flexion by 65° if compared with the Standard Mills position. Shoulder girdle forward flexion to 65° was hypothesized to decrease the mechanical tension in the brachial plexus by i) decreasing the distance between the lower cervical region and the axilla, ii) increasing the area of the thoracic outlet tunnel as the clavicle moves anteriorly away from the first and second ribs, while not modifying any other component of the Mills manipulation manoeuvre.

While all the tested muscles showed a highly significant decrease in EMG activity, the largest change was in muscles that may exert a protective effect on the radial nerve and its posterior interosseus branch by means of shortening their pathway in front of the elbow joint and shoulder. These muscles consist of biceps brachii, brachioradialis and upper trapezius. The results in this study are consistent with those of other investigations in which the shoulder girdle has been shown to elevate (95) and the upper trapezius muscle has been shown to participate in this effect (108) in response to the neurodynamic test for the brachial plexus and median nerve. The neurodynamic test for the median nerve has been shown by Kleinrensink et al. (82) to apply tensile force to this nerve into the axilla, but also the medial and lateral cords of the brachial plexus by a similar amount as has been shown to occur in the RNT in the same study. Based on this, shoulder girdle elevation may exert a protective effect in which the upper trapezius muscle activity produces a reduction in the distance between the lower cervical spine and the axilla, therefore reducing tension in the brachial plexus.

This Varied position encompassing shoulder forward flexion by 65° showed significantly less myoelectic activity in the test muscles, and was also reported to be the less painful one by all the tested subjects. However, we did not ask our subjects to precisely quantify the symptoms during the pre-manipulative stretch. This did not allow us to test for any correlation between the magnitude of pain and changes in myoelectic activity, after Balster and Jull (108).

The non-protective muscle, lower trapezius, showed a significant increase in myoelectric activity in the position involving shoulder 65° forward flexion. This may be interpreted in relation to its function as a scapular stabilizer in shoulder girdle abduction (109) and its contribution to posterior tilt and external rotation of the scapula during humeral elevation in standing or seated subjects (110). The opposite myoelectric trend recorded in the lower trapezius suggests that the overall changes in myoelectric activity in the test muscles were an expression of a specific protective response related to mechanical force production in the neural tissues, and not just the effect of a general increase of myoelectric activity.

### 6.2.3 Methodological Considerations

The myoelectric signals presented in this paper were recorded in different pre-manipulative positions to describe the protective reaction induced by neural stretching. In the actual literature the positioning of the electrodes between the innervation zone and the tendon is recommended (111,112). This is, because the motor unit action potentials propagate in both directions from the innervation zone and can therefore impact on the recorded myoelectric potentials in case the recording electrodes are on different sides of the innervation zone. The variance of the location of the innervation zones between different individuals advocates for the use of multichannel techniques including electrode grids to estimate the location of the innervation zone in different individuals. However, as discussed with the members of the Biosignal Analysis Group from University of Eastern Finland, being the here presented analysis based on within-subject comparison, the electrode positioning in respect to the individual innervation zone is not likely to have influenced the presented data on subjective muscular reaction to neural loading.

The myoelectric reaction of asymptomatic subjects was assessed in order to provide normative data that will allow for future clinical comparisons in patients with epicondylalgia. Further investigations should be conducted in tennis elbow patients before generalizing the presented results to a symptomatic population.

Following the presented data (III, IV) it seems evident that muscles can activate in function of nerve protection, i.e. increase their activity when the peripheral nerves undergo unacceptable amount of tension. It seems plausible that the muscles were reflexively activated in order to protect the peripheral nerves in the most logical way; by shortening their pathway and opposing the manipulation movement. The authors think this is the most interesting result in these studies (III and IV) and also an intriguing possibility that calls for planning further investigation to elucidate the exact mechanisms.

It could be hypothesized that certain muscle activity during the increase in mechanical tension in the peripheral nerves is mediated by a nociceptive flexor reflex. However, in Balster and Jull(108), the lack of correlation between the magnitude of painful symptoms at the end range elbow of extension and cervical contralateral lateral flexion stages (which does increase the tension in the nerves) and the collected EMG data on the ipsilateral upper trapezius during the performance of a neurodynamic test for the median nerve, suggests that the mechanism may be more complex. In articles III and IV, the Varied positions allowing for neural detensioning during Mills manipulation showed significantly less myoelectric activity in the test muscles. The Varied position encompassing shoulder forward flexion by 65° was also reported to be the less painful one by all the tested subjects (article IV). In order to check whether these reactions are indeed mediated by the nociceptive flexor reflex, it would be of use to explore whether magnitude of painful symptoms shows any correlation with magnitude of myoelectric activity in protective muscles. Moreover, it would be of interest to explore whether a delay exists between first onset of painful symptoms and onset of muscle protective activation in some muscles.

However, we did not ask our subjects to quantify the symptoms during the pre-manipulative stretch, and this does not allow us to test for any correlation between the magnitude of pain and changes in EMG activity, after Balster and Jull (108). This feature can be listed as a further limitation that needs to be corrected in future experiments.

### 6.2.4 **Implications and Future Directions**

The results gained from the neurophysiologic investigations seems to point to the fact that muscles may be activated for protection of peripheral nerves from tensile forces in the most logical way, by shortening the neural pathway and opposing joint movements toward further elongation of the nerve bedding.

In clinical practice, muscular spasm is a pathognomic sign frequently found in patients with compressive peripheral neuropathies during physical testing. In this line of research in neurophysiology we seek to understand the origin of such spasm. Particularly, elucidate whether this phenomenon can be mediated by adverse mechanical forces acting on mechanosensitive nerves. To do so, and to solve some of the limitations listed in the previous chapter (6.2.3) the author of this doctoral thesis decided to further investigate the specificity of, and measure quantitative parameters of, such muscular activation in response to mechanical testing of peripheral nerves in asymptomatic subjects in order to establish normative responses.

In these new investigations the author sought to explore whether this muscular activation in response to mechanical loading of the peripheral nervous system may bear some features of specificity and modulation. This was achieved by testing the muscular responses to the Radial neurodynamic test performed in opposite sequences (proximal and distal sequence).

The unpublished neurophysiological results presented in chapter 5.2.3.1 shows that the muscle activation patterns differed significantly between the test manoeuvres, leading to the conclusion that muscles near the joint first moved tend to become active before others. This event may find an explanation in the phenomenon of nerve convergence in which nerves slide in the body toward the joint at which tension is being applied and may be tensioned stronger and for longer time around the joint that is moved first (17). By extension, it seems reasonable that muscles nearby the joint moved first become active before others. The onset of muscle activation always appeared near the first onset of pain, with muscle activation starting before the first onset of painful symptoms in the great majority of cases (89%). This results do question the notion of a NFR-based mechanism.

Furthermore, from the unpublished neurophysiological results presented in chapter 5.2.3.2 it is evident that the continuous increase of mean amplitude values (MAV) and the concomitant continuous decrease of myoelectric mean frequency (MNF) toward the end of each radial nerve tension manoeuvre does indicate genuine muscular contraction in response to neural mechanical loading, but also modulation of muscular response. It emerges that this muscular activation seems to increase continuously, and motor units activation seems to synchronize continuously, following the increase in tensile stress into and onto the nerve in response to the RNT. These records differ significantly from those collected during strong stretch of biceps brachii muscle, indicating that muscular stretch itself may not be responsible for the presented phenomenon.

The data seem to not to support the common theory of reflex mediated muscle activation in response to mechanical loading of nerves, and does indeed support the idea that the mechanism is modulated and more complex than originally thought.

As mentioned earlier, the existence of nerve terminals in the connective tissue of peripheral nerves sensitive to mechanical forces, and that could produce ectopic electrogenesis at the peripheral nerve level, has already been demonstrated by Hromada (85) and Bove and Light(86). This represents the basic information underpinning the hypothesis that muscles can be directly activated to protect peripheral nerves from tensile and compressive mechanical loads. It may also be hypothesized that propioceptive signals from the joint capsules may facilitate such response.

These new insights warrant for further investigations aimed at exploring the neural pathways that would allow for such manifestation. If such a specific pathway will be proven to exist, a new peripheral mechanism that may cause muscular hypertonia may be described, and alternative pharmacological and physical therapies may be designed for neurological patients showing hypertonia.

### *6.2.4.1 Future directions*

As mentioned earlier, these data seem not to support the common theory of reflex mediated muscle activation in response to mechanical loading of nerves, and support the idea that the mechanism is modulated and more complex than originally thought.

It remains to understand which neural pathway may allow for such specific and modulated muscle activation for neural protection. It is of interest to understand these neural protective mechanisms and discover the neural pathway allowing for modulated muscle activation in function of neural protection, which will in turn allow us to and hypothesize further developments in treatment of hypertonia.

Following this, two main aims of this line of research in neurophysiology can be shaped:

i) Improve the accuracy and specificity of neural tensile tests that are used in musculoskeletal medicine for diagnosis of medical conditions such as radiculopathies and canalicular syndromes

ii) Explore and define the exact neural pathway allowing for such specific and modulated muscle activation in function of neural protection.

Further experiments are already scheduled to be performed in a joined collaboration between the:

- Biosignal Analysis Group from University of Eastern Finland, with Dr Saara Rissanen
- Department of Physical and Rehabilitation Medicine of Kuopio University Hospital, with Marinko Rade and Prof Olavi Airaksinen

- Department of Physical and Rehabilitation Medicine of Tampere University Hospital, with Dr Markku Kankaanpää
- Neurodynamic Solutions from Adelaide (Australia), with Michael Shacklock

We do believe that the line of research n. 2 is innovative and has great development potential, and are thus going to invest further efforts in it.

# 7 Conclusions

In this doctoral thesis the author has introduced the rationale underpinning two lines of research and their possible future developments.

The author of this dissertation presented arguments to support the notion that:

- Nerves move, and that their movements can be quantified using non-invasive techniques,
- The human body does have some innate mechanisms to protect nerves from excessive mechanical forces,
- These mechanisms can be investigated and quantified using non-invasive methods.

With these results, we hypothesize that the sliding of neural structures in anatomical tunnels and canals may be a protective effect which preserves the spinal cord, neural roots and peripheral nerves from strain and compression. If this were true, the preservation of a free longitudinal and transverse sliding of the neural structures in these tunnels and canals might be the *conditio sine qua non* for maintaining an asymptomatic situation. On the other hand, if sliding mechanisms fails to protect nerves from such mechanical forces, it seems that muscles can be activated in function of neural protection by simply i) avoiding further elongation of neural bed, ii) shortening the neural pathway in order to decrease tensile stress.

Following the assumption that improved knowledge of the local mechanics will lead to improved diagnostics and treatment selection, these new information can provide clinical advantages allowing informed decision making in terms of diagnosis and treatment planning, as well as the design of new diagnostic algorithms. Also new lines of research that expands the presented knowledge can be designed, with the final aim of fully understand the neural adaptation mechanisms and innate means of protection of nerves against adverse mechanical forces.

In these seemingly different lines of research, different research methodologies have been presented to investigate the same thing: the innate mechanisms that the human body employs to protect the nerves from adverse mechanical forces. These two lines took birth from the author's firm belief that in order to explore normal neural mechanisms, the principle of *no- harm* has to be respected. That is, the investigation methodologies have to be non-invasive.

Before designing these lines, the author engaged in courses organized by the Department of Physics of University of Eastern Finland in order to fully understand the principles of the devices he was going to employ. The newly acquired knowledge allowed for several problem solving sessions, and most of all, allowed the author of this doctoral thesis to recognize soon enough bad research designs. It takes time and knowledge to admit our own mistakes soon enough, and it is for this reasons that I am particularly grateful to this department.

An additional value of this thesis is represented by the new information presented in the literature review on the codification of the Straight Leg Raise test. As the author of this thesis speaks Croatian fluently, he was able to retrieve an article published by Laza Lazarević in the Serbian Archives of Medicine in 1880 and in which the execution of the SLR seem to be described for the first time in a scientific journal. As this publication outdates the J.J. Fort's one by one year, it seems that the authorship of this widely used test should be reconsidered.

As stated in the introduction chapter, the aim of this dissertation was not only to present plain data, but to try to shift the clinician's concept of nerves passively enclosed in tunnels delimited by bones, ligaments and muscles, to the concept of nerves sliding and moving freely in those tunnels in order to avoid potentially harmful mechanical forces as tension and compression arising from interfacing structures, and increase the awareness of the fact that those movements can be measured, understood, predicted and also possibly used at our advantage in our everyday clinical practice. If this was achieved, then this thesis has served its purpose.

# 8 References

(1) Sunderland S, Bradley KC. Stress-strain phenomena in denervated peripheral nerve trunks. Brain 1961;84(1):125-127.

(2) Sunderland S, Bradley KC. Stress-strain phenomena in human peripheral nerve trunks. Brain 1961;84(1):102-119.

(3) Sunderland S, Bradley KC. Stress-strain phenomena in human spinal nerve roots. Brain 1961;84(1):120-124.

(4) Sunderland S. Nerves Injuries and Their Repair: A Critical Appraisal. Edinburgh: Churchill Livingstone; 1991.

(5) Lundborg G, Rydevik B. Effects of stretching the tibial nerve of the rabbit. A preliminary study of the intraneural circulation and the barrier function of the perineurium. Journal of Bone and Joint Surgery - Series B 1973;55(2):390-401.

(6) Ogata K, Naito M. Blood flow of peripheral nerve effects of dissection stretching and compression. J Hand Surg 1986;11(1):10-14.

(7) Soderberg GL. Kinesiology: Application to pathological motion. Baltimore: Williams & Wilkins; 1986.

(8) McLellan DL, Swash M. Longitudinal sliding of the median nerve during movements of the upper limb. Journal of neurology, neurosurgery, and psychiatry 1976;39(6):566-70.

(9) Wilgis EFS, Murphy R. The significance of longitudinal excursion in peripheral nerves. Hand Clin 1986;2(4):761-766.

(10) Gelberman RH, Szabo RM, Williamson RV, Hargens AR, Yaru NC, Minteer-Convery MA. Tissue pressure threshold for peripheral nerve viability. Clin Orthop 1983;No. 178:285-291.

(11) Nakamichi K, Tachibana S. Transverse sliding of the median nerve beneath the flexor retinaculum. J Hand Surg 1992;17 B(2):213-216.

(12) Greening J, Smart S, Leary R, Hall-Craggs M, O'Higgins P, Lynn B. Reduced movement of median nerve in carpal tunnel during wrist flexion in patients with non-specific arm pain. Lancet 1999;354(9174):217-218.

(13) Yoshii Y, Villarraga HR, Henderson J, Zhao C, An K-, Amadio PC. Ultrasound assessment of the displacement and deformation of the median nerve in the human carpal tunnel with active finger motion. Journal of Bone and Joint Surgery - Series A 2009;91(12):2922-2930.

(14) Yoshii Y, Ishii T, Tung W-, Sakai S, Amadio PC. Median nerve deformation and displacement in the carpal tunnel during finger motion. Journal of Orthopaedic Research 2013;31(12):1876-1880.

(15) Wertsch JJ, Melvin J. Median nerve anatomy and entrapment syndromes: A review. Arch Phys Med Rehabil 1982;63(12):623-627.

(16) Bilecenoglu B, Uz A, Karalezli N. Possible anatomic structures causing entrapment neuropathies of the median nerve: An anatomic study. Acta Orthop Belg 2005;71(2):169-176.

(17) Shacklock M. Clinical neurodynamics, a new system of musculoskeletal treatment. Oxford: Elsevier; 2005.

(18) Lluch AL. Thickening of the synovium of the digital flexor tendons: Cause or consequence of the carpal tunnel syndrome? J Hand Surg 1992;17 B(2):209-212.

(19) Sud V, Tucci MA, Freeland AE, Smith WT, Grinspun K. Absorptive properties of synovium harvested from the carpal tunnel. Microsurgery 2002;22(7):316-319.

(20) Ettema AM, Amadio PC, Zhao C, Wold LE, An KN. A histological and immunohistochemical study of the subsynovial connective tissue in idiopathic carpal tunnel syndrome. Journal of Bone and Joint Surgery - Series A 2004;86(7):1458-1466.

(21) Ettema AM, Zhao C, Amadio PC, O'Byrne MM, An KN. Gliding characteristics of flexor tendon and tenosynovium in carpal tunnel syndrome: A pilot study. Clinical Anatomy 2007;20(3):292-299.

(22) Zhao C, Ettema AM, Osamura N, Berglund LJ, An KN, Amadio PC. Gliding characteristics between flexor tendons and surrounding tissues in the carpal tunnel: A biomechanical cadaver study. Journal of Orthopaedic Research 2007;25(2):185-190.

(23) Van Doesburg MHM, Van Der Molen AM, Henderson J, Cha SS, An KN, Amadio PC. Sonographic measurements of subsynovial connective tissue thickness in patients with carpal tunnel syndrome. Journal of Ultrasound in Medicine 2012;31(1):31-36.

(24) van Doesburg MHM, Henderson J, Mink van der Molen AB, An KN, Amadio PC. Transverse plane tendon and median nerve motion in the carpal tunnel: Ultrasound comparison of carpal tunnel syndrome patients and healthy volunteers. PLoS ONE 2012;7(5).

(25) Bogduk N, Twomey L. The clinical anatomy of the lumbar spine. New York: Churchill Livingstone; 1991.

(26) Singh V. Anatomy of Abdomen and Lower Limb. New Delhi: Elsevier India; 2011.

(27) Hansen JT. Netter's Clinical Anatomy. 3rd Edition ed. Philadelphia: Elsevier Saunders; 2014.

(28) Pope MH, Novotny JE. Spinal biomechanics. J Biomech Eng 1993;115(4 B):569-574.

(29) Smith SA, Massie JB, Chesnut R, Garfin SR. Straight leg raising: Anatomical effects on the spinal nerve root without and with fusion. Spine 1993;18(8):992-999.

(30) Lasègue CH. Considérations sur Ia sciatique . Arch Gén de Méd 1864;2 (Série 6, Tome 4):558-580.

(31) De Beurmann L. Note sur un signe peu connu de la sciatique. Recherches expérimentales. Arch de Phvsiol, Norm et Pathol 1884;3 (Série 3):375-380.

(32) Sjöqvist O. The Mechanism of Origin of Lasègue's Sign. Acta Psychiat et Neurol 1947(Supplementum 4):290-297.

(33) Woodhall B, Hayes GJ. The Well-Leg-Raising Test of Fajersztajn in the Diagnosis of Ruptured Lumbar Intervertebral Disc. Journal of Bone and Joint Surgery 1950;32:786-792.

(34) Forst JJ. Contribution à l'Étude Clinique de Ia Sciatique: Thèse pour le Doctorat en Médecine. Paris: Faculté de Médecine de Paris 1881;N.33.

(35) Lazarević LK. Ischias postica contunnii - jedan prilog za njenu diferencijalnu dijagnozu. Srpski arhiv za celokupno lekarstvo 1880;7:23-35.

(36) Inman VT, Saunders JB. The Clinico-Anatomical Aspects of the Lumbosacral Region. Radiology 1942;38:669-678.

(37) Falconer MA, McGeorge M, Begg AC. Observations of the cause and mechanism of symptom production in sciatica and low back pain. J Neurol Neurosurg Psychiatry 1948;11:12-26.

(38) Charnley J. Orthopaedic sign in the diagnosis of disc protrusion: with special reference to the straight-leg-raising test. Lancet 1951;27:186-192.

(39) Goddard MD, Reid JD. Movements induced by straight leg raising in the lumbosacral region. J Neurol Neurosurg Psychiatry 1965;28:12-18.

(40) Brieg A, Marions O. Biomechanics of the lumbosacral nerve roots. Acta Radiologica diagnosis 1962;1:1141-1160.

(41) Kobayashi S, Shizu N, Suzuki Y, Asai T, Yoshizawa H. Changes in nerve root motion and intraradicular blood flow during an intraoperative straight-leg-raising test. Spine 2003;28(13):1427-1434.

(42) Kobayashi S, Takeno K, Yayama T, Awara K, Miyazaki T, Guerrero A, et al. Pathomechanisms of sciatica in lumbar disc herniation: Effect of periradicular adhesive tissue on electrophysiological values by an intraoperative straight leg raising test. Spine 2010;35(22):2004-2014.

(43) Trolard P. Recherches sur L'Anatomie des Meninges Spinales, des Nerfs Sacre et du Filum Terminale dans le Canal Sacre. Arch Physiol Normal Pathol 1888;4:191-199.

(44) Hofmann M. Die Befestigung der Dura Mater im Wirbelcanal. Arch F Anat Physiol 1898:403-410.

(45) De Peretti F, Micalef JP, Bourgeon A, Argenson C, Rabischong P. Biomechanics of the lumbar spinal nerve roots and the first sacral root within the intervertebral foramina. Surgical and Radiologic Anatomy 1989;11(3):221-225.

(46) Grimes PF, Massie JB, Garfin SR. Anatomic and biomechanical analysis of the lower lumbar foraminal ligaments. Spine 2000;25(16):2009-2014.

(47) Gilbert KK, Brismée JM, Collins DL, James CR, Shah RV, Sawyer SF, et al. 2006 Young investigator award winner: Lumbosacral nerve root displacement and strain: Part 1. A novel measurement technique during straight leg raise in unembalmed cadavers. Spine 2007;32(14):1513-1520.

(48) Gilbert KK, Brismée JM, Collins DL, James CR, Shah RV, Sawyer SF, et al. 2006 Young investigator award winner: Lumbosacral nerve root displacement and strain: Part 2. A comparison of 2 straight leg raise conditions in unembalmed cadavers. Spine 2007;32(14):1521-1525.

(49) Graham GE. Intraoperative straight-leg raising during laminectomy and disk excision for sciatica. Clin Orthop 1981(154):343-344.

(50) Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81(9):646-656.

(51) Jonsson B, Stromqvist B. The straight leg raising test and the severity of symptoms in lumbar disc herniation: A preoperative and postoperative evaluation. Spine 1995;20(1):27-30.

(52) Shacklock M. Neurodynamics. Physiotherapy 1995;81(1):9-16.

(53) Breig A, Troup JDG. Biomechanical considerations in the straight-leg-raising test. Cadaveric and clinical studies of the effects of medial hip rotation. Spine 1979;4(3):242-250.

(54) Van der Windt Daniëlle AWM, Simons E, Riphagen Ingrid I, Ammendolia C, Verhagen Arianne P, Laslett M, et al. Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain. 2010(2).

(55) Brieg A. Adverse Mechanical Tension in the Central Nervous System. New York: John Wiley & Sons Inc; April 1978.

(56) Shacklock M. Biomechanics of the Nervous System: Breig Revisited. Adelaide: Neurodynamic Solutions NDS; 2007.

(57) Brown MA, Semelka RC. MRI: Basic Principles and Applications. New York: John Wiley & Sons, Inc.; 1999.

(58) Westbrook K. MRI at a Glance. Oxford: Blackwell Science Ltd,; 2002.

(59) McRobbie DW, Moore EA, Graves MJ, Prince MR. MRI from picture to proton. Second edition ed. Cambridge: Cambridge University Press; 2006.

(60) Gruchow HW, Pelletier D. An epidemiologic study of tennis elbow. Incidence, recurrence, and effectiveness of prevention strategies. Am J Sports Med 1979;7(4):234-238.

(61) Noteboom T, Cruver R, Keller J, Kellogg B, Nitz AJ. Tennis elbow: A review. J Orthop Sports Phys Ther 1994;19(6):357-366.

(62) McHardy A, Pollard H, Luo K. Golf injuries: A review of the literature. Sports Medicine 2006;36(2):171-187.

(63) Stockard AR. Elbow injuries in golf. J Am Osteopath Assoc 2001;101(9):509-516.

(64) Mills GP. Treatment of tennis elbow. British Medical Journal 1928;1:12-13.

(65) Cyriax J. Textbook of Orthopaedic medicine, Vol 1. 8th edition ed. London: Baillière Tindal; 1982. p. 119-180.

(66) Greenfield C, Webster V. Chronic lateral epicondylitis: survey of current practice in the outpatient departments in Scotland. Physiotherapy 2002;88(10):578-594.

(67) Kesson M, Atkins E. Orthopaedic medicine, a practical approach. 2nd Edition ed. Edinburgh: Elsevie; 2005. p. 207-211.

(68) Cyriax J. Textbook of Orthopaedic medicine, Vol.2. 11th edition ed. London: Baillière Tindall; 1984. p. 112.

(69) Atkins E, Kerr J, Goodlad E. . A practical approach to orthopaedic medicine. 3rd Edition ed. Edinburgh: Churchill Livingstone - Elsevier; 2010. p. 142-145.

(70) Bragard K. Die nervendehnung als diagnostisches prinzip ergibt eine reihe neuer nervenphanomene. . Miinchener Medizinische Wochenschrift 1929;76:1999-2003.

(71) Von Lanz T, Wachsmuth W. Praktische Anatomie. Ein lehr und Hilfsfuch der Anatomischen Grundlagen Ärtslichen, Handelns.. Berlin: Springer-Verlag; 1959.

(72) Breig A, Marions O. Biomechanics of the Lumbosacral Nerve Roots. Acta Radiol Diagn 1963;1:1141-1160.

(73) Elvey RL. Brachial plexus tension tests and the pathoanatomical origin of arm pain. In: Idczak R, editor. Aspects of manipulative therapy. Melbourne, Australia: Lincoln Institute of Health Sciences; 1979. p. 105-110.

(74) Butler D. The Sensitive Nervous System. Adelaide: NOI Press; 2000.

(75) Kenneally M, Rubenach H, Elvey R. The upper limb tension test: the SLR test of the arm. In: Grant R, editor. Physical Therapy of the Cervical and Thoracic Spine New York: Churchill Livingstone; 1988. p. 167-194.

(76) Butler D, Gifford L. The concept of adverse mechanical tension in the nervous system. Part 1: testing for 'dural tension'. Physiotherapy 1989;75(11):622-629.

(77) Butler D. Mobilisation of the Nervous System. Edinburgh: Churchill Livingstone; 1991.

(78) Elvey RL. Treatment of arm pain associated with abnormal brachial plexus tension. Australian Journal of Physiotherapy 1986;32(4):225-230.

(79) Zöch G, Beer R, Reihsner R, Millesi H. Anpassung des N. medianus an extreme Beugung und Streckung der oberen Extremität. Acta Chirurgica Austriaca 1986;5:491-495.

(80) Selvaratnam P, Glasgow E, Matyas T. Strain effects on the nerve roots of brachial plexus. Journal of Anatomy 1988;161:260-264.

(81) Selvaratnam PJ, Matyas TA, Glasgow EF. Noninvasive discrimination of brachial plexus involvement in upper limb pain. Spine 1994;19(1):26-33.

(82) Kleinrensink GJ, Stoeckart R, Mulder PG, Hoek G, Broek T, Vleeming A, et al. Upper limb tension test as tools in the diagnosis of nerve and plexus lesions. Anatomical and biomechanical aspects. Clinical Biomechanics 2000(15):9-14.

(83) Mackinnon S, Dellon A. Surgery of the Peripheral Nerve. New York: Thieme; 1988.

(84) Yaxley G, Jull G. A modified upper limb tension test: an investigation of responses in normal sybjects. Australian Journal of Physiotherapy 1991;27(3):143-152.

(85) Hromada J. On the Nerve Supply of the Connective Tissue of Some Peripheral Nervous System Components. Acta Anat 1963;55:343-351.

(86) Bove GM, Light AR. Unmyelinated nociceptors of rat paraspinal tissues. J Neurophysiol 1995;73(5):1752-1762.

(87) Porter RW, Trailescu IF. Diurnal changes in straight leg raising. Spine 1990;15(2):103-106.

(88) Rade M, Könönen M, Vanninen R, Marttila J, Shacklock M, Kankaanpää M, et al. 2014 young investigator award winner: In vivo magnetic resonance imaging measurement of spinal cord displacement in the thoracolumbar region of asymptomatic subjects: Part 1: Straight leg raise test. Spine 2014;39(16):1288-1293.

(89) Rade M, Könönen M, Vanninen R, Marttila J, Shacklock M, Kankaanpää M, et al. 2014 young investigator award winner: In vivo magnetic resonance imaging measurement of spinal cord displacement in the thoracolumbar region of asymptomatic subjects: Part 2: Comparison between unilateral and bilateral straight leg raise tests. Spine 2014;39(16):1294-1300.

(90) Dilley A, Lynn B, Greening J, DeLeon N. Quantitative in vivo studies of median nerve sliding in response to wrist, shoulder and neck movements. Clinical Biomechanics ,2003;18:899-907.

(91) Coppieters MW, Hough AD, Dilley A. Different nerve-gliding exercises induce different magnitudes of median nerve longitudinal excursion: an in vivo study using dynamic ultrasound imaging. J Orthop Sports Phys Ther 2009 Mar;39(3):164-171.

(92) Coppieters MW, Van de Velde M, Stappaerts KH. Positioning in anesthesiology: toward a better understanding of stretch-induced perioperative neuropathies. Anesthesiology 2002 Jul;97(1):75-81.

(93) Coppieters MW. Shoulder restraints as a potential cause for stretch neuropathies: biomechanical support for the impact of shoulder girdle depression and arm abduction on nerve strain. Anesthesiology 2006 Jun;104(6):1351-1352.

(94) Coppieters MW, Stappaerts KH, Everaert DG, Staes FF. Addition of test components during neurodynamic testing: effect on range of motion and sensory responses. J Orthop Sports Phys Ther 2001 May;31(5):226-35; discussion 236-7.

(95) Coppieters MW, Stappaerts KH, Wouters LL, Janssens K. Aberrant protective force generation during neural provocation testing and the effect of treatment in patients with neurogenic cervicobrachial pain. J Manipulative Physiol Ther 2003 Feb;26(2):99-106.

(96) Van Hoof T, Vangestel C, Forward M, Verhaeghe B, Van Thilborgh L, Plasschaert F, et al. The impact of muscular variation on the neurodynamic test for the median nerve in a healthy population with Langer's axillary arch. Journal of Manipulative and Physiological Therapeutics 2008;31(6):474-483.

(97) Hermens HJ, Freriks B, Merletti R. SENIAM: Raccomandazioni europee per l'elettromiografia di superficie. Torino: C.L.U.T. Edition.; 2000.

(98) Hashimoto T, Shindo M, Morita H, Yanagisawa N, Ikeda S. On the errors in assessment of severity of involuntary movements using surface EM G. J Electromyography Kinesiol 2005;15:316-322.

(99) Rissanen SM, Kankaanpää M, Meigal A, Tarvainen MP, Nuutinen J, Tarkka IM, et al. Surface EMG and acceleration signals in Parkinson's disease: feature extraction and cluster analysis. Med Biol Eng Comput 2008;46:849–858.

(100) Rissanen SM, Kankaanpää M, Tarvainen MP, Meigal AY, Nuutinen J, Tarkka IM, et al. Analysis of dynamic voluntary muscle contractions in Parkinson's disease. IEEE Transactions on Biomedical Engineering 2009;56(9):2280-2288.

(101) Jaberzadeh S, Scutter S, Nazeran H.
Mechanosensitivity of the median nerve and mechanically produced motor responses during Upper Limb Neurodynamic Test 1. Physiotherapy 2005;91:94-100.

(102) Wu G, Van Der Helm FCT, Veeger HEJ, Makhsous M, Van Roy P, Anglin C, et al. ISB recommendation on definitions of joint coordinate systems of various joints for the reporting of human joint motion - Part II: Shoulder, elbow, wrist and hand. J Biomech 2005;38(5):981-992.

(103) Heck CV, Hendryson IE, Rowe CR. Joint Motion: Method of Measuring and Recording. 14th reprint ed. Edinburgh: The American Academy of Orthopaedic Surgeons - Churchill Livingstone; 1991. p. 10-11.

(104) Haninec P, Szeder V. Reconstruction of elbow flexion by transposition of pedicled long head of triceps brachii muscle. Acta Chir Plast 1999;41(3):82-86.

(105) Lim AYT, Pereira BP, Kumar VP. The long head of the triceps brachii as a free functioning muscle transfer. Plast Reconstr Surg 2001;107(7):1746-1752.

(106) Nee RJ, Yang CH, Liang CC, Tseng GF, Coppieters MW. Impact of order of movement on nerve strain and longitudinal excursion: a biomechanical study with implications for neurodynamic test sequencing. Man Ther 2010 Aug;15(4):376-381.

(107) Günal I, Köse N, Erdogan O, Göktürk E, Seber S. Normal Range of Motion of the Joints of the Upper Extremity in Male Subjects, with Special Reference to Side. J Bone Joint Surg Am 1996;78:1401-1404.

(108) Balster SM, Jull GA. Upper trapezius muscle activity during the brachial plexus tension test in asymptomatic subjects. Man Ther 1997;2(3):144-149.

(109) Johnson GR, Pandyan AD. The activity in the three regions of the trapezius under controlled loading conditions - An experimental and modelling study. Clin Biomech 2005;20(2):155-161.

(110) Ludewig PM, Cook TM, Nawoczenski DA. Three-dimensional scapular orientation and muscle activity at selected positions of humeral elevation. J Orthop Sports Phys Ther 1996;24(2):57-65.

(111) Mesin L, Merletti R, Rainoldi A. Surface EMG: The issue of electrode location. Journal of Electromyography and Kinesiology 2009;19(5):719-726.

(112) Rodriguez-Falces J, Negro F, Gonzalez-Izal M, Farina D. Spatial distribution of surface action potentials generated by individual motor units in the human biceps brachii muscle. Journal of Electromyography and Kinesiology 2013;23(4):766-777.

**MARINKO RADE**

# *Between Neuroradiology and Neurophysiology: New Insights in Neural Mechanisms*

This thesis presents new data on the subject of neural protective mechanisms, particularly in aspects that have not been studied before, namely spinal cord movement and muscular protective effects during limb movements that produce excursion of nerve tissues. The aim is to try to shift the clinician's concept of nerves passively enclosed in tunnels delimited by bones, ligaments and muscles, to the concept of nerves sliding and moving freely in those tunnels in order to avoid potentially harmful mechanical forces as tension and compression arising from interfacing structures and maintain an asymptomatic situation, and increase the awareness of the fact that those movements can be measured, understood, predicted and also used at our advantage in our everyday clinical practice. If this will be achieved, then this thesis will have served its purpose.

UNIVERSITY OF
EASTERN FINLAND

PUBLICATIONS OF THE UNIVERSITY OF EASTERN FINLAND
*Dissertations in Health Sciences*

ISBN 978-952-61-1740-9