Experimental and Clinical Neck Pain

effects on dynamic cervical joint motion and pressure pain sensitivity

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BY
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DISSERTATION SUBMITTED 2019

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CV

Ning Qu obtained his Bachelor degree in Clinical Medicine from Xiamen University (China) in 2012. After the graduation, Ning Qu was recomendated to continue studing in Faculty of Medicine of Jilin University (China). During the same period (2012 to 2015), Ning Qu also worked in the Orthopedics department in the second affiliated hospital of Jilin University. In 2016, he was supported by China Scholarship Council (CSC) to start his PhD in SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark.

ENGLISH SUMMARY

Neck pain is a global health issue. It significantly affects the life quality of patients and consequently causes a dramatic economic burden to society. Neck pain is a multifactorial disease influenced by many biological, psychological and psychosocial factors. Nevertheless, many researchers propose that neck pain should have a local pathoanatomical basis. However, a large portion of neck pain is classified as non-specific, since the source of neck pain is rarely identified.

The assessment of dynamic cervical joint motion is supposed to reveal more impairments of neck pain at the individual cervical joint levels when compared with motion assessments on static and end-range radiographs. In addition, pressure pain sensitivity is widely investigated in patients with neck pain and applied to subgroup patients with neck pain. These two parameters also show potential diagnostic values of reflecting the sources of neck pain. Additionally, persistent motor and sensory changes may lead to the recurrence of neck pain. However, dynamic cervical joint motion patterns and pressure pain sensitivity of patients with recurrent neck pain remains unstudied.

The thesis aimed to investigate the effects of pain originating from different cervical structures on dynamic cervical joint motion and pressure pain thresholds (PPTs) and to investigate dynamic cervical joint motion patterns and PPTs in patients with recurrent neck pain. Experimental deep and superficial cervical muscle pain were applied in study I and experimental inter-spinous ligament pain was applied in study II. Patients with recurrent neck pain and matched healthy controls were recruited in study III. Video-fluoroscopy was used to record cervical flexion and extension movements. Dynamic cervical joint motion parameters were extracted, which included pro-directional motion, anti-directional motion, joint motion variability, and total joint motion. PPTs were measured over bilateral C2/C3 and C5/C6 facet joints (study I-III) and the right tibialis anterior (TA) (Study III) by a pressure algometer.

Results of study I showed that: 1) deep cervical muscle pain redistributed anti-directional motion between C3/C4 and C6/C7 during cervical extension while superficial cervical muscle pain decreased the overall anti-directional motion, pro-directional motion, and joint motion variability during cervical extension; 2) deep cervical muscle pain increased PPTs over bilateral C2/C3 and left C5/C6 facet joints and superficial cervical muscle pain increased PPTs over bilateral C2/C3 and C5/C6 facet joints. Results of study II showed that: 1) inter-spinous ligament pain redistributed anti-directional motion and joint motion variability between C2/C3 and C4/C5 during cervical extension; 2) inter-spinous ligament pain increased PPTs over the left C2/C3 facet joints. Results of study III showed that: 1) patients with recurrent neck pain decreased anti-directional motion at C2/C3 and C3/C4 and increased anti-directional motion at C5/C6 and C6/C7 during cervical extension and increased the overall anti-directional motion during cervical flexion; 2) no differences in PPTs over bilateral C2/C3 and C5/C6 facet joints and the right TA were found between patients with recurrent neck pain and healthy controls.

In conclusion, different effects on anti-directional motion were demonstrated when pain originated in the deep cervical muscle, superficial cervical muscle, and inter-spinous ligament. Patients with recurrent neck pain showed altered anti-directional motion patterns compared with healthy controls. However, experimental cervical muscle and ligament pain decreased the pressure pain sensitivity over different cervical facet joints and patients with recurrent neck pain showed no localized and widespread hyperalgesia. The findings in the thesis indicated that the anti-directional motion was the most sensitive to experimental and clinical neck pain and investigations of anti-directional motion may contribute to the diagnosis of neck pain when attempting to identify the pain sources.

DANSK RESUME

Nakkesmerter er et globalt sundhedsproblem. Nakkesmerter kan påvirke livskvaliteten og medfører tabt arbejdskraft og dermed være en økonomisk byrde for samfundet. Nakkesmerter er en multifaktuel sygdom som influeres af flere biologiske, fysiologiske og psykiske faktorer. På trods af dette mener flere forskere at nakkesmerter har en lokal patologisk årsag. På trods af dette, bliver en stor del af nakkesmerter defineret som ikke-specifik, eftersom årsagen til smerten sjældent bliver identificeret.

Undersøgelse af dynamisk cervikal ledbevægelse formodes at kunne identificere skader bedre ved de enkelte cervikal led sammenlignet med statiske røntgenbilleder i ydrestillinger. Yderligere tryk sensibilitet undersøgelser er bredt anvendt på patienter med nakkesmerter og kan anvendes til at subgroupere patienter. Disse to parametre viser også potentielle diagnostiske værdier for at reflektere årsagen til nakkesmerter. Derudover kan vedvarende motoriske og sensoriske ændringer føre til gentagende nakkesmerter. Imidlertid er dynamiske cervikale ledbevægelsesmønstre og tryksmerterfølsomhed hos patienter med tilbagevendende nakkesmerter ikke undersøgt.

Formålet for denne afhandling var at undersøge effekten af smerte fra forskellige cervicale strukturer på dynamisk cervicalled bevægelse og mekanisk trykfølsomhed (PPT) og undersøge hvordan disse parameter er i blandt patienter med tilbagevendende nakkesmerter. Eksperimental cervical muskelsmerte var anvendt i studie I og eksperimentel inter-spinøs ligament smerte blev anvendt i undersøgelse II. Patienter med tilbagevendende nakkesmerter og matchede raske kontroller blev rekrutteret i undersøgelse III. Video-fluoroskopi blev anvendt til at spore cervikal fleksion og ekstension. Dynamiske cervikale ledbevægelsesparametre blev ekstraheret, som inkluderede pro-retningsbestemt bevægelse, anti-retningsbestemt bevægelse, ledbevægelsesvariabilitet og total ledbevægelse. PPT'er blev målt over bilaterale C2 / C3 og C5 / C6 facetled (undersøgelse I-III) og højre tibialis anterior (TA) (undersøgelse III) ved hjælp af et trykalegometer.

Resultater af undersøgelse I viste, at: 1) dyb cervikale muskelsmerter omdistribuerede anti-retningsbevægelse mellem C3 / C4 og C6 / C7 under cervikal ekstension, mens overfladisk cervicalmuskel smerte mindskede den samlede anti-retningsbevægelse, pro-directional bevægelse og ledbevægelse variation under cervikal ekstension; 2) dybe cervikale muskelsmerter øgede PPT'er over bilaterale C2 / C3 og venstre C5 / C6 facetled og overfladiske cervical muskelsmerter og øgede PPT'er over bilaterale C2 / C3 og C5 / C6 facetled. Resultaterne af undersøgelse II viste, at: 1) inter-spinøs ligamentsmerter om distribuerede anti-retningsbevægelse og variation i ledbevægelsen mellem C2 / C3 og C4 / C5 under cervikal ekstension; 2) inter-spinøs ligament smerte øgede PPT over venstre C2 / C3 facetled. Resultaterne af undersøgelse III viste, at: 1) patienter med tilbagevendende nakkesmerter nedsatte deres anti-retningsbevægelse ved C2 / C3 og C3 / C4 og øgede deres anti-retningsbestemte bevægelse ved C5 / C6 og C6 / C7 under ekstension af det cervicale led og øgede den samlede anti- retningsbevægelse under cervical fleksion; 2) der blev ikke fundet nogen forskelle i PPT'er i forhold til bilaterale C2 / C3 og C5 / C6 facetled og den højre TA mellem patienter med tilbagevendende nakkesmerter og raske kontroller.

Forskellige effekter på anti-retningsbestemt bevægelse blev demonstreret, når smerter stammede i den dybe cervikale muskel, den overfladiske cervikale muskel og det inter-spinøse ledbånd. Patienter med tilbagevendende nakkesmerter viste ændret anti-retningsbestemte bevægelsesmønstre sammenlignet med raske kontroller. Imidlertid nedsatte eksperimentel cervikal muskelsmerter, ligamentsmerter og tryk sensibilitet over forskellige led i cervikale facetter, og patienter med tilbagevendende nakkesmerter viste ingen lokal og udbredt hyperalgesi. Resultaterne i afhandlingen indikerede, at den anti-retningsbestemte bevægelse var den mest følsomme over for eksperimentelle og kliniske nakkesmerter, og undersøgelser af anti-directional bevægelse kan bidrage til diagnosen af nakkesmerter, når man forsøger at identificere smertekilderne.

PREFACE

The PhD thesis includes three independent studies which are referred to as study I-III in the text. The three studies were conducted between 2016 and 2019 at Center for Sensory Motor Interaction (SMI), Department of Health and Science Technology, Faculty of Medicine, Aalborg University, Denmark and Vejgaard Chiropractic Clinic, Aalborg, Denmark. The thesis is based on the results of the three studies:

Study I

Ning Qu, Rene Lindstrøm, Rogerio Pessoto Hirata, Thomas Graven-Nielsen. Origin of neck pain and direction of movement influence dynamic cervical joint motion and pressure pain sensitivity. *Clin Biomech*. 2019, 61: 120-128

Study II

Ning Qu, Rene Lindstrøm, Thomas Graven-Nielsen, Rogerio Pessoto Hirata. Experimental cervical inter-spinous ligament pain altered cervical joint motion during dynamic extension movement and decreased pressure pain sensitivity in the neck. *Clin Biomech*. 2019, 65: 65-72

Study III

Ning Qu, Thomas Graven-Nielsen, Rene Lindstrøm, Victoria Blogg, Rogerio Pessoto Hirata. Recurrent neck pain patients exhibit altered joint motion pattern during cervical flexion and extension movements. *Clin Biomech*. 2019. Accepted.

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ABBREVIATION

ROM	Range of motion
PPT	Pressure pain threshold
CNS	Central nervous system
ICR	Instantaneous center of rotation
NRS	Numerical rating scale
NDI	Neck disability index
TA	Tibialis anterior
EMG	Electromyogram
SD	Standard deviation
SEM	Standard error of measurement
MDC	Minimal detectable change
ICC	intra-class correlation coefficient
RM-ANOVA	Repeated-measures analysis of variance

CONTENTS

CHAPTER 1. INTRODUCTION

1.1. OVERVIEW OF NECK PAIN

Neck pain is defined as pain perceived in the anatomic region of the neck[1, 2]. Neck pain is one of the most commonly reported musculoskeletal disorders and causes a substantial economic burden due to primary health care, absence from work and compensations[3, 4]. Around fifty percent of the adult population experience at least one episode of neck pain during their lifetime[5]. The 12-month prevalence of neck pain has been predominantly reported between 30% and 50%[5, 6]. Additionally, neck pain ranks fourth in leading causes of the global disabilities[7]. People aged 25 to 64 are the most frequently affected by neck pain[8]. The number of years lived with disability from neck pain causes increased 21.4% from the year 2007 to 2017[8]. Besides, the remission rate of neck pain at 1 year ranges from 33% to 65%[9], and approximate 50% to 75% of patients experiencing one episode of neck pain are more likely to report another episode in 1 to 5 years[10].

1.2. REQUIREMENTS IN DIAGNOSTIC EVALUATIONS OF NECK PAIN

One of the challenges in the management of neck pain is how to diagnose the causes of neck pain and provide effective therapies[11, 12]. Diagnosis is of fundamental importance in determining the therapeutic approach of neck pain. However, neck pain is a multifactorial disease influenced by many biological, psychological and psychosocial factors, which makes it difficult to identify the main contributors and their relevance to the consequences of neck pain[10, 13]. A large portion of neck pain is classified as non-specific[13, 14], since the underlying etiology of neck pain remains unclear[15]. In the absence of a clear pathological etiology, therapies tend to focus on addressing the symptoms or the physical impairments of neck pain. Therefore, the effects of current therapies on neck pain are heterogeneous[16-19]. Therefore, better diagnostic evaluations of neck pain are needed and will benefit the management of neck pain.

Although the psychological and psychosocial components of neck pain have attracted increasing attentions over the past years, the biological component is still under great research emphases and efforts have also been made to explore the biomechanical causes of neck pain[2, 13, 20, 21]. Many researchers propose that neck pain should have a local pathoanatomical basis which could be identified[1]. However, given the complexity of the cervical structures (muscles, ligaments, discs and facet joints, etc.), identifying the pain sources of neck pain is clinically challenging. As a consequence, potential injuries in these structures may be ignored and left without proper treatments, which may contribute to a further episode of neck pain.

The diagnosis of neck pain is normally based on clinical assessments of the signs and symptoms of neck pain. Several issues are preventing clinicians from linking the clinical assessments to the contribution of a specific cervical tissue in patients with neck pain. One is that the causal relationship between pain and the clinical presentations could not be clarified in most of the patients with neck pain. It remains unclear whether neck pain causes the clinical presentations or the clinical presentations cause neck pain. Another one is that the current parameters are not capable of reflecting the causes of neck pain in terms of anatomical site, pathology and mechanisms[11, 22], and they are not always capable of differentiating patients with neck pain from healthy subjects[23].

Dynamic cervical joint motion parameters during neck movements are supposed to reveal more impairments related to neck pain at individual cervical joint levels when comparing with motion assessments made on static and end-range radiographs[24-28]. In addition, pressure pain sensitivity is widely investigated in patients with neck pain and applied to subgroup patients with neck pain[29-35]. These two parameters also show potential diagnostic values of reflecting the sources of neck pain[36-39].

Motor and sensory systems are mostly affected in patients with neck pain. The multifactorial nature of neck pain determines that one single assessment may not be sufficient to make the diagnosis of neck pain and making the diagnosis of neck pain needs to combine the results of several assessments. Therefore, it is of clinical advantages to simultaneously investigate the effects of neck pain on motor and sensory perspectives. A better understanding of the effects of neck pain on dynamic cervical joint motion and pressure pain sensitivity may help to improve the diagnosis and treatment of neck pain.

1.3. CERVICAL MUSCLES AND LIGAMENTS

A substantial number of patients with neck pain are assumed to have a biomechanical cause related with muscular and ligamentous factors[12, 40]. Cervical ligaments and muscles are the potential sources of neck pain, however, the current imaging tools (e.g. Magnetic Resonance Imaging (MRI), computed tomography (CT) and ultrasound) could not completely identify the structural damage especially when there are no major histologic changes[2, 13]. It is important to differentiate cervical muscle dysfunctions from cervical ligament dysfunctions, since injuries in these two structures require different treatments[20, 41]. Dysfunctions of cervical muscles were widely reported in patients with neck pain in previous studies[42, 43]. Deep cervical muscles normally showed decreased activity while superficial cervical muscles showed increased activity in patients with neck pain[42, 43]. Additionally, cervical ligament dysfunctions also caused alterations in cervical muscle activities [44]. The functional roles of cervical muscles and ligaments in neck movements are different.

Three interactive systems are involved in the motor control of neck movements: the active system (cervical muscles), the passive system (vertebrae, intervertebral discs, ligaments, joint capsules, and facet joints, etc.) and the neuromuscular control system[45, 46]. Cervical muscles are the direct motion performers and dynamic stabilizers of the cervical joints while the cervical ligaments are crucial passive stabilizers[47, 48]. There are around 20 pairs of cervical muscles surrounding the cervical spine column including deep and superficial muscles[49]. The deep cervical muscles, typically attach to the cervical vertebrae directly with a small moment during neck movements, are supposed to control individual cervical joint motion (e.g. longus colli, longus capitis, and multifidus muscles)[49, 50]. Conversely, superficial cervical muscles normally cross several cervical vertebrae or the entire cervical spine and work as the posture maintainers and movement initiators (e.g. sternocleidomastoid and trapezius muscles). Therefore, superficial cervical muscles have no direct controls on individual cervical joints[49, 50]. Cervical ligaments do not have active functions as cervical muscles. Cervical ligaments were thought to only have mechanical roles[51]. However, the two systems are connected by ligamento-muscular reflex and neuromuscular control system[52-54]. Dysfunctions in cervical ligaments also affect the cervical muscle functions involved in the same neck movement[44]. The neuromuscular control system refers to the central and peripheral nervous systems controlled and reflex-mediated muscular contraction in response to the neck movements.

Deep and superficial cervical muscles are different in terms of anatomy, function, and density of nociceptors[49, 50, 55]. Previous experimental pain studies also showed that pain originating in the deep and superficial cervical muscles caused different recruitment strategies of cervical muscles during motor tasks, which indicated the different roles of deep and superficial cervical muscles in neck movements[56]. Neck pain was linked to altered motor control of neck movements but the extent to which deep and superficial muscle pain influences individual cervical joint motion during neck movements remains unstudied[57-61]. Exploration of this relationship may provide a rational background for treatments aiming specifically at deep and superficial cervical muscles in nonspecific neck patients[62, 63]. Cervical ligaments were traditionally supposed to have only mechanical roles, such as inter-spinous ligament which was historically considered to limit the cervical joint motion at the extremes of cervical flexion[28, 51]. However, emerging evidence showed that passive cervical tissues also provided proprioceptive information to the central nervous system (CNS) throughout the entire motion cycle as well as muscles and affected the neuromuscular control system[64, 65]. Investigating the effects of cervical ligament pain on dynamic cervical joint motion during neck movements may provide valuable information to the diagnosis of ligament injuries.

1.4. CERVICAL PROPRIOCEPTION

The proprioception, afferent sensory information concerning the sense of position, movement, force, and effort, is essential to the neuromuscular control system and could be influenced by pain[66]. Both active and passive cervical structures provide proprioception to the CNS[64, 65]. Pain originating in cervical structures will lead to proprioceptive deficits and result in altered movement patterns and each cervical structure has its functional role in a specific neck movement[67]. The dynamic cervical joint motion during neck movements depends on instant proprioceptive feedbacks from each cervical structure[64, 65]. Dynamic cervical joint motion, therefore, is supposed to be sensitive to reflect the dysfunction of a specific cervical structure. Previous studies have demonstrated proprioceptors in both cervical muscles and ligaments and the densities of proprioceptors are different between cervical structures[55, 68-70]. However, it remains unclear if pain sources will have different effects on the dynamic cervical joint motion parameters[71].

1.5. ADVANTAGES OF DYNAMIC CERVICAL JOINT MOTION

Cervical range of motion (ROM) has been routinely assessed in the clinical practice to assist clinicians with diagnosis, treatment, and prognosis of neck disorders[15, 67, 72]. Neck pain is normally associated with reduced cervical ROM[73-77]. However, most of the previous studies only investigated the cervical ROM or regional cervical ROM (upper, middle and lower cervical spine regions) but individual cervical joint motions could not be obtained from those assessments. Cervical joint motion reflects the conditions of the surrounding soft tissues. Assessments of cervical joint motion can provide more information to identify dysfunctions related to neck pain at the individual cervical joint levels compared with cervical ROM[78-81]. Additionally, the assessment of cervical joint motion is also applied to evaluate the efficiency of physical treatments and surgeries operated on the neck[23, 82]. However, previous imaging studies were limited to static and end-range radiographs, the assessments based on which cannot reflect the dynamic characteristics of neck activities in daily life, especially during the middle motion ranges of neck movements[83]. Anderst et al. (2013) demonstrated the maximum cervical joint motion occurred before reaching the end of the cervical flexion and extension and cervical joints did not reach their maximum range of motion simultaneously[84]. The cervical ROM and cervical joint motion assessed on static and end-range radiographs could not always show differences between patients with neck pain and healthy controls, which indicated they may not be sensitive enough to detect the functional cervical disorders[23, 85, 86]. Furthermore, weak relationships were demonstrated previously between neck pain symptoms and motion assessments on static and end-range radiographs[15, 87]. Therefore, there is an increasing demand to drive the researches to explore dynamic characteristics of neck movements, where the abnormal motions and dysfunctions were postulated to occur (**Appendix A**). Dynamic characteristics of neck movements have not been completely understood. However, the investigation of dynamic motion parameters is supposed to provide valuable information for the diagnosis and treatment of neck pain[88, 89].

With regards to dynamic motion parameters, Sjolander et al. (2008) and Bahat, Weiss, & Laufer (2010) both demonstrated reduced motion velocity and smoothness in patients with neck pain compared to healthy controls but without differences in cervical ROM between the two groups[61, 90]. These studies again implied the dynamic motion parameters were more informative and sensitive to neck pain compared with motion assessments on static and end-range radiographs. However, these studies only investigated the entire cervical spine that the dynamic motion status of individual cervical joints is still incompletely understood. Researchers have started to investigate dynamic cervical joint motion during cervical flexion and extension separately or during the full range of flexion-extension[26, 27, 91-95]. Wu et al. (2007, 2010) have studied cervical joint motion during three and ten even ranges of neck movements in the sagittal plane in healthy subjects[27, 95]. They demonstrated the patterns of cervical joint motion during cervical flexion and extension were non-linear and the cervical joint motion was unevenly distributed among different ranges of neck movements and the contribution to the cervical ROM was different between cervical joints[27, 95]. Anderst et al. (2013, 2015) investigated cervical joint motion during the full range of flexion-extension in healthy subjects[91, 92]. They demonstrated similar non-linear cervical joint motion patterns and the contribution to cervical ROM varied between cervical joints during different ranges of neck movements[91, 92].

Among these studies, Wang et al. (2017) showed that the cervical joints commonly presented reversal motions to the intended movement direction during cervical flexion and extension[94]. They defined the motion opposite to the primary movement direction as anti-directional motion and defined the motion along with the primary movement direction as pro-directional motion[94]. The anti-directional motion phenomenon is a unique feature of the neck which is described but not quantified previously[39]. Wang et al. (2017) further quantified the anti- and pro-directional motion and showed that the anti-directional motion was approximately 40% of the pro-directional motion[94]. This finding may explain why no significant difference in cervical joint motion was found between patients and healthy subjects in some previous studies[61, 90]. The cervical joint motion consists of anti-directional motion and pro-directional motion. The anti-directional motion can be explained by changes in the relative position between the force vector and the instantaneous center of rotation (ICR) of the cervical vertebrae during neck movements[39]. Wang et al. (2018) further demonstrated the cervical joint motion patterns during flexion and extension were repeatable[96]. Therefore, dynamic cervical joint motion parameters, such as the anti-directional motion, were thought to be important to understand impairments related to neck pain.

1.6. PRESSURE PAIN SENSITIVITY

The International Association for the Study of Pain (IASP) defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”[97]. Pain

sensitivity could be assessed by a range of thermal, electrical, chemical and mechanical methods, of which the most commonly used in researches is the mechanical stimuli[98]. Pressure pain threshold (PPT) is defined as the minimal amount of pressure producing the detectable pain sensation[99]. Changes in PPTs reflect the underlying pain processing mechanisms of different pain conditions and assist clinicians with the diagnosis of neck pain[31, 100, 101]. Moreover, PPTs are also used to predict the prognosis of neck pain[33, 102]. The decrease in PPTs indicates enhanced responses to the mechanical painful stimulus and the phenomenon is defined as hyperalgesia, while the increase in PPTs indicates weakened responses to the mechanical painful stimulus which is defined as hypoalgesia[103-105]. Localized hyperalgesia over the injury tissue reflects the sensitization of peripheral nociceptors[103, 104, 106]. On the other hand, hyperalgesia over a remote area out of the original injury tissue is likely to reflect augmented central pain processing mechanisms[33, 107]. The hyperalgesia over a remote area is defined as widespread hyperalgesia. Patients showing widespread hyperalgesia normally have poor recovery and may develop into chronic neck pain [33, 102, 108]. Although the changes in pressure pain sensitivity were showed to be pain sources related[36-38, 109, 110], the relationship between pain sources of neck pain and changes in pressure pain sensitivity has never been investigated. Different results were demonstrated in PPTs over areas out of the pain site when experimental pain was induced in different structures[36-38]. However, experimental pain induced in deep muscles and tendons/ligaments was prone to decrease PPTs over the areas out of the pain site[36-38]. Additionally, patients with neck pain normally showed localized hyperalgesia in the neck, while widespread hyperalgesia was only demonstrated in some subgroups of patients with neck pain and little is known about the pressure pain sensitivity in patients with recurrent neck pain[29, 30]. Widespread hyperalgesia indicates a poor recovery from neck pain which may lead to the recurrence of neck pain[111]. Investigations of localized and widespread hyperalgesia in patients with recurrent neck pain may be of clinical importance which may contribute to a better understanding on the recurrence of neck pain.

1.7. EXPERIMENTAL NECK PAIN MODELS AND RECURRENT NECK PAIN

The experimental pain models could solve the issue of the unclear causal relationships between pain sources and motor/sensory alterations in patients with neck pain. By applying experimental neck pain models, it is possible to clarify the effects of pain originating in a specific cervical structure on dynamic cervical joint motion and pressure pain sensitivity[112-114]. The recurrent neck pain is chosen because the acute neck pain will either recover or become recurrent and the recurrence rate of neck pain is high[115]. The previous episode of neck pain is a strong risk factor for the further recurrences of neck pain[10, 116, 117]. Therefore, the pain sources of patients with recurrent neck pain were thought not to have been properly addressed. Previous studies demonstrated that alterations in motor control and sensory systems did not return to the normal level when the pain was gone, which indicated the persistent motor and sensory changes may lead to the recurrence of neck pain[60, 118-120]. However, previous studies mainly investigated the alterations of muscle activity or muscle recruitment patterns in patients with neck pain. Whether the cervical joint motion is affected by the changes of cervical muscle activities remains unclear. Additionally, when neck pain becomes chronic, more tissues and factors may be involved which will consequently be difficult to identify the initial pain sources. Therefore, a better understanding of recurrent neck pain may help to prevent patients from developing into chronic neck pain.

1.8. AIMS OF THE PHD THESIS

The thesis aimed to investigate the effects of neck pain on dynamic cervical joint motion and pressure pain sensitivity in experimental neck pain models and recurrent neck pain patients. The overview of the PhD thesis was shown in **Fig.1**.

Three research questions were raised and answered from the underlying studies:

Research question 1: Does the pain originating in deep and superficial cervical muscles have different effects on dynamic cervical joint motion and pressure pain sensitivity over cervical facet joints?

Research question 2: Does the pain originating in cervical ligaments affect dynamic cervical joint motion and pressure pain sensitivity over cervical facet joints?

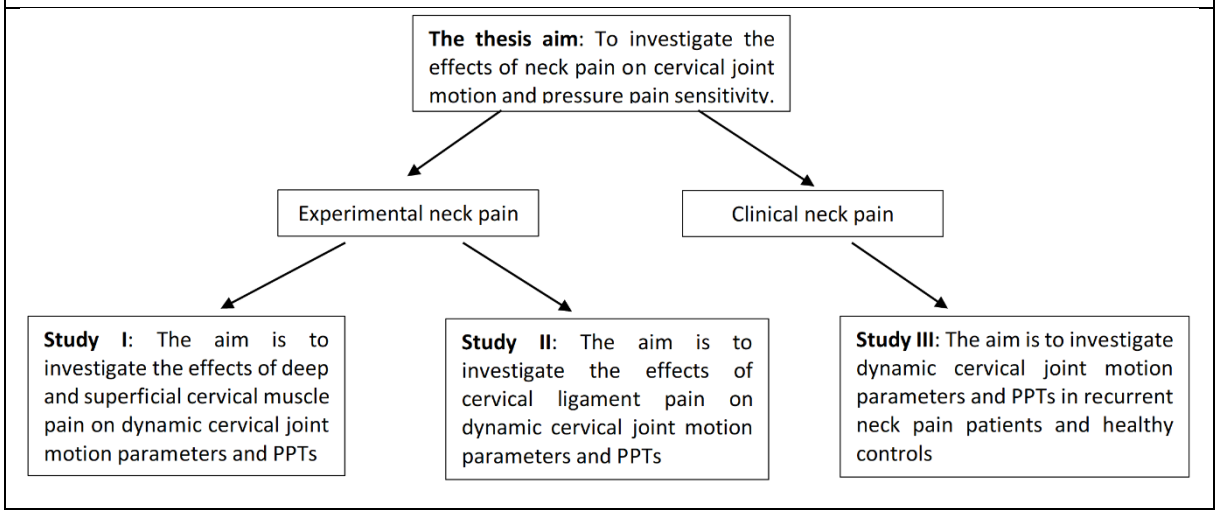
Research question 3: Do patients with recurrent neck pain show altered dynamic cervical joint motion patterns and pressure pain sensitivity when compared with healthy controls?

Study I: the aim is to investigate the effects of deep and superficial cervical muscle pain on dynamic cervical joint motion parameters and PPTs over bilateral C2/C3 and C5/C6 facet joints.

Study II: the aim is to investigate the effects of cervical inter-spinous ligament pain on dynamic cervical joint motion parameters and PPTs over bilateral C2/C3 and C5/C6 facet joints.

Study III: the aim is to investigate dynamic cervical joint motion parameters and PPTs over bilateral C2/C3 and C5/C6 facet joints and right tibialis anterior (TA) in patients with recurrent neck pain and healthy controls.

Figure 1. The overview of the PhD thesis



1.9. HYPOTHESES

The overall hypothesis: neck pain will significantly affect dynamic cervical joint motion patterns and pressure pain sensitivity compared with either pain free conditions (study I and study II) or healthy match controls (study III).

To answer the specific research questions, the following hypotheses were proposed for each of the three studies:

Hypotheses of **Study I**:

1) Deep cervical muscle pain will significantly affect individual cervical joint motion;

2) Superficial cervical muscle pain will significantly affect the entire neck motion;

3) Deep cervical muscle pain will significantly decrease PPTs over bilateral C2/C3 and C5/C6 facet joints;

4) Superficial cervical muscle pain will significantly increase PPTs over bilateral C2/C3 and C5/C6 facet joints

Hypotheses of **Study II**:

1) Cervical inter-spinous ligament pain will significantly affect individual cervical joint motion;

2) Cervical inter-spinous ligament pain will significantly decrease PPTs over bilateral C2/C3 and C5/C6 facet joints.

Hypotheses of **Study III**:

1) Patients with recurrent neck pain will show significant alteration in dynamic cervical joint motion patterns when compared with healthy controls;

2) Patients with recurrent neck pain will show a significant decrease of PPTs over bilateral C2/C3 and C5/C6 facet joints and over the right TA when compared with healthy controls.

CHAPTER 2. OVERVIEW OF STUDY DESIGNS, SAMPLE SIZES AND STATISTICS

2.1. STUDY DESIGNS

Study I: A repeated-measure study design was used with the application of experimental cervical muscle pain models in a healthy subjects group (**Fig.2**). Subjects were to attend two experimental sessions separated by a seven-day interval. In the first session, baselines of PPTs over the cervical facet joints and fluoroscopy videos of neck movements were first measured. During the assessment of neck movements, the subjects were instructed to flex and extend their neck from the self-determined neutral position to the maximal end-range position. After the baseline assessments, the experimental pain was induced either in the multifidus muscle or in the trapezius muscle by injecting 0.5 ml of hypertonic saline (5.8%). The PPTs over the cervical facet joints and fluoroscopy videos of neck movements were measured again after the injection. Pain intensity, pain duration and pain distribution of the experimental pain were recorded after the injection. In the second session, the subjects underwent the same procedures but experimental pain was induced in the previously unused cervical muscle. The injection order of the two cervical muscles was randomized across the two experimental sessions. A 7- day washout interval was chosen to mitigate the potential effects of the previous injection.

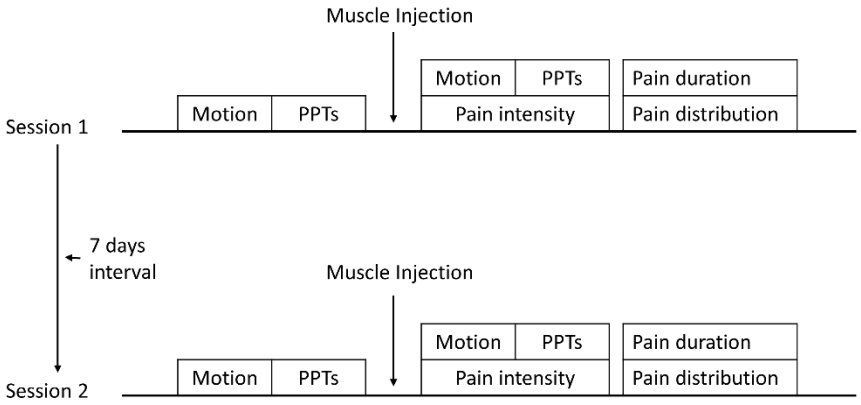


Figure 2. The experiment flow of study I. Motion represents cervical flexion and extension movements; PPTs: pressure pain thresholds.

Study II: The study design was the same as study I (**Fig.3**). However, the experimental cervical ligament pain model was applied instead of the experimental cervical muscle pain model in a healthy subjects group. The study contained two experimental sessions separated by a seven-day interval. In the first session, baselines of PPTs over the cervical facet joints and fluoroscopy videos of cervical flexion and extension were first measured. After the baseline assessments, either 0.2 ml of hypertonic saline (5.8%) or isotonic saline (0.9%) was injected into the C4/C5 inter-spinous ligament. The hypertonic saline injection was used to induce experimental pain, while the isotonic saline injection was used as a control condition. The PPTs over the cervical facet joints and fluoroscopy videos of neck movements were measured again after the injection. Similarly, pain intensity, pain duration, and pain distribution were recorded after the injection. In the second session, the subjects underwent the same procedures but with the injection of the previously unused saline concentration. The injection order of the two saline concentrations was randomized across the two experimental sessions. A 7- day washout interval was chosen to mitigate the potential effects of the previous injection.

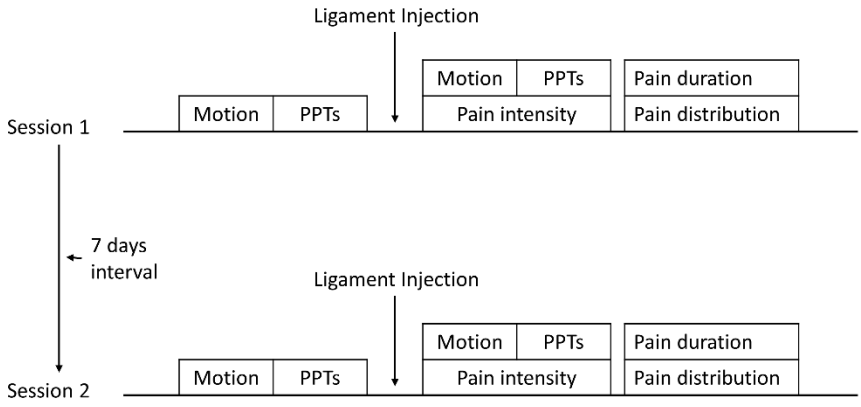


Figure 3. The experiment flow of study II. Motion represents cervical flexion and extension movements; PPTs: pressure pain thresholds.

Study III: Two groups of participants were recruited: one recurrent neck pain patient group and one age- and gender-matched healthy control group. Patients were examined during their recurrence of neck pain. Patients were assessed in terms of PPTs over cervical facet joints and the right TA, fluoroscopy videos of cervical flexion and extension, neck disability index (NDI), pain intensity and pain distribution. The healthy controls were assessed for PPTs over cervical facet joints and the right TA, and fluoroscopy videos of cervical flexion and extension (**Fig.4**).

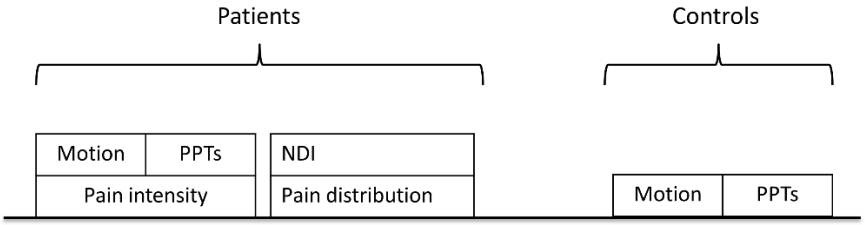


Figure 4. The experiment flow of study III. Motion represents cervical flexion and extension movements; PPTs: pressure pain thresholds; NDI: neck disability index.

The assessment parameters applied in three studies were summarized in **Table 1**.

Table 1. The overview of assessments in the three studies.

Parameters	**Study I**	**Study II**	**Study III**
Pain intensity	✓	✓	✓
Pain duration	✓	✓	
Pain distribution	✓	✓	✓
NDI			✓
PPTs	✓	✓	✓
Motion	✓	✓	✓

Motion: cervical flexion and extension movements; PPTs: pressure pain thresholds; NDI: neck disability index.

2.2. SAMPLE SIZES AND PARTICIPANTS RECRUITMENT

Study I and study II: No previous studies have investigated the new developed cervical joint motion parameters (anti-directional motion, pro-directional motion, total joint motion, and joint motion variability) in either experimental pain studies or patients with neck pain. Therefore, there is no prior information from which to base a sample size calculation. Therefore, the effect size of 0.25 was chosen to calculate the sample size in study I and study II. At a significance level of 0.05, power of 0.9 and effect size of 0.25, it was calculated that a minimum of fourteen participants was required for a repeated measure design study (G*Power, version 3.1). To allow for one drop out, fifteen participants were recruited for study I and study II respectively. Although some previous studies have shown a slight gender effect on neck movements (e.g. primary extension) in healthy subjects[121], the gender balance was not controlled in study I and study II since the aim was to investigate the effect of experimental neck pain on cervical joint motion in a repeated-measure designed study.

Inclusion criteria: Healthy participants were included if they had no neck pain for the last three months.

Exclusion criteria: Healthy participants were excluded if they had: (1) Cervical trauma or surgery, (2) Cervical musculoskeletal diseases, (3) Psychosocial profile (depressive, bipolar, anxiety, etc.) that would affect the responsiveness to the pain, (4) Inability to cooperate and (5) Possibility of pregnancy.

Study I: Nine male and six female healthy participants were recruited (age: 25.1years (SD 4.7), height: 172.7 cm (SD 11.6) and weight: 70.0 kg (SD 13.6).

Study II: Eleven male and four female healthy participants were recruited (age: 27.4 years (SD 6.5), height: 173.7 cm (SD 11.5) and weight: 73.6 kg (SD 11.8).

Study III: The sample size was calculated based on motion findings in the previous experimental neck pain studies published by our research team[24, 28]. The effect sizes of the experimental neck pain on cervical joint motion parameters (anti-directional motion, pro-directional motion, total joint motion, and joint motion variability) at individual cervical joint levels ranged from 29.9% to 71.1%[24, 28]. Considering the high inter-variability in patients, the effect sizes of clinical neck pain on the cervical joint motion parameters were assumed to be smaller when compared with experimental neck pain. A 20% change in individual cervical joint motion is assumed to be clinically relevant[122]. In order to have enough power to detect significant alterations in all the cervical joint motion parameters, the effect size of 0.2 was chosen to calculate the sample size. At a significance level of 0.05, power of 0.9 and effect size of 0.2, it was calculated that a minimum of seventeen participants was required in each group (G*Power, version 3.1). To allow for one drop out, eighteen participants in each group were recruited.

Inclusion criteria: Patients were defined to have recurrent neck pain and included in the study if they met the following criteria: 1) at least three self-reported episodes of neck pain separated by episodes of pain remission during the last 12 months; 2) the pain symptoms last more than 24 hours with limited activities of daily living during episodes of neck pain; 3) pain remission episodes last at least 1 month without the pain symptoms; 4) the patient had a diagnosis of non-specific neck pain. Additionally, patients were to be examined during the episode of neck pain in the study and the pain rating was required to be higher than 3/10 on the 10-cm Numerical Rating Scale (NRS) anchored with “no pain” at 0 cm and “the worst possible pain” at 10 cm. Healthy participants were included if they had no neck pain for the last three months.

Exclusion criteria: Patients were excluded if they had any 1) Spinal pathology and radiating signs, 2) Other musculoskeletal diseases, 3) Neurological disorders, 4) History of cervical fractures or whiplash, 5) Cervical spine surgery, 6) Systematic diseases and 7) Recent or current pregnancies. Healthy participants were excluded if they had: (1) Cervical trauma or surgery, (2) Cervical musculoskeletal diseases, (3) Psychosocial profile (depressive, bipolar, anxiety, etc.) that would affect responsiveness to pain, (4) Inability to cooperate and (5) Possibility of pregnancy.

Study III: Eighteen patients (eleven females) with recurrent neck pain (age: 34.7 years (SD 11.4), height: 171.5 cm (SD 7.7), weight: 71.9 kg (SD 14.8) and BMI: 24.2 kg/m^2 (SD 3.6)) and eighteen (eleven females) age- and gender-matched healthy controls (age: 34.6 years (SD 12.3), height: 168.1 cm (SD 9.9), weight: 64.3 kg (SD 14.3) and BMI: 22.6 kg/m^2 (SD 3.2)) were recruited.

2.3. STATISTICAL ANALYSIS

Statistical analyses were performed in SPSS (IBM Statistics 24). Before statistical comparisons, all data were tested for normality by the Kolmogorov-Smirnov test and the normality of the data was confirmed. Additionally, the sphericity was tested by the Mauchly's test. If the assumption of sphericity was violated, Greenhouse-Geisser corrections were used.

The pain distribution, peak pain intensity, and pain duration were compared between conditions in study I and study II by paired t-test (Study I: between multifidus and trapezius muscle pain; Study II: between hypertonic saline and isotonic saline injections).

PPTs were analyzed separately for each condition in study I and study II (Study I: multifidus and trapezius muscle pain; Study II: hypertonic saline and isotonic saline) by two-way repeated-measures analysis of variance (RM-ANOVA) with two within-group factors: Measurement site (right C2/C3, left C2/C3, right C5/C6 and left C5/C6) and Condition (before pain, during pain). For study III, PPTs were analyzed by two-way RM-ANOVA with Measurement site (right C2/C3, left C2/C3, right C5/C6, left C5/C6 and TA) as the within-group factor and Group (patient, control) as the between-group factor.

The dynamic cervical joint motion parameters were analyzed separately for flexion and extension in each condition in study I and study II (Study I: multifidus and trapezius muscle pain; Study II: hypertonic saline and isotonic saline) by two-way RM-ANOVA with two within-group factors: Joint (C0/C1, C2/C3, C3/C4, C4/C5, C5/C6 and C6/C7) and Condition (before pain, during pain). For study III, the dynamic cervical joint motion parameters were analyzed separately for flexion and extension by two-way RM-ANOVA with Joint (C0/C1, C1/C2, C2/C3, C3/C4, C4/C5, C5/C6 and C6/C7) as the within-group factor and Group (patient, control) as the between-group factor.

All ANOVAs were corrected for the family-wise error. If the significance remained, a Bonferroni post hoc analysis was performed for multilevel comparisons. P-values < 0.05 were considered as significant.

CHAPTER 3. CHARACTERISTICS OF EXPERIMENTAL AND CLINICAL NECK PAIN

3.1. EXPERIMENTAL NECK PAIN MODELS

Most previous studies investigating motor and sensory changes in patients with neck pain were not able to tell if the pain caused the motor/sensory alterations or the pain was the result of the motor/sensory alterations[123]. Human experimental pain models have been extensively applied to explore the cause-effect relationship between pain and motor/sensory alterations[105, 112, 113, 124-126]. One advantage of experimental pain models is that the pain quality is comparable to the clinical pain[104, 127]. Another advantage of experimental pain models is that the pain is standardized and clears up the confounding factors usually found in patients[104]. Back in the 1940s, the injection of hypertonic saline was initially used to induce experimental muscle pain[128]. Since then, the hypertonic saline injection was applied in different human tissues to establish different experimental pain models[36-38, 109]. Normally, the injection of isotonic saline into the same tissue was used as a control condition[56, 113, 129, 130]. In this PhD thesis, the experimental muscle and ligament pain models were applied in study I and study II, respectively. All the injections in study I and study II were conducted by an experienced radiographer under the ultrasound guide. The location of the target structure was confirmed by NQ and the radiographer together. Ultrasound-guide injection was widely applied in previous experimental pain studies and the ultrasonography showed acceptable reliability and validity in assessing cervical structures[131-134].

3.1.1. DEEP AND SUPERFICIAL MUSCLE PAIN

In study I, the experimental pain was induced by injecting 0.5 ml of sterile hypertonic saline (5.8%) in the right cervical multifidus and trapezius muscles, respectively. The injection site of the right multifidus muscle was the deepest layer at the C4 level. The muscle fasciculation lies between the right articular pillar of C5/C6 joint and the right side of C3 laminae. The C4 spinous process was first identified by palpation and the ultrasound scanner was then placed over the C4 spinous process in the horizontal plane. The examiner slid the ultrasound scanner to the right side with 1 cm away from the midline. The target multifidus fasciculation was located at the junction between the spinous process and the vertebral laminae. The needle was proceeded to the junction directly (**Fig.5**). The injection site of the right trapezius muscle was located at the midpoint of C7 spinous process and the right acromion. The hypertonic saline was injected slowly into the multifidus and trapezius muscles.

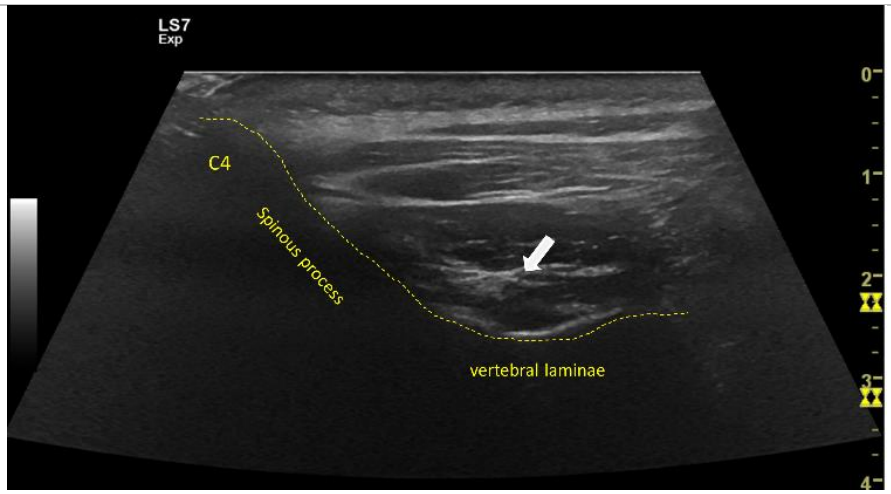


Figure 5. The injection site of the right multifidus muscle at C4 level under ultrasound guide in the view of the horizontal plane. The white arrow indicated the location of the multifidus muscle. The dash line indicated the outline of C4 spinous processes and the right vertebral laminar.

3.1.2. INTER-SPINOUS LIGAMENT PAIN

The density and sensitivity of nociceptive afferents in ligaments are higher than those in cervical muscles[37, 109, 135]. Therefore, lower volumes of hypertonic saline should be applied in order to induce comparable pain intensity as with cervical muscle pain[28, 109]. In study II, the experimental pain was induced by injecting 0.2 ml of sterile hypertonic saline (5.8%) in the C4/C5 inter-spinous ligament. A 0.2 ml of sterile isotonic saline (0.9%) was injected in the same inter-spinous ligament as a control condition. The subjects needed to keep their neck at a flexion position to tighten the neck skin and enlarge the space between the two adjacent cervical spinous processes. The examiner first palpated the C4 spinous process to determine the general injection location and then used the ultrasound scanner to confirm the accurate location. The ultrasound scanner was placed in the sagittal plane along the midline, the C4, C5 and C6 spinous processes were identified in the view (**Fig.6**). Then the ultrasound scanner was slid to the top of C5 spinous process to make space for the injection. During the injection, the needle was against the C5 spinous process with 45 degrees to the direction of the spinous process. The needle went through several layers including skin, subcutaneous tissue, and supra-spinous ligament. When the needle reached the supra-spinous ligament, the examiner would feel a strong resistance and needed to increase the force to reach the middle part of the C4/C5 inter-spinous ligament. The hypertonic saline and the isotonic saline were injected slowly into the inter-spinous ligament.

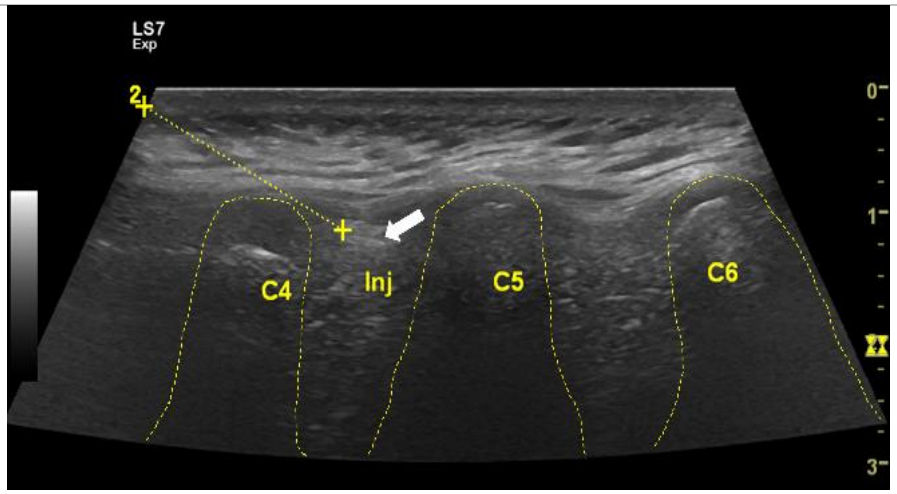


Figure 6. The injection site of C4/C5 inter-spinous ligament under ultrasound guide in the view of the sagittal plane. The white arrow indicated the location of the inter-spinous ligament and the hypertonic saline. The dash lines indicated the outlines of C4, C5 and C6 cervical spinous processes. Inj: injection site.

3.2. ASSESSMENT OF PAIN PARAMETERS

Pain is commonly characterized by its intensity, duration, and distribution. Pain intensity could be assessed by several tools, of which the Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Verbal Rating Scale (VRS) and Faces Pain Scale-Revised (FPS-R) are commonly used by clinicians and researchers[136]. Among those measurement tools, the NRS was the most sensitive and responsive tool which can be administered verbally or graphically for self-completion[136, 137]. The NRS is an 11-point numeric scale anchored with 'no pain' at 0 cm and 'worst pain imaginable' at 10 cm[136, 137]. The NRS is a valid tool with high reliability to assess pain intensity in clinical settings and researches[136, 137]. In study I and study II, the pain intensity was recorded every minute after the injections until the pain vanished in each experimental session. The peak pain intensity was extracted for the final analysis. In study III, the pain intensity of patients with recurrent neck pain was recorded at the beginning of the study. Pain duration was calculated as the time from the onset of the pain to the disappearance of the pain after injections in study I and study II. Pain distribution is a useful sign that helps clinicians to understand the pathology of neck pain and classify patients with neck pain[138]. Pain distribution was drawn on a body chart at the end of each session by participants in study I and study II[24, 28]. In study III, the pain distribution of patients with recurrent neck

pain was recorded at the beginning of the study. Pain distribution was extracted into data in arbitrary units (a.u.) via VistaMetrix (version.1.38.0; SkillCrest, LLC, Tucson, AZ, USA) for analysis[24, 28, 113].

3.3. ASSESSMENT OF FUNCTIONAL DISABILITY

Patients with neck pain are usually associated with different levels of functional disabilities[123-125]. Neck Disability Index (NDI) questionnaire is a standardized instrument for assessing the severity of disabilities caused by neck pain and shows good reliability and validity[139]. The NDI includes 10 items with 6 score-different selections under each (0: no disability, 5: disability). The total score out of 50 was calculated. Lower NDI score indicates lower pain and disability, and vice versa. According to the total score, the disability was classified into five levels: 0-4 = none; 5-14 = mild; 15-24 = moderate; 25-34 = severe; over 34 = complete disability[140]. Patients with recurrent neck pain in study III completed the NDI questionnaire at the beginning of the study. The average NDI score of the patients with recurrent neck pain is 16.7. The NDI was previously reported to be related to PPTs and neck motion functions[100, 141-143].

3.4. COMPARISON BETWEEN EXPERIMENTAL AND CLINICAL NECK PAIN

3.4.1. PAIN INTENSITY AND DURATION

Hypertonic saline injection produces the pain sensation by depolarizing membranes of the nociceptors in cervical tissues[144, 145]. The pain sensation following hypertonic saline injections is resulted from the activation of group III (Adelta-fiber) and group IV (C-fiber) nociceptors[146-148]. These types of nociceptors are found in both muscles and ligaments[36, 109, 149-151]. Different words have been used to describe the experimental pain sensation following hypertonic saline injection such as pressing, drilling, annoying, throbbing, aching, sharp and sore, etc.[109, 152, 153]. The muscle pain was mostly described as cramp-like and diffuse-aching, while the ligament pain was mostly described as aching, sharp and throbbing[109]. The deep and superficial cervical muscle pain induced by hypertonic saline showed similar patterns of pain intensity against time (**Fig.7**)[24]. The pain characteristics of experimental and clinical neck pain were summarized in **Table 2**. The peak pain intensity was 6.1 ± 2.1 cm for multifidus muscle pain and 5.5 ± 2.2 cm for trapezius muscle pain (Study I)[24]. The pain duration was 8.3 ± 1.7 minutes for multifidus muscle pain and 7.9 ± 2.3 minutes for trapezius muscle pain (Study I)[24]. The pain intensity and pain duration were consistent with previous experimental muscle pain models[56, 112, 113, 152]. Previous studies showed that hypertonic saline injection in the deep back muscles produced higher pain intensity compared to the same volume of hypertonic saline injected in the superficial back muscles[110]. Although pain induced in the deep cervical muscle (Multifidus) showed a slightly higher peak pain intensity compared to pain induced in the superficial cervical muscle (Trapezius) following the injection of hypertonic saline, the difference was not statistically significant[24]. The variations of pain intensity following the uniform injection of hypertonic saline (volume and concentration) may be explained by the different density and sensitivity of nociceptive afferents between deep and superficial cervical muscles[154-156]. The duration of experimental pain induced by hypertonic saline may depend on the absorbing rate of the substance or the spreading rate to nearby tissues[109, 155]. Tissues containing a rich vascular system and surrounded by loose connective tissues could increase the absorbing process and result in a shorter pain duration compared with tissues lacking vascularities[109, 155].

The peak pain intensity after hypertonic saline injection in the inter-spinous ligament was 5.0 ± 2.2 cm and the pain duration was 7.8 ± 3.2 minutes (Study II)[28]. Previous studies have shown that the same volume of hypertonic saline produced different pain intensities and pain distributions when injected in different anatomical structures[36, 109, 110]. Normally, the experimental pain induced in ligaments showed higher pain intensity compared with muscles[36, 109], which indicated the density and sensitivity of nociceptive afferents in ligaments are higher than in muscles[37, 109, 135]. Additionally, the pain duration following hypertonic saline injection in ligaments was longer compared with the pain duration following the same volume of hypertonic saline injection in muscles[36, 109]. Therefore, in order to produce comparable pain characteristics between the cervical inter-spinous ligament and cervical muscles, a lower volume (0.2ml) of hypertonic saline was used which was less than 1/2 compared to the volume (0.5ml) applied in experimental cervical muscle pain models. The peak pain intensity and pain duration of experimental ligament pain were comparable to what was found in the above mentioned experimental cervical muscle pain. The injection of isotonic saline in the inter-spinous ligament (Study II) produced a quite low peak pain intensity (0.9 ± 1.2cm) and short pain duration (1.7± 2.6 minutes)[28]. The pain following the injection of isotonic saline lasted around 9 minutes in **Fig.7** and was due to one subject reporting a low pain intensity for a long duration (Study II)[28]. The isotonic saline was normally used as a control condition when exploring the relationship between pain and motor/sensory effects[56, 112]. The short pain duration and low pain intensity of isotonic saline injection in inter-spinous ligament indicated the pain induced by hypertonic saline was not related to the osmotic effect[109].

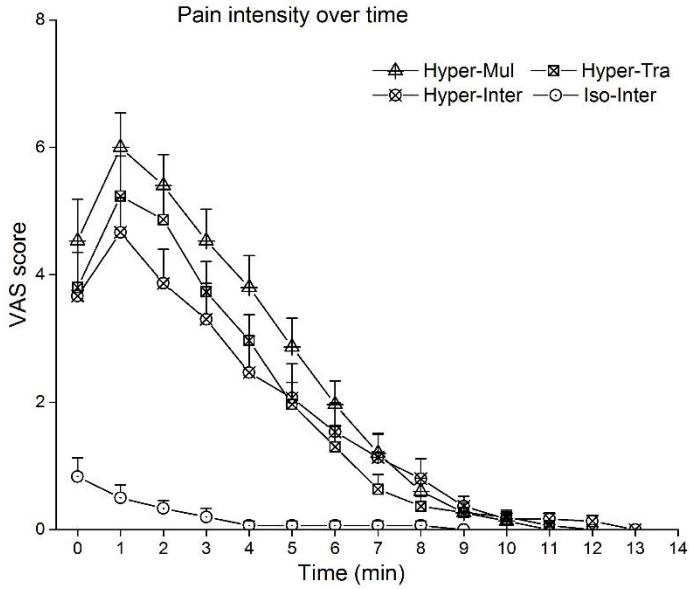


Figure 7. Pain intensity after injection of hypertonic or isotonic saline in cervical muscles (Study I) and inter-spinous ligament (Study II). Hyper: hypertonic saline; Iso: isotonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; min: minute.

Table 2. Pain characteristics of experimental and clinical neck pain

	Peak pain intensity (cm)	**Pain duration (min)**
Hyper-Mul	6.1 ± 2.1	8.3 ± 1.7
Hyper-Tra	5.5 ± 2.2	7.9 ± 2.3
Hyper-Inter	5.0 ± 2.2	7.8± 3.2
Iso-Inter	0.9 ± 1.2	1.7± 2.6
Recurrent neck pain patients	5.1 ± 1.3	

Hyper: hypertonic saline; Iso: isotonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament. Data were obtained from Study I-III.

Previous studies reported a large range in terms of the pain intensity in patients with neck pain (1.5 - 6.4 cm using NRS or equivalent score in similar pain evaluation tools)[58, 74, 90, 102, 157-160]. Some researchers did not even report the pain intensity of the patients with neck pain in their studies according to different research aims[161-164]. Among those studies reporting the pain intensity, the inclusion criteria with respect to pain intensity of patients with neck pain were mostly not clarified[58, 74, 90, 102, 157-159]. Although a few previous studies have shown the potential relationship between pain intensity and motor/sensory outputs[142, 165, 166], no standard on pain intensity of patients with neck pain was established when studying the motor and sensory effects of neck pain. However, it is widely

accepted that the minimal pain intensity of patients with neck pain should be at least 3cm on a 10 cm numerical rating scale (NRS) [160-164]. In the thesis, the pain intensity of patients with recurrent neck pain was 5.1 ± 1.3 cm (Study III). In addition, the experimental pain models applied in the thesis are comparable to clinical neck pain in terms of pain quality and intensity.

3.4.2. PAIN DISTRIBUTION

The pain distribution following the hypertonic saline injection is normally characterized by the local pain area around the injection site and the referred pain area remote from the injection site. The local pain area results from stimulating the local peripheral nociceptors, while the referred pain area is related to the central sensitization mechanism[105]. Previous experimental pain studies showed that the hypertonic saline injections in different structures resulted in various patterns of pain distributions[36-38, 109, 167]. The intrinsic variation in the density of nerve innervations between structures may account for the difference in the patterns of pain distributions[154, 166, 168]. Moreover, experimental pain induced by the hypertonic saline injection may also affect dorsal horn neurons of different spinal segment levels and result in different referred pain distribution patterns[37, 128]. Additionally, the experimental pain distribution was reported to correlate with the pain intensity in the injection site[105]. The higher the pain intensity, the larger the pain distribution[105]. In the thesis, the distribution of cervical multifidus and trapezius muscle pain was confined to the posterolateral neck area of the injection side (**Fig.8 A and B**). The trapezius muscle pain distributed to the midline of the neck from the injection site but only covered the lower cervical spine region. Three out of 15 subjects (20%) showed referred pain following hypertonic saline injection into the trapezius muscle. The manifestation of trapezius muscle pain distribution was similar to the findings of previous studies applying the same experimental trapezius muscle pain model[130, 152, 169]. The experimental multifidus muscle pain distributed to the right shoulder region from the injection site and six out of 15 subjects (40%) showed referred pain. The distribution of multifidus muscle pain seems larger than trapezius muscle pain but without a statistical significance. As previous studies indicated, the small variation in pain distribution could be the result of variations in the pain intensity between multifidus muscle pain and trapezius muscle pain[105].

The pain distribution following the injection of hypertonic and isotonic saline in the inter-spinous ligament centrally located around the injection site (**Fig.8 C**). The localized pain distributions were consistent with previous studies[109, 170]. The reason could be that the inter-spinous ligament locates in a narrow space between two adjacent spinous processes[171]. Five out of 15 subjects (33%) showed referred pain areas to the shoulder region following the hypertonic saline injection. With respect to the isotonic saline injection, two out of 15 subjects (13%) showed large pain distribution after the injection, while 5 subjects (33%) showed a local tiny pain area and the rest of the subjects showed no pain at all (**Fig.8 D**).

The pain distribution of patients with recurrent neck pain was much larger than any experimental pain model in the thesis (**Fig.8 E**). The pain distribution of patients with recurrent neck pain covered the entire posterior and most lateral area of the neck, the bilateral posterior shoulder regions and the upper thoracic spine region. The larger pain distribution in patients with neck pain compared with experimental pain models following one single injection of hypertonic saline was expected, since clinical neck pain is more complex than experimental neck pain. The patients with neck pain may have multiple painful foci and serious psychological features (e.g. anxiety and depression)[172, 173], both of which affected the pain processing pathway and may explain the large pain distribution in patients with recurrent neck pain.

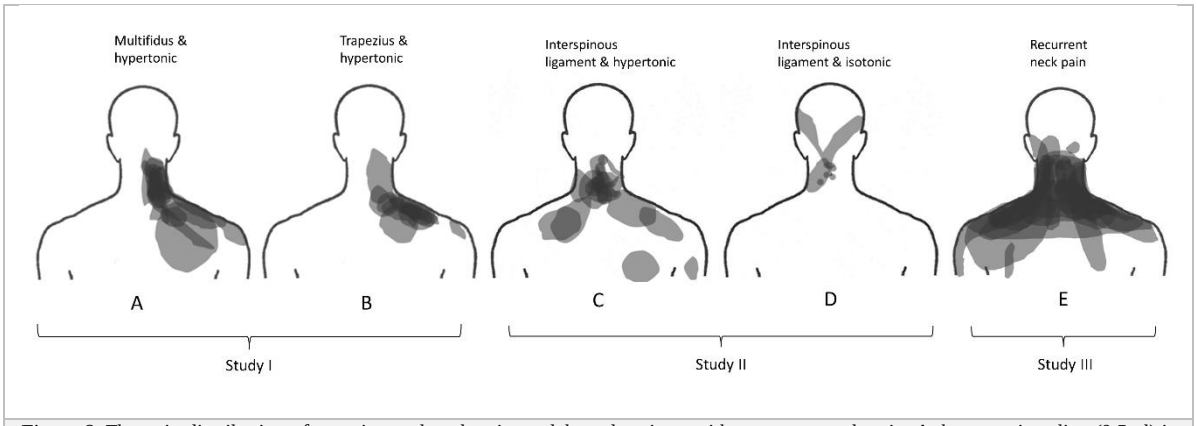


Figure 8. The pain distribution of experimental neck pain models and patients with recurrent neck pain. A: hypertonic saline (0.5ml) in multifidus muscle; B: hypertonic saline (0.5ml) in trapezius muscle; C: hypertonic saline (0.2ml) in C4/C5 inter-spinous ligament; D：isotonic saline (0.2ml) in C4/C5 inter-spinous ligament; E: recurrent neck pain patients. Data were obtained from Study I-III.

In summary, experimental cervical muscle and ligament pain showed comparable pain intensity and duration. Additionally, the experimental neck pain was comparable to clinical neck pain in terms of pain quality and intensity. The experimental multifidus and trapezius muscle pain were confined to the posterolateral neck area of the injection side, while the inter-spinous ligament pain centrally located around the injection site. The patients with recurrent neck pain showed larger pain distribution compared to any experimental neck pain models in the thesis.

CHAPTER 4. PRESSURE PAIN SENSITIVITY AND NECK PAIN

4.1. ASSESSMENT OF PRESSURE PAIN SENSITIVITY

Pressure pain thresholds (PPTs) measured by the pressure algometer were widely applied to quantify pain sensitivities in both healthy subjects and patients with neck pain and the method showed high reliability and validity[174-178]. Three repetitions are recommended if researchers want to track changes of PPTs across study sessions[178]. In all studies (Study I-III), the PPTs were measured over bilateral C2/C3 and C5/C6 cervical facet joints with the subjects in a prone position and relaxed their neck. In addition, the PPTs over the muscle belly of the right TA were assessed to evaluate the potential widespread hyperalgesia of patients with recurrent neck pain in study III. The measurements were assessed by using a pressure algometer (Algometer, Somedic Production AB, Sollentuna, Sweden) with a 1 cm^2 round rubber tip. The pressure algometer was placed perpendicular to the tissue surface and the pressure was constantly delivered with a speed of 30kPa/s during the measurements. Subjects were asked to press the handheld button connected to the pressure algometer when they felt the pressure sensation became detectably painful. Each site was assessed three times and the three assessments were used in determining the average for the further analysis. A 30s resting period was taken between two assessments. The procedure was in line with the previous studies[179]. The PPTs were measured by NQ alone. NQ was not blind to the test conditions (before injection or after injection) or the patients with recurrent neck pain, because NQ needed to assist the radiographer to do the injection and confirm the location of the target cervical structure.

4.2. EFFECTS OF NECK PAIN ON PRESSURE PAIN SENSITIVITY

The significant results of PPTs are summarized in **Table 3.** Hypertonic saline injection in the deep cervical muscle (Multifidus) increased the PPTs over bilateral C2/C3 facet joints and left C5/C6 facet joint compared with before injection. Hypertonic saline injection in the superficial muscle (Trapezius) increased the overall PPTs over the cervical facet joints compared with before injection (**Table 4**). Hypertonic saline injection in the inter-spinous ligament increased the PPTs over the left C2/C3 facet joint, while isotonic saline injection in the inter-spinous ligament showed no changes in PPTs over the cervical facet joints (**Table 4**). Contrary to the hypothesis, no difference was found in PPTs over the cervical facet joints and the TA between patients with recurrent neck pain and healthy controls (**Table 5**).

Table 3. The overview of altered PPTs in three studies

Parameters	**Study I**				**Study II**				**Study III**	
	Hyper-Mul		**Hyper-Tra**		**Hyper-Inter**		**Iso-Inter**			
PPTs	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
C2/C3	✓	✓	✓	✓	✓					
C5/C6	✓		✓	✓						

Hyper: hypertonic saline; Iso: isotonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament. ✓indicates a statistical difference.

4.2.1. EXPERIMENTAL NECK PAIN

The investigation of PPTs helps clinicians to understand the underlying pain processing mechanisms involved in neck pain[31, 100, 101]. In previous studies, experimental pain induced in different human tissues caused various manifestations of changes in PPTs. Gibson et al. (2006) demonstrated that hypertonic saline injection in the tendon, tendon-bone junction and muscle belly of tibialis anterior muscle increased or did not change PPTs over the areas

out of the injection site during pain[36]. Izumi et al. (2014) demonstrated hypertonic saline induced pain in the gluteus medius tendon and gluteus medius muscle were likely to decrease PPTs over the areas out of the injection site while hypertonic saline induced pain in the adductor longus tendon was likely to increase PPTs over the areas out of the injection site during pain [37]. Additionally, the changes in PPTs also depends on the location of measurement sites. Palsson et al. (2012) demonstrated hypertonic saline induced pain in the long posterior sacroiliac ligament decreased PPTs over the area 1 cm lateral to the spinous process of S2 during pain but did not change PPTs over the rest of measurement sites [38]. However, no previous studies have reported whether changes in PPTs over the cervical facet joints will be different when the pain originates in different cervical tissues. The findings may contribute to the experimental neck pain models investigating pain sensitivity and help clinicians to better understand the sensory effects of neck pain. The results showed experimental cervical muscle and ligament pain increased or did not change PPTs over bilateral C2/C3 and C5/C6 facet joints (Study I-II)[24, 28]. In agreement with the hypothesis, experimental trapezius muscle pain increased overall PPTs over the bilateral C2/C3 and C5/C6 facet joints (Study I)[24]. Contrary to the hypotheses, experimental multifidus muscle pain increased PPTs over the bilateral C2/C3 and left C5/C6 facet joints (Study I) and experimental inter-spinous ligament pain increased PPTs over the left C2/C3 facet joint (Study II)[24, 28]. These results imply that pain sources may influence the pain sensitivity over cervical facet joints. As indicated in a previous review paper, the pain intensity following hypertonic saline injection influenced the pain sensitivity of deep human tissues[105]. Studies with the peak pain intensity below 6 cm after injections commonly reported that PPTs increased or remained unchanged compared with the before injection condition, while studies with the peak pain intensity above 7 cm were more likely to show decreased PPTs compared with the before injection condition[105]. In study I and study II, the peak pain intensity remains below or slightly over 6 cm, which may explain the increased and unchanged PPTs over the bilateral C2/C3 and C5/C6 facet joints. Additionally, the time point of the measurement after injections may be related to the changes in PPTs. Previous studies have indicated the descending inhibitory and facilitatory modulations of the spinal nociceptive processes simultaneously existed during pain and played a crucial role in modulating the pressure pain sensitivity in experimental pain models[152]. Ge et al. (2003) suggested that enhanced descending inhibitory and facilitatory mechanisms were activated simultaneously but predominated in different phases during experimental pain[152]. Descending facilitatory mechanisms were more likely to predominate in the early phase and descending inhibitory mechanisms predominated later[152]. Therefore, the various findings of pressure pain sensitivity in previous studies probably resulted from the shift between the inhibition and facilitation mechanisms[126]. The increased, decreased and unchanged PPTs could co-exist in the same experimental pain study[37, 38]. In both study I and study II, the PPT measurements were conducted almost at the end of the pain because of the motion tasks after the injection. The measurements coincided approximately with the descending inhibitory mechanism phase and presented as increased PPTs. Interestingly, the alterations in PPTs were more often demonstrated over the upper facet joints (C2/C3) and the non-injected side (left side) of the neck. The inherent difference of pain sensitivity in different areas of human body may account for these findings[168, 180, 181]. The upper spine region is generally more sensitive than the lower spine region[168, 181]. It was reported in one previous study that the PPTs over neck and head were the lowest among 29 measurement sites over different areas of the human body[180]. Moreover, most of the subjects in the experimental pain models are right hand dominant (80% in study I, 93% in study II) and this may explain why findings were more likely to be demonstrated over cervical facet joints on the left side[180, 182].

In summary, hypertonic saline induced experimental neck pain in multifidus muscle, trapezius muscle and inter-spinous ligament caused unchanged or increased PPTs over the bilateral C2/C3 and C5/C6 facet joints. The affected area was different according to the pain sources. The upper cervical facet joints and the non-injected side of the neck were more likely to be affected. The results indicated the descending inhibitory mechanism may predominate during PPTs measurement and the differences of inherent pain sensitivity over different areas of the human body.

Table 4. Pressure pain thresholds over different sites before and after injection of hypertonic or isotonic saline into the cervical muscles and ligaments.

	Study I				**Study II**			
	Hyper-Mul		**Hyper-Tra**		**Hyper-Inter**		**Iso-Inter**	
	Pre	Post	Pre	Post#	Pre	Post	Pre	Post
Right C2/C3	256.4±137.2	283.1±141.4*	240.4±102.4	279.5±131.3	209.1±97.1	213.1±93.8	222.8±138.2	244.3±153.5
Left C2/C3	263.0±129.1	298.9±144.8*	244.7±92.8	277.4±139.8	198.9±67.6	230.8±92.1*	229.8±129.2	245.2±148.2
Right C5/C6	283.8±150.6	277.9±134.4	274.6±126.5	319.5±162.0	237.2±96.1	237.8±102.8	244.6±132.6	253.1±161.6
Left C5/C6	298.5±163.1	322.2±161.9*	280.8±124.1	315.9±153.1	220.9±67.5	234.1±81.5	246.2±135.6	248.9±146.4

*Values were expressed as mean ± SD; Hyper: hypertonic saline; Iso: isotonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: interspinous ligament. *indicated the statistical interaction effect between before and after injections. # indicates the statistical main effect between before and after injections. Data were obtained from Study I and Study II.*

4.2.2. CLINICAL NECK PAIN

Contrary to the hypothesis, localized and widespread hyperalgesia was not found in patients with recurrent neck pain. To the best of our knowledge, no previous studies have investigated pressure pain sensitivity in patients with recurrent neck pain (**Appendix B**). Therefore, no direct data of pain sensitivity in the same type of patients with neck pain were available to be compared with. However, similar results of no localized and widespread hyperalgesia were demonstrated in recurrent low back pain patients when compared with healthy controls[183, 184]. This evidence may imply a similar pain processing mechanism in patients with recurrent pain.

Localized hyperalgesia normally reflects the sensitizations of peripheral nociceptors which may result from injury of the neck tissues[185]. No localized hyperalgesia may indicate less sensitization of peripheral nociceptors in patients with recurrent neck pain (Study III). Patients with recurrent neck pain showed a developing pattern with episodes of fluctuating pain and disability[115]. The measurements of PPTs were conducted during the recurrence episode in the thesis, therefore, recoveries of the injured tissues in the previous remission episode may result in less sensitization of the peripheral nociceptor. The current findings were contrasted to previous studies showing localized hyperalgesia over the cervical spine region in patients with neck pain compared with healthy controls[29, 30, 186]. The methodology differences including the measurement sites and the measurement devices may be one of the explanations for the inconsistent findings, for instance, the baselines of pain sensitivity are diverse among neck structures[180, 181]. Even in the same group of patients with neck pain, the initial pain locations may be different between patients and different from the standardized measurement sites. Additionally, Johnston et al. (2008) compared PPTs over the cervical spine region between office workers with neck pain and healthy controls and found that participants with a high level of neck pain and disability were more prone to show low PPTs[100]. Similarly, Sterling et al. (2004) demonstrated localized hyperalgesia over the cervical spine in acute whiplash patients with moderate and severe pain intensity and disability instead of patients with mild pain intensity and disability when compared to healthy controls[187]. Although the relationship between PPTs and the pain characteristics remains incompletely understood[188], these previous studies indicated PPTs may be negatively correlated to the level of the pain intensity and disability[100, 187]. In study III, the mean pain intensity is 5.1 ± 1.3 cm and the mean NDI score of patients with recurrent neck pain is only 16.7 (**Section 2.3**). Therefore, the relatively low pain intensity and disability may explain no differences in PPTs over the cervical spine between patients with recurrent neck pain and healthy controls. Lastly, the injury mechanisms and the associated symptoms of neck pain may also contribute to the inconsistent findings in PPTs among previous studies[29, 30, 32, 136, 187].

Measuring PPTs over the TA was commonly applied to detect widespread hyperalgesia in patients with neck pain. Widespread hyperalgesia indicates the central sensitization, to be more specific, the impairment of the descending inhibitory control on the pain processing[189]. The current findings did not imply the widespread hyperalgesia in patients with recurrent neck pain, as no difference in PPTs over the TA were found between patients with recurrent neck pain and healthy controls (Study III). Previously, the widespread hyperalgesia was mostly demonstrated in chronic and whiplash-associated neck pain patients and occasionally in the non-specific neck pain patients[29-32, 35, 100, 190, 191]. In a previous review paper, the author concluded there was a lack of evidence for the central sensitization in idiopathic and non-traumatic neck pain[192]. The above-mentioned low NDI score may also be a factor influencing the development of the widespread hyperalgesia in patients with neck pain[100]. Additionally, the persistent nociceptive stimulus was a main contributor to the development of the widespread hyperalgesia[126]. Javanshir et al. (2010) also highlighted the existence of different sensitization mechanisms between chronic and acute non-specific neck pain patients, and chronic neck pain patients showed widespread hyperalgesia instead of acute neck pain patients[34]. However, patients with recurrent neck pain showed intermittent remission episodes without the maintenance of nociceptive stimulations, which may explain the absence of widespread hyperalgesia. Additionally, Madrid et al. (2016) implied the widespread enhanced sensitivity response to the pressure was related to the neuropathic symptoms[30], which is also not a feature of the patients with recurrent neck pain in the thesis. Although previous studies tried to subgroup patients with neck pain and differentiate them from healthy subjects based on the manifestations of pain sensitivity, the PPTs seem not to be a sensitive parameter for patients with recurrent neck pain[183, 184].

Previous studies demonstrated that the widespread hyperalgesia indicated a poor recovery of neck pain[33, 102, 108]. No findings in localized and widespread hyperalgesia, in turn, may explain the recurrent nature of neck pain. Goubert et al. (2017) proposed that the pain processing may be more efficient in recurrent low back pain patients

compared with healthy controls, which help patients quickly recover from the pain episode and prevent the development into chronic pain[183].

Table 5. Pressure pain thresholds over different sites between patients with recurrent neck pain and healthy controls

	Patients	**Controls**
Right C2/C3	236.8±149.3	270.5±118.2
Left C2/C3	239.8±137.3	271.7±97.6
Right C5/C6	227.7±157.2	267.3±101.9
Left C5/C6	222.7±132.8	262.9±102.3
Right TA	372.6±224.7	382.4±184.6

Values expressed as mean± SD. TA: Tibialis anterior. Data were obtained from Study III.

In summary, no localized and widespread hyperalgesia was demonstrated in the patients with recurrent neck pain in the thesis. The natural course, low NDI score and no associated neuropathic symptoms of the patients with recurrent neck pain in the thesis could be the explanations for these findings. The PPTs may not be a sensitive parameter to differentiate patients with recurrent neck pain from the healthy controls.

CHAPTER 5. CERVICAL JOINT MOTION AND NECK PAIN

5.1. ASSESSMENT OF NECK MOVEMENTS

5.1.1. MEASUREMENT TECHNIQUE

Many techniques have been applied to capture dynamic neck movements including virtual reality, digital camera, biplane X-ray system, electro-goniometer, inclinometers and video-fluoroscopy[83, 85, 91, 94, 96, 193-195]. The techniques using indirect markers, such as skin surface markers, are generally limited to the measurement of the gross cervical range of motion. They are unable to assess accurate individual cervical joint motion even at the static positions, not to mention during dynamic neck movements. In contrast, methods identifying and tracking direct landmarks of cervical vertebrae on radiographic images are considered accurate methods to measure cervical joint motions[196].

Video-fluoroscopy is an X-ray based technique and allows the real-time tracking of individual cervical joint motion during dynamic neck movements with low radiation doses[24, 27, 28, 94, 96, 197, 198]. Video-fluoroscopy takes multiple frames of the cervical spine per second and enables the identification of cervical vertebrae frame by frame on the fluoroscopic motion sequence. Individual cervical joint motion can be calculated between any two frames regardless of where the frame occurred during neck movements[27, 93, 95, 96]. Measurement of the cervical joint motion via video-fluoroscopy has been previously reported with high reproducibility and reliability[95, 198]. Therefore, video-fluoroscopy was applied in this PhD thesis to assess cervical joint motion during neck movements.

5.1.2. STANDARDIZED PROTOCOLS

The methodologic factors which may influence the measurement of cervical joint motion need to be considered and addressed carefully before the assessments of neck movements, since standardized experimental methods promise good results and make the results comparable between studies[199, 200]. With respect to the movement performance, both active and passive cervical ROM were applied in previous studies. The active motion refers to the spontaneous motion performed by participants themselves, while the passive motion refers to the motion assisted by the researchers or external control tools[27, 93, 94, 96, 200, 201]. Although differences between assessments of active and passive motion were observed previously, there is no consensus on which type of motion assessment is better when evaluating the motor effects of neck pain[67, 202]. However, the active motion is under the physiological loads derived from the surrounding soft tissues and controlled by the neuromuscular system, which is representative of neck activities in the daily life[199]. Therefore, active motion assessment was used in this PhD thesis. Additionally, the starting position of the neck movements also needs to be considered. The neutral position is defined as *the posture of the spine in which the overall internal stress in the spinal column and the muscular effort to hold the posture are the minimal*[203]. In the sagittal plane, the neutral position of the neck is simply the point midway between flexion and extension. In previous studies, the neutral position of the neck was determined by the participants themselves or adjusted by the researchers[94, 96]. However, the researcher-assisted method may change alignment of the cervical joints at the neutral position which can affect the cervical joint motion pattern[204]. Some studies also investigated cervical joint motion from the maximal flexion to the maximal extension and from the maximal extension to the maximal flexion to avoid determining the neutral position[91, 92]. However, the internal stress and the muscular efforts of the neck at the maximal range position is significant, which may make the neck move in a totally different pattern compared with the motion started at the neutral position. There is also no uniformed standard on the starting position of the neck movements[67, 202]. The self-determined neutral position was applied in this PhD thesis since most of the daily neck activities started from the neutral position and the aim was to investigate cervical flexion and extension respectively[83]. Moreover, the self-determined method also reflects the proprioceptive ability of the participants to resume their neck neutral position which could be affected by neck pain[93].

For studies in this PhD thesis, the motion assessments were conducted in a room shielding X-ray (**Fig.9**). The subjects were seated in a chair with a backrest which was placed between the image intensifier and the X-ray transmitter of the fluoroscopy machine and kept their hips, knees, and ankles at 90 degrees. The trunk of subjects was restricted by straps attached to the chair to reduce movements from the thoracic spine and their right shoulder was directly against the image intensifier. The subjects wore a pair of glasses with four steel balls which were used

to represent the bottom of the occipital condyles. A continuous line on the floor, wall, and ceiling was used to guide the flexion and extension movements and reduce the out-of-plane motions. A cross symbol on the front wall was adjusted to the eye level of the subjects to remind them of the initial neutral position. The subjects were instructed to flex and extend their necks from the self-determined neutral position to the maximal range position (**Fig.9**). Cervical flexion and extension videos were collected at 25 frames per second by the video-fluoroscope system (Philips BV Libra, 2006, Netherland) with 45 KV, 208 mA, 6.0ms X-ray pulses. The motion tasks were practiced in advance to ensure a continuous and steady pace of flexion and extension motions. The fluoroscopic videos were recorded and stored in a computer software (Honestech VHS to DVD 3.0 SE).

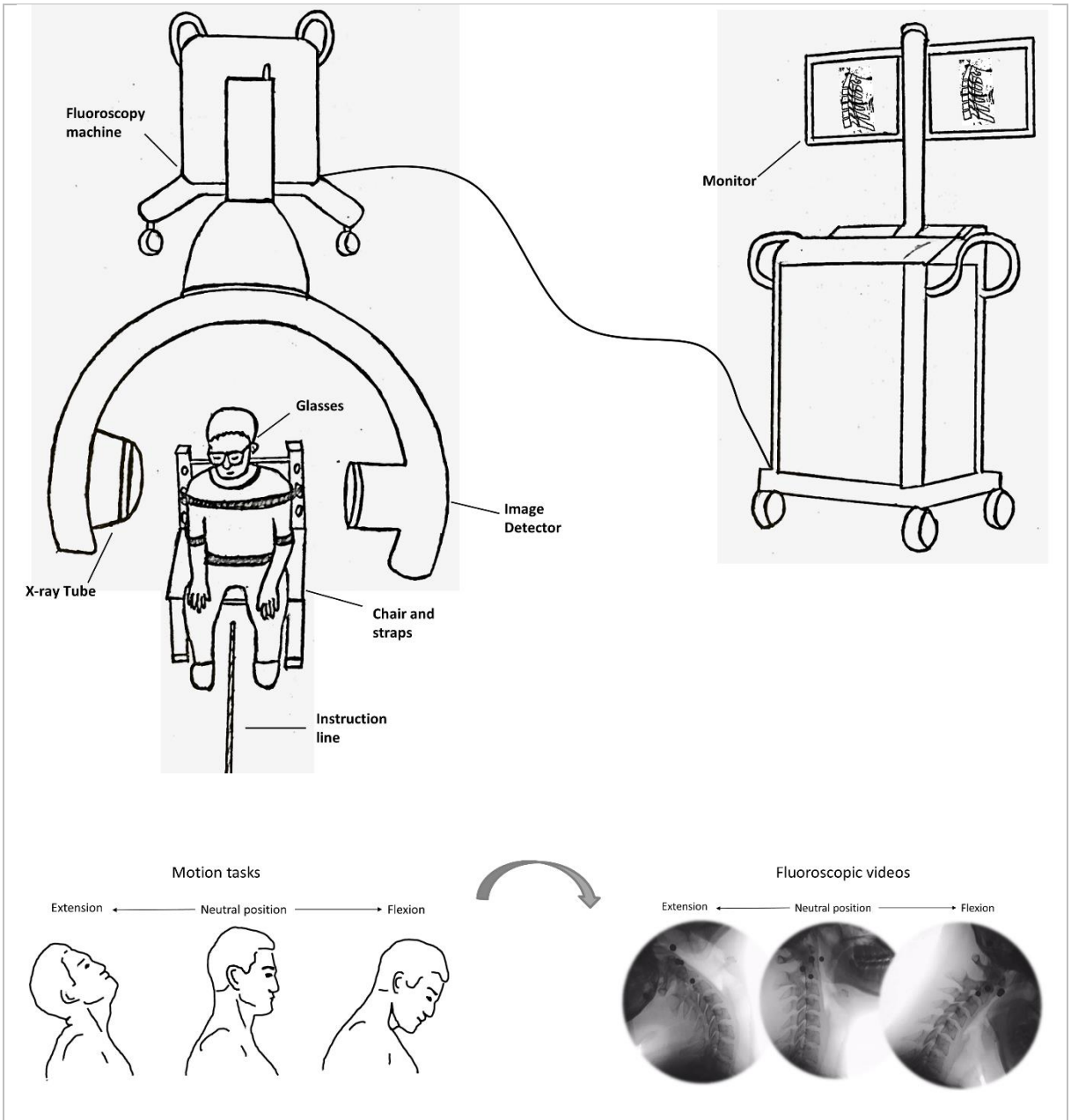


Figure 9. The set-up in the clinic and the motion tasks. The fluoroscopy machine was placed in a room shielding X-ray. A monitor in the adjacent room was connected to the fluoroscopy machine. During the data collection, examiners switched on the fluoroscopy machine, instructed participants on the motion tasks and recorded the fluoroscopic videos in the adjacent room without exposure to X-ray. Participants were instructed to flex and extend their neck from the neutral position to the maximal range position. Flexion and extension movements were recorded separately.

5.1.3. MOTION PARAMETERS EXTRACTION

For studies in this PhD thesis, the fluoroscopic videos were digitalized frame by frame in a custom Matlab (2015b) program. The program of identifying cervical vertebrae landmarks was developed from the approach initiated by Frobin et al (2002)[196]. For the occipital condyles (C0), four external steel balls attached to the pair of glasses were marked. The centers of medullary marrow cavities of the anterior and posterior arch were marked on C1 vertebra. The two inferior corners were marked on C2 vertebra. The four corners of C3-C6 vertebrae were marked. The two superior corners were marked on C7 vertebra. The marking procedure has been showed to have good reliability and low average marking errors[196, 198]. The landmarks of each cervical vertebra (C0-C7) were used to calculate the mid-plane of the vertebrae. For C0, the mid-plane was defined as the line connecting the midpoint of the two anterior external markers and the midpoint of the two posterior external markers. For C3-C6, the mid-plane was defined as the line connecting the midpoints of two anterior markers and the two posterior landmarks. For C1, C2 and C7 the line connecting the two landmarks was used as the mid-plane.

Two adjacent cervical vertebrae formed the basic motion unit of the neck, which was called cervical joint. The angle between two adjacent mid-planes was defined as joint angle. As pre-programed, joint angles during cervical extension were produced in positive numbers and joint angles during cervical flexion were produced in negative numbers. The change in angles of the same joint during neck movements was defined as the joint motion. Therefore, the anti-directional motion of cervical joints was recognized as negative numbers during cervical extension and positive numbers during cervical flexion (**Fig.10**).

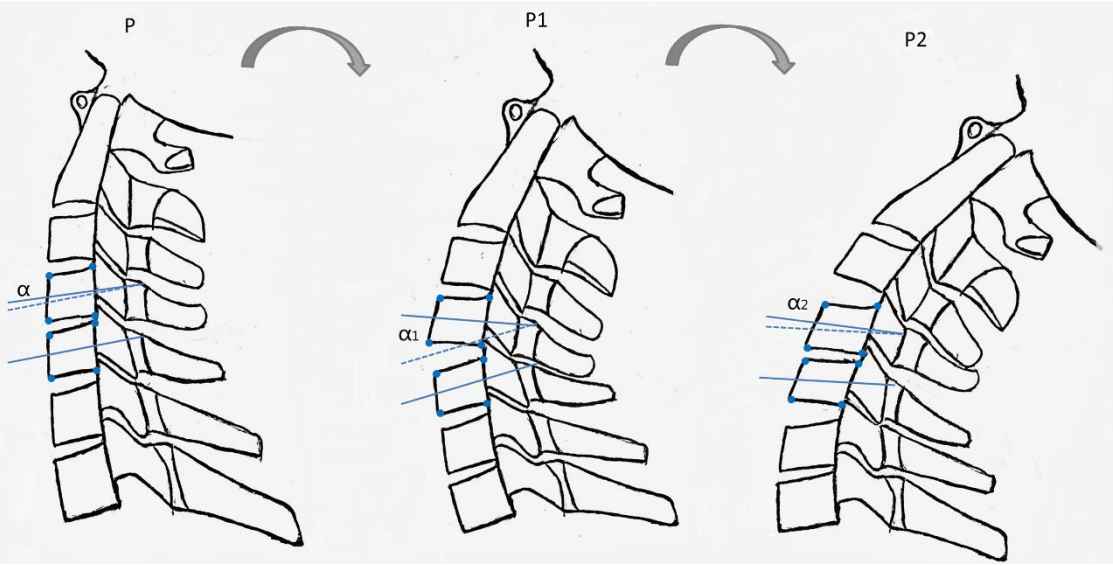


Figure 10. Illustration of anti-directional motion and pro-directional motion during cervical extension. P, P1 and P2 represents three positions of the cervical spine during extension and α, α1 and α2 represents joint angles of C4/C5 at the corresponding position. The C4/C5 joint angle increased from P to P1 when the cervical ROM increased in the extension direction. Therefore, C4/C5 joint motion from P to P1 calculated as α1- α was along with the motion direction and was defined as Pro-directional motion. Conversely, the C4/C5 joint angle decreased from P1 to P2 when the cervical ROM increased in the extension direction. C4/C5 joint motion from P1 to P2 calculated as α2-α1 was opposite to the motion direction and was defined as Anti-directional motion. The definitions are the same with respect to cervical flexion.

In the thesis, the cervical joint motion parameters were extracted during 10 even epochs of cervical flexion and extension movements. The detailed extraction procedure from the fluoroscopy videos to the final cervical joint motion in degrees was shown in **Fig.11**. For each fluoroscopy video, the starting and ending frames of the neck movement together with 9 frames in the middle range of the neck movement were selected, which separated the neck movement into 10 even epochs. After identifying the landmarks on each frame, cervical joint motions during 10 epochs were obtained[24, 28, 93, 94, 96]. The cervical joint motion parameters were calculated based on the typical

dataset. In the thesis, the collections of fluoroscopic videos of neck movements were conducted by NQ. NQ was not blind to the test conditions (before injection or after injection) or the patients with recurrent neck pain, because NQ needed to assist the radiographer to do the injection and confirm the location of the target cervical structure. Additionally, NQ did the marking procedure and motion extractions alone. The cervical joint motion parameters analyzed in the three studies were summarized in **Table 6**.

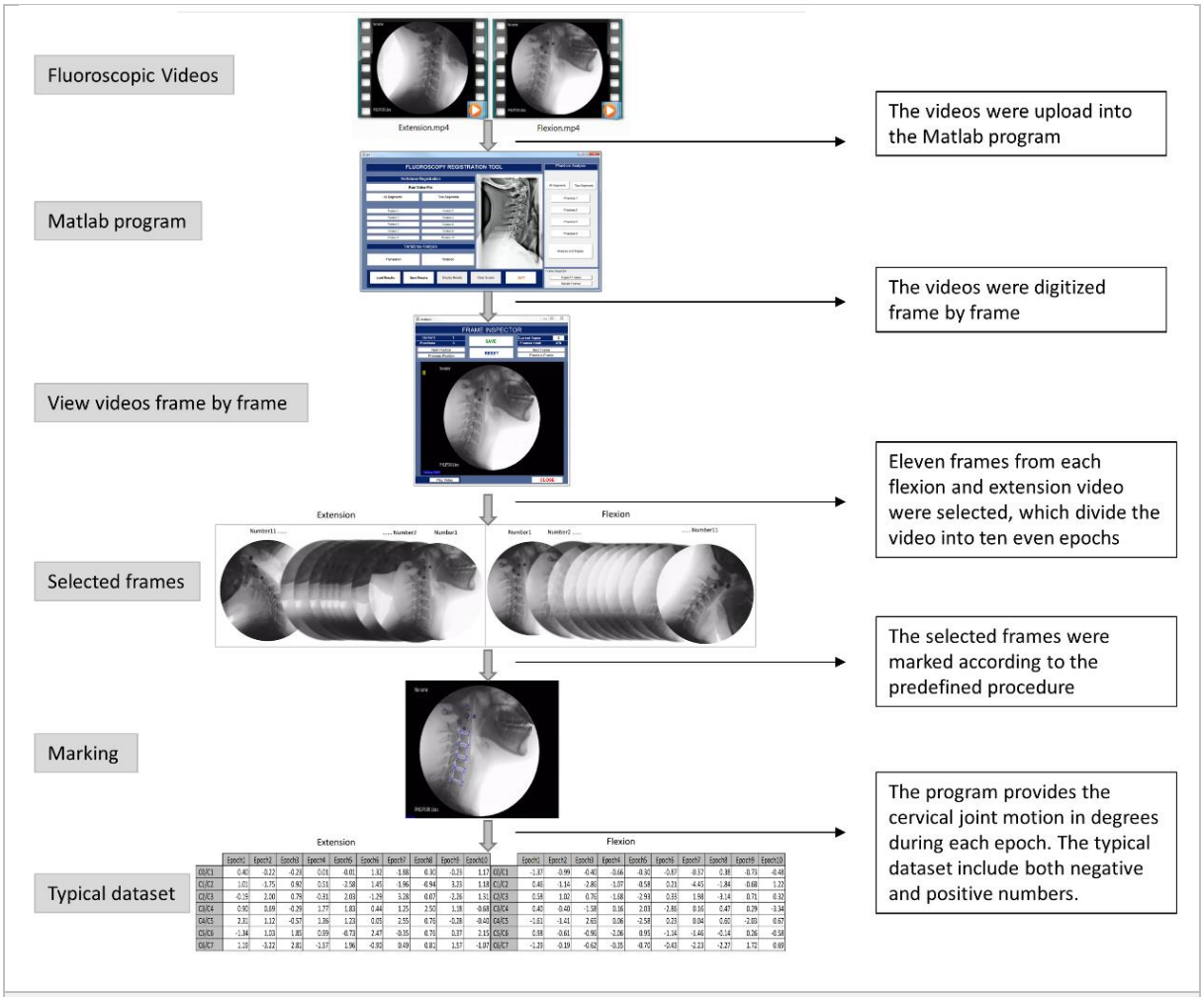


Figure 11. Data extraction procedure from the fluoroscopic videos to the typical datasets.

Table 6. The overview of motion parameters assessed in three studies

Parameters	Definition	Extraction method
Anti-directional motion	Joint motion opposite to the primary motion direction	The sum across 10 epochs
Pro-directional motion	Joint motion along with the primary motion direction	The sum across 10 epochs
Joint motion variability	The variance of joint motions during movements	The variance across 10 epochs
Total joint motion	The sum of pro-directional and anti-directional motion	The sum across 10 epochs

5.1.4. ACCURACY AND RELIABILITY OF THE MEASUREMENT

The cervical spine is a relatively inaccessible structure which makes direct measurements on cervical joint motion impossible. Video-fluoroscopy allows researchers and clinicians to work on the fluoroscopic images and extract cervical joint motion by identifying landmarks of the cervical vertebrae. The accuracy and reliability of the measurement method are important for interpreting the results. Therefore, the measurement method should be valid before its application in researches.

The landmark identification method applied in the thesis was derived from the approach proposed by Frobin et al. (2002)[196]. The high reproducibility of the marking method was previously reported by Plocharski et al. (2018)[198]. Plocharski et al. (2018) reported the marking error at individual cervical joint levels on static and dynamic fluoroscopic images when marked by examiners with and without radiography experience separately[198]. The average marking error across examiners and images was −0.12° with a range from −1.00° to 1.61° and the average SD was 0.88° with a range from 0.27° to 1.19°. The average marking error and SD were smaller than the average inter-examiner marking error and SD reported by Frobin et al. (2002) which is 0.18° and 1.98° respectively[196]. Additionally, the average marking error was smaller than the average marking error of intra- and inter-examiner reported by Wu et al. (2007) which was 2.44° and 2.66° respectively[205]. With respect to the marking method in the thesis, large marking errors were demonstrated at C0/C1 (0.57°), C1/C2 (1.61°), C2/C3 and C6/C7 (-1.00°) on dynamic fluoroscopic images and at C1/C2 (-0.68°) on static fluoroscopic images when marked by the examiners with radiography experience[198]. The marking errors at the rest of the cervical joints were all below 0.50° (ranging from 0.04° to – 0.47°) despite the type of fluoroscopic images and examiners[198].

For the reliability of the measurement, intra-class correlation coefficient (ICC) values of the inter-examiner and intra-examiner for marking on static fluoroscopic images were both 0.95 and ICC values of the inter-examiner and intra-examiner for marking on dynamic fluoroscopic images were 0.96 and 0.98, respectively[198]. Additionally, Wu et al. (2007) reported the ICC values of intra-examiner and inter-examiner for marking were 0.936 and 0.898 respectively[205].

However, the above-mentioned measurement errors and reliability were for single fluoroscopic image marking. The reliability of marking a single fluoroscopic image is fundamental for the further calculation of complicated cervical joint motion parameters. The extraction of dynamic cervical joint motion parameters in the thesis requires marking eleven static and dynamic fluoroscopic images. In order to obtain the accuracy and reliability of the measurement method for the dynamic cervical joint motion parameters in this thesis (anti-directional motion, pro-directional motion, total joint motion, and joint motion variability), the lead investigator (NQ) marked one fluoroscopic video three times and calculated: 1) the intra-class correlation coefficient (ICC); 2) standard error of measurement (SEM); and 3) minimal detectable change (MDC). The ICC was calculated to evaluate the test-retest reliability of the lead investigator (NQ). The ICC value was interpreted in five levels: 0-0.40 = unacceptable, 0.41-0.60 = moderate, 0.61-0.80 = substantial and 0.81-1.00 = almost perfect[206]. The SEM is a widely applied indicator of the measurement error. A small value of SEM indicates the low measurement error and the high reliability of the measurement method. The MDC is defined as the minimal changes beyond the measurement error of a specific measurement method with a 95% confidence level. Changes exceeding the MDC could be interpreted as the true significance and are of clinical relevance.

The SEM and the MDC were calculated according to the following formulas:

$$MDC = 1.96 \times \sqrt{2} \times SEM$$

$$SEM = SD \times \sqrt{(1 - ICC)}$$

Where the SD is the standard deviation of measurement.

The ICC, SEM, and MDC of the dynamic cervical joint motion parameters at the individual joint level and overall level are presented in **Table 7**. The ICC for anti-directional motion is 0.882, for pro-directional motion is 0.931, for total joint motion is 0.949 and for joint motion variability is 0.895. According to the agreement levels rating proposed by Landis and Koch, the ICCs in the thesis indicate almost perfect reliabilities[206]. The ICC results for total joint motion is the highest among the four cervical joint motion parameters. This is in accordance with findings published by Plocharski et al. (2018) that the marking errors on dynamic fluoroscopic images are larger than the marking errors on static fluoroscopic images. The calculation of total joint motion mainly needs the data

from two static fluoroscopic images at the beginning and end of the neck movements, while the calculations for the rest of the motion parameters need both data from static and dynamic fluoroscopic images.

The SEM and MDC values are relatively small in **Table 7**, which indicates the low measurement errors and high reliability of the measurement method. Plocharski et al. (2018) have reported that the SD of the measurement error ranges from 0.88° to 1.16° across cervical joints and the ICCs were all higher than 0.95[198]. According to the formulas (MDC = 1.96× √2 × SEM, SEM = SD × √ (1 - ICC)), the MDC value in the paper published by Plocharski et al. could be calculated. The MDC value ranges from 0.55° to 0.72°, if the 0.95 ICC value is applied. The MDC value range (from 0.26° to 1.61°) in the thesis is comparable to what Wang et al. (2017) reported when the same measurement method was applied in their study, where the MDC value at individual cervical joint motion ranges from 0.35° to 1.17° and the average MDC value is 0.73[93]. Additionally, the motion differences observed at the individual cervical level in the thesis were all larger than the corresponding MDCs which indicated the results were reflective of the true differences.

Table 7. ICC, SEM and MDC of different cervical joint motion parameters.

	ICC		C0/C1	C1/C2	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	Overall
Anti	0.882	SEM	0.27	0.43	0.45	0.45	0.26	0.40	0.30	1.40
		MDC	0.75	1.20	1.25	1.25	0.71	1.11	0.83	3.88
Pro	0.931	SEM	0.32	0.21	0.31	0.47	0.34	0.58	0.42	0.65
		MDC	0.88	0.58	0.86	1.31	0.95	1.61	1.17	1.79
Total	0.949	SEM	0.12	0.10	0.09	0.31	0.39	0.45	0.37	0.26
		MDC	0.33	0.28	0.26	0.86	1.09	1.24	1.03	0.71
Vari	0.895	SEM	0.19	0.30	0.42	0.36	0.38	0.18	0.14	1.20
		MDC	0.52	0.84	1.17	1.00	1.05	0.50	0.38	3.32

Anti: anti-directional motion; Pro: pro-directional motion; Total: total joint motion; Vari: joint motion variability; ICC: intra-class correlation coefficient.

In summary, the low marking errors and good reliability within examiners supported the feasibility of the current measurement method in assessing cervical joint motion. The motion differences observed at individual cervical joint levels in study I-III were larger than the marking error and MDC at the corresponding cervical joint. Therefore, the findings of dynamic cervical joint motion indicated a real difference and may be of clinical relevance.

5.2. THE MOTION BASELINES

Theoretically, the true values of cervical joint motion in vivo could never be obtained, but the extremely close values could be calculated by averaging many repetitive measurements results on cervical joint motion in a large enough healthy population sample.

There are five healthy motion baselines in the thesis, two in study I (baselines before injection in trapezius and multifidus muscles), two in study II (baselines before injection of hypertonic and isotonic saline) and one in study III (baseline of the healthy controls). The variabilities among those baselines existed. With respect to the study designs, study I and study II were to investigate the cervical joint motion before and after the injections, in which the participants acted as their own controls. The study III was to investigate cervical joint motion between patients with recurrent neck pain and a healthy group matched for gender, age, and BMI, which were reported to influence cervical joint motion[121]. Therefore, the results of each study were concluded according to its own baseline and there is no requirement for similar baselines across two sessions within the same study or across studies.

Moreover, Wang et al. (2018) have reported the acceptable repeatability of cervical joint motion during cervical flexion and extension with a 20s interval and a one-week interval[96]. The motion differences between two repetitions were reported to be normally distributed[96]. The average motion difference with a 20s interval was 0.00° ± 2.98° for flexion and 0.00° ± 3.05° for extension[96]. The average motion difference with a one-week interval was 0.02° ± 2.56° for flexion and 0.05° ± 2.40° for extension[96].

Nevertheless, two different types of variabilities in motion baselines need to be considered in the thesis.

1) The variability between baselines measured with a one-week interval in the same study.
2) The variability between baselines across studies.

For the baselines within the same study, the variability was mainly the collective result of measurement error and the intrinsic motion variability of subjects. For the baselines across studies, the structural variability (disc degeneration, cervical curvature, etc.) and the physical factors influencing neck movements (gender, age and BMI, etc.) between different samples also account for the variability in addition to the two above mentioned aspects[121].

The measurement errors normally result from the measurement equipment, the quality of movement performances and the marking procedure. The measurement equipment was the same across studies in the thesis and efforts were spent to train subjects to ensure a standard movement performance with good qualities. Additionally, previously reported low marking errors and high ICCs within and between examiners which indicated the marking procedure and the examiners are reliable in the thesis[198]. Therefore, the variability between baselines within the same study mainly reflects the normal motion variability of the subjects.

In the thesis, most of the motion findings were demonstrated in anti-directional motion during cervical extension. Therefore, the baseline differences and motion changes of anti-directional motion during cervical extension in study I and study II were provided in **Table 8**. It was demonstrated that the changes of anti-directional motion during pain conditions in study I and study II were all larger than the difference between the two baselines. The results in **Table 8** indicated that the effect of experimental neck pain on cervical joint motion was larger than the normal motion variability between repetitions.

Table 8: Baseline differences and motion changes of anti-directional motion during cervical extension in study I and study II

Study I	C0/C1	C1/C2	C2/C3	C3/C4	C4/C5	C5/C6	C6/C7	Overall
$Baseline_{study\ I}$	0.17	0.77	0.21	1.47	0.70	0.49	0.73	2.73
Multifidus	-0.03	-0.08	1.43	-1.73*	-0.11	-0.45	1.79*	0.82
Trapezius	0.27	0.55	2.13	0.40	1.60	0.42	0.71	6.07*
Study II								
$Baseline_{study\ II}$	0.59	0.26	0.12	0.86	1.28	0.26	1.19	2.61
Hypertonic	0.08	0.34	-2.62*	0.80	1.61*	0.60	-0.26	0.55

*The blue rows indicate baseline differences in study I and study II. The orange rows indicate the motion changes from the baselines during pain conditions. $Baseline_{study\ I}$: absolute difference between baselines in study I. $Baseline_{study\ II}$: absolute difference between baselines in study II. Multifidus: motion changes from the baseline during multifidus muscle pain; Trapezius: motion changes from the baseline during trapezius muscle pain; Hypertonic: motion changes from the baseline after injection of hypertonic saline in the inter-spinous ligament. * indicates the significant difference.*

In summary, the baselines within the same study and across studies are not required to be similar according to the study designs. The cervical joint motion during cervical flexion and extension with 20s interval and one-week interval were reported to be repeatable. The motion changes of anti-directional motion during pain conditions in study I and study II were all larger than the difference between the two baselines. Nevertheless, we recommend interpretation of the results with respect to the corresponding baseline. The structural variability (disc degeneration and cervical curvature, etc.) and the physical factors influencing neck movements (gender, age and BMI, etc.) are different between samples in the three studies, which result in a large variability between baselines across studies. Cautions should be paid when comparing the results with baselines across studies.

5.3. EFFECTS OF NECK PAIN ON CERVICAL JOINT MOTION

Among the dynamic cervical joint motion parameters in the PhD thesis, anti-directional motion is the most sensitive parameter to experimental and clinical neck pain, followed by joint motion variability. The anti-directional motion may indicate the fine adjustments of neuromuscular control on cervical joint motion during cervical flexion and extension[24, 28, 94]. Therefore, altered neuromuscular control strategy during neck pain may be reflected by changes in the anti-directional motion[24, 28, 94]. Deep cervical muscle pain, superficial cervical muscle pain and cervical inter-spinous ligament pain showed different effects on cervical joint motion. Interestingly, most of the results were found during cervical extension movement. Only clinical neck pain showed effects on cervical joint motion during both cervical flexion and extension movements. The significant findings in dynamic cervical joint motion parameters are summarized in **Table 9**. Additionally, anti-directional motion, pro-directional motion, joint motion variability and total joint motion during cervical flexion and extension were showed in **Fig.12-19**. The figures showing no changes of dynamic cervical joint motion parameters were presented in **Appendix C**.

Table 9. The overview of significant alterations in cervical joint motion parameters of three studies

Parameters	Study I				Study II				Study III	
	Hyper-Mul		Hyper-Tra		Hyper-Inter		Iso-Inter			
	Flex	Ext	Flex	Ext	Flex	Ext	Flex	Ext	Flex	Ext
Anti-directional motion		✓		✓		✓			✓	✓
Joint motion variability				✓		✓				✓
Pro-directional motion				✓						
Total joint motion										

Hyper: hypertonic saline; Iso: isotonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament. Flex: flexion; Ext: extension. ✓indicates a statistical difference.

5.3.1. DIFFERENCES BETWEEN DEEP VS SUPERFICIAL MUSCLE PAIN EFFECTS ON CERVICAL JOINT MOTION

Cervical muscles are the direct performers of the neuromuscular control system. The normal functions of cervical muscles and the coordination between cervical muscles ensure the dynamic stability of the cervical spine during neck movements[207]. With respect to the anatomical features, deep and superficial cervical muscles were supposed to have different functions in cervical joint motion. Deep cervical muscles normally have small ranges and direct attachments to the cervical vertebrae[49, 50]. Additionally, they are very rich of proprioceptors and play a crucial role in the sense of cervical joint position during neck movements[55, 208]. Therefore, deep cervical muscles are supposed to control individual cervical joints, while superficial muscles normally have a large range crossing several cervical joins and are believed to be motion initiators[49, 50]. Functions of deep and superficial cervical muscles were widely reported to be impaired in the presence of experimental and clinical neck pain[114]. Patients with neck pain are normally associated with decreased activity of the deep cervical muscles and increased activity of the superficial cervical muscles[43, 114, 157, 209, 210]. In hypertonic saline induced experimental neck pain studies, the injected muscle generally showed decreased activity with decreased or increased activity of the other relevant muscles[129].

In study I, deep cervical muscle pain increased the anti-directional motion of C3/C4 and decreased the anti-directional motion of C6/C7 during cervical extension while superficial cervical muscle pain decreased the overall anti-directional motion during cervical extension (**Fig.12**). Additionally, superficial cervical muscle pain also

decreased the overall pro-directional motion and joint motion variability during cervical extension (**Fig.13, Fig.14**). The findings indicated deep cervical muscle pain had effects on individual cervical joint motion while superficial cervical muscle pain had effects on the entire neck motion[24]. Similar results were demonstrated in previous studies[56, 211]. Yoo et al. (2014) found that patients with trapezius muscle pain showed decreased motion of the entire neck but patients with levator scapular muscle pain only showed decreased motion of the upper cervical region[211]. In addition, experimental neck pain induced in deep and superficial cervical muscles was reported to cause different motor control strategies to maintain the isometric cervical force[56].

The cervical spine is a multi-joint structure and the joints interact with each other. Therefore, there is a compensation mechanism within the cervical spine[81, 212, 218]. Changes in motion of one cervical joint will consequently affect all the other joints but the effect sizes are various between joints[81, 212, 218]. Therefore, the motion change at C6/C7 could be the compensative response to the initial motion changes at C3/C4 during cervical extension (Study I). The compensative effect of a cervical joint is also related to the biological situation of the joint, such as disc degeneration and sagittal alignment which may affect the cervical joint motion[213]. The findings in study I indicated the cervical joint motion pattern may be related to the pain sources. When the pain was induced in the deep cervical muscle, the overall anti-directional motion during cervical extension was maintained with motion redistribution between joints C6/C7 and C3/C4 (Study I). In contrast, the superficial cervical muscle pain decreased the overall anti-directional motion, pro-directional motion, and joint motion variability during cervical extension, which may indicate the effect of neck pain has been beyond the compensative ability of the cervical spine (Study I). This finding reinforces the difference between pain induced in deep and superficial cervical muscles.

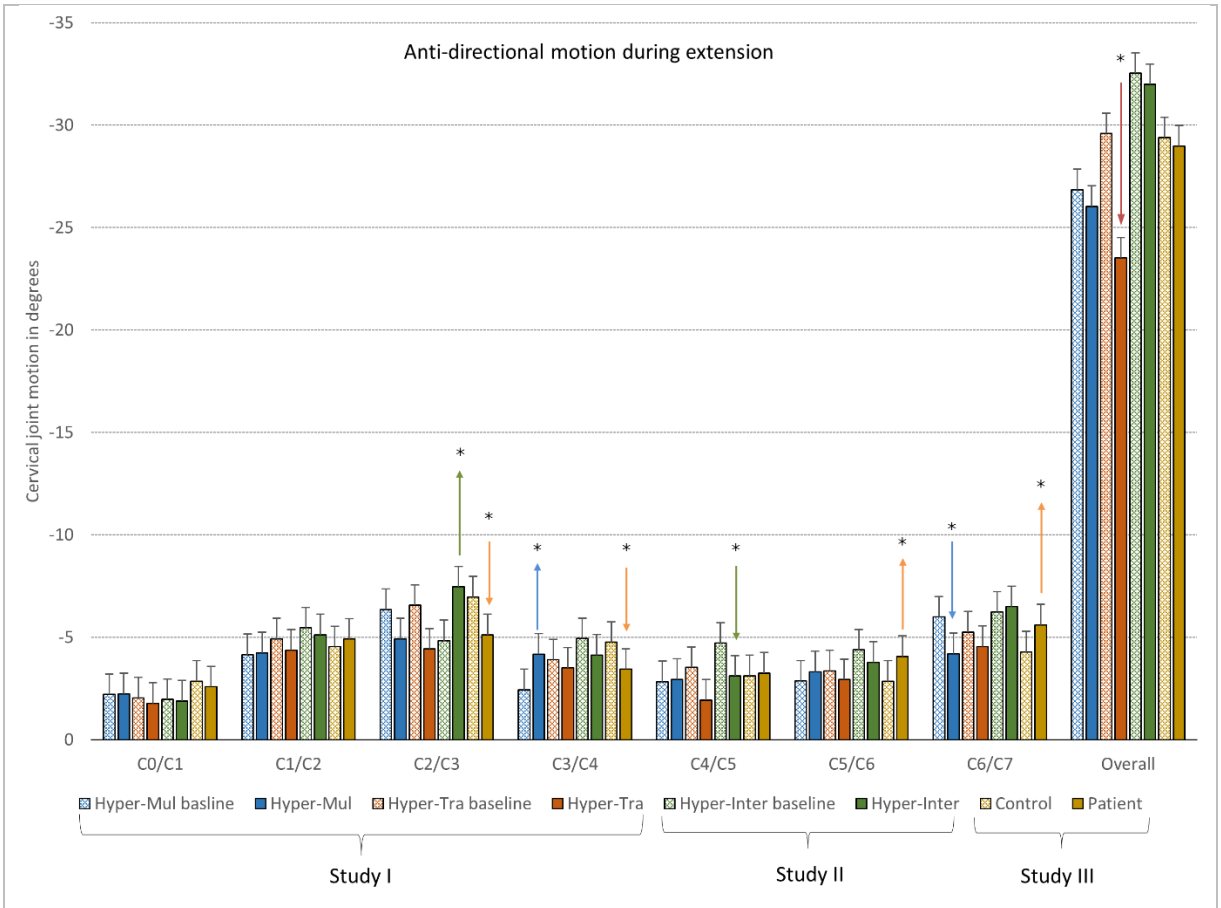


*Figure 12. Anti-directional motion during cervical extension with different pain conditions. Hyper: hypertonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; Control: healthy control; Patients: patients with recurrent neck pain. The direction of the arrow indicated the increasing or decreasing changes compared with the baselines. Significant differences compared with before pain: * P < 0.05. Data were obtained from Study I-III.*

Many studies have shown previously that neck pain impaired the synergistic modular control of cervical muscles[129]. Therefore, the changes in the anti-directional motion during cervical extension may result from the altered recruitment strategies of cervical muscles during pain conditions[129, 214]. The previous studies have demonstrated redistributed muscle activity during experimental pain conditions or when the spinal tissue creep[114, 215]. The central nervous system assumed the spine was unstable under pain conditions, therefore, more spinal muscles were activated to keep the spinal stability[46]. The musculoskeletal dysfunctions during pain could alter tissue loading, the direction, and the magnitude of joint forces and contribute to the altered cervical joint motion patterns[47, 48, 216].

However, no previous studies have shown dynamic electromyogram (EMG) data of cervical muscles correlating to cervical joint motion during neck movements. Nevertheless, the results of a lumbar motion study have shown the relationship between individual lumbar joint motion during epochs of lumbar movement and the activities of the deep and superficial low back muscles[217]. The increase of lumbar joint motion was synchronously accompanied by decreased activity of deep lumbar muscles and increased activity of superficial lumbar muscles[217]. Moreover, the activity of deep lumbar muscles alone was correlated to changes of individual lumbar joint motion[217]. The findings in Study I showed that deep cervical muscle pain had effects on the individual cervical joint motion while superficial cervical muscles had effects on the entire neck motion. Therefore, the increased anti-directional motion at C3/C4 may be mainly resulted from the altered activity of the multifidus muscle and caused the motion compensation at C6/C7 to maintain normal cervical extension[81, 212, 218]. Additionally, the results also indicated that cervical joint motion may depend on the coordination between deep and superficial cervical muscles. The decreased overall anti-directional motion, pro-directional motion, and joint motion variability during trapezius muscle pain may derive from the altered motor control strategy between deep and superficial cervical muscle[56]. The trapezius muscle does not allow direct controls on the individual cervical joint, the activity of deep cervical muscles may also be altered during the trapezius muscle pain[24, 214]. Cagnie et al. have shown that experimental pain induced in the right upper trapezius muscle caused reduced activities of bilateral multifidus and semispinalis

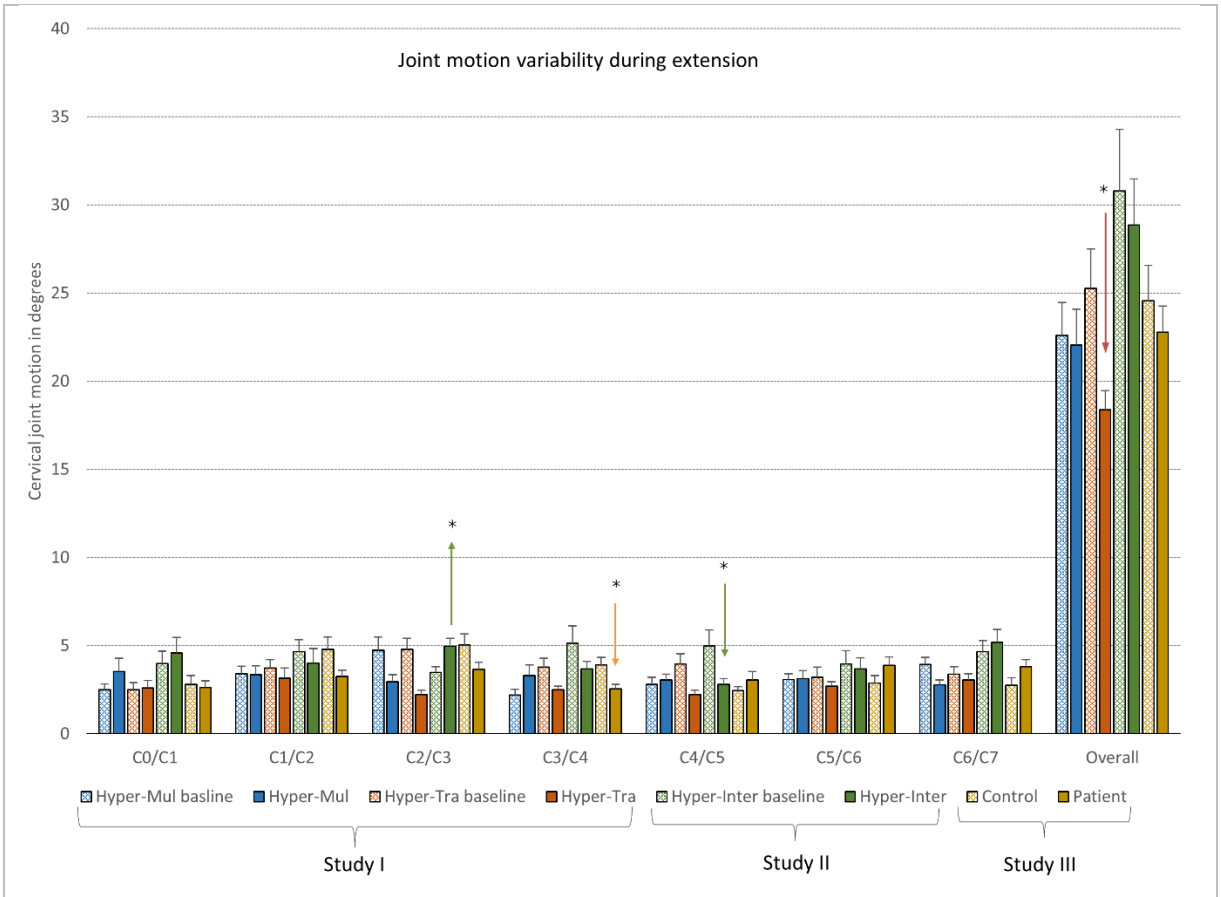


*Figure 13. Joint motion variability during cervical extension with different pain conditions. Hyper: hypertonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; Control: healthy control; Patients: patients with recurrent neck pain. The direction of the arrow indicated the increasing or decreasing changes compared with the baselines. Significant differences compared with before pain: * P < 0.05. Data were obtained from Study I-III.*

cervicis muscles at C7/T1 level during the extension exercise[214]. This may explain the decreased anti-directional motion and pro-directional motion over all cervical joints of cervical extension during trapezius muscle pain.

In study I, the total joint motion was comparable to the motion of individual cervical joints assessed at static upright and end-range positions of cervical flexion and extension in previous studies[23, 82, 219]. No significant findings were demonstrated in the total joint motion of flexion and extension during deep and superficial cervical muscle pain (**Appendix C: Fig.16, Fig.17**). The results were in line with previous studies showing that dynamic motion parameters during neck movements revealed more impairments related to neck pain compared to motion parameters assessed at static and end-range positions of neck movemnets[26, 27, 61]. In addition, total joint motion consists of two motion parts: anti-directional motion and pro-directional motion[94]. Therefore, the changes of total joint motion during experimental pain rely on the changes in both anti-directional and pro-directional motion, which may explain the unchanged total joint motion during deep and superficial cervical muscle pain.

The motion alterations during experimental neck pain were all found during the cervical extension movement (**Table 9**). The results indicated that the effects of deep and superficial cervical muscle pain may be direction-dependent. Falla et al. (2006) also demonstrated that the motor control strategies are different between flexion and extension directions during the experimental neck pain[56]. This may be related to the functional role of the cervical muscle (agonist or antagonist) during cervical flexion and extension[56]. In study I, the trapezius and multifidus muscle both play an agonist role during cervical extension. Therefore, both deep and superficial muscle pain in study I may mainly affect the synergistic modular control of cervical muscles during cervical extension[220].

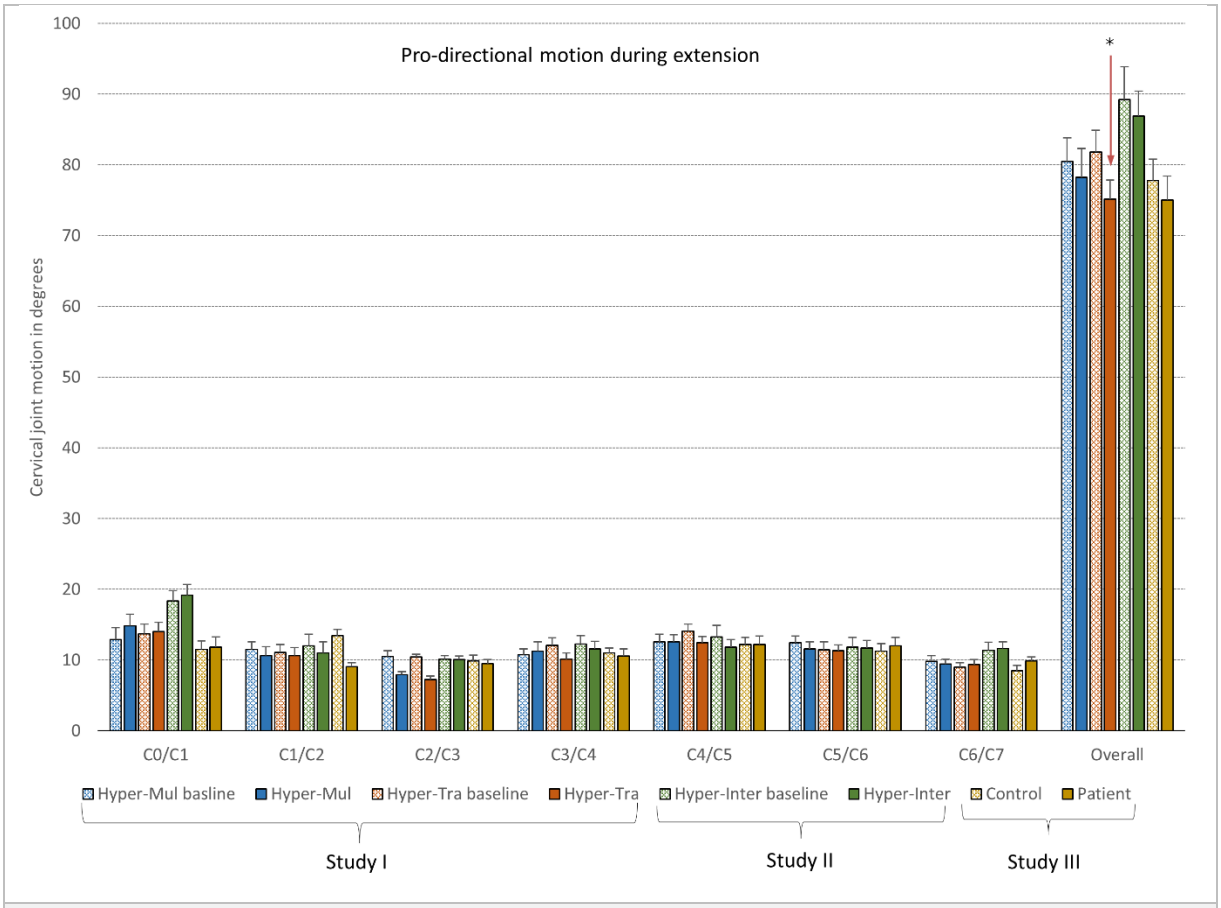


*Figure 14. Pro-directional motion during cervical extension with different pain conditions. Hyper: hypertonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; Control: healthy control; Patients: patients with recurrent neck pain. The direction of the arrow indicated the increasing or decreasing changes compared with the baselines. Significant differences compared with before pain: * P < 0.05. Data were obtained from Study I-III.*

In summary, deep cervical muscle pain showed effects on individual cervical joint motion and superficial cervical muscle pain showed effects on the entire neck motion during cervical extension movement. The findings indicated the potential different motor control strategies of the neck when the pain originated in deep and superficial cervical muscles. Additionally, the findings in dynamic cervical joint motion may be explained by the altered activity of cervical muscles and the impaired synergistic modular control of cervical muscles during pain conditions. Most of the motion alterations were found during cervical extension movement indicates the effects of deep and superficial cervical muscle pain may be direction-dependent.

5.3.2. DIFFERENCES BETWEEN LIGAMENT VS MUSCLE PAIN EFFECTS ON CERVICAL JOINT MOTION

Inter-spinous ligaments have no direct active functions, like cervical muscles, to control cervical joint motion. However, previous studies demonstrated mechanoreceptors embedded in various ligament structures and the afferent input ascending to the CNS contributed to proprioception, motor control, and joint stability[221]. Abnormal signals from mechanoreceptors in ligaments could modify the neuromuscular control system and eventually result in altered motion patterns[197, 222, 223].

In study II, the inter-spinous ligament pain induced by hypertonic saline showed effects to decrease the anti-directional motion of C4/C5 and consequently increase the anti-directional motion of C2/C3 during the cervical extension movement (**Fig.12**). Additionally, the joint motion variability decreased at C4/C5 and increased at C2/C3 during cervical extension movement (**Fig.13**). However, the injection of an equal volume of isotonic saline in the same inter-spinous ligament did not cause any significant alterations in dynamic cervical joint motion parameters (**Table 9**). The decreased anti-directional motion at C4/C5 of cervical extension implied a restrictive motor control strategy at C4/C5 during experimental inter-spinous ligament pain. The finding was in line with previous studies showing that patients with neck pain conducted neck movements in a more restrictive and rigid strategy compared to healthy subjects, although different motor outputs were assessed[58, 59]. The ligaments were functionally connected to the surrounding muscles by the ligamento-muscular reflex[44, 224]. Paraspinal muscles (such as multifidus muscle) could be activated by a stimulus in ligaments and restrict the segmental cervical joint motion during neck movements[44, 52, 53, 225]. Therefore, experimental pain induced in the inter-spinous ligament may cause the activation of deep cervical muscles and resulted in a decrease of anti-directional motion at the injected joint during cervical extension movement[44, 52, 53, 225]. Consequently, the increased anti-directional motion at C2/C3 may be due to the compensative mechanism within the cervical spine which was well stated in previous studies in patients associated with different pathological conditions of the cervical spine[81, 212, 218].

In contrast to the effects of superficial cervical muscle pain on the entire neck motion (Study I), the inter-spinous ligament pain (Study II) showed similar effects to deep cervical muscle pain on individual cervical joint motion (**Fig.12**). The results indicated that the pain induced in the inter-spinous ligament may affect the deep cervical muscles more than the superficial cervical muscles during cervical extension[225]. Although deep cervical muscle pain and inter-spinous ligament pain both redistributed the anti-directional motion between joints during cervical extension, the effects were different with respect to the alterations of anti-directional motion at the joint close to the injection site. Deep cervical muscle pain decreased the anti-directional motion at C3/C4 during cervical extension movement, while inter-spinous ligaments pain increased the anti-directional motion at C4/C5 during cervical extension movement (**Fig.12**). The different motion responses at the joint close to the injection site implied the underlying mechanisms may be different when experimental pain were induced in muscle tissues and ligament tissues of the neck. The increase of anti-directional motion at C3/C4 during deep cervical muscle pain was suggestive of a less control on the joint[24]. While the decrease of anti-directional motion at C4/C5 during inter-spinous ligament pain indicated a restrictive motor control strategy which was consistent with previous studies showing general restrictive strategies in patients with neck pain regardless of the pain source[58, 59]. Previous studies have shown that stimulations in ligaments activated the surrounding muscles and restricted the given joint motion[52, 53, 225]. On the contrary, the muscle injected with hypertonic saline normally showed decreased activity during motor tasks[129] Therefore, it is reasonable to speculate that the neuromuscular control system may increase the activity of the deep cervical muscles and decrease the anti-directional motion when the pain originated in the inter-spinous ligament[225]. Conversely, if the pain originated in the deep cervical muscles, the neuromuscular control system was unable to increase the activity of the painful muscle and resulted in the increased anti-directional motion of the joint[129].

In line with deep and superficial cervical muscle pain, inter-spinous ligament pain caused no changes in the total joint motion both during flexion and extension (**Appendix C: Fig.16, Fig.17**). However, inter-spinous ligament pain increased joint motion variability at C2/C3 and decreased it at C4/C5 during cervical extension which was different from the effect of multifidus muscle pain (**Fig.12**). The joint motion variability is calculated based on anti-directional motion and pro-directional motion. Therefore, the changes in joint motion variability may be explained by changes in anti-directional motion at C2/C3 and C4/C5 (Study II). Together with results demonstrated during superficial cervical muscle pain that the overall joint motion variability decreased during cervical extension with decrease in the overall anti-directional motion and pro-directional motion (Study I), the joint motion variability can be affected by both anti-directional motion and pro-directional motion but may be more sensitive to changes in the anti-directional motion.

In summary, experimental pain induced in the inter-spinous ligament showed effects on individual cervical joint motion during cervical extension which was similar to the effects of deep cervical muscle pain. Although both inter-spinous ligament pain and deep cervical muscle pain redistributed anti-directional motion between joints during cervical extension, the effects were different with respect to the changes of anti-directional motion at the joint close to the injection site. The increase of anti-directional motion at C3/C4 during deep cervical muscle pain was suggestive of a strategy of less control on the joint. While the decrease of anti-directional motion at C4/C5 during inter-spinous ligament pain indicated a restrictive control on the joint. The findings indicated the underlying motor control strategy may be different when experimental pain was induced in the muscle and ligament tissues of the cervical spine.

5.3.3. DIFFERENCES BETWEEN EXPERIMENTAL VS CLINICAL NECK PAIN EFFECTS ON CERVICAL JOINT MOTION

Patients with neck pain have been widely reported to show altered motion patterns compared with healthy controls when conducting the same motor task[58, 61, 86, 90, 226, 227], although different motor outputs were measured between studies. Patients with neck pain normally have reduced ROM, reduced peak velocity, reduced mean velocity, reduced smoothness of movement, reduced reposition acuity, larger ROM-variability, reduced conjunct motion, increased joint position error, poor movement control and a lower degree of movement coordination when comparing with healthy controls[58, 61, 86, 90, 226, 227]. However, those studies either reported quantitative parameters at static positions of the neck or dynamic qualitative parameters assessing the entire neck. The quantitative assessment of dynamic cervical joint motion parameters during neck movements in patients with neck pain was seldom studied. Emerging studies have shown that the patterns of cervical joint motion during cervical flexion and extension are not linear[24, 27, 28, 94, 96, 197, 198].

In study III, patients with recurrent neck pain showed decreased anti-directional motion at C2/C3 and C3/C4 and increased anti-directional motion at C5/C6 and C6/C7 during cervical extension movement (**Fig.12**) and increased overall anti-directional motion during cervical flexion movement compared to healthy controls (**Fig.15**). The redistribution of anti-directional motion between joints during cervical extension was also demonstrated in experimental deep cervical muscle pain (Study I) and experimental inter-spinous ligament pain (Study II) models in the thesis, but the clinical neck pain affected more cervical joints compared with experimental neck pain. Patients with recurrent neck pain increased the overall anti-directional motion during cervical flexion, which indicated an effect on the entire neck motion. The experimental superficial muscle pain also showed effects on the entire neck motion, but it decreased the overall anti-directional motion during cervical extension (Study I). Normally, the clinical neck pain is complex with multiple pain foci[172], which is different from the one pain focus in experimental neck pain models in the thesis. Additionally, the larger pain distribution of patients with recurrent neck pain compared with the experimental pain models (**Section 3.4.2**) may explain why more cervical joints were affected in recurrent neck pain when compared to the experimental pain models. However, since the pain sources of patients with recurrent neck pain are unable to be located, the causal relationship between the decreased anti-directional motion of middle cervical joints and the increased anti-directional motion of lower cervical joints during cervical extension remains unclear. Impaired functions of cervical extensor and flexor muscles were extensively reported in patients with neck pain[43, 50, 228], which was different from the experimental superficial cervical muscle pain model that pain was only induced in one superficial extensor muscle. The potential difference in the impaired muscles and the consequent motor control strategies between clinical neck pain and experimental

neck pain may explain the increased overall anti-directional motion during cervical flexion in patients with recurrent neck pain.

According to our previous studies, deep cervical muscle pain and inter-spinous ligament pain redistributed anti-directional motion between cervical joints and superficial cervical muscle pain decreased the overall anti-directional motion (Study I and Study II)[24, 28]. Moreover, the cervical joint motion was more likely to be affected during cervical extension when the pain was induced in the extensor muscles[24, 28]. Therefore, the finding that both flexion and extension movements were affected in patients with recurrent neck pain indicated both flexor and extensor muscles may be impaired in patients with recurrent neck pain, and most probably they were superficial flexor and deep extensor muscles.

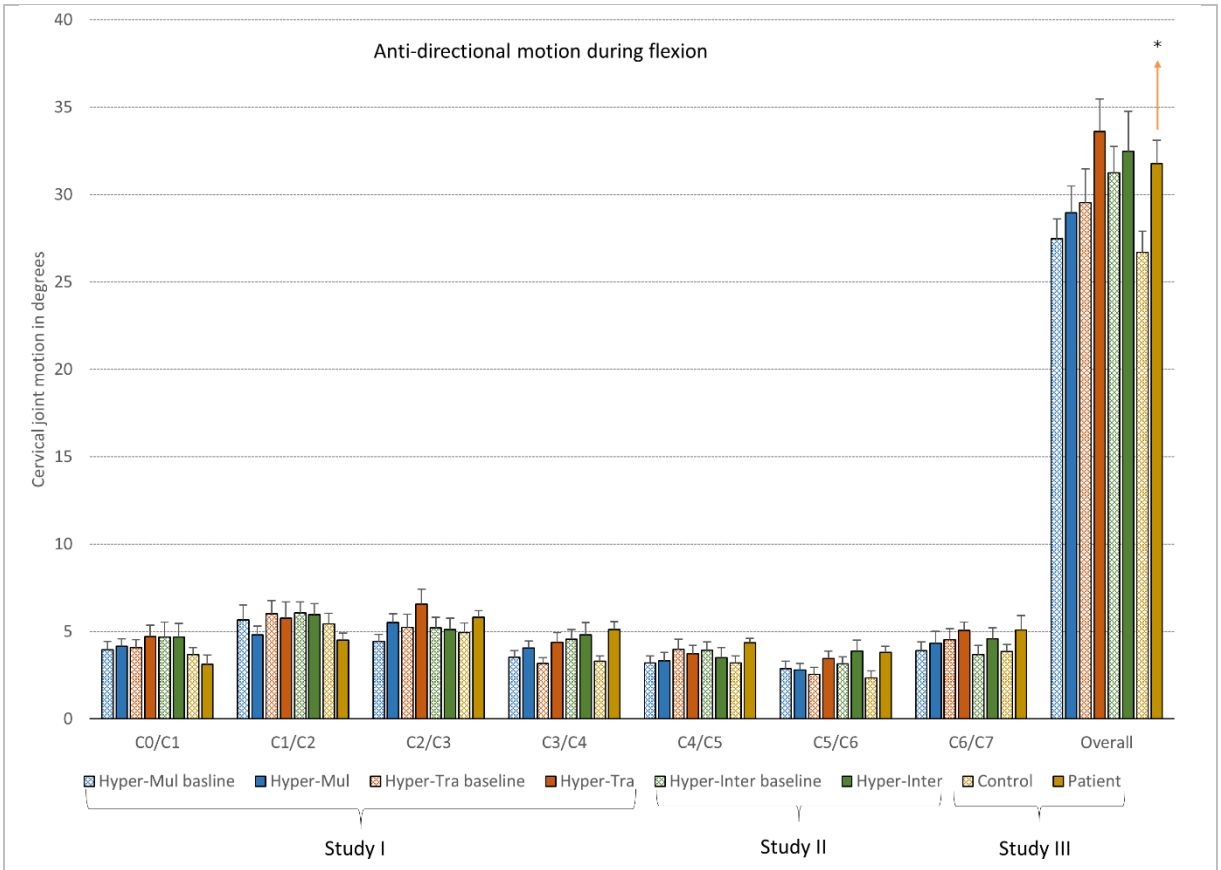


*Figure 15. Anti-directional motion during cervical flexion with different pain conditions. Hyper: hypertonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; Control: healthy control; Patients: patients with recurrent neck pain. The direction of the arrow indicated the increasing or decreasing changes compared with the baselines. Significant differences compared with before pain: * P < 0.05. Data were obtained from Study I-III.*

No difference in the total joint motion was demonstrated between patients with recurrent neck pain and healthy controls. The result was analogous to our own experimental pain studies (Study I and Study II). Additionally, the result agreed with a previous clinical neck pain study that the assessment of total joint motion was sometimes unable to find the motion difference between patients with neck pain and healthy controls[231]. In light of such observations, dynamic cervical joint motion parameters during neck movements were inclined to reveal more motion impairments related to neck pain compared with motion parameters measured at the static and end range of neck movements[61, 90, 231].

In addition, neck pain is a multifactorial disease which is influenced by many biological and psychosocial factors[13, 14]. The current study could not completely exclude the effects of other potential factors. For instance, patients with neck pain were presumably different from healthy subjects with experimental induced neck pain regarding the

psychosocial states (e.g. anxiety, depression, catastrophizing, fear-avoidance behavior, distress), which may contribute to the different motor effects between clinical neck pain and experimental neck pain[142, 229, 230].

In summary, the patients with recurrent neck pain showed altered patterns of dynamic cervical joint motion compared with healthy controls. The anti-directional motion was redistributed between the middle and lower cervical spine during extension movement and the overall anti-directional motion decreased during cervical flexion movement in patients with recurrent neck pain compared with healthy controls. Clinical neck pain affected more cervical joints compared with experimental neck pain and affected both cervical flexion and extension movements.

5.3.4. DIFFERENCES OF NECK PAIN EFFECTS ON CERVICAL JOINT MOTION BETWEEN FLEXION VS EXTENSION

In study I and study II, all the motion alterations were found during cervical extension movement[24, 28]. In study III, the motion alterations were found during both flexion and extension movements, but the alterations were different between flexion and extension movements. The evidence suggested that the effect of neck pain may be direction-dependent. In healthy subjects, previously studies have shown that cervical joint motion patterns are not linear and are different between cervical flexion and extension movements[27, 91, 92, 94, 95]. Similarly, previous studies demonstrated that the motor control strategies of cervical flexion and extension movements are different during experimental pain conditions[56, 232]. When the experimental pain was induced in ether the flexor muscle or the extensor muscle, the cervical flexion movement depends on the coordination between agonist and antagonist muscles and the cervical extension depends on the coordination between agonist and the synergistic muscles[56]. Rudolfsson et al. (2012) also demonstrated that the cervical joint motion was affected differently between flexion and extension movements in patients with neck pain[74]. The upper cervical joint motion reduced during cervical extension while the lower cervical joint motion reduced during cervical flexion in patients with neck pain[74]. The anatomical differences between anterior and posterior cervical structures may be the reason motor demands are different between flexion and extension movements[199]. Cheng et al. (2008, 2014) further demonstrated different patterns in the co-contraction of cervical muscles between cervical flexion and extension movements[57, 233]. Additionally, the cervical joints do not move simultaneously during neck movements[27, 91]. The upper cervical joints start first during the flexion movement and the lower cervical joints start first during the extension movement[27, 91]. The opposite moving order of cervical joints requires different motor control strategies for cervical flexion and extension.

In summary, the effects of neck pain on the cervical joint motion may be direction-dependent. The anatomical differences between anterior and posterior cervical structures may explain the different motor demands between cervical flexion and extension movements.

5.3.5. THE SENSITIVE JOINT MOTION PARAMETER TO NECK PAIN

Many different motor outputs (maximal force, submaximal force, ROM, speed and smoothness, etc.) were investigated in previous experimental and clinical neck pain studies, which either reduced or unchanged during the pain conditions[56, 61, 85, 90, 129, 209, 234]. These motor outputs were not able to reflect the effect of impairments in specific cervical structures. One reason is that they were gross motor outputs and/or measured at a static position, which reduced the weight of individual cervical structure in the motor outputs. Another reason is due to the complicated compensative mechanism within the cervical spine[56, 129, 234]. The motor deficit of one cervical structure will be compensated by another structure and may finally result in unchanged gross motor outputs. Therefore, the motor deficit from individual cervical structure could not be detected by measuring the gross motor outputs. Conversely, dynamic cervical joint motion during neck movements requires continuous sensory inputs regarding the position, speed and loading status of the cervical spine from the related cervical structures[64, 65], which could be more representative of the motor deficit of individual cervical structures.`

The anti-directional motion is a common healthy motion phenomenon of the cervical spine, which could be demonstrated by investigating cervical joint motion during dynamic neck movements[24, 27, 94, 95]. Whether a cervical joints experienced flexion or extension depends on the relative position between the force vector and the instantaneous center of rotation (ICR) of the cervical vertebra[39, 235, 236]. If the force vector is behind the ICR of a vertebra during cervical flexion, the vertebra will extend, and vice versa[39]. Additionally, the cervical joints do not move simultaneously during neck movements, while the cervical flexion movement starts from the upper joints and the cervical extension movement starts from the lower joints[27, 91]. The cervical joints moving early may need to adjust anti-directionally to keep the cervical stability or keep the proper loading spread during neck movements[39]. The location of the ICR changed with the range of motion and are different between cervical vertebrae[25]. The location of the ICR is sensitive to the disc degeneration and the ligament damage[236]. The location of the ICR was also previously demonstrated to be more sensitive to neck pain compared with cervical ROM and translation[237], which may explain more findings were found in the anti-directional motion than other motion parameters in the thesis.

In summary, the anti-directional motion is a healthy motion phenomenon of the cervical spine and is the most sensitive motion parameter affected by experimental neck pain and clinical neck pain in the thesis. The alterations in anti-directional motion may be explained by changes in the location of the ICR during neck pain.

5.3.6. MULTIFACTORIAL NATURE OF NECK PAIN

The thesis mainly investigated motor and sensory perspectives of neck pain. However, neck pain is a complex multifactorial disease and many factors other than the motor and sensory aspects must be considered. George Engel proposed the biopsychosocial model in mid-20th century[238, 239], after which the biological, psychological and psychosocial factors of a disease were investigated individually or jointly. The biopsychosocial model was widely accepted in the neck pain studies[240]. Within the biological component, changes in muscle morphology[241, 242], altered muscle activities[162, 210, 215, 243, 244], motor impairments[143, 245-247], morphological and functional brain alterations[248] were commonly found in patients with neck pain. For the psychological perspective, psychological distress which included depression, anxiety, obsessive-compulsive, hostility, mental illness, illness worrying, and coping strategy, etc. were showed in association with the development of neck pain[10, 249, 250]. For the psychosocial perspective, positive relationships were reported between neck pain and high quantitative job demands, poor social support, low job control, low skill discretion, and low job satisfaction[251]. Other factors, such as age, gender, pain intensity, duration of the current episode of neck pain, a previous history of neck problems, co-existing shoulder problems and other musculoskeletal disorders were also reported to influence neck pain[116, 252].

Several psychological and psychosocial factors were also reported to influence the neck movements. A negative correlation was previously demonstrated between the pain catastrophizing scale and the cervical ROM[253]. In addition, the fear of movement was also negatively correlated to the cervical ROM[142]. The healthy subjects in study I-III were screened to exclude preexistent psychological factors which may influence the cervical joint motion. However, the psychological status of patients with recurrent neck pain was not evaluated in the thesis. Therefore, the potential effects of psychological factors on dynamic cervical joint motion in study III could not be eliminated. Nevertheless, the psychological factors were mainly reported to influence the cervical ROM. The effects of those psychological factors on the individual cervical joint motion remain unclear. Additionally, no significant difference in the cervical ROM was demonstrated in the thesis. As stated earlier, the observed findings of dynamic cervical joint motion in experimental and clinical neck pain may be related to several factors, the study was not designed to check the effects of these factors on dynamic cervical joint motion rather than neck pain.

CHAPTER 6. LIMITATIONS

1. The thesis only investigated dynamic cervical joint motion in the sagittal plane. However, the cervical joint motion is three-dimensional. The motion in the sagittal plane is associated with axial rotation and lateral bending [58, 59, 254], which may have led to discrepancies in the angles extracted via two-dimensional analysis. A solution to this limitation would be a better control for the out of plane motion or a method to investigate the differences between the 3D multi-planar motion and the uni-planar motion.

2. Degeneration of cervical structures is an age-related issue which starts from the second decade of life and has been shown to affect cervical joint motion[80, 255]. Similarly, the curvature of the neck was related to cervical joint motion[80, 204]. However, the results of the thesis were not adjusted for these factors due to the small sample sizes. A solution for this limitation would be an evaluation of the degeneration status and the curvature of the neck of participants and doing subgroup analysis on cervical joint motion according to classifications of the degeneration status and the curvature of the neck[256].

3. The manual marking method used in the thesis requires great accuracy, hence one of the most common errors in extracting cervical joint motion during flexion and extension is the marking error made by the examiner [257]. Additionally, the manual marking method is time-consuming. All the fluoroscopic videos were only marked one time and only 10 epochs of cervical joint motion during the neck movements were analyzed due to this limitation. The limitation could be solved by applying automatic cervical vertebrae tracking techniques. With the application of the automatic cervical vertebrae tracking techniques, it would be possible to analyze more epochs and even the full image sequences of the neck movements with a shorter time compared with manual marking procedure. However, the automatic cervical vertebrae tracking techniques are not well developed and they make large measurement errors at present[258].

4. The subjects in study I and study II only represented a young healthy population sample. However, factors such as age, gender, and BMI were reported to influence neck motion patterns [121]. A solution for this will be evaluating the difference in cervical joint motion between different age ranges, gender, and BMI in a larger population. Additionally, the healthy subjects in study I-III were recruited if they had no neck pain within the last 3 months. There was a risk that those healthy subjects were actually in the remission period of recurrent neck pain, since the remission period of patients with recurrent neck pain could last longer than 3 months. However, this may happen probably during the first remission episode, when the participant does not realize it is recurrent neck pain. Additionally, the participants were screened for the history of cervical muscular disease, which makes the risk very low.

5. The variability of motion baselines existed between different studies and the standard motion baseline was absent. Repeated measurements on cervical joint motion in a large healthy sample could help to establish the standard motion baseline.

CHAPTER 7. FUTURE PERSPECTIVES

1. The thesis investigated cervical joint motion during experimental pain induced in the extensor muscles and inter-spinous ligament. However, the cervical spine is a complex structure which includes many muscles, ligaments, bones, and discs, etc. Further studies may focus on the effects of pain induced in other cervical structures, such as cervical flexors or supra-spinous ligament, on dynamic cervical joint motion. The results may help to indicate the potential pain sources of different clinical neck pain conditions. Additionally, clinical neck pain is more complex when compared with experimental neck pain. Future studies could investigate the motor effects of more complicated neck pain conditions, such as pain induced at bilateral sides of the neck, a combination of extensor pain and flexor pain or a combination of ligament pain and muscle pain.

2. Anti-directional motion is a parameter, which is sensitive to potential motion differences between patients with recurrent neck pain and healthy controls in the thesis. However, the thesis only studied patients during their recurrence episodes of neck pain. The motion characteristics of the same patient group before they had neck pain or during the remission episodes were not available. Further studies should investigate the cervical joint motion in patients with recurrent neck pain during both remission and recurrence episodes to check if the motion alterations are persistent. The findings may shed new light on the causes of the recurrence of neck pain.

3. The dynamic cervical joint motion parameters should be further studied in different types of patients with neck pain, for instance, acute neck pain, chronic neck pain and whiplash-associated neck pain, etc.[14]. The results may indicate if the anti-directional motion could be applied to subgroup patients with neck pain and design efficient target treatments. Further, dynamic cervical joint motion parameters before and after treatments or surgeries on patients with neck pain should be investigated. The results may indicate the efficiency of the treatment and surgery. Additionally, the results may help to understand the postoperative complications, such as the accelerated adjacent disc degeneration after single cervical joint fusion surgery. The accelerated adjacent disc degeneration may be related to the altered pattern of anti-directional motion.

4. The thesis investigated the effects of neck pain on dynamic cervical joint motion and pressure pain sensitivity. However, the cervical joint motion is mainly controlled by cervical muscles and the muscle recruitment pattern during neck movements may be important for the understanding of cervical joint motion alterations in patients with neck pain [217]. Therefore, further studies may investigate the cervical muscle activity and dynamic cervical joint motion simultaneously. Clarification of the relationship between these two perspectives may help to understand the complexity of the neck movements and explain the findings in the thesis.

CHAPTER 8. CLINICAL IMPLICATIONS

The results of the thesis showed some implications for clinical practice and future researches.

The thesis proposed an alternative motion assessment method of neck pain which may supplement the traditional assessment methods in the future. The results indicated that investigations of dynamic cervical joint motion during neck movements may reveal the impairments of neck pain which could not be reflected by assessments at static and end ranges of the neck movements. Dynamic cervical joint motion parameters, especially the anti-directional motion, may be sensitive to neck pain. Although it is too early to state the diagnostic value and further applications of this parameter in clinical practice, assessing dynamic cervical joint motion showed the potential to locate the motion impairments of neck pain at the individual cervical joint levels, and to some extents, reflect the pain sources in the surrounding soft structures. Therefore, assessment of dynamic cervical joint motion may help clinicians to identify the pain sources in non-specific neck pain patients or whiplash patients which were supposed to be related to soft tissue damage and may provide target treatments and evaluate the effect of treatments in the future. However, it should be kept in mind that neck pain is a multifactorial biopsychosocial disease that the parameters themselves could not stand alone and should be considered with other assessment parameters to get a comprehensive overview of neck pain.

Previous studies widely demonstrated an altered motor control strategy in patients with neck pain in terms of muscle activity[114, 157, 210], however, whether the changes in cervical muscle activity affect cervical motion remains unclear. The results provided supports to the clinical treatments on deep and superficial cervical muscle dysfunctions and implied that the dysfunctions of deep and superficial muscle needed to be addressed in patients with neck pain. Additionally, the deep cervical muscles are important for the dynamic stability of individual cervical joints during neck movements[232].

The results indicated that the cervical ligament injury also affected the dynamic cervical joint motion. It challenges the previous notions that the cervical inter-spinous ligament merely contributes to the restriction of cervical flexion at the end of the motion[51]. The ligament injuries were assumed to be the sources of chronic neck pain, such as chronic whiplash disorders[259]. Therefore, the results may help clinicians to identify the ligament injury in the acute phase of neck pain, design target treatments and prevent the pain from becoming chronic in the future.

The anti-directional motion was able to differentiate patients with recurrent neck pain from healthy controls in the thesis. Thus the pattern of anti-directional motion may in the future be used to subgroup patients with neck pain. The thesis has shown that pain originating in cervical muscles and ligaments affected dynamic cervical joint motion patterns. Therefore, soft tissue damage during cervical spinal surgeries may need to be considered by orthopedic surgeons and the emphasis also needs to be on how to reconstruct the cervical structures. Improper reconstruction of cervical structures may lead to abnormal cervical joint motion patterns which may contribute to postoperative complications and postoperative neck pain.

The thesis showed that the cervical joint motion patterns during neck movements are nonlinear with scattered anti-directional motions, which is consistent with previous studies[24, 28, 94, 96]. The thesis provided biomechanical background knowledge of cervical joint motion during neck movements, which may help to design better cervical implants in the future. For example, the artificial discs may be required to maintain the dynamic characteristics of cervical joint motion during neck movements.

CHAPTER 9. CONCLUSIONS

The results and conclusions of the PhD thesis were summarized in **Fig.20**, which was in line with the aims in **Fig.1**.

Three aims of the thesis were: 1) to investigate the effects of deep and superficial cervical muscle pain on dynamic cervical joint motion parameters and PPTs over bilateral C2/C3 and C5/C6 facet joints (Study I); 2) to investigate the effects of cervical ligament pain on dynamic cervical joint motion parameters and PPTs over bilateral C2/C3 and C5/C6 facet joints (Study II); 3) to investigate dynamic cervical joint motion parameters and PPTs over bilateral C2/C3 and C5/C6 facet joints and right TA between patients with recurrent neck pain and healthy controls (Study III).

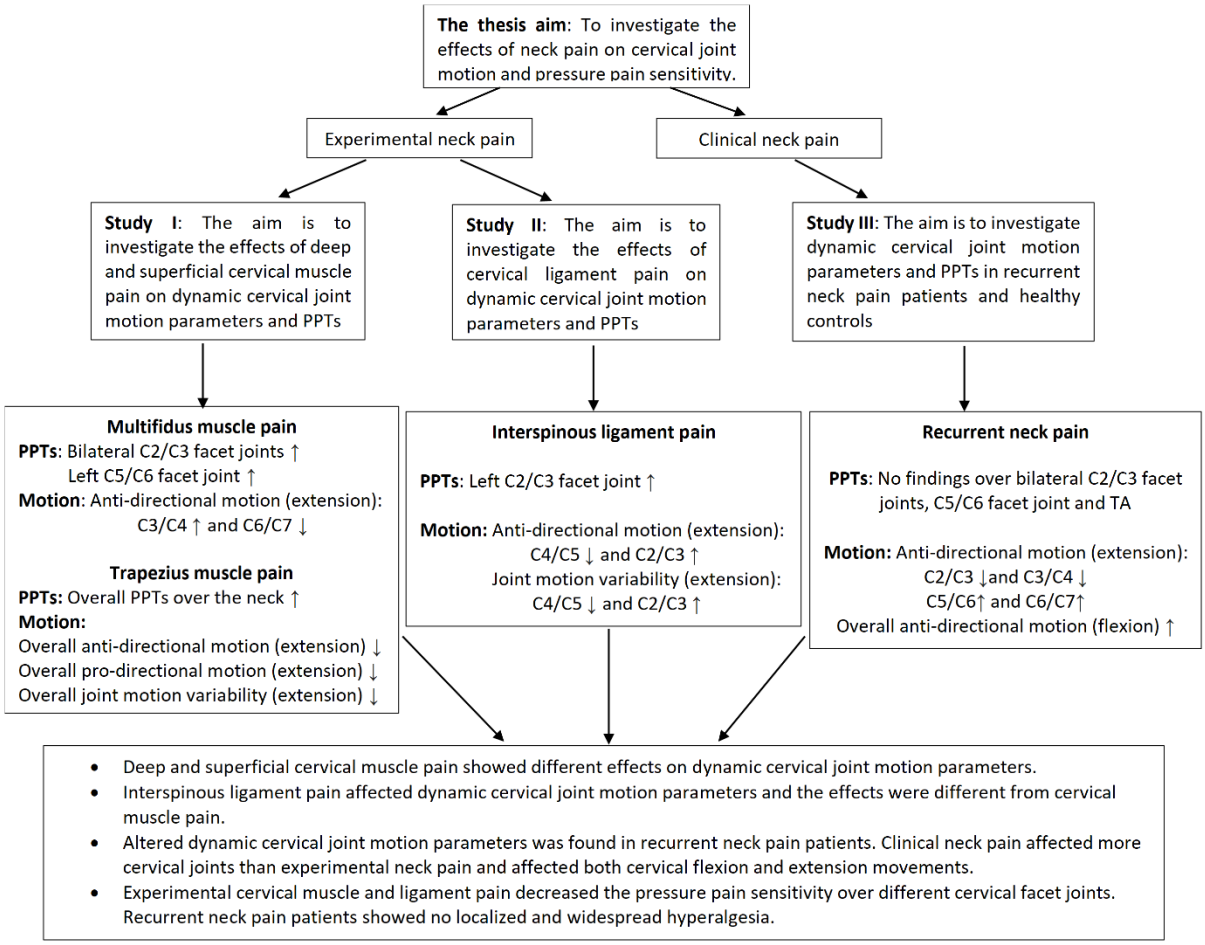
The results of study I and study II showed that pain originating from cervical muscles and ligaments affected dynamic cervical joint motion. Deep cervical muscle pain and cervical inter-spinous ligament pain both significantly affected individual cervical joint motion. Deep cervical muscle pain redistributed anti-directional motion between cervical joints during extension and the cervical inter-spinous ligament pain redistributed the anti-directional motion, and joint motion variability between cervical joints during extension. Superficial cervical muscle pain significantly affected the entire neck motion by reducing the overall anti-directional motion, pro-directional motion and joint motion variability during extension. Moreover, the effects on dynamic cervical joint motion were influenced by the pain sources. Additionally, cervical muscle and ligament pain significantly increased PPTs over different cervical facet joints.

The results of study III showed that patients with recurrent neck pain had a significantly different anti-directional motion pattern during cervical flexion and extension compared with healthy controls and no significant difference in PPTs over cervical facet joints and TA were found between patients with recurrent neck pain and healthy controls.

The findings of the PhD thesis indicated that pain originating in different cervical structures showed different effects on dynamic cervical joint motion. The anti-directional motion was the most sensitive motion parameter to experimental and clinical neck pain in the thesis. Investigations of anti-directional motion in patients with neck pain may contribute to the diagnosis of neck pain with possibilities to reflect the pain sources.

The studies in the thesis are basic descriptive studies (Phase 1). The results in the thesis could not be applied directly to the clinical practice. Although the motion difference was demonstrated between patients with neck pain and healthy controls in the thesis, the results should not be over-interpreted. There is a long way for a parameter to be transferred from the basic science to clinical practice.

Figure 20. *The summary of the results in the thesis.*



CHAPTER 10. APPENDICES

Appendix A: Overview of studies investigating dynamic motion of the cervical spine

The appendix A is a summary of studies investigating dynamic motion of the cervical spine in both patients with cervical spine disorders and healthy controls by applying different devices. The types of patients include chronic nonspecific neck pain, whiplash associated disorder (WAD) and patients after single-level anterior arthrodesis surgery. The devices include Cineradiography, Video-fluoroscopy, Electromagnetic tracking system, Virtual reality (VR) assessment system, Biplane X-ray system, Dual fluoroscopic system, and Robotic DSA system.

Authors	Title	Participants	Parameters	Devices used to assess neck movement
Hino et al. 1999	Dynamic Motion Analysis of Normal and Unstable Cervical Spines Using Cineradiography	Patients with cervical spine disorders & Healthy controls	Angular motion pattern & longitudinal displacement pattern	Cineradiography (Arritechno 35, Arritechno, Germany)
Wu et al. 2007	The quantitative measurements of the intervertebral angulation and translation during cervical flexion and extension	Healthy participants	Intervertebral translation	Video-fluoroscopy system (Diagnost 97, Philips Corporation)
Woodhouse et al. 2008	Altered motor control patterns in whiplash and chronic neck pain	Whiplash associated disorder (WAD) patients & Chronic neck pain patients & Healthy controls	Conjunct motion in the two associated planes & ROM-variability &	3 Space Fastrak (Polhemus, Inc, Colchester, Vermont, USA)
Sjolander et al. 2008	Sensorimotor disturbances in chronic neck pain--range of motion, peak velocity, smoothness of movement, and repositioning acuity	Insidious neck pain patients & Whiplash associated disorder (WAD) patients & Healthy controls	Range of motion and peak velocity & Smoothness of movement & ROM-Variability & Repositioning acuity and bias &	Electromagnetic tracking system (FASTRAK™, Polhemus Inc, USA)
Bahat et al. 2010	The effect of neck pain on cervical kinematics, as assessed in a virtual environment	Chronic neck pain patients & Healthy controls	Response time & Peak and mean velocity & Number of velocity peaks & Time to peak velocity percentage	Virtual reality (VR) assessment system
Wu et al. 2010	Segmental percentage contributions of cervical spine during	Healthy participants	Percentage contribution of each segmental level to overall ROM	Video-fluoroscopy system (Diagnost 97,

	different motion ranges of flexion and extension			Philips Corporation)
Anderst et al. 2013	Cervical motion segment percent contributions to flexion-extension during continuous functional movement in control subjects and arthrodesis patients	Single-level (C5/C6) anterior arthrodesis patients & Healthy controls	Cervical motion segment contributions for every 1% increment of total ROM	Biplane X-ray system & High-resolution CT scans
Anderst et al. 2013	Six-degrees-of-freedom cervical spine range of motion during dynamic flexion-extension after single-level anterior arthrodesis: comparison with asymptomatic control subjects.	Single-level (C5/C6) anterior arthrodesis patients & Healthy controls	Maximum and minimum range of motion and translation during static and dynamic flexion and extension	Biplane X-ray system & High-resolution CT scans
Tsang et al. 2013	Movement coordination and differential kinematics of the cervical and thoracic spines in people with chronic neck pain	Chronic neck pain patients & Healthy controls	Angular displacement & Velocity & Acceleration	Electromagnetic tracking device (Fastrak, Polhemus Inc., Colchester, VT, USA)
Anderst et al. 2013	Motion path of the instant center of rotation in the cervical spine during in vivo dynamic flexion-extension: Implications for artificial disc design and evaluation of motion quality after arthrodesis	Single-level (C5/C6) anterior arthrodesis patients & Healthy controls	Motion Path of the Instant Center of Rotation	Biplane X-ray system & High-resolution CT scans
Anderst et al. 2013	Cervical spine intervertebral kinematics with respect to the head are different during flexion and extension motions	Healthy participants	Relative angle at each intervertebral motion segment for every 1% increment of head motion.	Biplane X-ray system & High-resolution CT scans
Anderst et al. 2014	Continuous cervical spine kinematics during in vivo dynamic flexion-extension	Single-level (C5/C6) anterior arthrodesis patients & Healthy participants	Continuous motion path	Biplane X-ray system & High-resolution CT scans

Lin et al. 2014	In vivo three-dimensional intervertebral kinematics of the subaxial cervical spine during seated axial rotation and lateral bending via a fluoroscopy-to-CT registration approach	Healthy participants	Coupled intervertebral motions	Biplane fluoroscope (Allura Xper FD10/10, Philips Medical Systems, Netherlands) & CT scan
Bahat et al. 2015	Interactive cervical motion kinematics: Sensitivity, specificity and clinically significant values for identifying kinematic impairments in patients with chronic neck pain	Chronic neck pain patients & Healthy controls	Peak and mean velocity & Number of velocity peaks & Time to peak velocity percentage & Head movement accuracy	Virtual reality (VR) assessment system
Meisingset et al. 2015	Evidence for a general stiffening motor control pattern in neck pain: A cross sectional Pathophysiology of musculoskeletal disorders	Neck pain patients & Healthy controls	Trajectory movement control	Liberty electromagnetic motion tracker system (Polhemus, Inc, Colchester, Vermont, USA)
Anderst et al. 2015	Three-dimensional intervertebral kinematics in the healthy young adult cervical spine during dynamic functional loading	Healthy participants	Range of motion & Helical axis of motion (HAM)	Biplane X-ray system & High-resolution CT scans
Anderst et al. 2015	Cervical motion segment contributions to head motion during flexion\ extension, lateral bending, and axial rotation	Healthy participants	Cervical motion segment contributions to the primary head rotation	Biplane X-ray system & High-resolution CT scans
Mao et al. 2016	Dimensional changes of the neuroforamina in subaxial cervical spine during in vivo dynamic flexion-extension	Healthy participants	Dimensional changes of cervical neuroforamina	Dual fluoroscopic system (BV Pulsera, Phillips, Bothell, WA, USA) & MRI scan
Seo et al. 2016	Dynamic intervertebral body angle of the lower cervical spine during protracted head extension using	Healthy participants	Cobb angle of cervical joint	Video-fluoroscopy system (ARCADIS Orbic, Siemens, USA)

	measured by fluoroscopy			
Tsang et al. 2016	Relationship between neck acceleration and muscle activation in people with chronic neck pain: Implications for functional disability	Chronic neck pain patients & Healthy controls	Acceleration/deceleration of cervical spine	Electromagnetic tracking device (Fastrak, Polhemus Inc. Colchester, VT, USA)
Ren et al. 2016	The Study of Cobb Angular Velocity in Cervical Spine during Dynamic Extension–Flexion	Healthy participants	Cobb angular velocity (CAV)	Robotic DSA system (Artis_one XA82008; Siemens Medical Solution, Germany)
Wang et al. 2017	Cervical flexion and extension include anti-directional cervical joint motion in healthy adults	Healthy participants	Anti-directional motion & Pro-directional motion	Video-fluoroscopy (BV Libra, Philips, Netherlands)
Wang et al. 2017	Repeatability of Cervical Joint Flexion and Extension Within and Between Days	Healthy participants	Repeatability of cervical motions within-day or between-day	Video-fluoroscopy (BV Libra, Philips, Netherlands)
Chang et al. 2017	Dynamic measurements of cervical neural foramina during neck movements in asymptomatic young volunteers	Healthy participants	Dimensional changes of cervical neuroforamina	Biplane X-ray system & High-resolution CT scans
College et al. 2017	Ranges of Cervical Intervertebral Disc Deformation During an In Vivo Dynamic Flexion – Extension of the Neck	Healthy participants	Disc height and range of motion of individual cervical joint	Dual fluoroscopic imaging system (BV PulseraVR, Phillips, Bothell, WA) & MR scan
Lemmers et al. 2018	Three-dimensional kinematics of the cervical spine using an electromagnetic tracking device. differences between healthy subjects and subjects with non-specific neck pain	Non-specific neck pain patients & Healthy controls	Range of motion & Motion coupling patterns & Ratio & Speed, acceleration and rhythm & Jerk motion	Flock of Birds electromagnetic tracking system (Ascension Technologies, Shelburne, USA©)

Appendix B: Overview of studies investigating PPTs in patients with neck pain and healthy controls.

The appendix B is a summary of studies comparing PPTs between neck pain patients and healthy controls. All the studies investigated the PPTs of the neck in different measurement sites and most of the studies investigated the PPTs at distal measure site (TA).

Authors	Title	Participants	Measurement sites
Sterling et al. 2002	Pressure pain thresholds in chronic whiplash associated disorder: further evidence of altered central pain processing	Patients with chronic whiplash-associated disorders& Healthy controls	Bilateral C1/C2, C2/C3 and C5/C6 facet joint & Greater occipital nerve & Median nerve trunk & Radial nerve trunk & Ulnar nerve trunk & TA
Sterling et al. 2003	Sensory hypersensitivity occurs soon after whiplash injury and is associated with poor recovery	Whiplash patients & Healthy controls	Bilateral C2/C3 and C5/C6 facet joint & Median nerve & TA
Sterling et al. 2004	Characterization of acute whiplash-associated disorders	Whiplash patients & Healthy controls	Bilateral C2/C3 and C5/C6 facet joint & Median nerve & TA
Scott et al. 2005	Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain	Patients with chronic whiplash-associated disorders & Patients with chronic idiopathic neck pain & Healthy controls.	C2/C3 and C5/C6 facet joint & Median, radial, and ulnar nerves & TA
Johnston et al. 2008	Quantitative sensory measures distinguish office workers with varying levels of neck pain and disability	Female office workers with neck pain & Healthy controls	Median nerve site & levator scapulae & trapezius muscles & posterior neck & TA
Chien et al. 2008	Whiplash (Grade II) and cervical radiculopathy share a similar sensory presentation: An investigation using quantitative sensory testing	Chronic whiplash & Patients with cervical radiculopathy & Healthy controls	Bilateral C5/C6 facet joints & Median nerve & TA
Chien et al. 2009	Hypoaesthesia occurs with sensory hypersensitivity in chronic whiplash–further evidence of a neuropathic condition	Chronic whiplash & Healthy controls	Bilateral C2/C3 and C5/C6 facet joint & Median nerve & TA
Javanshir et al. 2010	Exploration of somatosensory impairments in subjects with mechanical idiopathic neck pain: A preliminary study.	Patients with acute neck pain & Patients with chronic neck pain & Healthy controls	Supraorbital, mental, median, ulnar and radial nerves & C5/C6 Facet joint & The second metacarpal & TA

Chien et al. 2010	Sensory hypoaesthesia is a feature of chronic whiplash but not chronic idiopathic neck pain	Patients with chronic WAD & Patients with chronic idiopathic neck pain & Healthy controls	Bilateral C5/C6 Facet joint & Nerve trunk of the median nerve & TA
La Touche et al. 2010	Bilateral Mechanical-Pain Sensitivity Over the Trigeminal Region in Patients with Chronic Mechanical Neck Pain ´	Patients with neck pain & Healthy controls	Bilateral masseter, temporalis, and upper trapezius muscle & C5/C6 facet joint & TA
Tampin et al. 2012	Quantitative sensory testing somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with nonspecific neck–arm pain	Patients with cervical radiculopathy & patients with nonspecific neck–arm pain associated with heightened nerve mechanosensitivity & patients with fibromyalgia (FM) & Healthy controls	Maximal pain area & Dermatome & Foot
Fernández-Pérez et al. 2012	Muscle trigger points, pressure pain threshold, and cervical range of motion in patients with high level of disability related to acute whiplash injury	Acute whiplash-associated disorders (WADs) & Healthy controls	Bilateral C5/C6 facet joints & Second metacarpal & TA
Schomacher et al. 2013	Localized pressure pain sensitivity is associated with lower activation of the semispinalis cervicis muscle in patients with chronic neck pain	Chronic nonspecific neck pain patients & Healthy controls	C2/C3 and C5/C6 facet joint
Uthaikhup et al. 2015	Altered pain sensitivity in elderly women with chronic neck pain	Patients with idiopathic neck pain & Healthy controls	C5/C6 facet joints & TA
Madrid et al. 2016	Widespread pressure pain hyperalgesia in chronic nonspecific neck pain with neuropathic features: A descriptive cross-sectional study.	Chronic nonspecific neck pain patients with and without neuropathic features & Healthy controls	Suboccipital muscle & Upper trapezius muscle & Lateral epicondyle & TA

Appendix C: Figures showing no changes in joint motion parameters

Figure 13 showed the total joint motion during cervical extension with different pain conditions. No difference was found for individual and overall total joint motion during cervical extension between any experimental pain condition and their baseline (Study I and Study II). There was no difference found in total joint motion during cervical extension between patients with recurrent neck pain and healthy controls (Study III).

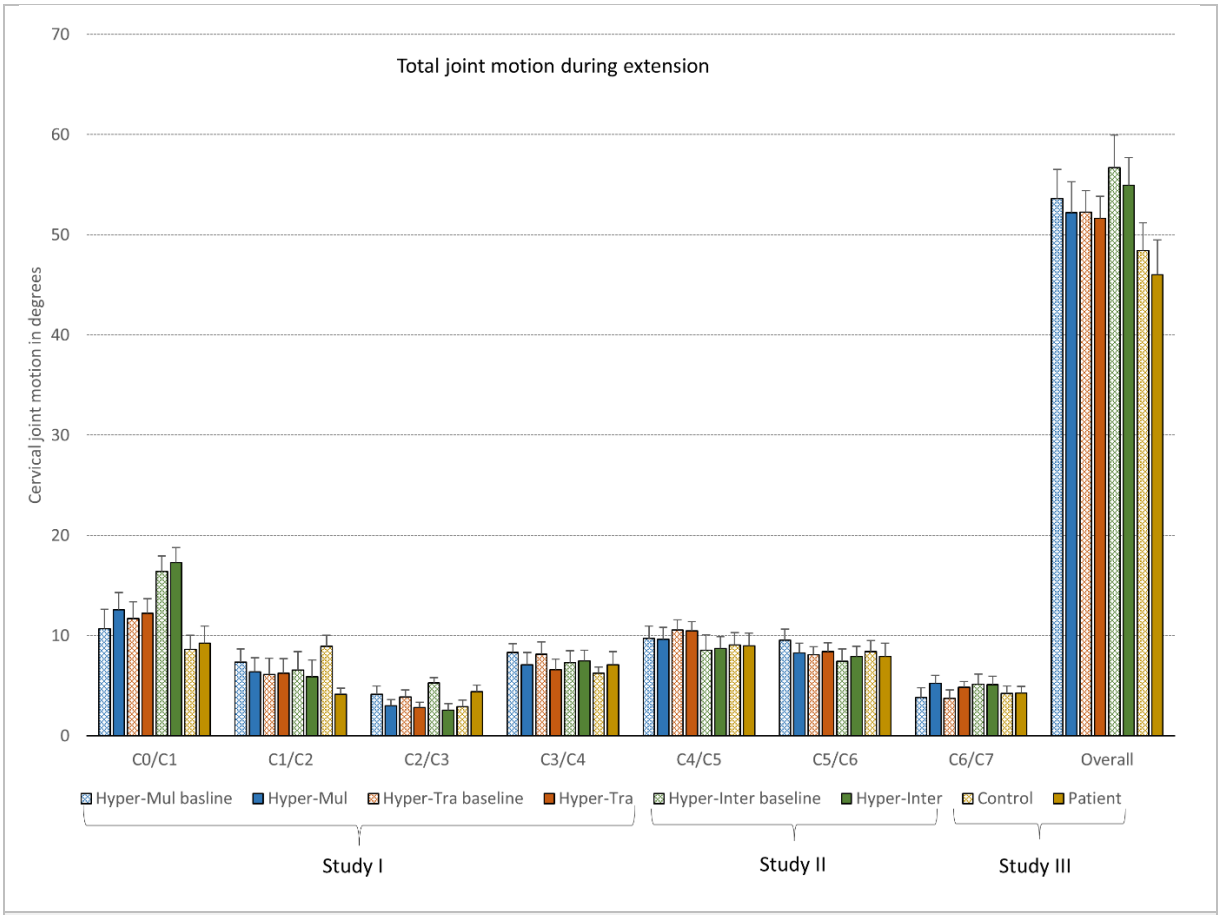


Figure 16. Total joint motion during cervical extension with different pain conditions. Hyper: hypertonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; Control: healthy control; Patients: patients with recurrent neck pain. Data were obtained from Study I-III.

Figure 14 showed the total joint motion during cervical flexion with different pain conditions. No difference was found for individual and overall total joint motion during cervical flexion between any experimental pain condition and their baseline (Study I and Study II). There was no difference found in total joint motion during cervical flexion between patients with recurrent neck pain and healthy controls (Study III).

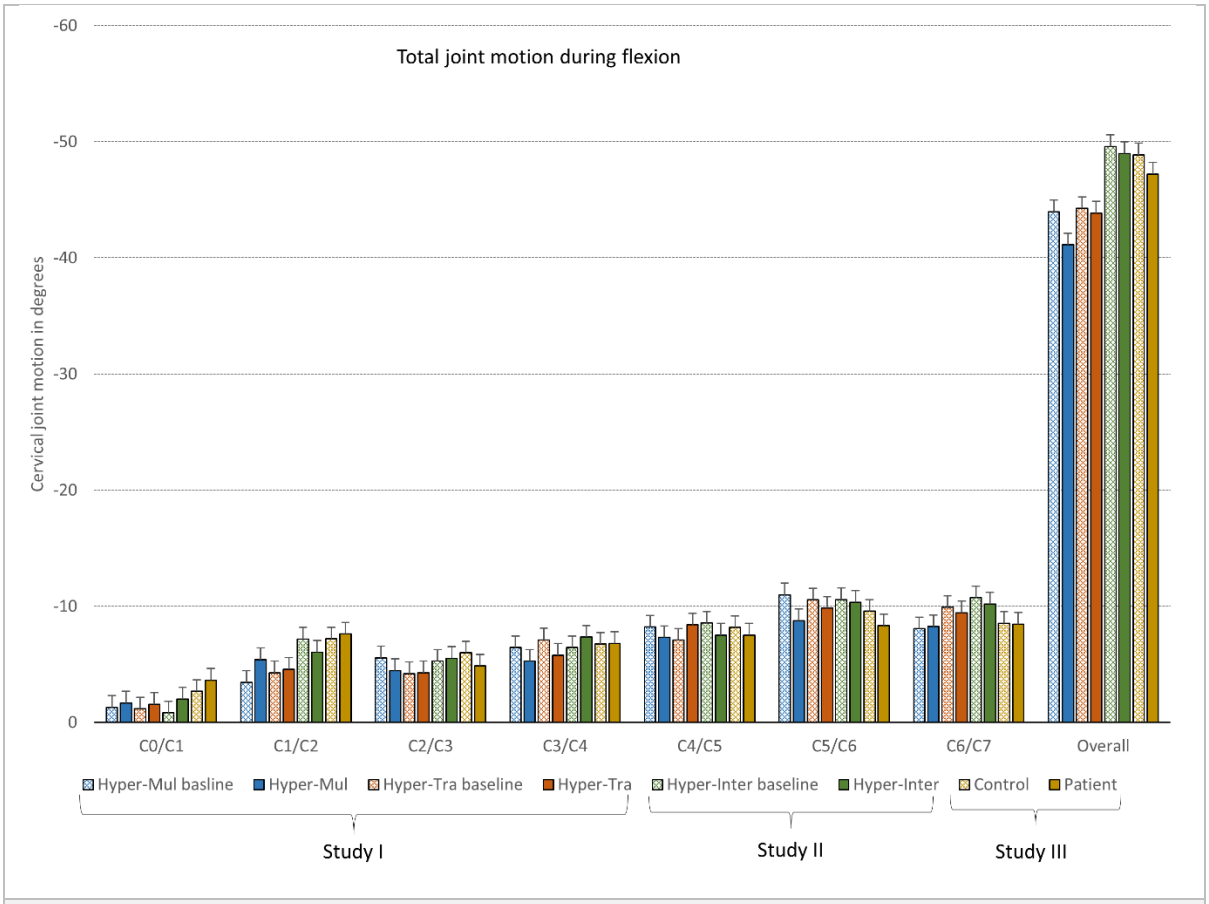


Figure 17. Total joint motion during cervical flexion with different pain conditions. Hyper: hypertonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; Control: healthy control; Patients: patients with recurrent neck pain. Data were obtained from Study I-III.

Figure 15 showed the joint motion variability during cervical flexion with different pain conditions. No difference was found for individual and overall joint motion variability during cervical flexion between any experimental pain condition and their baseline (Study I and Study II). There was no difference found in joint motion variability during cervical flexion between patients with recurrent neck pain and healthy controls (Study III).

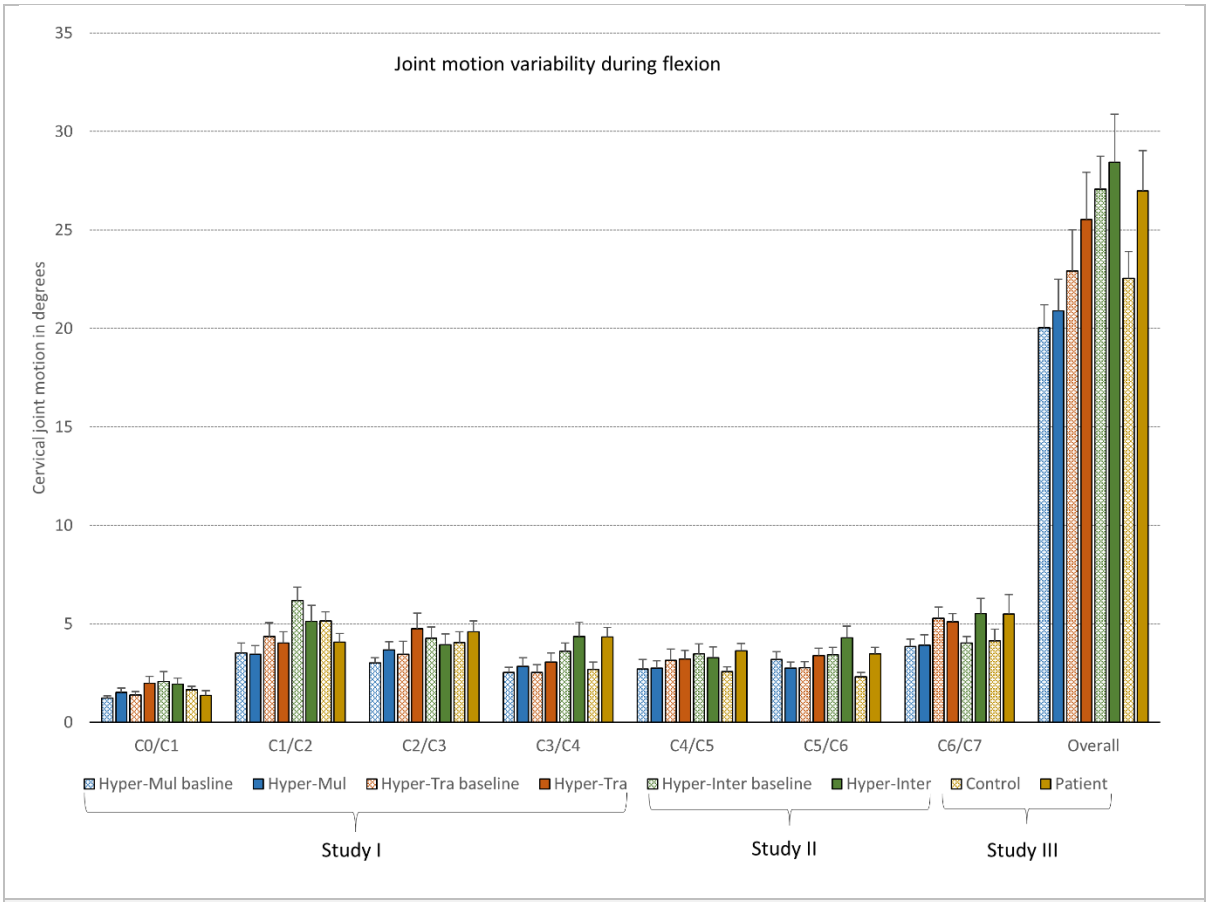


Figure 18. Joint motion variability during cervical flexion with different pain conditions. Hyper: hypertonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; Control: healthy control; Patients: patients with recurrent neck pain. Data were obtained from Study I-III.

Figure 16 showed the pro-directional motion during cervical flexion with different pain conditions. No difference was found for individual and overall pro-directional motion during cervical flexion between any experimental pain condition and their baseline (Study I and Study II). There was no difference found in pro-directional motion during cervical flexion between patients with recurrent neck pain and healthy controls (Study III).

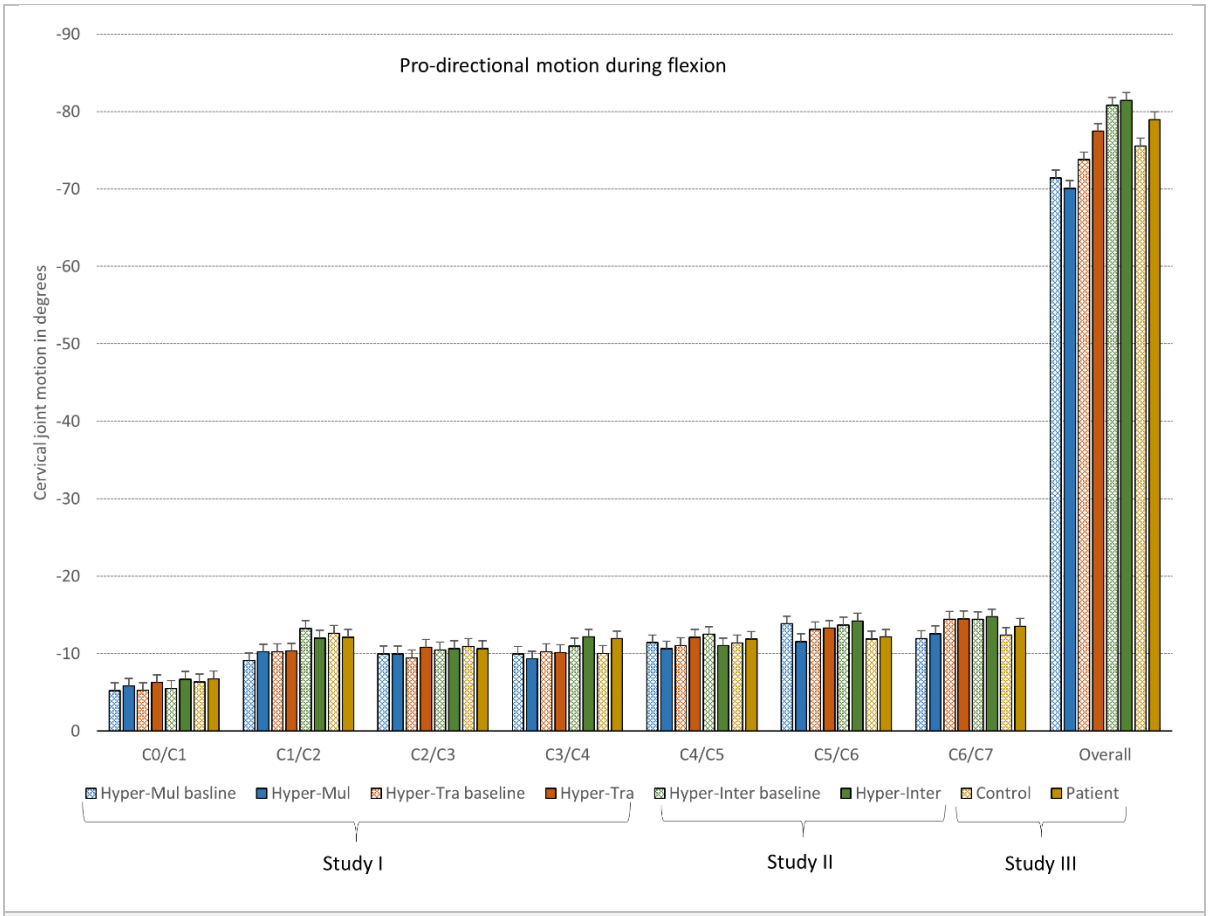


Figure 19. Pro-directional motion during cervical flexion with different pain conditions. Hyper: hypertonic saline; Mul: multifidus muscle; Tra: trapezius muscle; Inter: inter-spinous ligament; Control: healthy control; Patients: patients with recurrent neck pain. Data were obtained from Study I-III.

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