Cervical Radiofrequency Neurotomy Reduces Central Hyperexcitability and Improves Neck Movement in Individuals with Chronic Whiplash

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Running Title: Cervical Radiofrequency Neurotomy Reduces Central Hyperexcitability
ABSTRACT:

Objective:

This study aims to determine if cervical medial branch radiofrequency neurotomy reduces psychophysical indicators of augmented central pain processing, and improves motor function in individuals with chronic whiplash symptoms.

Design:

Prospective observational study of consecutive patients with healthy control comparison.

Setting:

Tertiary spinal intervention centre in Calgary, Alberta, Canada.

Subjects:

Fifty-three individuals with chronic whiplash and disorder symptoms (Grade 2). 30 healthy controls.

Methods:

Measures were made at four time points: two prior to radiofrequency neurotomy and 1- and 3-months post radiofrequency neurotomy. Measures included: comprehensive quantitative sensory testing (including brachial plexus provocation test); nociceptive flexion reflex; and motor function (cervical range of movement; superficial neck flexor activity during the cranio-cervical flexion test). Self-report pain and disability measures were also collected. One-way repeated measures analysis of variance and Friedman’s tests were performed to investigate the effect of time on the above measures. Differences between the whiplash and healthy control groups were investigated with two-tailed independent samples t-test or Mann-Whitney tests.
Results:

Following cervical radiofrequency neurotomy there were significant early (within 1-month) and sustained (3-months) improvements in pain, disability, local and widespread hyperalgesia to pressure and thermal stimuli; nociceptive flexor reflex threshold, and brachial plexus provocation test responses as well as increased neck range of motion (all \( p < 0.0001 \)). A non-significant trend for reduced muscle activity with the cranio-cervical flexion test (\( p > 0.13 \)) was measured.

Conclusions.

Attenuation of psychophysical measures of augmented central pain processing and improved cervical movement imply that these processes are maintained by peripheral nociceptive input.

Keywords: Whiplash, Radiofrequency Neurotomy, Central Sensitization, Quantitative Sensory Testing, Peripheral Nociception
INTRODUCTION:

Approximately 50% of individuals who sustain a whiplash injury will continue to report ongoing neck pain and disability 12 months later [1]. Chronic whiplash associated disorder (WAD) is characterised by sensory disturbances (widespread hypersensitivity) [2-4] and heightened spinal cord flexor withdrawal responses [5,6], both indicative of augmented central nociceptive processing [7]. Changes in motor function are also evident with reduced neck range of movement and altered muscle recruitment patterns [8,9].

The processes underlying and contributing to these features are not clear. Whilst it is generally accepted that sensory features result from augmented central nociceptive processing (central hyperexcitability) [10,11], there is much debate as to whether these are driven by an ongoing peripheral nociceptive source [12-14] or are self-maintaining due to neuroplastic changes in the central nervous system [7]. Previous studies of patients with painful hip or knee osteoarthritis demonstrated improvement in sensory measures following successful arthroplastic surgery, indicating that central pain processes are being maintained by peripheral nociceptive input [15,16].

Similarly, persistence of motor changes following whiplash injury, such as morphometric muscular changes, local muscular weakness and loss of range of movement, suggests the presence of ongoing peripheral mechanisms [17-21]. However, these changes cannot be separated from changes in central nervous system control; with neuromotor performance in individuals with neck pain associated with reorganization of control strategies [22-24].
Whilst tissue damage usually cannot be detected in the patient with WAD with current imaging techniques, evidence to date suggests that a peripheral lesion of some kind is likely to be present [25-27]. Most available evidence would support the cervical facet joint as one source of nociception in individuals with chronic WAD [28-30]. Animal studies have demonstrated that cervical facet joint injury may be responsible for hypersensitivity and increased neuronal excitability [31-34]. Injury to the facet joint has also been implicated in local muscle responses in a cat model [35]. Modulating nociception from facet joints is possible via medial branch blocks (MBB) or radiofrequency neurotomy (RFN). There are suggestions that MBB or RFN may attenuate sensory hypersensitivity [36-38]; although the evidence is weak, with studies involving limited subjects, measures or procedures; or only investigating immediate post-procedure effects. Thus the role of the cervical facet joint in regard to sensory and motor changes in chronic WAD requires further investigation, with a wider range of measures of central hyperexcitability, and inclusion of measures of motor function.

The aim of this study was to investigate changes in measures of central hyperexcitability following RFN of cervical spine facet joints in individuals with chronic WAD. We also investigated changes in motor function following the same procedure. The null hypothesis is that reducing nociception via RFN would not result in changes in psychophysical indicators of central hyperexcitability or changes in motor function.
METHODS:

Design:

A prospective cohort study design was employed at a tertiary spinal intervention centre in Calgary, Alberta, Canada. Participants included individuals with chronic WAD who underwent RFN, following a successful response to cervical facet joint blockade. A healthy control (HC) cohort was also investigated to provide comparative data. Individuals with WAD attended the research laboratory at four time points: one month following cervical facet joint injections (double blockade procedure), immediately prior to receiving RFN, one month following RFN, and three months following RFN. HC individuals attended one session of laboratory testing.

Participants:

Inclusion Criteria:

Consecutive participants were recruited from individuals aged 18-65 years with WAD Grade II of a duration greater than 6 months post motor vehicle collision (MVC) following successful response (greater than 50% of neck pain relief) to cervical facet joint blockade (intra-articular block followed by confirmatory medial branch block) [40], who subsequently underwent RFN.

HC individuals with no previous history of neck pain, whiplash injury or recent treatment for musculoskeletal pain (within previous 2 years) were recruited from advertisements placed around the spinal intervention centre.
Exclusion Criteria:

Individuals were excluded from the study if they were classifiable as WAD Grade III (neurological deficit) or IV (fracture or dislocation) [39]; sustained a concussion or loss of consciousness as a result of the trauma; or if they were not fluent in spoken or written English. All the participants were unpaid volunteers. Ethical clearance for this study was granted from the institutional medical research ethics committees (University of Calgary and University of Queensland) in 2009. All participants provided informed consent.

Outcome Measures

Quantitative Sensory Tests:

Pressure Pain Thresholds

Pressure pain thresholds (PPTs) were measured using a pressure algometer (Somedic AB, Farsta, Sweden). The probe size was 1 cm² and the rate of application was 40 kPa/sec. PPTs were measured over the articular pillars of C5/6 bilaterally (which is the most prevalent facet joint involved in neck pain, not involving headaches) following whiplash trauma);[30] over the median nerve trunks anterior to the elbow bilaterally, and at a bilateral remote site (upper one third of the muscle belly of tibialis anterior) as previously described in investigations of chronic WAD [4]. The participants were requested to push a button when the sensation of pressure first became painful. Three recordings were taken at each site and the mean value for each site used in the analysis.
Nociceptive Flexion Reflex

The nociceptive flexion reflex (NFR) is a polysynaptic spinal withdrawal reflex that is elicited following activation of nociceptive A-delta afferents [41]. It was performed via electrical stimulation through bipolar surface Ag/AgCl-electrodes (inter electrode distance approximately 2 cm), which were placed just distal to the left lateral malleolus of the ankle (innervation area of the sural nerve). EMG reflex responses to electrical stimulation were recorded from the middle of the biceps femoris muscle using Ag/AgCl-electrodes. The participant lay prone and a wedge was placed under the ankle to obtain 30 degrees knee flexion. The EMG signal was amplified and low-pass filtered 0-500Hz by a Multichannel EMG (Noraxon, Scottsdale AZ). Stimulation and recording was controlled and analyzed with custom software developed specifically for this test. A 25ms, train-of-five, 1ms, square-wave impulse (perceived as a single stimulus), was delivered by a computer-controlled constant current stimulator (Digitimer DS7A, England).

The current intensity was increased from 2mA in steps of 2mA until a reflex was elicited. The program delivered the impulses at random time intervals, so that the participants were not aware of when the stimulus was going to be applied. In this way, voluntary muscle contraction due to stimulus anticipation was avoided. A reflex response was defined using the standardized peak (NFR interval peak z score) EMG activity from biceps femoris as recommended [42]. The NFR Interval Peak z score is the NFR interval peak (EMG activity 90 to 150ms post-stimulation interval)—baseline mean (60ms before stimulation)/baseline SD. Rhudy and France [43], suggest a NFR interval peak z score of greater that 10.32 be used to define a reflex response. The 90 to 150ms interval was chosen as it avoids possible contamination by low threshold cutaneous
flexor reflex, startle reactions, and voluntary movements [43]. The current intensity required to elicit a reflex response was defined as the NFR threshold.

*Thermal Pain Thresholds*

Thermal pain thresholds were measured bilaterally over the cervical spine using the TSA II Neurosensory Analyzer (Medoc Advanced Medical Systems; Minneapolis, MN, USA). The thermodode was placed over the skin of the mid cervical region and preset to 32°C, with the rate of temperature change being 1°C per second. To identify cold pain thresholds (CPT) and heat pain thresholds (HPT), participants were asked to push a switch when the cold or warm sensation first became painful [44]. Triplicate recordings were taken at each site and the mean value for each site used in the analysis.

*Brachial Plexus Provocation Test*

The brachial plexus provocation test (BPPT) was performed in the following sequence: gentle shoulder girdle depression, glenohumeral abduction and external rotation in the coronal plane, forearm supination, wrist and finger extension, and elbow extension [45]. The range of elbow extension was measured at the participants’ pain threshold using a standard goniometer aligned along the mid humeral shaft, medial epicondyle, and ulnar styloid [46]. If the participant did not experience pain, the test was continued until end of available range. Hypersensitive responses to this test have been demonstrated in chronic whiplash [47,48], together with excellent intra-therapist reliability [49].
Motor Measures:

Range of Motion

Active cervical range of motion (ROM) was measured using electromagnetic motion sensors (Fastrak, Polhemus, USA) [8]. One sensor was placed over the C7 spinous process and the other attached to the top of a light skull cap firmly fitted to the participant’s head, such that the second sensor sat on the vertex. Three trials were performed in each direction (flexion, extension, left and right rotation) and the means of the three trials were used in analysis. A computer program was developed to convert the Euler angles into degrees of freedom of motion of the vertex relative to C7. The Fastrak has previously been used in trials of neck pain and whiplash participants [50] and has shown to be accurate within +/- 0.2 degrees [51].

Cranio-cervical Flexion Test

Surface EMG (Noraxon Tele Myo 900) was used to measure the activity of superficial neck flexor muscles (sternocleidomastoid - SCM) during the five incremental stages of the cranio-cervical flexion test (CCFT) as described by Jull [9]. The test was performed in supine and used a pressure biofeedback device (Stabilizer, Chattanooga, USA) placed sub-occipitally behind the neck to guide performance. It was inflated to a baseline of 20mmHg and participants performed cranio-cervical flexion to increase the pressure by five progressive increments of 2mmHg (22mmHg-30mmHg). Each pressure level was maintained for 10s and participants rested for 15s between each stage. Myoelectric signals were collected from the SCM muscles using Ag–AgCl electrodes (Noraxon, USA) in a bipolar configuration (inter electrode distance approximately 2 cm).
Electrodes were positioned along the lower one-third of the muscle bellies of the SCM [52]. Signals were amplified and filtered by a 500Hz low pass filter (Noraxon TeleMyo 900, Scottsdale AZ) and sampled at 2000Hz (National Instruments DAQ PCI-6221). EMG data were analyzed as follows: The maximum root mean squared (RMS) value was identified for each trace using a 1s sliding window, incremented in 100ms steps. RMS values were normalized for each participant, by dividing the 1s maximum RMS from each level of the CCFT by the 1s maximum RMS during a standardized head lift. The baseline EMG data (RMS value) obtained at rest (20mmHg) was subtracted from the measured EMG at each level of this test. The normalized RMS data for the left and right SCMs were averaged for analysis [9,50].

**Questionnaires:**

Measures included a description of symptoms, symptom dominance (unilateral or bilateral) and severity, crash parameters, treatments since the crash, compensation status, list of medications and demographic variables including gender, age, marital status, employment status, education level and duration of neck pain as per a standard clinical examination.

A single item visual analogue scale (VAS: 0-10cm) was used to measure the participants’ current pain intensity in the cervical spine (as perceived anywhere in the posterior region of the cervical spine, from the superior nuchal line to the first thoracic spinous process) with (0) described as ‘No Pain’ and (10) as ‘Worst Pain Imaginable’.

Self-reported pain and disability was measured in whiplash participants with the Neck Disability Index (NDI) [53]. The NDI consists of 10 items addressing functional activities such as personal...
care, lifting, reading, work, driving, sleeping, and recreational activities and also pain intensity, concentration, and headache which are rated from no disability (0) to total disability (5). The overall score (out of 100) is calculated by totalling the responses of each individual item and multiplying by 2. A higher score indicates greater pain and disability. It is the questionnaire most utilized in WAD research [54].

Procedure:
Participants were assessed on all outcome measures at the following time points: (t1) at a time period when their familiar baseline neck pain was present (when symptoms returned following successful cervical facet joint double blockade) [38]; (t2): immediately prior to receiving RFN; t(3) one month following RFN and t(4): 3 months following RFN. Attendance at two time points prior to receiving RFN allowed us to determine if time alone (t(1) vs. t(2)) resulted in improvements in measures, prior to RFN being performed (Figure 1).

Participants first completed all questionnaires, after which a standard protocol was used for the order of tests [55]. The participants were seated, the Fastrak sensors applied and ROM was measured. They were instructed to assume a comfortable position looking straight ahead, then to perform each movement three times, moving at a comfortable speed as far as possible and to return to the start position between each repetition. The order of movements assessed were flexion, extension, left rotation and right rotation. The participants were then positioned supine, EMG electrodes were applied, and the CCFT was performed. For all of the following bilateral tests, the left side was measured first. PPTs were measured in the following order: tibialis anterior, median nerves and C5/6. Thermal pain thresholds were then measured over the cervical
spine, HPTs followed by CPTs. These were followed by the BPPT. The NFR was the final testing procedure. The same examiner tested all participants. No feedback or cues were given to the participants regarding their performance on any tests.

RFN Procedure:
Details of the RFN procedure are provided in Appendix 1.

Data Analysis:
Data were analyzed with Stata 9.0 statistical software. Based on our previous research [38], utilizing the standard deviation of changes observed (in distal PPT pre/post interventional procedure), our statistical calculations indicated that this study required 26 participants (with 80% power at 5% level of significance) to adequately detect a minimally clinically important difference for the primary outcome measures (change in PPT in Tibialis Anterior, change in CPT, or change in NFR threshold). Further participants were recruited in the whiplash group to power a further study.

Assumptions of normality, non-multicollinearity, and homoscedasticity were tested through examination of histograms, box plot graphs, correlation matrices, and a plot of predicted to residual values, respectively. If the data were not normally distributed, transformation of the data was applied. PPT, BPPT, NFR threshold and CCFT data required log transformation. Despite various transformations being attempted, normality for CPT and HPT was unable to be achieved (primarily due to floor and ceiling effects). A paired t-test was used to determine within participant side-to-side differences for all measures and followed by the exploratory
analysis for all the measures. As no side-to-side differences were found (PPT, CPT, HPT and BPPT), the data from each side were averaged and the mean data used for analysis.

All assumptions for repeated measures ANOVA were satisfied, except for HPT and CPT. One-way repeated measures analysis of variance (ANOVA) was performed to investigate the effect of time (four levels: one month following cervical facet blockade; one month prior to receiving RFN; one month following RFN, and three months following RFN) on the following log-transformed measures: PPT, BPPT, NFR, and CCFT, and normally distributed ROM. Non-parametric Friedman’s repeated measures test was used to analyze the effects of time on CPT and HPT. The baseline data for each dependent measure was entered into each ANOVA (but not Friedman’s) analysis as a covariate. As this did not alter the significance of any of the results, further mention of baseline adjustment will not be made.

For ease of interpretation, results are presented using non-transformed data for medians and interquartile ranges, with probability estimates taken from analyses using transformed data. Where there was a significant difference over time, post hoc tests of simple effects were performed to determine where these differences occurred. Significance level was set at 0.05 with Bonferroni adjustments used where appropriate. When the Friedman test was significant, multiple Wilcoxon Signed Rank tests were performed with Bonferroni adjustment (p < 0.008) utilized to determine where those differences occurred. Differences between the whiplash and healthy control (HC) groups were investigated with two-tailed independent samples t-test or Mann-Whitney tests (for CPT and HPT respectively).
The data were assessed for effect size using Cohen’s $d$ for normally distributed data, and Cliff’s Delta for non-parametric analyzed data [56]. The established convention rates were used. A Cohen’s $d$ effect size of $0 < 0.50$ is small, a size of $0.50$ to $< 0.80$ is moderate, and $> 0.80$ is large [57]. The corresponding effect sizes for Cliff’s Delta are: $< 0.147$ is small; between $0.148$ and $0.33$ is moderate, and $> 0.33$ is large [58]. Effect size was calculated utilizing $t(4)$, being the primary end point of this study; and $t(2)$, the time period immediately prior to receiving RFN.

RESULTS:

Participants:
Fifty-eight individuals had a successful response to the cervical facet joint double blockade and agreed to participate in the study. Four individuals subsequently withdrew before undergoing RFN (three individuals declined to proceed with RFN, and one individual sustained other traumatic injuries from a skiing accident). Thus, 54 individuals underwent RFN.

At the one month review period following RFN ($t(3)$), one individual sustained neuritis (this was the only side effect noted for the duration of the study); and thus was unable to attend for further analysis. Thus, 53 individuals (36 female, 17 male; mean age = 44.7 +/- 10.9 (SD) years) were included in the study. Three individuals were unable to attend the three month review (one pregnancy, two lost to follow up), although all data until that point was included in the analysis. The collision vectors reported were: rear-end impacts (51%), frontal impacts (23%), side impacts (21%) and combined (6%) vectors. Twenty-eight participants (53%) were involved in ongoing compensation claims; 30 (57%) reported the presence of other musculoskeletal symptoms (i.e. headaches (44%), low back pain (34%), thoracic spine pain (21%), shoulder/arm pain (21%) and
jaw pain (8%)); 27 (51%) were university educated; 41 (77%) were fully employed throughout
the course of the study, and 39 (74%) reported that they were married or in a long-term
supportive relationship.

The median [range] duration of symptoms post whiplash injury was 43 [9 – 195] months.
Following the initial cervical facet double blockade procedure, there was a mean (+/-SD) wait of
10.4 (+/-4.5) months until RFN was performed. All participants received treatment following the
MVC. Thirty-one participants (58%) were receiving conservative treatment at the time of
participation in the study. Twenty-six participants (49%) had previously attended the local
health authority multi-disciplinary chronic pain centre.

The most common facet joint involved was C2/3 (41%), followed by C6/7 (28%) and C5/6
(24%). C3/4 (11%) and C4/5 (4%) were less often involved. Bilateral facet joint involvement
was present in 31% of individuals, whilst 36% of individuals had involvement of both an upper
cervical (C2-4) and lower cervical intervertebral segment (C4-7).

Following RFN, medication usage decreased as follows: anti-inflammatory medication (from
45% of individuals to 36%); simple over-the-counter analgesics (34% to 23%); various narcotic
medications (26% to 19%); anti-convulsants (19% to 13%); selective serotonin reuptake
inhibitors (13% to 8%), tri-cyclic antidepressants (13% to 6%), with slight increase in usage of
selective norepinephrine reuptake inhibitors (8% to 13%).
Table 1 presents the demographic, pain and disability characteristics for the participants at the four measurement time points.

**Pain and Disability:**

Repeated measures ANOVA revealed a significant main effect of time for VAS (Table 1). Post-hoc tests of simple effects showed no significant difference in pain scores before RFN (t(1) and t(2)); with early (t(3): one month following RFN) and sustained (t(4): three months after receiving RFN) reductions in pain following RFN with no difference between t(3) and t(4). Similarly, there was a main effect of time for NDI scores (Table 1). Post-hoc tests mirrored the results for VAS scores, with reductions in self-reported disability following RFN, with no significant differences in the time periods prior to or following RFN respectively.

The effect sizes were large for both pain (Cohen’s $d$: 1.34 (95%CI: 1.13,1.55)) and disability measures (Cohen’s $d$: 1.00 (95%CI: 0.79,1.21)).

**Pressure Pain Thresholds (PPT):**

There was a significant main effect of time for PPT at all sites (Table 2). PPTs at tibialis anterior and median nerve sites demonstrated early and sustained increases following RFN; with no difference in PPTs prior to or following RFN. Similar results (early and sustained increases following RFN with no differences prior to or following RFN) were demonstrated at the cervical
spine site, with one slight difference, that being no significant difference measured between t(2) and t(3) (p=0.27). The effect sizes were moderate for all sites measured (Table 2).

In comparison to the healthy control group, PPTs at all sites were lower in the whiplash group prior to undergoing RFN (81 d.f., p<0.0001). Following RFN (t(4)), there were no differences between the WAD group and controls at the median nerve and tibialis anterior sites (78 d.f., p>0.18), but PPT at the cervical spine remained lower in the WAD group (t_{78}=2.26, p=0.013).

**Nociceptive Flexion Reflex (NFR):**

There was a significant main effect of time for NFR threshold (Table 2). Post-hoc tests showed that there was no significant difference in NFR thresholds before RFN. There was a significant increase in NFR thresholds between the time periods prior to RFN, and following RFN (except for t(2) to t(4): p=0.056). There were no significant differences in NFR thresholds following RFN. The effect size was small: Cohen’s $d = 0.40$ (Table 2).

There was no significant difference between the healthy control group and the whiplash group at t(4): $t_{78} = 0.67$, p=0.51 but NFR threshold was lower in the WAD group prior to RFN (t(2): $t_{81} = 2.97$, p=0.004).
Cold Pain Thresholds (CPT):

There was a significant effect of time for CPT (Table 3). Post-hoc analyses revealed that significant reductions in cold hyperalgesia (lower CPTs) were measured post-RFN. There were no significant differences in CPTs measured before receiving RFN or following RFN. Effect sizes were large: Cliff’s Delta = 0.38.

Prior to undergoing RFN, the WAD group demonstrated a significantly elevated CPT (20.8°C) compared to the healthy controls (3.5°C, Table 2; Mann–Whitney $U = -4.89$, $n_{\text{WAD}} = 53$, $n_{\text{HC}} = 30$, p<0.0001). At t(4), median CPTs in the whiplash group were significantly higher than those of controls (p=0.003; Table 3).

Heat Pain Thresholds (HPT):

There was a significant time effect for HPT (Table 3). Post-hoc analysis revealed that significant increased HPTs followed RFN. There were no significant differences in HPTs measured in the time periods prior to or following RFN. The effect sizes were large: Cliff’s Delta = 0.41 (Table 3).

Prior to undergoing RFN, the WAD group showed lower HPT compared to controls (Mann–Whitney $U = 4.43$, $n_{\text{WAD}} = 53$, $n_{\text{HC}} = 30$, p<0.0001; Table 2) but there was no difference between the groups following RFN (p=0.17; Table 3).
Brachial Plexus Pain Provocation Test (BPPT):

There was a significant main effect of time for elbow extension ROM with the BPPT (Table 2). Post-hoc analysis revealed that there were no significant differences measured prior to RFN. Elbow extension ROM increased following RFN, but there were no significant differences in the two time points following RFN. The effect size was large: Cohen’s $d$: 1.21 (Table 2).

The WAD group showed less elbow extension ROM compared to controls both prior to ($t_{81} = -9.2, p<0.0001$) and following RFN ($t_{67} = -2.61, p=0.011$; Table 2).

Range of Motion (ROM):

There were significant differences over time for cervical ROM ($F_{3,153}=104.4, p<0.0001$). Post-hoc analysis showed no change in cervical ROM between t(1) and t(2) ($p=1.00$), but cervical ROM significantly improved following RFN (both early: $t(3)$ ($p<0.0001$), and three months later: $t(4)$; $p<0.0001$). No significant differences in ROM were measured between t(3) and t(4) ($p=1.00$). A large effect size was present: Cohen’s $d$: 1.78 (95% CI: 1.52, 2.04).

Both prior to and following RFN, the WAD group showed less cervical ROM compared to the healthy controls ($p<0.0001$).
Cranio-cervical Flexion Test (CCFT):

There was a significant main effect of time for s EMG at 24mmHg, 26mmHg and 28mmHg levels of the CCFT (Table 4). No significant effect of time was found for the 22mmHg and 30mmHg levels. Post-hoc tests of simple effects were not significant. Thus, a general trend for reduced EMG was evident at the 24mmHg, 26mmHg and 28mmHg levels of the CCFT.

Prior to RFN, the WAD group demonstrated increased EMG levels compared to the controls at all levels of the CCFT (p<0.05), except for 30mmHg (p=0.053). Following RFN, there was no significant difference between the WAD and healthy control groups for any level of the CCFT (p>0.084).

DISCUSSION:

The results of this study demonstrated that individuals with chronic WAD who underwent successful cervical RFN show significant and sustained reductions in sensory hypersensitivity (mechanical and thermal), spinal cord hyperexcitability, improved responses to the BPPT and cervical ROM with trends towards improved cervical muscle control. Attenuation of widespread sensory hypersensitivity, spinal cord hyperexcitability and measures of motor function after RFN suggests that nociception from the cervical facet joint contributes to augmented central nociceptive processing and movement dysfunction in patients with chronic WAD.

Post-mortem studies have previously demonstrated that cervical facet joints are injured in motor vehicle crashes (MVC) [59-62], with clinical studies confirming the facet joint as a candidate for
ongoing nociception in patients with chronic WAD [28,30]. Biomechanical studies of cadavers and human volunteers have demonstrated how these injuries may occur [63-70]. Animal studies have shown that facet joint capsule stretch resulting from whiplash loading [71] has the potential to initiate physiological and behavioural responses including nociceptive afferent activation and after-discharge [31,71-75]; release of inflammatory mediators resulting in peripheral sensitization [32]; and alterations in neuronal excitability in the spinal cord [33,73,76-78]. The results of our study, where hyperalgesic responses were effectively modulated following the reduction of facet joint nociception, would support the results of these animal studies demonstrating a relationship between the facet joint and ongoing hyperalgesic responses in WAD.

Other studies in humans with chronic musculoskeletal pain have attempted to elucidate the relationship between peripheral mechanisms (persistent nociception) and augmented central processes. In studies of painful osteoarthritis, participants demonstrated central nervous system hyperexcitability prior to undergoing arthroplasty of the hip or knee which was reversed after arthroplastic surgery and subsequent pain relief [15,16], implicating the role of ongoing afferent nociception in augmentation of central pain processes. The influence of peripheral mechanisms driving central mechanisms was also demonstrated in a recent study involving individuals with chronic low back pain [79]. Following successful reduction in pain with surgery or facet joint injections; functional MRI scans demonstrated a reversal of functional and structural brain abnormalities, which did not occur in those who did not respond to treatment [79]. Thus, it appears that successfully reducing nociception, results in changes in central pain processing mechanisms.
Previous studies have investigated the effects of RFN on sensory measures in patients with WAD to some extent. Consistent with our findings, Prushansky et al. [37] and Chua et al. [36], demonstrated that PPTs measured over the cervical spine increased following RFN and this may reflect local hypoalgesia related to the anaesthetic procedure to the neck and decreased focal sensitization of peripheral structures. Our finding of decreased heat hyperalgesia may also support this proposal, as heat hyperalgesia is thought to reflect nociceptor sensitization, and also be an indicator of peripheral sensitization [80,81]. Chua et al. [36] found no change in PPTs at remote sites. In contrast, we found that PPTs at sites remote to the neck also increased, indicating that RFN has the capacity to modulate central as well as peripheral nociceptive processing. This discrepancy in study findings could be explained by the low sample size (n=9) of Chua’s study [36], in view of large variance in distal PPT measurements [38,82]. We previously demonstrated immediate (within hours) increases in PPTs at sites away from the site of injury (neck) in patients with chronic WAD [38]. The current study replicated these findings but demonstrated that these effects were sustained to at least three months post procedure and exceeded published minimal detectable changes (MDC) [83]. The current study findings also differed from those of our previous study. In the former study, PPT measures of the whiplash group remained lower than that of controls post-MBB, whilst in the current study, measures largely returned to those of the HC group. This may be due to the duration of pain relief in this study (3 months compared to 1-2 hours), or possibly due to participant variability in their health characteristics.

In addition to changes in PPT, we found sustained increases in NFR threshold following RFN, indicating reduced excitability of the spinal cord reflexes; reduced hyperalgesic response to the
BPPT, together with decreased cold and heat hyperalgesia. Cold sensitivity has been postulated to occur as a result of sensitized afferent fibres or dorsal horn neurons, with possible underlying insular cortex dysfunction [84,85]. Dorsal horn sensitization has also been suggested as an underlying mechanism of heat hyperalgesia [16], whilst BPPT reactivity has been interpreted to reflect hyperalgesic motor and sensory responses as a consequence of central sensitization [86,87]. Thus, reduction of cold hyperalgesia, concomitant improvements in PPT at distal sites of uninjured tissues (tibialis anterior and median nerves), especially when combined with reduction of spinal cord hyperexcitability (increased NFR threshold) and improvement in BPPT hyperalgesia, would suggest that peripheral nociception contributes to these processes. Most of the sensory measures of the WAD group were no longer different from control data following RFN. The exceptions to this were CPT and BBPT responses, which remained more sensitive than the healthy controls at the follow-up time points, although the values for these two measures were within 95% confidence intervals of published normative data [4,88].

Individuals with chronic WAD consistently demonstrate the presence of persistent motor dysfunction [8,17,50,89-91], most noticeable in those with increased levels of pain and disability [8,50]. In longitudinal studies, motor dysfunction has remained unchanged over time [50,92], with only modest improvements in ROM, pain and disability demonstrated following a course of multimodal physiotherapy [93]. The changes measured were not significantly different to a self-management group (advice booklet and exercise) [93]. In contrast, our study demonstrated a large and significant improvement in ROM following RFN with concurrent large reductions in pain and disability. There was also a trend toward improvement in performance of the CCFT, with changes not quite reaching statistical significance. However, following RFN, no significant
difference in test performance was measured between the HC and WAD groups, indicating that
the improvements measured were relevant. Hence, the reduction of nociception resulted in
certain CCFT improvements occurring. Given that individuals continued to report ongoing mild
levels of pain, further improvement could be postulated to occur if further pain reduction was
possible. However, these results are also consistent with findings in previous research, where,
despite resolution of pain and disability in some participants, deficits in performance of the
CCFT remained [50]. Thus, the remaining motor impairment in this group with chronic neck
pain probably reflects both local changes in muscle properties as well as changes in central
neuromotor control [19,22-24].

Individuals in our study continued to present with mild to moderate levels of pain and disability,
one- to three-months following RFN. These results are consistent with other studies, when
comparing similar time periods post-RFN [37,94]. At first glance, these results may not seem as
promising as Lord et al. [95], where complete relief of pain was reported in the days following
the procedure. In our study, only 4 patients reported complete relief of pain 1-month following
RFN (with an additional 10 individuals reporting ≤ 1/10 pain). However, when comparing
results at 3-months post-RFN, they are similar, with both studies finding approximately 60% of
participants reporting maintained relief of pain of at least 50% [95]. Nevertheless, the mild to
moderate levels of pain and disability reported at one and three months may be as a result of
ongoing nociception from structures other than the facet joints influenced by RFN [96].
Additionally, ongoing disability could be related to factors such as persistent motor dysfunction
(ongoing reduced ROM when compared to the healthy control participants and impaired motor
control demonstrated via the CCFT) and persistent psychological distress [97].
There are some limitations in this study. We investigated 54 consecutive individuals undergoing RFN after successful response to facet joint double blockade. Selection of patients for, and performance of RFN differed slightly from the stringent guidelines established by the International Spine Intervention Society [98,99]. Another limitation of the study was that it was not possible to blind the assessor to the status of the patient or the aims of the study. This may have introduced bias, thus indicating some caution with interpretation of study findings.

CONCLUSIONS.

Cervical RFN resulted in increased NFR thresholds, increases in local (mechanical and thermal) and remote (mechanical) pain thresholds as well as improvement in cervical ROM. These results indicate that augmented central nociceptive processes and movement loss are maintained by peripheral nociception arising from the cervical facet joints.

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Disclosures:

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Conflict of Interest:

The authors do not have any conflicts of interest to disclose.
REFERENCES:


**Table 1:** Demographics of participants and changes in pain and disability over time in the WAD participants

<table>
<thead>
<tr>
<th>Gender (F/M)</th>
<th>Age (yrs +/- SD)</th>
<th>Duration of symptoms Mths (median) [25,75]</th>
<th>VAS (+/- SD) (0-100mm)</th>
<th>NDI (+/- SD) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAD: 36/17</td>
<td>44.7 (10.9)</td>
<td>43 [30,69]</td>
<td>t(1): 58 (19)†</td>
<td>t(1): 42 (15)¥</td>
</tr>
<tr>
<td>HC: 21/9</td>
<td>44.2 (9.7)</td>
<td></td>
<td>t(2): 55 (19)</td>
<td>t(2): 43 (16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t(3): 25 (20)†*</td>
<td>t(3): 29 (16)†**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t(4): 25 (21)†*¥</td>
<td>t(4): 27 (16)†*¥</td>
</tr>
</tbody>
</table>

**Legend:** WAD = Whiplash and Associated Disorder; HC = Healthy Controls; VAS = Visual Analogue Scale; NDI = Neck Disability Index; t(1) = time-point 1 (admission to study following cervical facet joint injection double blockade); t(2) = time-point 2 (immediately prior to receiving radiofrequency neurotomy); t(3) = time-point 3 (one month following radiofrequency neurotomy); t(4) = time-point 4 (three months following radiofrequency neurotomy); † p<0.001 (between t(1) and t(x)); * p<0.0001 (between t(2) and t(x)); ¥ p=1.00 (between t(1 and 2), or t(3 and 4), or post-RFN)
Table 2: Summary of sensory measures over time in WAD participants vs. healthy controls

<table>
<thead>
<tr>
<th>Time (n)</th>
<th>t(1) (53)</th>
<th>t(2) (53)</th>
<th>t(3) (53)</th>
<th>t(4) (50)</th>
<th>Healthy Controls</th>
<th>Effect Size Cohen’s d (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPT (kPa)</strong> Median [IQR]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cervical</strong></td>
<td>186 [142,228]</td>
<td>199 [139,253]</td>
<td>236 [178,304]</td>
<td>293 [191,352]</td>
<td>344 [285,415]</td>
<td>0.74 (0.54,0.94)</td>
</tr>
<tr>
<td><em>P values</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;-----p=1.00-----&gt;</td>
<td>&lt;----------p=0.037----------&gt;</td>
<td>&lt;----------p&lt;0.005----------&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median N</strong></td>
<td>242 [183,286]</td>
<td>253 [179,312]</td>
<td>307 [242,379]</td>
<td>338 [252,426]</td>
<td>371 [297,428]</td>
<td>0.73 (0.53,0.93)</td>
</tr>
<tr>
<td><em>P values</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;-----p=1.00-----&gt;</td>
<td>&lt;----------p&lt;0.01----------&gt;</td>
<td>&lt;----------p=0.023----------&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tib Ant</strong></td>
<td>328 [282,398]</td>
<td>350 [285,436]</td>
<td>428 [363,549]</td>
<td>511 [360,657]</td>
<td>563 [462,728]</td>
<td>0.73 (0.53,0.93)</td>
</tr>
<tr>
<td><em>P values</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;-----p=1.00-----&gt;</td>
<td>&lt;----------p&lt;0.005----------&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NFR (mA)</strong> Median [IQR]</td>
<td>12 [6,18]</td>
<td>12 [6,20]</td>
<td>18 [10,30]</td>
<td>16 [8,38]</td>
<td>21 [10,38]</td>
<td>0.40 (0.20,0.60)</td>
</tr>
<tr>
<td><em>P values</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;-----p=1.00-----&gt;</td>
<td>&lt;----------p&lt;0.013----------&gt;</td>
<td>&lt;----------p&lt;0.035----------&gt;</td>
<td>&lt;----------p&lt;0.056----------&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td>&lt;-----p=1.00-----&gt;</td>
</tr>
<tr>
<td><em>P values</em></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;-----p=1.00-----&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td>&lt;----------p&lt;0.001----------&gt;</td>
<td>&lt;-----p=1.00-----&gt;</td>
</tr>
</tbody>
</table>
Legend: WAD = Whiplash and Associated Disorders; PPT = Pressure Pain Threshold; kPa = kilopascal; IQR = Interquartile Range; Median N = Median Nerve; Tib Ant = Tibialis Anterior; NFR = Nociceptor Flexor Reflex; mA = milliamperes; BPPT = Brachial Plexus Provocation Test; °elb ext ROM = degrees of elbow extension Range of Motion; CI = Confidence Interval, **Bolded P values** denote statistical significance
Table 3: Summary of thermal pain thresholds over time in WAD participants vs. healthy controls

<table>
<thead>
<tr>
<th>Time (n)</th>
<th>CPT (°C)</th>
<th>Healthy Controls</th>
<th>Effect Size</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19.6 [11.3,25.3]</td>
<td>20.8 [11.0,24.7]</td>
<td>12.6 [4.9,17.8]</td>
<td>9.7 [3.6,17.0]</td>
</tr>
<tr>
<td>P values</td>
<td>&lt;-----p=0.51----&gt;</td>
<td>&lt;------------------p&lt;0.0001--------------------&gt;</td>
<td>&lt;---p=0.0001--&gt;</td>
<td>&lt;-------p&lt;0.001--------&gt;</td>
</tr>
<tr>
<td>HPT (°C)</td>
<td>42.6 [40.3,45.0]</td>
<td>43.5 [41.8,45.9]</td>
<td>46.7 [43.7,48.1]</td>
<td>46.6 [44.0,48.4]</td>
</tr>
<tr>
<td>P values</td>
<td>&lt;-----p=0.04-----&gt;</td>
<td>&lt;------------------p&lt;0.0001--------------------&gt;</td>
<td>&lt;---p=0.0001--&gt;</td>
<td>&lt;-------p&lt;0.001--------&gt;</td>
</tr>
</tbody>
</table>

Legend: WAD = Whiplash and Associated Disorders; CPT = Cold Pain Threshold; HPT = Heat Pain Threshold; °C = degrees Celsius; IQR = Interquartile Range; Bolded P values denote statistical significance
Table 4: CCFT RMS values (medians [IQR]) over time for WAD Participants vs. healthy controls

<table>
<thead>
<tr>
<th>Time (n)</th>
<th>t(1)</th>
<th>t(2)</th>
<th>t(3)</th>
<th>t(4)</th>
<th>ANOVA P value</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>22mmHg</td>
<td>0.08</td>
<td>0.07</td>
<td>0.07</td>
<td>0.06</td>
<td>0.057</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>[0.03,0.26]</td>
<td>[0.04,0.15]</td>
<td>[0.03,0.16]</td>
<td>[0.02,0.15]</td>
<td></td>
<td>[0.02,0.08]</td>
</tr>
<tr>
<td>24mmHg</td>
<td>0.13</td>
<td>0.16</td>
<td>0.10</td>
<td>0.12</td>
<td>0.044</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>[0.05,0.31]</td>
<td>[0.07,0.31]</td>
<td>[0.05,0.21]</td>
<td>[0.04,0.21]</td>
<td></td>
<td>[0.03,0.19]</td>
</tr>
<tr>
<td>26mmHg</td>
<td>0.16</td>
<td>0.26</td>
<td>0.15</td>
<td>0.18</td>
<td>0.013</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>[0.07,0.42]</td>
<td>[0.14,0.66]</td>
<td>[0.06,0.39]</td>
<td>[0.05,0.28]</td>
<td></td>
<td>[0.06,0.23]</td>
</tr>
<tr>
<td>28mmHg</td>
<td>0.30</td>
<td>0.34</td>
<td>0.29</td>
<td>0.27</td>
<td>0.015</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>[0.15,0.52]</td>
<td>[0.16,0.72]</td>
<td>[0.12,0.53]</td>
<td>[0.09,0.50]</td>
<td></td>
<td>[0.10,0.30]</td>
</tr>
<tr>
<td>30mmHg</td>
<td>0.53</td>
<td>0.55</td>
<td>0.37</td>
<td>0.35</td>
<td>0.067</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>[0.17,0.82]</td>
<td>[0.21,0.86]</td>
<td>[0.16,0.69]</td>
<td>[0.10,0.71]</td>
<td></td>
<td>[0.10,0.46]</td>
</tr>
</tbody>
</table>

Legend: WAD = Whiplash and Associated Disorders; mmHg = millimetres mercury; RMS = Root Mean Square; t(1) = time-point 1 = one month after receiving cervical facet joint blockade; t(2) = time-point 2 = immediately prior to receiving radiofrequency neurotomy; t(3) = time-point 3 = one month following radiofrequency neurotomy; t(4) = time-point 4 = three months following radiofrequency neurotomy; Bolded P values denote statistical significance