The effect of aerobic exercise on pain and neurosensory modulation in healthy participants and with chronic pain disorder

By

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# Table of contents

Acknowledgments ................................................................................................................. 2  
Table of contents .................................................................................................................. 3  
List of figures .......................................................................................................................... 13  
List of tables ........................................................................................................................... 18  
List of abbreviations .............................................................................................................. 20  
Glossary .................................................................................................................................. 22  
Publications from this thesis .................................................................................................. 23  
Certificate of authorship ........................................................................................................ 24  
Prologue ................................................................................................................................. 25  

**Chapter 1: Introduction** ........................................................................................................ 26  
1.1 Exercise and experimental pain inhibition ........................................................................ 29  
1.2 Chronic pain ...................................................................................................................... 29  
1.3 Economic and social impact of chronic pain ..................................................................... 31  
1.4 Exercise rehabilitation ..................................................................................................... 32  
1.5 Exercise and chronic pain ............................................................................................... 33  
1.6 Psychological status and exercise rehabilitation ............................................................. 35  
1.7 Exercise programme adherence ....................................................................................... 36  
1.8 Reduced experimental pain parameters with exercise rehabilitation ............................. 36  
1.9 The pain network ............................................................................................................ 37  
1.10 Central sensitisation in chronic pain ............................................................................. 37  
1.11 Summary ....................................................................................................................... 39  

**Chapter 2: Review of literature** ............................................................................................. 41  
2.1 Classification of pain ....................................................................................................... 44
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.1</td>
<td>Acute pain</td>
<td>44</td>
</tr>
<tr>
<td>2.1.2</td>
<td>Chronic pain</td>
<td>45</td>
</tr>
<tr>
<td>2.1.3</td>
<td>Epidemiology of chronic pain</td>
<td>47</td>
</tr>
<tr>
<td>2.1.4</td>
<td>Comorbidity in chronic pain disorder</td>
<td>49</td>
</tr>
<tr>
<td>2.1.5</td>
<td>Chronic pain disorder as an independent disease</td>
<td>50</td>
</tr>
<tr>
<td>2.2</td>
<td>Pain theories and models</td>
<td>51</td>
</tr>
<tr>
<td>2.2.1</td>
<td>Specificity theory of pain</td>
<td>52</td>
</tr>
<tr>
<td>2.2.2</td>
<td>Pattern theory of pain</td>
<td>53</td>
</tr>
<tr>
<td>2.2.3</td>
<td>Affect theory of pain</td>
<td>56</td>
</tr>
<tr>
<td>2.2.4</td>
<td>Gate-control theory of pain</td>
<td>57</td>
</tr>
<tr>
<td>2.2.5</td>
<td>Multi-dimensional theories of pain</td>
<td>60</td>
</tr>
<tr>
<td>2.2.6</td>
<td>The bio-psycho-social model of pain</td>
<td>61</td>
</tr>
<tr>
<td>2.2.7</td>
<td>Fear avoidance model</td>
<td>63</td>
</tr>
<tr>
<td>2.3</td>
<td>Pain neurophysiology</td>
<td>64</td>
</tr>
<tr>
<td>2.3.1</td>
<td>Nociceptive fiber populations</td>
<td>66</td>
</tr>
<tr>
<td>2.3.2</td>
<td>Sensations elicited by nociceptor activation</td>
<td>69</td>
</tr>
<tr>
<td>2.3.3</td>
<td>Nociceptive transmission</td>
<td>69</td>
</tr>
<tr>
<td>2.3.4</td>
<td>Activation and sensitisation of the primary afferents</td>
<td>71</td>
</tr>
<tr>
<td>2.3.5</td>
<td>Nociceptive transmission in the spinal cord</td>
<td>73</td>
</tr>
<tr>
<td>2.3.6</td>
<td>Neurotransmitters and receptors in nociceptive transmission</td>
<td>77</td>
</tr>
<tr>
<td>2.3.7</td>
<td>Ascending pain pathways in the spinal cord</td>
<td>78</td>
</tr>
<tr>
<td>2.3.8</td>
<td>Mid-brain processing of nociceptive information</td>
<td>82</td>
</tr>
<tr>
<td>2.3.9</td>
<td>Ascending tracts and cortical projections</td>
<td>83</td>
</tr>
<tr>
<td>2.3.10</td>
<td>Integration of pain in the cerebral cortex and sub-cortical regions</td>
<td>86</td>
</tr>
<tr>
<td>2.3.11</td>
<td>The pain network</td>
<td>86</td>
</tr>
<tr>
<td>2.3.12</td>
<td>The lateral and medial pain system</td>
<td>87</td>
</tr>
</tbody>
</table>
2.4 Pain modulation ........................................................................................................... 89

2.5 Endogenous pain inhibition ......................................................................................... 90
  2.5.1 Noradrenergic neurons ......................................................................................... 93
  2.5.2 Dopaminergic pathways ...................................................................................... 94
  2.5.3 Serotonergic pathways ......................................................................................... 94
  2.5.4 Opioids and pain inhibition .................................................................................. 95
  2.5.5 Placebo analgesia ............................................................................................... 97
  2.5.6 Gate-control theory and pain inhibition ............................................................... 98
  2.5.7 Stress induced analgesia ..................................................................................... 99
  2.5.8 Diffuse noxious inhibitory controls ..................................................................... 100
  2.5.9 The endocannabinoid system .............................................................................. 103

2.6 Exogenous pain inhibition ......................................................................................... 104

2.7 Experimental noxious stimuli ................................................................................... 106
  2.7.1 Electrical stimuli .................................................................................................. 107
  2.7.2 Mechanical pressure stimuli ................................................................................ 108
  2.7.3 Laser stimuli ....................................................................................................... 112
  2.7.4 Cold stimuli ......................................................................................................... 112
  2.7.5 Heat stimulation .................................................................................................. 113
  2.7.6 Chemical irritants ............................................................................................... 114
  2.7.7 Ischaemia ........................................................................................................... 115

2.8 The measurement of pain ........................................................................................ 117
  2.8.1 The scaling of pain perception ............................................................................ 118
  2.8.2 Pain threshold ...................................................................................................... 120
  2.8.3 Pain tolerance ...................................................................................................... 122
  2.8.4 Dual and multi-dimensional pain scales .............................................................. 123
  2.8.5 Magill pain questionnaire ..................................................................................... 124
2.8.6 Pain and lifestyle impact questionnaires ........................................ 125
2.8.7 Behavioural measures of pain ....................................................... 126
2.8.8 Neurophysiological correlates of pain ........................................... 127
2.8.9 Microneurography of nociceptor activity ...................................... 128
2.8.10 Nociceptive reflexes ................................................................. 129
2.8.11 Cerebral evoked potentials to experimental noxious stimuli .......... 132
2.8.12 Brain imaging of pain ............................................................... 135
2.9 Chronic pain pathophysiology and neurosensory characteristics ...... 144
  2.9.1 Nociceptive pain ................................................................. 145
  2.9.2 Ischemic pain ................................................................. 145
  2.9.3 Visceral pain ................................................................. 146
  2.9.4 Neuropathic pain .............................................................. 146
  2.9.5 Non-specific chronic pain ..................................................... 149
  2.9.6 Central changes in chronic pain ............................................. 152
  2.9.7 Sensitisation in chronic pain disorder .................................... 153
  2.9.8 Central neurochemical changes in chronic pain ....................... 156
  2.9.9 Experimental pain assessments in chronic pain disorder .......... 157
  2.9.10 Brain imaging in chronic pain ............................................ 161
  2.9.11 Chronic pain management .................................................. 165
  2.9.12 Behaviour modification in chronic pain disorder ..................... 167
  2.9.13 Physical exercise rehabilitation in chronic pain management .... 168
2.10 Physical exercise and pain modulation ........................................ 170
  2.10.1 Aerobic exercise and experimental pain parameters ................. 171
  2.10.2 Isometric exercise and experimental pain parameters .......... 180
  2.10.3 Eccentric exercise and experimental pain parameters ........... 183
  2.10.4 Resistance exercise and experimental pain parameters .......... 184
2.10.5 Passive movement and experimental pain parameters ............... 186
2.10.6 Long-term exercise training and experimental pain parameters ........... 186
2.11 Physical exercise rehabilitation for chronic pain .......................... 190
  2.11.1 Acute effects of exercise in chronic pain participants .................. 190
  2.11.2 Effects of exercise rehabilitation for persons with chronic pain ........ 198
2.12 Summary of literature review ........................................... 209
  2.12.1 Exercise induced pain-inhibition in healthy participants ............... 210
  2.12.2 Exercise induced pain-inhibition in participants with chronic pain .... 213

Chapter 3: Research proposal and design ....................................... 216
  3.1 Justification of thesis .................................................. 217
  3.2 Purpose of the thesis .................................................. 219
  3.3 Delineation of thesis .................................................. 219
  3.4 Hypotheses ............................................................ 220
    3.4.1 Purpose of study one ............................................. 221
    3.4.2 Purpose of study two ............................................. 222
    3.4.4 Purpose of study three .......................................... 223
    3.4.5 Purpose of study four .......................................... 223

Chapter 4: Reliability of the nociceptive withdrawal reflex (NWR) threshold and association with pain threshold ........................................... 224
  4.1 Abstract ............................................................. 225
  4.2 Introduction ........................................................... 226
  4.3 Methodology ........................................................... 228
    4.3.1 Participants ....................................................... 228
    4.3.2 Experimental design ............................................. 228
    4.3.3 Electrode site preparation and position .................................. 229
    4.3.4 Laboratory apparatus ............................................ 230
Chapter 5: Aerobic exercise attenuates cerebral event related potentials to nociceptive events

5.1 Abstract .................................................................................................................. 249

5.2 Introduction ............................................................................................................. 250

5.3 Methods .................................................................................................................. 253
  5.3.1 Participants .......................................................................................................... 253
  5.3.2 Study design ......................................................................................................... 253
  5.3.3 Assessment of maximum exercise oxygen consumption .................................. 254
  5.3.4 Nociceptive withdrawal reflex threshold assessment ........................................ 255
  5.3.5 Pain threshold assessment .................................................................................. 257
  5.3.6 Cerebral event related potentials ...................................................................... 258
  5.3.7 Aerobic exercise ................................................................................................. 261
  5.3.8 Statistical analysis ............................................................................................. 261

5.4 Results ................................................................................................................... 262
  5.4.1 Aerobic exercise responses ................................................................................ 262
5.4.2 Nociceptive withdrawal reflex threshold and pain threshold assessment 262
5.4.3 EMG peak signal amplitude at the nociceptive withdrawal reflex threshold and pain threshold ......................................................... 263
5.4.4 Signal latency checks for cerebral event related potentials .......... 266
5.4.5 CEP at the NWR threshold .................................................. 266
5.4.6 CEP at pain threshold ......................................................... 267
5.5 Discussion ................................................................................. 271
5.5.1 Conclusion .............................................................................. 275

Chapter 6: Effects of moderate-intensity aerobic exercise rehabilitation for chronic pain disorder .................................................. 276
6.1 Abstract .................................................................................. 277
6.2 Introduction ............................................................................... 278
6.3 Methodology ............................................................................ 280
  6.3.1 Ethics statement .................................................................. 280
  6.3.2 Participants .......................................................................... 280
  6.3.3 Experimental design ............................................................ 281
  6.3.4 Exercise programme adherence, modality, frequency, intensity, and perceptual responses .......................................................... 282
  6.3.5 Health status and anthropometric characteristics .................. 283
  6.3.6 Functional capacity and cardiovascular fitness ....................... 283
  6.3.7 Pressure pain threshold ....................................................... 284
  6.3.8 Electrocutaneous pain threshold ........................................... 285
  6.3.9 Nociceptive withdrawal reflex threshold ............................... 286
  6.3.10 Pain report and lifestyle impact assessment .......................... 287
  6.3.11 The 10-month follow-up assessments .................................... 288
  6.3.12 Statistical analysis .............................................................. 288
7.5.2 Regional brain analysis ................................................................. 339
7.5.3 Perceptual and regional brain responses at following aerobic exercise rehabilitation ................................................................. 340
7.5.4 Anticipation................................................................................. 341
7.5.5 Reduced neuronal activity in caudate ......................................... 342
7.5.6 Thalamus .................................................................................. 342
7.5.7 Insula – A pattern of connectivity between temporal lobe and basal ganglia .............................................................................. 343
7.5.8 BOLD signal analysis ................................................................. 344
7.5.9 Summary................................................................................... 345

Chapter 8: Conclusion .................................................................. 346

8.1 Study 1: Reliability of the nociceptive withdrawal reflex threshold ........................................................................... 348
  8.1.1 Study 1: Research question addressed ........................................ 349
  8.1.2 Study 1: Major finding ............................................................... 350
  8.1.3 Study 1: Limitations ................................................................. 350

8.2 Study 2: Reduced cerebral event related potentials to nociceptive stimuli following aerobic exercise .............................................................................. 351
  8.2.1 Study 2: Research question addressed ........................................ 351
  8.2.2 Study 2: Major finding ............................................................... 352
  8.2.3 Study 2: Limitations ................................................................. 353

8.3 Study 3: Effects of moderate intensity aerobic exercise rehabilitation for chronic pain disorder .............................................................................. 354
  8.3.1 Study 3: Research question addressed ........................................ 355
  8.3.2 Study 3: Major findings .............................................................. 356
  8.3.3 Study 3: Limitations ................................................................. 360
8.4 Study 4: Functional brain responses and perceptual rating to somatic-pressure stimulation in chronic pain and healthy participants before and after exercise rehabilitation................................................................. 361
8.4.1 Study 4: Research question addressed........................................... 361
8.4.2 Study 4: Major finding .................................................................... 363
8.4.3 Study 4: Limitations......................................................................... 363
8.5 Summary............................................................................................ 364
8.6 Future research directions.................................................................... 366
Reference list ........................................................................................ 368
Appendix 1 ......................................................................................... 441
   Pain sensation scale................................................................. 441
Appendix 2 ......................................................................................... 442
   Rating of perceived exertion (RPE)............................... 442
Appendix 3 ......................................................................................... 443
   Muscle pain intensity scale (MPI)....................................... 443
Appendix 4 ......................................................................................... 444
   Study health screening questionnaire.......................... 444
List of figures

**Figure 2.1**: Organisation of the dorsal horn laminae and the ascending pathways in the spinal cord ......................................................... 75

**Figure 2.2**: The neospinothalamic (direct) and paleospinothalamic (indirect) pathways of the anterolateral system projecting discriminative and non-discriminative pain ........................................................................................................ 81

**Figure 2.3**: Sagittal plane schematic of ascending pathways, subcortical structures, and cerebral cortical structures associated with pain processing ................................................................. 85

**Figure 2.4**: Functional MRI responses (% contrast) in human primary visual cortex (● mean, error bars ± standard error mean) plotted against average neural firing rates in monkey primary visual cortex (line). ................................................................. 139

**Figure 2.5**: Major brain regions active during a painful experience, highlighted as bilaterally active, with increased activation in the contralateral hemisphere (orange) ........................................................................................................... 143

**Figure 2.6**: Active brain regions during functional MRI scanning between chronic pain and control participants during similar pressure stimulation ........................................... 164

**Figure 4.1**: Showing the subject setup for recording the lower limb nociceptive withdrawal reflex A) and the electromyogram setup B) ................................................................................................. 233

**Figure 4.2**: The between-trials measurement analysis for the NWR reflex threshold and Pain threshold. The trials were separated by a mean of 4.3 ± 2.9 days. The measurement analysis was performed by comparing the threshold assessment in Measurement A for each trial .................................................................................. 239
**Figure 4.3:** The within-trial measurement analysis of the NWR reflex threshold and Pain threshold. The repeated threshold assessments (Measurement A and Measurement B) were separated by a 20 min rest interval within each trial. 241

**Figure 4.4:** The correlation between the NWR reflex threshold and the Pain threshold within each trial. 243

**Figure 5.1:** Showing a participant performing aerobic exercise with EEG electrocap in place for the Pre and Post exercise recording of cerebral event related potentials to nociceptive events. 260

**Figure 5.2:** Mean CEP peak amplitude at the nociceptive withdrawal reflex threshold for N1 (A) and P1 (B) at Pre, Post1 (5 min), and Post2 (15 min) for High (70% VO$_2$ max) and Low intensity aerobic exercise (30% of VO$_2$ max), * significant difference between Pre-Post2 for exercise ($P<0.001$). 268

**Figure 5.3:** Mean CEP peak amplitude at pain threshold for N1 (A) and P1 (B) at Pre, Post1 (5 min), and Post2 (15 min) for High (70% VO$_2$ max) and Low intensity aerobic exercise (30% VO$_2$ max). 269

**Figure 5.4:** A) A sample EMG signal at the Nociceptive withdrawal reflex threshold. The vertical axis represents the voltage and the stimulus (electrocutaneous) onset. The nociceptive withdrawal reflex timeframe window is depicted between .9 and 1.5 s (horizontal axis). B) A sample CEP at 140 V. The vertical axis represents the voltage and the stimulus onset. The horizontal axis represents the time in milliseconds. 270

**Figure 6.1:** Showing the timeline for the Pre and Post assessments and the appraisal performed during exercise rehabilitation over 12 weeks. 290

**Figure 6.2:** Pre and Post aerobic exercise rehabilitation within the chronic pain group and the control group for Health Status (SF36), Body composition (% body fat), Functional capacity (6-min walk, power output, Exercise muscle pain intensity), Cardiovascular fitness (HR/Watt), and Experimental pain parameters (PPT, EPT,
NWR threshold). Results are expressed as Cohen’s $d$ with 95 percent confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful difference. A Cohen’s $d$ above 0.2 or below -0.2 represents a meaningful difference.

**Figure 6.3:** A) Mean exercise power output (W), B) Heart Rate (beats/min), and C) Muscle pain intensity rating (0-10 units) during exercise at moderate intensity (RPE of 12) in chronic pain and control participants at Start, Mid, and End of 12-weeks of aerobic exercise rehabilitation.

**Figure 6.4:** Chronic pain compared to the control group at Pre aerobic exercise intervention for Health Status (SF36), Body composition (% body fat), Functional capacity (6 min walk test, Power output, Muscle pain intensity (0-10 units), Cardiovascular fitness (HR/Watt), and Experimental pain parameters (PPT, EPT, and NWR threshold). Results are expressed as Cohen’s $d$ with 95 percent confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful difference. A Cohen’s $d$ above 0.2 or below -0.2 represents a meaningful difference. Higher scores indicate the chronic pain group was higher than the healthy controls.

**Figure 6.5:** Comparison for the Magill pain questionnaire (MPQ) and Fibromyalgia impact questionnaire (FIQ) between Start-Mid and Start-End of aerobic exercise rehabilitation in the chronic pain group. Results are expressed as Cohen’s $d$ with 95 percent confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful difference. A Cohen’s $d$ above 0.2 or below -0.2 represents a meaningful difference.

**Figure 6.6:** Comparisons for the Health status (SF36), Magill Pain Questionnaire (MPQ), and Fibromyalgia Impact Questionnaire (FIQ) between Post-10Month follow-up in the chronic pain group. Results are expressed as Cohen’s $d$ with 95 percent confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful difference. A Cohen’s $d$ above 0.2 or below -0.2 represents a meaningful difference.
confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful difference. A Cohen's $d$ (●) above 0.2 or below -0.2 represents a meaningful difference ................................................................. 303

**Figure 7.1:** A) Showing participant setup and somatic pressure site prior to functional MRI scanning B) showing the 2 kg somatic pressure stimulus positioned on the mid-thigh......................................................................................................................... 321

**Figure 7.2:** Mean perceptual rating (0-10 units) to the somatic-pressure stimulus during functional brain imaging in chronic pain and control participants at Pre and Post aerobic exercise rehabilitation. Group comparison between chronic pain and control at Pre * ($P=0.018$) and Post ** ($P=0.007$)......................................................... 327

**Figure 7.3:** Neuronal areas of enhanced activity (ChronicPre>ControlPre) amongst the regions of interest (display threshold; $P<0.05$, 5 voxels).............................................. 328

**Figure 7.4:** Neuronal areas of enhanced activity (ControlPre>ChronicPre) amongst the regions of interest (display threshold; $P<0.05$, 5 voxels).............................................. 329

**Figure 7.5:** Neuronal areas of enhanced activity (ChronicPost>ControlPost) amongst the regions of interest (display threshold; $P<0.05$, 5 voxels).............................................. 330

**Figure 7.6:** Neuronal areas of enhanced activity (ControlPost>ChronicPost) amongst the regions of interest (display threshold; $P<0.05$, 5 voxels).............................................. 331

**Figure 7.7:** Percent BOLD signal change within the regions of interest between the chronic pain and the control group (between-group analysis) at Pre and Post aerobic exercise rehabilitation. Results are expressed as Cohen's $d$ (●) with 95 percent confidence interval (horizontal bars). The vertical dotted lines represent the threshold ($± 0.2$) for the smallest meaningful difference. A Cohen's $d$ (●) above 0.2 or below -0.2 represents a meaningful difference (enhanced neuronal activation or deactivation) in the BOLD signal in the chronic pain group compared to the control group................................................................. 336
Figure 7.8: Percent BOLD signal change in the regions of interest between Pre and Post aerobic exercise rehabilitation (within-group analysis) for the chronic pain and the control group. Results are expressed as Cohen’s $d$ (●) with 95 percent confidence interval (horizontal bars). The vertical dotted lines represent the threshold (± 0.2) for the smallest meaningful difference. A Cohen’s $d$ (●) above 0.2 or below -0.2 represents a meaningful difference (enhanced neuronal activation or deactivation) in the BOLD signal for the chronic pain group compared to the control group. ........ 337
List of tables

Table 2.1: Classification of afferent fibers. .......................................................... 68

Table 2.2: Showing a sample of research studies examining the relationship between exercise and experimental pain parameters in healthy participants ..................... 194

Table 2.3: Showing a sample of research studies examining the acute effects of exercise on experimental pain parameters in participants with chronic pain .......... 205

Table 2.4: Showing a sample of research studies on examining the effects of exercise rehabilitation on experimental and clinical pain outcomes in participants with chronic pain.................................................................................................................. 207

Table 4.1: The mean electrotactaneous intensity (V±SD) for the NWR reflex threshold and Pain threshold between-trials (Trials 1, 2 & 3) and within-trials (Measurement A and Measurement B). The between-trials period were separated by a mean of 4.3 ± 2.9 days. The within-trial period was separated by a 20 minute rest interval .......... 236

Table 4.2: The mean coefficient of variation (CoV%) for the NWR-T and PT for each subject.......................................................................................................................... 237

Table 5.1: The nociceptive withdrawal reflex threshold and pain threshold (mean Volts ± SD) at Pre, Post1, and Post2 aerobic exercise. High and Low intensity aerobic exercise were performed on separate occasions ........................................ 264

Table 5.2: Mean peak EMG signal amplitude at the nociceptive withdrawal reflex threshold and pain threshold for Pre, Post1, and Post2 High and Low intensity aerobic exercise .............................................................................................................. 265

Table 6.1: Characteristics of the chronic pain and control group prior to aerobic exercise rehabilitation. Data are expressed as mean ± SD.............................................. 300
Table 7.1: Group characteristics prior to aerobic exercise rehabilitation. Data are presented as mean ± SD. *Group comparisons between chronic pain and control, P<0.05.

Table 7.2: Results for peak voxels amongst the regions of interest prior to exercise rehabilitation*

Table 7.3: Results for peak voxels amongst the regions of interest following exercise rehabilitation.
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>rACC</td>
<td>Rostral anterior cingulated cortex</td>
</tr>
<tr>
<td>AER</td>
<td>Aerobic exercise rehabilitation</td>
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<tr>
<td>BOLD</td>
<td>Blood oxygen-level dependent</td>
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<td>CEPs</td>
<td>Cerebral event related potentials</td>
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<tr>
<td>DMN</td>
<td>Default mode network</td>
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<tr>
<td>DNICs</td>
<td>Diffuse noxious inhibitory controls</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>EMG</td>
<td>Electromyogram</td>
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<tr>
<td>FIQ</td>
<td>Fibromyalgia impact questionnaire</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
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<td>IC</td>
<td>Insula cortex</td>
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<td>IASP</td>
<td>International association for the study of pain</td>
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<td>MPI</td>
<td>Muscle pain intensity</td>
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<td>MPQ</td>
<td>Magill pain questionnaire</td>
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<td>NMDA</td>
<td>N-methyl-d-aspartic acid</td>
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<td>NRM</td>
<td>Nucleus raphe magnus</td>
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<tr>
<td>NWR</td>
<td>Nociceptive withdrawal reflex</td>
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</tr>
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<td>Somatosensory evoked potentials</td>
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<td>Stress induced analgesia</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>VO$_{2\text{max}}$</td>
<td>Maximum volume of oxygen uptake</td>
</tr>
<tr>
<td><strong>Glossary</strong></td>
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<tr>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td><strong>Nociceptive withdrawal reflex</strong></td>
<td>A polysynaptic sensorimotor withdrawal reflex that emerges in response to stimulation of nociceptive fibers</td>
</tr>
<tr>
<td><strong>Pain sensitivity</strong></td>
<td>The verbal rating or behavioural response to an experimental pain stimulus</td>
</tr>
<tr>
<td><strong>Pain threshold</strong></td>
<td>The minimum level of experimental noxious stimulation that reliably elicits a pain response</td>
</tr>
<tr>
<td><strong>Pain tolerance</strong></td>
<td>The time that a continuous stimulus is endured, or the maximally tolerated stimulus intensity</td>
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</table>
Publications from this thesis

The following research study has been published based on data from this thesis:

Certificate of authorship

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Chapter 1: Introduction

Prologue

The function of endogenous pain-inhibiting systems is well recognised in the research literature, however, the underlying central mechanisms following physical exercise and the application in exercise rehabilitation has not been fully elucidated. Previous research shows that spinal anti-nociceptive and central pain-inhibitory systems contribute to mediating experimental pain responses (Basbaum & Fields, 1984). Currently, there is a paucity of research literature that explicates the neurosensory processing of nociceptive information in healthy participants following physical exertion. This information is important in advancing the understanding of the processes that lead to the inhibition of pain. Moreover, this information can initiate further understanding into the development of exercise rehabilitation programming for persons with chronic pain disorder.

Previous research shows that the central nervous systems undergoes structural and functional changes in persons suffering with persistent pain conditions (Lee & Tracey, 2010). It has been proposed that part of the underlying pain processing mechanism in chronic pain disorder is of central hypersensitivity (Lim, Sterling, Stone, & Vicenzino, 2011). Physical exercise rehabilitation has the potential to impede and alleviate the changes in the central nervous system as well attenuate clinical pain report in persons with chronic pain disorder. In order to develop a series of research studies to elucidate the function of pain inhibitory systems following physical exercise, it is necessary to develop a review of the past and present pain literature. Therefore the purpose of this thesis is to further explicate the function of central pain inhibitory systems in healthy participants following acute physical exercise and in persons with chronic pain disorder following physical rehabilitation.
Chapter 1: Introduction
Observations from researchers and clinicians have widely recognised an association between pain and exercise. In laboratory-based research, physical exertion has shown to mediate experimental pain parameters such as pain threshold and tolerance. In the clinical context, physical exercise rehabilitation has been shown to influence pain report in persons with chronic pain. The effect of physical activity on pain is of interest in exercise and pain research due to the potential function of endogenous pain control systems and in the development of physical rehabilitation programmes for persons with chronic pain disorder.

The continuation of exercise despite a significant injury such as a fractured bone, suggests that pain is endogenously mediated under certain conditions (Colt & Spyropoulos, 1979). It has been proposed that the inhibition of pain under these circumstances is performed by the function of endogenous pain-inhibiting systems. In order to assess the inhibition of pain following physical exertion, experimental pain stimuli are applied under controlled research conditions. Attenuation of the perception of experimental noxious stimuli has been observed during and after exercise (Kemppainen, Pertovaara, Huopaniemi, Johansson, & Karonen, 1985) and is referred to as exercise-induced hypoalgesia (Koltyn, 2002). Observations of exercise-induced hypoalgesia have been performed under various experimental conditions and protocols (Cook & Koltyn, 2000; Koltyn, 2000). The mechanisms underlying the attenuation of pain with exercise are not fully understood, however, several possibilities have been proposed (O’Connor & Cook, 1999).
In order to assess the function of endogenous pain mediating systems, pain needs to be reliably measured. Pain is a subjective experience that is not directly quantifiable. Only perceptual and behavioural responses to pain can be observed and measured. This means that verbal reports and communications are assigned in pain research to represent the private, multidimensional, and otherwise inaccessible pain experience (Lee & Tracey, 2010). The difficulty with this subjective method is the potential difference between the report of pain and the actual perception. In the research and clinical setting, this is overcome by applying reliable and valid measurement procedures in order to assess pain and treatment effects.

Studies on pain and exercise can be grouped into two broad areas: investigations into the use of experimentally induced pain during and after exercise; and the assessment of clinical pain and functional outcomes following exercise rehabilitation. Experimentally induced pain requires the use of controlled noxious stimuli to evoke and assess pain before and after intervention such as physical exercise. Typically, experimental pain stimuli such as electrocutaneous and somatic-mechanical pressure are applied in exercise and pain research settings to assess the function of the pain system. In the clinical pain context, physical exercise rehabilitation is often recommended as a therapeutic intervention for managing persistent pain conditions and improving function in persons with chronic pain disorder.
1.1 Exercise and experimental pain inhibition

Physical exercise has previously shown to reduce experimental noxious stimuli during concurrent activity in healthy participants (Kemppainen, Paalasmaa, Pertovaara, Allila, & Johansson, 1990). A transient sensory attenuation of experimental noxious (Droste, Greenlee, Schreck, & Roskamm, 1991) and innocuous stimuli (Paalasmaa, Kemppainen, & Pertovaara, 1991) has also been observed in the post-exercise period (O’Connor & Cook, 1999), however, this has not been consistently demonstrated (Ruble et al., 2005). The attenuation of pain in the post-exercise period has been linked with cerebral (Olausson et al., 1984) and spinal (Guieu, Blin, Pouget, & Serratrice, 1992) pain control systems. Pain modulation following exercise has also been demonstrated in animal models (Li, Rhodes, Girard, Gammie, & Garland, 2004; Shyu, Andersson, & Thoren, 1982). Observations of pain inhibition following exercise is of interest due to the limited understanding of the function of endogenous pain control systems and for the development of exercise rehabilitation programmes for chronic pain disorder.

1.2 Chronic pain

Chronic pain has emerged as a distinct phenomenon in comparison to acute pain. Chronic pain is defined as continuous pain that persists for three of the last six months (Blyth et al., 2001; Siddall & Cousins, 2004). The point of division between acute to chronic pain is often depicted as three months (Merskey & Bogduk, 1994). This length of time is distinguished by the period for inflammation to subside and for healing to complete. When pain persists beyond this period then it is considered as
chronic pain. In the classification of low back pain, chronic pain is pain that lasts for more than six months (Long, 1999). In a large-scale epidemiological study with more than 40,000 participants, chronic pain was classified as persistent pain for at least six months (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Landmark, Romundstad, Borchgrevink, Kaasa, & Dale, 2011). In research on idiopathic low-back pain, a minimum pain duration of three months was applied (Giesecke et al., 2004). Currently there is no consensus timeline for pain to be classified as chronic pain, although three months is often the point of division between acute and chronic pain (Merskey & Bogduk, 1994).

Chronic pain represents a significant impact on the health care system. Population based studies show that up to 20% of the adult population report moderate to severe chronic pain (Blyth, et al., 2001; Breivik, et al., 2006). Despite the significance of this problem and advances in our understanding of pain mechanisms, the pace at which new treatments have been made available for chronic pain has been slow. Persons with persistent pain that seek health care are often not treated effectively (Katz & Barkin, 2010). Standard treatments for chronic pain provide only temporary relief. For example, to achieve continual pain relief, multiple doses of non-steroidal anti-inflammatory drugs such as acetamenophin is required, however, this contributes to non-compliance (Katz, 2002). Moreover, a significant proportion of persons with chronic pain choose not to receive medication due to the side-effects and ineffective pain-relief (Breivik, et al., 2006).

A significant barrier to overcome is that chronic pain is often not viewed as a physical illness worthy of treatment. Chronic pain continues to be perceived as a ‘characterologic’ disorder rather than a medical disease (Brookoff, 2000). Historically,
chronic pain has been labelled as a syndrome or group of syndromes, however, accumulating evidence from neuroimaging studies indicates that chronic pain can be classified as a disease (Tracey & Bushnell, 2009). Previous research shows that the peripheral and central nervous systems undergo structural and functional changes such as neurodegeneration and central hypersensitivity (Lee & Tracey, 2010). Knowledge of the structural and functional changes that occur with persistent pain can be applied in exercise therapy in order to optimize the rehabilitation of persons with chronic pain.

1.3 Economic and social impact of chronic pain

The burden of chronic pain is substantial for both the patient and society. In a large scale population survey in Australia comprising 17,543 interviews, chronic pain was reported in 17.1% of males and 20% of females (Blyth, et al., 2001). Among the respondents who reported chronic pain, 12.3% indicated that the pain was causing some degree of interference with daily activities. Across 16 countries, 19% of 46,394 respondents reported pain for more than 6 months (Breivik, et al., 2006). In the chronic pain respondents, intermittent pain was reported at 54% and constant pain at 46%. Moreover, the rate of depression among persons surveyed with chronic pain was 21%, while 61% reported that they were less able or unable to work outside of home. The financial cost to society has been estimated at $150 billion per annum in the USA and €200 billion in Europe (Tracey & Bushnell, 2009). In 2007, 3.2 million Australians reported experiencing chronic pain at an estimated cost of $34.4 (AU) billion (Access Economics, 2007).
Due to the impact of chronic pain on large numbers of people, persistent pain is a significant medical-health care problem that results in substantial health care costs. Although a variety of pharmacologic treatments are available, chronic pain remains inadequately treated. Current pharmaceutical options are limited with respect to pain relief and are associated with significant side-effects. Many pharmacological treatment options provide pain relief for 4-6 hours, however, multiple doses are required for continued pain relief. The inconvenience of multiple doses prevents many from achieving adequate pain relief (Katz & Barkin, 2010). Other limitations to pharmacological treatment include undesirable gastrointestinal effects, adverse cardiovascular changes, toxicity, and addiction (Whelton, 2000; Wolfe, Lichtenstein, & Singh, 1999). Additionally, improvements in functional status with pharmacological treatment have not been consistently demonstrated (Staiger, Gaster, Sullivan, & A Deyo, 2003).

1.4 Exercise rehabilitation

Exercise rehabilitation is defined as the restoration and/or maintenance of physical function to enable an individual to perform activities of daily living (ADL) without high levels of fatigue and stress (Rimmer, 1994). The prescription of a physical exercise programme as a medical treatment and as a form of rehabilitation is a long-standing notion that has gained acceptance in the clinical setting. Exercise-based rehabilitation programmes were initially found to be clinically effective in treating cardiovascular disease and musculoskeletal injuries (Hellénius & Sundberg, 2011; Moore, 2004). Gradually, rationales for medically directed exercise for treating and reducing the risk of chronic diseases were developed for diabetes, obesity, depression, and cancer (Thompson et al., 2003). Substantial evidence has
accumulated to show that physical exercise has the potential to alleviate pain and restore function in persons with chronic pain.

1.5 Exercise and chronic pain

Persons with chronic pain often present with decreased levels of physical fitness, diminished health status, and reduced functional capacity. Assessments for cardiorespiratory fitness show decreased performance in persons with chronic pain compared to healthy persons (Bennett et al., 1989; Cook, Nagelkirk, Poluri, Mores, & Natelson, 2006). Health status is substantially reduced (Neziri, Andersen, et al., 2010) and measures of functional capacity are significantly lower compared to healthy participants (Mannerkorpi, Svantesson, Carlsson, & Ekdahl, 1999).

An exercise prescription, as in other types of prescription, requires a dose, frequency, duration of treatment, therapeutic goal, and anticipatory side-effects (ACSM, 2006). In the context of chronic pain management, the current understanding of optimal exercise prescription for alleviating pain, maintaining programme adherence, and minimising the potential side-effects is limited. Moreover, little attention has been paid towards the emergence of pain during exercise and its potential role in adherence to exercise rehabilitation programmes for persons with chronic pain.

In healthy participants, threshold for muscle pain during aerobic exercise was shown to appear at a mean of 50% of peak power output and oxygen consumption (Cook, O’Connor, Eubanks, Smith, & Lee, 1997). During aerobic exercise, chronic pain participants have been shown to reveal greater increases in leg muscle pain
compared to healthy control participants (Cook, Stegner, & Ellingson, 2010). Further research is required to ascertain the acute and long-term effects of exercise in chronic pain participants in the context of muscle pain responses during exercise and the long-term effects of exercise programming on clinical pain and health outcomes.

Previous research indicates that long-term exercise programming reduces clinical pain, improves function, and enhances health-related components in persons with chronic pain disorder (Busch, Barber, Overend, Peloso, & Schachter, 2009). Individuals with chronic pain are often sedentary with reduced functional capacity. Limitations in the ability to perform daily living activities are reported to be high in persons with chronic pain (Hawley & Wolfe, 1991). In addition to reducing pain, the potential benefits of exercise rehabilitation for persons with chronic pain are closely associated with improvements in functional capacity and quality of life (Busch, et al., 2009).

Regular physical activity has been associated with a lower prevalence of chronic pain rates in epidemiological research (Landmark, et al., 2011). Previous studies on exercise programme intervention for chronic pain participants show favourable pain report outcomes (Busch, et al., 2009; Choi, Verbeek, Tam, & Jiang, 2010; Hurkmans, van der Giesen, Vliet Vlieland, Schoones, & Van den Ende, 2009; Roddy et al., 2005) and improved health-related components (Gowans et al., 2001; Richards & Scott, 2002; Valim et al., 2003).

Research into the effects of exercise on chronic pain requires the use of pain measurement and reporting tools in order to assess the efficacy of exercise-intervention for chronic pain disorder. Studies combining experimental pain
assessment and pain appraisal enable comparisons between functional pain processing and clinical pain evaluation to explicate pain outcomes. The potential for research on the pain-relieving effects of exercise is to contribute towards understanding pain mechanisms and in the development of optimal exercise prescription in the management of chronic pain.

1.6 Psychological status and exercise rehabilitation

Chronic pain has been associated with reduced emotional status and high rates of depression. In a large scale population-based survey of chronic pain participants, 21% of respondents were diagnosed with depression and psychological distress (Breivik, et al., 2006). Enhanced psychological distress has been identified as a potential pathway in which influences the development of persistent pain. It has been shown that symptoms of depression and stress partially determine how pain influences chronic disability (Hall et al., 2011). Hence, chronic pain often coincides with disturbances in the affective state (Toblin, Mack, Perveen, & Paulozzi, 2011) and this further perpetuates the pain condition (Hamilton, Karoly, & Kitzman, 2004; Hummel, Lu, Cummons, & Whiteside, 2008; Linton et al., 2011; Schmidt-Wilcke et al., 2006; Staud, Vierck, Robinson, & Price, 2006; Tang et al., 2008; Vlaeyen & Linton, 2000).

Exercise intervention has the potential to improve physical function and psychological status for persons with chronic pain (IASP, 1998). Previous research has shown substantial improvements in mental health components among chronic pain participants following exercise rehabilitation (Bircan, Karasel, Akgun, El, & Alper, 2008; Sañudo et al., 2010). On this basis, improvements in functional capacity and
psychological status during exercise rehabilitation may contribute towards reduced pain and chronicity in persons with chronic pain disorder.

1.7 Exercise programme adherence

Exercise programme adherence is a significant problem for chronic pain participants (Linton, Hellsing, & Bergström, 1996). The reason for low exercise programme adherence amongst persons with chronic pain is attributed to an acute exacerbation of pain and fatigue in the post-exercise period (Richards & Scott, 2002; van Santen et al., 2002). Currently there is a lack of information on the optimum exercise prescription for persons with chronic pain. Previous research shows that chronic pain participants report elevated muscle pain ratings during exercise (Cook & Stegner, 2007). Therefore, it is possible that exercise prescription for chronic pain participants may require amendments in order to minimise muscle pain during exercise and to maintain programme adherence.

1.8 Reduced experimental pain parameters with exercise rehabilitation

Several forms of intervention strategies are often applied to treat chronic pain conditions including exercise rehabilitation (Melzack & Turk, 1998). Several studies show that exercise rehabilitation reduces clinical pain report in persons with chronic pain (Carbonell-Baeza et al., 2010; Choi, et al., 2010). The mechanisms for the reduced pain in persons with chronic pain following exercise rehabilitation are not fully understood. It has been suggested that exercise diminishes pain through a process of neurologic or physiologic desensitisation of the pain-producing tissue
(Imamura, Cassius, & Fregni, 2009; Rainville et al., 2004; Rainville, Jouve, Hartigan, Martinez, & Hipona, 2002). On this basis, exercise rehabilitation may reveal favourable changes in experimental pain parameters associated with reduced tissue sensitivity. In support of this, previous research shows improvements in experimental pain parameters, such as pain threshold, following exercise rehabilitation among persons with chronic pain disorder (Carbonell-Baeza, et al., 2010).

1.9 The pain network

Technological advances allow the non-invasive assessment of brain activity by functional brain resonance imaging during experimental pain stimulation. Pain is a complex subjective experience that involves neuronal activity in a widely distributed network of brain regions known as the pain matrix (Tracey & Mantyh, 2007). Previous research shows functional differences in brain activity amongst participants with chronic pain disorder (Pujol et al., 2009). Currently there is lack of research on the effects of exercise rehabilitation on the functional brain responses in the pain matrix amongst persons with chronic pain disorder. A plausible basis for the reduced pain report in chronic pain disorder following exercise rehabilitation is that physical activity restores the function of the network of brain regions associated with pain processing.

1.10 Central sensitisation in chronic pain

Accumulating evidence supports a correlation between experimental pain sensitivity and chronic pain disorder including low-back pain (O'Neill, Kjaer, Graven-Nielsen, Manniche, & Arendt-Nielsen, 2011), fibromyalgia (Staud, Nagel, Robinson, & Price,
2009), complex regional pain, and temporomandibular pain (Maixner, Fillingim, Booker, & Sigurdsson, 1995). In a longitudinal study conducted over 12 years, experimental pressure pain threshold corresponded with the development of chronic pain in tension-type headache (Buchgreitz, Lyngberg, Bendtsen, & Jensen, 2008). Collectively, these studies indicate that enhanced sensitivity to experimental somatic stimuli is associated with persistent pain input from chronic pain. In support of this premise, afferent input from peripheral sources has been shown to dynamically maintain central sensitisation and account for the widespread somatic hypersensitivity in persons with chronic pain disorder (Staud, et al., 2009).

It has been proposed that a commonality of central hyperexcitability exists between various chronic pain disorders (Curatolo, Arendt-Nielsen, & Petersen-Felix, 2006; Phillips & Clauw, 2011; Woolf, 2011). Several studies point towards enhanced sensitisation of the central pain system in participants with chronic pain (Graven-Nielsen & Arendt-Nielsen, 2010). Representation of central sensitisation is shown by the recruitment of previously sub-threshold synaptic inputs to produce an augmented output. Pain under central sensitisation arises spontaneously, can be elicited by normally innocuous stimuli, is augmented and prolonged in response to noxious stimuli, and spreads beyond the site of injury (Latremoliere & Woolf, 2009). Spatially generalised hypersensitivity and hyperalgesia has been identified in various chronic pain disorders (Vierck Jr, 2006). Accumulating evidence is showing that chronic pain is associated with elevated spinal excitability (Lim, et al., 2011; Neziri, Haesler, et al., 2010) among participants with chronic pain disorder.

Quantitative sensory testing such as pain threshold assessment is based on the participants’ voluntary responses. Pain threshold assessment is subject to conscious
or involuntary symptom exaggeration. In contrast, experimental pain-related events such as the nociceptive withdrawal reflex are considered a direct measure of the excitability of the central nervous system (Sandrini, Arrigo, Bono, & Nappi, 1993; Skljarevski & Ramadan, 2002; Willer, 1977). A lower nociceptive withdrawal reflex threshold in persons with chronic pain suggests the notion of a central hypersensitivity in chronic pain disorder.

1.11 Summary

There are several links between physical exercise and pain. In the area of pain inhibition, exercise has been shown to reduce experimental pain parameters. Since pain is a subjective experience, its measurement is often based on perceptual rating. At present, there is a lack of information on neurophysiological correlates of pain and the reliability and validity of these measures. Moreover, the application of pain-related neurophysiological events could advance the understanding of the mechanisms underlying exercise-induced pain inhibition.

Exercise rehabilitation has been shown to reduce pain and improve health and functional capacity in persons with chronic pain. A side-effect of exercise is the presence of muscle pain during physical exertion. Pain in muscle tissue during acute physical exertion has been shown to develop in healthy participants (Cook, et al., 1997) and in persons with chronic pain. Muscle pain during exercise in persons with chronic pain is substantially elevated compared to healthy pain-free participants (Cook & Stegner, 2007). Presently, there is a lack of information on the optimum exercise prescription for curtailing muscle pain during exercise and maintaining exercise programme adherence in persons with chronic pain.
The state of understanding on the interaction between pain and the brain is undergoing a veritable revolution, with new surprising observations accumulating at a fast pace (Apkarian, Hashmi, & Baliki, 2011). Repeated activation of pain pathways such as in chronic pain induces physiochemical changes in neural pathways of the spinal cord to amplify pain signals and diminish the function of intrinsic pain-inhibiting systems (Brookoff, 2000). Changes in the nervous system by the original injury may cause an inability to return to normal function. Previous research shows that exercise rehabilitation reduces experimental and clinical pain parameters in persons with chronic pain. On this basis, it is plausible that exercise rehabilitation reduces somatic tissue sensitivity and central sensitisation in persons with chronic pain. Moreover, there is a lack of information on the functional changes in regions of the central nervous system associated with central sensitisation. It is possible that exercise rehabilitation mediates the central processing of sensory information in persons with chronic pain. This information is important in developing an understanding of how exercise rehabilitation attenuates somatic tissue sensitivity in persons with chronic pain.

From the present literature on pain and exercise, there is substantial scope for further investigation into the modulation of pain by physical exertion. Firstly, there is a capacity to expand the potential of neurophysiological correlates to pain and apply this in the exercise context. Additionally, there is further research opportunity to elucidate the potential mechanisms of pain modulation in healthy participants and in chronic pain disorder. A review of literature in chapter two will address these areas and then provide a sequence of hypotheses to be experimentally evaluated in a series of studies.
Chapter 2: Review of literature
Review of literature

Prior to conducting research on the relationship between physical exercise and pain, it is important to provide a historical context along with the present understanding of pain. Historically, pain has been variably understood. Originally pain was assumed to be an emotion, similar to pleasure and fear. In this context, Aristotle categorised pain as an “affect”, separating pain from the primary senses. Pain and pleasure were viewed as passions of the soul rather than a primary sense (Basbaum & Bushnell, 2009). In contrast, Descartes (1664) illustrated a nerve to brain sensory pathway in the transmission of a burning stimulus on the skin to a pain qualia (Apkarian, et al., 2011). This posits that pain is part of the conscious sensory experience of feeling. The dichotomy between affect and sensory in the dialogue of pain persists to this day.

Early experiments tended to isolate a pain sense, but in dealing simply with sensory thresholds, these studies failed to represent much of what pain is thought to be in everyday life. As such, two sets of descriptions and understandings of what is called pain developed (Bartley, 1982). One definition was in the vocabulary of the experimental psychologists, and the other was the view that clinicians espoused. Pain terms developed with the use of experimental stimuli and clinical assessment tools (IASP, 2011). For example, analgesia refers to an absence of pain response to a stimulus which would normally be painful. Hyperalgesia refers to increased pain from a stimulus that normally provokes pain, and allodynia refers to pain after stimulation which is not normally painful.
Pain is a conscious experience communicated by language (Lee & Tracey, 2010). The International Association for the Study of Pain (IASP) has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (IASP, 1979). This definition highlights the multi-dimensionality of pain in that the experience of pain encompasses sensory, cognitive, and emotional components. Moreover, the relationship between tissue damage and pain is variable, such that the size of an injury is not a reliable guide as to how much pain an individual experiences or reports. In many instances, people report pain in the absence of tissue damage (IASP, 2011).

The signals the body sends from an injury are referred to as nociceptive signals. These signals are conveyed to the central nervous system by nerve fibers known as nociceptors. The nociceptive signals are experienced as pain when they reach the conscious brain and the person interprets them as pain. Pain is a conscious experience, whereas nociception refers to the unconscious detection of noxious stimuli (Bartholomew, Lewis, Linder, & Cook, 1996). The interpretation of nociceptive signals as pain is influenced by factors including past experience, beliefs, and the context in which pain is being experienced. As such, pain is a complicated trait because it is an aggregate of peripheral and central nervous system dynamics, stress responsiveness, and inflammatory state (Diatchenko, Nackley, Tchivileva, Shabalina, & Maixner, 2007).

In a rare phenotype, the complete inability to sense pain is recognised as a congenital insensitivity to pain. In this condition, patients do not perceive pain due to
a dysfunction in the sensory-discriminative pain components (Cox et al., 2006). In contrast, a congenital indifference to pain is where there is a loss of the affective-motivational component to pain. In this situation, there is a general recognition of pain, however, there are no withdrawal responses. These individuals are severely compromised, and often die in childhood due to a failure to perceive injury and infection (Nagasako, Oaklander, & Dworkin, 2003).

2.1 Classification of pain

Pain arises from a variety of sources that can be classified into three broad categories: transient; acute; and chronic (Loeser & Melzack, 1999). Transient pain is a brief pain that has a rapid onset and departure. Procedures such as venipuncture or immunisation are examples of transient pain. Transient pain is also the most common pain induced by experimental noxious stimuli. This pain is projected by pain receptors, known as nociceptors, from tissue to the central nervous system. The term ‘nociception’ is a physiological term used to describe the neural processes of encoding and processing noxious stimuli (Loeser & Treede, 2008).

2.1.1 Acute pain

Acute pain is elicited by substantial injury of body tissue. This type of pain is present following physical trauma, surgical interventions, and in some diseases. In acute pain, nociceptors are activated at the site of injury and a persistence of pain presents usually over a few days or weeks. Acute pain subsides with the process of healing. Pain can be identified as acute or inflammatory when produced by tissue injury and/or immune system activation. Pain that is associated with inflammation falls into
the category of nociceptive pain due to the activity of nociceptors. It should be noted that peripheral nociception should not be confused with pain, since each can occur without the other (Loeser & Treede, 2008). In situations of local anaesthesia, there is peripheral nociception without pain, and in thalamic pain there is pain without peripheral nociception.

Acute pain can also be elicited by skeletal muscle contraction. Specialised nociceptors have been shown to be activated under ischemic conditions in animal models (Mense & Stahnke, 1983). Pain has been shown to emerge during isometric muscle contraction at 25% of maximum force output during a hand-grip task (Caldwell & Smith, 1966). It has been suggested that nociceptors elicit pain during intermittent claudication and during tonic muscle contractions (Mense, 2007). During intense skeletal muscle contraction, tissue pH is reduced and several metabolites are expressed. The release of lactic acid and inflammatory mediators may sensitise and excite nociceptors and give rise to the sensation of pain during exercise (O'Connor & Cook, 1999). Distinct muscle pain has been shown to emerge at about 58% of maximum exercise work capacity during cycling activity (Hamilton, Killian, Summers, & Jones, 1996) and has been observed to positively accelerate with increasing exercise workload (Cook, et al., 1997). Muscle pain intensity at volitional exhaustion was rated at ‘very strong pain’ amongst healthy participants.

2.1.2 Chronic pain

Chronic pain is recognised when pain is persistent, when the process of repair has apparently ended, or when there is a failure of tissues to properly heal. The IASP defines chronic pain as pain without apparent biological value that has persisted
beyond the normal tissue healing time, usually taken to be three months (IASP, 1986).

Chronic pain can transpire from persistent or recurrent nociceptive, neural, or inflammatory activity. Additionally, in some persistent pain conditions such as fibromyalgia and non-specific low back pain, chronic pain is reported without apparent tissue inflammation, nociceptive activity, or nerve lesion (Woolf, 2011). In this context, pain that persists has no clear aetiological factor. It should be noted that the term ‘chronic pain syndrome’ is a generalised term which usually implies a pattern of persistent pain that may or may not have arisen from organic causes. The unifying symptom of chronic pain is persistent pain, regardless of known or unknown causes. A task force on the taxonomy for chronic pain by the IASP has developed an extensive description and list of chronic pain syndromes with specific and non-specific aetiology (Merskey & Bogduk, 1994).

Aside from known or unknown aetiology, persistent pain beyond 3-6 months is classified as chronic pain (Merskey & Bogduk, 1994). In another definition, however, chronic pain is defined as continuous pain for three of the last six months (Blyth, et al., 2001; Siddall & Cousins, 2004). In a large scale epidemiological study, chronic pain was defined as pain lasting more than six months, having pain in the last month, and having pain intensity of at least 5 points in a 0-10 point scale (Breivik, et al., 2006). In the recruitment of low back pain patients for functional magnetic imaging, at least 12 weeks duration of pain was required (Giesecke, et al., 2004). Based on no fixed duration, chronic pain has also been defined as pain that extends beyond the expected period of healing (Turk & Okifuji, 2001). The expected duration of healing is, however, ambiguous. In chronic inflammatory conditions such as rheumatoid
arthritis and osteoarthritis, normal healing has not occurred. Currently, there is no agreed timeline for chronic pain diagnosis, although three to six months is often applied.

### 2.1.3 Epidemiology of chronic pain

Large scale population based studies show that chronic pain is amongst the most disabling and costly afflictions in North America, Europe, and Australia (Harstall & Ospina, 2003). In developing countries, data on the prevalence of chronic pain is not available, however, it is likely to be equally important (IASP, 2003). Across 15 European countries, an average of 19% of the population surveyed reported having chronic pain (Breivik, et al., 2006). The prevalence of chronic pain in Australia is at 19% (Blyth, et al., 2001) with the total cost of chronic pain estimated at $34.4 billion, or $10,847 per person with chronic pain (Access Economics, 2007). The prevalence of chronic pain in Australia is comparable or higher than a number of health priority areas including cardiovascular disease, cancer, musculoskeletal diseases, injuries, asthma, and diabetes. Persons with chronic pain often use medical resources extensively and are commonly disabled by pain. Chronic pain is also associated with decreases of 45% and 23% in overall physical and mental health, respectively (Katz & Barkin, 2010).

In a large-scale survey of 46,394 persons with chronic pain, 42% reported osteoarthritis and rheumatoid arthritis as the pathogenesis of persistent pain (Breivik, et al., 2006). Spinal degeneration, disc erosion, or fractures of the spine accounted for 20%, and trauma or surgery were reported amongst 15% of respondents. Approximately 10% of adults report severe chronic pain (Harstall & Ospina, 2003),
with chronic back pain being the most predominant contributor to this population (Atkinson, 2004). Twelve percent of respondents with chronic pain reported that they did not know the cause of their pain (Breivik, et al., 2006). Based on these studies, the majority of chronic pain disorders stem from organic causes such as ongoing or recurrent inflammation resulting in concomitant nociceptive activity. A substantial proportion of persons, however, do not know the cause for their chronic pain.

Epidemiological studies demonstrate that chronic pain is a highly prevalent condition that severely impacts the individuals’ health status and healthcare services. Successful treatment outcomes for persons with chronic pain are difficult to achieve (Smith, Macfarlane, & Torrance, 2007). In the U.S.A., approximately 20-30% of Americans suffer from chronic pain, and more than 60% of chronic pain respondents report to have suffered from persistent pain for at least five years (Glickman-Simon, 2006).

Epidemiological studies of low-back pain have revealed demographic factors such as female gender, older age, and lower socioeconomic status are associated with a higher risk of the future onset of chronic pain (Macfarlane, 2006). Individual factors such as psychological distress and lifestyle, including low physical activity, obesity, and smoking are also associated with the report of back pain. These factors have also been shown to predict the onset of chronic pain (Thomas et al., 1999).

In a review of epidemiological research on sex differences in pain report, women show a higher prevalence for many clinical pain conditions compared to men, including musculoskeletal, neuropathic, abdominal, and migraine-related conditions (Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009). In one study across
17 countries with a total sample size of 85,052 adults (Tsang et al., 2008), the prevalence of any musculoskeletal chronic pain condition was higher among females (45%) compared to males (31%). In a large scale sample study using de-identified medical reports from 72,000 hospital patient records, diagnosis sex-specific differences were found with reported pain (Ruau, Liu, Clark, Angst, & Butte, 2012). The most significant differences occurred in female patients with disorders of the musculoskeletal, circulatory, respiratory, and digestive system. Moreover, consistent with previous reviews, current human findings on experimental pain parameters in females, show greater pain sensitivity compared to males (Fillingim, et al., 2009). This was also observed in clinical pain models involving intramuscular injection of algesic (pain evoking) substances and temporal summation of repeated pain stimulation.

### 2.1.4 Comorbidity in chronic pain disorder

Several health disorders contribute to the risk of developing chronic pain, known as comorbid conditions. The quality of life in chronic pain disorder is significantly reduced when comorbid with physical or mental health conditions (Asmundson & Katz, 2009). In a population based survey (N=12,488), a quarter of respondents with chronic pain reported two or more comorbid conditions (Dominick, Blyth, & Nicholas, 2012). Chronic pain was associated with physical conditions including arthritis, migraine, osteoporosis, heart disease, and bowel disease. Moreover, anxiety/depression was shown to interact synergistically with arthritis and neck/back pain disorders to increase the risk of chronic pain.

A positive association has also been observed between chronic pain and major depression (Arnow et al., 2006). Among those with major depressive disorder (MDD),
a significant higher proportion reported chronic pain (66% versus 43%) compared to those without MDD (N=5,808). Additionally, disabling chronic pain was present in 41% of those with MDD compared to 10% without MDD. These results show that chronic pain is more common among those with major depression. One explanation for this is associated with the high presence of panic disorder in respondents with both MDD and disabling chronic pain. Here, it is possible that catastrophic thoughts in MDD, contributes to chronic pain disability.

2.1.5 Chronic pain disorder as an independent disease

Historically, chronic pain has been labelled as a syndrome, however, data from neuroimaging research indicates that both structural and functional changes take place with persistent pain (Tracey & Bushnell, 2009). Evidence is accumulating showing that chronic pain should be recognised as an independent condition and not ‘merely’ a consequence or symptom of an underlying condition. Continuing nociceptive input results in a multitude of consequences ranging from changes in receptor function, mood dysfunction, inappropriate cognitions, and social disruptions that impact on the individual (Siddall & Cousins, 2004). The persistent changes in sensory, emotional, and psychological function supports the notion that chronic pain is an independent condition that can no longer be regarded as a passive symptom of organic dysfunction.

Advances in genotyping methods have provided a rapidly increasing list of genes associated with persistent pain conditions. Temporomandibular joint disorder (TMJD) is a common pain disorder associated with pain in the muscles involved in mastication and the temporomandibular joint. TMJD is linked with genetic dysfunction
associated with transporters, transcription regulators, and receptors (Diatchenko, et al., 2007). Other chronic pain disorders associated with genetic variations include fibromyalgia, low back pain, and osteoarthritis. The multifactorial composition of these phenotypes is in line with several genetic variants that are shaped by environmental pressures.

2.2 Pain theories and models

During antiquity, pain had no significance other than signalling specific disorders. Remedies were devised to alleviate pain that consisted of blood-letting, topical ointments, exercise, sulphur rubs, hot seawater baths, and diet (Hardcastle, 1999). Galen (2nd century AD) argued that pain is a sense, similar to touch, and this view is prevalent throughout pain literature.

The majority of pain theory and research for the past three hundred years has emphasised the mechanistic nature of pain. In specificity theory, pain sensation was directly associated with peripheral physical damage and the pathways to the brain for the conscious perception of pain. Until the mid-1960's, the history of research into the biology of pain was typified by attempts to isolate specific pain fibers and receptors which formed a unique and complete system. The understanding of pain was significantly progressed when a more comprehensive theory proposed ascending and descending pathways that project nociceptive signals and regulate pain. Here, Melzack and Wall (1965) proposed the gate control theory of pain.
2.2.1 Specificity theory of pain

Pain research and therapy has been dominated by specificity theory. This theory proposed that pain is a specific sensation and that the intensity of pain is proportional to the extent of tissue damage. This implies a linear causality between injury and pain, and between the stimulus and response. Descartes (1664) proposed that the causation from injury to pain acts in the same way as a bell-ringing mechanism where “by pulling at one end of a rope one makes to strike at the same instant a bell which hangs at the other end” (Melzack & Wall, 1996). A limitation of this theory is that in pain-cases which could not be accounted for, such as in persons with chronic pain or phantom limb pain, were commonly referred to psychiatrists (Horn & Munafo, 1997).

Modern specificity theories further evolved by adding that the brain received information about external stimuli only via the sensory nerves. Müller (1842) proposed that a straight-through system from the sensory organ to the brain centre was responsible for sensation. Since the cortex is seemingly at the ‘top’ of the nervous system, a search was made for cortical centres in pain control.

A more complete specificity theory of pain was developed by von Frey (1894). This theory proposed that pain was one of four sensory inputs including touch, cold, warmth, and pain, each with a direct singular anatomical pathway to a specific site in the brain. It was concluded by von Frey that pain receptors were free-nerve endings since they were found almost everywhere on the skin. Other investigators sought to find specific pain pathways (Keele, 1957) from receptors to the spinal cord and then
the brain. This research again relied on the Cartesian model in that there was a direct link between a peripheral receptor and a specific brain site, which was anatomically incorrect (Melzack, 1999).

Extensions to von Frey’s theory included the ascription of unique types of pain (sharp versus dull, for example) to different pain fiber types such as Aδ and C-fiber pain. The spinothalamic tract was also identified as crucial for the transmission of pain information and has since been referred as the ‘pain pathway’. It was proposed that the brain centre for pain was located in the thalamus because cortical lesions or excisions rarely abolish or may exacerbate pain (Head, 1920). Thus the thalamus was held to contain the pain centre and the cortex to exert inhibitory control over it. There is continued research on the processing of pain information in the brainstem and thalamus (Leite-Almeida, Valle-Fernandes, & Almeida, 2006; Zambreanu, Wise, Brooks, Iannetti, & Tracey, 2005).

### 2.2.2 Pattern theory of pain

Limitations to specificity theory in explaining pain in various clinical contexts began to be identified. The assumption that there exists a direct and invariant relationship between a physical stimulus and a sensation was insufficient in many pain cases. Similar tissue damage does not necessarily result in similar pain across individuals, and this is in part due to a constellation of social, cultural, and psychological variables (Horn & Munafo, 1997).

Causalgia is characterised by very intense episodes of burning pain and a pathological sensitivity to neutral stimuli following the healing of a physical injury, and
neuralgia which is brought about by peripheral nerve damage from viral infection, diabetes, poor circulation, vitamin deficiency, or poison ingestion, provide a dramatic refutation of the concept of a fixed, direct-line pain system. In these conditions, gentle touch, vibration, and other non-noxious stimuli elicit excruciating pain or sometimes spontaneous pain in certain patients (Melzack & Wall, 1996). In pain conditions such as tabes dorsalis, which occurs in late-stage syphilis resulting in a degeneration of the sensory neurons, an unusual burning pain arises in response to repeated touch by an innocuous stimulus. The aetiology was later characterised by a degeneration in the dorsal spinal cord and dorsal roots, and one of its major symptoms is the temporal and spatial summation of somatic input to enhance pain signalling (Noordenbos, 1959).

The studies on tabes dorsalis patients suggested that some form of central summation process was required if pain mechanisms were to be fully understood (Goldsheider, 1884). The important feature of this new theory was that transmission of peripheral sensory information was summated at the dorsal horn, with pain information being transmitted only if the level of output at the dorsal horn exceeded a threshold. This theory was the first to recognise that the dorsal horn played an active role in the modulation of pain. However, patterning theory suggests that the sensation of pain is the result of spatial and temporal patterns of neural transmission. The theory proposed that free nerve endings are alike and non-specific, as opposed to specialised pain fibers for transmitting pain information.

Pattern theory was extended by the development of central summation theory (Livinstone, 1943). This theory proposed that reverberatory circuits comprised of closed, self-exciting loops of neurons in the gray matter of the spinal cord were
triggered by pathological stimulation of sensory nerves. This theory was powerful in explaining phantom limb pain, where initial damage to the limb or the trauma associated with removal, initiates abnormal firing patterns in reverberatory circuits in the dorsal horn of the spinal cord. These circuits send volleys of nerve impulses to the brain that give rise to pain. In addition, emotional disturbance may evoke activity that feeds into the abnormal neuron pools. Local anaesthetic injections or physiotherapy can be applied to modulate the sensory input and reinstate normal cord activity. There is no physiological evidence of functional reverberatory circuits, however, Livingston’s concept of sensory modulation to control pain has had a powerful impact on subsequent ideas (Melzack & Wall, 1996).

In peripheral pattern theory (Sinclair, 1955; Weddell, 1955), pain was considered to be due to excessive peripheral stimulation, since it proposed that all fiber endings were alike, and intense stimulation of non-specific receptors produces a pattern of nerve impulses which is translated centrally as pain. While this theory ignored the physiological receptor-fiber specialisation, it also did not account for pain states such as phantom limb, causalgia, and the neuralgias.

A further extension of summation theory is sensory interaction theory. This theory proposed that summation is prevented in normal subjects by a dedicated input-modulating system. Pain information is inhibited by the faster transmitting, large-diameter sensory fibers, with transmission to the central nervous system being a result of the balance of activity between these groups of fibers. A relative increase in the number of small-diameter fibers compared to large-diameter fibers would result in increased pain information transmission, greater summation, and excessive pathological pain. Under pathological conditions, the fast system loses its dominance.
over the slow pain transmission, and the result is pain states such as diffuse burning pain (Bishop, 1959) or hyperalgesia (Noordenbos, 1959). This is consistent with the physiological evidence that there is a relative increased loss of large fiber function following nerve damage (Waldram, 2003). This theory markedly extended the explanation for pain phenomena compared to simple specificity theories. Sensory interaction theory explained the failure of spinal cord lesions in abolishing pathological pain states. Sensory interaction theories were developed primarily in the late 1950’s and may be regarded as a paradigm shift towards the Gate-control theory of pain.

2.2.3 Affect theory of pain

At the turn of the 19th century considerable debate was centred on the question of pain specificity. For instance, von Frey (1894) argued for specific pain receptors, while Goldsheider (1884) contended that pain was produced by excessive skin stimulation and central summation. Both theories were based on pain being a sensory modality. Affect theory was proposed by Marshall (1894), with links to Aristotle, posited that pain ‘...is an emotional quality that colours all sensory events’ (Melzack & Wall, 2008, p. 161). Moreover, this theory accepted the existence of a pricking-cutting sense, however, pain was considered distinctly different.

Affect theory proposes that pain is a strong negative affective quality that brings forth pain behaviours such as limb withdrawal and protective actions. The behavioural outcome to pain is to typically commit the most effective course of action to stop it. In chronic pain, guarding and protective actions are often displayed. The study of pain behaviours encompasses emotion and motivation, however, the development of
sensory physiology and psychophysics has overshadowed the role of affective and motivational processes in pain.

### 2.2.4 Gate-control theory of pain

From a growing body of evidence it was apparent that Specificity and Patterning theories did not independently account for several pain states including the persistence of pain after healing, the influence of psychological processes such as anxiety on pain and response, and the high degree of specialisation of pain receptor-fiber types and pathways to the central nervous system. Specificity and Patterning theories remained prevalent until Melzack and Wall, inspired by Head’s work (Head, 1920), proposed the Gate-control theory of pain (Melzack & Wall, 1965). At the core of the theory is the gate, a neural mechanism in the spinal cord which modulates the passage of pain information from the periphery to the central nervous system. Nociceptive signals from the periphery are modulated at the gate and then allowed to pass, before the individual is in pain.

The degree to which the gate is open or closed is dependent on signals from peripheral nerves and descending signals from the central nervous system. Ascending signals are comprised of action potentials from large-diameter fibers (Aβ) and small diameter fibers (Aδ and C-fibers). The theory proposed that large and small fiber input into the dorsal horn of the spinal cord were delivered to ‘transmission cells’ (T cells). These cells transmitted peripheral information to local reflex circuits and to the brain (Melzack & Wall, 1996). Later research showed that input from large fibers to the spinal cord are the most common in signalling injury (Yaksh, 1986). Additionally, the proposed dorsal horn T cells have been replaced with the
identification of several interneurons, projection cells, and marginal cells (Shepherd, 1994).

The cells in the spinal cord respond to light pressure on the skin and increase their frequency of response as the pressure of the stimulus increases in intensity, such as during a strong pinch. A minority of cells in the spinal cord only respond when small afferent fibers are stimulated. These cells are known as nociceptive specific cells. Another group of cells respond only to low intensity pressure stimuli. Gate-control theory proposed that several different fiber types converge in the spinal cord and pain is triggered when the firing rate of any group of cells exceeded a critical level determined by the properties of the brain.

Gate-control theory accommodated for the effect of descending input on the function of the spinal cord. It had been known for some time that descending input into the spinal cord modulate spinal reflexes through the work by Sherrington (1906). Stimulation of midbrain and medulla sites also revealed an inhibition of spinal cord cells (Taub, 1964). In addition, it was demonstrated that a powerful tonic inhibition flowed from the brainstem to the spinal cord (Wall, 1967). The nature of the descending signals, while being the most visionary element of Gate-control theory, was intended to account for the role of psychological factors, such as anxiety, on pain response. There is an abundance of evidence indicating that attention, anxiety, past experience and personality among others, can modulate the relationship between physical pathology and pain (Horn & Munafo, 1997). Although the specifics of the modulation of pain transmission remain open to debate and the theory has been enhanced and diversified, the concept of a gate is no longer controversial.
Gate-control theory proposed that the extent to which signals flow through the spinal cord is determined by the amount of excitatory and inhibitory input at the spinal cord. Large-diameter peripheral afferents can excite as well as inhibit spinal cord function (Wall, 1964). This double effect is related to a spatial separation of inputs conveyed by large-diameter fibers. The inhibitory activity has been shown to occur in the substantia gelatinosa of the dorsal horn (Wall, 1964) and for this reason it was proposed that the inhibitory and excitatory interneurons are located in the substantia gelatinosa (Melzack & Wall, 1996).

Inhibitory activity has been shown to occur at the terminals of afferent nerve fibers, which attenuates ascending transmission in the spinal cord (Wall, 1964). It is generally agreed that the presynaptic inhibition involves the chemical gamma-aminobutyric acid (GABA), released from cells in the dorsal laminae causing a depolarisation of afferent terminals and leads to a decreased excitatory effect. Opioids are also released by cells in the substantia gelatinosa in the form of enkephalins and dynorphins. These are released in response to descending inhibitory input. Post synaptic inhibition, in which inhibitory cells act directly on dorsal horn cells, has also been reported (Melzack & Wall, 1996). Additionally, ascending messages to the brain can influence the descending controls, creating a loop from spinal cord to brain and back to spinal cord.

In summary, the activity of large peripheral nerve fibers has an inhibitory effect on spinal cord substantia gelatinosa cells and dampens ascending pain signals. Small fiber input can overcome this inhibition resulting in prolonged firing of spinal cord ascending pain signal, the duration of which may increase with each successive volley (Stimmel, 1983). The net result of the interplay between large and small
afferent activity is modulated by descending central systems and by ascending
peripheral systems, comprise the physiological basis for pain transmission.

The strength of gate-control theory relies on its ability to integrate psychological,
behavioural and physiological elements and present them as different levels of
explanation of a single holistic system (Schneider & Karoly, 1983). A large part of the
value of this new conception of pain mechanisms is the ability to account for the pain
experienced during injury and pain being felt without apparent injury. Additionally,
gate control theory forced the medical and biological sciences to accept the brain as
an active system that filters, selects and modulates inputs (Melzack, 1999).

2.2.5 Multi-dimensional theories of pain

The breadth of the pain experience, highlighted in pain descriptors such as sharp,
dull and aching, verifies the variety of qualities inherent in pain. The conceptual
nature of pain and its functional significance are emphasised in the definition
provided by the IASP in that pain is “An unpleasant sensory and emotional
experience associated with actual or potential tissue damage, or described in terms
of such damage” (Merskey, 1979). This definition highlights the multi-dimensionality
of pain, from its sensory qualities, its unpleasantness, and its emotional
consequences. These considerations have led to the development of three major
psychological dimensions of pain: sensory-discriminative, motivational-affective, and
cognitive-evaluative (Melzack & Casey, 1968).

The dimensions of the pain experience are subserved by physiologically specialised
systems in the brain. The sensory-discriminative dimension of pain is served by the
rapidly conducting spinal systems. Activities in the reticular and limbic system influence the unpleasantness of pain and are served by slowly conducting spinal systems (Frot, Mauguière, Magnin, & Garcia-Larrea, 2008). Perception of a noxious stimulus in terms of size, location, and intensity is performed by the lateral pain system. In contrast, the negative emotional state associated with the noxious stimulation is performed by the medial pain system (Kanda et al., 2000). The cognitive-evaluative component of pain is driven by neocortical or higher central nervous system processes (Melzack & Katz, 1999). Interaction between the multiple dimensions of pain enables the capacity to integrate the location, magnitude, spatiotemporal properties, past experiences, and behavioural reactions to pain.

The Loeser model of pain is a multi-conceptual interpretation of the pain experience (Loeser & Melzack, 1999). This model posits that the pain experience comprises of four different categories: nociception, pain, suffering, and pain behaviour. These categories are considered parallel systems, each with the capacity to influence each other. Pain behaviour is the observable outcome in the pain experience. Associated with pain behaviour is suffering which is observed through behavioural outcomes such as splinting, moaning, limping, or taking pain medication. Underlying suffering is the actual pain and below this is the actual source of pain, nociception.

### 2.2.6 The bio-psycho-social model of pain

The bio-psycho-social approach posits that the experience of pain is determined by interactions amongst biological, psychological, and social factors that together influence a person’s perception of pain and response to pain (Hadjistavropoulos & Craig, 2004). Psychological factors comprise the cognitive circumstances and
affective components of the pain experience. Social factors comprise the collective and cultural context, and the biological factors include the nociceptive and inflammatory mechanisms of pain. The bio-psycho-social model of pain implicitly supports the notion that “…societal, lifestyle, and molecular explanations of disease are interconnected and mutually reinforcing, not stark alternatives locked in mortal combat against each other” (Poole & Rothman, 1998).

Bio-psycho-social models of pain have progressed to explain pain phenomena in persons with persistent pain. This approach has important implications for pain treatment and management. The model predicts that if biological, personal and/or environmental factors appear to be contributing to an emerging chronic pain condition, then as many as possible of these components should be addressed in any intervention to prevent the pain from becoming disabling (Linton, 2002). The inability to do so risks creating a major long term health problem with all its likely complications and costs.

Bio-psycho-social treatments address a range of physical, psychological, and social components of chronic pain (Nielson & Weir, 2001). Multimodal bio-psycho-social treatments such as cognitive-behavioural and/or behavioural modification have been shown to be effective treatments for persons with chronic pain for up to 12 months. There are, however, few predictors of treatment success and more research is required.
2.2.7 Fear avoidance model

Chronic pain is compounded by psychological and behavioural changes (Vlaeyen & Linton, 2000). The fear avoidance model provides an account of the development of chronic pain following an acute injury. Fear-avoidance, which refers to the avoidance of movements or activities based on fear, is proposed as a central mechanism for the development of persistent pain (Vlaeyen & Linton, 2000). A failure to control fear contributes to the chronicity of pain and suffering (Leeuw et al., 2007). In this context, fear of pain is a consequence of pain catastrophising, whereby there is an increase in activity intolerance (Sullivan et al., 2002). Moreover, prediction of pain intensity was robustly performed by psychological assessments for fear of pain (Parr et al., 2012) in an experimental pain model. Measures of disability correlated more closely with pain catastrophising and fear of movement.

Accumulating evidence seems to corroborate the idea that fear of pain or (re)injury is more disabling than pain itself. In one study, approximately 20-40% of the relationship between pain and disability was accounted for by the fear avoidance model (Kamper et al., 2011). Fear of movement, kinesiophobia, appears to explain the variance in pain when the duration of pain is greater than one year (Boersma & Linton, 2005). Here, three stages of chronicity were defined by pain as less than one year (N=48), between 1-3 years (N=47), and greater than three years (N=89). The results from the Boersma & Linton (2005) study indicate that the time point in the development of chronic pain is an important aspect in explaining the relationship between psychological components and function.
2.3 Pain neurophysiology

Early 20\textsuperscript{th} century discourse in sensory neurophysiology was centred on whether specialised damage-sensitive neurons or high-level input from sensory neurons evoked a sensation of pain (Liu, Oh, & Wood, 2011). Work by Perl (1968, 2007) and Iggo (1960) affirmed the existence of damage-sensing neurons by their response to noxious stimuli. These neurons were classified as nociceptors, based on research by Sherrington (1910) on the nociceptive flexion reflex. The term nociceptor is derived from the Latin word \textit{noxious} which refers to damaging or harmful to the body.

In order of decreasing size, axons from sensory afferent receptors are designated A\textsubscript{\textalpha} (group I), A\textbeta (group II), A\textdelta (group III), and C (group IV), although sensory nerves from skin lack the largest diameter A\textalpha group of axons (Ringkamp & Meyer, 2009). Myelinated fibers are large and produce the fastest nerve impulse conduction which include the A-fiber group of neurons. Group I fibers comprise the primary endings from muscle spindles (Ia) and golgi tendon organs (Ib), (Hunt, 1954a). Cutaneous A\textbeta fibers comprise the group II fibers although in muscle, group II fibers have substantial distribution to muscle spindles (Hunt, 1954b), and there is some functional crossover with the A\textdelta conduction velocity (Djouhri & Lawson, 2004). The A\textdelta fibers are thinly myelinated, while the C-fibers are unmyelinated (Jay, 2007).

The nomenclature with Roman numerals (group I-IV) are based on nerve fiber diameter and initially referred to muscle afferents (Lloyd, 1943), although, is now applied to depict afferents from muscle, joint tendons, and fascia. The A-fiber sub-
classification with Greek alphabet is based on nerve conduction velocity. Fibers that innervate regions of the head and body arise from cell bodies located in the trigeminal and dorsal root ganglion, respectively. The large diameter cell bodies give rise to the $A\beta$ fibers which detect innocuous stimuli from skin, muscle, and joints (Julius & Basbaum, 2001). They transmit information associated with pressure, touch, and vibration.

There is a negative relationship between mechanical threshold and conduction velocity of sensory afferents. Fibers with lower mechanical threshold show higher conduction velocities (Mense, 2009). The characteristics of the afferent fibers that transmit information from tissues of the body are shown in Table 2.1. Afferent information from the group Ia and Ib fibers in skeletal muscle innervate sensory endings that include annulo-spray muscle spindle and Golgi tendon apparatus, respectively. Group II fibers are large myelinated fibers and originate from skin and the proprioceptive muscle spindle flower-spray sensory endings (Holmes, 1993).
2.3.1 Nociceptive fiber populations

The small and medium diameter cell bodies give rise to most of the nociceptors, although about 20% of the large Aβ fibers have revealed nociceptive functions in animal models (Djouhri & Lawson, 2004). Most of the afferents that transmit pain-related information, known as nociceptors, are of small diameter or primary afferents (Ribeiro-da-Silva & Koninck, 2009). There are two types of nociceptors, the thinly myelinated, more rapidly conducting Aδ (group III) afferents, and the slow conducting, unmyelinated C-fibers (or group IV) afferents. The Aδ and C-fibers mediate ‘first’ and ‘second’ pain, respectively, which correspond with the rapid, acute, sharp pain and the delayed more diffuse pain evoked by noxious stimuli.

Nociceptive signals are primarily conveyed by the Aδ and C-fibers. Although there are differences between muscles and species, skeletal muscle is dense with group Aδ and especially C-fiber afferents. The C-fibers are far more numerous than the Aδ fibers (Holmes, 1993). These non-myelinated sensory fibers are 4-5 times more numerous than the myelinated fibers in sensory nerves (Iggo, 1960). The C-fibers are distributed in most tissues of the body, however, the Aδ fibers are distributed throughout the body surface, muscles, and joints. C-fibers are also located along the walls of arterioles and in the surrounding connective tissue. These fibers are also activated during muscular contraction and may function as ‘ergoreceptors’ during the circulatory adjustments and respiratory responses to muscular exercise (Kniffki, Mense, & Schmidt, 1981).
At least two sub-types of Aδ nociceptors have been identified which can be distinguished by their response to noxious mechanical pressure or intense heat and mechanical pressure (Jay, 2007). In general, the A-fiber nociceptors perform similarly to the C-fibers but do this more robustly. If a nociceptive fiber responds to heat and mechanical stimuli then the fiber will, in most situations, also respond to chemical stimuli (Davis, Meyer, & Campbell, 1993). Therefore, the nomenclature for C-fiber and A-fiber mechano-heat sensitive nociceptors is CMH and the AMH, respectively. Most C-fiber nociceptors are polymodal in that they respond to noxious chemical, heat, and mechanical stimuli (Mense, 2009). A small number of C-fibers are non-nociceptive and convey either innocuous mechanical or thermal information (Ribeiro-da-Silva & Koninck, 2009). Some nociceptors remain silent unless sensitised by tissue injury (Schmidt et al., 1995).
**Table 2.1:** Classification of afferent fibers.

<table>
<thead>
<tr>
<th>Fiber type</th>
<th>Size (μm)</th>
<th>Myelination</th>
<th>Conduction (m/s)</th>
<th>Receptors innervated (% contribution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aα (I)</td>
<td>Large (6-17)</td>
<td>Heavy</td>
<td>15-60</td>
<td>Mechanoreceptors</td>
</tr>
<tr>
<td>Aβ (II)</td>
<td>Large (6-17)</td>
<td>Heavy</td>
<td>15-60</td>
<td>Mechanoreceptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nociceptors (20%)*</td>
</tr>
<tr>
<td>Aδ (III)</td>
<td>Small (1-5)</td>
<td>Thin</td>
<td>10-25</td>
<td>Mechanoreceptors (75%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nociceptors (25%, mechanical, thermal, chemical)**</td>
</tr>
<tr>
<td>C- (IV)</td>
<td>Small (0.3-1)</td>
<td>None</td>
<td>0.4-1</td>
<td>Mechanoreceptors (50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nociceptors (50%, mechanical, thermal, chemical, silent)**</td>
</tr>
</tbody>
</table>

Adapted from Stimmel (1983); *Djourhi and Lawson (2004); **Julius and Basbaum (2001)
2.3.2 Sensations elicited by nociceptor activation

Stimulation of nociceptors elicits sensations depending on nociceptor type and location. In skin, stimulation of Aδ nociceptors results in a sharp, pricking, and stabbing type pain. Stimulation of C-fiber nociceptors in skin results in a dull, burning, and aching-type pain that gradually increases in intensity. In muscle, however, stimulation of Aδ or C-fiber nociceptors results in a dull-aching or cramping-type pain (Marchettini, Simone, Caputi, & Ochoa, 1996).

The C-fibers respond preferentially to endogenous noxious substances released during tissue injury such as from cuts or crushing injury. A sub-population of C-fiber nociceptors have been identified as responding preferentially to muscular contractions under ischemic conditions (Mense, 1993b). Compared to other sensory neurons, nociceptors are equipped with a repertoire of transduction pathways that enable these cells to respond to several stimuli.

2.3.3 Nociceptive transmission

Nociceptors are present in most body tissues, including the skin, bone, muscle, most internal organs, blood vessels, and the heart. They are notably absent from the brain, except for the meninges, liver, lung parenchyma, and cartilage (Mense, 2009). The nociceptors are unencapsulated free nerve endings with unmyelinated or finely myelinated neurons which conduct nociceptive information to the central nervous system. Most nociceptors are polymodal nociceptors, capable of responding to several types of stimuli including mechanical, thermal, and chemical (Ringkamp &
Meyer, 2009). Many nociceptors also show selectivity in their responses to different stimuli and are activated by either strong mechanical stimulation (mechanical nociceptors), extremes in temperature (thermal nociceptors), or chemical substances released in response to injury (chemo-nociceptors) and ischemia.

The Aδ fibers are finely myelinated and have conduction velocities of 10-25 m/s. They respond to mechanical deformation and are described as high-threshold mechanoreceptors. The Aδ fibers subserve prickling, bright, well-localised pain and are also stimulated by firm pressure or cutting (Stannard & Booth, 1998).

The C-fibers are unmyelinated and have slower conduction velocities of 0.4-1 m/s. These fibers respond to a variety of noxious inputs and are known as polymodal nociceptors. C-fibers subserve burning or aching sensations, which is poorly localised (Holmes, 1993). These receptors are also called mechano-thermal receptors because, in addition to responding to strong mechanical stimuli, they are also responsive to severe thermal stimuli.

In a normal subject, a noxious stimulus evokes an immediate sensation of sharp well-localised pain, which is conveyed by Aδ fibers. After a second or so, a second more intense, less well-localised pain arises and is associated with the slower conducting C-fiber nociceptors (Basbaum & Jessell, 2000). These sensations are called first and second pains, and are mediated by the different conduction and projection characteristics of the primary afferent fibers.

Interactions between central processes initiated by afferent fibers are complex. Several human trials have demonstrated the suppressive effect of tactile and
vibrotactile stimulation on various forms of pain and pain-related evoked responses (Melzack & Wall, 1965; Nahra & Plaghki, 2003). In the opposite paradigm, heat-induced pain has been shown to diminish vibrotactile perception (Apkarian, Stea, & Bolanowski, 1994). Previous research demonstrates both inhibitory and excitatory postsynaptic responses of nocireceptive dorsal horn neurons, including inhibitory interactions mediated through the activation of Aδ and C-fibers (Liu, Morton, Azkue, Zimmermann, & Sandkühler, 1998). Additionally, activation of Aδ fibers suppresses the cortical response mediated by C-fibers (Bromm & Treede, 1987). More recently, cortical responses to preferential Aδ and C-fiber stimulation have been shown to be attenuated whenever either cortical response preceded the other (Tran, Matre, & Casey, 2008).

2.3.4 Activation and sensitisation of the primary afferents

Substances which increase the activation or sensitivity of group III and IV afferent fibers are known as algesics. Several biochemicals have been identified as sensitising or activating Aδ and C-fibers. These biochemical mediators are expressed from a variety of sites including cells that are damaged, thrombocytes, primary afferent fibers, and injury related immunoresponsive cells (Ringkamp & Meyer, 2009). Nociceptors comprise a multitude of receptor molecules for endogenous pain-producing substances. Increased sensitisation of nociceptive receptors results in increased spontaneous nerve activity, decreased activation threshold, and a prolonged firing response to a supra-threshold stimulus (Mense, 1993a, 1993b).

Peripheral tissue injury leads to the localised release of inflammatory mediators including serotonin, histamine, prostaglandins, bradykinin, cytokines, and glutamate
(Ringkamp & Meyer, 2009). These substances precipitate a sensitisation of peripheral receptors and alter the response characteristics of nociceptor terminals. They also activate normally inactive or “silent” nociceptors (Schmidt, et al., 1995).

The inflammatory response also triggers gene expression in the dorsal root ganglion to increase the synthesis of peripheral receptors (Curatolo, et al., 2006). Continued nociceptive activity from localised inflammation also leads to the Aβ fibers synthesising C-fiber type receptors and they begin to function with C-fiber characteristics (Neumann, Doubell, Leslie, & Woolf, 1996). These sensitising events mediate primary hyperalgesia, which is characterised by a localised reduction in pain threshold and enhanced pain to suprathreshold stimuli (Curatolo, et al., 2006).

Peripheral sensitisation that initiates increased nociceptive activity leads to a reversible plasticity in the spinal cord, known as central sensitisation. Prolonged nociceptive input from inflammatory pain increases the excitability of central neurons through the elevated expression of N-methyl-d-aspartic acid (NMDA) receptors (Woolf & Thompson, 1991) that is associated with the secretion of cyclooxygenase-2 (COX-2) in the spinal cord (Curatolo, et al., 2006). In nerve injury, a depression of pain inhibitory mechanisms is observed by a reduction in the secretion of gamma-aminobutyric acid (GABA), increase in cholecystokinin, and reduced GABA and opioid receptors (Woolf & Mannion, 1999). Structural changes take place whereby the Aβ fibers sprout from deeper dorsal horn layers into superficial layers where C-fibers terminate (Mannion & Woolf, 2000). Together, these events expand the cutaneous receptive field and amplify the ascending nociceptive input to supraspinal regions.
2.3.5 Nociceptive transmission in the spinal cord

The nociceptor terminations join to form axons whose cell bodies are in the dorsal root ganglia or trigeminal cranial ganglion. The central terminations of peripheral fibers are in the dorsal horn of the spinal cord. The majority enter the ventrolateral bundle of the dorsal root, located laterally from the group II larger-diameter myelinated Aβ fibers. About 30% of the unmyelinated C-fibers enter the ventral root of the spinal cord and terminate in the dorsal root (Stannard & Booth, 1998). Some nociceptor fibers bifurcate into ascending and descending branches and terminate in the dorsal horn at one or two segments above or below the original entry.

The dorsal horn of the spinal cord comprises a series of laminae that receive input from the periphery in accordance to fiber size (Rexed, 1952). Six laminae are recognised in receiving nociceptive input in the dorsal horn. The organisation of dorsal horn neurons are presented in Figure 2.1. Prior to entering the spinal cord, large fibers become spatially organised to comprise the medial division and the small fibers form the lateral division (Stimmel, 1983). The superficial dorsal horn comprising layers I (marginal layer) and II (substantia gelatinosa) are of particular importance in the spinal processing of pain-related information and forwarding onto ascending destinations (Ribeiro-da-Silva & Koninck, 2009).

High threshold Aδ and C-fibers terminate predominantly in lamina I and II, with some terminating in lamina V (Woolf & Salter, 2006). The large myelinated group I (Aα) and group II (Aβ) fibers terminate within excitatory synapses in lamina II through to VI of the dorsal horn. Cells in lamina II and III form an inhibitory circuit to the connections from the marginal layer. These cells do not primarily transmit nociceptive
stimuli, however, activation of these cells increases the inhibitory action in lamina II and III. Clinically, the inhibitory action of the large myelinated fibers on pain can be observed during a cut on a finger. Pain can be inhibited by applying local pressure to nearby structures which activates the large myelinated fibers.

The neurons in the superficial layers of the dorsal horn respond exclusively to nociceptive stimulation and they are termed ‘nociceptive specific’ neurons. Deeper layers of the dorsal horn are activated by both nociceptive stimuli and by non-nociceptive stimuli including light-touch sensations, and are known as ‘non-specific nociceptive neurons’ or as ‘convergent neurons’ (Cambier, 1995).

The small afferent nociceptive fibers course the tract of Lissauer (fasciculus dorsolateralis) before penetrating the gray matter of the dorsal horn and terminate in the marginal layer, lamina I (La Motte, 1977). These cells relay homeostatic information associated with physiological status of body tissues including pain, temperature and itch. Lamina I neurons relate many aspects of the ongoing physiological status of the tissues of the body (Craig, 2002). Cells in lamina IV-V receive input primarily from large diameter Aβ fibers and some from the nociceptive Aδ and C-fibers (Willis, 1985). Most of these cells are the wide dynamic range nociceptive cell because they respond to both high and low threshold stimuli.
Figure 2.1: Organisation of the dorsal horn laminae and the ascending pathways in the spinal cord

Adapted from Stimmel (1983)
Two classes of nociceptive neurons have been identified in the spinal cord. The first class are neurons that respond to gentle cutaneous stimuli and increase their discharge when the stimulus becomes noxious. The second class neurons respond exclusively to noxious stimuli. The first class neurons, known as nociceptive non-specific neurons, are identified as wide dynamic range, lamina V type, convergent, class 2, polymodal, multimodal, or multireceptive neurons (Besson & Chaouch, 1987). The majority of wide dynamic range neurons have convergent input. Some wide dynamic neurons combine low-threshold activity from skin mechanoreceptors and nociceptors with proprioceptive and/or visceral input (Devor, 2003). Activity in wide dynamic range neurons can evoke pain through rapid firing. The second class neuron is designated as nociceptive specific. This neuron is identified as class V neuron, high-threshold neuron, class 3 neuron, or nociceptive neuron.

From the first relay in the dorsal horn, ascending pathways distribute nociceptive input to higher processing centres and terminate in the cerebral cortex with one or several relay stations in serial connections along the way (Lima, 2009). Many projection neurons located in lamina I send axons to the caudal ventrolateral medulla, parabrachial area, periaqueductal gray matter, and the thalamus (Todd, 2002). The multitude of ascending nociceptive pathways makes it difficult to attribute a functional meaning to each one, although the role of each pathway has been depicted by the connections to the target site.
2.3.6 Neurotransmitters and receptors in nociceptive transmission

Nociceptive afferents terminate predominantly in laminae I and II. Histochemical analysis of the dorsal horn and dorsal root has revealed the presence of a large number of transmitter substances. The knowledge base on the morphological properties of these neurons is incomplete. Nociceptive afferent neurons that have small cell bodies, the C-fiber afferents, are divided into peptidergic and non-peptidergic neurons (Ribeiro-da-Silva & Koninck, 2009). The peptidergic neurons contain substance P, calcitonin gene related peptide (CGRP), and somatostatin. Non-peptidergic neurons contain fluoride-resistant acid phosphatase (FRAP), demonstrated in 30-50% of dorsal root ganglion cells. Neurons with large cell bodies contain phosphorylated heavy chain neurofilament protein (NF200) and are considered to represent the myelinated Aδ afferents.

The primary neurotransmitter for pain is the neurokinin substance P (Todd, 2002). This neurotransmitter is a prototype for other peptides contained in peripheral sensory nerve fibers. Substance P is the most important neurotransmitter of sensory information including noxious stimulation (Julius & Basbaum, 2001). Another significant neurotransmitter associated with nociceptive transmission is CRGP. The majority of CGRP-containing neurons are classified as nociceptive. Somatostatin is also expressed in a limited number of dorsal root ganglion cells that respond to noxious thermal stimuli (Tiseo, Adler, & Liu-Chen, 1990).

Receptors for excitatory amino acids (EAA) including glutamate and aspartate are closely associated with nociceptive transmission at pre-synaptic and post-synaptic
sites. Activity in the afferent terminals leads to the release of substance P and CGRP, both of which enhance the EAA action and are considered to modulate nociceptive signalling (Carlton, 2001). These are expressed in approximately half of the dorsal root ganglia cells (Yaksh, 1999). Several other transmitters and receptors have been shown to play a role in the responsiveness of nociceptors centrally and peripherally including opioid and vanilloid receptors (Meyer, Ringkamp, Campbell, & Raja, 2006).

### 2.3.7 Ascending pain pathways in the spinal cord

Nociceptive, thermal, and non-discriminatory touch information are projected to higher brain centers by the anterolateral system through direct and indirect pathways (Patestas & Gartner, 2006). The direct and indirect pathways of the anterolateral system are shown in Figure 2.2. Functionally, nociceptive information from A\(\delta\) fibers is propagated through the dorsal horn of the spinal cord by direct pathways to the neospinothalamic tract and to motor neurons. Nociceptive information from C-fiber activity is relayed by the indirect pathway through the paleospinothalamic tract toward sites involved in arousal, autonomic, and the emotional aspects of pain. First-order neuronal cell bodies are located in the dorsal root ganglion. From the first-order neurons, nociceptive information is transmitted to second-order neurons with cell bodies located at the dorsal horn of the spinal cord and cranial sensory nuclei. Cell bodies for third-order neurons are located in the thalamus and ascend to the somatosensory cortex.

The rapid transmission of large fiber impulses from touch receptors and proprioceptors to the brain is performed by the lemniscal system. This system offers
identification and subsequent modulation of response to noxious stimuli by inhibiting the transmission of nociceptive information from A\textsubscript{\textdelta} and C-fibers. Nociceptive information is transmitted to the dorsal horn through the tract of Lissauer. This tract relays nociceptive information from the lateral division of the dorsal root as well as axons from the substantia gelatinosa (Kerr, 1975).

The ascending pathway important for pain includes projections to the thalamus through the spinothalamic tract. This tract is concentrated in the lateral funiculus and the anterior funiculus, comprising the lateral spinothalamic tract and anterior spinothalamic tract, respectively (Craig, 2002). It is accepted that the lateral spinothalamic tract originates predominantly from lamina I cells with the anterior spinothalamic tract originating from deeper laminae V and VI cells (Dostrovsky & Craig, 2006). Pain signals are projected to the contralateral side through the dorsal and ventral spinal commissures, although some project ipsilaterally.

Multiple pain-signalling systems in the spinal cord are involved in conveying nociceptive information to higher centers. These include the postsynaptic fibers of the dorsal columns, spinocervical tract, neospinothalamic tract, paleospinothalamic tract, and the spinoreticular system (Dennis & Melzack, 1977). The first three systems are considered the ‘lateral pain system’ in that they rapidly convey intensity and location-based nociceptive information. The paleospinothalamic and the spinoreticular tract are considered the ‘medial pain system’, which conduct signals more slowly.

The classical view is of a dual distribution of nociceptive input in that sharp, short, fast-acting pain is projected through the direct lateral neospinothalamic pathway and diffuse, poorly localised pain is conveyed by the indirect medial paleospinothalamic
pathway (Lima, 2009). Fibers of the lateral neospinothalamic tract project to the ventrolateral and posterolateral thalamic sensory nuclei (Willis, 1985). The thalamic nuclei project nociceptive information to the primary (S1) and secondary (S2) somatosensory cortex. This pathway has been considered responsible for sensory aspects of pain including spatial and temporal discriminative components for pain and touch sensation (Price & Dubner, 1977).

The paleospinothalamic tract, also referred as the spinoreticular tract, comprises mainly short fibers that project to the reticular formation of the medial spinal cord, the lateral pons, the midbrain, and to medial thalamic nuclei (Casey, Jones, Kerr, & Casey, 1978). These pathways serve as relays in the medial spinothalamic system (Lima, 2009). This tract is active in suprasegmental reflex responses by generating aversive motivation and other non-discriminative aspects of pain. The affective components for pain are thought to be predominantly mediated by the ‘medial pain system’ through projections to the medial thalamus, anterior cingulate cortex, and the anterior insula (Sprenger et al., 2006).

Ascending pain information is also conveyed by projections to the medulla and brainstem, the spinomedullary and spinobulbar tracts, respectively (Dostrovsky & Craig, 2006). Indirect pathways to the forebrain through the brainstem include the postsynaptic dorsal column (PSDC) and the spinocervicothalamic (SCT) pathway. The main feature with the ascending pathways is the multiplicity in terms of the supraspinal regions that are targeted. This has been viewed as a means for eliciting a multitude of responses to noxious events that involve autonomic, motor, affective, and cognitive behaviours.
Figure 2.2: The neospinothalamic (direct) and paleospinothalamic (indirect) pathways of the anterolateral system projecting discriminative and non-discriminative pain

**Key:** VPL, ventroposterior lateral; VPI, ventroposterior intermediate; S1, primary somatosensory cortex; S2, secondary somatosensory cortex

Adapted from Patestas and Gartner (2006)
2.3.8 Mid-brain processing of nociceptive information

The spinothalamic tract terminates in six distinct regions of the thalamus (Dostrovsky & Craig, 2006). The thalamus receives fibers that terminate in the posterior nuclear complex of the thalamus from the ventral lateral quadrant of the spinal cord and parts of the lateral spinothalamic tract (Trevino, Coulter, & Willis, 1973). This region is considered part of a specific pain pathway involved in discriminative pain sensation, with cells responding to noxious and non-noxious stimuli. The lateral thalamus is involved in the discriminative sensory aspects of pain and the medial thalamus in the emotional, motivational aspects of pain (Albe-Fessar, Berkley, Kruger, Ralston III, & Willis Jr, 1985). The densest spinothalamic termination includes the posterior part of the ventral medial nucleus which has projections to the insula and is considered to constitute interoception of the physiological state of the body.

Spinobulbar projections to the brainstem are important for the integration of nociceptive activity with processes that subserve homeostasis and behavioural state (Dostrovsky & Craig, 2006). These tracts are particularly important for integrating nociceptive information with arousal and autonomic processes and conveying this to the forebrain, after brainstem processing (Tracey & Mantyh, 2007). As such, these pathways play a role in the pain experience.

Terminations of ascending spinobulbar projections include the catecholamine cell groups (A1-A7), parabrachial nucleus, periaqueductal gray, and brainstem reticular formation. Several of these termination sites are associated with antinociceptive
activity. Other possible direct projections of nociceptive activity include pathways to the hypothalamus and ventral forebrain, which may engage inhibitory interneurons.

The reticular formation in the medulla, together with the pons, are the major recipients of a wide variety of sensory input including a number of cells responding only to noxious stimulation. Cells within the reticular formation, such as the nucleus reticularis gigantocellularis, are considered to be a relay site for pain in the spinoreticulothalamic system when activated by noxious somatic A\(\delta\) fiber input (Collins & Randt, 1960). The connection of the reticular formation with the hypothalamus and the limbic system suggests that these connections may impact on motivational and affective states associated with human pain.

Reticular formation neurons from the bulbar reticular region also project to the medial and intralaminar nuclei of the thalamus, the periaqueductal gray (PAG), and the posterior hypothalamus to reach the mesencephalic reticular formation. These pathways are important with respect to the function of descending control systems (Stimmel, 1983). Neurons of the mesencephalic reticular system participate in supraspinal pain modulation. The medullary dorsal reticular nucleus is reciprocally connected with the spinal dorsal horn, is populated mainly by nociceptive neurons, and regulates spinal nociceptive processing (Leite-Almeida, et al., 2006).

### 2.3.9 Ascending tracts and cortical projections

From the dorsal horn of the spinal cord, nociceptive information is transmitted contralaterally through the spinothalamic tract (STT) to the thalamus and the spinoreticular (spinoparabrachial) and spinomesencephalic tracts to the medulla and
brainstem. The thalamus is the main relay site for nociceptive information. The thalamus has anatomical and functional divisions through connections with specific spinal cord laminae. Signals from peripheral noxious stimuli reach thalamic nuclei including the ventroposterior lateral (VPL), ventroposterior inferior (VPI), and mediodorsal (MD) nucleus (Kakigi et al., 2005). Ascending pathways to the thalamus and projections to cortical regions are depicted in Figure 2.3. In this figure, the VPI and VPL transmit to primary somatosensory (Nelson & Kaas, 1981) and secondary somatosensory cortex (Friedman & Murray, 1986). The MD nucleus projects to the cingulate cortex (Vogt, Pandya, & Rosene, 1987). The thalamus also projects to the insula from VPI and basal ventromedial (VMb) nuclei (Friedman & Murray, 1986).

The cerebral cortex receives thalamic neurons concerned with nociceptive information which project to the retroinsular cortex as well as the striatum. The primary somatosensory cortex projects to secondary somatosensory (Vogt & Pandya, 1978) and cingulate cortex (Friedman, Murray, O'Neill, & Mishkin, 1986). The insula also projects to secondary somatosensory (Mesulam & Mufson, 1982) and cingulate cortex (Vogt & Pandya, 1987). Neocortical processes impact on sensory, affective, and motivational dimensions of pain by evaluating peripheral sensations. Available evidence suggests that the primary area for receiving somatosensory information in the cortex, the S1, is not essential for recognition of pain (Melzack & Casey, 1968). This area plays a role in modulating cognitive and non-cognitive features of pain and to evaluate the sensation through associations based on prior experiences (Bonica, 1977).
**Figure 2.3**: Sagittal plane schematic of ascending pathways, subcortical structures, and cerebral cortical structures associated with pain processing.

**Key**: ACC, anterior cingulate cortex; AMYG, amygdala; HT, hypothalamus; MDvc, ventrocaudal part of the medial dorsal nucleus; M1, primary motor cortex; NS, nociceptive specific neuron; PAG, periaqueductal gray; PB, parabrachial nucleus of the dorsolateral pons; PCC, posterior cingulate cortex; PF, prefrontal cortex; PO, ventromedial part of the posterior nuclear complex; PPC, posterior parietal complex; S1 and S2, primary and secondary somatosensory cortical areas; SMA, supplementary motor area; VPL, ventroposterior lateral nucleus; WDR, wide dynamic range neuron

Adapted from Price, Hirsh, & Robinson (2009).
2.3.10 Integration of pain in the cerebral cortex and sub-cortical regions

Pain is generally believed to occur at the cortical level, although a role for the thalamus and the brainstem in mediating some aspects of pain perception cannot be completely excluded (Dostrovsky, 2000). Pain is an unpleasant conscious awareness of a noxious sensation that is modulated by a complex set of emotional, environmental, and psychophysiological variables. Therefore, pain influences brain processing at many levels including attention, information selection, learning, and anticipation (Ingvar & Hsieh, 1999).

2.3.11 The pain network

Recent brain imaging data provide clear evidence of the common regions found active during acute pain (Apkarian, Bushnell, Treede, & Zubieta, 2005). These areas are illustrated in Figure 2.3 and include the primary and secondary somatosensory, insular, anterior cingulate, and pre-frontal cortices, as well as the thalamus. Together, these areas are considered as a pain network, or ‘pain matrix’, after Melzack’s neuromatrix concept was proposed (Melzack, 1999). Depending on the set of circumstances for the individual, brain regions also active during acute pain stimulation include the basal ganglia, cerebellum, amygdala, hippocampus, and areas within the parietal and temporal cortices. It should be noted that there is continued debate on whether there is a unitary set of brain regions that equates to the presence of pain. This is especially true for chronic pain conditions that show unique brain activity patterns (Apkarian, et al., 2011).
2.3.12 The lateral and medial pain system

The spinothalamic tract consists of the lateral and medial pain systems. The lateral pain system terminates in the somatosensory cortex and participates in the sensory discrimination of pain and the medial system terminates in the anterior cingulate cortex (ACC) and insular cortex (IC) to mediate affective components of pain (Senba, Imbe, & Okamoto, 2008). When noxious stimuli are relayed to the dorsal horn of the spinal cord, the discriminatory content is relayed to the anterior nuclei of the thalamus. The noxious message is also directed to the medial nuclei of the thalamus, and to the limbic and fronto-cingular cortex regions. The characteristics of the ascending information are determined by the integration which occurs in the dorsal horn.

The presentation of a noxious stimulus activates multiple cortical regions. Noxious and innocuous somatosensory input to the thalamus are relayed to the primary and secondary somatosensory cortices (Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994). The S1 and S2 cortices code spatial, temporal, and intensive characteristics of noxious and innocuous somatosensory stimuli. It has been indicated that these characteristics could subserve the sensory-discriminative dimension of pain processing (Hofbauer, Rainville, Duncan, & Bushnell, 2001). Together, the S1 and S2 cortices comprise the final pathway for the lateral pain system (Ingvar & Hsieh, 1999).

The ACC and the IC are also cortical regions that are active during human brain imaging studies of pain. These regions are components of the limbic system and are
considered as areas for processing the affective-motivational dimension of pain. Painful stimuli elicit evoked potentials over the human anterior cingulate gyrus (Hutchison, Davis, Lozano, Tasker, & Dostrovsky, 1999). This may be associated with the role of anterior cingulate cortex in cognitive processes such as attention. The insular cortex has been implicated in the subjective experience of pain through the regulation of autonomic functions (Augustine, 1996). The ACC is part of the medial pain system. The posterior ACC seems to be associated with the affective-evaluative dimension of pain and the anterior ACC associated with non-specific attention and arousal (Kwan, Crawley, Mikulis, & Davis, 2000). In the animal model, it has been demonstrated that lesion of the somatosensory cortex alters the sensory component of pain, however, pain affect behaviour remained intact (Uhelski, Davis, & Fuchs, 2012).

The view of pain transmission through nociceptors to the spinal cord, from spinal cord to the thalamus, and from the thalamus to the somatosensory cortex for processing is simplistic and does not explain several pain conditions. Individuals who have lost a limb do not have nociceptors and often present with intense pain. This condition is known as phantom limb pain (Melzack, 1990). Moreover, surgical removal of structures considered important in pain processing such as the thalamus and the somatosensory cortical areas have failed to alleviate chronic pain. Instead, nociception and pain processing spans throughout several regions of the spinal cord and brain.
2.4 Pain modulation

Data from patients entering an emergency clinic show that 37% of patients stated that they did not feel pain at the time of injury. Most of these patients reported the onset of pain within an hour of injury, although the delays were up to nine hours or more in some patients (Melzack, Wall, & Ty, 1982). In contrast, sensitivity to innocuous stimuli can be perceived as painful, as shown in conditions of alldynia (Nagi, Rubin, Chelvanayagam, Macefield, & Mahns, 2011). These data suggest a functional endogenous modulation of pain and that the relationship between injury and pain is highly variable.

Pain is integrated and modulated by diverse mechanisms. The brain possesses a highly organised descending system that is associated with modulating pain transmission. Descending control systems mediate synaptic transmission of sensory fibers at the dorsal horn as well as modulating ascending transmission at every level of the neuroaxis (Holdcroft & Jaggar, 2005). Descending pain modulatory systems comprise of anatomical networks that modulate nociceptive processing mostly at the level of the dorsal horn to produce either facilitation (pronociception) or inhibition (antinociception), (Tracey & Mantyh, 2007). It is presumed that the systems which facilitate or inhibit pain will enhance the chances for survival.

It is generally accepted that convergent neurons in the dorsal horn of the spinal cord and its homologue for the face, the trigeminal nucleus caudalis, play an important role in the transmission of nociceptive messages toward supraspinal regions (Villanueva & Le Bars, 1995). Brain stem neuronal circuits exert inhibitory control on
spinal cord nociceptive transmission. These neurons can be activated by both non-
noxious and noxious stimuli and their activities are under the influence of different
modulatory mechanisms from segmental, propriospinal, and supraspinal centres.
Functional studies show extensive evidence that brain stem modulatory circuits exert
a bidirectional control and that pain facilitation is also a significant part of their
function (Neubert, Kincaid, & Heinricher, 2004).

Higher brain functioning has been shown to contribute to endogenous pain control.
Psychological factors such as arousal, attention, and expectation influence central
nervous system circuits involved in pain modulation. Pain transmission depends on
the balance between inhibitory and facilitatory influences on somatosensory neural
circuits (Holdcroft & Jaggar, 2005). Previous research shows that attention and
emotions differentially alter the sensory and affective dimensions of pain perception
and apparently implicate different brain circuits (Villemure & Schweinhardt, 2010).

## 2.5 Endogenous pain inhibition

The endogenous pain inhibiting systems are often classified as either opioid or non-
opioid inhibiting systems. The non-opioid based systems appear to be involved in
analgesia related to low pain levels, whereas analgesia related to high pain levels is
more associated with the endogenous opioid systems (Flor, Birbaumer, Schulz,
Grüsser, & Mucha, 2002). The pain-inhibitory circuitry for opioid analgesia includes
the PAG, which produces autonomic fight-flight responses. Evidence has now
accumulated showing a variety of brain regions involved in descending modulation
and include the ACC, IC, amygdala, hypothalamus, PAG, nucleus cuneiformis,
(NCF), and rostral ventromedial medulla (RVM), (Tracey & Mantyh, 2007). Three
major brain structures associated with descending inhibitory signals to the spinal cord include the PAG, RVM, and the dorsolateral pontine tegmental area (DLTP). Descending input to the spinal cord from supraspinal structures has long been accepted as a major pathway for modulating sensory input.

The PAG integrates ascending nociceptive input from the dorsal horn with the limbic forebrain and diencephalon. Electrical stimulation of the PAG in the rat has been shown to produce analgesia sufficient for surgical procedures to be carried out, with no evidence of discomfort in fully conscious animals (Reynolds, 1969). This became known as stimulation produced analgesia (SPA) and has been subsequently confirmed in humans (Hosobuchi, Adams, & Linchitz, 1977). The discovery of the pain-modulating effect of the PAG was a critical advance in understanding the mechanism for pain modulation.

The PAG receives input from the medial prefrontal cortex, insular cortex, hypothalamus and the amygdala. Opioid administration to the PAG has been shown to stimulate the descending pain modulatory neurons (Yaksh, 1997). The PAG projects minimally to the spinal cord. The modulation of nociceptive activity in the spinal cord by the PAG is largely by connections to the RVM. The RVM includes the nucleus raphe magnus (NRM) and the reticular formation. Electrical stimulation or microinjection of opioids or excitatory amino acids into the RVM produces analgesia and inhibits spinal dorsal horn neuronal responses to noxious stimulation (Basbaum & Fields, 1984).

The PAG-RVM connection evokes synaptic inhibition on ascending pain-signalling neurons in the spinal cord. The RVM is a major source of serotonin in the spinal cord.
Direct spinal application of serotonin has been shown to inhibit nociceptive dorsal horn neurons (Jordan, Kenshalo, Martin, Haber, & Willis, 1978). The termination zone for many RVM axons is located within the superficial and deep layers of the dorsal horn. These terminals matched the region where nociceptors terminated, suggesting that the RVM specifically modulates nociceptive primary afferent targets in the dorsal horn (Basbaum & Fields, 1978). The terminals of RVM in the spinal cord are dense in lamina I, II and V. Inhibitory interneurons have been shown to be present in lamina I and II.

Noxious stimuli have been shown to stimulate the anterior cingulate. The medial prefrontal cortex belongs to the ACC and previous research shows antinociceptive effects during prefrontal cortex stimulation (Hardy, 1985). Motivational and affective components of pain perception have been linked to the ACC. Direct stimulation of the ACC has been shown to significantly inhibit the responses of spinal dorsal horn neurons to noxious mechanical stimuli (Senapati et al., 2005). Bilateral projections from the anterior cingulate to the PAG may account for the reduced response in dorsal horn neurons.

The neurophysiological circuit for exercise-induced pain inhibition has not been fully elucidated. A potential mechanism for attenuation of pain following exercise exists within the dorsal horn of the spinal cord. In order to elicit brainstem descending antinociceptive signalling in the spinal cord, it is necessary to evoke ascending pain signals. In this context, it is possible that the pain elicited from muscle tissue during exercise may potentially evoke a brainstem antinociceptive circuit within the spinal cord. In one study, it was observed that the threshold for the nociceptive withdrawal reflex was elevated following aerobic exercise (Guieu, et al., 1992). This suggests that exercise induces antinociception within the spinal cord.
2.5.1 Noradrenergic neurons

The third brain region that plays a role in pain-modulation is the dorsolateral pontine tegmental area (DLPT). The DLPT includes the nucleus cuneiformis which has reciprocal noradrenergic containing connections to the RVM and to the spinal cord. The major sources of noradrenergic projections to the spinal cord include the locus coeruleus, the A5, and the A7 group neurons. Direct spinal application of norepinephrine has been shown to selectively inhibit nociceptive dorsal horn projection neurons (Belcher, Ryall, & Schaffner, 1978). In the animal model, noradrenergic involvement with the PAG was associated with inhibition of dorsal horn cell activity (Peng, Lin, & Willis, 1996).

The DLPT also receives input from lamina I of the dorsal horn (Fields & Basbaum, 1999). Neurons in Lamina I project to some cells of the DLPT and the RVM to become activated and others to become inhibited. The cells that become activated with noxious stimulation are termed ‘on-cells’ and the cells that become inhibited are termed ‘off-cells’. The on-cells have been shown to facilitate nociceptive transmission and off-cells inhibit nociceptive transmission. On- and off-cells of the RVM project to lamina I, II, and V of the dorsal horn. Opioid administration in the RVM inhibits the activity of on-cells and activates the off-cells (Basbaum & Fields, 1978). The activity of the off-cells is most consistently related to suppression of nociceptive transmission in the spinal cord.
2.5.2 Dopaminergic pathways

Expectations of pain and reward are also implicated in the modulation of pain responses through dopaminergic pathways. Previous research indicates that the activation of the nucleus accumbens, an area in the brain that expresses dopamine, was shown to mediate placebo analgesia (Scott et al., 2007). The results from 14 healthy participants show that the individual variation in the activity of the nucleus accumbens accounted for 28% of the placebo analgesia. These results also advance the understanding of expectation in pain relief within clinical trials on chronic pain (Tracey & Mantyh, 2007).

2.5.3 Serotonergic pathways

Acute and chronic exposure to noxious stimuli has been shown to activate serotonergic neurons. Manipulation of serotonergic pathways has been shown to mediate stress induced analgesia following exposure to noxious stimuli (Millan, 2002). Traditionally, the action of serotonin has been considered as inhibiting the flow of nociceptive activity, however, there is some evidence showing that the serotonergic activity facilitates nociceptive activity (Zhang, Yang, Gao, & Wu, 2001). In this respect, serotonin may not invariably inhibit nociceptive signalling, but rather elicits a range of pro- and anti-nociceptive actions (Millan, 2002).
2.5.4 Opioids and pain inhibition

The control of nociceptor transmission along nociceptive pathways is mediated by three groups of endogenous opioids known as enkephalins, endorphins, and dynorphins (Brunton, Lazo, & Parker, 1990). Nociceptor signals from peripheral tissues stimulates the release of endorphins in the PAG and the release of enkephalins in the NRM of the brainstem (Brookoff, 2000). Nerve cells containing β-endorphin are located in the arcuate nucleus of the hypothalamus, with extensive projections throughout the brain including the nucleus tractus solitarius in the brain stem. Another β-endorphin system is located in the anterior pituitary, where it is co-released with adrenocortocotropic hormone into systemic circulation (Hoffman, Jonsdottir, & Thorén, 1996).

Endorphins inhibit pain signalling by binding to μ-opioid receptors located on pre-synaptic nerve terminals of nociceptors and post-synaptic surfaces of dorsal horn neurons in the spinal cord. Enkephalins from the NRM bind to δ-opioid receptors on inhibitory interneurons in the substantia gelatinosa resulting in a release of GABA to dampen nociceptor signalling (Brookoff, 2000). Dynorphin is released by spinal interneurons and binds to κ-opioid receptors to precipitate closure of calcium channels that relay nociceptive signals to the brain. In spinal cord cells, the release of enkephalin also triggers the discharge of substances that inhibit pain signalling such as norepinephrine, relaxin, and oxytocin.

Almost all brain areas contain opiate receptors, with the exception of the cerebellum. Also dense clusters of receptors are present at synaptic areas of the ventral
spinothalamic tract, the substantia gelatinosa of the spinal cord, PAG, intralamina nuclei of the thalamus, extrapyramidal system, with the amygdala being one densely populated with opiate receptors (Bunney et al., 1979). In the central nervous system, β-endorphins bind predominantly to µ-opioid receptors associated with descending pain control circuits including the amygdala, mesencephalic reticular formation, PAG, and the RVM (Miller, 2005; Sprouse-Blum, Smith, Sugai, & Parsa, 2010). Additionally, β-endorphin binding to µ-opioid receptors inhibits the release of GABA, resulting in an increase in central dopamine.

Opioid receptors have been observed on peripheral terminals of afferent fibers (Stein et al., 1990). Peripheral analgesia by opioids appears to be part of a physiological antinociceptive system based on the amount of endogenous opioids found in inflamed tissue. Inflammatory cells such as macrophages, monocytes and lymphocytes express opioid peptides (Przewlocki et al., 1992). Interleukin 1β and corticotropin releasing hormone originating from inflamed tissue induce the release of endogenous opioids and antinociception (Schäffer, Carter, & Stein, 1994). Since the number and location of certain receptors has been shown to be dynamic, this suggests that nociception can be modified before the signals reach the spinal cord (Carlton & Coggeshall, 1988). Peripherally, β-endorphins bind predominantly to µ-receptors at pre and post-synaptic nerve terminals (Sprouse-Blum, et al., 2010). Through a cascade of events, this results in the inhibition of the release of substance P, a primary pain neurotransmitter.

It has been proposed that the mechanism for exercise-induced pain inhibition is by an increase in the concentration of β-endorphin (Droste, Meyer-Blankenburg, Greenlee, & Roskamm, 1988). In contrast, pain thresholds (N=10) did not correlate
with plasma β–endorphin levels following exercise (Droste, et al., 1991). Similarly, changes in pain perception were only partly attributed to endogenous opioid systems (Janal, Colt, Clark, & Glusman, 1984), as assessed by plasma concentration of β-endorphin. It should be noted that plasma and central concentrations of β-endorphin are not necessarily correlated (Radosevich et al., 1989) and therefore plasma β-endorphin may not reflect changes in pain perception from central β-endorphin release.

### 2.5.5 Placebo analgesia

The anticipation of pain has been shown to mediate a placebo-induced pain inhibition by enhanced opioid release. Expectations of pain have been associated with enhanced activity of the prefrontal cortex (PFC). This region of the brain has been associated with activity in classic pain processing regions including the thalamus, insula, and anterior cingulate (Tracey & Mantyh, 2007). Stronger PFC activation has been shown to correlate with greater placebo-induced pain relief by reductions in neural activity within the pain processing regions (Wager et al., 2004). Moreover, activity in opioid-receptor rich areas located in the rostral anterior cortex and the anterior insula were more extensively activated during opioid treatment compared to placebo (Petrovic et al., 2010). Together, these results suggest that placebo-analgesia is partially mediated by the endogenous opioid system and that prefrontal mechanisms can influence descending pain-control systems and subsequently pain perception.
2.5.6 Gate-control theory and pain inhibition

Pain evoked by activity in nociceptors can be modulated by the simultaneous activity of low-threshold mechoreceptors in skin. Gate-control theory (Melzack & Wall, 1965) proposed that a pain inhibitory dorsal horn interneuron is activated by fibers conveying tactile information. This can be observed when pain in the skin can frequently be relieved by gently stimulating the skin around the hurt area by light brushing, massaging, or tickling. The neurons of the dorsal horn projecting up the spinothalamic tract are excited by both large-diameter myelinated sensory neurons and by unmyelinated pain fibers. The projection neuron is also inhibited by an interneuron, and the interneuron is both excited by large sensory fiber input and inhibited by nociceptive fiber input.

Concurrent activation of large mechanoreceptive axons mediates the activity of interneurons in the dorsal horn and suppresses nociceptive signals. The tactile pathway inhibits the pain pathway. This modulation is not limited to a simple competition among afferent stimuli, as a multitude of descending inputs from the brain may incite neurons in the dorsal horn to modulate nociceptive impulses. The pro-nociceptive mechanisms vie with the anti-nociceptive mechanisms, and the perception of pain results from this interchange (Rey, 1995). Gate-control theory has been imprecise in elucidating the spinal cord circuits, however, the idea of a specific neuronal cord circuit for pain transmission and modulation is well accepted.
2.5.7 Stress induced analgesia

Exposure to stress reduces pain responses and is referred to as stress induced analgesia (SIA). The reduction in pain is mediated by descending pain-inhibitory circuits and is an indicator of centrally mediated pain control (Amit & Galina, 1986; Butler & Finn, 2009). Based on results from fMRI in 21 healthy participants, an increase in pain tolerance and threshold following stress induction was shown to correlate with enhanced activation in several brain regions (Yilmaz et al., 2010). The increase in pain tolerance was shown to be associated with activation in the rostral anterior cingulate, while pain unpleasantness was associated with activity in the dorsal anterior cingulate cortex. These results indicate that stress induced analgesia activates similar brain regions associated with placebo analgesia and analgesia triggered by diffuse noxious inhibitory controls.

It has been shown that exposure to aversive and/or noxious stimuli engages defensive systems that inhibit nociceptive reflexes (Meagher, Chen, Salinas, & Grau, 1993). These inhibitory effects are not mediated by a single system but an array of neural systems that function at multiple levels of the neuro-axis to regulate pain (Millan, 2002). The measurement of spinal reflexes in the rat following exposure to an aversive shock generally produces an increase in tail-flick latencies, known as antinociception (Grau, Hyson, Maier, Madden, & Barchas, 1981).

Relatively brief-moderate electrophysiological shocks have been shown to activate forebrain-dependent systems to inhibit spinal reflexes via lower brainstem systems such as the PAG (Fields & Basbaum, 1999). This system relies on an opioid synapse
and is referred to as the spinal-opioid system. More severe shocks directly engage brainstem and spinal antinociceptive mechanisms in the absence of the forebrain and is not mediated by an opioid synapse (Meagher, Grau, & King, 1990). This system is referred to as the brainstem-nonopioid system. Functionally, relatively mild shock stimuli will engage a forebrain-dependent antinociception, whereas more severe stimuli will engage multiple antinociceptive systems (Crown, Grau, & Meagher, 2004).

The co-release of β-endorphin and adrenocorticotropin hormone in conditions of stress, including physical exercise (Goldfarb & Jamurtas, 1997), has led to the notion of exercise induced hypoalgesia (Janal, et al., 1984). Enhanced plasma levels of β-endorphin have been observed with exercise above 60% of maximum oxygen consumption, with peak values at 15-min post-exercise (Hoffman, et al., 1996). A confounding factor for studies on exercise and plasma levels of β-endorphin are that peripheral levels do not reflect central nervous system opioid activity (Baker et al., 1997) and that opioid receptors are not fully antagonised by blocking agents such as naloxone (Hoffman, et al., 1996).

### 2.5.8 Diffuse noxious inhibitory controls

Diffuse noxious inhibitory controls (DNICs) refers to the supraspinal neural substrates mediating inhibition of nociception generated by other nociceptive stimuli (Le Bars, Dickenson, Besson, & Björklund, 1982; Le Bars & Willer, 2009). The onset of DNICs is observed when a strong painful stimulus is applied and subsequently decreases pain responsiveness in other body regions, heterotopically. Reductions in pain responsiveness with DNICs share similarities with stress induced analgesia (Butler &
Finn, 2009). In this context, DNICs involves endogenous bottom-up analgesic modulation of pain (Reidler et al., 2012).

DNICs mediate noxious signalling at the spinal level. When noxious signalling ascends, supraspinal structures such as the subnucleus reticularis dorsalis of the caudal medulla mediate descending inhibition of lamina I neurons in the spinal cord (Villanueva, 2009; Villanueva, Bouhassira, & Le Bars, 1996). The DNICs act specifically on spinal and trigeminal wide dynamic range neurons including those projecting to the thalamus (Dickenson & Le Bars, 1987). The wide dynamic range neurons, also designated as class 2 or multireceptive neurons, are activated by both innocuous and nociceptive inputs through A and C-fibers. DNICs act by a postsynaptic inhibitory mechanism involving hyperpolarisation of the neural membrane (Le Bars & Willer, 2009).

In animal models, the responses of wide dynamic range neurons to nociceptive stimuli are inhibited in an intensity-dependent and long-lasting action when conditioning nociceptive stimuli are applied to heterotopic areas of the body (Hanai, 1998; Ness & Gebhart, 1991). An important common finding in these studies is that the inhibition generated by an innocuous stimulus occurs at the spinal segmental level, whereas inhibition generated by nociceptive stimulus has been demonstrated to be organised at segmental, intraspinal, and supraspinal levels.

Counterirritation, also referred as nocigenic inhibition, or ‘pain inhibits pain’ effect is defined as the inhibition of neural, behavioural, or reflex responses to a nociceptive test stimulus produced by another concomitant nociceptive stimulus (Piché, Arsenault, & Rainville, 2009; Price & McHaffie, 1988). Counterirritation has been
suggested to depend on specific neurophysiological mechanisms involving endogenous modulatory systems at the spinal cord. It has been proposed that counterirritation is due to the increased activation of diffuse noxious inhibitory controls, although supraspinal mechanisms may take place depending on the pathophysiology of clinical pain (Bouhassira, Danziger, Attal, & Guirimand, 2003).

Elevated pain thresholds have been demonstrated following DNIC induction in a group of 15 healthy participants (Reidler, et al., 2012). The results also demonstrated that transcranial direct current stimulation of the motor cortex in healthy participants resulted in elevated pain threshold. Moreover, an additive effect on increasing the pain threshold was observed when motor cortex stimulation was combined with DNICs.

A potential mechanism for the activation of diffuse noxious inhibitory controls is physical exercise. Acute muscle pain is elicited by exercise at or above 50% of maximal work capacity (Hamilton, et al., 1996), and reaches levels of ‘very strong pain’ at volitional exhaustion (Cook, et al., 1997). The pain elicited by intense muscle contraction during exercise may launch central anti-nociceptive mechanisms and result in the inhibition of experimental pain parameters in the post exercise period (Koltyn, 2002). There is some evidence that the nociceptive withdrawal reflex signal is attenuated following exercise, however, measures of pain rating were not assessed (Guieu, et al., 1992). Further research is required to explicate the effects of exercise on the nociceptive signal and verbal pain responses to experimental noxious stimuli.
2.5.9 The endocannabinoid system

Endocannabinoid signalling is distributed throughout the brain and is involved in regulating excitatory and inhibitory neurotransmitters. The presence of this system in the hypothalamus and limbic structures such as the amygdala suggests that this regulates the neuroendocrine and behavioural responses to stress (Hill et al., 2010). Previous research indicates that the endocannabinoid signalling acts to suppress hypothalamic-pituitary-adrenal (HPA) axis activity through concerted actions within the prefrontal cortex, amygdala, and hypothalamus (Hill & Tasker, 2012).

Receptors for cannabinoids have been shown to be both peripherally and centrally located. Peripherally, the general effect for cannabinoids is for neuronal inhibition. Endocannabinoids have also been shown to centrally modulate pain (Dietrich & McDaniel, 2004). Receptors for endocannabinoids in the dorsal horn have been shown to reduce pain from noxious heat in the rat model (Hohmann, Tsou, & Walker, 1999). Central antinociceptive brain circuits activated by endocannabinoids have been demonstrated in the RVM (Meng, Manning, Martin, & Fields, 1998) and in the PAG (Ho et al., 2011). The efficacy for cannabinoids in antinociception is similar to morphine (Dietrich & McDaniel, 2004).

Previous research shows that aerobic exercise of moderate intensity activates the endocannabinoid system (Sparling, Giuffrida, Piomelli, Rosskopf, & Dietrich, 2003). Physical exercise activates stress systems and it is possible that this launches the endocannabinoid system. The presence of this system following exercise suggests a new mechanism for exercise-induced pain inhibition (Dietrich & McDaniel, 2004).
Antinociception following exercise appears to be more consistent with the endocannabinoid system compared to the opioid system due to the peripheral antinociceptive mechanisms associated with endocannabinoids.

### 2.6 Exogenous pain inhibition

Pharmacological intervention for pain includes drugs such as aspirin, lignocaine, and opiates. Aspirin is a mild analgesic acting by way of blocking the peripheral release of prostaglandins and inflammatory mediators, thereby reducing the sensitivity of nociceptors. Lignocaine peripherally blocks ion channels in the cell membrane that convey the propagation of action potentials from populations of both sensory and motor neurons (Toates, 2007). Opiates are chemically similar to endogenous opioids and exert a similar effect. Opiates target receptor sites and block the transmission of nociceptive signals at the spinal cord and in the brain.

Activity within large-myelinated sensory axons opposes the transmission of nociceptive neurons in the spinal cord. The antidromic effect of the large afferents has led to the development of pain therapeutic techniques such as transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), and deep brain stimulation (Simpson, Meyerson, & Linderoth, 2006). TENS involves applying weak electrical signals at the skin corresponding to the affected area. This procedure aims to excite the large-myelinated afferents and avert the activity of the small diameter afferents. SCS requires the implantation of a percutaneous lead in the dorsal epidural space and are applied for treatments in neuropathic and ischemic pain. The mechanism for the reduced pain in SCS are not fully understood, however, multiple
mechanisms may be operating sequentially and simultaneously (Oakley & Prager, 2002).

Deep brain stimulation procedures have been applied in the management of persistent pain that is resistant to other therapies. Surgical implantation of stimulating electrodes that predominantly target the sensory thalamic nuclei, periaqueductal/periventricular gray region, and more recently the precentral area and motor cortex (Simpson, et al., 2006). Evidence is accumulating showing that stimulation of the thalamic nuclei is effective for neuropathic pain and the periventricular gray is effective for nociceptive forms of pain. Deep brain stimulation of medial thalamus and periventricular gray has also been applied for treatment of chronic low back pain.
2.7 Experimental noxious stimuli

Pain research requiring experimentally induced pain procedures offers a degree of experimental control not found in studies of clinical pain. Although experimentally induced pain cannot simulate the severity or impact of clinical pain, the procedure offers a degree of control and measurement not possible with clinical pain assessment (Gracely, 1983). Experimental pain procedures performed on pain-free individuals and persons with chronic pain also explicates the experience of pain that is not possible in controlled studies of laboratory animals. The application of noxious stimuli to induce pain enables the pain experience to be evaluated by a number of verbal, behavioural, and physiological measures. Consequently it is recognised that experimental pain procedures approaches an understanding of pain mechanisms that is not available in clinical pain evaluation.

The properties of experimental noxious stimuli should produce a distinct pain sensation and a relation between stimulus and pain intensity. An ideal pain stimulus has properties that elicits desirable traits (Beecher, 1959). Pain stimuli should provoke minimal tissue damage and reveal an analgesic dose relationship. A diverse range of noxious stimuli have been applied to induce pain in humans and animals. Stimuli such as heat, cold, electricity, cutaneous pressure, and ischaemia have been employed to assess pain and analgesia.

A consensus on the ideal noxious stimulus for inducing experimental pain is not apparent in pain research. Experimental pain stimuli differ along multiple dimensions including time course (phasic versus tonic), site and depth of stimulation (cutaneous...
versus deep), site location (regionalised versus generalised), and potential response (perception versus behavioural withdrawal).

2.7.1 Electrical stimuli

The most common method of inducing an experimental pain stimulus is by electrical stimulation. Electrical stimuli are applied to skin, muscle, gastric sites, or directly to peripheral and central nerves (Gracely, 1999b). When electrical recording techniques were first developed it was demonstrated in animal experiments that under physiological conditions, pain is induced only when the stimuli are strong enough to recruit nociceptive fibers (Gasser & Erlanger, 1929). The low intensity electrical stimuli excite mechanoreceptive afferent nerve fibers that do not evoke pain. Pain is evoked by electrical stimulation at an intensity that is sufficient to recruit nociceptive fibers.

Previous research in healthy participants (N=10) indicates that electrical stimuli can elicit reliable pain responses in the course of a day (Notermans, 1966). The variance in electrocutaneous pain threshold was shown to be less than 20%. However, in another research trial (Lund et al., 2005), the between-day percentage agreement in electrocutaneous pain threshold (N=48) was shown to be 49%. Despite some evidence showing the reliability of electrical stimuli for inducing pain, this type of stimulus has limitations. Firstly, electrical stimuli excite the afferent pathway in an unnatural synchronised manner. These stimuli excite the full spectrum of afferent nerve fibers and do not specifically activate pain fibers, unless non-pain afferent fibers are blocked. Secondly, electrical stimulation bypasses the sensory nerve
endings and so information on the transduction process is lost (Handwerker & Kobal, 1993).

Several investigations have employed electrical stimuli to assess pain processing before, during, and after exercise (Droste, et al., 1991; Kemppainen, et al., 1985; Olausson, et al., 1984). In one of the earliest experimental investigations on electrical stimulation and exercise, experimental pain was induced on dental pulp during bicycle ergometer activity (Pertovaara, Huopaniemi, Virtanen, & Johansson, 1984). The advantage of dental stimulation is the selective recruitment of nociceptive fibers within dental pulp. This procedure requires applying a cathode to an intact upper tooth through a metal cylinder which is glued to the tooth. Electrical stimuli were delivered by constant current pulses of 10 ms duration at a frequency of 5 Hz to six participants. The results revealed that pain was inhibited during exercise. These studies indicate that electrical stimuli are often applied in exercise and pain research.

### 2.7.2 Mechanical pressure stimuli

Mechanical stimuli are a common form of experimental pain which include the use of needles, spicules, and pressure devices. Mechanical pressure evokes pain by deformation of the skin above bone or soft tissue sites (Fischer, 1986). Mechanical somatic pressure protocols include constant load or increasing load. In constant load protocols, a set mechanical pressure is applied to a site while verbal pain ratings are recorded (Koltyn, Trine, Stegner, & Tobar, 2001). With increasing pressure load protocols, the pressure applied to a site is augmented until pain parameters such as the threshold or tolerance are established. Typically, mechanical pressure is applied by an algometer on a site until the pain threshold is indicated by the participant.
communicating verbally or behaviourally such as pressing a button. Pressure algometers consist of a pressure sensitive strain-gauge and rod applicator and rubber tip with a diameter of 10 mm which made contact with the skin (Kosek, Ekholm, & Nordemar, 1993).

Several studies, show that experimental somatic mechanical-pressure pain is a reliable measure in normal subjects (Fischer, 1987; Ohrbach & Gale, 1989). Stimulus control with mechanical pressure is potentially problematic because tissue elasticity, application rate, and degree of compression can influence results (Jensen, Anderson, Olesen, & Lindblom, 1986). Moreover, repeated measurements performed over four consecutive days (N=19), showed an overall declining trend in threshold (Jones, Kilgour, & Comtois, 2007). Here, it was proposed that a centrally mediated alteration in pressure pain sensation could contribute to the decline in pressure pain threshold with serial measurements over consecutive days.

Assessments of mechanical pain thresholds have been performed in healthy (Koltyn, Garvin, Gardiner, & Nelson, 1996) and in chronic pain participants (Kosek, Ekholm, & Hansson, 1996a) to assess the function of the pain system. Under resting conditions and in healthy participants, a high reliability has been observed for pressure pain threshold between various target sites (Fischer, 1987), between trials (Nussbaum & Downes, 1998; Ohrbach & Gale, 1989) and across different raters (Chesterton, Sim, Wright, & Foster, 2007). In contrast, there is evidence showing that repeated pressure pain testing (N=19) lowers the threshold compared to baseline (Jones, et al., 2007). Similarly, a large variance in pressure pain threshold (N=28) was observed in the measurement of one area within short time intervals (Hogeweg, Langereis, Bernards, Faber, & Helders, 1992). The results also showed no significant
difference between the same points on either side of the body ($r= .74 – .93$), nor was there a difference between observers. Significant differences in pressure pain threshold were shown in the peripheral joints compared to the paravertebral points. These studies show that pressure pain thresholds can significantly vary when repeated within a short time interval and that there are distinct differences between different areas of the body.

Pressure pain threshold assessment has been applied to determine tissue sensitivity in chronic pain disorder (Mikkelsson, Latikka, Kautiainen, Isomeri, & Isomaki, 1992; Reeves, Jaeger, & Graffradford, 1986). In chronic pain fibromyalgia, tissue tenderness is assessed by pressure pain threshold assessment across 18 tenderpoints for diagnostic purposes (Wolfe, Smythe, Yunus, & et al., 1990). The threshold for pressure pain has been shown to be reliable amongst persons with chronic pain (Russell, 1998), and has been used to assess treatment effects (Fischer, 1998). In one study, the pressure pain threshold was assessed in three groups consisting of regional chronic pain ($N=60$), widespread chronic pain ($N=60$), and in sixty healthy controls (Granges & Littlejohn, 1993). The results indicated that there was a generalised sensitivity in the pain system across different chronic pain disorders compared to healthy controls. In another study with 245 participants (Gupta et al., 2007), the number of tender points, as measured by mechanical pressure threshold, was associated with the onset of chronic widespread pain.

Assessment for pressure pain threshold in chronic pain participants, however, has not been shown to closely match with clinical pain intensity (Staud, 2005). Moreover, there is evidence showing that in 27% of respondents ($N=24$), there is an increase in pressure pain threshold with repeated testing (Greenspan & McGillis, 1994).
Moreover, there is some evidence showing that manual pressure of muscle (palpation) is open to subjective bias (Branch, Carlson, & Okeson, 2000). Here, the influence of clinician bias on the report of pain was investigated in 40 patients. The results from this study show that patient reports of pain were influenced by biased clinician statements.

In the classification of chronic pain fibromyalgia, generalised pain and multiple painful regions, amongst other symptoms such as sleep disturbance, fatigue, and stiffness are identified with this syndrome (Wolfe et al., 1990). Tenderpoint examination for determining multiple painful regions is performed by palpation over 18 sites across the body or by dolorimetry (pressure algometer). Tenderness at a pressure of approximately 4 kg in at least 11 of 18 tenderpoints provided the most sensitive, specific, accurate criteria for diagnosis. The bilateral tenderpoints include the muscle insertion at the occiput, intertransverse spaces at C5-C7, trapezius at the midpoint of the upper border, supraspinatus at origin above scapula spine near medial border, paraspinous at 3 cm lateral to the midline at the level of the mid-scapula, 2nd rib at the second costochondral junctions, lateral epicondyle at 2 cm distal to the epicondyles, gluteal at the upper outer quadrants of buttocks in the anterior fold, greater trochanter posterior to the trochanteric prominence, medial fat pad of the knee proximal to the joint line. The new criteria for diagnosing fibromyalgia by the American College of Rheumatology, however, have removed these tenderpoints as the central defining element (Wolfe, 2010).
2.7.3 Laser stimuli

Laser stimuli have been used in pain research to selectively activate the Aδ and C-fiber free nerve endings and avert activation of the Aβ heavily myelinated fibers. Brief radiant heat pulses are generated by infrared laser (Bromm & Treede, 1984). Laser induced pain consists of an immediate stinging component followed by a burning pain which lasts several seconds. It has been demonstrated, however, that the cerebral evoked potentials from laser-induced nociceptor activity are not unique to the nociceptive system (Iannetti, Hughes, Lee, & Mouraux, 2008), but are associated with multimodal networks involved in sensory integration (Mouraux & Iannetti, 2009). Results from nine healthy participants showed that the magnitude of the multimodal response was correlated with the subjective rating of the saliency of the signal. The correlation was irrespective of the sensory system, suggesting an involvement of the attention and arousal system. This indicates that the generation of cerebral evoked potentials from laser stimuli are not nociceptive specific, although may indirectly reflect the function of the afferent nociceptive system.

2.7.4 Cold stimuli

Studies on pain have administered noxious cooling as a stimulus for evoking pain. Cold stimuli are applied by contact thermodes, coolant sprays or by immersion in water. These methods can be divided into those eliciting a discreet stimulus or continuous stimulation. A common method for administering continuous cold stimulation is the cold pressure test. This test involves immersion of a limb in very
cold water (0-4°C). The cold-pressor test evokes a severe pain that increases rapidly and can be tolerated for only a few minutes (Gracely, 1999b).

The cold-pressure test is often used to evoke pain, however, in clinical trials the test has shown a low reliability (Blasco & Bayes, 1988). Vascular reactions to cold strongly affect the pain intensity during cutaneous vasoconstriction. During prolonged cooling, the vasoconstriction is followed by a vasodilation, and pain begins to plateau (Kreh, Anton, Gilly, & Handwerker, 1984). Individual differences in the vasomotor activity to cold may be a reason for the unreliability of the cold pressure test. Results from 26 healthy participants during the cold-pressor test revealed that there were differences in gender, with males reporting longer times (Mitchell, MacDonald, & Brodie, 2004). Moreover, the study showed significant main effects for temperature. Equipment for precise constant temperature of circulating water was recommended to ensure comparable and reliable results.

### 2.7.5 Heat stimulation

Experimental noxious stimuli are also delivered by heat stimulation. Contact thermodes on the skin administer a temperature increase that is proportional to the magnitude and direction of the stimulating current (Kenshalo & Bergen, 1975). Other methods of delivering a heat stimulus include argon laser or CO₂ (Gracely, 1999b). The rate of change in heat is fast with electrically heated units. A thermister at the thermode-skin interface provides precise and controllable stimulation. Pain induced by radiant heat was widely used by Hardy et al, who developed heat delivery methodological procedures (Hardy, Wolff, & Goodell, 1952).
Noxious radiant heat procedures have been shown to be prone to artifact. In rat experiments it has been shown that the tail-flick latency during heat stimulation depends on the tail temperature and blood flow (Berge, Garcia-Carbrera, & Hole, 1988). Even when skin surface temperature is controlled, results can differ depending on the heat application wavelength during radiation or thermod contact with skin. Laser beams have also been used to apply fast rising temperatures to skin (Bromm & Treede, 1984). However, this procedure may also excite sensitive mechanoreceptors and warmth receptors in addition to nociceptors due to the changes in tissue turgor induced by laser beams.

2.7.6 Chemical irritants

Chemical substances have been administered to elicit pain in humans and animals. Chemical substances have been shown to selectively excite pain nerve endings in humans by intracutaneous injection, topical application, or application to blistered skin (Handwerker & Kobal, 1993). Substances such as mustard oil and capsaicin, the pungent ingredient in chilli pepper, are applied topically or intradermally to assess hyperalgesia (Simone, Baumann, & LaMotte, 1989). Chemical substances have been administered to teeth, to the eye, or injected intramuscularly. The degree of stimulus control is generally low in that the capacity to instantaneously remove the stimulus is limited, although new methods such as CO₂ delivery on nasal mucosa cells and manipulating tissue pH offer controlled and repeatable chemical stimulation.

Research using chemical stimulation is useful in specific types of pain research. The application of chemical irritants provides a model of prolonged pain. In one study, the topical application of algogenic substances was employed to compare the latency of
chemically evoked discharges from microneurographic recordings and concurrent subjective sensations (Adriaensen, Gybels, Handwerker, & Van Hees, 1980). From these results, it was shown that a summation of input from nociceptors was required to elicit pain sensations.

### 2.7.7 Ischaemia

Experimental pain has been elicited by arresting the blood flow in the arm during isometric or dynamic hand exercise. Blood flow is occluded by a pressure cuff. This procedure was performed in 45 participants and induced ischaemic pain in the forearm muscles (Smith, Egbert, Markowitz, Mosteller, & Beecher, 1966). The ischaemic pain increased in intensity when muscle contractile activity was performed by squeezing a hand exerciser for 20 repetitions. The pain intensity was shown to increase from slight, moderately distressing, very distressing, and unbearable during 20 hand compressions.

Two separate components of pain have been identified during the ischemic pain test. Amongst 17 participants, the ischaemic pain test was shown to elicit pressure pain from the cuff and ischaemic pain in the forearm during hand compressions (Pertovaara, Nurmikko, & Pöntinen, 1984). The ischaemic pain was attributed to the accumulation of metabolites that sensitised neurons subserving the sensory-discriminative aspect of pain (Price & Dubner, 1977). Under successive determinations, the test was considered reliable and useful in pain research although should be applied with caution in persons with cardiovascular disease (Pertovaara, Nurmikko, et al., 1984).
Ischaemic pain has been experimentally applied to assess pain parameters before and after long-term exercise training (Scott & Gijbers, 1981) and following acute exercise (Black, Chesher, & Starmer, 1979). Here, experimental ischaemia was induced in the arm in one participant by inflating a sphygmomanometer cuff to a pressure of 200 mmHg. This procedure also required the subject to hand-compress a rubber bulb using the ischemic arm with a force sufficient to maintain 200 mmHg of pressure. In another study, experimental ischaemic pain was induced in 24 chronic pain participants (Sternbach, Deems, Timmermans, & Huey, 1977). The results showed that the pain estimates were too small to discriminate differences in analgesic drug responses.
2.8 The measurement of pain

“Measure what is measurable, and make measurable what is not so” may be an apt Galilean dictum in the measurement of pain (Lee & Tracey, 2010, p. 125). Firstly, a framework of what is to be measured needs to be established. Pain is a subjective experience that is not directly quantifiable. By its very nature, pain is difficult to assess, investigate, manage, and treat. This is because of a raft of factors that influence nociceptive processing and result in amplifying, attenuating, and colouring the pain experience (Tracey & Mantyh, 2007). Pain has been shown to demonstrate complex interactions with cognitive functions (Oosterman, Dijkerman, Kessels, & Scherder, 2010), emotions (Rhudy, Williams, McCabe, Rambo, & Russell, 2006), and sociocultural factors (Hsieh, Tripp, & Ji, 2011).

Response to pain can be observed and assessed by communication of the subjective experience. Whether such assessments of pain represent quantitative measures for research remains controversial (Lee & Tracey, 2010). Further difficulty in the assessment of pain is the potential difference between the perception of the pain experience and the behavioural report. There is no simple thermometer that can objectively measure how much pain an individual experiences. The reliability of pain measurement tools seems to validate the assessment of the pain experience. Statistical methods for analysing reliability such as the intraclass correlation coefficient, are used to assess the agreement between examiners and serial measures of pain (Dworkin & Whitney, 1992).
2.8.1 The scaling of pain perception

The scaling of pain assumes that a participant can quantify the sensation on a psychophysical scale. Pain rating scales are administered to assess experimental and clinical pain parameters. Common responses include discrete numerical (0-10), category scales (mild, moderate, severe), continuous response such as the visual analogue scale (VAS), magnitude estimation, and cross-modality matching (Gracely, 1999b).

Category scales and the VAS are the most widely used in clinical and experimental pain trials. The pain VAS is a unidimensional measure of pain intensity used in diverse populations (Hawker, Mian, Kendzerska, & French, 2011). The application of the VAS requires a 10 cm line labelled at one end with ‘no pain’ and the other with ‘most intense pain imaginable’. Subjects indicate the pain magnitude by marking the 10 cm line at the appropriate point. The validity and reliability of the VAS in pain research has been demonstrated among several pain assessment scales (Jensen, Karoly, & Braver, 1986). Results in 75 chronic pain participants showed that the scales yield similar scores in the intensity of pain. The use of VAS has been successful for assessing sensory intensity, the unpleasantness of experimental pain sensation, and for assessing pain interventions (Price, 1988).

Several types of category scales have been employed to assess pain intensity in pain research. The simplest category scale includes the four-point ‘none, mild, moderate, and severe’. Another scale, the numerical scale of 1-10, can also offer descriptive categories during pain measurement. Most category scales are confined
by fixed end-points which can introduce biases associated with the limited availability of categories (O'Connor & Cook, 1999). In addition, category scales are confounded by the memory of pre-treatment pain category responses.

Some of the limitations of psychophysical scaling methods using bounded responses have been overcome. The Method of magnitude estimation has an unbounded response range and may be less sensitive to biases associated with bounded scales (Gracely, 1999b). This scaling method requires subjects to assign a number to the first stimulus and to judge subsequent stimuli in proportion to the first stimulus.

Pain measurement procedures can be grouped into two categories: one that requires the use of verbal report to assess the pain experience, and the second method requires the measurement of non-verbal pain responses. The measurement of pain using verbal report applies the principles of psychophysics. Pain psychophysics commenced with assessing verbal responses for tactile and pressure stimulation from the studies of von Frey (1897). Pain research using principles of psychophysics determines relations between an experimental stimulus and the perception of the stimulus (Handwerker & Kobal, 1993).

The validity of four pain intensity rating scales in 127 healthy participants was assessed using the cold-pressor test (Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011). Numerical rating, VAS, verbal rating, and faces pain scales were assessed using correlation and mixed-design repeated measures. The findings provide strong support for validity of all four scales. Moreover, the numerical rating scale was shown to be the most responsive followed by the VAS. These results are consistent with previous findings showing that the VAS and numerical rating scales are most
responsive, due perhaps to the number and availability of response levels in these scales.

The psychophysical assessment of pain requires the collection of pain report from persons presented with experimental noxious stimuli or with clinical pain. Most of the research on human pain has assessed pain as a single sensory dimension that quantifies pain intensity. The measurement of pain intensity is performed by applying psychophysical assessments such as the pain threshold, pain tolerance, or by scaling the perception of pain magnitude.

### 2.8.2 Pain threshold

A central concept in psychophysics is that of the sensory threshold. In pain psychophysics, several types of thresholds have been employed including pain threshold and pain tolerance. Pain threshold is defined as the minimum amount of experimental stimulation that reliably evokes a report of pain (Gracely, 1999b). The pain threshold is evoked by a stimulus and is not at a level which induces suffering. Noxious stimulation at or near threshold produces minimal aversive reactions and are well tolerated. The pain threshold is expressed in physical units of stimulus intensity or time of pain onset.

The threshold for pain requires a judgment about the emergence of pain sensation following the delivery of an experimental stimulus. In pain measurement research, this presents the semantic problem of whether a faint burning or stinging sensation is painful or not (Mumford & Bowsher, 1976). This can manifest as pain response either
being sooner or later, lower or higher to a given stimulus intensity. Hence the pain threshold is not a discrete event but a probability function (Gracely, 1999b).

The subjective criteria used to determine pain onset varies between and within individuals. While experimental pain induction methods have been shown to provide scientifically acceptable reliability, the repeatability differs with the type of noxious stimulus and the methodological procedure. The measurement of pain threshold using cutaneous electrical stimulation has been demonstrated to have the highest reliability with a coefficient of $\leq 0.95$ for immediate test-retest and $\geq 0.85$ for between-sessions (Wolff, 1983). In 28 healthy males and females, no significant differences in pain threshold were observed.

The methodology for determining the pain threshold has included procedures such as the Method of limits, Method of adjustment and the Method of constant stimuli. The Method of limits requires the delivery of single stimulus events in ascending or descending order (Gracely, 1999b). The stimulus intensity is either increased or decreased in small steps until the stimulus is perceived as painful. The participant indicates by verbal response or pressing a button when the stimulus intensity is painful. In the Method of adjustment, the subject regulates the stimulus intensity until pain threshold is determined. The Method of constant stimuli requires the presentation of a set of fixed stimuli in a random sequence.

An alternative psychophysical approach to measuring thresholds is provided by Sensory decision theory. This theory was introduced in sensory threshold research to distinguish weak signals from a noisy background (Green & Swets, 1966). In pain research, Sensory decision theory is used to quantify the capacity to discriminate...
between different levels of repeatedly applied stimuli. In Sensory decision theory analysis, two parameters are derived which represent the ratio of the probabilities of the responses under different stimulus intensities. One parameter represents the pure discriminative aspect or the sensory acuity of the pain stimulus. The second parameter is the report criterion. This is recognised as a measure of the response bias, associated with the non-sensory components of pain (Clark & Yang, 1983). Sensory decision theory advanced the understanding of non-sensory decision factors contributing to pain response.

In pain threshold research, the application of Sensory decision theory does present problems arising from the plasticity of pain. The many stimulus repetitions required in Sensory decision theory can alter the stability of the pain response (Butler & Finn, 2009). A repeated administration of acute experimental noxious episodes launches pain-inhibitory systems (Hollins, Harper, & Maixner, 2011) and this can confound results for intervention trials.

2.8.3 Pain tolerance

Pain tolerance is defined as the time that a continuous stimulus is endured, or the maximally tolerated stimulus intensity (Gracely, 1999b). For example, in one study participants were required to verbally indicate when the maximum surface pressure on the mid-tibia was attained during 5 s increments (Bartholomew, et al., 1996). The pain tolerance was presented as the maximum pressure in mmHg. As in pain threshold measurement, the assessment of pain tolerance is confounded by response bias. Investigations on pain tolerance research are less common than pain threshold measurements. The measurement of pain tolerance presents components
of pain that reflect motivational and cognitive dimensions (Melzack, 1985). The tolerance of a painful stimulus has been shown to be related to a separate endurance factor which is not associated with sensory intensity (Wolff, 1971). In several experiments on pain tolerance, a ceiling tolerance limit is required due to the potential for tissue damage or injury (Bartholomew, et al., 1996).

### 2.8.4 Dual and multi-dimensional pain scales

Pain is recognised as a somatic sensation and a powerful feeling state that has affective and reactive components (Wall, 1979). Pain reporting instruments have been developed to assess the breadth of the pain experience through dual or multi-dimensional scales. Uni-dimensional measures of pain assess the intensity of pain sensation. Dual and multiple dimensional pain scales capture the non-sensory components of pain (Gracely, 1999b). Pain studies using dual component pain assessment require separate scales for the sensory intensity and ‘hedonic’ scales of pleasantness-unpleasantness. Multi-dimensional pain scales emphasise the differences between pain components by distinguishing the features which separate various pain conditions.

The non-sensory components of pain are depicted as the affective, evaluative, reactive, and the emotional components. The number and structure of the non-sensory pain components has not been firmly established. Pain research using dual measures of pain have revealed non-parallel changes in the pain components (Gracely, McGrath, & Dubner, 1978). Manipulation of the internal state such as during conditions of elevated core temperature (Mower, 1976) has been shown to
modify the affective component of pain without altering judgments of sensory intensity.

In one study, a multi-dimensional scaling analysis was performed on the distinctiveness of the sensory, emotional, and motivational dimensions of pain (Clark, Janal, Hoben, & Carroll, 2001). Correlations were demonstrated between psychological tests and noxious stimulation. The results from 41 male participants show that pain is heavily influenced by the individual’s emotional and motivational state.

2.8.5 Magill pain questionnaire

Pain is comprised of a variety of qualities such as deep or superficial, pricking or dull, burning or aching. The breadth of the pain experience is captured by multi-dimensional scales. The Magill pain questionnaire (MPQ) is the most widely used multi-dimensional instrument. This instrument is comprised of 78 pain descriptors classified into 20 categories (Melzack, 1975). The MPQ assesses multi-dimensional components of pain that comprises an Affective, Sensory, Evaluative, and a Total pain score. Examples of word descriptors for Affective, Sensory, and Evaluative pain components include ‘tiring’, ‘sharp’, and ‘miserable’, respectively. The MPQ has been applied in both experimental and clinical pain contexts. A substantial body of literature shows strong evidence for the construct validity and reliability of the instrument (Melzack, 2005).

The MPQ has also been shown to differentiate between various chronic pain disorders (Dubuisson & Melzack, 1976). Here the MPQ was administered to 95
patients with one of eight known chronic pain disorders. The results showed that the instrument was able to correctly classify the different pain conditions in 77% of cases. In another study, the MPQ was administered to 138 patients who felt pain immediately after an injury or when pain emerged after a delay period (Melzack, et al., 1982). The results revealed a normal distribution of sensory pain scores, however, in chronic pain patients the affective pain scores from the injury were elevated compared to patients without chronic pain.

In exercise and chronic pain research, the MPQ has been applied to assess the efficacy of exercise intervention on clinical pain outcomes in 132 participants with chronic pain fibromyalgia (Richards & Scott, 2002). The results showed that the exercise group had greater reductions in the MPQ scores compared to the non-exercising relaxation group following three months of exercise intervention.

### 2.8.6 Pain and lifestyle impact questionnaires

Persistent pain has previously been associated with a reduced functional capacity (Mannerkorpi, et al., 1999). The impact of chronic pain on lifestyle and activities of daily living is assessed by instruments such as the Fibromyalgia impact questionnaire (FIQ). The FIQ is applied in chronic pain research to assess the overall impact of pain on lifestyle, function, and disability (Bennett, 2005). Measures within the FIQ include a Total score, Physical impairment, and Fatigue scores. The FIQ has been extensively used in chronic pain research and has shown to have credible construct validity, reliable test-retest characteristics, and a good sensitivity in demonstrating therapeutic change. In exercise and chronic pain research, the FIQ has been applied to assess the efficacy of exercise intervention amongst chronic
pain participants (Gowans, deHueck, Voss, Silaj, & Abbey, 2004). In this study, 30 subjects with chronic pain were assigned to an aerobic exercise intervention programme. The results showed improvements in FIQ scores at 6 and 12 months following aerobic exercise intervention.

2.8.7 Behavioural measures of pain

The assessment of non-verbal pain responses requires the measurement of physiological or behavioural correlates of pain. Concerns about the reliability and validity of verbal pain reporting methods have stimulated the development of 'objective pain measurement' techniques that involve non-verbal assessments. However, non-verbal pain assessment techniques are also problematic in that they lack the face validity of verbal report (Gracely, 1999b). Moreover, non-verbal pain assessments are often compared with verbal report to establish the concurrent validity.

Pain is typically defined by its subjective sensory qualities, however, it can also be understood by the behavioural responses that are elicited. In animal models, this includes the motivation to escape, terminate, or avoid tissue-damaging processes (Baliki, Geha, Fields, & Apkarian, 2010). A painful stimulus often elicits stereotypical behaviours. The assessment of pain behaviour has been employed to determine the magnitude of stimulus-evoked pain sensation. Pain reaction time is the latency between pain stimulus onset and movement. The latency to pain stimuli has been shown to be related to stimulus intensity (Kenshalo, Anton, & Dubner, 1989). Here, four participants were presented with different increasing heat intensity stimuli. The results show that the reaction time to pain was best fitted by a logarithmic function.
Facial expression has been shown to correlate with physical effort during fatiguing eccentric exercise (de Morree & Marcora, 2010) and in constant-load cycling (de Morree & Marcora, 2012). Studies of facial and pain expressions from photographs have been employed to assess pain in chronic pain disorder such as low back pain (Keefe & Block, 1982). Facial expressive behaviour during experimental stimuli have also been shown to determine pain magnitude (LeResche, 1982). In the absence of verbal report, it has been suggested that facial expression accompanying pain could serve as an accurate measure of pain (LeResche & Dworkin, 1984). Using experimental pain procedures in 41 participants, facial expression was shown to reveal consistent non-verbal responses included brow lowering, tightening and closing of eye lids, nose wrinkling, and upper lip raising (Prkachin, 1992). These findings indicate that facial actions could be reliably applied to assess pain intensity. The Faces pain scale has been shown to be appropriate for use in assessing acute pain in children from age four or five onward (Hicks, von Baeyer, Spafford, van Korlaar, & Goodenough, 2001).

2.8.8 Neurophysiological correlates of pain

Several studies on pain measurement have investigated the association between pain and autonomic responses. Pain measurement research has evaluated the efficacy of autonomic responses in assessing pain intensity using experimental stimuli. Studies on autonomic responses include measures such as heart rate, skin conductance, and temperature. These autonomic responses are responsive to pain, however, they show association and dissociation with pain intensity (Bromm & Scharein, 1982). In a review on autonomic nervous system responses to painful
stimulation, it was concluded that no single autonomic response measure can provide an infallible indicator of pain (Hilgard & Morgan, 1975).

As the basic vehicle of pain is the neuronal system, neurophysiological techniques have been developed or adapted for the evaluation of pain in human subjects and patients (Bromm & Lorenz, 1998). The majority of physiological measures of pain have examined the neurophysiological correlates of pain. Several techniques have been developed to capture activity in peripheral nociceptive fibers and in central pain networks. These include microneurography, reflexes, evoked potentials, and brain imaging procedures.

2.8.9 Microneurography of nociceptor activity

Neurophysiological recording techniques such as microneurography provide a means of recording the activity of nociceptive fibers. This procedure also offers the opportunity to directly correlate neural activity evoked by experimental stimuli, with the subjects’ verbal reports of the sensation (Torebjork, LaMotte, & Robinson, 1984). Microstimulation of nociceptive fibers has been shown to elicit burning pain or sharp pain in accordance with the type of fiber stimulated (Konietzny, Perl, Trevino, Light, & Hensel, 1981). In this study, different populations of cutaneous afferents were electrostimulated in four participants. The afferents were separated based on conduction velocity. These results show a functional specificity of peripheral nerve fiber terminals that underlies the different sensory modalities.

Studies employing microneurography recordings have investigated the relationship between the loss of sensory modalities and progressive nerve blockade. During
selective pressure blockade of myelinated fibers there is a loss of cold sensation (Yarnitsky & Ochoa, 1990). During this stage, low temperatures at 6 °C produce a burning sensation which is attributed to a release of cold nociceptor input. Also pinprick stimuli have been shown to lose their sharp character when all A-fibers are blocked, however, the sense of warmth and burning pain remained as long as the C-fibers were conducting (Mackenzie, Burke, Skuse, & Lethlean, 1975). These results affirm the functional differences between fibers in eliciting pain sensations.

Microneurography has been applied to assess the conduction of cutaneous C-fibers (Serra, Campero, Ochoa, & Bostock, 1999). The results revealed three sub-classes of C-fibers are differentiated by the responses to non-noxious cold and electrical stimulation. Additionally, microneurography is the only technique available for recording spontaneous nociceptive activity such as in diseased peripheral nociceptors. It has been shown that in microneurographic recordings from patients with neuropathic pain are characterised by much greater than normal spontaneous C-fiber nerve activity (Serra et al., 2012). In these studies, it is important to match the groups by age. During a nerve a block, it has been demonstrated that elderly adults rely on C-fiber input whereas younger adults rely on additional A-fiber input when reporting pain (Chakour, Gibson, Bradbeer, & Helme, 1996).

2.8.10 Nociceptive reflexes

At the beginning of the 20th century, Sherrington observed that painful electrical stimulation of the limb in experimental animals produced a withdrawal reflex and defined this as the nociceptive flexion reflex (Sherrington, 1910). The first human
study was published in 1960 (Kugelberg, Eklund, & Grimby, 1960) and was based on
the use of electrical stimuli and electromyographic responses.

The nociceptive flexion reflex, also known as the RIII reflex or nociceptive withdrawal
reflex (NWR), is a polysynaptic withdrawal reflex that emerges in response to painful
stimulation of nociceptive fibers (Sandrini et al., 2005). This procedure has been
shown to elicit relatively stable, stimulus-induced, physiological responses
(Skljarevski & Ramadan, 2002). The NWR is typically evoked by transcutaneous or
percutaneous electrostimulation of the sural nerve in humans. The electromyographic
response of the biceps femoris muscle during sural nerve electrostimulation reveals a
biphasic wave with a latency of 90-150 ms from stimulus onset (Willer, Boureau, &
Albe-Fessard, 1979).

Substantial evidence has accumulated supporting the nociceptive withdrawal reflex
as a relatively objective pain-measuring tool (Skljarevski & Ramadan, 2002). The
intensity of electro-stimulation required to elicit the nociceptive flexion reflex is used
as an objective measure of the sensitivity of the nociceptive system. Previous
research has shown that the nociceptive withdrawal reflex threshold is highly
correlated with the pain threshold under standardised resting conditions (Dowman,
1993; Willer, 1977). In 14 healthy participants, the coefficient of determination
between pain threshold and the nociceptive withdrawal reflex was .93 (Micalos,
Drinkwater, Cannon, Arendt-Nielsen, & Marino, 2009). Therefore, the NWR threshold
accounts for 93% of the variance in the electrocutaneous pain threshold.

In a review study, it has been indicated that the NWR might constitute a tool to
investigate pain processing at spinal and supraspinal levels under pharmacological
and pathological pain conditions (Sandrini, et al., 2005). The responsiveness of the nociceptive withdrawal reflex has been used as an indirect measure of supraspinal modulation of nociceptive transmission (French, France, France, & Arnott, 2005).

In exercise and pain research, the NWR has been applied to investigate exercise-induced pain inhibition (Guieu, et al., 1992). The nociceptive withdrawal reflex was assessed before and after aerobic cycling exercise in six healthy participants. The results show an increase in the threshold for the nociceptive withdrawal reflex following aerobic exercise. This suggests that exercise attenuates pain within the spinal cord. Further research is required to elucidate the supraspinal transmission of nociceptive signals following exercise.

The NWR has been indicated as a measure of central hyper-excitability in persons with chronic pain. In 22 patients with chronic pain fibromyalgia and 27 patients with chronic neck whiplash pain, a significantly lower nociceptive withdrawal reflex threshold was observed in both groups compared to healthy controls (N=29), (Banic et al., 2004). It has been suggested that central hyper-excitability may, in part, explain the underlying mechanisms for various chronic pain disorders (Lim, et al., 2011). Potentially, the NWR threshold provides a tool for assessing central hyper-excitability in chronic pain disorder.

The threshold for the nociceptive withdrawal reflex has been shown to be lower in persons with chronic tension-type headache compared to healthy controls (Langemark, Bach, Jensen, & Olesen, 1993). In contrast, no difference in NWR threshold was observed between 53 chronic pain and 17 pain-free control participants (Boureau, Luu, & Doubrere, 1991). Moreover, the study also indicated
that there was no correlation between the NWR threshold and clinical pain scores. In a recent study, however, a generalised expansion of nociceptive fields and reduced threshold has been observed in 20 chronic pain patients (Neziri, Haesler, et al., 2010). Together, these results indicate that the nociceptive withdrawal reflex constitutes an important research tool for investigating pain processing in healthy participants and in chronic pain disorder.

### 2.8.11 Cerebral evoked potentials to experimental noxious stimuli

The delivery of a controlled noxious stimulus has been shown to elicit a synchronised response in the electroencephalogram (EEG), (Treede, Kief, Holzer, & Bromm, 1988). The evoked response reveals a waveform that is characterised by the amplitude and latency of the component peaks known as somatosensory evoked potentials (SEPs), cerebral event related potentials (CEPs), or cortical evoked potentials (Gracely, 2006). Brief somatosensory evoked potentials from noxious stimulation produces a biphasic potential consisting of a peak late negative (N) at 120 ms and a positive (P) at 230 ms, with a maximum at the vertex (Bromm & Lorenz, 1998). The early components of the waveform have been associated with the sensory intensity. Later components of the evoked potentials have been associated with the perceptual processing of the pain stimulus (Bromm & Scharein, 1982).

The characteristics of the CEPs were shown to be dependent on the type of stimulus, laser or electrotaneous, and were influenced by preceding A-fiber input (Mouraux & Plaghki, 2007). Blocking the activation of the faster Aβ nociceptor fibers has been shown to result in C-fiber latencies of 750-1150 ms when stimulating the hand dorsum with heat laser stimuli (Magerl, Ali, Ellrich, Meyer, & Treede, 1999). This has
led to the premise that Aδ nociceptive input may inhibit cortical processes associated with C-fiber input (Plaghki & Mouraux, 2002).

Measures of cortical activity evoked by brief electrical or laser stimuli include both the amplitude and latency of prominent positive and negative peaks. The SEP components are correlated with the magnitude of subjective pain reports (Chudler & Dong, 1983; Kanda et al., 2002; Svensson, Beydoun, Morrow, & Casey, 1997). During experimental pain intervention procedure such as pharmacological and non-pharmacological treatments, the amplitude of the cortical evoked potentials has corresponded with the extent of pain inhibition. The amplitude of the late SEP components and pain ratings were investigated following the administration of opioid based compounds (Bromm, Ganzel, Herrmann, Meier, & Scharein, 1987). Here, 80 intracutaneous electrical stimuli were delivered at 200% and 300% above pain threshold before and after treatment. The results show a significant and parallel reduction in pain ratings and SEP components.

The association between cortical evoked potentials and pain report has not been evident under all experimental conditions (Lorenz & Garcia-Larrea, 2003). Evoked potentials are influenced by arousal, attention, movement, stimulus parameters, and sedatives. Passive and active movement (N=17) has been shown to attenuate evoked potentials without changing verbal report (Kakigi, Matsuda, & Kuroda, 1993). The dissociation between cortical evoked potentials and pain report has been attributed to differences in the processing of the affective components of pain (Gracely, 1999b).
Observations of the relationship between the intensity of pain perception and magnitude of laser evoked potentials has led to the notion that these responses are a direct correlate of the neural activity responsible for coding pain intensity in the cortex. In contrast, recent evidence shows that the responses observed in the EEG are not determined by the perception of pain, but mainly by the saliency of the nociceptive stimulus (Iannetti, et al., 2008). Laser evoked potentials have been applied in pain research due to the preferential recruitment of nociceptive specific afferents. In contrast, somatosensory evoked potentials are thought to be generated by both non-nociceptive and nociceptive afferents. Recent evidence (N=9) shows that the laser evoked potentials do not reflect nociceptive-specific neural activity (Mouraux & Iannetti, 2009). Instead, the laser evoked potentials were explained by a combination of multimodal neural activities that were somatosensory-specific, but not nociceptive-specific. The subjective pain ratings correlated with the saliency of the stimulus, suggesting that these responses are more involved with arousal and attentional reorientation.

Brain potentials elicited by brief noxious stimulation have been shown to be abnormal in chronic pain patients. Cortical evoked-potentials to brief stimuli revealed higher amplitudes in 10 chronic pain participants compared to 10 pain-free age-matched controls (Lorenz, Grasedyck, & Bromm, 1996). Changes in EEG power spectra were observed to occur earlier in chronic pain patients compared to healthy controls during a cold-pressure test (Stevens, Batra, Bartels, & Schwarz, 2000). Although there are limited data, the available evidence suggests abnormal EEG patterns during noxious stimulation in chronic pain participants. This suggests that chronic pain may be associated with dysfunctional processing of pain signalling.
2.8.12 Brain imaging of pain

Advances in technology allow for the non-invasive imaging of brain activity. Brain imaging procedures such as positron emission tomography (PET) and functional magnetic resonance imaging (Garcia-Larrea et al., 2000; Peyron, Laurent, & Garcia-Larrea, 2000) offer spatial information of pain processing. Other methods include the measurement of changes in regional cerebral blood flow using single-photon emission tomography, spectroscopy, and echo planar imaging (EPI). Imaging of pain processing in the brain has predominantly been performed by PET and functional magnetic resonance imaging (fMRI) methods.

Local changes in cerebral blood flow in response to experimental stimuli have been detected by fMRI. These images offer greater acuity over PET scanning. The method requires evoking changes in brain neuronal activity, typically by an external noxious stimulus or by provoking a clinical symptom. Procedures for fMRI infer neuronal activity by the changes in regional cerebral blood flow. The most common method of fMRI is by blood oxygen level-dependent (BOLD) imaging. Levels of oxygen in blood provide a signal since oxygenated haemoglobin has different magnetic properties compared to deoxygenated blood (Gracely, 1999a; Pauling & Coryell, 1936). The BOLD signal indirectly measures neuronal activity by the coupling with the haemodynamic response (Jezzard, Matthews, & Smith, 2001). The exact nature of this coupling remains largely unknown (Arthurs & Boniface, 2002). Previous research indicates a predominantly linear correlation between the haemodynamic response and neuronal activity (Heeger, Huk, Geisler, & Albrecht, 2000), although this was not found in all animal experiments (Ances, Zarahn, Greenberg, & Detre, 2000).
Details underlying the process between neuronal activity and metabolic demand are only partially understood. The emerging haemodynamic response model posits that the increase in neuronal activity results in a decrease in oxyhaemoglobin and increase in deoxyhaemoglobin concentration due to demand for oxygen (Fox, Raichle, Mintun, & Dence, 1988). After a delay of approximately 2 s there is a large increase in local blood flow which provides glucose for synaptic consumption. This overcompensates for the amount of oxygen being extracted so that an oversupply of oxygenated blood is delivered (Heeger & Ress, 2002). Astrocytes surrounding synapses and capillaries have an important role in neurotransmitter recycling since they also rely on glucose metabolism. Here, it has been proposed that changes in local blood flow are due to demand for glucose by astrocytes, regardless of the blood oxygenation. A subthreshold activity may be reflected in the fMRI signal which is not part of neuronal firing and this may confound the data.

An alternative view is that the local blood flow responses serve to deliver oxygen to the neurons (Heeger & Ress, 2002). This view is supported by evidence showing that only a small percentage of energy is used by astrocytes (Attwell & Laughlin, 2001). Instead, it is proposed local blood flow changes trigger metabolic by-products of neuronal activity such as nitric oxide or from within blood vessels, as shown by the initial dip in blood oxygenation. Another possibility is that the enhanced blood flow is triggered by a combination of astrocyte, neuronal, and blood vessel by-products from elevated metabolism.

The various possible measurements of neuronal activity may also influence the predictive capacity of fMRI. For instance, the relationship between the average firing rate of neuronal sub-populations, the current source density, and synchronous
spiking activity has not been fully detailed. Most fMRI studies infer the underlying neuronal activity based on the fMRI response. In a compelling study showing a quantitative link between fMRI and neuronal responses, fMRI responses in human primary visual cortex were plotted against firing rates in monkey primary visual cortex (Rees, Friston, & Koch, 2000). When these results are plotted together, as illustrated in Figure 2.4, a proportional relationship between fMRI response and average neuronal firing rate is demonstrated.

Typically a block-design paradigm is used in fMRI procedures to compare brain responses between a stimulus ‘on’ period with a non-stimulus ‘off’ period. The time-frame for the ‘on’ and ‘off’ epoch is about 30 s to ensure that activations of interest and physiological noise are minimised (Ingvar & Hsieh, 1999). The stimulus ‘on’ and ‘off’ epoch has differed between studies. In one study, a 4 kg/cm\(^2\) mechanical pressure ‘on’ period over the thumb was applied for nine seconds and the ‘off’ period was 21 s in nine chronic pain and nine healthy control participants (Pujol, et al., 2009). In another study the ‘on’ and ‘off’ period was alternated at 25 s with a blunt mechanical stimulus that was repeated over 12 intervals (Gracely et al., 2004).

A large number of brain imaging studies have been conducted to assess supraspinal processing of experimental pain stimuli. Brief heat, electrocutaneous, laser, and somatic mechanical pressure stimuli have been shown to reliably activate a network of brain structures. Due to the complexity of pain, a widely distributed network of brain structures are shown to be activate during experimental pain stimulation (Bushnell & Apkarian, 2006; Derbyshire et al., 1997).
A pain “neuromatrix” was described by Melzack (1999) and has been termed the “pain matrix” (Tracey & Johns, 2010; Tracey & Mantyh, 2007) to refer to the common brain regions that are active during acute pain experiences. Based on meta-analysis of human data, these areas include primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices as well as the thalamus (Apkarian, et al., 2005). These regions are depicted in Figure 2.5. Depending on the circumstances, other regions involved in the experience of pain include the basal ganglia, cerebellum, amygdala, hippocampus, and areas within the parietal and temporal cortices. None of these activation sites are unique to pain, however, when activated collectively, they result in the sensory, emotional, cognitive, and motivational perception of pain (Tracey & Johns, 2010).
Figure 2.4: Functional MRI responses (% contrast) in human primary visual cortex (● mean, error bars ± standard error mean) plotted against average neural firing rates in monkey primary visual cortex (line).

Adapted from Heeger et al (2000)
The network of brain sites comprising the pain matrix, however, is not unequivocally defined. Other brain regions may be recruited to attenuate or exacerbate the pain experience depending on contextual, cognitive, and emotional factors (Tracey & Mantyh, 2007). The core neuroanatomical components of the pain matrix, however, can be thought of as having a lateral (sensory-discriminatory) and a medial (affective-cognitive-evaluative) division (Albe-Fessar, et al., 1985). The medial pain system has been shown to react to pain in parallel with neuroendocrine systems and result in affective pain responses through activation in bilateral perigenual cingulate and orbitofrontal cortices, contralateral (right) amygdala, ipsilateral (left) hypothalamus, posterior insula, motor cortex, and the frontal pole (Kulkarni et al., 2005). In contrast, the lateral pain system is mainly associated with the localisation of pain through activation in the contralateral (right) primary somatosensory and inferior parietal cortices. These results tend to suggest a clear division of function within the neural pain matrix.

Experimental pain intensity has been shown to be encoded throughout the pain matrix (Derbyshire, et al., 1997). Anatomical and physiological evidence shows that distinct cortical regions are involved in the sensory and affective components of pain. In contrast, it has been shown that components of the affective medial pain system (N=10, healthy subjects), such as the anterior cingulate cortex, are also contributing to the sensory aspects of the pain experience (Hofbauer, et al., 2001). Individuals grouped as highly pain-sensitive exhibit more frequent and more robust pain-induced activation of the primary somatosensory cortex, anterior cingulate cortex, and prefrontal cortex compared to the insensitive individuals (Coghill, McHaffie, & Yen, 2003). Here, as pain becomes more intense then it also becomes more unpleasant.
Anatomical connections between anterior cingulate cortex, insula cortex, and somatosensory cortices indicate that these regions are highly interactive when encoding pain (Friedman, et al., 1986). Brain imaging was performed to assess non-pharmacological pain control strategies such as suggestion on the perception of unpleasantness of tonic heat stimuli across 11 sessions (Rainville, Duncan, Price, Carrier, & Bushnell, 1997). The results demonstrate a corresponding increase or decrease in affective pain response through activation of the anterior cingulate cortex. An absence of change in the sensory component of pain perception argues for a significant involvement of the affective component in the anterior cingulate cortex. This suggests that there is at least a partial segregation between affect and sensation, with the anterior cingulate cortex showing more activity with the emotional experience.

An investigation was performed using fMRI to explore the central mechanisms during the ‘psychophysical plateau’ following temporal summation of noxious contact cutaneous heat stimulation in ten healthy participants (Tran, Wang, Tandon, Hernandez-Garcia, & Casey, 2010). During the protocol, the heat stimulus was perceived as being increasingly painful from five to ten seconds, revealing temporal summation. The increasing perceptual response, however, reaches a plateau as the stimulus duration increases from 10-20 seconds. It has been suggested that peripheral or central mechanisms, or a combination of both mediate the perception of pain to elicit a psychophysical plateau during the period. Results from the study show a recruitment of thalamocortical circuits that participate in the modulation of pain-related cortical responses and the temporal summation of heat pain.
An fMRI analysis was performed on a Yoga master who claims not to feel pain during meditation (Kakigi, et al., 2005). The results show that during meditation, activity levels in the secondary somatosensory-insula cortex and cingulate cortex were slightly increased but did not reach levels of significance. Interestingly, activity in the thalamus was decreased, although did not reach levels of significance. The study concluded that changes in thalamic activity, possibly by modulation below the thalamus or at the cerebral cortex and cingulate cortex, may be responsible for the reduced pain perception during meditation.

In summary, an array of method's are applied in research to measure the pain experience. Since pain is a multidimensional experience, then several methods have been developed to assess the sensory, emotional, and cognitive components. The visual analogue scale and category scales for pain remain the most widely used in clinical and experimental settings. However, these are often limited to the unidimensional assessment of pain intensity. Multidimensional pain scales and lifestyle impact questionnaires offer the ability to capture the breadth of the pain experience in the experimental context and in chronic pain disorder. Additionally, appraisal of the function of the neural system in pain processing has the potential to further elucidate the dispensation of pain signals. As follows, the function of the afferent pathway, spinal cord, and the supraspinal processing of pain signals can be assessed by techniques such as microneurography, nociceptive reflexes, and cerebral evoked potentials.
Figure 2.5: Major brain regions active during a painful experience, highlighted as bilaterally active, with increased activation in the contralateral hemisphere (orange).
Adapted from Tracey & Mantyh (2007)
2.9 Chronic pain pathophysiology and neurosensory characteristics

Chronic pain is apparent when pain continues long after the immediate, or acute, pain-causing stimulus has receded. It can follow surgery or injury, and is associated with rheumatoid arthritis and cancer. Three months is the most common point of division from acute to chronic pain, however, six months may be preferred in research settings (Merskey & Bogduk, 1994). Typically, inflammation from acute injury such as a laceration, or incision will heal with the union of separated tissues, however, a longer period of healing is required for peripheral nerves to grow back after trauma. Chronic pain is recognised when repair processes have ended and pain persists (Turk & Okifuji, 2001).

Chronic pain is a heterogenous group of clinical conditions that are aetiologically diverse. The most prevalent type of persistent pain is musculoskeletal in nature, including low back pain and arthritis (Glickman-Simon, 2006). Other common chronic pains include diabetic neuropathy, headache syndromes, and spinal stenosis. It is also recognised that in many chronic pain syndromes, normal healing is not apparent. In conditions such as rheumatoid arthritis, osteoarthritis, and spinal stenosis, the repair processes do not take place. In persistent migraine, there is remission or healing and is followed by a recurrence. In these conditions, chronic pain stems from recurring inflammation, autoimmune disorder, and/or a failure for tissues to properly heal.
2.9.1 Nociceptive pain

Chronic pain conditions are grouped as nociceptive, neuropathic, visceral, ischemic, or a combination of aetiologies (Brookoff, 2000). Nociceptive pain is associated with the activity of nociceptors. Persistent pain from nociceptive activity arises from ongoing or recurring inflammation such as in conditions of arthritis, cancer, or spinal cord tumors. Nociceptive pain can be somatic or visceral and responds to treatment with opioids and non-steroidal anti-inflammatory drugs (Katz & Barkin, 2010).

Somatic nociceptive pain is described as being sharp, shooting, throbbing, burning, stinging, or cutting that arises from conditions such as arthritis, bony metastases of cancer, or surgery (Bryant & Knights, 2011).

2.9.2 Ischemic pain

Chronic ischemic pain is a leading cause of pain in the lower extremities due to insufficient blood supply. This type of pain is neither typically visible nor felt at the source. Ischemic diseases resulting in chronic pain are often caused by arteriosclerosis due to hypertension or diabetes (Devulder et al., 2011). Ischemic pain has been shown to comprise of neuropathic or nociceptive components, depending on whether there is critical limb ischemia or claudication (Rüger et al., 2008).

The perception of experimentally induced ischemic pain has been shown to be mediated by mental health status including major depression and adjustment disorder (Boettger & Bär, 2007). Here, 15 patients with depression were assessed
with experimental ischaemic pain. The results showed that depressive symptomatology alters pain sensitivity.

### 2.9.3 Visceral pain

Visceral pain stems from nociceptive or inflammatory activity or a combination of both in organ tissue (Paine, Kishor, Worthen, Gregory, & Aziz, 2009). Visceral pain is commonly diffuse in character and poorly localised (Gebhart & Bielfeldt, 2009). This type of pain is the most common produced by disease. The neurological mechanisms and the perception of visceral pain differ from somatic pain (Cervero & Laird, 1999). In addition, the mechanisms for visceral pain differ between organs and organ systems.

### 2.9.4 Neuropathic pain

Neuropathic or neurogenic pain can arise from abnormal nerve activity either in the periphery, central nervous system, or in the central nervous system after peripheral injury. A recent definition posits that neuropathic pain arises from a direct consequence of a lesion or disease affecting the somatosensory system (Treede et al., 2008). Damage to sensory neurons manifests as spontaneous pain, stimulus-independent, or pain hypersensitivity (Woolf & Mannion, 1999). This results in hyperalgesia, whereby there is an increased pain response. Additionally there is the presence of allodynia, whereby the sensation of pain is elicited by a non-noxious stimulus. Chronic pain from neuropathic sources corresponds to pain resulting from trauma and many other sources including diabetes, HIV infection, and stroke (Knotkova, Cruciani, Tronnier, & Rasche, 2012). In phantom limb pain, research and
Lesions in peripheral nerve, spinal cord, brainstem, thalamus, lenticular, and cerebral cortex have been associated with neuropathic pain (Peyron et al., 2004). Symptoms of neuropathic pain include deep tissue hyperalgesia, burning, and prickling. A proportion of these individuals develop chronic neuropathic pain. The impairment of discriminative sensations including tactile, thermal, kinesthetic, and nociceptive results in ‘deafferentiation pain’ where pain is experienced in the region where the other sensation was felt (Albe-Fessar, et al., 1985). This type of pain does not respond to opiate drugs or anti-inflammatory agents and is far more difficult to treat compared to nociceptive pain.

The development of chronic pain in painful neuropathy is associated with incomplete peripheral nerve regeneration following nerve injury (Taylor, Anastakis, & Davis, 2010). Neuropathic pain is mediated by peripheral nerve impairment (Landerholm & Hansson, 2011) and concurs with functional changes in the central nervous system (Hsieh, Belfrage, Stone-Elander, Hansson, & Ingvar, 1995; Moisset & Bouhassira, 2007; Peyron, et al., 2004). Here, it has been shown that firing of C-nociceptors as based on the occurrence of multiple spiking and spontaneous activity, was observed in nine neuropathic pain patients during microneurographic recording (Schmidt et al., 2012). Axonal hyperexcitability and spontaneous activity of nociceptors was observed in the neuropathic pain patients. A direct mechanistic link between multiple spiking and hyperalgesia in neuropathic pain remains to be shown.
The causes of neuropathic pain symptoms includes alterations in gene transcription, protein expression, ion-channel organisation, trophic factors, and dysregulated metabolites in the dorsal horn of the spinal cord (Patti et al., 2012). Excessive sensitivity of central neurons develops, known as central sensitisation, which outlasts the injury. These functional changes in the spinal cord in the later stages of neuropathic pain have an important role in precipitating long-term changes in pain sensitivity (Hunt & Mantyh, 2001).

In one study on chronic widespread pain (N=81), neuropathic pain symptoms corresponded with experimental pain parameters (Amris, Jespersen, & Bliddal, 2010). Neuropathic pain symptoms were associated with the presence of tender points around the body. The study concluded that assessments for neuropathic pain are a useful diagnostic tool for identifying patients with chronic widespread pain.

Available treatment options for neuropathic pain are limited and are associated with undesirable side effects. Complete therapeutic relief is rare. Pharmacological treatments for neuropathic pain, as approved by regulatory agencies, may not have efficacy in all neuropathic pain conditions (Dworkin et al., 2011). In phantom limb pain, peripheral and central neuroplastic changes contribute to pain that is largely neuropathic (Knotkova, et al., 2012). Non-pharmacological strategies for phantom limb pain may include transcranial direct current stimulation, which has shown clinical potential in some neuropathic pain syndromes (Lefaucheur, Drouot, & Nguyen, 2001). Pharmacological treatment for neuropathic pain includes tricyclic or serotonin and norepinephrine uptake inhibitors, antidepressants, and anticonvulsants which all have limited efficacy and undesirable side effects (Kingery, 1997).
2.9.5 Non-specific chronic pain

In conditions such as widespread chronic pain, fibromyalgia, and in many low back pain syndromes there is no initial primary peripheral abnormality. A common feature amongst these pain syndromes is that they show somatic symptoms without an associated medical condition (Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005). The association between physical abnormality and the individual report of chronic pain is often ambiguous and poorly correlated. In chronic low back pain, 85% of patients in primary care cannot reliably attribute a specific disease or structural abnormality to the cause of pain (Chou et al., 2007; van Tulder, Assendelft, Koes, & Bouter, 1997). Chronic back pain remains poorly understood and few treatments have been validated.

Acute back pain often resolves within three months, however, up to 15% will report persistent pain after one year (Atkinson, 2004). Most chronic low back pain patients have no definitive anatomic abnormality (Deyo & Weinstein, 2001). The mechanisms behind the pathogenesis of chronic back pain are unknown. Persistence of pain beyond the period of expected healing is proposed to result from neuronal hyperactivity, dysfunction of modulatory or inhibitory systems, and central sensitisation resulting in abnormal processing of normal afferent traffic.

The evidence for a psychogenic aetiology in the development of chronic pain in conditions such as low back pain and fibromyalgia is not substantial. It has been proposed, however, that susceptibility to chronic pain is in part due to genetically determined hyper-responsiveness to stress (van Houdenhove & Egle, 2004). This
model posits that ongoing psycho-social stress coupled with painful injury, infection, or traumatic experience leads to long-term disturbances in the stress-regulating, pain-processing, and immune systems.

Psychological factors play an important role in chronic pain (Siddall & Cousins, 2004). Persistent pain experienced without nociceptive input, sometimes referred to as psychogenic pain, is not less real than “physically” defined pain (Tracey & Mantyh, 2007). Neuroimaging studies have highlighted the physiological reality of such experiences due to the extensive neural activation that occurs (Pujol, et al., 2009). A degree of overlap exists with psychological factors in that chronic pain leads to psychological and behavioural changes, consisting of muscle guarding, abnormal movement, and disuse syndrome. Report of persistent pain, regardless of aetiology, leads to the chronic pain state, which is defined by preoccupation with pain, depression, anxiety, and disability (Long, 1999).

There is a growing body of evidence amongst chronic pain patients showing that the attentional system is biased in favour of pain-related stimuli. In a meta-analysis of 10 studies, attentional bias to pain-related stimuli in chronic pain patients was evident with a small to medium effect size of 0.36 (Schoth, Nunes, & Liossi, 2012). Currently it is uncertain as to whether this has a causal role in the maintenance of chronic pain or whether it is an epiphenomenon (Liossi, 2012).

An inability to identify a specific cause for persistent pain should not be assumed to insinuate that the pain is imaginary or non-existent. The relationship between tissue damage and pain is variable and involves a number of personal and environmental factors (Flor & Hermann, 2004). Moreover, genetic factors do not account for the
transition into chronic pain, however, is important in the large inter-individual variation in pain response amongst cause-specific pain conditions (Tegeder et al., 2006). This may help to explain why some individuals progress to persistent pain while others do not. Previous research shows that pain catastrophising and neuroticism were significantly elevated in patients that developed chronic pain (Taylor, et al., 2010). It is possible that these psychological factors act cortically to influence pain perception and the propensity to develop and maintain chronic pain.

Fibromyalgia is a chronic pain disorder characterised by diffuse widespread musculoskeletal aching and stiffness and multiple tender points (Wolfe, 2010; Wolfe, Smythe, Yunus, Bennett, et al., 1990). There are no consistent muscle abnormalities, inflammation, or neuropathic sources that would explain the pain associated with fibromyalgia. Continuing debate is suggestive that fibromyalgia is a psycho-social condition (Gordon, 2003; Hadler, 2003). Previous research shows a strong association between psychogenic seizure and a history of chronic pain or fibromyalgia (Benbadis, 2005). Alternative models posit that fibromyalgia reflects an underlying central sensitisation and abnormal pain sensitivity (Bradley, McKendree-Smith, Alarcón, & Cianfrini, 2002).

Previous studies show a strong familial aggregation of fibromyalgia and related conditions, suggesting the importance of genetic factors in the development of chronic pain disorder (Buskila, 2007). Additionally, temporal summation of pain, or wind-up, has been proposed as a potential mechanism for the maintenance of chronic pain (Staud, Price, Robinson, Mauderli, & Vierck, 2004). Accumulating research suggests that chronic pain fibromyalgia is maintained by tonic input from deep tissues such as muscle and joints in combination with central sensitisation.
mechanisms (Desmeules et al., 2003; Price & Staud, 2005). Most fibromyalgia patients attribute an acute injury, athletic injury, repetitive work related injury, or another pain state to the onset of fibromyalgia, while others may relate this to the onset of stress, infections, and toxins.

Previous functional imaging research in nine patients with chronic pain fibromyalgia show dysfunctional responses in brain regions associated with pain processing (Pujol, et al., 2009). Research on experimentally induced pain in persons with chronic pain fibromyalgia has indicated a state of central sensitisation that may be associated with abnormal sensory processing (Bennett, 1996). An alternative neurogenic model has also developed which proposes that functional dysregulation of central pain pathways may account for many of the clinical manifestations of fibromyalgia (Kwiatek et al., 2000).

2.9.6 Central changes in chronic pain

Although functional changes in pain states have been the focus of many studies and symposia, less attention has been paid to the tremendous potential for central plasticity at the structural level, connectivity, and the representation of pain. The key spinal neurotransmitter involved in the transmission of pain signals is glutamate. Two receptors for glutamate are involved in acute and chronic pain, including the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors, respectively (Katz & Barkin, 2010). In chronic pain, sustained levels of glutamate result in activation of NMDA receptors which leads to the release of pro-inflammatory molecules and the activation of other receptors that amplify the pain signal (Watkins & Jane, 2006). This hypersensitisation of the pain-sensing system can lead to
hyperalgesia and allodynia and marks the transition from acute to chronic pain (Brookoff, 2000).

The activation of NMDA receptors causes spinal neurons relaying nociceptive signals to be stimulated with less peripheral input, a phenomenon known as wind-up. Functionally, less glutamate is required to transmit the nociceptive signal and more antinociceptive input is required to inhibit nociceptive signalling (Brookoff, 2000). Endorphins and other naturally occurring pain-relievers cannot keep up with the demand and essentially lose their effectiveness. Moreover, repeated administration of opioids results in the development of tolerance and pro-nociceptive processes that contributes to a decrease in analgesic efficacy (Ballantyne & Shin, 2008).

2.9.7 Sensitisation in chronic pain disorder

Sensitisation refers to increased responsiveness of nociceptive neurons to their normal input and/or a response to normally subthreshold input (IASP, 2011). This can be observed as a decrease in threshold or as an increased supra-threshold response. Central sensitisation is a potential mechanism involved in the transition from acute to chronic widespread pain (Graven-Nielsen & Arendt-Nielsen, 2010). Tissue healing and repair is promoted by the pro-nociceptive influence of the brainstem during inflammation and injury. Tissue damage that results in long-lasting hypersensitivity serves to promote healing and protect body parts from re-injury. A continued hypersensitivity that outlasts the process of healing may become itself a disease (Bromm & Lorenz, 1998). A sustained facilitation of nociception that fails to resolve with tissue healing may be responsible for chronic pain (Porreca, Ossipov, & Gebhart, 2002). Based on this premise, the sustained activation of descending
modulatory pathways that facilitate pain transmission could underlie the transition from acute to chronic pain.

Ongoing pain signalling from prolonged pain initiates physiochemical changes in neural pain pathways. These changes cause pain pathways to be hypersensitive to pain signals. A shift in the membrane receptor profile in dorsal horn neurons of the spinal cord is the first step in hypersensitisation (Brookoff, 2000). Enhanced synaptic transmission leads to a reduction in pain threshold, an amplification of pain responses, and a spread of pain sensitivity to non-injured areas, known as central sensitisation (Ji, Kohno, Moore, & Woolf, 2003). A sensitivity to noxious and innocuous experimental stimuli is evident across a range of chronic pain disorders and may be a unifying concept (Yunus, 2007).

Peripheral sensitisation from an inflammatory response arises from tissue injury and results in an enhanced sensitivity of nociceptive fibers and cutaneous Aβ fibers. These sensitising events mediate primary hyperalgesia, resulting in a reduced threshold for pain and enhanced pain to suprathreshold stimuli (LaMotte, Thalhammer, Torebjork, & Robinson, 1982). A secondary hyperalgesia results when a prolonged afferent nociceptive input to the spinal cord causes a reversible increase in the excitability of sensory neurons in the dorsal horn of the spinal cord (Woolf & Salter, 2000). This may be responsible for the enhanced pain experience in tissues with no apparent injury and at locations beyond the site of injury in chronic pain.

Central sensitisation is characterised by increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold afferent input (Loeser & Treede, 2008). Hyperalgesia is a psychophysical term that refers to
conditions of increased pain sensitivity. As such, the definition of hyperalgesia parallels that of the physiological expression ‘sensitisation’. Persistent activation of pain pathways from ongoing pain induces physiochemical changes in neural pathways of the spinal cord that render them simultaneously hypersensitive to ongoing pain signals and resistant to intrinsic inhibitors of pain (Brookoff, 2000).

The hyper-excitability of dorsal horn neurons in central sensitisation reduces the threshold for eliciting Aδ and C-fiber pain. Aβ fibers transmit mechanical stimuli, which do not produce pain under normal conditions, however, activate the hyper-excitabile dorsal horn neurons, ultimately resulting in pain sensation known as allodynia (Coderre, Katz, Vaccarino, & Melzack, 1993; Latremoliere & Woolf, 2009). These alterations are likely to substantially contribute to persistent pain states (Curatolo, et al., 2006). In the animal model, chronic ischemic pain has been shown to induce central changes in the spinal cord and contralateral mechanical allodynia (Kwak et al., 2009).

A supraspinal contribution to central sensitisation in humans has been observed in neuroimaging research. In 15 healthy volunteers, regions showing enhanced activation following experimentally induced hypersensitisation were observed in the mesencephalic reticular formation (Lee, Zambreanu, Menon, & Tracey, 2008; Zambreanu, et al., 2005). These data suggest that activity in brainstem mesencephalic-pontine reticular formation represents a neural correlate for states of central sensitisation. A sustained activation of descending modulatory pathways that facilitate pain transmission could underlie states of chronic pain (Porreca, et al., 2002). Converging evidence indicates that some abnormal chronic pain states depend on descending facilitatory drive from supraspinal sites such as the
rostroventromedial medulla. The sustained facilitatory influence of these sites is consistent with the behavioural manifestations of chronic pain states.

2.9.8 Central neurochemical changes in chronic pain

Emerging evidence shows that supraspinal regions are associated with functional changes in the neurosensory system in chronic pain. It has been revealed that enhanced activity in the mesencephalic-pontine reticular formation during opioid withdrawal induces a central sensitisation and subsequent hyperalgesia (Wanigasekera, Lee, Rogers, Hu, & Tracey, 2011). This region is part of a descending pain modulatory system. These results suggest that in susceptible persons, central mechanisms regulate opioid induced hyperalgesia and that this might have relevance in chronic pain conditions where a peripheral origin for pain is absent.

Abnormal changes in brain neurochemistry in persons with chronic pain have been observed during ligand-based PET studies (Lee & Tracey, 2010). Previous research has revealed a decrease in central opioid (Harris et al., 2007; Jones, Watabe, Cunningham, & Jones, 2004) and dopamine (Wood, Patterson, et al., 2007) receptor sites in patients with chronic pain. These neurochemical abnormalities have been demonstrated amongst various chronic pain conditions including non-specific chronic pain. In fibromyalgia patients, reduced dopamine release from basal ganglia following an external noxious stimulus has been observed compared to healthy participants (Wood, Schweinhardt, et al., 2007). Moreover, reduced concentrations of the excitatory neurotransmitter glutamate in the contralateral insula amongst chronic pain
patients have been correlated with the extent of the experimental and clinical pain experienced (Harris et al., 2008).

2.9.9 Experimental pain assessments in chronic pain disorder

Considerable evidence is accumulating showing a sensitivity to noxious stimuli in a range of chronic pain conditions (Lim, et al., 2011). Enhanced sensitivity to noxious stimuli may contribute to a wide range of chronic pain disorders through central hyper-excitability from sustained noxious input. Direct measurements of activity in spinal cord or brain neurons cannot be performed and therefore direct evidence for neuronal hyper-excitability in persons with chronic pain is not available. Indirect assessment of hyper-excitability is performed by quantitative sensory tests (Curatolo, et al., 2006). Sensory hyper-sensitivity has been observed in various chronic pain syndromes using psychophysical (Curatolo et al., 2001; Sarlani & Greenspan, 2003; Sorensen, Graven-Nielsen, Henriksson, Bengtsson, & Arendt-Nielsen, 1998) and electrophysiological testing procedures (Banic, et al., 2004; Desmeules, et al., 2003; Neziri, Haesler, et al., 2010).

Persons with chronic pain often display a reduced threshold to experimental pain stimuli (Neziri, Haesler, et al., 2010; O'Neill, et al., 2011). These results have been observed amongst participants with chronic whiplash, fibromyalgia, low back, and temporomandibular pain. Together, these findings suggest that chronic pain is associated with a widespread hypersensitivity, possibly through central sensitisation (Costigan & Woolf, 2000; Desmeules, et al., 2003; Giesecke, et al., 2004; Graven-Nielsen & Arendt-Nielsen, 2010; Latremoliere & Woolf, 2009; Lim, et al., 2011; Neziri, Haesler, et al., 2010), or deficiencies in the pain inhibitory system (Bruehl, Chung,
Ward, & Johnson, 2004; Gebhart, 2004; Lautenbacher & Rollman, 1997; Normand et al., 2010). Functional and anatomical brain neuroimaging research supports the notion that an altered interaction of pro- and anti-nociceptive mechanisms may contribute to the development or maintenance of chronic pain states (Bingel & Tracey, 2008).

A potential mechanism for enhanced sensitivity to experimental pain stimuli is through elevated excitability in the spinal cord. The hyper-excitability involves exaggerated responses, known as wind-up, of the dorsal horn neurons. Wind-up in humans can be investigated by repeated nociceptive stimuli, known as temporal summation, whereby there is increasing pain reaction to a repeated stimulus (Arendt-Nielsen & Petersen-Felix, 1995). Several studies have observed enhanced pain responses and elevated temporal summation in chronic pain participants compared to healthy controls (Staud, Bovee, Robinson, & Price, 2008; Staud & Spaeth, 2008; Staud, Vierck, Cannon, Mauderli, & Price, 2001).

The nociceptive withdrawal reflex has been applied as a measure of spinal cord excitability and hypersensitivity in persons with chronic pain. It has been shown that in participants with chronic pain following whiplash injury and in fibromyalgia that the threshold for nociceptive withdrawal reflex is reduced compared to pain-free controls (Banic, et al., 2004). Moreover, it has been observed that there is a general expansion of nociceptive reflex fields, possibly through a widespread central hypersensitivity in chronic pain (Neziri, Haesler, et al., 2010). In one study, however, the nociceptive withdrawal reflex, pain threshold and tolerance in 53 chronic pain participants did not differ compared to 17 healthy controls (Boureau, et al., 1991). This study highlights limitations in that the groups differed in age and that the chronic
pain participants were selected based on a low drug intake. From the weight of available evidence, a central hypersensitivity is more often observed amongst chronic pain participants.

The mechanism for the development of hypersensitivity in chronic pain is likely to be from central nervous system plasticity. This potentially involves a neuroanatomical reorganisation of dorsal horn laminae of the spinal cord by the sprouting of myelinated axons from laminae III and IV into laminae II (Kohama, Ishikawa, & Kocsis, 2000; Mannion & Woolf, 2000), as observed following nerve injury in animal models. Additionally, modification of pain transmission by transcriptional changes in the profile of receptors and transmitters within the dorsal horn following nerve injury and inflammation is also proposed (Woolf & Salter, 2000). Another model posits that nerve injury appears to lead to neuronal cell death in the superficial layer of the dorsal horn (Azkue, Zimmermann, Hsieh, & Herdegen, 1998). This leads to a disinhibition of afferent signalling and precipitates a facilitation of pain transmission.

Central hypersensitivity in the spinal cord could explain exaggerated pain in the presence of minimal and undetectable tissue damage. There is a lack of diagnostic criteria for identifying the presence of central sensitisation in persons with chronic pain, however, several studies have identified this phenomenon as contributing to the pain phenotype (Woolf, 2011).

Persistent widespread pain has a negative influence on the outcome for chronic low back pain. Previous research shows that the number of tender points, a measure of widespread somatic pressure hypersensitivity, was shown to be positively associated with the intensity of low back pain (Jensen, Nielsen, & Stengaard-Pedersen, 2010). The results amongst 326 patients also revealed that chronic low back pain was more
often associated with disturbed pain regulation than disc degeneration. In addition, somatic pressure hyperalgesia was also demonstrated in 264 persons with long lasting back pain but not with recent back pain (O'Neill, et al., 2011). The study concluded that pressure pain threshold decreases as a consequence of long-lasting pain, however, this did not constitute a separate risk factor for chronic pain.

Several studies show enhanced pain sensitivity in persons with fibromyalgia (Gracely, Grant, & Giesecke, 2003; McDermid, Rollman, & McCain, 1996; Mikkelsson, et al., 1992; Sorensen, et al., 1998). The mechanism behind the enhanced pain sensitivity is not fully understood, however, perturbations of central nociceptive mechanisms have been implicated in the pathogenesis of fibromyalgia (Arroyo & Cohen, 1993). A functional deficit in the endogenous pain inhibitory system has been observed (Julien, Goffaux, Arsenault, & Marchand, 2005). Additionally, it has also been shown that a perceptual pattern of hypervigilance is one of a number of predisposing factors in the onset of fibromyalgia (McDermid, et al., 1996).

Recent evidence shows a new population of afferent C-fibers that are implicated in ongoing pain signalling in an inflammatory animal model (Seal et al., 2009). These fibers were shown to be specialised in sending signals to the central nervous system by responding to low threshold mechanical stimuli. The study revealed that they are recruited in a spinal dorsal root ganglion pain circuit, resulting in light touch becoming a painful stimulus. These neurons may be routing innocuous touch sensations to the pain pathway in chronic pain conditions.

Pain evoked brain potentials to noxious stimuli in chronic pain patients has shown to be altered compared to healthy controls. In a study on chronic pain fibromyalgia, the
sensation of pain and the associated electroencephalographic patterns were shown to appear significantly earlier compared to healthy controls (Stevens, et al., 2000). These results further corroborate the notion of dysfunctional pain processing in patients with chronic pain.

2.9.10 Brain imaging in chronic pain

Advances in imaging technology allow for the assessment of pain processing in the brain amongst participants with chronic pain. These studies have revealed structural and functional differences in the brain of persons with chronic pain. A reorganisation of the cortical body map has been demonstrated in patients with low back pain (Flor, Braun, Elbert, & Birbaumer, 1997). Additionally, decreased prefrontal and thalamic gray matter density has been shown in persons with chronic pain. The reduced gray matter volume was shown to correspond with the duration of pain in participants with chronic pain (Apkarian et al., 2004). A loss in gray matter volume suggests that chronic pain could be considered as a neurodegenerative disorder.

Based on accumulating evidence, enhanced activation in the prefrontal, frontal, and insular cortex is consistently observed across a range of chronic pain conditions (Tracey & Mantyh, 2007). Using meta-analysis techniques, clinical pain appears to be more prominent in brain regions that are located rostrally in the anterior insula compared to nociceptive pain induced in healthy participants (Schweinhardt et al., 2006). The neurodegenerative and functional changes in the brain amongst persons with chronic pain suggests an underlying central disorder across multiple chronic pain syndromes (Lee & Tracey, 2010; Tracey & Bushnell, 2009).
The influence of emotional and cognitive factors on descending pain modulatory systems in persons with chronic pain is not fully understood. Based on animal studies, connections between brainstem structures comprising descending pathways have been shown with the anterior insula (Fields, Basbaum, & Heinricher, 2006). Activity in the anterior insula has been shown to appear during pain and during states of anxiety, depression, and fear. This circuit might explain how emotions and mood influence pain perception. In a study with 16 chronic pain participants, a standard somatic pressure stimulus resulted in augmented pain processing in several regions of the brain, as shown in Figure 2.6, compared to 16 healthy controls (Gracely, Petzke, Wolf, & Clauw, 2002). Additionally, the results showed an attenuation of responses within the caudate nucleus. These augmented brain responses in the chronic pain group may lead towards understanding the consequences and causes of chronic pain syndrome. Moreover, it is not known how interventions such as exercise rehabilitation may modulate these responses in chronic pain disorder.

Elevated activity in the medial pre-frontal cortex and the rostral anterior cingulate cortex during spontaneous pain has been demonstrated in persons with chronic pain (Baliki et al., 2006). In chronic pain participants, fluctuations within the medial pre-frontal cortex and parts of the default mode network (DMN) were shown to be synchronous with changes in spontaneous pain during a pain-rating task (Baliki, Baria, & Apkarian, 2011). These results suggest that chronic pain results in abnormal patterns in the resting brain.

The DMN involves a set of brain regions that include the medial prefrontal cortex, medial temporal cortex, and posterior cingulate cortex/retrosplenial cortex (Lee & Tracey, 2010). These sites are active during the resting state and possibly reflect...
intrinsic properties of brain organisation (Raichle & Snyder, 2007). Previous research shows that chronic pain has a widespread impact on overall brain function, and is possibly associated with disruptions of the DMN. This may underlie the cognitive and behavioural impairments accompanying chronic pain (Baliki, Geha, Apkarian, & Chialvo, 2008).

Previous research shows that exercise can induce changes in brain responses. In one study on chronic low back pain, it was revealed that pain physiology education resulted in reduced brain activation in areas outside of the primary somatosensory cortex during a voluntary muscle trunk task (Moseley, 2005). These results suggest that the reduced brain activation may be due to a decrease in the threat value of the physical exercise task. Moreover, improved regional brain activation has been observed in stroke patients following exercise ambulatory activity over 6-months (Luft et al., 2008). Further studies are required to ascertain the brain adaptations with exercise rehabilitation and the chronic pain condition.
Figure 2.6: Active brain regions during functional MRI scanning between chronic pain and control participants during similar pressure stimulation. Regions in which the response is greater in chronic pain patients compared to healthy controls are highlighted by arrows and red colouration. Regions in which healthy controls are more active compared to chronic pain patients are highlighted by arrows and green colouration (top right).

Key: MFG, medial frontal gyrus; IPL, inferior parietal lobule; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; PCC, Posterior cingulate cortex; STG, superior temporal gyrus

Adapted from Gracely et al., (2002).
Previous research shows that changes in pain intensity in chronic pain participants using predictors such as pain-related fear and catastrophising were able to account for 25% of the variance (Peters, Vlaeyen, & Weber, 2005). In contrast, brain imaging in persons with chronic pain reveals a more robust relationship. Results from brain imaging shows that chronic pain is associated with altered brain neurochemistry (Grachev, Fredrickson, & Apkarian, 2000). These results are consistent with enhanced activity in the medial pre-frontal cortex activity and rostral anterior cingulate cortex. These brain parameters accounted over 70–80% of the variance for pain intensity and duration among chronic pain participants (Baliki, et al., 2006).

2.9.11 Chronic pain management

Evidence based research into the treatment efficacy in chronic pain is limited. Little attention has been directed in determining whether evidence of efficacy in one particular condition can be extrapolated to others (Dworkin, et al., 2011). Currently there is no cure for chronic pain and so treatment is centred on managing pain. In this context, the treatment focus for chronic pain is for the relief or control of pain as well as limiting its impact on functional activities and reducing the level of disability. In many cases, the emphasis is based on a coordinated, multidisciplinary care programme, since no single treatment is likely to be sufficient (Access Economics, 2007). Moreover, simply addressing pain severity is unlikely to be adequate in promoting improvements in functional capacity and health components.

Opiates such as morphine and heroin remain the ‘gold standard’ in pain relief but they work only temporarily for those with chronic pain. Continuous application of low-
dose opioid is the standard in pain therapy (Drdla-Schutting, Benrath, Wunderbaldinger, & Sandkühler, 2012). Research on the efficacy of opioid treatment for chronic pain, however, indicates a loss of analgesic efficacy in the long-term (Ballantyne & Shin, 2008). Initial pain relief by opioid therapy is effective, however, changes in pharmacological tolerance, opioid-induced hyperalgesia, and psychological factors leads to a loss in opioid analgesic efficacy. In chronic low back pain, the available evidence suggests that pharmacological interventions, non-steroidal anti-inflammatory drugs, and muscle relaxants are effective in the short term (Macfarlane, Jones, & Hannaford, 2006).

Studies on the long-term safety and efficacy of opioid medication such as oxycodone for chronic pain treatment are lacking in high quality data. Most clinical trials have lasted no longer than three months. In a six month observational study of chronic back pain patients and opioid use, it was noted that the drugs remained beneficial, although, parameters such as addiction were not assessed and many participants dropped out (Maxmen, 2012).

Treatment strategies such as neuromodulation techniques involving repetitive transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS) have revealed some short-term analgesic benefits in chronic pain participants (Fenton, Palmieri, Boggio, Fanning, & Fregni, 2009; Lefaucheur, Drouot, Ménard-Lefaucheur, Keravel, & Nguyen, 2006; Mendonca et al., 2011). Some evidence shows that daily treatment of TMS for two weeks reduces pain scores and depression in 10 chronic pain participants (Short et al., 2011). Further studies are required to address questions such as stimulation parameters, site of stimulation, and the duration of effects (Lima & Fregni, 2008).
2.9.12 Behaviour modification in chronic pain disorder

In chronic back pain research, there is relatively little available evidence on the effectiveness of behavioural or multidisciplinary treatment programmes. These programmes are based on the bio-psycho-social model of physical, psychological, and social influences on pain (Macfarlane, et al., 2006). In one study on the behavioural treatment for back pain, the results showed improved function at 9-12 months but not at six weeks (Fordyce, Brockway, Bergman, & Spengler, 1986). In a meta-analysis, results show that cognitive and behavioural therapies did not differ from other active therapies for outcomes in low back pain (Turner, 1996).

The biomedical model in the treatment for chronic non-specific low back pain has been challenged (O'Sullivan, 2012). This model is underpinned by physical therapies, opioid medications, spinal injections, disc replacement, and fusion surgery (Deyo, Mirza, Turner, & Martin, 2009). Mounting evidence from randomised controlled trials shows that positive outcomes in chronic low back pain are predicted by changes in psychological status, fear avoidance beliefs, and a belief in self-efficacy in controlling pain (Mannion et al., 2001; Woby, Urmston, & Watson, 2007).
2.9.13 Physical exercise rehabilitation in chronic pain management

Neuroplastic changes leading to hypersensitivity in the central nervous system suggests that this has an important role in the development and maintenance of chronic pain (Flor, 2003). Therapy modalities for central hypersensitivity in chronic pain are largely unexplored. The limited evidence available and everyday practice show, at best, modest efficacy of the available treatment modalities for central hypersensitivity. The gap between basic knowledge and clinical benefits remains large and requires further research (Curatolo, et al., 2006). Current available therapies yield limited success in treating chronic pain. In contrast, physical activity has often shown to be effective in pain management for persons with chronic pain (Friedberg, Williams, & Collinge, 2012; Macfarlane, et al., 2006). Despite this, there is limited evidence available for optimum exercise prescription in persons with chronic pain. Additionally, there is incomplete evidence on the central changes with exercise rehabilitation in chronic pain. Previous studies on stroke, show that long-term exercise intervention can mediate central nervous system plasticity and this suggests a mechanism to optimise therapy (Forrester, Wheaton, & Luft, 2008).

Previous research indicates that certain types of physical exercise may be beneficial for clinical pain outcomes in participants with chronic pain. It has been shown that physical exercise elicits a short-lasting increase in clinical pain which rapidly declines during rest periods (Staud, Robinson, Weyl, & Price, 2010). Enhanced pain during exercise has allayed concerns that exercise produces prolonged exacerbation of pain in chronic pain participants.
Chronic pain is often associated with increased incidence of depression, fear of re-injury, and avoidance of activity (kinesiophobia). These factors predispose the individual with chronic pain to general deconditioning and this further perpetuates the chronic pain state. Systematic reviews for physical exercise rehabilitation have shown exercise programming to be moderately effective in pain management including back pain and fibromyalgia pain (Busch, et al., 2009; Mior, 2001). Despite the accumulating evidence for the effectiveness of exercise in chronic pain management, review studies often conclude that there is a lack of information on the optimal exercise prescription for pain reduction, exercise programme adherence, and functional outcomes (Busch, et al., 2009; Gowans & deHueck, 2004; Mior, 2001).
2.10 Physical exercise and pain modulation

Anecdotes from dancers, gymnasts, and athletes who continue strenuous exercise despite severe injuries (Harringe, Lindblad, & Werner, 2004) and later report that they felt little or no pain have led to the premise that exercise inhibits pain. There is accumulating evidence showing that exercise does inhibit the response to experimental pain stimuli (Koltyn, 2002). Exercise induced pain inhibition is characterised by a decrease in the responsiveness to experimental noxious stimuli. This involves a reduced verbal rating to a standard noxious stimulus following physical exercise.

Much of the research investigating the relationship between exercise and experimental pain has been performed amongst pain-free individuals. The bulk of this research has examined the acute effects of exercise on the pain threshold. Additionally, pain responses to a standard weight stimulus, such as 3 kg for 2 min have also been applied (Koltyn, et al., 2001). A sample series of studies between exercise and experimental pain outcomes in healthy participants is shown in Table 2.2. From this, various exercise protocols and experimental pain procedures have been applied in the research setting to assess exercise-induced pain inhibition.

The inhibitory effect of exercise on pain has not been observed in every study or with every type of noxious stimulus. Several forms of noxious stimuli have been applied to assess the effect of exercise on experimental pain. Similarly the exercise protocol has varied significantly between studies. The following provides a review of the
methodological procedures for measuring the relationship between exercise and experimental pain response in healthy individuals and in persons with chronic pain.

Most of the research between exercise and experimental pain have applied measures of pain threshold. There is also some evidence that exercise increases the threshold for the nociceptive flexion reflex (Guieu, et al., 1992). Modulation of the nociceptive flexion reflex threshold has been shown in animal models to be mediated by supraspinal descending pain inhibitory circuits (Schomburg, 1990). Since exercise activates the central stress system, the inhibition of the nociceptive flexion reflex has been proposed to be linked to stress induced analgesia (Guieu, et al., 1992). Stress induced analgesia has been associated with pain inhibitory mechanisms related to endogenous adrenergic, serotonergic, dopaminergic, and opioid descending systems.

2.10.1 Aerobic exercise and experimental pain parameters

Aerobic exercise requires large muscular repetitive movement activity that elicits a heart rate of at least 55-60% of maximum predicted heart rate or 60-65% of maximum oxygen uptake (VO₂ max), (ACSM, 1998). Isometric exercise involves the development of muscle tension without joint movement, and resistance exercise involves muscle contraction and joint movement against a weight-load (ACSM, 2006). The effects of physical activity including aerobic, isometric, and resistance exercise on experimental pain parameters have been investigated under acute and long-term training protocols. Experimental pain parameters have been investigated following aerobic activity involving running and cycling exercise to examine pain inhibition.
One of the earliest investigations on aerobic exercise-induced pain inhibition was performed in a case study during running exercise (Black, et al., 1979). The exercise protocol required the subject to run for 40 min, a distance of approximately 5 km, in 15 trials over six months. Pain was experimentally induced by arm compression-ischemia before and after each exercise trial. The pain threshold and pain intensity were assessed by verbal reports during arm ischemia while compression of a rubber bulb by the ipsilateral hand maintained a pressure of 200 mmHg. The results revealed that 40 min of running exercise induced a significant increase in the pain threshold and reduced the pain intensity ratings associated with arm ischaemia. Limitation in this study was that only one participant was assessed and that the workload was not accurately quantified. Moreover, since the experimental pain was induced by compression-ischemia, caution must be considered since the vascular changes following exercise could have affected the pain response.

Aerobic running exercise was observed to induce pain inhibition in 15 trained runners following a 1.6 km run at a self selected pace (Haier, Quaid, & Mills, 1981). In order to assess whether the pain inhibition was induced by endogenous opioid release, the subjects were injected with 10 mg naloxone (an opioid blocker) or a placebo within a double blind procedure. The results revealed that both placebo and naloxone trials reported a significant increase in time to pain response at immediately after exercise but not at 10 min post-exercise compared to pre-exercise. While the limitation in this study is that the exercise workload was not accurately measured, it is of note that the opioid blocker did not diminish the pain inhibition following exercise. This suggests that the pain inhibition immediately following exercise is not associated
with the endogenous opioid system. Moreover, this study also indicates that the pain inhibition following exercise is evident within a short transient period.

A limitation in many exercise and pain inhibition research studies is that of response bias. The application of sensory decision theory analysis on pain stimuli before and after running exercise was investigated to assess pain inhibition in 12 runners after running 10.1 km at a self-selected intensity (Janal, et al., 1984). The study also included the effects of naloxone (an opioid blocker) on pain following exercise. Noxious stimulation included radiant heat, ischemic pain, and cold-pain tolerance. The results show that there was a significant decrease in the sensory discriminability to radiant heat stimuli and a reduced ischemic pain report at 20 min following exercise, however, the cold-pain tolerance test did not reveal a pain inhibition. Using sensory discriminatory analysis during the radiant heat tests, this study was able to assess response bias following exercise. Response bias is a limitation in using verbal pain reports following exercise since the subjects attitude can change. By showing there was no change in response bias, this study revealed a reduced pain report following exercise for the radiant heat stimuli. Moreover, these results also revealed that the endogenous opioid system may be partly involved in deep pain inhibition (reduced response to ischemia) but not in superficial (radiant heat on skin) pain inhibition following exercise.

Further research using signal detection theory with radiant heat stimuli on pain report following exercise was investigated in 22 trained runners and a control group (Fuller & Robinson, 1993). This procedure eliminated the possibility of pre-exercise pain testing influencing the post-exercise pain report, as seen in previous research (Padawer & Levine, 1992). The subjects completed running exercise for 9.6 km in 30
min and the control group performed quiet rest for 40 min. The results show that the ability to discriminate between temperatures (44 and 46 °C) was significantly reduced following exercise compared with the no-exercise condition. The aerobic exercise, however, did not reveal a difference in the ability to discriminate between higher temperatures (46 and 48 °C). This suggests that aerobic exercise induces a mild analgesic effect which is not evident with intensely painful stimuli. Moreover, the results also revealed that in three subjects there was no decrease in thermal discriminability. It is possible that this may be due to differences in the relative exercise workload between subjects since the exercise intensity was self-selected.

Previous research on the relationship between exercise and experimental pain has been performed between different exercise modalities. Pressure pain thresholds were investigated following treadmill running at a heart rate of 65-75% of the pre-determined heart rate reserve and following isometric exercise in 12 subjects on separate occasions (Drury, Stuempfle, Shannon, & Miller, 2004). The results show that the pressure pain threshold was significantly increased following treadmill running and isometric exercise compared to the pre-exercise value. These results indicate that different modalities of exercise can illicit experimental pain inhibition.

The influence of exercise intensity on experimental pain inhibition has not been fully detailed. In one study, the exercise intensity and duration were manipulated to assess the effect on pressure pain rating following treadmill running (Hoffman et al., 2004). Exercise intensity was set at 75% of maximal oxygen uptake (VO₂ max) for 10 min, 75% of VO₂ max for 30 min, 50% of VO₂ max for 10 min, 50% of VO₂ max for 30 min on separate occasions and in random order. Pressure pain ratings were measured using a VAS scale during a 2 min pressure pain stimulus on the index
finger at immediately before treadmill exercise, at 5 min, and at 30 min after treadmill exercise. The results show that pressure pain ratings were significantly decreased compared to pre-exercise values at 5 min after treadmill exercise at 75% of VO$_2$ max. These results indicate that pain inhibition following exercise is dose dependent in that high intensity aerobic exercise is required to elicit an inhibitory response. However, the exercise induced pain inhibition rapidly dissipates soon after exercise and is not present at 30 min post-exercise. Moreover, this exercise intensity would exacerbate pain symptomology in participants with chronic pain (Mengshoel, Vollestad, & Forre, 1995).

Several studies have investigated exercise-induced pain inhibition during cycling exercise. The advantage of stationary cycling is that experimental pain parameters can be assessed during exercise. Dental pain thresholds using electrical stimuli were assessed in six healthy male subjects before, during, and after cycling exercise (Pertovaara, Huopaniemi, et al., 1984). Distinct exercise intensities were performed for eight minutes at 50, 100, 150 and 200 W. Subjects performed the 200 W at an average intensity of 70.7% of VO$_2$ max. The results show that dental pain thresholds increased with increasing workloads, however, a statistically significant increase was evident only at 200 W. The dental pain threshold remained elevated up to 30 min following exercise, however, one subject did not show an increase in pain threshold. This study further supports the notion that a minimum exercise intensity is required to elicit experimental pain inhibition and that this response is not consistent in all participants. In contrast to previous research, however, this study shows a long lasting effect of pain inhibition of at least 30 min following exercise.
Dental pain thresholds using electro-stimuli and blood plasma levels of stress hormones were assessed in seven male subjects during and after cycling exercise (Kemppainen, et al., 1985). The exercise intensity was set at four different workloads in a stepwise order from 100, 200, 250 and 300 W. The results show that the average dental pain threshold was significantly elevated at an exercise intensity of 250 W and 300 W compared with the pre-exercise threshold. Increases in dental pain threshold varied from 6% to 114%. This study reveals that pain thresholds were significantly elevated during aerobic exercise when the intensity is at least 250 W. The post-exercise pain threshold, however, was not significantly different to pre-exercise. Moreover, the results from this study show that plasma levels of stress hormones were not associated with pain thresholds in the post-exercise period.

A possible mechanism for exercise-induced pain inhibition is by proprioceptive attenuation of nociceptive signalling. To determine the effect of muscle afferent and proprioceptive activity on pain inhibitory systems, cycling exercise was performed at two different pedal frequencies of 40 and 70 rpm at each workload in a counterbalanced order (Kemppainen, et al., 1985). Cutaneous thermal sensitivity was assessed during cycling exercise with different cycling cadences and exercise intensities. Five subjects performed ramped cycling exercise at 100, 150, 200 and 250 W for eight minutes. Thermal limens (the interval between warm and cool thresholds) were determined at the leg, forearm, and hand before exercise, at each workload, and at 15 min post-exercise. The rate of temperature change was 2.2 °C/s between 20-50 °C. This study reveals that thermal limens increased significantly as a function of increasing work load that is independent of pedal frequency. Moreover, the cutaneous sensitivity was shown to be reduced at the leg site in the post—exercise period. This suggests that exercise may inhibit cutaneous sensitivity in
areas that have a lower cortical representation such as the leg compared to the forearm and hand.

Cycling exercise was also the mode of activity for assessing tactile threshold, thermal limen, and heat pain threshold during and after cycling at 100, 150, 200, 250 W (Paalasmaa, et al., 1991). Eleven subjects performed workloads at an average of 36.5%, 54.5%, 73.3% and 91.3% of their VO\textsubscript{2} max. The results show a load dependent increase in the heat pain threshold that was significantly elevated from pre-exercise at 250 W, however, this was not shown to be elevated in the post-exercise period at 30 min. In contrast, the tactile threshold was shown to be elevated at immediately after and at 30 min post-exercise. This indicates that exercise may attenuate sensitivity from large afferents but does not attenuate small fiber activity such as nociceptors in the post-exercise period.

Experimental pain thresholds and opioid blockade was investigated during stepwise cycling exercise in order to explicate the effect of endogenous opioids (Droste, et al., 1991). Ten healthy male subjects performed cycling exercise at 100 W which was incremented by 50 W every 3 min until exhaustion. Dental pulp and finger pain thresholds by electro-stimuli were determined prior to exercise, during sub-maximum exercise, prior to exhaustion, and up to 60 min after exercise. The study included a double blind procedure for injecting 20 mg naloxone in 20 ml of 0.9% saline (an opiate blocker) or an equivalent amount in saline solution. The results revealed that the pain thresholds for finger and dental pulp were significantly increased during exercise in both the placebo and naloxone trial. The pain threshold elevation was most pronounced during maximal exertion and remained elevated 10-15 min after exercise. Pain thresholds returned to pre-exercise values at 60 min after exercise.
Since pain threshold remained elevated in the naloxone trial, these results suggest that the exercise-induced pain inhibition is mediated by non-opioid mechanisms. This data supports previous research (Haier, et al., 1981; Janal, et al., 1984) indicating that the pain inhibition is not directly associated with plasma endorphin levels in the post-exercise period. In a fMRI study of pain responses following running exercise, central opioidergic inhibition of experimental pain was implicated by activation in the PAG and rACC, although pain threshold was not elevated (Scheef et al., 2012).

The effect of exercise intensity and pre-exposure to experimental pain stimulation on exercise-induced pain inhibition was assessed in 91 healthy participants (Padawer & Levine, 1992). Experimental pain was induced by the cold pressor test in a between-group experimental design. The first design compared the post-exercise cold-pain ratings with two control groups comprised of a group performing low exercise intensity and a non-exercise group. No significant difference in cold-pain rating was shown between groups. The second design comprised a Solomon 4-group design where cold-pain responses were compared with groups having pre-exercise pain exposure and no pre-exercise pain exposure. The exercise intensity was set at 70% of age-predicted maximum heart rate for a period of 20 min. The results revealed that there was no cold-pain inhibition due to cycling exercise, however, a significant effect for pre-exposure to the cold-pain test procedure was evident. These results suggest that the cold-pain inhibition following cycling exercise is a result of the pre-exercise exposure to the pain stimulus. A major limitation in this study is that the method of cold-pressor testing has been shown to be unreliable in pain studies (Blasco & Bayes, 1988).
Cold-pain sensitivity was assessed in jet fighter pilots before and after cycle ergometer exercise (Kemppainen, Hämäläinen, & Könönen, 1998). Cycling exercise was increased stepwise from 50, 100, 150, and 200 W with each workload performed for 8 min. The cold-pain sensitivity was determined before exercise, at 200 W, and at 60 minutes after exercise. The experiment included two groups (N=16) comprising fighter pilots with a previous history of acute in-flight neck pain and a group with no history of neck pain. The pre-exercise results revealed that there was no difference in cold-pain threshold or response between groups. Cycling exercise at 200 W elicited a significant increase in cold pain threshold only in the group with a previous history of neck pain, however, both groups showed a significant decrease in VAS pain responses. The results show that exercise–induced pain inhibition is enhanced during exercise at 200 W in individuals with a history of acute pain episodes. In addition, the post-exercise pain measures at 60 min did not show an increase in pain threshold or reduction in pain response. This study implies that the inhibition of experimental pain during exercise is influenced by previous experience with clinical pain.

Pressure pain threshold and pain rating were assessed before and after cycling exercise at a pre-determined level of aerobic capacity (Koltyn, et al., 1996). Sixteen subjects (14 male, 2 female) performed cycling exercise for 30 min at 75% of VO$_2$max or quiet rest. The order was counterbalanced and randomly assigned on different days. Pressure pain thresholds were assessed before and after exercise and during quiet rest. The results show that the pressure pain threshold was significantly elevated at 5 and 15 min post-exercise compared with quiet rest. By using a separate control procedure, this method accounted for the possibility that previous exposure to pain stimuli may induce analgesia (Padawer & Levine, 1992). In
addition, the results show that pressure pain threshold and pain ratings were remained significantly elevated near 15 min following exercise at 75% of VO$_2$ max.

2.10.2 Isometric exercise and experimental pain parameters

In order to determine whether different exercise modalities inhibit experimental sensory events, tactile thresholds, thermal limens, and heat pain thresholds were assessed during and after isometric exercise (Paalasmaa, et al., 1991). This form of exercise involves muscle tension in the absence of limb or joint movement. Eleven subjects performed isometric exercise (right foot dorsiflexion) at 30% and 70% of the maximum force for two minutes with a five minute rest period between each load. The results show that heat pain thresholds and tactile thresholds were not significantly modified by isometric exercise at 30% or 70% of maximum voluntary isometric force. In contrast, the cutaneous thermal sensitivity was shown to decrease during isometric exercise in the exercising leg. It is possible that isometric exercise in this study did not mediate the ratings of the experimental stimuli due to the activation of a relatively small muscle mass rather than a large muscle mass.

Pressure pain thresholds were assessed during and after isometric leg exercise in 14 healthy female subjects (Kosek & Ekholm, 1995). The participants were required to maintain an isometric contraction of the quadriceps at 25% of the maximum voluntary isometric force until exhaustion or until a maximum of 5 min. Pressure pain thresholds were determined at sites on the quadriceps muscles before exercise, every 30 s during exercise, at 2.5 min and 5 min after exercise. Furthermore, a mild anaesthetic cream was applied on the site to assess the effects of cutaneous input on pressure pain threshold. Pressure pain thresholds increased significantly at the
start of contraction and continued to increase until the middle of the contractile period, then remained at this level during the contractile period. Following exercise, the pressure pain thresholds decreased, however, remained significantly above pre-exercise levels up to 5 min following exercise. Moreover, the results from this study indicate that input from cutaneous and deeper tissues interacts with nociceptive activity from the pressure stimulus as shown by the higher pre-exercise pressure pain threshold with the anaesthetic cream.

The effect of isometric exercise on pain threshold was assessed on exercising and non-exercising limbs (Kosek & Lundberg, 2003). Twenty four healthy subjects with a mean age of 24.4 years performed isometric contraction of the quadriceps with a load weight of 1 kg attached to the ankle until exhaustion or for a maximum of 10 min. Pressure pain thresholds were assessed on the contracting quadriceps femoris, the bilateral non-contracting quadriceps femoris, and the non-contracting infraspinatus muscle sites. The results reveal a significant increase in pressure pain threshold at the contracting muscle, at the resting contralateral muscle, and at a distant resting muscle site. Together these data show that isometric exercise elicits a segmental (within the exercising limb) and plurisegmental (in non-exercising limbs) modulation of pressure pain threshold during exercise but not at 30 min post-exercise. Furthermore, this study posits that the pain inhibition may be induced from the activation of diffuse noxious inhibitory controls by the muscle ischemia from isometric exercise. A limitation here is that levels of muscle pain intensity were not assessed during exercise and this could have provided further insight into the level of isometric muscle pain required to elicit pain inhibitory mechanisms.
To assess the potential difference in experimental pain perception between men and women to exercise, pressure pain thresholds were assessed in 15 men and 16 women before and after isometric hand grip exercise (Koltyn, et al., 2001). The estimated sample size (Kraemer & Thieman, 1987) required to detect differences between men and women in pain thresholds was determined prior to the participant recruitment. Participants performed isometric exercise on a hand grip dynamometer at maximum strength for 5 s and at 40-50% of maximum strength for 2 min. Pressure pain thresholds and pain ratings were assessed before and after isometric exercise. Pain ratings were determined every 15 s during the constant pressure pain stimulus period. The results revealed that the pain threshold was increased after isometric exercise in women but not in men. Pain ratings were found to be lower after maximum isometric exercise in both men and women. This study also showed that there was a lower pre-exercise pain threshold in women compared to men, however, isometric exercise produced a significant increase in pain threshold in women but not in men. It was indicated that these differences may be associated with blood pressure regulation between men and women (Campbell, Hughes, Girdler, Maixner, & Sherwood, 2004).

In a comparative study between isometric and aerobic exercise, pressure pain threshold was measured before and after isometric hand grip exercise and treadmill running performed on separate occasions (Drury, et al., 2004). The results indicate a statistically significant increase in the pressure pain threshold after isometric exercise and after treadmill exercise compared with the pre-exercise values. Moreover, treadmill exercise was shown to induce a greater increase in pain threshold compared to isometric exercise. A limitation in the study is that differences in
workload between isometric and aerobic exercise were not quantified. This may account for the high pressure pain threshold observed with treadmill exercise.

To determine the relationship between isometric exercise, experimental pain, and muscle fatigue, pressure pain threshold was assessed in the trapezius and deltoid muscles before and after an isometric arm endurance task (Persson, Hansson, Kalliomäki, Moritz, & Sjölund, 2000). The subjects included 25 healthy females performing isometric endurance exercise by abducting the arm to 90 degrees in the scapular plane with a one kg weight fixated around the wrist. Muscle fatigue was assessed by a time series of electromyographic responses. The results showed that pressure pain thresholds were increased bilaterally immediately after exercise, although the increase was more pronounced within the exercise side. This study also demonstrated that pressure pain threshold remained elevated at 10 min after exercise, however, this was not associated with muscle fatigue. It is possible central nervous system descending antinociceptive systems may mediate the bilateral experimental pain inhibition (Le Bars & Willer, 2009).

2.10.3 Eccentric exercise and experimental pain parameters

There is insufficient information on the effects of eccentric exercise on experimental pain. Eccentric exercise elicits muscle tension under conditions whereby the joint or limb is extending, such as during landing activities following a jump. This form of exercise also induces muscle soreness at 24-48 hr after exercise (Miles & Clarkson, 1994; Nosaka, Newton, & Sacco, 2002). In one study, pressure pain tolerance was assessed in 15 healthy (mean age 22 ± 2.6 SD years) untrained female subjects before and after downhill running exercise (Baker, Kelly, & Eston, 1997). The
subjects performed one bout of downhill running set at -12% gradient for 40 min at an intensity of 60% of age-related maximum heart rate reserve. The pressure pain tolerance was determined along the rectus femoris muscle belly and the myotendinous junctions at two days prior to, immediately after, and each day for three days, after eccentric running exercise. Results show that the pressure pain tolerance immediately after exercise were not significantly different compared with before exercise. The pressure pain tolerance at 24 hrs and at 72 hrs after exercise, however, showed a significant decrease in sites across the muscle belly and myotendinous junctions, suggesting an increased tenderness. This study also demonstrated that eccentric exercise did not attenuate experimental pain immediately following exercise, however, pain tolerance was assessed rather than pain threshold. It has been indicated that pain tolerance presents a specific pain factor that is not associated with sensory intensity (Wolff, 1971).

2.10.4 Resistance exercise and experimental pain parameters

Resistance exercise involves muscle contractions requiring flexion and extension of joints under conditions of increased resistance such as lifting and lowering a weight. Pressure pain responses were investigated before and after ordinary weight lifting exercise in 12 men who exercised regularly (Bartholomew, et al., 1996). The exercise protocol involved either resistance exercise, circuit weight training, or stationary aerobic cycling for a total of 20 min. The exercise intensity was assessed by participants rating the pain intensity of the exercise. The average pain rating experienced during the exercise was ranked as 59 ± 22.6 on a 100 point scale and the average perceived effort was rated at 13.2 ± 2.9 on Borg’s scale of 6-19, which reflects a moderate exercise effort. Pain thresholds and pain tolerance were
determined by application of gross pressure on the medial surface of the dominant leg. The subjects also performed a 20 min quiet rest period in a counterbalanced, randomly assigned order, separated by at least 1 hr but no more than 3 days. The results show a significant increase in pain tolerance but not pain threshold following 20 minutes of moderate level exercise. Limitations in the study were that initially 22 participants were excluded from the data analysis since they reached the maximum allowable limit for the gross pressure device. This indicates that the sample size would have been reduced and would have reduced the ability to generalise the results. Moreover, the exercise workload was not quantified and four participants performed aerobic exercise. This mixed sample of exercise modality would further limit the use of these results, although this research does demonstrate that self-selected exercise can increase the tolerance to pain.

In order to assess the effect of resistance exercise on pain thresholds and pain ratings (Koltyn & Abogast, 1998), six women and seven men with a previous history of resistance training performed a pre-determined exercise load. The resistance exercise consisted of 45 minutes of lifting three sets of 10 repetitions at 75% of one repetition maximum. Pain responses were assessed by application of a three kg constant load pressure on the middle digit. Pressure pain threshold and pain responses were determined before resistance training exercise, five and 15 minutes after exercise. The results reveal that the pain threshold was significantly increased and the pain rating was decreased at five minutes after resistance exercise compared with quiet rest. This study also shows that resistance exercise elicits a transient inhibition of experimental pain response in the post-exercise period which returns to baseline within 15 min.
2.10.5 Passive movement and experimental pain parameters

It has been indicated that low threshold mechanoreceptors may project to central nervous anti-nociceptive systems and that this may result in attenuation of experimental stimulation (Zusman, Edwards, & Donaghy, 1989). In one study, the effect of passive movement exercise on experimental pain was assessed following 30 min of electrically driven cycling (Nielsen, Mortensen, Sorensen, Simonsen, & Graven-Nielsen, 2009). Experimental deep-tissue muscle pain was induced by chemical injection of hypertonic saline in a control repeated measures design. Experimental pressure pain thresholds were also assessed on the injection site. The results show that passive movement exercise increased the pressure pain threshold and reduced the deep-tissue muscle pain. This research demonstrates the capacity for passive movement exercise to induce analgesia, possibly through activation of low threshold mechanoreceptors and descending pain inhibitory pathways.

2.10.6 Long-term exercise training and experimental pain parameters

There is a paucity of evidence showing the long-term effects of exercise training on experimental pain parameters in healthy individuals. Moreover, there are few studies which have performed comparisons between physically trained and untrained groups to determine differences in pain parameters. In a review paper of 15 studies involving 899 athletes and non-athletes, were assessed for the perception of experimental pain parameters (Tesarz, Schuster, Hartmann, Gerhardt, & Eich, 2012). The results revealed that athletes possessed higher pain tolerance, however, pain threshold was not significantly different. It remains to be clarified as to whether physical training
reduces pain sensitivity or that athletes engage in physical activity because of differences in pain perception.

Pain perceptual parameters such as the pain threshold and pain tolerance using the cold-pressor test were investigated in 52 professional ballet-dancers and 53 age-matched non-dancers (Tajet-Foxell & Rose, 1995). Psychological variables such as coping style and neuroticism were assessed prior to the cold-pressor test. The results show that the ballet-dancers had a significantly higher cold-pain threshold and tolerance than non-dancers. Significantly higher pain experience measures were reported in the ballet-dance group during the cold-pain test. This study demonstrates that the ballet-dancers experienced cold-pain more acutely than the non-dancers, however, the ballet-dancers demonstrated a greater capacity to encounter pain. Interestingly, the measures of psychological variables did not account for differences between groups. Instead, it was contended that the greater exposure to physical training and increased fitness results in higher pain threshold and tolerance in the ballet-dancers.

A range of experimental pain stimuli were delivered to a group of trained athletes and non-athletes (Manning & Fillingim, 2002). Experimental pain stimuli for pressure, ischemia, and cold temperature were presented to 24 athletes and 24 non-athletes in a gender balanced design. The analysis indicated an increased ischemic pain tolerance and increased cold-pain threshold and tolerance in athletes compared to non-athletes. This study also involved interviews with athletes, and proposed that the athletes were able to compare the experimental pain stimuli with previous pain experiences during training. Moreover, this enabled athletes to use specific coping strategies when confronted with pain experiences.
To compare pain sensitivity in habitual runners, a series of experimental pain tests were performed in 12 trained men and 18 normally active controls (Janal, Glusman, Kuhl, & Clark, 1994). The trained group consisted of athletes training at least 30 km/week for 3 months. Pain was assessed by the cold-pressor test, heat pain sensitivity, and ischemic stimulation between the running group and a control group. The results revealed that for the cold-pressor test, runners reported significantly longer latencies for cold immersion sensations compared with the control group. There was no difference between the runners and the control group for the heat pain test and the ischaemic pain test. Overall, this study shows that the running group did not demonstrate a reduced sensitivity to experimental pain stimuli compared to the control group. A shortcoming in this study is the lack of data comparing the aerobic capacity between groups. Additionally, a physical activity diary was also not conducted in both groups, and this limits that ability to generalise the results in comparing athletes with non-athletes.

Experimental pain parameters were assessed in swimmers during a training season (Scott & Gijbers, 1981). The study investigated the ischaemic pain threshold and tolerance in three groups of subjects comprised of 30 national-level swimmers, 30 club-level swimmers, and 26 non-competitive athletes. The national-level swimmers were tested twice during the peak of their training season and a third time at the beginning of the next training season. The results show that there was no difference between groups for pain threshold, however, results for pain tolerance show that the national level swimmers were higher than the club-level swimmers and the non-competitive athletes. Club-level swimmers indicated a pain tolerance that was significantly higher than non-competitive athletes. Moreover, the results also
revealed that the pain tolerance in national-level swimmers increased according to the stage of training season. This study highlights that physical training in elite athletes enhances the tolerance to experimental pain according to the training status. It was also indicated that the ischemic pain stimulus mimicked the type of pain normally experienced during physical training.
2.11 Physical exercise rehabilitation for chronic pain

There is accumulating evidence that physical exercise rehabilitation elicits favourable pain report outcomes (Ambrose, Lyden, & Claw, 2003; Busch, et al., 2009; Carbonell-Baeza, et al., 2010; de Jong et al., 2003; Gowans, et al., 2004; Hurkmans, et al., 2009; Meiworm, Jakob, Walker, Peter, & Keul, 2000; Roddy, et al., 2005) and enhanced health-related components (Gowans, et al., 2001; Richards & Scott, 2002; Valim, et al., 2003) in persons with chronic pain disorder. In addition to reduced clinical pain report, there is some evidence showing that exercise rehabilitation mediates experimental pain parameters such as pressure pain threshold. A reduction in somatic pressure sensitivity in chronic pain participants suggests that aerobic exercise rehabilitation enhances the function of the endogenous pain inhibiting systems or desensitises the sensory pathway.

2.11.1 Acute effects of exercise in chronic pain participants

Previous research has applied various exercise protocols for the therapeutic treatment of pain, experimental pain assessment, and functional improvements in chronic pain participants. Advantages of applying experimental pain assessments in chronic pain participants following exercise is that this provides further understanding on the function of the pain system under different conditions. A sample series of studies on the acute effects of exercise in chronic pain participants is depicted in Table 2.3.
Pressure pain thresholds in 21 persons with chronic low back pain and 31 healthy control persons were assessed before and after sub-maximal cycling exercise (Meeus, Roussel, Truijen, & Nijs, 2010). The results show that there was no difference in pressure pain threshold between groups before exercise. Both groups revealed an increase in pressure pain threshold following exercise, with no difference observed between groups. Limitations in the study indicate that the participants had a variable exercise dose and this may have influenced the outcome for experimental pain assessment.

Experimental pain ratings were investigated in 10 persons with chronic low back pain following aerobic exercise at 50% and at 70% of maximum oxygen uptake (Hoffman, Shepanski, Mackenzie, & Clifford, 2005). The results show that there was a long-lasting attenuation of experimental pain ratings for up to 30 min amongst the chronic pain participants. Interestingly, the baseline measures of pressure pain ratings were similar to the control group, which is in contrast to other studies on chronic back pain participants (Giesecke, et al., 2004). It is possible that this difference may be due to the low to moderate levels of disability chosen as the subject sample for chronic low back pain.

Increased experimental heat pain sensitivity has been observed in 15 persons with chronic musculoskeletal pain compared to 17 healthy controls following aerobic exercise at 70% of peak oxygen consumption (Cook, et al., 2010). An interesting part of the methodology is that the data included pain-affect ratings. The results show that acute exercise influences the suffering components to experimental pain to a greater extent than the sensory components in persons with chronic pain. This information may be applicable in exercise prescription for persons with chronic pain.
The effects of acute aerobic exercise on experimental pressure pain threshold were investigated in persons with chronic whiplash pain (Van Oosterwijck, Nijs, Meeus, Van Loo, & Paul, 2012). Aerobic exercise was performed at 75% of age-predicted target heart rate and at a self-paced, physiologically limited exercise intensity. It was shown that in both types of exercise there was a decline in pressure pain threshold except that the pressure pain threshold was elevated for the calf muscle during self-paced exercise. In contrast, the pressure pain threshold was observed to increase in the healthy control group in both types of exercise. A deterioration of chronic whiplash associated symptoms was reported post-exercise, however, this was less prominent in the self-paced exercise group. These results suggest an impaired endogenous pain inhibition during exercise in persons with chronic whiplash disorder. Moreover, self-paced exercise appears to elicit less severe symptoms in the post-exercise period.

Pressure pain thresholds were determined in patients with fibromyalgia and healthy controls during isometric leg exercise (Kosek, et al., 1996a). Fourteen patients with fibromyalgia and 14 healthy controls participated in the study. Isometric exercise was performed at 22% of maximal isometric strength until exhaustion. The exercise was limited to a maximum of five minutes. The pressure pain thresholds were determined over the quadriceps femoris muscle before, during and after isometric exercise. The results show a decrease in pressure pain threshold during the contractile period in patients with fibromyalgia. The pressure pain thresholds remained below pre-contraction values at five minutes after exercise. The pressure pain threshold increased during the contractile period in healthy persons and remained elevated at five minutes after isometric exercise.
Individuals with unilateral chronic shoulder pain were assessed for pressure pain threshold and clinical pain scores following an isometric fatiguing endurance task (Persson, Hansson, Kalliomaki, & Sjolund, 2003). The results revealed a bilateral long-lasting 20 min increase in pressure pain threshold following exercise, however, there was an increase in shoulder pain intensity after the test. These results suggest that exercise may launch central anti-nociceptive systems, possibly through diffuse noxious inhibitory controls.

The effects of isometric exercise on thermal pain ratings and pressure pain thresholds were determined in 12 fibromyalgia and 11 healthy subjects (Staud, Robinson, & Price, 2005). The isometric exercise required 90 s of sustained handgrip exercise at 30% of maximal voluntary contraction. Supra-threshold thermal pain ratings and pressure pain threshold were determined over both forearms before and during isometric exercise. The results show a decrease in thermal ratings and an increase in pressure pain threshold in healthy subjects. These changes were observed in the local and non-exercising forearm. In contrast, the fibromyalgia patients observed opposite effects compared with healthy subjects.
Table 2.2: Showing a sample of research studies examining the relationship between exercise and experimental pain parameters in healthy participants

**Key:** N=number of participants; PPT, pressure pain threshold; VO_2 max, maximum oxygen uptake, HRR, heart rate reserve; HR, heart rate; RM, repetition maximum

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulus</th>
<th>Exercise</th>
<th>Participants</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>(Black, et al., 1979)</td>
<td>Ischaemic pain rating</td>
<td>Aerobic running, 40 min</td>
<td>N=1</td>
<td>Increased ischaemic pain threshold, reduced pain ratings</td>
</tr>
<tr>
<td>(Janal, et al., 1984)</td>
<td>Heat pain, Ischaemic pain, cold-pain tolerance</td>
<td>Aerobic running, ~50 min, ~85% of VO_2 max</td>
<td>N=12</td>
<td>No change in cold pain, reduced heat and ischaemic report</td>
</tr>
<tr>
<td>(Fuller &amp; Robinson, 1993)</td>
<td>Heat stimuli</td>
<td>Aerobic running, ~30 min</td>
<td>N=22</td>
<td>Reduced discriminability for low temperature but no change for high temperature</td>
</tr>
<tr>
<td>(Drury, et al., 2004)</td>
<td>Pressure pain threshold</td>
<td>Aerobic, 65-75% of HRR</td>
<td>N=12</td>
<td>Increased PPT</td>
</tr>
<tr>
<td>(Hoffman, et al., 2004)</td>
<td>Pressure pain ratings</td>
<td>Aerobic, 50% &amp; 75% of VO_2 max</td>
<td>N=12</td>
<td>Reduced pressure pain ratings for 75% VO_2 max at 5 min post but not at 30 min post exercise</td>
</tr>
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### Table 2.2: continued

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<tr>
<th>Study</th>
<th>Stimulus</th>
<th>Exercise</th>
<th>Participants</th>
<th>Results</th>
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<tbody>
<tr>
<td>(Pertovaara, Huopaniemi, et al., 1984)</td>
<td>Dental pain threshold</td>
<td>Incremental cycling up to 200 W</td>
<td>N=6</td>
<td>Elevated dental pain threshold at 200 W for up to 30 min post exercise</td>
</tr>
<tr>
<td>(Kemppainen, et al., 1985)</td>
<td>Dental pain threshold, thermal sensitivity</td>
<td>Incremental cycling up to 300 W</td>
<td>N=7</td>
<td>6-114% increase in dental pain threshold from 250 W, Elevated dental pain threshold at 15 min post-exercise in 4 subjects, reduced thermal sensitivity</td>
</tr>
<tr>
<td>(Paalasmaa, et al., 1991)</td>
<td>Heat pain threshold, thermal sensitivity</td>
<td>Incremental cycling up to 91% of VO₂ max</td>
<td>N=11</td>
<td>Increased heat pain threshold only at the highest workload produced an increase in heat pain threshold, reduced thermal sensitivity, return to baseline at 30 min post exercise</td>
</tr>
<tr>
<td>(Padawer &amp; Levine, 1992)</td>
<td>Cold-pressor test</td>
<td>20 min cycling at 70% of predicted maximum HR</td>
<td>N=91 (7 groups)</td>
<td>No hypoalgesic effect for exercise. A hypoalgesic effect from repeated cold-pressor testing</td>
</tr>
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Table 2.2: continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulus</th>
<th>Exercise</th>
<th>Participants</th>
<th>Results</th>
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<tbody>
<tr>
<td>(Droste, et al., 1991)</td>
<td>Electrocutaneous and dental pulp electrical thresholds</td>
<td>Incremental cycling until exhaustion</td>
<td>N=10 males</td>
<td>Increased threshold for electrocutaneous and dental pulp at 10-15 min post-exercise. Return to baseline at 60 min</td>
</tr>
<tr>
<td>(Kemppainen, et al., 1998)</td>
<td>Cold-pressor test</td>
<td>Incremental cycling until 200 W (65-70% of VO₂ max)</td>
<td>N=16 (2 groups)</td>
<td>Reduced pain intensity and unpleasantness scores during 200 W exercise. Elevated pain threshold only in the group with previous history of clinical pain</td>
</tr>
<tr>
<td>(Koltyn, et al., 1996)</td>
<td>Pressure pain threshold, Pressure pain ratings</td>
<td>30 min cycling at 75% of VO₂ max</td>
<td>N=16</td>
<td>Increased PPT at 5 min and 15 min post-exercise. Reduced pain ratings at 5 min post-exercise</td>
</tr>
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Table 2.2: continued  

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<thead>
<tr>
<th>Study</th>
<th>Stimulus</th>
<th>Exercise</th>
<th>Participants</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>(Paalasmaa, et al., 1991)</td>
<td>Tactile threshold, thermal limen (thermal sensitivity), heat pain threshold</td>
<td>5 min isometric leg exercise at 30% and 70% of maximum force output</td>
<td>N=11</td>
<td>Reduced thermal sensitivity in the exercising leg</td>
</tr>
<tr>
<td>(Drury, et al., 2004)</td>
<td>Pressure pain threshold</td>
<td>Isometric hand grip</td>
<td>N=12</td>
<td>14.4% increase in pressure pain threshold immediately after exercise</td>
</tr>
<tr>
<td>(Koltyn &amp; Abogast, 1998)</td>
<td>Pressure pain threshold, pressure pain responses</td>
<td>Resistance exercise (3 sets, 10 reps, 75% of 1RM)</td>
<td>N=13</td>
<td>Increased pressure pain threshold and reduced pain ratings at 5 min post. No difference in pressure pain threshold at 15 min post exercise</td>
</tr>
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</table>
2.11.2 Effects of exercise rehabilitation for persons with chronic pain

Most of the research on exercise rehabilitation for persons with chronic pain has focused on using aerobic or resistance-exercise modalities for treatment. A sample series of studies showing the effects of exercise rehabilitation on experimental and clinical pain outcomes in chronic pain participants is shown in Table 2.4. In one study, the effect of exercise rehabilitation on pain parameters in chronic pain participants (N=103) was assessed in four exercise intervention groups and a control group (Waling, Sundelin, Ahlgren, & Järnholm, 2000). Exercise intervention groups included strength training, endurance training, and co-ordination training. Each exercise group participated three times per week for 10 weeks. Pressure pain thresholds were measured at six trigger-points in the trapezius muscle with a pressure algometer. The results show that pressure pain thresholds increased and clinical pain report was significantly reduced after exercise intervention. Moreover, all three exercise programmes showed similar reductions in pain, which suggests that the type of exercise is of less importance to achieve reductions in pain.

The effect of 12 weeks of aerobic exercise on pain parameters was assessed in 27 patients with fibromyalgia (Meiworm, et al., 2000). The exercise training included jogging, walking, cycling, or swimming for an average of 25 min two to three times a week at 50% of maximal aerobic oxygen uptake. The study included 12 sedentary fibromyalgia patients as controls. The results show that the mean number of tender points, pressure pain threshold of gluteal tender point, and the painful body surface decreased significantly in the exercise group. Pain parameters remained unchanged.
in the control group. The subjective pain condition was shown to deteriorate in two patients but was improved in 17 patients.

The effectiveness of resistance exercise and stretching on intensity of neck pain was assessed in 393 female office workers with chronic neck pain (Viljanen et al., 2003). The participants were randomly assigned to either an exercise group, a relaxation training group, or an ordinary activity group. The resistance training was comprised of dumbbell exercises performed to activate large muscle groups in the neck and shoulder. The resistance exercises and relaxation exercises were performed over 12 weeks. The results revealed that there was no significant difference in neck pain between groups. The study concluded that dynamic muscle training and relaxation training do not lead to better improvements in neck pain compared with ordinary activity.

A 20-week general fitness exercise programme was performed by 18 chronic pain participants twice per week. This study also included a non-exercising control group for statistical comparisons. The results showed no significant differences in general pain scores and fatigue following the rehabilitation programme. Limitations in this study are that the exercise intensity was not quantified and that there was a 38% drop-out rate in the exercising group.

Pain parameters were assessed in women with fibromyalgia following 12 weeks of strength training (Kingsley et al., 2005). Twenty nine women with fibromyalgia were randomly assigned to an exercise programme or a non-exercise control group. The strength training programme was performed two times per week, using 11 exercises with one set of 8-12 repetitions at 40-60% of maximum force output. The number of
tender points and myalgic score using a pain scale were assessed by a rheumatologist. The fibromyalgia was assessed by the Fibromyalgia Impact Questionnaire. The results revealed a significant increase in strength and functional capacity in the exercise group, however, tender point sensitivity and fibromyalgia impact questionnaire score did not change.

A between and within group comparison was performed for cardiovascular exercise rehabilitation and flexibility exercise over 20 weeks amongst 42 persons with fibromyalgia (McCain, Bell, Mai, & Halliday, 1988). The results for the cardiovascular training group show a significant improvement in cardiovascular fitness and experimental pain threshold compared to the flexibility training group. The clinical pain scores, however, did not significantly decline despite a downward trend. Interestingly, this study used a group exercise approach, rather than individualised instruction, and this resulted in a high 90% compliance rate amongst the chronic pain participants.

The effect of neck muscle endurance and strength training was investigated in women with chronic neck pain (Ylinen et al., 2005). The study included 180 women with chronic, non-specific neck pain. The subjects were randomised into three groups comprised of neck muscle endurance training, neck muscle strength training and a control group. The groups participated in the study over 12 months. The groups were assessed for pressure pain threshold and neck pain was determined by visual analogue scale. The results show that both training groups revealed an increase in the pressure pain thresholds compared with the pre-training baseline. The pressure pain thresholds did not change in the control group. A follow up study revealed a dose-response relationship between exercise training and perceived neck pain. In
addition, the study revealed that the decrease in neck pain correlated positively with the amount of physical training.

Persons with chronic neck pain were prescribed resistance exercise or endurance exercise in a 12-day exercise rehabilitation programme which was continued by self-guided exercise for 12 months (Nikander et al., 2006). The results show that declines in neck pain and disability correlated positively with the amount of training. Both training groups revealed a decline in neck pain and disability. An interesting finding in the study revealed a low drop-out rate, possibly from the self-guided exercise programme following the initial 12-day exercise guidelines. These results suggest that self-paced exercise results in improved pain outcomes and enhanced programme adherence rates.

A 10-week exercise intervention study was performed in participants with chronic trapezius myalgia and in healthy controls (Nielsen et al., 2010). The participants performed either resistance exercise or general fitness activity. In accord with previous research, the chronic pain group had lower pressure pain thresholds in distant unaffected muscles compared to the healthy control group. Both the resistance exercise and general fitness training groups observed improvements in pressure pain thresholds. In new finding in this study revealed that resistance exercise was shown to improve pressure pain thresholds at the painful muscle sites compared to general fitness training. In this study, however, results for baseline and post-exercise intervention clinical pain scores were not reported.

In a multidisciplinary study, 25 chronic pain fibromyalgia participants underwent a three week intensive aerobic exercise rehabilitation combined with a cognitive based
therapy programme (Suman et al., 2009). Clinical pain and pressure pain assessments were favourably improved for up to 12 months after the programme. These results show the long-term efficacy of multidisciplinary programmes. Moreover, the study concluded that the inclusion of physical exercise as a coping strategy for chronic pain acceptance the long-term effects of the intervention.

Yoga exercise has been used as a treatment for a variety of chronic conditions in which pain is a predominant feature. Intervention research for chronic pain participants has also included the effects of yoga exercise (Curtis, Osadchuk, & Katz, 2011). The exercise protocol involved yoga activity for 75 min, twice per week, over eight weeks. Results from this study show a reduction in clinical pain report, reduced pain catastrophising, and alterations in cortisol levels following the yoga intervention. A limitation in the study was the lack of a control group for between group comparisons.

In a three month multidisciplinary exercise intervention study, 75 women with fibromyalgia pain were allocated to low-moderate intensity pool, land-based, and psychological sessions or usual care group (Carbonell-Baeza, et al., 2010). The results showed significant improvements in pressure pain thresholds at several points compared to the usual care group, despite no changes in physical fitness. In another study of 123 fibromyalgia participants, an inverse association of pressure pain tender points was shown with total distance walked in six minutes (6-min walk test) and chair stand test (Carbonell-Baeza, Aparicio, Sjostrom, Ruiz, & Delgado-Fernandez, 2011). Additionally, weight status (body mass index) appeared to also play a role in the association between experimental pain scores and functional assessments. These results suggest that targeting functional capacity and weight
status in chronic pain may present important goals for exercise rehabilitation in chronic pain management.

The effects of high and low intensity aerobic fitness training over 20 weeks were investigated in 37 patients with chronic pain fibromyalgia (van Santen, et al., 2002). The results showed a low participation rate in both the high and low intensity exercise groups. Most important reasons for this included an increased post-exercise pain and fatigue, time consumption, and stress. For high intensity exercise a significant increase in VAS global pain score was shown, however, a decrease VAS pain score was shown for low intensity exercise. These results suggest that high intensity aerobic exercise is associated with an exacerbation of pain symptomology in chronic pain participants.

On another study it was demonstrated that chronic pain patients had no difference in cardiovascular fitness compared to a healthy control group, however, it was shown that the chronic pain group had a much higher rating of perceived exertion during exercise (Mengshoel, et al., 1995). The results also showed that muscle pain after exercise remained elevated in the chronic pain group for at least 24 hours.

In a cycling exercise test, participants with chronic pain (N=181) observed only a 63% maximum increase in heart rate compared to the predicted heart rate (Norregaard, Bulow, Lykkegaard, Mehlisen, & Danneskiold-Samsooe, 1997). The study concluded that the exercise status of chronic pain participants was related to the pain scores during exercise rather than the physical capacity or effort.
In another study, preferred aerobic exercise intensity was compared with prescribed exercise in 21 chronic pain participants (Newcomb, Koltyn, Morgan, & Cook, 2011). The study concluded that the preferred exercise intensity model demonstrated a significant reduction in pain symptoms after exercise. Moreover, the study found a much larger effect in pain threshold increase following the preferred exercise intensity.

In a review study on the efficacy of aerobic exercise in chronic pain fibromyalgia, it was indicated that some studies did not sufficiently report the exercise protocol (Häuser et al., 2010). In many studies the prescribed exercise intensity was not reported or was not assessed by heart rate telemetry. Additionally, the attendance rates were inconsistently reported. Therefore, recommendations on an effective aerobic exercise programme were not possible.

The association between exercise and pain has been highlighted through the previous research on the acute and long-term effects of exercise participation among healthy participants and in persons with chronic pain disorder. Physical exercise has revealed a capacity to favourably modulate experimental pain and chronic pain symptoms, although, this has not been consistently demonstrated.
Table 2.3: Showing a sample of research studies examining the acute effects of exercise on experimental pain parameters in participants with chronic pain

**Key:** VO$_2$, maximum oxygen uptake; N, number of participants; W, power output in Watts

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulus</th>
<th>Exercise</th>
<th>Participants</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>(Meeus, et al., 2010)</td>
<td>Pressure pain threshold</td>
<td>Incremental cycling up to 130 W</td>
<td>N=21 chronic low back pain, N=31 healthy</td>
<td>Increase pressure pain threshold in both groups</td>
</tr>
<tr>
<td>(Hoffman, et al., 2005)</td>
<td>Pressure pain ratings</td>
<td>Cycling exercise at 50% and 70% of VO$_2$ max</td>
<td>N=10 chronic low back pain</td>
<td>Reduced pressure pain ratings immediately after and at 32 min after exercise</td>
</tr>
<tr>
<td>(Cook, et al., 2010)</td>
<td>Heat pain sensitivity, Exercise muscle pain ratings</td>
<td>Cycling at 70% of peak oxygen consumption</td>
<td>N=15 chronic musculoskeletal pain, N=17 control</td>
<td>Increased heat sensitivity, Increased exercise muscle pain sensitivity compared to healthy group</td>
</tr>
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<th>Study</th>
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<th>Participants</th>
<th>Result</th>
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<tbody>
<tr>
<td>(Van Oosterwijck, et al., 2012)</td>
<td>Pressure pain threshold, exercise pain ratings</td>
<td>Cycling at 75% of maximal predicted heart rate</td>
<td>N=22 chronic whiplash disorder, N=22 control</td>
<td>Reduced pressure pain threshold in chronic pain group. Increased pressure pain threshold in control group. Reduced exercise pain ratings at self-paced exercise</td>
</tr>
<tr>
<td>(Kosek, et al., 1996a)</td>
<td>Pressure pain threshold</td>
<td>Isometric exercise at 22% of maximal force output</td>
<td>N=14 Chronic pain fibromyalgia, N=14 control</td>
<td>Reduced pressure pain threshold in chronic pain. Increased pressure pain in control group</td>
</tr>
<tr>
<td>(Staud, et al., 2005)</td>
<td>Thermal pain rating, Pressure pain threshold</td>
<td>90s of isometric exercise at 30% of maximum force output</td>
<td>N=12 chronic pain fibromyalgia, N=11 control</td>
<td>Increased thermal ratings and decreased pressure pain threshold in chronic pain group. Decreased thermal ratings and increased pressure pain threshold in control</td>
</tr>
</tbody>
</table>
Table 2.4: Showing a sample of research studies on examining the effects of exercise rehabilitation on experimental and clinical pain outcomes in participants with chronic pain

**Key**: VAS, visual analog scale; N, number of participants

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<tr>
<th>Study</th>
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<th>Exercise</th>
<th>Participants</th>
<th>Result</th>
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<tbody>
<tr>
<td>(Waling, et al., 2000)</td>
<td>Pressure pain threshold, VAS for clinical pain</td>
<td>Strength training, muscular endurance, coordination, 10 weeks</td>
<td>N=103 trapezius myalgia (3 groups) N=21 control</td>
<td>For all exercise groups a significant increase in pressure pain threshold in some locations. Reduction in trapezius myalgia VAS scores</td>
</tr>
<tr>
<td>(McCain, et al., 1988)</td>
<td>VAS for clinical pain</td>
<td>20 week cardiovascular fitness, flexibility exercise</td>
<td>N=42 chronic pain fibromyalgia</td>
<td>Trend for reduced VAS in the cardiovascular group,</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>(Carbonell-Baeza, et al., 2010)</td>
<td>Pressure pain threshold</td>
<td>12 week low-moderate intensity exercise</td>
<td>N=33 chronic pain fibromyalgia (exercise) N=32 chronic pain fibromyalgia usual care</td>
<td>Increased pressure pain threshold in several points for exercise group. No change in physical fitness.</td>
</tr>
<tr>
<td>(van Santen, et al., 2002)</td>
<td>VAS global pain score Number of tender points</td>
<td>2 supervised session per week, 20 weeks High and low intensity exercise groups</td>
<td>N=19 fibromyalgia, high intensity exercise and N=18 fibromyalgia low intensity exercise</td>
<td>Increased global VAS clinical pain score for high intensity exercise. Improved cardiovascular fitness for high intensity exercise.</td>
</tr>
</tbody>
</table>
2.12 Summary of literature review

Previous studies highlight the neurosensory ascending pathways for pain and the mechanisms by which pain is modulated. Peripherally, nociceptor populations transmit noxious information through Aδ and C-fibers to the dorsal horn of the spinal cord. The dorsal horn is a significant site in which nociceptive signalling is mediated by descending supraspinal contribution and by concomitant A-fiber input. Nociceptive signalling is projected to the thalamus and to supraspinal regions by direct and indirect pathways. Ascending nociceptive information becomes painful through the interaction between a network of brain sites including the somatosensory cortex, and sites involved in affect and autonomic processing.

Nociceptive signalling is mediated at the dorsal horn by pro- and anti-nociceptive descending modulation. Supraspinal mediation of pain involves endogenous systems that are opioid and non-opioid based. Inhibition of nociceptive activity in the spinal cord is largely performed by the PAG-RVM connections. Terminals of RVM neuron have been shown in the superficial and deep lamina of the dorsal horn. Ascending nociceptive signalling has been shown to stimulate the anterior cingulate cortex and this has been indirectly linked to descending inhibitory activity of the dorsal horn neurons through connections with the PAG.

Chronic pain refers to ongoing pain, typically considered beyond three months. The aetiology of chronic pain is not fully understood, however, ongoing nociceptive input from inflammatory, visceral, or neurogenic input results in central changes in pain processing. Non-specific, or psychogenic chronic pain involves persistent pain with
no apparent organic cause. Regardless of whether chronic pain is from known or unknown organic causes, extensive evidence shows central changes in pain processing takes place in the chronic pain condition.

Chronic pain has far-reaching effects that extend beyond the neurophysiological components. These effects include changes in psychological status, fear of re-injury, avoidance of activity, loss of self-esteem, and depression (Mior, 2001). Prescription of extended rest has now been replaced with prescription for exercise and functional restoration programmes to return the patient to normal activities. There is substantial evidence supporting the premise that active exercise achieves long-term relief of pain and related disability. There is, however, a shortage of information on the optimal prescription for the exercise-based rehabilitation in chronic pain disorder.

Accumulating evidence shows that persistent pain results in widespread somatic hypersensitivity, possibly through changes in central sensitivity. Dysfunctional descending inhibition is a significant characteristic of central sensitisation. Therefore, it is likely that these central changes, together with adverse changes in psychological status and the development of fear of pain and kinesiophobia, results in the ongoing chronicity of pain in chronic pain disorder.

2.12.1 Exercise induced pain-inhibition in healthy participants

Based on the available literature on healthy participants, exercise has predominantly shown to inhibit experimental pain parameters. Acute physical exercise has been shown to increase the pain threshold and reduce the pain intensity rating to experimental noxious stimulation. The inhibition of pain appears to be exercise-dose
and duration dependent. Following running exercise, the threshold to elicit an exercise-induced pain inhibition was shown to be at least 50% of VO$_2$ max for a minimum of 10 min (Hoffman, et al., 2004). During cycling exercise, pain thresholds were observed to be significantly increased at an intensity of 200 W, which was equivalent to 70% of maximum oxygen uptake (Pertovaara, Huopaniemi, et al., 1984). Similarly, increases in pain thresholds were observed in healthy participants during isometric exercise (Drury, et al., 2004; Kosek & Ekholm, 1995), although eccentric exercise appears to lower pressure pain thresholds through increased muscle sensitivity at 24 and 48 hours following exercise (S. J. Baker, et al., 1997).

The mechanisms underlying exercise-induced pain inhibition are not fully understood. Possible candidates for pain inhibition following exercise are the endogenous opioids and the stress hormones such as adrenocorticotropic hormone (Angelopoulos et al., 1995; Kemppainen, et al., 1990). The endogenous opioid, β-endorphin, is released into circulation by the pituitary gland and to central sites by the hypothalamus. Exercise of sufficient intensity and duration has been demonstrated to increase circulating β-endorphin levels (Goldfarb & Jamurtas, 1997; Schwarz & Kindermann, 1992; Taylor et al., 1994). A poor correlation between circulating plasma β-endorphin concentration and cerebrospinal fluid, however, limits the use of plasma-endorphin concentration to assess the relationship between pain and central nervous system opioid activity (D. G. Baker, et al., 1997).

In the animal model, cerebrospinal fluid endorphin and corticotropic hormone concentrations were shown to be enhanced during low intensity but not high intensity aerobic exercise (Radosevich, et al., 1989). In contrast, plasma concentrations of endorphin and corticotropin were shown to be elevated during high intensity exercise.
Previous studies on the effects of opioid and corticotrophin blockade on pain parameters in persons following exercise show mixed results (Droste, et al., 1991; Kemppainen, et al., 1990; Pertovaara, Huopaniemi, et al., 1984). Together, these results show that plasma levels of opioid concentration are not closely matched with perceptual responses to noxious stimuli.

In contrast to the plasma endorphin research on pain and exercise, there is little research showing the acute effects of exercise on the central neurosensory processing of noxious input in healthy persons. It is possible that acute exercise mediates central processing of nociceptive input at segmental and/or at supraspinal sites. The functional status of the spinal cord excitability and mediation of nociceptive signalling can be assessed by measuring the nociceptive withdrawal reflex. One study has shown that the threshold for the nociceptive withdrawal reflex threshold was significantly elevated after aerobic cycling exercise at 50% of maximum oxygen consumption in healthy participants (Guieu, et al., 1992). This suggests that aerobic exercise reduces the excitability of the spinal cord and that this may be associated with the function of endogenous pain inhibiting systems. Further research is required to elucidate the role of the spinal cord and supraspinal networks in mediating pain inhibition following exercise.

The potential mechanisms by which exercise triggers pain inhibitory systems are not known. It has been suggested that exercise evokes central antinociceptive systems (Persson, et al., 2003). In this context, intense skeletal muscle contraction induces muscle pain and this evokes the function of diffuse noxious inhibitory controls. The activation of diffuse inhibitory controls by muscle pain during exercise may evoke a central inhibition of noxious stimuli in the post-exercise period.
Another potential candidate mechanism for antinociception following acute exercise is through stress induced analgesia. In this context, physical exercise elicits a stress response which induces descending opioid-based inhibition of dorsal horn neurons. It is possible to assess the function of this antinociceptive system by determining changes in neurosensory events at the spinal cord and at the cerebral level following acute physical exercise. Here, the excitability of the spinal cord can be assessed by the nociceptive withdrawal reflex. Supraspinal processing of noxious stimuli can be assessed by capturing cerebral event related potentials to nociceptive events. Together, the concomitant assessment of the nociceptive withdrawal reflex and cerebral event related potentials could further explicate the function of the pain inhibitory systems following aerobic exercise in healthy participants.

2.12.2 Exercise induced pain-inhibition in participants with chronic pain

From the available literature, acute exercise has predominantly shown to increase the sensitivity to experimental pain in participants with chronic pain disorder. In contrast to chronic pain participants, acute exercise in healthy subjects has shown to reduce experimental pain sensitivity. This suggests a dysfunction of the endogenous pain inhibitory system to acute exercise in persons with chronic pain disorder (Van Oosterwijck, et al., 2012). In contrast, long-term exercise rehabilitation has been shown to decrease experimental pain sensitivity and reduce clinical pain report in participants with chronic pain. These outcomes, however, appear to be dependent on the exercise prescription. Under current models of exercise prescription, clinical pain symptoms are exacerbated in persons with chronic pain disorder (Newcomb, et al., 2011).
Much of the research on exercise for chronic pain has been based on applying existing cardiovascular based exercise prescription protocols. Aversive consequences of exercise are often reported by chronic pain participants and this is a deterrent to compliance with therapeutic protocols. A potential alternative prescription for exercise in chronic pain participants is to limit exercise intensity based on the symptomology during exercise. This method of prescription could minimise the elevated pain during exercise and improve programme adherence.

The mechanism for reduced experimental and clinical pain following exercise rehabilitation in chronic pain participants is not fully understood. It is possible that exercise rehabilitation restores the functional excitability of the spinal cord by reducing the sensitisation of central mechanisms for pain signalling. Potential pathways for this include the enhancement of the function of the opioid system (Droste, et al., 1991) or by forebrain dependent antinociception (Crown, et al., 2004). Further research is required to examine the role of exercise in modifying the function of the central nervous system and central sensitisation in chronic pain patients.

Another potential research pathway for the reduced clinical pain report following exercise rehabilitation for persons with chronic pain disorder is through changes in psychological status (Valim, et al., 2003). The endogenous opioid system is silent in normal physiological conditions and becomes active under conditions such as physical exercise. Pain inhibition has been associated with the various classes of endorphins, however, these peptides are also associated with positive changes in behaviour and mood (Hoffman, et al., 1996). Regular physical activity has been shown to be inversely correlated with the prevalence of depression and anxiety.
disorders (Goodwin, 2003). Therefore, it is possible that physical exercise may favourably mediate chronic pain report through positive changes in psychological status. Additionally, prescribing exercise that is mediated to pain symptomology could potentially alleviate a fear of movement, kinesiophobia, and thereby reduce clinical pain report and experimental pain sensitivity through positive changes in psychological status.

The rational for exercise rehabilitation for persons with chronic pain is not straightforward. Acute exercise has shown to exacerbate symptoms and lower experimental pain thresholds. Additionally, exercise rehabilitation programmes have often revealed low levels of compliance amongst chronic pain participants. Improvements in cardiovascular fitness through prescribed exercise programming are not always correlated with reductions in pain report (Valim, et al., 2003). Based on previous research evidence, there is support for the notion that moderate to low levels of exercise intensity are associated with reduced pain report in chronic pain participants (Newcomb, et al., 2011). Currently, there is a lack of information on the exercise work capability and pain symptomology during exercise amongst chronic pain participants.

In conclusion, there is potential for further research in the function of spinal and cerebral antinociceptive systems following exercise. Based on the available literature, aerobic exercise may engage antinociception and pain inhibition through descending spinal input and cerebral modulation of pain signalling. Additionally, further research is required to elucidate central hypersensitivity and the optimal exercise prescription in persons with chronic pain disorder.
Chapter 3: Research proposal and design
3.1 Justification of thesis

It is proposed that the present research investigates the relationship between pain-inhibition and exercise through a series of studies that explicates the function of the pain system in healthy participants and in persons with chronic pain disorder.

Studies on pain rely on the assessment of pain through subjective judgment. In pain research, reliable measurement protocols are required in order to observe treatment effects. Currently there is a lack of information on the reliability and validity of pain-related neurophysiological events. The nociceptive withdrawal reflex is a spinal mediated reflex that launches motor activity by threshold excitation of nociceptive afferent fibers. The nociceptive withdrawal reflex can be a useful procedure in pain research in order to examine the effects of treatment on spinal cord excitability. For example, a reliable nociceptive withdrawal reflex protocol would be of use in order to examine the effect of intervention such as physical exercise on spinal-mediated pain inhibition. The reliability of the nociceptive withdrawal reflex and the association with pain has not been fully detailed.

Although several studies show that exercise inhibits experimental pain parameters, few studies have examined the mechanisms behind exercise-induced pain inhibition. The existence of spinal and suprapinal endogenous pain mediating systems is well recognised, however, it is not clear whether these are activated by exercise. There is a lack of information on the changes of experimental pain parameters alongside neurophysiological pain-related events following physical exercise. Through the measurement of spinal-mediated nociceptive withdrawal reflexes and cerebral event
related potentials, it is possible to examine the function of pain-inhibitory mechanisms in the spinal cord and in the brain following physical exercise. This could elucidate the function of endogenous pain-inhibiting mechanisms in the spinal cord and in supraspinal regions following physical exercise.

Exercise is often recommended for persons with chronic pain. Several studies show that exercise rehabilitation has favourable outcomes on pain report, functional capacity, health, and experimental pain outcomes. In contrast, previous research has shown an exacerbation of clinical pain outcomes and low programme adherence in participants with chronic pain disorder. Few studies, however, have examined the optimal prescription for exercise workload and programme adherence in persons with chronic pain. By assessing pain and workload responses during exercise it is possible to develop a prescription for exercise rehabilitation that optimises programme adherence, improves functional capacity, enhances health components, and reduces pain report in persons with chronic pain.

There is a lack of information on combined pain report and experimental pain parameters following exercise rehabilitation in persons with chronic pain. Accumulating research evidence shows a general trend of augmented baseline sensory responses among persons with chronic pain. Enhanced experimental sensory responses in persons with chronic pain are revealed by elevated sensitivity to experimental pain stimuli compared to healthy persons. Previous research shows that exercise rehabilitation reduces the sensitivity to experimental pain stimuli in persons with chronic pain. Few studies have examined the effects of exercise rehabilitation on central sensitivity through experimental pain parameters and functional brain imaging in persons with chronic pain.
3.2 Purpose of the thesis

Based on the available literature between exercise and pain inhibition, aerobic exercise appears to be the most consistently demonstrated modality of physical activity to attenuate experimental pain parameters in healthy participants and reduce pain report in persons with chronic pain. Therefore, the principle purpose of the present thesis is to examine the effects of aerobic exercise on pain and neurosensory modulation in healthy participants and in persons with chronic pain disorder. In order to examine these effects, the thesis has four specific purposes, each of which are addressed in four separate but interrelated studies.

3.3 Delineation of thesis

The present thesis consists of four inter-related studies. Study one examines the reliability of the nociceptive withdrawal reflex threshold and the association of this measure with the electrocutaneous pain threshold. Study two examines the effect of aerobic exercise on experimental pain threshold together with measures of pain-related events including the nociceptive withdrawal reflex and cerebral event related potentials. Furthermore, study two examines the influence of the intensity of aerobic exercise on pain threshold and pain-related events. The purpose of this is to elucidate the potential mechanisms for pain inhibition in the spinal cord and in supraspinal structures. Study three examines the effect of aerobic exercise rehabilitation on pain, health, functional, and experimental pain outcomes in persons with chronic pain. Study four examines the functional brain responses to somatic-
pressure stimulation in chronic pain and healthy participants before and after exercise rehabilitation. The participants in study three were also involved in study four.

### 3.4 Hypotheses

Based on the previous research literature, aerobic exercise appears to inhibit pain in healthy persons and reduces clinical pain in persons with chronic pain disorder. Most of these studies have not included neurophysiological measures of pain-related events alongside perceptual responses in order support the findings and to ascertain the mechanisms behind exercise-induced pain inhibition. The overall research premise is that physical exercise mediates pain parameters in healthy persons and in persons with chronic pain disorder. Therefore, the following hypotheses are proposed:

1. The nociceptive withdrawal reflex is a reliable pain-related neurophysiological event and is associated with the pain threshold. Since the nociceptive withdrawal reflex has the potential to explicate changes in spinal cord excitability following exercise, the reliability of this neurophysiological event and association with the pain threshold needs to be determined.

2. Acute aerobic exercise attenuates experimental pain and pain-related neurophysiological events in healthy participants. Since aerobic exercise has been shown to attenuate the perception of experimental pain in healthy participants, then the potential changes in neurophysiological events such as the nociceptive withdrawal reflex and cerebral event related potentials need to
be determined to further ascertain the mechanisms for exercise-induced pain inhibition.

3. Moderate-intensity aerobic exercise rehabilitation reduces pain, enhances health outcomes, and improves functional capacity in persons with chronic pain disorder. Since moderate intensity aerobic exercise has been shown to improve exercise programme adherence in chronic pain participants, it is necessary to determine whether this exercise prescription has favourable outcomes on pain, health, and functional capacity.

4. Aerobic exercise rehabilitation favourably modulates brain-related processing of somatosensory stimulation in persons with chronic pain. Chronic pain disorder has been associated with increased somatic sensitivity. Since aerobic exercise rehabilitation has been shown to be associated with reduced experimental pain sensitivity, then it is expected to observe functional changes in the brain associated with the central processing of somatosensory signals following aerobic exercise rehabilitation.

3.4.1 Purpose of study one

The purpose of study one is to determine the reliability of the nociceptive flexion reflex threshold and assess the association with pain threshold. A potential neurophysiological correlate of pain is the nociceptive flexion reflex. While the nociceptive flexion reflex has been investigated in many studies, there is a lack of information on the within and between trial reliability. This information is important since a reliable pain-related event such as the nociceptive flexion reflex threshold
would be useful in studies that examine the effect of exercise intervention on pain parameters.

### 3.4.2 Purpose of study two

The purpose of study two is to determine the acute effect of aerobic exercise on experimental pain and pain-related neurophysiological events. Parameters such as the pain threshold, the nociceptive withdrawal reflex threshold, and cerebral event related potentials are to be assessed before and after acute aerobic exercise. While several studies have shown that aerobic exercise inhibits experimental pain parameters, there is a lack of information showing the effect of exercise on pain-related neurophysiological events. This information is important since it would further elucidate the potential mechanism behind exercise-induced pain inhibition. The nociceptive withdrawal reflex threshold could examine the function of the spinal cord in exercise-induced pain inhibition. Additionally, cerebral event related potentials would further explicate the outcome of nociceptive signalling in the cerebrum. Together this information could reveal the function of spinal and supraspinal mechanisms in pain modulation following aerobic exercise.
3.4.4 Purpose of study three

The purpose of study three is to determine the effect of moderate-intensity aerobic exercise rehabilitation on clinical pain, functional capacity, health, and experimental pain parameters in persons with chronic pain. A significant problem in exercise rehabilitation for persons with chronic pain is exercise-related muscle pain and programme adherence. Additionally, there is a lack of information on the optimum exercise prescription for persons with chronic pain. This information is important since exercise rehabilitation shows evidence of favourable outcomes for clinical pain, health, functional capacity, and experimental pain parameters in persons with chronic pain.

3.4.5 Purpose of study four

The purpose of study four is to determine the effect of somatic-pressure stimulation during functional brain imaging before and after aerobic exercise rehabilitation in persons with chronic pain. There is substantial evidence indicating hypersensitivity to experimental somatic stimuli in persons with chronic pain. Previous research shows that exercise rehabilitation reduces the sensitivity to experimental mechanical somatic pressure. There is a lack of information on the brain responses associated with central sensitisation in persons with chronic pain following aerobic exercise rehabilitation. Therefore, this study aims to examine the regional brain responses to somatic mechanical pressure stimulation before and after exercise rehabilitation in persons with chronic pain and compare this with healthy pain-free controls.
Chapter 4: Reliability of the nociceptive withdrawal reflex (NWR) threshold and association with pain threshold
4.1 Abstract

The purpose of this study was to assess the reliability of the nociceptive withdrawal reflex threshold (NWR-T) and Pain threshold in three repeated trials using electrocutaneous stimuli. Each trial was separated by a mean of $4.3 \pm 2.9$ days (between-trials) and included two repeated measurements (within-trial) of the NWR-T and the Pain threshold (PT) separated by 20 min. The participants were 14 healthy males (mean age $\pm$ SD, $23.5 \pm 5.3$ years). There was a significant difference between the NWR-T and PT. The reliability of the NWR-T and PT shows a between-trials coefficient of variance ($CV_{SEM}$) of 16.1% and 16.9%, respectively. The within-trial $CV_{SEM}$ for NWR-T and PT was 5.4% and 4.3%, respectively. There was a significant correlation between the NWR-T threshold and PT. The parallel association and correlation of the NWR-T with the PT suggests that the NWR-T is valid in experimental pain studies under standardised resting conditions.
4.2 Introduction

Acute noxious stimuli are administered in experimental and clinical settings to assess nociceptive transmission and pain sensation. An acute noxious stimulus to the foot evokes a flexor reflex and elicits a short, sharp pain sensation (Eklund, Grimby, & Kugelburg, 1959). A flexor reflex is initiated when a noxious stimulus is of sufficient intensity to project a sensorimotor reflex. Limb flexor reflexes are mediated by a widespread multi-sensorial network of afferents expressing a synergy of muscle activation through polysynaptic and multi-segmental spinal pathways (Schomburg, 1990). The motor function of the flexor reflex constitutes a limb withdrawal away from potential damage.

The flexor reflex when evoked by activation of nociceptive afferents has been termed the nociceptive flexion reflex, nociceptive withdrawal reflex or NWR reflex (Sandrini, et al., 2005; Skljarevski & Ramadan, 2002). The motor output of the NWR reflex is initiated by cutaneous nociceptive afferents via the spinal cord (Hugon, 1973). The latency of the NWR reflex corresponds with the signal conduction velocity of group III afferents (Ertekin, Ertekin, & Karcioğlu, 1975). Acute activation of nociceptive group III afferents evokes an NWR reflex (Wiesenefeld-Hallin, Hallin, & Persson, 1984) that is mediated by activity in type A alpha-beta (Willer & Albe-Fessard, 1983) and type IV afferents (Gronroos & Pertovaara, 1993). Consequently, the threshold for evoking the NWR reflex is a non-invasive procedure for identifying the activation onset of nociceptive afferents (Dowman, 1993).
The activation of cutaneous nociceptive afferents can be initiated by intense heat, mechanical, chemical, or tissue injury stimuli to elicit a pain sensation (Collins, Nulsen, & Randt, 1960). When induced by an acute electrocutaneous stimulus, the pain sensation is described as a “pinprick”, “sting” or “electric shock”. The minimum level of stimulation that reliably elicits a pain report is identified as the pain threshold (Gracely, 1999b). During controlled experimental conditions, the electrocutaneous pain threshold has been shown to correspond with the threshold of the NWR reflex (Willer, 1977). Therefore the NWR reflex is considered as a physiological measure of the pain related response (Dowman, 1991). In contrast, several studies have shown a disparity between the NWR reflex threshold and pain threshold (Boureau, et al., 1991; Bromm & Treede, 1980; Defrin, Peleg, Weingarden, Heruti, & Urca, 2007; France et al., 2005; Nord & Durkovic, 1988; Terkelsen, Andersen, Hansen, & Jensen, 2001; Willer, Roby, & Le Bars, 1984).

The threshold for the NWR reflex is subjected to differential processing compared with the pain threshold (Defrin, et al., 2007). For this reason, variance in the excitability of the NWR reflex is expected to be independent or in parallel with the pain threshold. Currently there are a paucity of data which provide for the reliability of the NWR reflex threshold and the concomitant assessment of pain threshold amongst successive trials. Therefore, the purpose of this study was to determine the reliability of the NWR reflex threshold and to assess the association with pain threshold in a series of repeated trials under resting conditions.
4.3 Methodology

4.3.1 Participants

The participants included 14 young healthy males (mean ± SD; age 23.5 ± 5.3; height 179 ± 6.3 cm; body weight 78.4 ± 7.1 kg). Participants were screened with a health questionnaire (Appendix 4). The exclusion criteria included the use of medications such as analgesics and anti-inflammatories, a prior history of leg/knee injury or surgery, acute and chronic disease. The study was conducted with the approval of Charles Sturt University Ethics in Human Research Committee and all subjects signed a letter of informed consent.

4.3.2 Experimental design

The experimental design was a within-subjects repeated measures procedure. Each subject participated in three trials separated by at least two days (mean ± SD; 4.3 ± 2.9 days). Each trial included two repeated measurements (Measurement A and Measurement B) of the NWR reflex threshold and Pain threshold separated by an interval of 20 minutes. The study was designed to minimise variations in the NWR reflex threshold from circadian rhythms (Sandrini et al., 1986), gender (Mylius, Kunz, Schepelmann, & Lautenbacher, 2005), temporal summation (Arendt-Nielsen, Brennum, Sindrup, & Bak, 1994) and exercise (Guieu, et al., 1992). Participants were instructed to maintain their regular daily activities during the period when the experimental trials were performed and to avoid aerobic exercise prior to each trial. Each trial was performed in a climate controlled laboratory (mean temperature and
relative humidity of 23.2 ± 2.1 °C and 25.2 ± 7.8 %, respectively) and the corresponding time of day.

### 4.3.3 Electrode site preparation and position

The procedure for electrode placement has been previously described (Willer, 1977), however, further methodological details are also outlined below. The placement of single differential electrodes was performed using anthropometric procedures at the beginning of each trial in order to minimise variation in electrode position. This procedure was performed by the same experimenter and included verifying the dominant leg, identifying the anatomical sites for electrode placement, and dermal preparation. The electrocutaneous stimulation site (ES) was located in the groove between the lateral malleolus of the fibula and the calcaneal tendon, over the retromalleolar pathway of the sural nerve. The surface electromyographic (EMG) recording site was on the biceps femoris long head muscle. This was located by identifying the biceps femoris tendon insertion on the lateral aspect of the popliteal space and measuring 1/3 of the distance to the ischial tuberosity towards the mid-gluteal fold. The reference electrode site was located on the lateral malleolus of the contralateral fibula. The electrode sites were prepared by shaving, dermal abrasion, and degreased with ethanol solution to achieve an impedance of less than 10,000 Ω between electrodes.

Two disposable (Ag/AgCl) adhesive press-stud electrodes (Meditrace, Chicopee, USA, 30 mm diameter with 22 mm diameter electrogel contact surface area) were applied at the ES and EMG sites. The electrodes were vertically aligned 30 mm apart from the centre of the disc, separated by the rim of the adhesive disk. The cathode
was connected inferior to the anode electrode. A single adhesive (Ag/AgCl) disposable press-stud electrode was positioned at the reference site following dermal preparation, on the contra-lateral malleolus of the fibula. The electrodes remained in position for Measurement A and B within each trial.

4.3.4 Laboratory apparatus

The EMG signal of biceps femoris muscle was digitally sampled at 2000 Hz using an analog-to-digital converter (Amlab, MR01C, Sydney, Australia). The raw EMG activity was low-pass filtered (25 Hz; 2\textsuperscript{nd} order quasi-butterworth filter with a slope of -40 dB/Dec). Similar filter parameters have been previously applied to assess the NWR reflex signal (Andersen, Jensen, Brennum, & Arendt-Nielsen, 1995). The digital sampling procedure simultaneously recorded the ES and the EMG signal.

4.3.5 Electrocutaneous stimulation procedure

Participants were seated on a reclined padded therapeutic lift-back table (Metron, Sydney, Australia) with the trunk reclined by 50° from the vertical and the lower limbs positioned horizontally on the padded table (Figure 4.1). A 10 s baseline EMG signal was recorded when participants were comfortably seated.

The electrocutaneous stimuli were delivered by a constant-voltage stimulator (Digitimer D185 MKIIa, Hertfordshire, UK) connected to a high grade electrical cable (Digitimer D185-HB4, Hertfordshire, UK), as previously applied in peripheral nerve and somatosensory research (Pelosi et al., 2002). Each electrocutaneous stimulus
was comprised of a volley of 8 x 1 ms rectangular pulses with an interspike interval of 2 ms delivered over 22 ms.

The NWR reflex threshold and pain threshold were determined by a modified staircase method (Willer, 1977). This procedure began by delivering a set of four 30 V electrostimuli at random-intervals of 5-15 s apart. Following each set of four electrostimuli, participants were requested to verbally rate the intensity of the sensation using a 0-10 category scale (Appendix 1). The numerical anchors and verbal descriptors were graded as 0=No sensation, 2=Slight sensation, 4=Moderate sensation, 6=Pain sensation, 8=Strong Pain sensation, 10=Pain tolerance. Participants were informed that a rating of 6 on the category scale represented the point at which the sensation was no longer tactile and was painful. A rating of 6 represented the pain threshold.

Following the first set of electrostimuli and verbal sensation scale rating, each subsequent set was increased by 20 V. This procedure continued until the NWR reflex threshold and pain threshold, or a upper limit of 7 on the sensation scale was observed. The pain threshold was represented by a verbal rating of 6 on the sensation scale. The threshold for the NWR reflex was defined by the presence of each of the following criteria: 1) an NWR reflex signal amplitude of at least 1.65 SD of the mean baseline resting EMG activity (France & Suchowiecki, 1999); 2) the voltage intensity that evoked at least three NWR reflexes from a set of four electrocutaneous stimuli (Willer, 1980); and 3) a post-stimulus reflex signal within a 90-150 ms time-frame (Rhudy, et al., 2006). A signal latency window of 90-150 ms is often applied in NWR reflex research to preclude signal contamination by non-nociceptive reflexes,
startle and/or voluntary responses (Rhudy, Williams, McCabe, Nguyên, & Rambo, 2005). This procedure may have included crosstalk from other knee flexor muscles.

Upon the initial observation of the NWR reflex, a decrement of 10 V was applied to assess the consistency of the NWR reflex signal at a reduced electrocutaneous intensity. This procedure differs slightly from the up-down stair-case method for measuring the NWR reflex threshold, however, this minimises pain-induced stress (Willer, 1980). A set of four NWR reflexes were digitally recorded when a consistent NWR reflex signal at threshold was observed.
Figure 4.1: Showing the subject setup for recording the lower limb nociceptive withdrawal reflex A) and the electromyogram setup B)
4.3.6 Signal analysis

The offline signal analysis included the measurement of the NWR signal latency for each of the four electrostimuli at the NWR reflex threshold and at the pain threshold. The signal latency was determined from the onset of the first spike-pulse of the electrocutaneous stimulus and the first inflection wave of the NWR reflex signal within the 90-150 ms post-stimulus period.

4.3.7 Statistical analysis

It is desirable to assess the degree of measurement reliability by using multiple statistical methods, as each has its own limitations. The more familiar paired t-test and ANOVA for a null hypothesis is not an appropriate test for establishing equivalence since a failure to reject the null hypothesis can arise from a lack of power. Therefore, several methods were applied to assess the reliability.

The coefficient of variation was determined for each subject from the between-trial and within-trial measurements. The between-trials and within-trial reliability of the NWR reflex threshold and pain threshold were evaluated using Bland-Altman agreement analysis (Bland & Altman, 1986), Standard error of measurement as a Coefficient of variation (CV_{SEM}), and the Intra class correlation coefficient (ICC). The CV_{SEM} was applied as it is a measure of the test stability between and within each trial. The between-trials reliability analysis was determined by comparing results among Measurement A for each trial. The within-trial reliability analysis was determined by comparing results between Measurement A and Measurement B.
within each trial. The ICC provides a measure of absolute agreement between repeated tests and is sensitive to systematic bias (Shrout & Fleiss, 1979). For the ICC analysis, the statistical software used was SPSS release 14.02 (SPSS, Inc) with a Two-way mixed model computation and the agreement definition set at Absolute. As a general guideline, values above .75 are indicative of good reliability (Portney & Watkins, 1993). An ICC reliability of .75 and above would show clinical application for the NWR and PT.

Data for the NWR reflex threshold and pain threshold are presented as mean ± SD. Comparison between the mean NWR reflex threshold and Pain threshold was assessed by repeated measures ANOVA, with significance level set at \( P<0.05 \). Partial eta-squared \( (\eta^2) \) was used as the effect size for F tests. Guidelines for interpreting \( \eta^2 \) are small=.01, medium=.06, large=.14 (Cohen, 1988).

### 4.4 Results

A total of 672 NWR reflexes (comprised of a set of four reflexes at the NWR reflex threshold and pain threshold in six repeated sessions for each participant) were digitally sampled at the NWR reflex threshold (NWR-T) and pain threshold (PT). The mean voltage (± SD) for the NWR-T and PT for the three trials are shown in Table 4.1. The mean NWR-T and PT was 110.6 V and 128.2 V, respectively. There was a significant difference between the mean NWR-T and the PT [\( F=31.8; \ df 1,13; \ P<0.001; \ \eta^2=0.41 \)]. The mean latency ± SD of the NWR reflex signal at the NWR-T and PT was 105 ± 13 ms and 102 ± 11 ms, respectively. The percent coefficient of variation for each subject for the NWR-T and PT within and between trials is shown in Table 4.2.
Table 4.1: The mean electrocutaneous intensity (V±SD) for the NWR reflex threshold and Pain threshold between-trials (Trials 1, 2 & 3) and within-trials (Measurement A and Measurement B). The between-trials period were separated by a mean of 4.3 ± 2.9 days. The within-trial period was separated by a 20 minute rest interval.

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
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<th>Trial 2</th>
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<th>Trial 3</th>
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<tbody>
<tr>
<td></td>
<td>NWR-T</td>
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<td>NWR-T</td>
<td>PT</td>
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<td>PT</td>
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<td>Measurement A</td>
<td>123.0 ± 53.7</td>
<td>132.5 ± 58.3</td>
<td>107.5 ± 45</td>
<td>128.6 ± 59.1</td>
<td>101.1 ± 45.2</td>
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<tr>
<td>Measurement B</td>
<td>123.6 ± 55.8</td>
<td>137.5 ± 60.8</td>
<td>105.0 ± 42.3</td>
<td>122.5 ± 54</td>
<td>102.5 ± 46.3</td>
<td>122.9 ± 50.1</td>
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<td>(V ± SD)</td>
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Table 4.2: The mean coefficient of variation (CoV%) for the NWR-T and PT for each subject

<table>
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<tr>
<th>Subject</th>
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<th>NWR-T Within trial CoV%</th>
<th>PT Between trial CoV%</th>
<th>PT Within trial CoV%</th>
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<td>5.2</td>
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<tr>
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4.4.1 Between-trials measurement analysis of the NWR reflex threshold and pain threshold

The between-trials analysis for the NWR reflex threshold reveals no systematic bias between measurements and that 89.5% of the data are within the limits of agreement (Figure 4.2). The mean between-trials coefficient of variation \((CV_{SEM})\) was 16.9 % and the mean between-trials ICC was .82.

The between-trials repeated measurement agreements for the PT reveals that a mean of 93% of the data are within the limits of agreements (Figure 4.2). The mean between-trials \(CV_{SEM}\) for PT was 16.1 %. The between-trials mean ICC for the measurement of the PT was .88.
Figure 4.2: The between-trials measurement analysis for the NWR reflex threshold and Pain threshold. The trials were separated by a mean of 4.3 ± 2.9 days. The measurement analysis was performed by comparing the threshold assessment in Measurement A for each trial.
4.4.2 Within-trial repeated measurement analysis of the NWR reflex threshold and pain threshold

The within-trial measurement analysis for the NWR reflex threshold was determined by comparing the threshold assessment for Measurement A and Measurement B within each trial. The graphical analysis (Figure 4.3) reveals a mean of 89.5% of the data were within the limits of agreement. The within-trials mean $CV_{SEM}$ and the ICC is 5.4% and .98, respectively.

The within-trials measurement analysis for PT reveals that a mean of 90.7% of data were situated within the limits of agreement (Figure 4.3). The within-trials mean $CV_{SEM}$ and ICC for PT was 4.3% and 0.98, respectively.
Chapter 4: Reliability of the nociceptive withdrawal reflex threshold and association with pain threshold

**Figure 4.3:** The within-trial measurement analysis of the NWR reflex threshold and Pain threshold. The repeated threshold assessments (Measurement A and Measurement B) were separated by a 20 min rest interval within each trial.
4.4.3 Correlation between the NWR reflex threshold and the pain threshold

The correlation between the NWR reflex threshold and the Pain threshold within each trial are shown in Figure 4.4. Each data point represents the intersection between the measurement of the NWR reflex threshold and the Pain threshold for each participant. The coefficient of determination, $r^2$, indicates the accuracy of the NWR reflex threshold for predicting the Pain threshold. The mean coefficient of determination between the NWR reflex threshold and Pain threshold is .93. Thus the NWR reflex threshold accounts for 93% of the variance in the Pain threshold.
Figure 4.4: The correlation between the NWR reflex threshold and the Pain threshold within each trial
4.5 Discussion

The novel finding in the present results show a reliable NWR reflex threshold that is closely associated with the electrocutaneous pain threshold. The present results show a significantly lower NWR reflex threshold compared with the pain threshold. The disparity between the NWR reflex threshold compared with the pain threshold may be due to the differential processing between sensorimotor reflexes and pain responses. Integration of the NWR reflex amongst sensory and motor fibers is carried out within the spinal cord (Baldissera, Hultborn, & Illert, 1981), however, the report of pain threshold requires an evaluation of the sensory signal as processed by the nervous system (Gracely, 1999b). Pain signals are processed within a central network of brain structures involved in cognitive and perceptual mediation of sensory information (Price, 2000). Therefore, pain is a subjective experience that is not simply determined by the extent of stimulation or nociceptive activity (Rhudy, et al., 2005).

It has previously been shown that the pain threshold under resting conditions varies substantially between trials (Lund, et al., 2005), however, a low variance in pain threshold has been observed when measured within a trial (Sang, Max, & Gracely, 2003). Not unlike previous findings, the present results show a substantial variance in pain threshold between trials of 16.1% and a low within-trial variance of 4.3%. The variance in pain threshold appears to be comparable with the variance in the NWR reflex threshold amongst the trials. This indicates that the variance in the pain threshold is also coupled with the changes in the NWR reflex threshold amongst the trials.
There was a substantial variance in the inter-individual threshold for the nociceptive withdrawal reflex and pain. Previous research shows a similar variance in thresholds between subjects (Guieu, et al., 1992; Jones, et al., 2007), although lower variances have been observed (Biurrun Manresa, Neziri, Curatolo, Arendt-Nielsen, & Andersen, 2011). Possible reasons for differences in the electrocutaneous pain threshold between subjects include the level of arousal (Haslam, 1967) and dissimilarity in the level of stress and anxiety (Hoeger Bement, Weyer, Keller, Harkins, & Hunter, 2010). Methodological limitations may also explain some of the between-trial measurement variance for the pain threshold and the NWR reflex threshold. The present study required the placement of new electrodes for each trial, however, the electrodes remained intact within the trial. Despite using surface anatomy procedures to maintain a consistent electrode position between trials, slight departures in electrode position may modify the level of neural activation by electrocutaneous stimulation.

The variation in the pain threshold and NWR reflex threshold may also be due changes in the central pain processing system between trials. It has been reported that a significant portion of the variance in pain rating is attributed to changes in the actual pain sensation (Rosier, Iadarola, & Coghill, 2002). Alterations in arousal and affective functioning, which are associated with central pain circuits, have been linked with changes in pain rating and the NWR reflex (Edwards et al., 2006; Rhudy, et al., 2005). Anticipation of very painful stimulation has been shown to increase the NWR threshold by involvement of endogenous opioid release (Willer, Dehen, & Cambier, 1981). Hence, it is possible that central changes in pain processing between trials may arbitrate expectations about noxious stimuli and alter the dispensation of noxious afferent information. This variance was notably present between trials 1 and
2 (Figure 4.2). It is possible that procedural familiarity and awareness was acquired by participants following trial 1 and this may have altered the arousal and affective functioning towards the electrocutaneous stimulation procedure in the ensuing trials. The implications for this are that interventions for modulating pain threshold will need to account for a potential 16% between-trial variance. Future studies could determine methods for minimising the effects of anxiety and arousal by including familiarity test sessions and standardised instructional tools.

The present results show a strong correlation between the NWR reflex threshold and pain threshold within each trial and confer with previous research (Willer, 1977). The coupling between the NWR reflex threshold and pain threshold is consistent throughout the trials. Compared with the present results, one study shows a lower correlation between the NWR reflex threshold and pain threshold (Boureau, et al., 1991). This may be due to differences in defining the thresholds for the NWR reflex and pain. The present study required that the NWR reflex was evoked in at least 75% of a set of threshold electrocutaneous stimuli (France & Suchowiecki, 1999), however, a 50% frequency of occurrence has also been applied (Boureau, et al., 1991). The present study defined pain threshold as the intensity at which the stimulus was no longer tactile and became painful. Previous research has defined pain threshold as the intensity level that elicited a minimum of 50% of a weak pain response (Boureau, et al., 1991). Here, the electrical intensity was defined as ‘light pricking’ and ‘weakly unpleasant’. Therefore, it might be expected that the degree of correlation between NWR reflex threshold and pain threshold is in part, a consequence of the method for defining the thresholds.
4.5.1 Conclusion

The present results show a within-trial measurement stability of the NWR reflex threshold that is experimentally reliable. There was a substantial between-trials variance for the NWR reflex threshold, however, this was comparable with the variance in pain threshold. The association of the NWR reflex threshold with the pain threshold suggests that the NWR reflex threshold is valid in experimental pain studies under standardised resting conditions. These data also suggest that interventions may need to account for a between-trial variance in pain threshold of 16.1% and a within-trial variance of 4.3%.
Chapter 5: Aerobic exercise attenuates cerebral event related potentials to nociceptive events
5.1 Abstract

The aim of this study was to assess the effect of acute aerobic exercise on cerebral and spinal processing of nociceptive events. Ten healthy participants performed 2 x 30 min bouts of cycling exercise at 70% and 30% of maximum oxygen consumption (VO$_{2\text{max}}$) on separate occasions, in a counter-balanced order. The nociceptive withdrawal reflex (NWR) threshold and pain threshold (PT) were assessed by graded electrocutaneous stimuli. Cerebral event related potentials (CEPs) to electrocutaneous stimuli were recorded at threshold for NWR and pain before and after exercise. The CEPs were grouped at NWR threshold and PT for Pre, Post1 (5 min) and Post2 (15 min) aerobic exercise at 70% and 30% VO$_{2\text{max}}$. Repeated measures ANOVA for CEP N1 peak amplitude at the NWR threshold revealed a significant difference amongst Pre, Post1, Post2 (N1, $F_{2,18}=5.423$, $P=0.033$). Pairwise comparisons between Pre-Post1 and Pre - Post2 revealed a significant decrease in N1 between Pre-Post2 ($P<0.001$), but no decrease between Pre-Post1 ($P=0.097$). There was no difference for N1 peak amplitude at the NWR threshold between exercise at 70% and 30% VO$_{2\text{max}}$ ($F_{1,9}=4.198$, $P=0.071$). There was no difference in the NWR threshold and the PT following aerobic exercise. These findings suggest that aerobic exercise attenuated nociceptive signalling at forebrain-cerebral sites but was not sufficient to mediate spinal antinociceptive mechanisms.
5.2 Introduction

Physical exercise has been shown to induce a transient increase in pain threshold in the post-exercise period (Droste, et al., 1991; Kemppainen, et al., 1990; Olausson, et al., 1984; Pertovaara, Huopaniemi, et al., 1984), however, this has not been consistently demonstrated (Droste, et al., 1988; Kemppainen, et al., 1985; Ruble, et al., 2005). Post-exercise attenuation of pain has been linked to opioid (Olausson et al., 1986; Olausson, et al., 1984) and spinal (Guieu, et al., 1992) pain inhibiting systems. The attenuation of pain following exercise is of interest in pain therapy and research due to the potential activation and function of endogenous pain mediating systems.

Exposure to stress reduces pain responses and is referred to as stress induced analgesia (SIA). The reduction of pain by SIA is mediated by descending pain-inhibitory circuits and is an indicator of supraspinal mediated pain control (Butler & Finn, 2009). Diffuse noxious inhibitory controls (DNICs) is revealed by a reduction in pain sensation to a noxious stimulus during or following another noxious stimulus in a different location on the body (Le Bars & Willer, 2002). Acute muscle pain is elicited by exercise at or above 50% of maximal work capacity (Hamilton, et al., 1996) and approaches “very strong pain” at volitional exhaustion (Cook, et al., 1997). Physical exercise may evoke pain inhibitory mechanisms through SIA and DNICs by the activation of stress systems and exercise induced muscle pain, respectively. Extremely intense pain activates spinal inhibitory circuits through DNIC’s whereas mild pain engages forebrain-dependent antinociception (Crown, et al., 2004).
As shown in chapter 4, the spinal-mediated nociceptive limb withdrawal reflex (NWR) threshold is reliable within-trial and corresponds with the pain threshold (Willer, 1977). The relevance of the NWR in pain research is that it represents a measure of spinal cord excitability and the function of the pain processing system (Skljarevski & Ramadan, 2002). The effect of aerobic exercise on the NWR has not been well documented, however, previous evidence shows that the threshold for the NWR is elevated following exercise at 50% of maximum aerobic capacity (Guieu, et al., 1992). In contrast, exercise at an average of 70% of maximum aerobic capacity was required to elicit changes in pain threshold (Pertovaara, Huopaniemi, et al., 1984).

These studies suggest that exercise may have a minimum dose response in altering the functioning of the pain processing system.

A potential mechanism for experimental pain inhibition is through DNIC’s, as evoked by elevated muscle pain from intense exercise (Persson, et al., 2003). Increased NWR threshold following aerobic suggests that exercise centrally attenuates nociceptive signalling within the spinal cord. This would imply that the function of exercise-induced antinociceptive systems is performed at the spinal cord level. Therefore, an attenuation of the nociceptive withdrawal reflex following aerobic exercise may be associated with spinal mediated diminution of the nociceptive signal rather than at supraspinal sites.

Cerebral event related potentials (CEPs) from acute noxious episodes can further explicate the transmission of nociceptive signalling through the central pathways (Kanda, et al., 2002; Treede, et al., 1988). Previous research shows that exercise involving small voluntary repetitive movement activity attenuates the CEP peak amplitude to electrocutaneous stimuli in the post-activity period (Murphy, Haavik
Taylor, Wilson, Oliphant, & Mathers, 2003). This suggests that physical activity may evoke a gating of somatosensory processing beyond the exercise period.

The concurrent assessment of cerebral and spinal events to nociceptive stimuli following aerobic exercise has not been fully elucidated. This procedure would enable the synchronised measurement of the nociceptive signal within the spinal cord and the processing of this signal at supraspinal levels within the cerebrum. Therefore, the purpose of this study was to evaluate cerebral and spinal events to nociceptive stimuli following aerobic exercise.
5.3 Methods

5.3.1 Participants

The participants included 10 healthy and physically active males (mean±SD; age 21.2 ± 3.4 years; body mass 77.1 ± 9.3 kg; height 179.5 ± 5.8 cm. Each participant was screened with a health questionnaire (Appendix 4). The exclusion criteria included the acute use of anti-inflammatory and analgesic medications, prior history of lower limb injury or surgery, acute infection and chronic disease. The study was conducted with the approval of the University Ethics in Human Research Committee (approval No: 2007/107) and all subjects signed a letter of informed consent.

5.3.2 Study design

A within-subjects experimental design was used whereby electrostimuli were delivered before and after acute exercise for each participant. An initial testing session was conducted to assess the maximum oxygen consumption (\(\text{VO}_2\max\)) prior to the aerobic exercise sessions. For the aerobic exercise sessions, each participant performed exercise for 30 min on a bicycle (Corsa, Avanti Bikes, Auckland, New Zealand) mounted on a stationary cycle trainer (Tacx Cycleforce Basic, Rotterdam, The Netherlands) with a power output display (SRM, Colorado Springs, USA) at 30% of \(\text{VO}_2\max\) (low intensity) and 70% \(\text{VO}_2\max\) (high intensity) on two separate occasions. An exercise intensity of 70% of \(\text{VO}_2\max\) was selected based on previous research on pain threshold elevation in the post-exercise period (Pertovaara,
Huopaniemi, et al., 1984). The sequence for low and high intensity aerobic exercise was counterbalanced amongst the participants to minimise an order effect. Each aerobic exercise session was performed in a climate controlled laboratory at the same time of day to minimise diurnal variation. The electrocutaneous pain threshold (PT), NWR threshold, Perceptual Magnitude Ratings (PMR), and CEPs were assessed by graded electrocutaneous (EC) stimuli before (Pre), 5 min post (Post1), and 15 min post (Post2) exercise. Participants were instructed to maintain their regular daily activities and to avoid exercise on the day when the experimental sessions were performed.

5.3.3 Assessment of maximum exercise oxygen consumption

Maximum exercise oxygen consumption was assessed by a metabolic measurement system (Par Medics, Pneumotach TrueOne 2400, Sandy, Utah, USA) connected to a Hans Rudolph valve (Hans Rudolph Inc., Shawnee, KS, USA) while performing cycling exercise on a stationary ergometer (Lode, Sport Excalibur, Groningen, Netherlands). The VO$_2$ assessment protocol began at 60 W and was incremented by 30 W at 3 min intervals until the oxygen uptake reached a maximum. The heart rate (HR) was recorded by a heart rate telemetry system (Polar RS200, Polar Electro, Kempele, Finland).
In order to synchronise the measurement of spinal and cerebral nociceptive processing, a specialised integrated system for capturing nociceptive reflexes and cerebral event related potentials following aerobic exercise was developed. The NWR threshold was determined while participants were seated on a reclined padded therapeutic lift-back table (Metron, Sydney, Australia) at Pre, Post1, and Post2 aerobic exercise. The electrocutaneous (EC) stimulation site was located on the retro-malleolar pathway of the sural nerve, posterior to the lateral malleolus of the fibula and anterior to the calcaneal tendon. A pair of disposable surface electrodes (Meditrace, Chicopee, USA, 30 mm diameter and 22 mm diameter electrogel contact surface area) were vertically positioned 30 mm apart over the sural nerve pathway. The cathode was connected inferior to the anode electrode. The electrodes remained intact for the duration of the exercise session and were regularly inspected for contact. The EC stimuli were delivered by a constant-voltage peripheral nerve stimulator (Digitimer D185-HB4, Hertfordshire, UK). A set of six EC stimuli were delivered at random intervals 5-15 s apart. Each single stimulus consisted of a train of 8 x 1 ms rectangular pulses with an interspike interval of 2 ms delivered over 22 ms.

Two disposable (Ag/AgCl) adhesive press-stud surface electrodes (Meditrace, Chicopee, USA, 30 mm diameter and 22 mm diameter electrogel contact surface area) were positioned over the biceps femoris muscle to record the electromyographic (EMG) response from the EC stimuli. A single adhesive (Ag/AgCl) disposable press-stud reference electrode was positioned on the contra-lateral
malleolus of the fibula. Each electrode site was prepared by shaving, dermal abrasion, and degreased with ethanol solution. The electrodes remained intact for the duration of the exercise session and were regularly inspected for consistent contact.

The EMG signal analysis for the NWR threshold was performed with Amlab II software (Amlab, Sydney, Australia). The EMG signal from biceps femoris muscle was digitally sampled at 2000 Hz using an analog-to-digital converter (Amlab, MR01C, Sydney, Australia). The raw EMG signal was amplified (1000x) and filtered (2nd order Butterworth). Similar parameters have been previously applied to determine the EMG signal for the NWR (Chan & Dallaire, 1989).

The EMG signal was digitally recorded for each set of six constant-voltage EC stimuli beginning at 20 V, followed by increments of 20 V until the appearance of the NWR EMG signal. Upon the initial observation of the NWR EMG signal, a decrease of 10 V was applied to assess the consistency of the signal at a reduced EC intensity in order to determine the lowest threshold for the NWR.

The threshold for the NWR was defined by 1) a nociceptive withdrawal reflex EMG signal amplitude of at least 1.6 SD of the mean baseline resting EMG activity, 2) the voltage intensity that evoked at least three NWR events from a set of six EC stimuli, 3) a post-stimulus reflex signal within a 90-150 ms time-frame. A signal window of 90-150 ms was applied in to preclude signal contamination by startle and/or voluntary responses. All NWR data were visually inspected for artefact. Offline data processing included the measure of the NWR EMG signal amplitude at the NWR threshold and
at pain threshold. EMG signal amplitude was determined from baseline to peak within the NWR window.

5.3.5 Pain threshold assessment

Perceptual magnitude ratings of EC stimuli were determined by the participants verbally rating the stimulus intensity following each set of six EC constant-voltage stimuli using a 0-10 category scale (Appendix 1). The numerical anchors and verbal descriptors were graded as 0=no sensation, 2=slight sensation, 4=moderate sensation, 6=pain sensation, 8=strong pain sensation, and 10=pain tolerance. Participants were instructed that a rating of ‘6’ on the category scale represented the point at which the sensation was no longer tactile and was painful (pain threshold). Each set of EC stimuli began at 20 V and was increased by 20 V until pain threshold was determined. A decrement of 10 V was applied to check the threshold measure for pain. Further increments were applied to achieve a verbal rating of ‘6’. The EMG signal for the nociceptive withdrawal reflexes were also recorded at pain threshold (PT).
5.3.6 Cerebral event related potentials

Participants were fitted with an EEG electrocap (Electrocap International Inc., Eaton, Ohio, USA) for recording the cerebral event related potentials (CEPs) during the assessment of the NWR threshold and pain threshold at Pre, Post1 and Post2 aerobic exercise (Figure 5.1). Instructions to minimise eye blink by focusing the eyes on a fixed point was provided for participants prior to the EC stimulation procedure. During aerobic exercise, the EEG electrocap was disconnected from the amplifier, however, remained fitted over the scalp. The EEG electrocap was reconnected immediately after exercise for the reassessment of the CEPs at Post1 and Post2.

The CEPs were recorded from electrodes mounted in the electrocap positioned over Fz, F3, F4, Cz, C3, C4, Pz, P3, and P4 in accordance with the international 10-20 system (Jasper, 1958). Impedances were maintained at 5 kiloOhms or less. The EEG signal was amplified using a 32 channel amplifier (NuAmps, Neuroscan Labs, El Paso, Texas, USA) with a bandpass of 0.01–30 Hz and gain of 19,000. The data were sampled at 2000 Hz by Neuroscan software version 4.3 (Neuroscan Labs, El Paso, Texas, USA) and referenced offline to average mastoid. Eye movements were recorded using two electrodes placed above and below the left eye.

The offline EEG signal processing was performed using EEG Display software version 5.0 (Fulham, 2005). Raw EEG signals were epoched between -200 to 600 ms from stimulus onset with baseline correction performed (-100 to 0 ms) and filtered for 50 Hz noise. Eye artefact correction was employed using the Gratton, Coles and Donchin procedure (Gratton, Coles, & Donchin, 1983). Trials with linear trend were
corrected and data with artefact were removed. Signal averaging was performed for each set of six randomly delivered EC stimuli at 20 V increments for Cz. The average Cz CEPs were grouped into blocks of trials at Pre, Post1, and Post2 at the NWR threshold and PT for high and low intensity aerobic exercise.

Data extraction for the CEPs was performed on peak amplitude and latency within each block of trials at the NWR threshold and Pain threshold. The CEP peak amplitude and latency were digitally exported from baseline to the peak signal. Checks for signal consistency were performed by visual inspection and statistical analysis of the peak signal latency between Pre, Post1, and Post2 for high and low intensity aerobic exercise.
Figure 5.1: Showing a participant performing aerobic exercise with EEG electrocap in place for the Pre and Post exercise recording of cerebral event related potentials to nociceptive events
5.3.7 Aerobic exercise

Following the assessment of baseline measures for NWR threshold, PT, and CEPs, each participant performed aerobic exercise by cycling for 30 min at either 30% (Low intensity) or 70% VO\textsubscript{2}\textsubscript{max} (High intensity) on separate occasions in a counterbalanced order. The participants were instructed to maintain the required power output throughout the aerobic exercise session, as shown by the power output display unit. The HR, Ratings of perceived exertion (RPE, Appendix 2), and the Muscle pain intensity (MPI, Appendix 3) were assessed every 2 min during exercise with the Borg category 6-20 scale (Borg, 1970), and by the 0-10 scale with verbal descriptors (Cook, et al., 1997), respectively. The metabolic load was indirectly determined by assessing capillary blood lactate concentration [BLa\textsuperscript{−}] at the finger site before and immediately after aerobic exercise by whole blood analyser (Radiometer Copenhagen, ABL 800 Flex).

5.3.8 Statistical analysis

Group comparisons between high and low intensity exercise were performed for [BLa\textsuperscript{−}], HR, RPE, and MPI. A 2 x 3 repeated measures ANOVA was performed for the NWR threshold, PT, EMG signal amplitude at the NWR threshold and PT, CEP peak signal amplitude and latency between exercise intensity (Exercise intensity: High, Low) and time points (Time: Pre, Post1, Post2). Additional checks were completed for data sphericity. Pairwise comparisons were performed where significance was observed. The level of significance set at \( P \leq 0.05 \) and data are presented as mean ± SD.
5.4 Results

5.4.1 Aerobic exercise responses

Each participant completed 30 min of aerobic cycling exercise at 30% and 70% of VO$_{2\text{max}}$ in a counterbalanced order on separate occasions. The mean VO$_{2\text{max}}$ was 3.5 ± 0.4 L/min and the predicted max HR was 198.8 ± 3.4 beats/min. Mean power output at 30% and 70% of VO$_{2\text{max}}$ was 84.5 ± 15.4 W and 186 ± 24 W, respectively. The high intensity aerobic exercise responses for [BLa] 6.4 ± 3.6 mmol/l, HR 151.8 ± 16.7 beats/min, RPE 13.5 ± 1.3, MPI 3.1 ± 1.1 and were significantly elevated compared to low intensity exercise where [BLa] was 2.0 ± 1.3, HR 106.4 ± 20.4 bpm, RPE 9.9 ± 3.2, and MPI 1.2 ± 2.0 ($P < 0.05$).

5.4.2 Nociceptive withdrawal reflex threshold and pain threshold assessment

A sample raw EMG signal at the nociceptive withdrawal reflex threshold is shown in Figure 5.4. The mean threshold (V) data for the NWR and PT before and after high and low intensity aerobic exercise are shown in Table 5.1. There was no statistical difference between high and low intensity exercise ($F_{1,9}=0.4$, $P=0.57$) and time ($F_{2,18}=0.6$, $P=0.58$) for the NWR threshold. There was no difference in the pain threshold for exercise intensity ($F_{1,9}=0.2$, $P=0.89$) and time ($F_{2,18}=0.5$, $P=0.60$) and there was no exercise intensity by time interaction for the NWR threshold and pain threshold.
5.4.3 EMG peak signal amplitude at the nociceptive withdrawal reflex threshold and pain threshold

The mean EMG peak signal amplitude (V) at the NWR threshold and PT following High and Low intensity aerobic exercise are shown in Table 5.2. There was no difference in the EMG signal amplitude at the NWR threshold for exercise intensity ($F_{1,9}=1.5, P=0.25$) and time ($F_{2,18}<0.1, P=0.96$). Additionally, the EMG signal amplitude at the PT shows no difference for exercise intensity ($F_{1,9}<0.1, P=0.85$) and time ($F_{2,18}=1.1, P=0.35$). There was also no exercise intensity by time interaction for pain threshold.
Chapter 5: Aerobic exercise attenuates cerebral event related potentials to nociceptive events

### Table 5.1: The nociceptive withdrawal reflex threshold and pain threshold (mean Volts ± SD) at Pre, Post1, and Post2

Aerobic exercise. High and Low intensity aerobic exercise were performed on separate occasions

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<th>Pain threshold</th>
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<td>Pre</td>
<td>Post1</td>
</tr>
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<td>High</td>
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</tr>
<tr>
<td>Low</td>
<td>99.0 ± 22.8</td>
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</tr>
</tbody>
</table>

**Key:** Pre=before exercise; Post1=5 min post exercise; Post2=15 min post exercise; High=exercise at 70% of VO$_2$ max; Low=exercise at 30% of VO$_2$ max
Table 5.2: Mean peak EMG signal amplitude at the nociceptive withdrawal reflex threshold and pain threshold for Pre, Post1, and Post2 High and Low intensity aerobic exercise

<table>
<thead>
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<th>Key: Pre=before exercise; Post1=5 min post exercise; Post2=15 min post exercise; High=exercise at 70% of VO\textsubscript{2 max}; Low=exercise at 30% of VO\textsubscript{2 max}</th>
<th>NWR threshold EMG Amplitude (V ± SD)</th>
<th>Pain threshold EMG Amplitude (V ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post1</td>
</tr>
<tr>
<td>High</td>
<td>0.00439 ± 0.00245</td>
<td>0.00408 ± 0.00169</td>
</tr>
<tr>
<td>Low</td>
<td>0.00722 ± 0.00868</td>
<td>0.00688 ± 0.00666</td>
</tr>
</tbody>
</table>
5.4.4 Signal latency checks for cerebral event related potentials

Data inspection revealed a Cz negative peak (N1) and a positive peak (P1) between 100-200 ms and 230-350 ms, respectively. The peak signal latency for N1 and P1 revealed no significant difference between Pre, Post1, and Post2 (N1, $F_{8,72} = 1.2$, $P=0.3$, and P1, $F_{8,72} = 1.5$ $P=0.117$).

5.4.5 CEP at the NWR threshold

A sample raw CEP is shown in Figure 5.4. The Cz average CEP peak amplitude for N1 at the NWR threshold at Pre, Post1, and Post2 for High and Low intensity aerobic exercise is shown in Figure 5.2A. Results for N1 at the NWR threshold reveals a significant difference amongst Pre, Post1, Post2 (N1, $F_{2,18} = 5.4$, $P=0.033$). Pairwise comparisons between Pre - Post1 and Pre - Post2 reveals a significant decrease in N1 between Pre – Post2 ($P<0.001$) but no difference between Pre-Post1 ($P=0.097$). There was no difference between High and Low intensity exercise for N1 ($F_{1,9}=4.2$, $P=0.071$) and no interaction effect between exercise and time.

The Cz average CEP peak amplitude for P1 at the NWR threshold at Pre, Post1, and Post2 for High and Low intensity aerobic exercise is shown in Figure 5.2B. Results for P1 at the NWR threshold shows no difference between Pre, Post1, and Post2 (P1, $F_{2,18} = 3.5$, $P=0.052$). There was no difference between High and Low intensity exercise for P1 at the NWR threshold ($F_{1,9} <0.1$, $P=0.88$) and no interaction effect between exercise intensity and time.
5.4.6 CEP at pain threshold

The average CEP peak amplitude for N1 at the pain threshold for Pre, Post1, and Post2 High and Low intensity aerobic exercise is shown in Figure 5.3A. Results for N1 at the pain threshold reveals no significant difference amongst Pre, Post1, Post2 (N1, $F_{2,18}= 0.1$, $P=0.902$). There was no difference between High and Low intensity exercise for N1 ($F_{1,9}=4.0$, $P=0.078$) and no interaction effect for exercise intensity by time.

The average CEP peak amplitude for P1 at the pain threshold for Pre, Post1, and Post2 High and Low intensity aerobic exercise is shown in Figure 5.3B. Results for P1 at the pain threshold reveals no significant difference amongst Pre, Post1, Post2 (P1, $F_{2,18}= 1.7$, $P=0.21$). There was no difference between High and Low intensity exercise for P1 ($F_{1,9}=1.0$, $P=0.35$) and no interaction effect for exercise intensity by time.
Chapter 5: Aerobic exercise attenuates cerebral event related potentials to nociceptive events

**Figure 5.2:** Mean CEP peak amplitude at the nociceptive withdrawal reflex threshold for N1 (A) and P1 (B) at Pre, Post1 (5 min), and Post2 (15 min) for High (70% VO$_2$ max) and Low intensity aerobic exercise (30% of VO$_2$ max), * significant difference between Pre-Post2 for exercise ($P<0.001$)
Figure 5.3: Mean CEP peak amplitude at pain threshold for N1 (A) and P1 (B) at Pre, Post1 (5 min), and Post2 (15 min) for High (70% VO₂ max) and Low intensity aerobic exercise (30% VO₂ max).
Figure 5.4: A) A sample EMG signal at the Nociceptive withdrawal reflex threshold. The vertical axis represents the voltage and the stimulus (electrocutaneous) onset. The nociceptive withdrawal reflex timeframe window is depicted between .9 and 1.5 s (horizontal axis). B) A sample CEP at 140 V. The vertical axis represents the voltage and the stimulus onset. The horizontal axis represents the time in milliseconds.
5.5 Discussion

The novel findings in the present results show attenuation in the CEP N1 peak amplitude at the nociceptive withdrawal reflex threshold following aerobic exercise. A trend in CEP attenuation was observed for high intensity aerobic exercise compared to low intensity exercise, however, this was not statistically significant. There was no change in the nociceptive withdrawal reflex threshold following aerobic exercise. Therefore, the present results show attenuation of nociceptive events at the cerebral level but not at the spinal level or perceptually following aerobic exercise.

Reliability of CEPs is depicted in the signal consistency of the peaks (Babiloni et al., 2001). The present study performed signal checks to assess the consistency of the peak latency for N1 and P1 before and after exercise. These results show a consistent peak latency. Previous research reveals attenuation in early CEP components following a repetitive movement task (Murphy, et al., 2003). In contrast, the present study identified consistent late CEP peak components but not early components in the post-stimulus interval. It is possible that the observation of consistent late CEP components in the present study was due to differences in the stimulus delivery protocol. In contrast, previous research showed CEP attenuation by electrostimuli at an upper limb mixed nerve site (Murphy, et al., 2003). The exercise involved repetitive small muscle group activity in the hand, whereas the present study involved gross motor activity of the lower limbs. The stimuli in the present study were delivered at random intervals over a sensory nerve site in order to assess the lower limb NWR threshold and to avert attenuation in CEP components (Fujii et al., 1994).
The late N1 and P1 CEP components in the present study are evoked potentials previously observed during noxious stimulation (Miltner, Johnson, Braun, & Larbig, 1989). These components are largely expressed by the anterior attention network (Posner & Petersen, 1990) and have been associated with alterations in attention and arousal (Lorenz & Garcia-Larrea, 2003; Miltner, et al., 1989). Additionally, these sites have been associated with the sensory-discriminative and affective-motivational components of pain processing (Treede, Kenshalo, Gracely, & Jones, 1999). It has previously been shown that these late CEP peaks are not nociceptive specific, but are also elicited by non-nociceptive somatosensory stimuli (Downar, Crawley, Mikulis, & Davis, 2000; Mouraux & Iannetti, 2009). Since the late CEP components have previously been shown to be modulated by the attention network, it is possible that aerobic exercise in the present study attenuated these components by changes in arousal and attention following exercise (Oweis & Spinks, 2001; Tate & Petruzzello, 1995). Future studies could assess post-exercise arousal levels with CEP components to noxious stimuli in order to further elucidate the mechanisms underlying the attenuation in these CEP peaks.

An alternative possibility for the CEP attenuation in the post-exercise period is by enhanced endogenous endorphin release. Several studies using exogenous analgesic opioid compounds have revealed attenuation in the N1 and P1 CEP components (Benedetti, Chapman, Colpitts, & Chen, 1982; Bromm, et al., 1987; Buchsbaum, Davis, Coppola, & Naber, 1981; Chapman, Colpitts, Benedetti, & Butler, 1982), that were not dissimilar to the present findings. Forebrain sites such as the rostral anterior cingulate cortex have previously been implicated in opioid analgesia (Petrovic, Kalso, Petersson, & Ingvar, 2002) and this site has also been identified as a generator of these late CEP peaks (Babiloni, et al., 2001). In the present study, it is
possible that the attenuation in the late CEP peaks in the post-exercise period may be due to an enhanced expression of endogenous opioid-based endorphin compounds, however plasma endorphins were not assessed. A disparity between the plasma and central endorphin concentrations limits the use of this measure to infer the central effects on pain processing (D. G. Baker, et al., 1997).

Previous research shows that plasma endorphin concentration peaks at 15 min following aerobic exercise at above 60% of maximum oxygen uptake (Hoffman, et al., 1996; Schwarz & Kindermann, 1992; Taylor, et al., 1994). In accord with the present results, a more prominent effect in CEP attenuation was observed in the later 15 min post-exercise data. A limitation in the present study is that endorphin concentration was not assessed and that CEP attenuation was not observed at pain threshold. A trend for CEP attenuation at pain threshold following high intensity exercise was observed, however, this was not statistically significant. Future research could include suprathreshold noxious stimuli over longer intervals in the post-exercise period to further elucidate the effect of aerobic exercise on these late CEP components.

The present results show no change in the spinal mediated nociceptive withdrawal reflex threshold and signal amplitude following aerobic exercise. There was a substantial variance in the NWR threshold and signal amplitude amongst the participants which has been previously shown (Chan & Dallaire, 1989). The consistent NWR threshold following aerobic exercise corresponds with the non-significant effect on the pain threshold following aerobic exercise in the present results. In contrast, previous research shows that exercise at 50% of VO$_2$ max elevated the threshold for the nociceptive withdrawal reflex in the post-exercise period,
however, measures of pain threshold were not performed (Guieu, et al., 1992). In the present study, changes in cutaneous resistance from sweat and vasodilation during high intensity exercise may have influenced the neuroactivation from constant-voltage electrocutaneous stimuli in the post-exercise period. A reduced skin resistance following exercise may have masked a potential increase in the threshold for the nociceptive withdrawal reflex. Thus, a limitation in the present study is that the skin conductance, such as the inter-electrode resistance, was not assessed. Interestingly, there was no difference or trend in the nociceptive withdrawal reflex threshold between high and low intensity exercise, which suggests that changes in skin resistance may not have influenced the threshold.

It is possible that the high intensity exercise at 70% VO$_2$ max in the present study was not sufficient to enhance the pain threshold in the post-exercise period. Previous electrostimulation studies demonstrating an elevation of post-exercise pain threshold involved exercise that approached 85% of VO$_2$ max (Pertovaara, Huopaniemi, et al., 1984), or until physical exhaustion (Droste, et al., 1991). In one study, exercise was performed above 85% of VO$_2$ max, however, pain threshold was not elevated following exercise (Kemppainen, et al., 1985). The present study included physical exercise to activate stress induced analgesia by launching antinociceptive systems from elevated ratings of muscle pain (Persson, et al., 2003), however, the muscle pain may not have been sufficiently raised to mediate the spinal antinociception systems. Muscle pain during high intensity exercise ranged between mild to moderate. Additionally the metabolic load, as assessed by the blood lactate level, indicates that the exercise stress may not have been substantially raised despite the relative exercise workload. Future studies could standardise the exercise stress by establishing a set metabolic load or perceived level of muscle pain intensity.
There was a general trend of attenuation of CEP peak amplitudes in the post exercise period. A general decrease in peak amplitudes at pain threshold in the post exercise period was observed following high intensity exercise (Fig. 4.3), however, a statistically significant attenuation was observed only at the nociceptive withdrawal reflex threshold. It is possible that aerobic exercise may have engaged supraspinal-mediated antinociception, as observed by the attenuation in CEP components, but was not sufficient to launch spinal-mediated antinociception due to the consistent nociceptive withdrawal reflex threshold. A shortcoming with electrocutaneous stimuli at the sural nerve site in the present study is that the stimulus bypasses the nerve receptor endings and activates the peripheral nerve trunk. This would avert the assessment of potential changes in peripheral afferent receptor function following exercise.

5.5.1 Conclusion

In summary, the present results show that aerobic activity attenuates cerebral event related potentials to nociceptive stimuli at 15 min post exercise, however, the nociceptive withdrawal reflex and pain threshold were not mediated by exercise. These findings indicate that aerobic exercise attenuates nociceptive signalling at supraspinal levels in the post-exercise period but did not mediate spinal cord antinociception.
Chapter 6: Effects of moderate-intensity aerobic exercise rehabilitation for chronic pain disorder
6.1 Abstract

Since moderate intensity aerobic exercise has been shown to improve exercise programme adherence in chronic pain participants, it is necessary to determine whether this exercise prescription has favourable outcomes on pain, health, and functional capacity. Therefore, the purpose of this study was to compare the influence of aerobic exercise rehabilitation (AER) on pain and health-related outcomes in participants with chronic pain (CP). Eleven CP and eight pain-free control participants completed a 12-week supervised AER programme, 2 d wk\(^{-1}\), with perceived exertion set at moderate-intensity and muscle pain rating set to below somewhat strong pain. Dependent variables included programme adherence, health status (SF36), percent body fat, 6 min walk test, cardiovascular fitness (HR Watt\(^{-1}\)), exercise power output (Watts), experimental pain parameters (pressure pain [PPT], nociceptive withdrawal reflex [NWR-T], electrocutaneous pain threshold [PT]), and pain report (Magill Pain Questionnaire [MPQ]). Results are expressed as mean (%) with standardised effect size (Cohen’s \(d\)) and 95% confidence limits (95% CL) of the effect size. Results for programme adherence (mean ± SD) were 74 ± 24% and 93 ± 4.0% for CP and control participants, respectively. Following AER, CP participants improved 29% in SF36 total (\(d=0.57; 95\% \text{ CL}:-0.45–1.6\)), 5.1% in the 6 min walk test (\(d = 0.36; \text{CL}:-0.34–1.07\)), 16.7% increased Watts (\(d = 0.43; 95\% \text{ CL}:-0.02–0.88\)), 102% elevated pressure pain threshold (\(d=1.8; 95\% \text{ CL}:-0.8–2.7\)), 21.2% enhanced PT (\(d=0.49; 95\% \text{ CL}:-0.23–1.21\)), and 26% reduced MPQ total pain (\(d = -0.41; 95\% \text{ CL}:-1.15–0.33\)). At 10-months after AER, there was a 10% decline in SF36 total health (\(d=-0.21, 95\% \text{ CL}:-1.02–0.61\)) and 66% increase in MPQ total pain (\(d=0.84, 95\% \text{ CL}:-0.09–1.77\)) in the CP participants. Additionally, there was a 17% decline in physical activity patterns.
at 10-months after AER in the chronic pain group. In conclusion, moderate-intensity AER is associated with sufficient programme adherence to increase physical activity patterns, reduce pain, and improve health outcomes in participants with chronic pain.

### 6.2 Introduction

Pain that continues beyond the time normally associated with healing for an illness or initial injury is defined as chronic pain (Turk & Okifuji, 2001). Previous research shows that up to 19% of the general population report suffering from chronic pain (Breivik, et al., 2006). Chronic pain is a significant medical-health care problem that results in personal suffering, decreased productivity, and substantial health care costs (Katz & Barkin, 2010). Individuals with chronic pain often present with decreased levels of physical fitness, diminished health status, and reduced functional capacity (Häuser, et al., 2010). Moreover, persons with chronic pain often show elevated experimental pain responses (Lim, et al., 2011) and psychological distress (Hall, et al., 2011). Therefore, a range of health, functional, and pain assessments are required to evaluate treatment outcomes amongst chronic pain participants.

Exercise is often prescribed to alleviate pain and improve physical function (IASP, 1998) for individuals diagnosed with chronic pain, however, the mechanism for pain inhibition is not fully understood. As demonstrated in chapter 5, acute aerobic exercise attenuates the function of the pain processing system in healthy participants. Previous research on the effect of exercise intervention for persons with chronic pain have shown reduced pain report (Bircan, et al., 2008), enhanced health-related outcomes (Richards & Scott, 2002), and improved experimental pain assessment (Carbonell-Baeza, et al., 2010) following aerobic exercise rehabilitation.
(AER). In contrast, no improvement in pain report (Ramsay et al., 2000), or an exacerbation of pain (van Santen, et al., 2002) amongst chronic pain participants have been reported following AER. In one study, exercise guidelines for aerobic training were not achieved because chronic pain participants were unable to attain target heart rate levels due to elevated pain during exercise (Norregaard, et al., 1997). Currently, further research is required to elucidate the optimum level of exercise rehabilitation in persons with chronic pain (Häuser, et al., 2010).

Reduced exercise programme adherence has been identified as a significant problem in participants with chronic pain (Busch, et al., 2009). Low exercise programme adherence has been attributed to an exacerbation of pain and fatigue (van Santen, et al., 2002). In a review study, low intensity aerobic exercise was associated with both enhanced programme adherence and symptom improvement (Jones, Adams, Winters-Stone, & Burckhardt, 2006). On this basis, it is plausible that exercise rehabilitation that is mediated to the individual rating for exercise pain may show increased programme adherence, favourable changes in pain report, and enhanced health-related outcomes for persons with chronic pain.

Therefore the purpose of this study was to quantify the workload capacity and pain responses to moderate-intensity aerobic exercise and compare the influence of this exercise rehabilitation on health, function, and pain related outcomes in persons with chronic pain.
6.3 Methodology

6.3.1 Ethics statement

The research study was conducted with the approval of the University Ethics in Human Research Committee (approval number 08/07) and all subjects signed a letter of informed consent.

6.3.2 Participants

The participants included 11 individuals diagnosed with chronic pain (9 women and 2 men; mean age ± SD, 50 ± 11.8 years) and 8 pain-free control participants (7 women and 1 man; 49.6 ± 10 years). Participants with chronic pain (CP) included 8 with fibromyalgia pain, 2 with chronic back pain, and 1 individual with complex regional pain. The chronic pain participants were diagnosed with pain for a period of at least 12 months by a medical practitioner, rheumatologist, or pain specialist prior to participation in the study. Each participant was screened with a health questionnaire (Jenkinson, Coulter, & Wright, 1993) prior to the study. The exclusion criteria for CP participants were persons with acute inflammatory conditions, acute pain, nociceptive pain, or cancer pain. The healthy participants were required to be pain-free and with absence of illness or disease.

All CP participants reported regularly using over-the-counter anti-inflammatory and analgesic medications, four reported using prescription opioid based medicines, and
three chronic pain participants were using prescription medication for mild depression. Changes in medication protocol can confound pain test results, therefore CP participants maintained their standard medication for the duration of the study.

6.3.3 Experimental design

Previous research shows that moderate intensity aerobic exercise has higher exercise programme adherence in chronic pain participants (Häuser, et al., 2010), however, it is necessary to determine whether perceptual based exercise intensity has favourable outcomes on pain, health, and functional capacity. The design of the research was a within-group and between-group measurement procedure. Within-group measures were performed before (Pre) and after (Post) 12 weeks of exercise rehabilitation. Between group measures were performed amid the CP and control groups at Pre and Post exercise rehabilitation. A timeline of the Pre and Post measurements and the appraisal performed during exercise rehabilitation is shown in Figure 6.3. The measured outcomes included exercise programme adherence, health status, anthropometric characteristics, functional capacity, cardiovascular fitness, perceptual responses to exercise, electrocutaneous and pressure pain thresholds. Additionally, the chronic pain participants completed pain (Melzack, 2005) and lifestyle impact (Bennett, 2005) questionnaires at weekly intervals for the duration of the study.
A moderate-intensity aerobic exercise rehabilitation programme was designed to optimise programme adherence and exercise compliance. Each participant was supervised by an exercise programme specialist during each exercise session. Participants performed aerobic exercise by treadmill walking or recumbent cycling activity for 20 min, 2d\(^1\)wk\(^1\), for 12-weeks. The exercise intensity was performed at a level that elicited a Rating of perceived exertion (RPE) of 12 - above ‘Fairly Light-11’ and below ‘Somewhat Hard-13’ on the 6-20 category ratio scale (Borg, 1970), (Appendix 2). For the chronic pain participants, the Muscle pain intensity (MPI) rating during exercise was to be below ‘Somewhat Strong Pain-4’ on a 0-10 category ratio scale (Cook, et al., 1997), (Appendix 3). If the muscle pain intensity increased above 4, then the exercise intensity was reduced. The RPE and MPI were assessed at 2 min intervals during exercise. Participants were familiarised with the RPE and MPI perceptual scales prior to the AER. The exercise duration was increased from 10 to 20 min gradually during the initial 4-6 sessions. All participants were encouraged to perform 2-3 intervals of enhanced workload intensity for 1-2 min at approximately 20% above steady state exercise in order to stimulate increased work output and training adaptation. The exercise power output (Watts) and heart rate (HR) were recorded each minute during exercise. All exercise sessions were supervised and individually monitored by trained personnel. The adherence to the exercise programme was assessed by the attendance rate of the exercise sessions within the chronic pain and control groups. The attendance rate was determined by the percentage of exercise sessions that were completed within the duration of the study.
6.3.5 Health status and anthropometric characteristics

The health status for chronic pain and control participants was assessed by SF36 questionnaire (Jenkinson, et al., 1993) before and after the exercise intervention. The SF36 is a well recognised reliable tool in medical research and includes scores for total health and for physical, and mental health components. Anthropometric assessment for percent body fat before and after the AER were performed by whole-body dual x-ray absorptiometry (DXA) analysis (Norland XR-800, Fort Atkinson, WI, USA) with scan speed set at 260 mm/s and resolution at 13.0 mm x 6.5 mm.

6.3.6 Functional capacity and cardiovascular fitness

The functional capacity and cardiovascular fitness of the participants were assessed by the 6 min walk test and submaximal exercise heart rate response, respectively. Each participant was required to complete a 6 min walk test before and after the exercise programme intervention as a measure of functional capacity. The 6 min walk test has previously been shown to be associated with pain-related impairment in physical function (Carbonell-Baeza, Ruiz, Aparicio, Ortega, & Delgado-Fernández, 2011). However, a learning effect has been observed within a healthy population at two months following testing (Wu, Sanderson, & Bittner, 2003). Participants were encouraged to perform their peak walking speed for 6 min on a flat surface area while the distance walked was recorded.
Each participant performed a sub-maximal exercise test to assess the relative improvement in cardiovascular fitness before and after the exercise programme intervention. The sub-maximal exercise test was performed on a recumbent cycling ergometer. The exercise HR and power output (W) were recorded each minute during steady state at a workload that elicited an RPE of 12 and MPI of less than 4. The average exercise HR was determined during steady state before the AER. The same sub-maximum exercise power output (W) was repeated following the AER to compare the mean HR response to the same exercise power output.

6.3.7 Pressure pain threshold

The pain threshold to somatic mechanical pressure was assessed as a general measure of the pain system in chronic pain and control participants and to evaluate changes following exercise intervention. Pain threshold to mechanical pressure was determined by digital algometer (Force one, Wagner) with metal piston and 1 cm rubber disc before and after exercise intervention for each participant by the same tester. Pressure pain threshold (PPT) has been shown to be reproducible in chronic pain participants (Russell, 1998). The PPT was assessed bilaterally on 18 tenderpoints (Wolfe, Smythe, Yunus, Bennett, et al., 1990) for all participants. Each participant was familiarised with the algometer and the pain threshold measurement procedure prior to the assessments. The procedure required the participant to verbally respond by saying “yes” when the pressure progressed from being tactile to painful during increasing mechanical pressure. A mean PPT (kg) was determined from the 18 tenderpoints for each participant.
6.3.8 Electrocutaneous pain threshold

The electrocutaneous pain threshold (EPT) was determined by a peripheral nerve stimulator (digitimer d185-HB4, Hertfordshire, UK) delivering constant-voltage stimuli at the sural nerve site, located posterior to the lateral malleolus. A set of eight electrocutaneous stimuli were delivered at random a interval between 5-15 s apart. Each stimulus comprised a volley of eight 1 ms rectangular pulses with an interspike interval of 2 ms and delivered over 22 ms.

Participants verbally rated the intensity of the electrocutaneous sensation following a set of eight constant-voltage stimuli using a 0-10 category scale (Appendix 1). The numerical anchors and verbal descriptors were graded as 0=no sensation, 2=slight sensation, 4=moderate sensation, 6=pain sensation, 8=strong pain sensation and 10=pain tolerance (Appendix 1), as previously defined in chapter 5. Participants were instructed that a rating of 6 on the category scale represented the point at which the sensation was no longer considered tactile and was painful. A rating of 6 represented the electrocutaneous pain threshold. The first set of constant-voltage stimuli were delivered at 20 V and each subsequent set was increased by 20 V. Participants rated the intensity of sensation following each set of eight stimuli. Increments of 20 V continued until the electrocutaneous pain threshold was determined.
6.3.9 Nociceptive withdrawal reflex threshold

As previously demonstrated in chapter 4, the nociceptive withdrawal reflex (NWR) threshold has been shown to parallel the electrocutaneous pain threshold. The NWR threshold was determined during the assessment of the electrocutaneous pain threshold (Micalos, et al., 2009). The surface electromyographic (EMG) signal of biceps femoris muscle was digitally sampled at 2000 Hz using an analog-to-digital converter (Amlab, MR01C, Sydney, Australia) and filtered (2nd-order Butterworth) during the delivery of the electrocutaneous stimuli. The threshold for the NWR was defined by 1) a nociceptive reflex signal amplitude of at least 1.6 standard deviations of the mean baseline resting EMG activity, 2) the voltage intensity that evoked at least four NWR events from a set of eight electrocutaneous stimuli, and 3) a post-stimulus reflex signal within a 90-150 ms time-frame. A signal window of 90-150 ms is often applied in NWR research to preclude signal contamination by non-nociceptive reflexes, startle and/or voluntary responses. Upon the initial observation of the NWR threshold, a decrement of 10 V was applied to assess the consistency of the NWR signal at reduced electrocutaneous intensity. The threshold for the NWR was determined offline from the filtered EMG signal using Amlab II software (Amlab, Sydney, Australia).
6.3.10 Pain report and lifestyle impact assessment

Assessments on pain report and the impact of chronic pain on lifestyle were completed by chronic pain participants. Assessment of pain report was determined from the Magill pain questionnaire (MPQ), (Melzack, 2005). The MPQ includes a Total pain score and assesses multidimensional components of pain including Affective, Sensory, and Evaluate pain scores. The impact of pain on lifestyle and activities of daily living was assessed by the Fibromyalgia impact questionnaire (FIQ), (Bennett, 2005). The FIQ was applied to assess the overall impact of chronic pain on lifestyle, function, and disability. Measures within the FIQ include Total score, Physical Impairment, and Fatigue scores. The MPQ and the FIQ were completed each week for the duration of the study.
6.3.11 The 10-month follow-up assessments

At 10-months after the aerobic exercise rehabilitation, chronic pain participants completed the SF36, MPQ, and FIQ. This was to determine the extent to which the chronic pain participants returned to baseline levels and to affirm the changes in pain during AER.

6.3.12 Statistical analysis

In order to reveal progression for exercise capacity during rehabilitation, data for exercise programme adherence, power output, heart rate, and muscle pain intensity rating were averaged (mean ± SD) between 0-2 weeks (Start), in the middle two weeks (Mid), and in the final 2 weeks (End) of aerobic exercise rehabilitation.

Comparisons between chronic pain and control groups before (Pre) and after (Post) aerobic exercise rehabilitation were expressed with confidence limits and effect sizes (Hopkins, Marshall, Batterham, & Hanin, 2009). A standardised Cohen’s effect size ($d$) was determined for the mean as well as the lower 95% and upper 95% confidence limits (CL), (Cohen, 1988). Thresholds for qualitative descriptors for effect sizes are 0.2=small effect, 0.5=medium effect, 0.8=large effect. The application of standardised Cohen’s effect size and confidence limits has previously been performed in chronic pain and exercise rehabilitation research (Sañudo, et al., 2010). This procedure offers details on changes in measured outcomes that are clinically meaningful and relevant (Hopkins, et al., 2009). A variable with a confidence interval
that spans outside of the central median has a $P < 0.05$. Additionally, a reduction of approximately 30% or 2 points in the 11-point pain intensity numerical rating scale are found to represent an important difference in clinical trials of chronic pain therapies (Busch, et al., 2009). For the FIQ, an improvement of 14% in the total score indicates a clinically relevant change (Bennett, Bushmakin, Cappelleri, Zlateva, & Sadosky, 2009).

For the chronic pain group, confidence limits and effect sizes were calculated for the FIQ and MPQ total score and subscale scores between Start-Mid and Start-End of the aerobic exercise intervention. Additional 95% confidence limits and effects size analyses for MPQ, FIQ, and SF36 were performed between the completion of the aerobic exercise rehabilitation programme and 10-month follow-up.
Figure 6.1: Showing the timeline for the Pre and Post assessments and the appraisal performed during exercise rehabilitation over 12 weeks.
6.4 Results

6.4.1 Comparisons between Pre and Post aerobic exercise rehabilitation

Results for the effect size and confidence limits analyses between Pre and Post for the chronic pain and control group are shown in Figure 6.4. The health status in the chronic pain group revealed a moderate 29% improvement in the SF36 Total health (8.7 points, 95% CL: -6.9 to 24.4), moderate 29.3% enhanced SF36 Physical health (6.5 points, 95% CL: -7.2 to 20.1), and a small 21.4% improved SF36 Mental health component (7.6 points, 95% CL: -9.9 to 25.2) between Pre and Post AER. Substantial enhancements in health status components were not observed following the AER in the control group (all $d$ between -0.2 and 0.2). Assessment for body composition did not reveal substantial reductions in the percentage body fat between Pre and Post AER for the CP or the control group (all $d$ between -0.2 and 0.2).

Evaluation of cardiovascular function for the chronic pain group revealed a small 5.1% improvement for the 6 min walk distance (21.8 m, 95% CL: -20.4 to 64) and a small 16.7% increased exercise power output (8.4 W, 95% CL: -0.3 to 17) following the AER. The effect size in the HR per Watt for the chronic pain group is considered trivial (-0.2 bpm/W, CL: -0.3 to -0.03), however, there was a strong trend for a reduced heart rate response (-6.7%) to exercise. Assessment of the 6 min walk test between Pre and Post for the control group revealed a small 6.3% enhanced 6 min
walk distance (41 m, 95% CL: 28.7 to 53.4). Comparison of the Pre and Post HR per Watt for the control group revealed a small -12.2% reduced HR per Watt (-0.2 bpm, 95% CL: -0.3 to -0.1), and large 43.5% enhanced exercise power output (44.5 W, 95% CL: 13.5 to 75.6).

Experimental pain assessment in the chronic pain group between Pre and Post revealed a large 102% enhancement in the pressure pain threshold (2.1 kg, 95% CL: 0.9 to 3.2), a moderate 21% elevated electrocutaneous pain threshold (16.4 V, 95% CL -7.5 to 40.3), and a clinically trivial change in the nociceptive withdrawal reflex threshold (1.0 V, 95% CL: -14.5 to 16.5). Experimental pain assessment within the control group between Pre and Post AER revealed a large 81.8% elevated pressure pain threshold (2.9 kg, 95% CL: 2.1 to 3.8), a small -16% reduced NWR threshold (-15.0 V, 95% CL: -36.9 to 6.9), and a trivial change in the electrocutaneous pain threshold (-3.8 V, 95% CL: -32.3 to 24.8).

### 6.4.2 Pain and lifestyle impact questionnaire responses during aerobic exercise rehabilitation in chronic pain participants

Comparisons between Start and End of the AER for MPQ and FIQ within the chronic pain group are shown in Figure 6.5. Results for the MPQ reveals a moderate -34.1% reduction in the MPQ Total score for pain following the aerobic exercise rehabilitation between Start-Mid (-6.6 points, 95% CL: -13.8 to 0.6) and a small -26% reduction between Start-End (-5.0 points, 95% CL: -13.8 to 0.6) amongst the chronic pain participants. There was a small -36% reduction in the MPQ Affective pain scale between Start-Mid (-0.7 points, 95% CL: -1.9 to 0.4) and small -27% reduced MPQ Affective pain scale between Start-End (-0.6 points, 95% CL: -1.9 to 0.4). There was
a moderate -33.3% (-4.0 points, 95% CL: -8.0 to 0.1) and small -22.3% reduction (-2.7 points, 95% CL: -8.2 to 2.9) in the MPQ Sensory pain scale between Start-Mid and Start-End, respectively. There was a moderate -35.5% (-0.7 points, 95% CL: -1.3 to -0.1) and small -15% reduction (-0.3 points, 95% CL: -1.0 to 0.5) in the MPQ Evaluative pain scale between Start-Mid and Start-End, respectively.

The moderate effect size in the MPQ Total pain score in the present study is similar to the trends observed in previous research (Busch, et al., 2009), although in one study there was no change in chronic pain (Schachter, Busch, Peloso, & Sheppard, 2003). Based on the effect size of 0.5 shown in the present study, together with a statistical power of 0.8, then a sample size of 34 participants would be required for statistical significance set an alpha of 0.05. However, previous research on exercise intervention and chronic pain is predominantly based on group or home-based exercise prescription. In contrast, the present study set individually supervised exercise programming by a specialist and included measurements of pain, power output, and heart rate responses during exercise. For this reason, all participants in the present study were able to safely complete the exercise rehabilitation. Therefore pain exacerbation and a high dropout rate, which are typically reported (Rooks, Silverman, & Kantrowitz, 2002; van Santen, et al., 2002), was not a significant factor in the completion of the exercise rehabilitation.

Outcomes for the FIQ Total score show that there was a moderate -12.4% reduction between Start- Mid (-6.7 points, 95% CL: -14.7 to 1.3) and a small -6.8% reduction between Start-End (-3.7 points, 95% CL: -15.3 to 8.0) following AER amongst the chronic pain participants. Results for the FIQ Physical impairment scale revealed a trivial change between Start-Mid (0.1 points, 95% CL: -0.2 to 0.3) and Start-End (0.1
points, 95% CL: -0.2 to 0.3). The FIQ Fatigue scale revealed a small -15.7% reduced fatigue score between Start-Mid (-1.0 points, 95% CL: -2.1 to 0.2), however, there was trivial change between Start-End (0.2 points, CL: -1.0 to 1.5).

6.4.3 10-month follow-up assessments for the chronic pain participants

Eight chronic pain participants completed the health status, pain, and lifestyle impact questionnaires at 10-months after the AER. Results of the SF36, MPQ, and FIQ questionnaire at 10 months following the aerobic exercise rehabilitation are shown in Figure 6.6. Outcomes for the SF36 indicate that there was a small -10% decline in the SF36 Total health score (-3.9 points, 95% CL: -19.5 to 11.6) and small -11.5% reduction in the SF36 Mental health component (-5.0 points, 95% CL: -23.8 to 13.9), however, there was a trivial change in the SF36 Physical health component (-0.7 points, 95% CL: -12.6 to 11.3) at 10 months follow-up. Results for the MPQ at 10 months following the AER show that there was a large 66% increase in the MPQ Total pain score (9.9 points, 95% CL: -1.0 to 20.8), a large 62% elevation in MPQ Sensory score (5.9 points, 95% CL: -0.1 to 11.8), a moderate 74% rise in MPQ Affective score (1.4 points, 95% CL: -0.6 to 3.3), however, there was no change in the MPQ Evaluative score (0.04 points, 95% CL: -0.8 to 0.9). Results for the FIQ Total score (-0.5 points, 95% CL: -12.0 to 10.9) and the FIQ Physical impairment (-0.1 points, 95% CL: -0.4 to 0.2) show a trivial change between End and 10Month follow-up, respectively. The FIQ Fatigue score shows a small 8% rise (0.6 points, 95% CL: -0.6 to 1.7) between End and 10Month follow-up. Responses for the physical activity patterns in the FIQ show that there was a 17% decline following the AER. It is likely that there was decrease in physical activity patterns because of the
inaccessibility of a prescribed and supervised exercise program during the 10 month follow-up period.

**Figure 6.2:** Pre and Post aerobic exercise rehabilitation within the chronic pain group and the control group for Health Status (SF36), Body composition (% body fat), Functional capacity (6-min walk, power output, Exercise muscle pain intensity), Cardiovascular fitness (HR/Watt), and Experimental pain parameters (PPT, EPT, NWR threshold). Results are expressed as Cohen’s $d$ (●) with 95 percent confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful
difference. A Cohen’s $d$ (●) above 0.2 or below -0.2 represents a meaningful difference.
6.4.4 Between group comparisons

Physical characteristics of the chronic pain and control groups are shown in Table 6.1. All participants in the chronic pain and control group completed each of the Pre and Post assessments. The attendance rate for the CP group between Start-Mid was 92.4 ± 12.6% and between Start-End was 73.9 ± 23.7%. The attendance rate for the control group between Start-Mid was 96.9 ± 4.3% and between Start-End was 92.7 ± 4.0%.

The mean exercise power output (W), exercise HR (beats/min), and muscle pain intensity rating during exercise (0-10 units) as determined at Start, Mid, and End of aerobic exercise rehabilitation are shown in Figure 6.1. The mean exercise HR as a percentage of maximum HR for the chronic pain group was 65.9 ± 9.4% and for the control group was 73.7 ± 9.1%. The maximum HR was determined as 220 - Age in years.

Differences for the chronic pain compared to the control group at Pre exercise intervention expressed as Cohen’s d and 95% confidence limits are shown in Figure 6.2. Differences for the chronic pain group SF36 health status total, physical, and mental health were all large, consisting of -61.4% for SF36 Total, -70.6% SF36 Physical, and -52.2% SF36 Mental health components compared to the control group at Pre aerobic exercise rehabilitation. Mean difference and 95% CL between CP and control for SF36 Total, Physical, and Mental health components were -47 points, 95% CL: -60.8 to -33.3; -52.9 points, 95% CL: -64.5 to -41.2; and -38.9 points, 95% CL::56.6 to -21.3, respectively. Assessment for body characteristics at Pre revealed
a large 20% higher body fat percent for the chronic pain group compared to the control group (8%, 95% CL: 0.3 to 15.7).

Measurements of functional capacity and cardiovascular fitness in the chronic pain group compared to the control group at Pre revealed a large difference of -34.2% in the 6 min walk distance (-222.1 m, 95% CL: -294.8 to -149.4), -40.8% exercise power output (-36.2 W, 95% CL: -54.8 to -17.7), and 63.7% elevated HR per Watt (1 bpm, 95% CL: -0.1 to 2.0).

Assessments for muscle pain intensity during exercise at Pre for the chronic pain group compared to the control group revealed a large 4,115% elevated MPI (2.6 points, 95% CL: 1.8 to 3.4). The mean RPE for the chronic pain and control group was 11.9 ± 0.8 and 11.5 ± 0.9, respectively. Six chronic pain participants reached threshold muscle pain intensity during Pre aerobic exercise rehabilitation. Following the aerobic exercise rehabilitation, five chronic pain participants reached threshold muscle pain intensity. None of the control participants reached threshold for muscle pain intensity during exercise. This indicates that muscle pain intensity rating is an important consideration in exercise prescription for chronic pain participants.

Assessments of experimental pain for the chronic pain group revealed a large -43.8% reduced PPT (-1.6 kg, 95% CL: -2.6 to -0.5), a small -18.7% lower electrocutaneous pain threshold (-17.7 V, 95% CL: -59.3 to 23.9), and a small -14.6% reduced NWR threshold (-13.5 V, 95% CL: -56.8 to 29.8) compared to the control group at Pre aerobic exercise intervention. In two chronic pain participants, the NWR threshold was not measurable during assessment due to artefact.
Chapter 6: Effects of moderate intensity aerobic exercise rehabilitation for chronic pain disorder

Figure 6.3: A) Mean exercise power output (W), B) Heart Rate (beats/min), and C) Muscle pain intensity rating (0-10 units) during exercise at moderate intensity (RPE of 12) in chronic pain and control participants at Start, Mid, and End of 12-weeks of aerobic exercise rehabilitation
Table 6.1: Characteristics of the chronic pain and control group prior to aerobic exercise rehabilitation. Data are expressed as mean ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Chronic pain</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 ± 11.8</td>
<td>49.6 ± 9.9</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>98.7 ± 20</td>
<td>79.1 ± 5.0</td>
</tr>
<tr>
<td>Body fat %</td>
<td>47.9 ± 7.8</td>
<td>39.9 ± 8.0</td>
</tr>
<tr>
<td>6 Min Walk Test (m)</td>
<td>428.1 ± 59.8</td>
<td>650.1 ± 90.9</td>
</tr>
</tbody>
</table>
Figure 6.4: Chronic pain compared to the control group at Pre aerobic exercise intervention for Health Status (SF36), Body composition (% body fat), Functional capacity (6 min walk test, Power output, Muscle pain intensity (0-10 units), Cardiovascular fitness (HR/ Watt), and Experimental pain parameters (PPT, EPT, and NWR threshold). Results are expressed as Cohen’s $d$ (●) with 95 percent confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful difference. A Cohen’s $d$ (●) above 0.2 or below -0.2 represents a meaningful difference. Higher scores indicate the chronic pain group was higher than the healthy controls.
Figure 6.5: Comparison for the Magill pain questionnaire (MPQ) and Fibromyalgia impact questionnaire (FIQ) between Start-Mid and Start-End of aerobic exercise rehabilitation in the chronic pain group. Results are expressed as Cohen's $d$ ($\bullet$) with 95 percent confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful difference. A Cohen's $d$ ($\bullet$) above 0.2 or below -0.2 represents a meaningful difference.
Figure 6.6: Comparisons for the Health status (SF36), Magill Pain Questionnaire (MPQ), and Fibromyalgia Impact Questionnaire (FIQ) between Post-10Month follow-up in the chronic pain group. Results are expressed as Cohen's $d$ ($\bullet$) with 95 percent confidence interval (horizontal bars). The dotted vertical lines represent the threshold for the smallest meaningful difference. A Cohen’s $d$ ($\bullet$) above 0.2 or below -0.2 represents a meaningful difference.
6.5 Discussion

The present findings show that chronic pain participants were able to perform aerobic exercise at a moderate level of perceived exertion without excessive or prohibitive muscle pain. Intervention of moderate-intensity aerobic exercise rehabilitation revealed high programme attendance rate, enhanced health outcomes, and reduced pain amongst the chronic pain participants. Cardiovascular fitness was not substantially improved in the chronic pain group, however, there was a strong downward trend of -6.7% towards a reduced heart rate response to sub-maximal exercise. The leg power output was substantially improved by 16.7% and there was a reduced exercise muscle pain following the exercise intervention. Therefore, it is recommended that exercise prescription for participants with chronic pain is developed from a perceptual model that modulates exertion based on the level of muscle pain. This model of exercise rehabilitation can elicit substantial improvement in exercise capacity, health status, and reduced pain amongst persons with chronic pain disorder.

The present results show that muscle pain intensity during exercise for the chronic pain group was substantially elevated compared to the control group. The high muscle pain rating was associated with a lower exercise power output compared to the control group at the equivalent level of perceived exertion. This is in accord with previous research showing elevated muscle pain during exercise in chronic pain participants (Cook & Stegner, 2007). Elevated muscle pain typically results in low
exercise programme adherence amongst chronic pain participants. The exercise intensity in the present study, however, was mediated to minimise the muscle pain and to maintain exercise compliance. Although the improvement in cardiovascular fitness was not substantial in the chronic pain group, there was a substantial enhancement in the exercise power output and a concomitant reduction in muscle pain intensity rating during the AER. This suggests that exercise muscle pain may have limited the improvement in cardiovascular fitness, however, AER progressively reduced the exercise muscle pain and improved the power output. These results further support provisions for perceptually mediated exercise intensity due to enhanced muscle pain during AER in chronic pain participants.

The AER revealed a 5.1% improvement in the 6 min walk test in the chronic pain group. Previous studies have shown improvements in the 6 min walk test for chronic pain participants (Rooks, et al., 2002), however, no improvement following exercise intervention has also been observed (Sañudo, et al., 2010) has also been shown following exercise rehabilitation. The improved functional capacity in the present results may be associated with the increased power output and reduced exercise muscle pain following the AER. It is likely that the improvement in functional capacity in the chronic pain group was associated with enhanced exercise power output and reduced muscle pain intensity following the AER.

Levels of adherence to exercise programs for persons with chronic pain are generally low. Attendance rates for chronic pain participants in previous research range within 27-90% with a median of 67% (Häuser, et al., 2010). The level of programme adherence for chronic pain participants was high in the present study compared to previous research. Attrition rates, which refers to the level of participant drop-out from
the study, have been shown to range within 1-29% with an average of 12% in persons with CP (Burckhardt, 2006). All participants in the present study completed the AER programme with an average rate of 74% attendance. The high level of programme adherence in the present study may be attributed to the moderated muscle pain and exercise intensity during acute aerobic exercise in the chronic pain group. In accord with this, previous research shows that self-selected exercise intensity compared to fixed-intensity exercise reduces post-exercise pain compared to prescribed exercise for chronic pain participants (Newcomb, et al., 2011).

The health status in the chronic pain group was substantially lower compared to the control group. Several studies have shown improvements in both physical and psychological health components in chronic pain participants following AER (Sañudo, et al., 2010). The present results demonstrate an improvement in total health score for the chronic pain group, however, the mental health component showed less improvement compared to the physical health component. Previous research has also shown no improvement in mental health scores in chronic pain participants following AER (Bircan, et al., 2008; Richards & Scott, 2002), however, substantial improvements in mental health have been shown with strength training (Bircan, et al., 2008) and with multi-mode exercise programme intervention (Sañudo, et al., 2010). Enhanced health status with multi-mode exercise intervention compared to single-mode aerobic exercise intervention has been linked with a greater capacity to perform normal daily activities in chronic pain participants (Sañudo, et al., 2010). Therefore, further research is required to determine optimal exercise modes for enhancing both physical and mental health components in chronic pain participants.
Population based surveys have shown that chronic pain is associated with higher rates of obesity (Toblin, et al., 2011). Additionally, an association between body weight status and experimental pain sensitivity has been shown in chronic pain participants (Carbonell-Baeza, Aparicio, et al., 2011). Assessment for body characteristics prior to the AER in the present study show a higher body fat percentage for the chronic pain group compared to the control group, however, the AER did not lower the body fat percentage for the chronic pain group. Similarly, previous studies have shown no improvement in body composition following AER in chronic pain participants. The exact training dose required for weight control has not been defined, although, it has been indicated that moderate exercise training for at least 60 min on most days of the week is required for weight management (ACSM, 2010). Hence, participants in the present study did not meet sufficient exercise training for weight reduction, however, exercise is recognised as a key component for success in long-term weight management.

Previous research on experimental pain assessments show reduced pressure pain threshold (O'Neill, et al., 2011), decreased nociceptive withdrawal reflex threshold (Lim, et al., 2011; Neziri, Haesler, et al., 2010), and lower electrocutaneous pain threshold (Neziri, Haesler, et al., 2010) in chronic pain participants compared to healthy controls. In accord with previous research, the present results show enhanced experimental pain sensitivity amongst the chronic pain group compared to the healthy control group. An additional purpose of the present study was to observe potential changes in pain sensitivity by experimental pain assessment following AER. Previous studies show improvements in pressure pain threshold following AER in chronic pain (Carbonell-Baeza, et al., 2010), which suggests a reduced tissue
sensitivity. The present results reveal an increase in pressure and electrocutaneous
pain threshold but not for the NWR threshold in chronic pain participants. In accord
with the present results, a substantial enhancement in PPT threshold has also been
observed in chronic pain participants following AER (Sencan et al., 2004). The
reason for the disparity between the pain threshold assessments and the NWR
threshold following exercise rehabilitation in the present results is uncertain,
however, it is possible that participants were more willing to tolerate the perception of
the experimental pain stimulus which enhanced the pressure pain threshold. Further
studies are required to ascertain changes in the perception of experimental pain and
central sensitivity (NWR threshold and brain responses) in chronic pain participants
following AER.

Results for pain report amongst the chronic pain participants show that the total
score for pain (MPQ) and lifestyle impact (FIQ) were attenuated during the AER. The
pain questionnaire revealed a 26% to 34% decrease in total pain during the AER.
Previous studies on AER have shown reductions in pain report that ranged from no
improvement (Ramsay, et al., 2000) to 30% improvement (Burckhardt, 2006). The
reduced total pain score in the present study represents a clinically relevant change
(Farrar, Young, LaMoreaux, Werth, & Poole, 2001). The impact of chronic pain on
lifestyle as assessed by the total FIQ score was shown to be improved by 6% and
12%, however, this was below the 14% minimum clinically relevant change (Bennett,
et al., 2009). Additionally, the FIQ scale for physical impairment was not improved
during the AER in the present study. It is possible that the unaltered rating for
physical impairment in the present study may be associated with the capacity to
perform daily living activities. In contrast to aerobic exercise rehabilitation, previous
research shows that exercise strength training is associated with reduced physical
impairment and enhanced functional capacity in chronic pain participants (Sañudo, et al., 2010).

The MPQ and FIQ total scores showed substantial improvements at the mid-section of the AER but this was reduced in the later stage of the programme. A lower participation rate in the later stage of the AER may explain the reduced MPQ and FIQ scores. Anecdotal reports from chronic pain participants in the present study suggest a preference for different modes of physical activity during the exercise programme. In previous studies, multi-mode and combined aerobic exercise with strength training interventions have shown favourable outcomes for programme adherence and reduced pain amongst chronic pain participants (Sañudo, et al., 2010). Therefore, long-term exercise intervention programmes for chronic pain participants may require multi-mode physical activities that includes aerobic and strength development in order to maintain programme adherence and enhance the capacity for activities of daily living.

Due to limitations in recruiting chronic pain participants, the present study applied a Pre-Post intervention to assess the effects of AER. A non-exercising chronic pain group was not available for comparisons, however, the 10-month follow-up period enabled comparisons within the chronic pain group during a non-intervention phase. Outcomes for the 10-month follow-up show a general trend towards levels prior to the AER for health status and pain in the chronic pain participants. Results for mental and total health components showed a reduced status, while physical health was not changed. This indicates that the decline in total health status was more associated with a decrease in mental health status in the follow-up period. Additionally, the impact of pain on lifestyle, as assessed by the FIQ, indicates that fatigue scores were
substantially elevated in the follow-up period. An increase in pain scores within the MPQ was also evident in the follow-up period. These data support the theory that moderate aerobic exercise rehabilitation is associated with reduced pain and improved health outcomes during the intervention period.

### 6.5.1 Conclusion

In summary, the present study indicates that chronic pain participants can perform moderate-intensity aerobic exercise without excess pain, although this is based on a small sample size. Aerobic exercise activity mediated to acute exercise muscle pain levels was associated with substantial programme adherence and improved health outcomes in chronic pain participants. The cardiovascular fitness of the chronic pain group was not significantly enhanced, however, there was an improvement in power output and a reduction in exercise muscle pain during the aerobic exercise rehabilitation. Results for pain and lifestyle impact questionnaire revealed that the aerobic exercise rehabilitation was associated with reduced pain and impact of pain on lifestyle. In conclusion, moderate-intensity aerobic exercise rehabilitation is associated high programme adherence, reduced pain, and improved health outcomes in chronic pain participants.
Chapter 7: Somatic-pressure stimulation in chronic pain and healthy participants before and after exercise rehabilitation – A functional MRI study
7.1 Abstract

The purpose of this study was to assess the perceptual rating and functional brain responses to innocuous somatic-pressure following exercise rehabilitation in persons with chronic pain and pain-free controls. The subjects were 11 chronic pain and 8 pain-free controls who completed 12-weeks of supervised aerobic exercise rehabilitation. Perceptual rating and brain responses to 2 kg somatic pressure stimulation on the right mid-thigh were assessed before and after exercise rehabilitation by functional magnetic resonance imaging (fMRI). There was a significant difference in the perceptual rating to somatic pressure between chronic pain and control groups before ($P<0.018$) and after ($P<0.007$) exercise rehabilitation. There was no difference in the perceptual rating to somatic-pressure stimulation following exercise rehabilitation in the chronic pain or control group. Regions of interest analyses of fMRI data revealed an enhanced blood oxygen level dependent (BOLD) signal response in the superior temporal gyrus, basal ganglia, and insula for the chronic pain group compared to healthy controls. The control group revealed an increased BOLD response only in the caudate region compared to the chronic pain group. The enhanced brain activity in the chronic pain group may be associated with increased anticipation and pain catastrophising in the chronic pain group.
7.2 Introduction

Exercise rehabilitation has been shown to inhibit experimental pain response in persons with chronic pain disorder (Richards & Scott, 2002). As demonstrated in the previous chapter, an increased pressure pain threshold was observed in the chronic pain group following exercise rehabilitation. Technological advances allow the non-invasive assessment of brain activity in pain research through functional magnetic resonance imaging (fMRI). Pain is a subjective experience that involves neuronal activity in a widely distributed brain network (Lee & Tracey, 2010). Chronic pain refers to the persistence of pain beyond the period normally associated with healing for an illness or initial injury (Merskey & Bogduk, 1994; Siddall & Cousins, 2004). Chronic pain has been associated with altered cerebral activity (Kwiatek, et al., 2000; Tracey & Bushnell, 2009). Previous fMRI research on persons with chronic pain reveal dysfunctional responses in brain regions associated with the pain network during somatic stimulation (Pujol, et al., 2009).

Several studies show a sensitisation of the central pain network in participants with chronic pain disorder (Burgmer et al., 2009; Graven-Nielsen & Arendt-Nielsen, 2010; Woolf, 2011). Representation of central sensitisation is revealed by the recruitment of previously sub-threshold synaptic inputs to generate an augmented output. Pain under central sensitisation arises spontaneously, can be elicited by innocuous stimuli, is augmented and prolonged in response to noxious stimuli, and spreads beyond the site of injury (Latremoliere & Woolf, 2009). Allodynia and hyperalgesia has been identified in various chronic pain disorders (Vierck Jr, 2006).
A characteristic of central sensitisation in chronic pain is enhanced sensitivity to somatic mechanical pressure (Clauw et al., 1999; Kosek, Ekholm, & Hansson, 1996b). The somatic-pressure required to produce slightly intense pain is lower in persons with chronic pain compared to pain-free participants. Moreover, functional brain imaging reveals several common regions of enhanced neuronal activation when an equal amount of pressure-pain is applied amongst various chronic pain conditions (Giesecke, et al., 2004). Prominent brain regions showing enhanced neuronal activity include the contralateral primary (S1) and secondary (S2) somatosensory cortices, inferior parietal lobule, cerebellum, and ipsilateral S2 (Giesecke, et al., 2004). The same stimulus resulted in only a single activation in the contralateral S2 in pain-free controls. Additionally, enhanced brain neuronal activity has been observed in the basal ganglia, operculo-insula, inferior parietal cortex (Pujol, et al., 2009), and the pre-frontal cortex (Lee & Tracey, 2010) in persons with chronic pain disorder. Few studies have ascertained the functional brain responses during innocuous non-painful somatic-pressure stimulation (Gracely, et al., 2002). In order to further elucidate brain neuronal activation under central sensitisation, innocuous somatic-pressure may reveal central regions that prime the pain network in chronic pain. Areas of enhanced neuronal activity during innocuous stimulation have been previously observed in the medial frontal gyrus, insula, superior temporal gyrus, cerebellum, sensory cortex, and the cingulate (Gracely, et al., 2002).

The persistence of pain in chronic pain is associated with dysfunctional pain inhibition (Henderson et al., 2013; Jensen et al., 2009) and enhanced sensitisation (Bingel & Tracey, 2008; Porreca, et al., 2002). Previous research on somatic-pressure stimulation in chronic pain participants shows that exercise rehabilitation reduces tissue sensitivity (Carbonell-Baeza, et al., 2010). The mechanisms by which exercise
rehabilitation attenuates the sensitivity to somatic-pressure are not currently established. However, a plausible basis for the reduced somatic sensitivity in chronic pain disorder following exercise rehabilitation is by a functional restoration of the descending pain inhibition pathways and/or desensitisation of the pain network. The insular cortex is one site that has common connections with cardiovascular and pain regulatory functions (Bruehl & Chung, 2004; Randich & Maixner, 1984). Additionally, physical exercise may engage descending systems associated with antinociception. On this basis, exercise rehabilitation may favourably modulate brain responses associated with central sensitisation in chronic pain disorder.

The purpose of this study was to compare the perceptual and functional brain responses to innocuous somatic-pressure in persons with chronic pain and pain-free controls. We also examined if the perceptual and brain responses were mediated following 12-weeks of aerobic exercise rehabilitation.
7.3 Methodology

7.3.1 Participants

The participants included 11 individuals with chronic pain (CP) disorder (9 women and two men) and eight pain-free control participants (seven women and one man). Participants with chronic pain included eight subjects with fibromyalgia, two with back pain, and one individual with complex regional pain. Chronic pain participants were diagnosed by a general medical practitioner, rheumatologist, or pain specialist with persistent pain for a period of at least 12 months prior to participating in the present research study. Each participant was screened with a health questionnaire and physical activity profile. The exclusion criteria for chronic pain participants were persons with acute inflammatory conditions, acute pain, cancer pain, and inability to perform moderate-intensity aerobic exercise. The healthy participants were required to be pain-free and with absence of illness and disease.

The study was conducted with the approval of the University Ethics in Human Research Committee (approval number 08/07) and Area Health Ethics in Human Research Committee HREC2008/5/4.23(2753). Subjects were provided with study information and signed a letter of informed consent prior to the research participation.

All chronic pain participants reported regular use of non-prescription anti-inflammatory and analgesic medications, four reported using prescription opioid based medicine, and three chronic pain participants were using prescription medication for mild depression. The chronic pain participants maintained their regular
medication during the course of the study, however, abstained from medication for 12 hrs prior to functional brain imaging.

The health status for chronic pain and control participants was assessed by SF36 questionnaire (Jenkinson, et al., 1993; McHorney, Ware, Lu, & Sherbourne, 1994) and pain appraisal was assessed by the Magill Pain Questionnaire (MPQ), (Melzack, 2005) prior to the exercise rehabilitation programme. The pressure pain threshold (PPT) was assessed by algometer bilaterally on 18 tenderpoints (Harth & Nielson, 2007; Wolfe, Smythe, Yunus, Bennett, et al., 1990) for chronic pain and control participants before exercise rehabilitation by the same examiner. Each participant was familiarised with the algometer and the pain threshold measurement procedure prior to the assessment. The procedure required the participant to verbally respond by saying “yes” when the stimulus was no longer tactile and became painful during increasing somatic mechanical pressure. A mean PPT (kg) was determined from the 18 tenderpoints for each participant. The same experimenter assessed all of the participants in the study.

7.3.2 Experimental design

The design of the study is a comparative aged-matched cross-section involving within and between group analyses. Within group functional brain responses were performed for the chronic pain group before and after 12 weeks of aerobic exercise rehabilitation, and in the control group. Between group comparisons were performed amid the chronic pain group and control group before after aerobic exercise rehabilitation. The exercise intervention was completed by both the chronic pain and control participants and involved 20 min’s of supervised mild aerobic exercise
performed twice per week for 12 weeks. Leg power output (W) and heart rate (beats/min) were recorded at two min intervals during exercise. Each participant completed an fMRI before (Pre) and after 12-weeks of aerobic exercise rehabilitation (Post).

7.3.3 Functional magnetic resonance imaging acquisition

Participants were imaged on a 3T GE Signa Excite MR scanner (Milwaukee, WI) with an eight channel Medical devices head coil. The fMRI utilised a single shot EPI sequence (TR-3000 ms, TE-35 ms, 24 cm FOV, 4.00 mm slices, 39 slices, 128 x 128 matrix). The fMRI procedure was a block-design paradigm consisting five rest and five stimulus periods of 30 seconds each. Coronal 3D SPGR and T2 axial datasets were also acquired for structural brain information. Participants were imaged within two weeks prior to and within 1 week after aerobic exercise rehabilitation.

7.3.4 Somatic-pressure stimulation

Somatic-pressure stimulation was applied during the fMRI procedure. The somatic pressure consisted of a 2 kg mass with a flat surface contact diameter of 2 cm positioned on the anterior surface of the right mid-thigh (Figure 7.1B). This location was marked at the mid-point between the superior aspect of the patella and mid inguinal fold. The pressure stimulus at this site elicited a dull compression of the tissues between the superior surface of the thigh and femur. Participants were requested to rate the somatic-pressure sensation on the mid-thigh using a 0-10 sensory category ratio scale (Micalos, et al., 2009) immediately following the fMRI scanning procedure. The numerical anchors and verbal descriptors were graded as
0=no sensation, 2=slight sensation, 4=moderate sensation, 6=pain sensation, 8=strong pain sensation and 10=pain tolerance (Appendix 1). Prior to each fMRI scanning procedure, participants were familiarised with the numerical anchors and descriptors of the sensory scale.

Independent group comparisons were performed for the mean perceptual somatic-pressure rating between chronic pain and control groups. A paired sample t-test was performed between Pre and Post for the perceptual somatic-pressure rating.

### 7.3.5 Image pre-processing and analysis

Images were processed using Matlab version 7.11 (The MathWorks Inc, Natick, Mass) and Statistical Parametric Mapping software (SPM8; The Wellcome Department of Imaging Neuroscience, London). Data pre-processing consisted of motion correction using realignment, normalising to standard Montréal Neurological Institute (MNI) space, and smoothing using an 8 mm Gaussian kernel. Data were filtered using a high-pass filter (cut-off period of 128 seconds).

Pre-processed images for individual participants were then analysed in a first-level fixed effects analysis using a canonical hemodynamic response convolved box-car function to model the blood oxygen dependent (BOLD) response during stimulus. A contrast image of stimulus versus rest was derived for each participant at each time point. For the second-level analysis, a flexible factorial design using the contrast images was configured for the between and within group comparisons.
All voxel-wise comparisons were performed using a region of interest (ROI) approach defined with wfu-pickatlas software (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) with human atlas (Tzourio-Mazoyer et al., 2002). ROIs were selected based on previous research on chronic pain participants and included the basal ganglia (caudate, putamen, and pallidum), cerebellum, cingulate, frontal inferior operculum, frontal mid orbital, insula, sensory-motor cortex, superior temporal gyrus, and thalamus (Giesecke, et al., 2004; Gracely, et al., 2002; Lee & Tracey, 2010; Pujol, et al., 2009). All statistical evaluations were performed using an uncorrected $P<0.05$ and clusters were required to have at least 5 contiguous voxels. Spatial coordinates from the obtained maps were ascertained hierarchically to the nearest gray matter in Talairach space (Lancaster et al., 2000).

In addition to voxel level comparisons, we also evaluated changes in the regional BOLD signal. The BOLD signal change for each region of interest was extracted from individual participant data at Pre and Post aerobic exercise rehabilitation using Marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002). Comparisons between the chronic pain and control groups at Pre and Post and within each group between Pre and Post aerobic exercise rehabilitation for the heart rate response per watt and BOLD signal change are expressed with confidence limits and effect sizes (Shakespeare, Gebski, Veness, & Simes, 2001). A standardised Cohen’s effect size ($d$) was determined from the mean difference between Pre and Post with lower 95% and upper 95% confidence limits (Cohen, 1988). For qualitative description, effect sizes 0.2 and above were considered as a small effect, 0.5 as a medium effect, and 0.8 as a large effect.
Figure 7.1: A) Showing participant setup and somatic pressure site prior to functional MRI scanning B) showing the 2 kg somatic pressure stimulus positioned on the mid-thigh
7.4 Results

7.4.1 Group characteristics and perceptual response to somatic-pressure stimulation during fMRI

Details of the characteristics for the chronic pain and control group are shown in Table 6.1. Results for MPQ pain score, SF36 total health status, (mean ± SD) for the chronic pain and control group are listed in Table 7.1. Group comparisons between chronic pain and control at Pre reveal a significant difference for SF36 total health status ($P<0.001$, df=17).

Perceptual response to the standard somatic-pressure was assessed to affirm somatic-pressure hypersensitivity in the chronic pain group. The mean perceptual rating (sensory scale units ± SD) to the somatic-pressure stimulus during the fMRI scanning procedure for the chronic pain and control participants at Pre and Post aerobic exercise rehabilitation are shown in Figure 7.2. The chronic pain group revealed a 46% higher somatic-pressure rating compared to the control group during fMRI for the somatic-pressure stimulus (2 kg on the right mid-thigh) at Pre ($P=0.018$, df=17), and 50% higher somatic pressure rating at Post aerobic exercise rehabilitation ($P=0.007$, df=17). There was no difference between Pre and Post in the somatic-pressure rating ($P>0.05$) within the chronic pain and the control group.
7.4.2 Voxel based ROI analysis

Significant clusters with fMRI differences between the control and chronic pain group for the voxel based ROI analysis \((P<0.05\) uncorrected, 5 voxels) at pre-aerobic exercise rehabilitation are illustrated in Figures 7.3 - 7.4 and summarised in Table 7.2. The chronic group had greater fMRI activations in a number of clusters within the basal ganglia, cerebellum, insula, superior temporal gyrus and thalamus; while clusters with increased fMRI activation were seen in the basal ganglia, cerebellum, posterior and anterior cingulate, frontal inferior operculum and the insula for the control group. Although the basal ganglia, cerebellum and insula were common for the two comparisons, the location of the clusters within these regions were different.

Clusters with significant fMRI differences between the two groups at post exercise rehabilitation are illustrated in Figures 7.5 - 7.6 and summarised in Table 7.3. Similar to the fMRI activations at pre, the chronic group had greater fMRI activations in clusters within the basal ganglia, cerebellum, insula, superior temporal gyrus and thalamus. In addition, clusters within the anterior and posterior cingulate, frontal mid orbital, frontal inferior operculum and precentral cortex were seen at the post fMRI. For the control group, clusters within the basal ganglia, cerebellum, posterior cingulate, and thalamus displayed increased activation.
7.4.3 BOLD signal extraction from the regions of interest

Between-group comparisons of BOLD signal for the ROIs at Pre and Post are shown in Figure 7.7. Within-group comparisons of BOLD signal for the aerobic exercise intervention (Pre vs Post) for both the chronic and control groups are shown in Figure 7.8.

The BOLD signal analysis replicated most of the findings from the voxel based between group analysis at both Pre and Post fMRI. Similar to the voxel based analysis at Pre fMRI, the chronic pain group had increased BOLD signal (Cohen’s $d > 0.2$) within the right basal ganglia, left cerebellum, and bilateral superior temporal gyrus at Pre. In comparison, the controls had greater BOLD signal for the left frontal inferior operculum, bilateral anterior cingulate, and left frontal mid orbital region.

For the between-group fMRI at Post, only the chronic group was found to have significantly increased BOLD signal. These were for the bilateral basal ganglia, frontal inferior operculum, frontal mid orbital, superior temporal gyrus, insula, left sensory motor cortex and right anterior cingulate cortex. Unlike the voxel based analysis, no regions had increased BOLD signal for controls at Post. Notably, the effect sizes of the between group differences were much larger for the Post fMRI. The average effect size at Post was 0.29 compared to -0.02 at Pre.

For the Pre vs Post comparisons within each of the groups, the chronic pain group on average had large effect sizes (Post>Pre) in comparison to controls. The average effect size for the control was 0.17 and the chronic pain group 0.46. The chronic
group had large effect sizes within the anterior cingulate and right insula and medium
effect sizes within the bilateral basal ganglia, frontal mid orbital, frontal inferior
operculum, superior temporal gyrus and right thalamus. For the control group,
medium effects were seen within the bilateral basal ganglia, anterior cingulate,
thalamus, right superior temporal gyrus and left insula. Only the cerebellum for the
chronic pain group and the right frontal mid orbital for the control group had greater
BOLD signal at Pre in comparison to Post.
**Table 7.1:** Group characteristics prior to aerobic exercise rehabilitation. Data are presented as mean ± SD. *Group comparisons between chronic pain and control, P<0.05.

<table>
<thead>
<tr>
<th></th>
<th>Chronic pain</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.0 ± 12</td>
<td>49.6 ± 10</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>98.7 ± 20.2</td>
<td>79.1 ± 5.0</td>
</tr>
<tr>
<td>MPQ</td>
<td>19.2 ± 11.7</td>
<td>0</td>
</tr>
<tr>
<td>SF36*</td>
<td>29.6 ± 15.3</td>
<td>76.7 ± 12.1</td>
</tr>
</tbody>
</table>

**Key:** MPQ, Magill Pain Questionnaire; SF36, Short form health status questionnaire (*P <0.001*)
Figure 7.2: Mean perceptual rating (0-10 units) to the somatic-pressure stimulus during functional brain imaging in chronic pain and control participants at Pre and Post aerobic exercise rehabilitation. Group comparison between chronic pain and control at Pre * ($P=0.018$) and Post ** ($P=0.007$)
Figure 7.3: Neuronal areas of enhanced activity (ChronicPre>ControlPre) amongst the regions of interest (display threshold: \( P<0.05 \), 5 voxels)
Figure 7.4: Neuronal areas of enhanced activity (ControlPre>ChronicPre) amongst the regions of interest (display threshold: $P<0.05$, 5 voxels)
Chapter 7: Somatic-pressure stimulation in chronic pain and healthy participants before and after exercise rehabilitation – A functional MRI study

<table>
<thead>
<tr>
<th>Basal Ganglia</th>
<th>Cerebellum</th>
<th>Cingulate</th>
</tr>
</thead>
<tbody>
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<td><img src="image3" alt="Cingulate" /></td>
</tr>
<tr>
<td>Frontal Inferior Operculum</td>
<td>Frontal Mid Orbital</td>
<td>Insula</td>
</tr>
<tr>
<td><img src="image4" alt="Frontal Inferior Operculum" /></td>
<td><img src="image5" alt="Frontal Mid Orbital" /></td>
<td><img src="image6" alt="Insula" /></td>
</tr>
<tr>
<td>SensoryMotor</td>
<td>Superior Temporal Gyrus</td>
<td>Thalamus</td>
</tr>
<tr>
<td><img src="image7" alt="SensoryMotor" /></td>
<td><img src="image8" alt="Superior Temporal Gyrus" /></td>
<td><img src="image9" alt="Thalamus" /></td>
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</tbody>
</table>

**Figure 7.5:** Neuronal areas of enhanced activity (ChronicPost>ControlPost) amongst the regions of interest (display threshold; \(P<0.05\), 5 voxels)
Chapter 7: Somatic-pressure stimulation in chronic pain and healthy participants before and after exercise rehabilitation – A functional MRI study

<table>
<thead>
<tr>
<th>Basal Ganglia</th>
<th>Cerebellum</th>
<th>Cingulate</th>
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</thead>
<tbody>
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<tr>
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<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
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<table>
<thead>
<tr>
<th>Superior Temporal Gyrus</th>
<th>Thalamus</th>
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<tr>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
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</table>

**Figure 7.6**: Neuronal areas of enhanced activity (ControlPost>ChronicPost) amongst the regions of interest (display threshold; $P<0.05$, 5 voxels)
Chronic > Control

<table>
<thead>
<tr>
<th>Region</th>
<th>L/R</th>
<th>MNI coordinates (mm)</th>
<th>Cluster size</th>
<th>Z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal Ganglia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral globus pallidus/ Putamen</td>
<td>R</td>
<td>20 -2 2</td>
<td>42</td>
<td>2.45</td>
<td>0.007</td>
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<tr>
<td>Claustrum</td>
<td>R</td>
<td>26 16 -4</td>
<td>112</td>
<td>2.36</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Cerebellum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declive</td>
<td>L</td>
<td>-16 -68 -18</td>
<td>803*</td>
<td>2.83</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>12 -76 -18</td>
<td>803*</td>
<td>2.46</td>
<td>0.007</td>
</tr>
<tr>
<td>Culmen</td>
<td>L</td>
<td>-16 -68 -18</td>
<td>803*</td>
<td>2.83</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>12 -56 -16</td>
<td>185</td>
<td>2.50</td>
<td>0.006</td>
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<td>Inferior semi-lunar lobule</td>
<td>L</td>
<td>-4 -64 -40</td>
<td>63^</td>
<td>2.69</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>26 -82 -36</td>
<td>12'</td>
<td>1.89</td>
<td>0.029</td>
</tr>
<tr>
<td>Cerebellar tonsil</td>
<td>L</td>
<td>-2 -56 -42</td>
<td>63^</td>
<td>2.04</td>
<td>0.021</td>
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<tr>
<td>Tuber</td>
<td>L</td>
<td>-36 -80 -24</td>
<td>137</td>
<td>2.49</td>
<td>0.006</td>
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<td></td>
<td>R</td>
<td>22 -86 -30</td>
<td>12'</td>
<td>1.72</td>
<td>0.043</td>
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<td>Pyramis</td>
<td>R</td>
<td>26 -84 -32</td>
<td>12'</td>
<td>1.86</td>
<td>0.032</td>
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<td><strong>Insula</strong></td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>R</td>
<td>44 14 -12</td>
<td>78</td>
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<td>0.008</td>
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<td><strong>Superior Temporal Gyrus (BA22)</strong></td>
<td>R</td>
<td>56 -18 0</td>
<td>43</td>
<td>2.26</td>
<td>0.012</td>
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<tr>
<td></td>
<td>L</td>
<td>-58 -12 6</td>
<td>50</td>
<td>2.19</td>
<td>0.014</td>
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<tr>
<td><strong>Thalamus</strong></td>
<td></td>
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<td>Medial dorsal nucleus</td>
<td>R</td>
<td>6 -12 12</td>
<td>1.92</td>
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*^* - indicates same cluster
Table 7.2: continued

<table>
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<th>Control &gt; Chronic</th>
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<tr>
<td>Caudate</td>
<td>L</td>
<td>-8 16 12</td>
<td>89</td>
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<tr>
<td>Culmen</td>
<td>R</td>
<td>6 -46 4</td>
<td>8</td>
<td>2.71</td>
<td>0.003</td>
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<td></td>
<td>L</td>
<td>-4 -40 0</td>
<td>15</td>
<td>2.09</td>
<td>0.018</td>
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<tr>
<td><strong>Cingulate</strong></td>
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<tr>
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<td>175</td>
<td>3.41</td>
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<tr>
<td></td>
<td>L</td>
<td>-4 -42 10</td>
<td>30</td>
<td>2.69</td>
<td>0.004</td>
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<td>Anterior cingulate (BA24)</td>
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<tr>
<td>Inferior frontal gyrus (BA44)</td>
<td>L</td>
<td>-56 18 14</td>
<td>40</td>
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<td>0.016</td>
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<tr>
<td><strong>Insula (BA13)</strong></td>
<td>R</td>
<td>46 -12 4</td>
<td>41</td>
<td>2.18</td>
<td>0.014</td>
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</tbody>
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**Key:** * L/R=Left/Right side, BA=Brodmann area, MNI=Montreal Neurological Institute
Table 7.3: Results for peak voxels amongst the regions of interest following exercise rehabilitation

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI Coordinates (mm) (x y z)</th>
<th>Cluster Size</th>
<th>Z</th>
<th>p-value</th>
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<tr>
<td><strong>Chronic &gt; Control</strong></td>
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<tr>
<td><strong>Basal Ganglia</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>R  18 14 2</td>
<td>384*</td>
<td>2.67</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>L -28 -14 -2</td>
<td>43</td>
<td>2.21</td>
<td>0.013</td>
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<tr>
<td>Lateral globus pallidus</td>
<td>R  18 2 0</td>
<td>384*</td>
<td>2.58</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>L -12 6 -2</td>
<td>89</td>
<td>2.33</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Cerebellum</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Declive</td>
<td>R  40 -78 -22</td>
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<td></td>
<td>L -18 -84 -22</td>
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<td>Uvula</td>
<td>R  30 -84 -24</td>
<td>140^</td>
<td>2.27</td>
<td>0.012</td>
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<td>Culmen</td>
<td>R  10 -42 -6</td>
<td>36</td>
<td>2.26</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>L -18 -36 -18</td>
<td>11</td>
<td>2.20</td>
<td>0.014</td>
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<tr>
<td><strong>Cingulate</strong></td>
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<td></td>
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</tr>
<tr>
<td>Precuneus/Posterior Cingulate</td>
<td>R  14 -48 36</td>
<td>67</td>
<td>2.59</td>
<td>0.005</td>
</tr>
<tr>
<td>(BA31)</td>
<td></td>
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</tr>
<tr>
<td>Anterior cingulate (BA32)</td>
<td>R  10 38 14</td>
<td>20</td>
<td>2.08</td>
<td>0.019</td>
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<td><strong>Frontal Mid Orbital</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mid frontal gyrus (BA11)</td>
<td>R  38 48 -8</td>
<td>69</td>
<td>2.65</td>
<td>0.004</td>
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<td>L -32 34 -14</td>
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<td>2.10</td>
<td>0.018</td>
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<td>Superior frontal gyrus (BA 11)</td>
<td>R  22 40 -20</td>
<td>31</td>
<td>2.63</td>
<td>0.004</td>
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<td><strong>Frontal Inferior Operculum</strong></td>
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<td>Inferior frontal gyrus (BA45-47)</td>
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<td>108</td>
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<td><strong>Insula</strong></td>
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<td>Superior Temporal (BA38)/ Inferior frontal gyrus (BA45-47)</td>
<td>R 44 12 -12</td>
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<td>2.69</td>
<td>0.004</td>
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<tr>
<td>Insula</td>
<td>L -40 4 -4</td>
<td>279'</td>
<td>2.51</td>
<td>0.006</td>
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<td><strong>SensoryMotor</strong></td>
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<td>0.024</td>
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</tr>
<tr>
<td>BA 21/22/38/13</td>
<td>R  46 -12 -14</td>
<td>161</td>
<td>2.86</td>
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334
Table 7.3: continued

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<thead>
<tr>
<th>Thalamus</th>
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</tr>
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<tbody>
<tr>
<td>Medial geniculum body</td>
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<td>18</td>
<td>-22</td>
<td>-2</td>
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<tr>
<td>Ventral lateral nucleus</td>
<td>L</td>
<td>-8</td>
<td>-12</td>
<td>4</td>
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*"^*" - indicates same cluster

<table>
<thead>
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<tr>
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<td>20</td>
</tr>
<tr>
<td>Cerebellum</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nodule</td>
<td>R</td>
<td>2</td>
<td>-46</td>
<td>-32</td>
</tr>
<tr>
<td>Inferior semi-lunar lobule</td>
<td>R</td>
<td>34</td>
<td>-70</td>
<td>-40</td>
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<tr>
<td></td>
<td>L</td>
<td>-30</td>
<td>-64</td>
<td>-42</td>
</tr>
</tbody>
</table>

| Cingulate                                   |   |   |      |      |
| Posterior cingulate                         | R | 10 | -36 | 12  | 23 | 2.62 | 0.004 |
| Thalamus                                    | L | -12 | -30 | 12  | 11 | 2.24 | 0.012 |

**Key:** * L/R=Left/Right side, BA=Brodmann area, MNI=Montreal Neurological Institute
Chapter 7: Somatic-pressure stimulation in chronic pain and healthy participants before and after exercise rehabilitation – A functional MRI study

Figure 7.7: Percent BOLD signal change within the regions of interest between the chronic pain and the control group (between-group analysis) at Pre and Post aerobic exercise rehabilitation. Results are expressed as Cohen’s $d$ ($\bullet$) with 95 percent confidence interval (horizontal bars). The vertical dotted lines represent the threshold ($\pm 0.2$) for the smallest meaningful difference. A Cohen’s $d$ ($\bullet$) above 0.2 or below -0.2 represents a meaningful difference (enhanced neuronal activation or deactivation) in the BOLD signal in the chronic pain group compared to the control group.
Figure 7.8: Percent BOLD signal change in the regions of interest between Pre and Post aerobic exercise rehabilitation (within-group analysis) for the chronic pain and the control group. Results are expressed as Cohen’s $d$ (*) with 95 percent confidence interval (horizontal bars). The vertical dotted lines represent the threshold ($\pm 0.2$) for the smallest meaningful difference. A Cohen’s $d$ (*) above 0.2 or below -0.2 represents a meaningful difference (enhanced neuronal activation or deactivation) in the BOLD signal for the chronic pain group compared to the control group.
7.5 Discussion

The purpose of the study was to assess changes in cerebral processing and perceptual rating of somatic pressure stimulation in chronic pain and control participants before and after 12-weeks of exercise rehabilitation. The novel finding in the present results revealed that exercise rehabilitation elicited improvements in cardiovascular fitness but did not show a significant reduction in the perceptual rating of somatic pressure stimulation during fMRI. Additionally, the ROI and BOLD signal analyses revealed several regions of interest showing enhanced activity before and after exercise rehabilitation in the chronic pain group compared to the pain-free control group.

7.5.1 Perceptual rating to innocuous somatic-pressure stimulation

Previous research shows that the perceptual rating of painful somatic-pressure stimulation during functional brain imaging is elevated in patients with chronic pain compared to pain-free control participants (Pujol, et al., 2009) suggesting a central hypersensitivity. The present study replicated this finding using an innocuous, non-painful, somatic pressure stimulus. Enhanced perceptual rating of the somatic-pressure (Fig. 7.2) suggests the presence of central sensitization by augmentation of the somatosensory stimulus in the chronic pain participants. The enhanced perception of somatosensation has been associated with elevated neuronal activity in regions within the brain. Previous research indicates enhanced brain responses to innocuous somatic temperature stimuli (Cook et al., 2004) and somatic-pressure (Gracely, et al., 2002) in participants with chronic pain.
7.5.2 Regional brain analysis

Enhanced perception of a moderately painful stimulus has been associated with augmented brain responses during functional brain imaging in participants with various pain syndromes (Giesecke, et al., 2004). The present study, however, applied an innocuous somatic pressure-stimulus on the surface of the thigh. This stimulus resulted in an elevated verbal rating and more widespread neuronal responses in the chronic pain group compared to the control group. Similarly, more widespread neuronal activation has previously been observed during innocuous somatic-pressure stimulation amid several brain regions in chronic pain participants compared to control participants (Gracely, et al., 2002).

Prominent brain regions that were active within the chronic pain group in the present study prior to exercise rehabilitation included the superior temporal gyrus, basal ganglia (putamen, claustrum, pallidus), and cerebellum. Several of these brain regions have previously been associated with pain catastrophising (Gracely, et al., 2004). This involves a maladaptive coping strategy that exerts a negative influence on pain and pain-related outcomes (Bartley & Rhudy, 2008). Brain areas associated with pain catastrophising include the claustrum, cerebellum, putamen, and pallidus. Heightened pain experience by catastrophising may be a marker of pain anticipation (Sullivan et al., 2001). Neuronal activity in the cerebellum has been associated with pain anticipation while the claustrum has been coupled with the emotional aspects of pain (Gracely, et al., 2004). Both the cerebellum and claustrum were prominent neuronal activation sites in the chronic pain group compared to the control group.
Thus, it is possible that these brain regions were more active due to catastrophising in the chronic pain compared to the control group.

7.5.3 Perceptual and regional brain responses at following aerobic exercise rehabilitation

Previous studies have shown a reduction in the perceptual rating of somatic-pressure stimulation in chronic pain disorder following exercise rehabilitation (Carbonell-Baeza, et al., 2010). The perceptual rating to the innocuous somatic-pressure stimulus during brain imaging following aerobic exercise rehabilitation in the present study did not reveal a reduced response. One possible explanation for this outcome is that the pressure stimulus intensity was not sufficient to detect changes in somatosensation following exercise rehabilitation. On this basis, it would be expected to observe a consistent fMRI result following exercise rehabilitation. However, there was an increased number of neuronal activation sites in the chronic pain group following exercise rehabilitation compared to the control group. Additional active regions in the chronic pain group following exercise rehabilitation involved the frontal mid orbital, precentral gyrus, and the operculum. This was also reflected as an increased BOLD signal within most of these regions at Post.

A limitation in the present study is the variance in the duration of chronic pain amongst the patient group. Previous research shows that chronic pain is associated with neurodegenerative changes and that this corresponds with the duration of clinical pain (Apkarian, et al., 2004). The present study included patients with a duration for chronic pain of greater than one year. This may have provided a heterogenous sample and influenced the effects of exercise rehabilitation. For
example the effect size of the change in the rating of the somatic pressure stimulus for the chronic pain and control group was 0.2 and 0.07, respectively. Hence it is possible that the chronic pain participants may have undergone neurodegenerative changes in the duration of the study. Future studies could provide a more homogenous duration of chronic pain such as a pain duration of 1-3 years when investigating the effects of exercise rehabilitation.

7.5.4 Anticipation

Prominent brain regions that revealed consistently enhanced activity at Pre and Post in the chronic pain group included the basal ganglia, insula, and superior temporal gyrus. Notably, neuronal activity from the somatosensory-motor area was not prominent in the chronic pain group. This indicates that most of the brain response during the innocuous somatic-pressure was associated with activity in regions involved in anticipation. A prominent brain region involved in anticipation is the entorhinal complex (Fairhurst, Wiech, Dunckley, & Tracey, 2007), which incorporates areas in the medial temporal lobe (Ploghaus et al., 2001). Previous research shows direct projections between the superior temporal gyrus and the entorhinal cortex (Amaral, Insausti, & Cowan, 1983). Therefore, the increased anticipation of the somatic pressure stimulus could result in increased perceptual sensitivity. Activation in the superior temporal gyrus featured prominently in the present results in the chronic pain group and this has previously been observed in persons with chronic pain (Gracely, et al., 2002). Experimental pain studies show that anxiety-related increases in perceived pain are associated with activation in the entorhinal cortex of the hippocampus (Ploghaus, et al., 2001). Therefore, the increased number of
activation sites in the chronic pain group may be associated with enhanced anticipation during the fMRI scanning procedure.

7.5.5 Reduced neuronal activity in caudate

The present results reveal that neuronal activity in the caudate was consistently enhanced in the healthy control group compared to the chronic pain group at both Pre and Post aerobic exercise rehabilitation. Previous research has shown that regional blood flow activity in the caudate is reduced in chronic pain participants compared to control (Mountz et al., 1995). Enhanced activity in the caudate has previously been observed in healthy control compared to chronic pain participants (Gracely, et al., 2002), although this difference was not observed in another study using cerebral blood flow analysis (Kwiatek, et al., 2000). In pain research, activation in the caudate nucleus suggests that this may be a likely source for pain suppression (Wunderlich et al., 2011). The initiation of suppression of the feeling of pain was shown by activation of the caudate (Freund et al., 2009). Therefore, the present findings suggest a functional abnormality amid the caudate during innocuous pressure stimulation in persons with chronic pain disorder.

7.5.6 Thalamus

Enhanced thalamic activity during noxious stimulation has been observed in pain-free participants compared to patients with chronic pain disorder (Gracely, et al., 2002). The present results did not show a difference between the chronic pain and control group for thalamic activity. Previous research has shown that regional blood flow (Kwiatek, et al., 2000; Mountz, et al., 1995) and neuronal activity in the thalamus is
reduced in chronic pain participants compared to control (Jensen, et al., 2009). It has been suggested that thalamic response is inhibited in chronic pain due to a functional plasticity from input by persistent pain signalling. This is supported by research showing that reduced thalamic activity was elevated following analgesic treatment in chronic pain patients (Hsieh, et al., 1995). It is possible that the non-painful stimulus in the present study was not sufficient to reveal differences in thalamic activity in the chronic pain group.

7.5.7 Insula – A pattern of connectivity between temporal lobe and basal ganglia

Elevated neuronal activity in the insula has been observed in pain tasks (Apkarian, et al., 2005) and in non-painful tasks (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). Functional integration of sensorimotor, socio-emotional, and cognitive networks amid the insula may set a context for thoughts and actions. Baseline brain activity in the insula has been shown to predict subsequent pain-intensity ratings (Boly et al., 2007). The present results show enhanced BOLD signal in the insula for the chronic pain group compared to the control group. In the resting brain, networks between the insula, temporal cortex, and anterior cingulate primarily contribute to emotional aspects. The present results show consistently enhanced neuronal activity in the basal ganglia, insula, and the superior temporal gyrus within the chronic pain group compared to control group during innocuous stimulation. This suggests that activity between these three regions may be augmenting the somatosensory input and priming the pain network. On this basis, it is possible chronic pain results in a dysfunction of the somatosensory system rather than augmentation of the noxious signal.
7.5.8 BOLD signal analysis

Results for the BOLD signal analysis amongst the regions of interest in the chronic pain compared to the control group reinforce the results observed in the voxel based ROI analysis. Enhanced BOLD signal was evident in the superior temporal lobe, insula, and basal ganglia. Additionally, there was a trend towards reduced activity in the anterior cingulate and the frontal inferior operculum in the chronic pain group compared to control. Diminished activity in the anterior cingulate has been implicated as a site for impaired descending pain inhibition (Jensen, et al., 2009). In contrast, previous research also shows enhanced activity in the anterior cingulate (Pujol, et al., 2009) amongst participants with chronic pain disorder compared to controls. One reason for this discrepancy is that the BOLD signal activity from the anterior cingulate in the present study was assessed during innocuous pressure stimulation and not during painful stimulation. Additionally, the present study employed a conventional-model driven approach which may underestimate brain responses to the stimulus compared to a data-driven approach (Pujol, et al., 2009). Despite this limitation, neuronal activity from the superior temporal lobe, insula, and basal ganglia were consistently elevated in the chronic pain group.

Affective and cognitive factors such as attention, anxiety, and anticipation may mediate the perception of somatosensation. Limitations within the present study are that the influence of central factors such as emotion and cognitive components were not assessed. In one study, anxiety and depression were co-factored amongst participants and this revealed that cognitive and affective factors during the anticipation of pain played an important role in pain processing (Burgmer, et al.,
2009). It has been suggested that attentional mechanisms such as hyper-vigilance may influence the evoked cerebral response in structures similar to those observed in the present study (Gracely, et al., 2002). In a pain-matched design between chronic pain and control groups it was revealed that brain regions pertaining to the affective-motivational and sensory-discriminatory domains for pain processing did not differ between the groups (Jensen, et al., 2009). However, differences between groups were observed in the function of endogenous pain inhibition. The chronic pain participants revealed attenuated responses to pain provocation.

7.5.9 Summary

In summary, the present study showed that the innocuous stimulation in chronic pain participants revealed elevated perceptual sensitivity and enhanced brain activity compared to the healthy control group in brain regions associated with pain anticipation and emotion. The enhanced brain activity may be associated with central sensitisation and pain catastrophising in persons with chronic pain. Enhanced activity in the caudate was observed in the control group compared to the chronic pain group. Exercise rehabilitation did not reveal a reduction in the perceptual response or brain neuronal activity to innocuous stimulation. The enhanced brain activity following aerobic exercise rehabilitation may be associated with increased anticipation during the fMRI in the chronic pain group. Further research is required to reveal the neuronal events in central sensitisation and exercise rehabilitation amongst persons with chronic pain.
Conclusion

The relationship between exercise and pain has long been recognised by researchers and clinicians. The present thesis investigated the relationship between the function of the pain system and physical exercise through a series of research trials in pain-free participants and in persons with chronic pain disorder. In the context of the exercise and experimental pain research, exercise has previously been shown to attenuate pain in the post-exercise period in healthy participants. The attenuation of pain following physical exertion suggests that exercise engages pain-inhibitory systems. Physical exercise may inhibit experimental pain parameters through descending antinociceptive systems. The mechanism for exercise-induced pain inhibition is not fully detailed, however, the function of spinal and cerebral antinociceptive systems were investigated in the present thesis.

In the clinical context, exercise rehabilitation has shown to reduce pain report and attenuate experimental pain in persons with chronic pain. The multi-system benefit of physical activity has been recognised in health and medicine (Khan, 2011), however, the optimum exercise prescription and mechanism for pain relief has not been fully explored in chronic pain management. The prevalence of chronic pain is projected to increase as the population ages (Access Economics, 2007). For many persons with chronic pain disorder, persistent pain is not managed optimally and therefore there is a large scope for reducing the impact of chronic pain. Exercise rehabilitation has been shown to be one of the few consistent efficacious treatments for chronic pain disorder. Previous research indicates that exercise rehabilitation is associated with
improved clinical pain report, enhanced functional capacity, and favourable changes in health. Despite this, the optimal prescription for exercise rehabilitation in persons with chronic pain has not been extensively detailed. An exacerbation of pain amongst chronic pain participants (van Santen, et al., 2002) has been reported during exercise rehabilitation and this is associated with low programme adherence and reduced clinical outcomes.

The present thesis combined a series of research studies that were designed based on the previous literature to further explicate the function of the pain system with physical exercise. This research also involved determining the reliability of the nociceptive withdrawal reflex threshold as a measure of the sensitivity of the pain system.

8.1 Study 1: Reliability of the nociceptive withdrawal reflex threshold

The purpose of study one was to assess the reliability of the nociceptive withdrawal reflex threshold and to determine the association with pain threshold. Previous research on exercise-induced pain inhibition has shown that the repeated administration of acute experimental noxious episodes launches pain-inhibitory systems (Padawer & Levine, 1992). The experimental pain inhibition following exercise was associated with a pain-test reactivity to repeated administration of noxious episodes. Pain inhibition by reactivity to repeated noxious episodes has been associated with stress induced analgesia (Butler & Finn, 2009). In order to avert pain-test reactivity to repeated noxious episodes it was necessary to develop a reliable experimental noxious protocol.
Experimental pain measurement procedures require the subjective judgment of an experimental noxious stimulus. The present thesis included the development of a reliable experimental noxious protocol in order to assess the potential effects of exercise-induced pain inhibition. The results demonstrate that the pain threshold, as assessed by an acute series of electrocutaneous stimuli revealed a reliable within-trial reproducibility.

### 8.1.1 Study 1: Research question addressed

The nociceptive withdrawal reflex is a reliable pain-related neurophysiological event and is associated with the pain threshold.

Results from the reliability and correlation analysis for the nociceptive withdrawal reflex threshold shows a within trial reliability and strong association with pain threshold. Here, the hypothesis is accepted. In addition to the reliable assessment of the electrocutaneous pain threshold, the present thesis also developed a reliable and valid pain-related neurophysiological event in the assessment of the nociceptive withdrawal reflex threshold. The present results show that the nociceptive withdrawal reflex threshold was stable and reproducible within-trial. Additionally, the advantage of the nociceptive withdrawal reflex threshold over sensory threshold testing is that the reflex assesses spinal cord excitability. These data show that the nociceptive withdrawal reflex threshold can be applicable in assessing within-trial pain interventions such as physical exercise.
It was also shown that the nociceptive withdrawal reflex threshold presented a strong association with the electrocutaneous pain threshold. The high correlation between the nociceptive withdrawal reflex threshold and the pain threshold reflects the results of previous research and affirms the association between the percept for pain threshold and the neurophysiological correlate as the nociceptive withdrawal reflex. The association between the nociceptive withdrawal reflex threshold and the pain threshold suggests that the nociceptive withdrawal reflex threshold is valid in experimental pain studies under standardised resting conditions.

### 8.1.2 Study 1: Major finding

It was shown that the nociceptive withdrawal reflex threshold presented a strong association with the electrocutaneous pain threshold. Additionally, both the nociceptive withdrawal reflex and pain threshold revealed a substantial within-trial reliability. The association and correlation of the nociceptive withdrawal reflex threshold with the pain threshold suggests that the nociceptive withdrawal reflex is clinically valid in experimental pain studies under standardised resting conditions.

### 8.1.3 Study 1: Limitations

Application of electrocutaneous stimuli bypasses the nerve endings and excites the nerve truck directly. Therefore, this type of noxious stimulus is limited in that the function of the nerve ending is not fully investigated. Mechanical pressure and thermal pain assessments are able to naturally activate the full range of peripheral receptors, however, this method is prone to perceptual bias following an intervention.
8.2 Study 2: Reduced cerebral event related potentials to nociceptive stimuli following aerobic exercise

Previous research has shown that aerobic exercise increases the nociceptive withdrawal reflex threshold and pain threshold in healthy participants. The enhanced nociceptive withdrawal reflex threshold following exercise suggests a spinal mechanism for the attenuation of nociceptive signals. Additionally, reduced cortical responses to noxious somatic stimuli have also been observed following repetitive movement exercise. Therefore, the purpose of study two was to assess the effect of acute aerobic exercise on the perception of noxious stimuli with cortical and spinal pain-related events. As such, the electrocutaneous pain threshold, nociceptive withdrawal reflex threshold, and cerebral event related potentials were assessed before and after acute aerobic exercise in healthy participants. The advantage of applying measures of the nociceptive withdrawal reflex and pain threshold is that this can assess the function of the pain processing system and determine the effects of aerobic activity.

8.2.1 Study 2: Research question addressed

Aerobic exercise attenuates experimental pain and pain-related neurophysiological events

Acute aerobic exercise did not increase the electrocutaneous pain threshold and did not reduce the spinal cord excitability as determined by the nociceptive withdrawal reflex threshold. It was demonstrated that acute aerobic exercise inhibits cerebral
event related potentials to nociceptive events. Together, these data indicate that acute aerobic exercise mediates nociceptive signalling at supraspinal levels in healthy participants, however, does not mediate the pain or the nociceptive withdrawal reflex threshold. The hypothesis is partially accepted in that nociceptive signalling was attenuated at the cerebral level, however, did not mediate the electrocutaenous pain and nociceptive withdrawal reflex threshold.

8.2.2 Study 2: Major finding

Results on the acute effects of aerobic exercise on spinal and cerebral pain-related events shows a dampening of cerebral event related potentials, but not for spinal cord excitability. These data indicate that acute aerobic exercise mediates nociceptive signalling at supraspinal, but not at the spinal cord level in healthy participants.

The new finding in study two revealed that aerobic exercise significantly attenuated cerebral event related potentials to nociceptive events. It was shown that aerobic exercise resulted in the attenuation of the peak signal amplitude for cerebral event-related potentials to nociceptive stimuli following physical exercise. Previous research has indicated that these somatosensory signals are attenuated by changes in arousal and by exogenous opioid intervention. Aerobic exercise has previously been shown to mediate attention and to enhance opioid based endorphin release in the post-exercise period. Therefore, it is possible that aerobic exercise attenuated the cerebral event related potentials to nociceptive stimuli by altering arousal or by enhanced endogenous endorphin release in the post-exercise period.
In conclusion, acute aerobic exercise was shown to attenuate cerebral event related potentials, however, did not mediate the function of the spinal cord in processing experimental noxious stimuli. Therefore, these results show that aerobic exercise attenuates nociceptive signalling at supraspinal levels but did not mediate spinal cord excitability in the post-exercise period.

8.2.3 Study 2: Limitations

The results from study two also revealed that aerobic exercise did not enhance the nociceptive withdrawal reflex threshold or the pain threshold. Another possible reason for the non-effect on the nociceptive withdrawal reflex and pain threshold is that the exercise intensity was not sufficient to mediate these thresholds. The present study included an exercise intensity that has previously been shown to elevate the nociceptive withdrawal reflex threshold (Guieu, et al., 1992). While the exercise intensity was based on the relative aerobic capacity (70% of VO\textsubscript{2 max}), it is possible that this workload did not elicit sufficient exercise stress in order to activate antinociceptive systems. This is supported by the metabolic load, as assessed by blood lactate. Levels of blood lactate did not substantially increase with high intensity exercise in some participants.

Further limitation in the study is that changes in skin resistance may have masked the potential effect on spinal mediated nociceptive reflexes in the post-exercise period. Future studies could address these limitations to further elucidate the mechanisms for exercise-induced pain inhibition. Moreover, a shortcoming with electrostimuli is that the stimulus bypasses the nerve receptor ending and therefore averts possible changes in receptor function following exercise.
Measures of attention and arousal during experimental noxious stimulation in the present study were not recorded and may have been useful in accounting for the variance in pain parameters under resting conditions and following aerobic exercise. Additionally, acute aerobic exercise may have altered the skin resistance to constant-voltage electrocutaneous stimuli and therefore may have masked the effects of exercise on the nociceptive withdrawal reflex in study two. Use of constant-current stimuli, alongside recordings of inter-electrode resistance could provide further information on the potential changes in skin resistance following exercise.

8.3 Study 3: Effects of moderate intensity aerobic exercise rehabilitation for chronic pain disorder

Previous research shows that self-selected exercise intensity reduces post-exercise pain compared to prescribed exercise for chronic pain participants (Newcomb, et al., 2011). In one study, exercise guidelines for aerobic training were not achieved because chronic pain participants were unable to attain target heart rate levels due to elevated pain during exercise (Norregaard, et al., 1997). Currently, further research is required to elucidate the optimum level of exercise rehabilitation in persons with chronic pain (Häuser, et al., 2010).

Therefore the purpose of this study was to quantify the exercise capacity and pain responses to moderate-intensity aerobic exercise in persons with chronic pain. Additionally, the influence of this mode of exercise rehabilitation on clinical pain, health, functional capacity, and pain-related outcomes in persons with chronic pain was examined.
The results show that the chronic pain participants reported elevated levels of pain and reduced workload output during exercise compared to healthy participants. Applying an exercise prescription based on limiting the exercise-related pain in the present study resulted a high level of exercise programme adherence in the chronic pain participants showing compared to previous research using prescribed exercise intensity.

This type of exercise rehabilitation also resulted in significant reductions of clinical pain, enhanced health status, and improved functional outcomes. The cardiovascular fitness was slightly enhanced, and there was a substantial improvement in exercise power output during the exercise rehabilitation for the chronic pain group. These results indicate that moderate-intensity aerobic exercise rehabilitation for chronic pain participants is well-tolerated and has favourable outcomes for programme adherence and clinical pain report.

8.3.1 Study 3: Research question addressed

Moderate-intensity aerobic exercise rehabilitation reduces pain, enhances health outcomes, and improves functional capacity in persons with chronic pain disorder

Moderate-intensity aerobic exercise rehabilitation resulted in favourable changes in clinical pain, health status, and improvements in functional capacity in persons with chronic pain. The hypothesis is accepted.
8.3.2 Study 3: Major findings

The findings in this study show that physical exercise rehabilitation when mediated to minimise exercise-induced muscle pain was associated with high programme adherence. Despite the reduced exercise workload due to elevated muscle pain, the chronic pain participants showed significant improvements in leg power output, reduced clinical pain report, and improved health status during the exercise rehabilitation programme.

Moderate aerobic exercise rehabilitation showed improved outcomes in pain report in the chronic pain participants. The favourable changes in clinical pain report may be associated with substantial improvements in health status following the exercise rehabilitation in the chronic pain group. Interestingly, measures of physical impairment were not substantially improved following the aerobic exercise programme. In contrast, previous research shows that exercise intervention programmes involving resistance training are associated with improved outcomes in physical impairment (Sañudo, et al., 2010). Therefore, it is possible that exercise rehabilitation programmes for chronic pain participants may require moderate aerobic activity in combination with resistance-based activities in order to alleviate reductions in physical impairment and improve the ability to perform activities of daily living.

The increase in health status during exercise rehabilitation was shown in both physical and mental health components in the chronic pain group. Interestingly, at the 10-month follow up after exercise rehabilitation, the chronic pain group observed an increase in pain report and a decline in mental health status, however, the
physical health status remained stable. This suggests that changes in mental health status during exercise rehabilitation are more closely associated with clinical pain report in chronic pain participants. A possible mechanism for this is that with supervised controlled exercise conditions helps to alleviate a fear of movement, known as kinesiophobia. Results from the 10-month follow-up show a decline in physical activity patterns in the chronic pain group. This suggests that the physical activity patterns decreased during the unavailability of the supervised aerobic exercise rehabilitation program and that clinical pain report increased. Therefore, a reduction in clinical pain report during moderate-intensity aerobic exercise rehabilitation may be associated with increased physical activity patterns and improvements in psychological status in chronic pain participants.

Experimental pain assessments amongst the chronic pain participants revealed a difference between the perceived responses and pain-related neurophysiological events following exercise rehabilitation. The perceptual responses to experimental pain included the pressure pain threshold. Assessments for pain-related events included the nociceptive withdrawal reflex threshold. The results show a large increase in the pressure pain, however, there was no change in the nociceptive withdrawal reflex threshold in the chronic pain group. The increased pressure pain threshold is in accordance with the reduced clinical pain report in the chronic pain group following exercise rehabilitation. This suggests that physical rehabilitation reduces clinical pain and peripheral tissue sensitivity in chronic pain participants.

Assessment of spinal cord excitability through the nociceptive withdrawal reflex threshold revealed that this was not altered following exercise rehabilitation in the chronic pain group. This indicates that the aerobic exercise rehabilitation did not
mediate the functional excitability of the spinal cord. A possible reason for this is that a substantially lower nociceptive withdrawal reflex threshold in the chronic pain group compared to the healthy control group was not evident prior to the intervention. Non-difference in the baseline measure of the nociceptive withdrawal reflex threshold may be associated with the variance in the duration of chronic pain in the chronic pain group. The selection of chronic pain participants was based on chronic pain diagnosis of at least one year. It is possible that this timeline may not have been sufficient to observe a reduced nociceptive withdrawal reflex threshold.

Currently there is a lack of available information between the duration of chronic pain and the presence of central hypersensitivity (Lim, et al., 2011). Previous research indicates that neurodegenerative changes in the brain are associated with the duration of chronic pain (Apkarian, et al., 2004). It is possible that the duration of chronic pain and central hypersensitivity may be together associated. The results in the present study did not show an improvement in central hypersensitivity in the spinal cord as revealed by the nociceptive withdrawal reflex threshold following exercise rehabilitation. Some participants in the present study had chronic pain for more than 10 years while others were less than 2 years. Hence the development of central hypersensitive may have varied substantially in the chronic pain group. Future research in this area may require a more homogenous pain duration group such as within 1-3 years in order to ascertain central hypersensitivity and whether exercise can mediate this.

The increased pressure pain threshold in the chronic pain group may be due to a perceptual bias to somatic pressure pain. A limitation in the present study is the lack of a non-exercising chronic pain group, however, perceptual bias to pressure pain
threshold assessment is difficult to control in pain research since participants are unable to be blinded to the exercise intervention and proposed outcomes. Prior knowledge of the proposed study outcomes may result in a modification of behaviour due to the awareness of the experimental situation, known as a Hawthorn effect (De Amici, Klersy, Ramajoli, Brustia, & Politi, 2000). On this basis, the chronic pain participants were possibly more willing to tolerate experimental pressure pain stimulation following exercise rehabilitation. An alternative possibility is that exercise rehabilitation favourably alters somatic tissue sensitivity. Since the electrocutaneous stimulus for the nociceptive withdrawal reflex bypasses the nerve receptor ending, it is possible that pressure pain threshold assessment reflects changes in peripheral tissue sensitivity following exercise rehabilitation.

Additionally, it is possible that the exercise rehabilitation may favourably alter higher order cognition in the chronic pain group. In one study, positive changes in psychological status following exercise rehabilitation in chronic pain participants were attributed to completing the exercise programme without undue harm (Mannion, et al., 2001). Moreover, the results showed favourable changes in psychological distress and somatic symptom perception. The present study observed positive changes in psychological status in the chronic pain group and this may have influenced the tissue sensitivity and thus the experimental pressure pain assessment. Thus, aerobic exercise rehabilitation in the chronic pain group resulted in positive changes in psychological status, which may have mediated the perception of experimental pressure pain assessment.
8.3.3 Study 3: Limitations

The impact of exercise rehabilitation on aspects on the quality of life for chronic pain participants such as the use of medication and changes in sleep patterns is unknown. In the present study, chronic pain participants were required to maintain their regular medication, except to abstain for 12 hours prior to testing. This was to maintain a standard during the intervention period. There was limited data gathered on medication use and no data was collated on sleep patterns. Structured interviews, questionnaires, and focus groups could glean further information on the effects of exercise intervention on the quality of life in chronic pain participants.

The current sample size in the present study may not have been sufficient to detect differences between the chronic pain and control groups for the nociceptive withdrawal reflex threshold. It has been suggested that sample sizes of below N=10 may result in differences between groups not being detected and that sample sizes of above 20 are required to detect differences (Lim, et al., 2011). The present sample was N=11, and therefore there is the possibility that the statistical power may have been less than optimal. However, the limitation in accessing suitable candidates in the regional and geographical area presented difficulties in availability.
8.4 Study 4: Functional brain responses and perceptual rating to somatic-pressure stimulation in chronic pain and healthy participants before and after exercise rehabilitation

The persistence of pain beyond the period of expected healing is hypothesised to result from neuronal hyperactivity, changes in membrane excitability, dysfunction of modulatory or inhibitory systems, and central sensitisation (Atkinson, 2004). Previous research shows that chronic pain is associated with enhanced widespread somatic mechanical pressure sensitivity and that exercise rehabilitation reduces this sensitivity. Therefore, the purpose of study four was to compare the perceptual and functional brain responses to innocuous somatic-pressure in persons with chronic pain and pain-free controls. Furthermore, brain response to the same somatic stimulus was re-assessed after 12-weeks of aerobic exercise rehabilitation.

8.4.1 Study 4: Research question addressed

Aerobic exercise rehabilitation favourably modulates brain-related processing of somatosensory events in persons with chronic pain

Aerobic exercise rehabilitation did not attenuate brain-related processing of mechanical somatic-pressure stimulation during fMRI imaging in chronic pain participants. The hypothesis in rejected.
The present results show that exercise rehabilitation revealed significant improvements in clinical pain report, however, did not reveal a significant reduction in the perceptual rating of somatic pressure stimulation during brain imaging within the chronic pain group. Several brain sites were shown to have elevated activity before and after aerobic exercise rehabilitation in the chronic pain group compared to the healthy control group. This may explain the elevated perception of somatic-pressure in the chronic pain group. The voxel based analysis shows consistently enhanced neuronal activity in the basal ganglia, insula, and the superior temporal gyrus within the chronic pain group compared to control group during innocuous stimulation. These areas are associated with the medial pain system in processing the affectual components of pain.

Results from the BOLD signal analyses confirm the results from the voxel based analysis. Enhanced BOLD signal was evident in the superior temporal lobe, insula, and basal ganglia. The enhanced brain activity may be associated with central sensitisation and pain catastrophising in persons with chronic pain. Therefore, it is possible that activity between these three regions may be augmenting the somatosensory input and priming the pain network. In this way, negative emotion pervasively biases information processing in chronic pain participants (Hamilton, et al., 2004).
8.4.2 Study 4: Major finding

Results from the fMRI imaging showed enhanced neuronal activity in the basal ganglia, insula, and the superior temporal gyrus within the chronic pain group compared to control group. Additionally, the chronic pain group revealed reduced activity in the caudate compared to the control group. The aerobic exercise rehabilitation did not reveal a normalisation of brain responses to somatic-pressure sensitivity in the chronic pain group. The enhanced brain activity may be associated with central sensitisation and pain catastrophising in persons with chronic pain.

8.4.3 Study 4: Limitations

Measures of pain catastrophising were not appraised in the chronic pain participants during the fMRI imaging. This data could have further elucidated the altered brain responses to somatic-stimulation in the chronic pain group. Additionally, the inclusion criteria for chronic pain participants required persistent pain for at least one year. This would have led to a substantial variance in the number of years of persistent pain amongst the chronic pain participants. Recent research indicates that chronic pain results in structural changes in the brain that are associated with the number of years of persistent pain. The present results are deficient in reporting the number of years with chronic pain and this may have been useful in contextualising the findings in the present study.
8.5 Summary

Experimental measurement of the electrocutaneous pain threshold can be reliably performed under controlled conditions. The nociceptive withdrawal reflex threshold was shown to be a reliable within-trial. Additionally there was a high correlation between the pain threshold and the nociceptive withdrawal reflex threshold between trials. These results show that the nociceptive withdrawal reflex threshold is a valid pain-related measure under standardised resting conditions. The reliability and association of the nociceptive withdrawal reflex and association with pain threshold establishes the capacity for this measure to be applied with interventions such as aerobic exercise.

Assessments for experimental pain parameters and nociceptive withdrawal reflex threshold following acute aerobic exercise in healthy participants revealed that exercise attenuated cerebral but not spinal nociceptive events. The pain threshold and the nociceptive withdrawal reflex threshold were not elevated by aerobic exercise. These data show a supraspinal suppression of nociceptive events following aerobic exercise. While these results show only a mild effect following aerobic exercise, this also suggests that exercise mediates the processing of experimental nociceptive signals and points to potential mechanisms for exercise induced analgesia.

Physical exercise has predominantly been viewed as an activity for healthy people and not for the chronically ill (Moore, 2004). In contrast, accumulating evidence shows that physical exercise has favourable outcomes for persons with chronic pain.
The difficulty with this type of intervention is that it is often not adhered to due to the exacerbation of symptoms. The present findings show that moderate-intensity aerobic exercise is well tolerated in participants with chronic pain. This type of exercise prescription results in high programme adherence, reduced clinical pain report, increased functional capacity, and improvements in health outcomes. Therefore, during the prescription of aerobic exercise for persons with chronic pain, it is important to consider both the perceptual responses to exertion and muscle pain intensity in order to maintain program adherence and reduce clinical pain report.

Accumulating evidence shows that chronic pain is associated with central sensitisation and hypersensitivity to experimental noxious and innocuous stimuli. The present results indicate several brain regions that revealed elevated activity in the chronic pain group compared to the control group during somatic pressure stimulation prior to exercise rehabilitation. These results affirm a somatic hypersensitivity amongst the chronic pain participants. Previous research shows that exercise rehabilitation reduces the sensitivity to experimental somatic-pressure pain stimuli in chronic pain participants (Carbonell-Baeza, et al., 2010). In the present results, aerobic exercise rehabilitation did not reveal a reduction in the perceptual and brain responses to somatic-pressure fMRI scanning, however, this may be associated with pain catastrophising during the imaging procedure in the chronic pain group. Future research would require measures of pain catastrophising in chronic pain participants in order to capture the effects of this on brain responses to somatic-pressure stimulation.
8.6 Future research directions

The present results show that exercise at 30% and 70% of aerobic capacity was sufficient to initiate cerebral attenuation of nociceptive events but did not launch spinal antinociceptive systems in healthy participants. Pain inhibitory systems evoked by DNICs require strong pain to launch spinal antinociception. In order to further explicate the function of exercise-induced antinociceptive systems, it may be required to perform exercise at intensities that illicit strong muscle pain. Since isometric exercise may illicit intense muscle pain in a relatively stable position, this could be a more suitable model to evoke potential spinal and cerebral antinociceptive systems.

The analgesic effect of passive movement exercise on chronic pain has not been fully explored. Passive movement of limbs is performed by an electromechanical device which activates joint and limb peripheral afferent feedback to the central nervous system. In one study, passive movement exercise was shown to produce an immediate analgesic effect as demonstrated by improvements in pain ratings and enhanced pressure pain thresholds (Nielsen, et al., 2009). Such an activity may have efficacy in chronic pain conditions where the capacity to perform physical activity is limited.

Previous research shows that the prefrontal cortex is a major site of neurodegeneration in chronic pain participants (Apkarian, et al., 2004). Moreover, this site was shown to correspond with the duration of clinical pain in chronic pain participants. Since the prefrontal cortex is a site for regulating descending pain inhibitory activity (Lorenz, Minoshima, & Casey, 2003), it is possible that this
antinociceptive system deteriorates with persistent pain conditions. Future physical activity based studies could investigate this site with respect to a homogenous clinical pain duration group and assess its potential improvement or stabilisation with ongoing physical activity.

Psychological factors play an important role in chronic pain (Siddall & Cousins, 2004). Persistent pain, regardless of aetiology, leads to the chronic pain state, which is defined by preoccupation with pain, depression, anxiety, and disability (Long, 1999). In the chronic pain state, a fear of movement appears to explain the variance in pain with duration of greater than one year (Boersma & Linton, 2005). Further research is required to elucidate the failure to control fear and its contribution to pain chronicity. Currently, it is unknown as to which physical activity movements are best tolerated and are able to alleviate the fear of movement in persons with chronic pain.

Physical exercise engages descending pathways that are also associated with pain inhibition. Previous studies show that transcranial cortex stimulation can exert an inhibitory effect on pain in patients with chronic pain (Lima & Fregni, 2008). A previous transcranial magnetic stimulation study has shown that chronic pain is associated with defective intracortical inhibition, possibly through a motor cortex disinhibition (Lefaucheur, et al., 2006). Preliminary clinical trials have suggested that motor cortex stimulation may be effective for treating chronic pain disorders (Fenton, et al., 2009; Mendonca, et al., 2011). Future studies could further explicate the potential therapeutic mechanisms of transcranial cortex stimulation by combining this with measures of experimental pain and central sensitisation.
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386


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## Pain sensation scale

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<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>No sensation</td>
</tr>
<tr>
<td>2</td>
<td>Slight sensation</td>
</tr>
<tr>
<td>4</td>
<td>Moderate sensation</td>
</tr>
<tr>
<td>6</td>
<td>Pain sensation</td>
</tr>
<tr>
<td>8</td>
<td>Strong pain sensation</td>
</tr>
<tr>
<td>10</td>
<td>Pain tolerance</td>
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## Appendix 2

### Rating of perceived exertion (RPE)

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<th>Number</th>
<th>Description</th>
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<tr>
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<tr>
<td>7</td>
<td>Very, very light</td>
</tr>
<tr>
<td>8</td>
<td>Very light</td>
</tr>
<tr>
<td>9</td>
<td>Fairly light</td>
</tr>
<tr>
<td>10</td>
<td>Somewhat hard</td>
</tr>
<tr>
<td>11</td>
<td>Hard</td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Very hard</td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
<tr>
<td>15</td>
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<td>19</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3

Muscle pain intensity scale (MPI)

0 No pain at all

½ Very faint pain (just noticeable)

1 Weak pain

2 Mild pain

3 Moderate pain

4 Somewhat strong pain

5 Strong pain

7 Very strong pain

10 Extremely intense pain (almost unbearable)

• Unbearable pain
Appendix 4

Study health screening questionnaire

Name_______________________ Date____________________
Age___________ Ht (cm)_____________ Wt (kg)______________

1. Are you currently, or have you recently had a cold, flu or other respiratory chest infection?
   YES / NO

   *If yes, please give approximate date when started*

2. Are you recovering from an illness and/or operation? YES / NO

   *If yes, please give details of the illness and/or operation with approximate dates*

3. Are you pregnant, or have you had a baby in the last 12 months? YES / NO

   *If yes, please give the date when the baby is due or when the baby was born*

4. Do you consider yourself to be overweight? YES / NO

   *If yes, by approximately how much?*
5. How many units of alcohol do you consume each week?

6. Do you smoke? YES / NO
   If yes, how many cigarettes do you smoke each week?

7. Are you worried that any of the assessments may affect your health? YES / NO
   If yes, in what way?

8. Do you consider your health to be Poor / Fair / Good / Excellent?
   (Please circle where applicable).

9. Do you have respiratory problems such as asthma or bronchitis? YES / NO
   If yes, please give details and of any medication?

10. Has a doctor ever said you have heart trouble? YES / NO
11. Have you ever had angina pectoris or sharp pain or heavy pressure in your chest as a result of exercise, walking or other physical activity, such as climbing a flight of stairs?

YES / NO

12. Do you experience sharp pain or extreme tightness in your chest when you are hit by a cold blast of air? YES / NO

13. Have you ever experienced palpitations or rapid heart beat?

YES / NO

*If yes, please give the approximate date*

14. Have you ever had a real or suspected heart attack/coronary occlusion/myocardial infarction/coronary insufficiency/thrombosis? (Please circle one or more if applicable.) YES / NO

*If yes to any of these, please give dates*

15. Has more than one blood relative (parent, brother or sister first cousin) had a heart attack or coronary artery disease before the age of 60? YES / NO

*If yes, please state which member of your family*
16. Have you ever had rheumatic fever?
YES / NO
*If yes, please give approximate date*

17. Do you have diabetes/high blood pressure/sugar in your urine?
YES / NO *(Please circle where applicable).*

18. Do you have high blood pressure/hypertension?
YES / NO *(Please circle where applicable).*

19. Does any of your family have high blood pressure/hypertension?
YES / NO
*If yes, please state which member of your family*

20. Have you ever taken medication to lower your blood pressure?
YES / NO
*If yes, please state what medication and approximate dates*

21. Have you ever taken digitalis, quinine or any other drug for your heart?
YES / NO
*If yes, please give type of medication and approximate date when this was*

22. Have you ever taken nitroglycerine or any other tablet for chest pain - tablets that you take by placing under the tongue?
YES / NO
23. Have you ever had a resting or stress electrocardiogram that was not normal? 
   YES / NO

   *If yes, please give type of medication and approximate date when this was*

________________________________________________________________________________________

24. Have you ever taken any medication / been on a special diet to lower your blood 
   cholesterol? YES / NO

   *If yes, please give type of diet and or medication and approximate date when this was*

________________________________________________________________________________________

________________________________________________________________________________________

25. Do you have any other physical condition that is not covered by the above questions? 
   YES / NO

   *If yes, please state*

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________

________________________________________________________________________________________