Investigating the role of cognitive risk factors and underlying neurobiological processes associated with chronic low back pain

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Bachelor of Behavioural Neuroscience (Honours)

A thesis submitted for the degree of Doctor of Philosophy at
Monash University in 2019
Monash Alfred Psychiatry Research Centre
Central Clinical School
Faculty of Medicine, Nursing and Health Sciences
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Abstract

Low back pain is the leading cause of disability worldwide and has been associated with significant economic burden. Currently, the cause of the majority of low back pain cases cannot be identified and therefore, low back pain is classified as non-specific. This has led to significant heterogeneity within low back pain patients, making it difficult to prescribe specific treatments to those who are most likely to benefit. Thus, tailoring appropriate treatments based on the clinical presentation or symptoms of specific subgroups of low back pain may improve outcomes.

Cognitive factors play a significant role in the development and persistence of low back pain. Pain-related cognition, such as maladaptive beliefs about low back pain and poor subjective well-being, have been found to be associated with higher levels of low back pain and disability. However, their role in the development of persistent low back pain has not been examined. Furthermore, the brain mechanisms related to cognition have shown to be disrupted in chronic low back pain, although its implications on related cognitive processes are not well understood. To address these limitations, the overall aim of this thesis was to examine the role of pain-related cognition as well as underlying neural processes associated with cognitive processes in chronic low back pain. This was addressed in 5 high quality studies, including a systematic review and 4 experimental studies.

The first study was a comprehensive systematic review that examined the evidence for brain changes from magnetic resonance imaging (MRI) studies in chronic low back pain populations and considered the potential implications of these changes on cognition and emotion. The results showed that rather than disruptions in areas associated with nociceptive pain processes,
brain changes were predominantly observed in regions associated with self-referential and emotional processes, such as the default mode network (DMN). This review identified that the abnormalities of the brain may be related to disrupted cognitive and emotional processes that are the driving factors of chronic low back pain. Future studies are needed to explore these relationships further.

The second study investigated the role of beliefs about low back pain on high intensity low back pain in a prospective 2-year community-based cohort study. The results showed that individuals with negative beliefs about back pain and its consequences were more likely to experience persistent high intensity low back pain 2 years later. In particular, participants with persistent high intensity pain had more negative beliefs related to the long-term consequences of low back pain and their ability to return to work. This study provides evidence to support back beliefs as a potential target for future interventions of low back pain.

As an individual’s perceptions related to their health and well-being are also thought to influence low back pain outcomes, this was explored in the third study. A prospective cohort study examined how overall subjective well-being, and its subdomains, may affect persistent high pain intensity and high disability over 2 years. The results showed that lower levels of overall subjective well-being, in particular reduced general health and vitality were associated with persistent high pain. Reduced overall subjective well-being, as well as the general health and vitality, were associated with persistent disability. These findings suggest that strategies aimed at improving subjective well-being, particularly aspects related to general health and vitality may reduce vulnerability to persistent pain and disability.
As concluded in the first study (the systematic review), there are gaps in our understanding of the relationship between the brain changes observed in chronic low back pain and cognitive and emotional function. Therefore, the fourth study investigated the brain mechanisms that underpin cognitive reappraisal, an adaptive emotion regulation process involved in coping with aversive stimuli, including pain, as well as negative emotions. This was done using functional magnetic resonance imaging in a group of individuals with chronic low back pain compared to healthy controls. In this study, the differences in regional brain activations and functional connectivity (i.e., the strength of coactivation between regions) during a task that involves reappraising negative emotional stimuli. Corresponding levels of negative affect were also examined. The results showed that there were no group differences in regional brain activation or perceived negative affect, suggesting cognitive reappraisal may have been successful across all participants. However, reduced functional connectivity between key regions involved in cognitive reappraisal were observed in the chronic low back pain group compared to healthy controls. A follow-up analysis in the chronic low back pain group revealed that the altered connectivity positively correlated with the percent of reduced negative affect during reappraisal, suggesting effective cognitive reappraisal may be compromised. Therefore, this study provides novel evidence that demonstrated that the brain changes in chronic low back pain may impair cognitive processes important in coping with negative stimuli such as pain and emotional distress associated with low back pain.

The final study in this thesis aimed to further interrogate the findings in the systematic review that identified aberrant brain activity in the DMN, specifically, to determine the functional significance of these alterations. Currently, no studies have specifically explored the functional connectivity of two key brain regions involved in communication and integration within the DMN (referred to as hubs) (i.e., medial prefrontal cortex, posterior cingulate cortex) with limited understanding of how it affects related processes. Some studies suggest that altered
DMN connectivity may be related to pain catastrophizing in other chronic pain conditions; although, this has not been explored in chronic low back pain. Therefore, this study examined the functional connectivity in the two key hubs of the DMN during resting-state (i.e., in the absence of a task) and whether disruptions were associated with pain catastrophizing in chronic low back pain. Group comparisons showed the chronic low back pain group had reduced functional connectivity in both hubs to various regions of the brain, suggesting that the network communication and information integration of the DMN may be compromised. However, these differences were not related to pain catastrophizing, indicating that pain catastrophizing could possibly engage other networks.

The body of work presented in this thesis presents novel evidence for the influence of cognitive risk factors on patient outcomes and underlying neural processes in chronic low back pain. Negative beliefs related to the consequences of low back pain and poor subjective well-being were identified as potentially modifiable cognitive risk factors for persistent low back pain and disability. This thesis presented the first neuroimaging study to show that impaired brain functional connectivity reduced effective cognitive reappraisal in chronic low back pain. The results of the thesis also showed that disrupted connectivity was observed in two key hubs of the DMN in chronic low back pain, however, further studies need to determine its functional significance. Overall, these studies provide an important contribution to our understanding of the role of pain-related cognition and the brain mechanisms associated with chronic low back pain and therefore, provide new data to inform the classification of subgroups and the development of novel approaches for the management of chronic low back pain.
List of Publications and Outputs

Peer-reviewed papers published directly relevant to this thesis


Submitted manuscripts directly relevant to this thesis


Other publications during candidature


Conference poster presentations during candidature


Ng SK, Cicuttini FM, Wang Y, Wluka AE, Fitzgibbon BM & Urquhart DM. Negative beliefs about low back pain are associated with persistent high intensity low back pain. 10th Congress of European Pain Federation, Copenhagen, Denmark, 2017.

Conference oral presentations during candidature


Awards

Recipient of an Australian Government Research Training Program Scholarship

Monash Travel Grant for 10th Congress of European Pain Federation, 2017

Received Best Rapid Communication Award at Australian Pain Society, Sydney, 2018
Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers published in peer reviewed journals and two submitted publications. The core theme of the thesis is investigating the role of cognitive risk factors and the underlying brain mechanisms associated with chronic low back pain. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Central Clinical School under the supervision of Dr Bernadette Fitzgibbon, Associate Professor Donna Urquhart, Professor Paul Fitzgerald, Professor Flavia Cicuttini.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 2, 3, 4, 5 and 6 my contribution to the work involved the following: Review of appropriate literature, securing ethics approval, recruitment of participants, data collection, conducting data analysis, writing manuscripts. Supervisors and co-authors provided input into completed manuscript drafts.
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<td>The relationship between structural and functional brain changes and altered emotion and cognition in chronic low back pain brain changes: A systematic review of MRI and fMRI studies</td>
<td>Published</td>
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2) Prof Susan Davis. Review of manuscript (2%)  
3) Prof Robin Bell. Review of manuscript (2%)  
4) Dr Roslin Botelho. Data collection, review of manuscript (2%)  
5) Dr Bernadette Fitzgibbon. Supervisory input, review of manuscript (2%)  
6) A/Prof Donna Urquhart. Supervisory input, review of manuscript (10%) |
| 5   | Neural activity during reappraisal in chronic low back pain: A preliminary BOLD-fMRI and functional connectivity study | Submitted    | 1) A/Prof Donna Urquhart. Review of manuscript (1%)  
2) Prof Paul Fitzgerald. Review of manuscript (1%)  
3) Dr Melissa Kirkovski. Data analysis assistance, review of manuscript (2.5%)  
4) Prof Flavia Cicuttini. Supervisory input, review of manuscript (1%)  
5) Dr Jerome Maller. Data analysis assistance, review of manuscript (2.5%)  
6) Prof Peter Enticott. Review of manuscript (1%)  
7) Prof Susan Rossell. Review of manuscript (1%)  
8) Dr Bernadette Fitzgibbon. Data collection, supervisory input, |
## Investigating resting-state functional connectivity in key hubs of the default mode network in chronic low back pain

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I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.
Acknowledgements

I would like to take this opportunity to express my gratitude to everyone who has made this thesis possible. First and foremost, I would like to thank my team of supervisors for their guidance throughout my PhD. To my main supervisor, Dr Bernadette Fitzgibbon, I am truly grateful for your wonderful support and encouragement over the years. Although there were a lot of unexpected challenges, you helped me navigate the best way forward and always believed in me even when I doubted myself. You always find the right words to motivate me and get me excited about the work that I’ve done. I have been able to learn so much from you and I am a better researcher for it. Thank you for your all your hard work and patience. You are an amazing mentor and role model, and I could not have asked for a better supervisor.

I would also like to thank my supervisor, Associate Professor Donna Urquhart who has always been one call away to talk through any difficulties I have. Whether it is data analysis, writing papers or juggling between my PhD, work and personal life, you have given me sound advice each time that has helped me immensely. Your support and guidance have been invaluable, and I am extremely grateful.

A big thank you to my other supervisors, Professor Paul Fitzgerald and Professor Flavia Cicuttini. Despite your busy schedules, you have always made time for me. Your dedication towards research truly inspires me. It has been an absolute privilege to work with you all and I am very fortunate to be a part of 2 incredible teams.

I would also like extend my thanks the team at MAPrc: Caley, Xianwei, Sung, Greg, Aron, Kirsten, Melanie, Karyn, Laura, Caitlyn, Hannah, Freya, Aleks, Andrea and Robert. It has always
been so lovely seeing all your friendly faces every time I come into the office. I have no doubt you will all achieve great things in the years to come.

A special thanks to my friends and colleagues at the Musculoskeletal Unit: Molly, Tom, Sharmayne, Louisa, Aruna, Waruna, Clare, Bothaina, Monira, Yuanyuan and Anita. From day 1 when you first invited me to lunch, you have all provided a safe space where we can discuss and share our concerns or mutual dislike for systematic reviews. I have really enjoyed working with you all.

To my dear friends who have supported me throughout this PhD, your unwavering enthusiasm and positivity have got me through the tough times. Thank you for always listening while I contemplate my life choices at Pancake Parlour in the late hours of the evening.

Thank you to my family for their unconditional love and encouragement. To big brother and sister-in-law, Chun Hin and Anna, who always believed in me even when I was full of doubt and worry. Thank you for sharing your PhD wisdom and making sure we were well fed. To my little brother, Chun Kiu, you have had to listen to my frustrations despite having difficulties in your own PhD. Thank you for looking out for me and making sure we always have enough snacks! To my mum and sifu, who has been my biggest source of strength. Thank you for teaching me that behind every obstacle is a life lesson and to embrace every challenge that comes my way because it is a chance for personal growth. Without your support and wisdom, I would not be where I am today. Finally, to my partner Brian who has been along for this emotional rollercoaster with me, there are no words to express how thankful I am to have you in my corner. You have always been so patient and understanding, especially when I’ve had to work late or over the weekend. Whenever I was stressed, you encouraged me to keep moving forward (and always twirling). Thank you for making sure I enjoy the little things in life.
I would also like to formally acknowledge and thank the following people for their contribution to this thesis. Thank you to my co-authors, Dr Monira Hussain, Dr Yuanyuan Wang, Professor Anita Wluka, Professor Susan Davis, Professor Robin Bell, Dr Roslin Botlero, Dr Melissa Kirkovski, Dr Jerome Maller, Professor Peter Enticott and Professor Susan Rossell for their help and input towards each of the manuscripts that were produced in this thesis. Thank you to the participants who took the time to be involved in the studies. This research was supported by an Australian Government Research Training Program (RTP) Scholarship.
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<td>ACC</td>
<td>Anterior cingulate cortex</td>
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<td>ACP</td>
<td>American College of Physicians</td>
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<td>BBQ</td>
<td>Back Beliefs Questionnaire</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>BOLD</td>
<td>Blood oxygen level dependent</td>
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<td>CBT</td>
<td>Cognitive behavioural therapy</td>
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<tr>
<td>CLBP</td>
<td>Chronic low back pain</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CPG</td>
<td>Chronic Pain Grade Questionnaire</td>
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<tr>
<td>dACC</td>
<td>Dorsal anterior cingulate cortex</td>
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<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<tr>
<td>DMN</td>
<td>Default mode network</td>
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<tr>
<td>DMPFC</td>
<td>Dorsomedial prefrontal cortex</td>
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<td>DTI</td>
<td>Diffusion tensor imaging</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>EMG</td>
<td>Electromyography</td>
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<td>FBSS</td>
<td>Failed back surgery syndrome</td>
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<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>GM</td>
<td>Gray matter</td>
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<td>gPPI</td>
<td>Generalised psychophysiological interaction</td>
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<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
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<tr>
<td>IASP</td>
<td>International Association for the Study of Pain</td>
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<td>IPL</td>
<td>Inferior parietal lobule</td>
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<td>Abbreviation</td>
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<tr>
<td>MEP</td>
<td>Motor evoked potential</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>mPFC</td>
<td>Medial prefrontal cortex</td>
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<td>MVPA</td>
<td>Multivariate pattern analysis</td>
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<tr>
<td>NAA</td>
<td>N-acetyl-aspartate</td>
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<td>NAc</td>
<td>Nucleus accumbens</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<td>NIBS</td>
<td>Non-invasive brain stimulation</td>
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<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<td>OFC</td>
<td>Orbitofrontal cortex</td>
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<td>PAG</td>
<td>Periaqueductal gray</td>
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<td>PCC</td>
<td>Posterior cingulate cortex</td>
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<td>PGWB</td>
<td>Psychological and General Well-Being Index</td>
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<td>PPC</td>
<td>Posterior parietal cortex</td>
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<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<td>RVM</td>
<td>Rostral ventromedial medulla</td>
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<td>S1</td>
<td>Primary somatosensory cortex</td>
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<td>S2</td>
<td>Secondary somatosensory cortex</td>
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<tr>
<td>tDCS</td>
<td>Transcranial direct current stimulation</td>
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<td>TMS</td>
<td>Transcranial magnetic stimulation</td>
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<tr>
<td>VBM</td>
<td>Voxel-based morphometry</td>
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<td>WM</td>
<td>White matter</td>
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Chapter 1
Introduction and Overview

This thesis will investigate the role of cognitive risk factors and underlying neurobiological processes associated with chronic low back pain. This chapter will outline the global burden and the current limitations in understanding the potential causes and thus, the management of low back pain. A review of the current literature that has identified the various biological and psychosocial factors that contribute to the development and maintenance of chronic low back pain will be included, with specific focus on cognition and brain mechanisms.

1.1 Global burden of low back pain

Low back pain refers to pain, stiffness or muscle tension, located in the region bordered by the lower rib cage and the inferior gluteal folds that can occur with or without sciatica [1-3]. It is a significant health problem and currently the leading cause of disability worldwide [4]. According to the Global Burden of Disease reports, low back pain has a global point prevalence of 9.4% [5] and has accounted for 64.9 million years lived with disability (YLD) in 2017, an increase of 17.5% since 2007 [4]. In Australia, approximately $4.8 billion is spent on direct medical costs, including prescription medications, hospital expenses and use of healthcare services each year [6]. Moreover, work-related disability associated with low back pain results in increased work absence, welfare payments and reduced productivity, further contributing to the huge economic costs of low back pain [7-10].

While the majority of cases often resolve within 6 weeks of onset [11], it has been reported that approximately 33% of these cases will have a recurrence within the next 12 months [12].
Approximately 10% will develop into chronic low back pain where pain persists for more than 3 months [2, 13, 14]. In addition to persistent pain, individuals with chronic low back pain have poorer health-related quality of life (HRQOL) [15], lower perceived mental health [16], maladaptive cognitions towards pain such as catastrophizing [17] and fear of pain due to movement (i.e., kinesiophobia) [18] and have a higher prevalence of comorbid conditions including depression, anxiety and sleep disorders [19-21]. This leads to significantly higher medical costs for these individuals due to ongoing use of treatments, medications and health care services for chronic low back pain [15, 22], as well as comorbid conditions [21]. Consequently, patients often report increased social isolation and disconnect [23, 24], concerns about the ability to retain employment [25], as well as financial difficulties due to inefficient compensatory systems [26]. While low back pain has a significant impact on the individual and society, effective treatment and pain management for chronic low back pain remains limited [13, 27].

1.2 Classification and management of chronic low back pain

1.2.1 Classification

Individuals who present with low back pain are typically classified into 3 categories according to the diagnostic triage approach in attempts to identify the potential causes of pain [28]. Low back pain can be due to specific spinal pathology including vertebral fracture, malignancy, axial spondyloarthritis and spinal infection; however, these only account approximately 1% of cases [28, 29]. Another 5-10% of case are categorised as radicular syndrome, where pain is due to pathology in the nerve root of the spine. If patients cannot be classified into the previous 2 categories, they are diagnosed with non-specific low back pain as a clear cause cannot be identified. They represent the remaining 90% of cases, which consequently, accounts for the majority of chronic low back pain cases [13, 27, 28, 30]. As a result of this final category, non-
specific chronic low back pain is heterogeneous and includes a number of subgroups that may differ in their clinical presentation and aetiology. The predominant mechanisms that drive pain in patients may also range from nociception, neuropathic pain, central pain sensitisation or mixed types of pain [31], which may require different approaches to treatment [32, 33]. Therefore, there is a need to develop a system that further classifies patients into subgroups. Not only will this provide clinicians with a better understanding of the mechanisms driving low back pain, but it will inform appropriate interventions for improved outcomes.

1.2.2 Management

Currently, there is no cure for low back pain and effective treatments are limited. However, there are a number of interventions and management programs aimed to reduce pain, disability and secondary symptoms associated with persistent pain such as emotional distress [34]. Recent clinical practice guidelines from the National Institute for Health and Care Excellence (NICE) and the American College of Physicians (ACP) have outlined the appropriate course of treatment for low back pain. Given that most acute (i.e., > 2 weeks) and subacute (4 weeks to 3 months) cases of low back pain resolve over time, the current recommendations are to promote self-management of pain by providing information about the course of low back pain and encouraging normal function and activities [35, 36]. Non-pharmacological interventions including exercise programs, manual therapy (e.g., massage, acupuncture or spinal manipulation) and psychological interventions through cognitive behavioural therapy (CBT) or mindfulness-based stress reduction may also be recommended [35, 37, 38]. For patients who do not experience benefits from non-pharmacological interventions, pharmacological medications, such as non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants may be prescribed as a second-line of treatment [35, 37, 38]. Although, it has been suggested that analgesics should only be used to manage pain in order for patients to maintain normal function [39].
For patients who develop chronic low back pain, the guidelines recommend a combination of the physical, psychological, behavioural and social interventions within multidisciplinary pain programs [27, 40]. A Cochrane systematic review found that multidisciplinary interventions are more effective in improving pain and disability outcomes in chronic low back pain compared to the standard care provided by a healthcare professional (e.g., general practitioner) and physical treatments (e.g., exercise and manual therapies) alone [41]. However, the current programs are not only time consuming for patients, but the observed effects have only been small and short-term [1, 34, 41, 42]. Therefore, a better understanding of the other potential factors that influence chronic low back pain prognosis may contribute to improving the efficacy of future interventions.

1.3 Factors associated with chronic low back pain

Without an identifiable cause, the traditional biomedical approach, whereby the aetiology of low back pain is directly related to specific pathology, no longer provides an appropriate explanation about the mechanisms of chronic low back pain. Instead, chronic low back pain is now better conceptualised within the biopsychosocial model [32]. The biopsychosocial model proposes that pain is characterised by complex and dynamic interactions between biological (e.g., nociceptive processes, genetic composition and central nervous system processes), psychological (e.g., emotional and cognitive processes), social and environmental factors. These constructs exhibit a bidirectional relationship that influence each other and gives rise to a uniquely personal and complex experience of pain [27, 43].
1.3.1 Biological factors contributing to chronic low back pain

There are a number of biological factors that contribute to the aetiology of chronic low back pain. Biomechanical components related to structural impairments have been associated with chronic low back pain. While low back pain patients have a higher prevalence of disc pathology, such as disc bulge, disc extrusion and modic changes [44, 45], these are also present in pain-free individuals [46, 47]. Therefore, there is insufficient evidence to clearly establish that these degenerative changes are the primary cause of chronic low back pain [44, 47, 48]; although they are still important risk factors to consider in chronic low back pain [49]. Genetic predisposition may be another biological risk factor, involved in susceptibility and maintenance of chronic low back pain [43, 50]. A systematic review reported that the heritability of low back pain in twin studies was estimated to range between 21% and 67%, with a greater prediction for chronic low back pain than acute low back pain [51]. Furthermore, a meta-analysis of genome-wide association studies (GWAS) found genetic variants, specifically in the SOX5, CCDC26/GSDMC and DCC genes, were observed in chronic low back pain [52]. The SOX5 and CCDC26/GSDMC genes have been involved in development of spinal structures and lumbar disc degeneration [53, 54] while the DCC gene was associated with pain pathways [55]. Therefore, variations within these genes may contribute to the different phenotypes related to spinal pathology and pain perception in low back pain [52]. While these studies have demonstrated there is a genetic influence on chronic low back pain, they are not sufficient alone to explain the aetiology of this condition. Moreover, research in the field of neuroscience has established that central processes are key biological factors that also contribute to chronic low back pain.

1.3.1.1 Central processes involved in chronic low back pain

A strong body of research has emerged demonstrating that the pathways within the central nervous system (CNS) responsible for the perception and modulation of pain, including the
brain, brainstem and spinal cord, are disrupted in chronic low back pain. Typically, acute pain occurs when information from noxious stimuli is transmitted via nociceptors (e.g., A-delta and C fibres) to the dorsal horn of the spinal cord, which is then relayed to the brain [56, 57]. The experience of pain involves the activation of various brain regions, such as the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insula, anterior cingulate cortex (ACC), thalamus and prefrontal cortex [58-62]. The top-down modulation of pain (i.e., cortical regulation) is activated by psychological processes related to cognition and emotional states, via the descending pain modulatory systems, involving regions, including the periaqueductal gray (PAG), amygdala, rostral ventromedial medulla (RVM), ACC, insula and prefrontal regions [63, 64]. Overall, these studies have demonstrated that the brain regions involved in pain processes are extensive.

Alterations within these pain pathways are apparent in chronic low back pain, which may lead to impaired pain processes, such as central sensitisation. Central sensitisation refers to heightened pain signals that may be due to the lack of inhibition and/or increased excitability of the pain processes within the CNS, resulting in pain hypersensitivity [65]. There is moderate evidence to support this as chronic low back pain patients have developed hyperalgesia (i.e., reduced pain threshold due to sensitisation of nociceptors) in response to experimentally induced pain at regions outside of the lumbar regions [66, 67] as well as dysfunctional condition pain modulation [68] compared to healthy controls. Other studies demonstrated that when compared to healthy controls, individuals with chronic low back pain reported increased temporal summation (i.e., heightened sensitivity to repetitive pain stimulation that results in increased pain perception) [69, 70] while other studies showed no significant differences [71]. Furthermore, the use of neuroimaging techniques has identified various changes within the brain in chronic low back pain. For example, a recent systematic review of studies examining the metabolic concentrations throughout the brain using proton magnetic resonance
spectroscopy showed altered neurochemical profiles in chronic low back pain groups. Specifically, there were lower levels of N-acetyl-aspartate (NAA), glutamate and glucose in areas involved in processing nociceptive pain including the dorsolateral prefrontal cortex (DLPFC), primary motor cortex (M1), insula and ACC [72]. It has been argued that chronic low back pain may be the cause of the metabolic changes as exaggerated or ongoing neural activity may result in neurochemical changes [73]. Studies using electroencephalography (EEG; measures the small electrical currents from neuronal activity at different frequencies) showed that chronic low back pain patients had higher activity in the S1 (measured by the N80 response) compared to healthy controls [69], an area related to processing the sensory aspect of pain. Additionally, the neural oscillations within the sensorimotor regions that generally occur during noxious pain (i.e., alpha 8-13 Hz or beta 14-29 Hz) were not observed with the spontaneous fluctuations of back pain in chronic low back pain patients. Instead, low back pain showed increased gamma (60-90 Hz) oscillations in the prefrontal areas in chronic low back pain patients. As gamma oscillations are associated with subjective pain, these findings suggest that there may be a dissociation between the pain experienced in chronic low back pain and nociceptive processes [74].

Studies using transcranial magnetic stimulation (TMS), a neuromodulation method capable of probing neurobiological function, have also provided supporting evidence to show that the brain changes observed in chronic low back pain were associated with impaired spinal motor control. Stimulation of the M1 area that corresponds with lower regions of the back produces a motor evoked potential (MEP), recorded by electromyography (EMG); MEPs provide a measure of motor response, which is thought to reflect motor excitability. Indeed, studies have shown that individuals with chronic low back pain have significantly lower threshold required to produce an MEP [75, 76], delayed co-activation between stimulation of the M1 and muscle response [77] and reorganisation of the topographic representation of lower lumbar muscles.
in the M1 [76]. These studies indicate that the changes within M1 mechanisms may contribute to dysfunctional motor control. Overall, these studies present evidence that reflects a degree of maladaptive neuroplasticity that alters physiological processes that may potentially influence pain outcomes in chronic low back pain. In addition to these neuroimaging and brain stimulation modalities, structural and functional magnetic resonance imaging (MRI) protocols have become an increasingly popular method used to explore the integrity of the brain. MRI is a non-invasive imaging technique that has a high degree of spatial resolution as the ability to produce accurate images of brain structure and activity [78]. In the following section, the evidence of changes in brain structure and function observed in chronic low back pain demonstrated through MRI will be discussed.

1.3.1.2 MRI evidence of structural and functional brain changes in chronic low back pain

There is a growing body of evidence from MRI studies that have observed maladaptive reorganisation of brain in chronic low back pain that influence pain-related processes. A systematic review has highlighted that widespread structural and functional changes within the brain are observed in chronic low back pain [79]. Structural MRI comparing cortical thickness and gray matter (GM) volumes using voxel-based morphometry (VBM) have reported reduced GM volumes in areas implicated in pain perception and modulation, including the DLPFC, thalamus, insula and cingulate cortex in chronic low back pain [80-83]. While studies examining white matter (WM) are limited, the use of diffusion tensor imaging (DTI; measuring WM integrity through the changes in water diffusion in the brain) found that patients with disabling chronic low back pain had reduced WM integrity in the splenium of corpus callosum compared to patients with non-disabling chronic low back pain [84], suggesting that impairments in the anatomical pathways may impact low back pain outcomes.
Functional activity within the brain can be measured by functional magnetic resonance imaging (fMRI). This method is based on detecting the difference in the magnetic susceptibility of oxygenated blood required by active neurons and deoxygenated blood. As neural activity increases the concentration of oxygenated blood, it changes the ratio of oxygenated to deoxygenated blood, which is detected by the fMRI scanner as blood oxygenated level dependent (BOLD) signals [85, 86]. The BOLD response measures brain activity that can also be used to determine functional connectivity, which refers to temporal correlation of neural activity in various brain regions [87]. This is used to identify brain areas that coactivate together, suggesting communication between regions. The use of fMRI has shown to be a relatively reliable measure for brain activity and functional networks [88, 89]. Therefore, fMRI can be used to detect the patterns of brain activity in response to pain events (i.e., from experimentally induced noxious pain stimulation), during tasks that involve the use of psychological processes that modulate pain or during resting-state (i.e., in the absence of an external task) in chronic low back pain populations [58, 90].

Event-related fMRI studies have investigated the underlying neural processes in pain perception by examining the BOLD response during noxious stimulation in chronic low back pain. Chronic low back pain patients have exhibited lower pain thresholds, as well as heightened BOLD activity of brain regions involved in nociceptive pain, including the insula, posterior cingulate cortex (PCC), S1, S2 and the inferior parietal lobule (IPL), compared to healthy controls [91, 92]. This suggests there may be an upregulation of the network that processes nociceptive pain in chronic low back pain. Interestingly, the comparison of neural processes during noxious pain and the pain experienced in chronic low back pain activated different BOLD responses. Experimentally induced pain was linked to activity within the insula, a region typically associated with nociceptive pain perception [93]. In contrast, spontaneous fluctuations of low back pain have been characterised by the medial prefrontal cortex (mPFC),
an area related to self-referential and emotional processes [94, 95], in chronic low back pain patients [96]. These studies have demonstrated that the underlying neural mechanisms involved in chronic low back pain may be different to nociceptive or acute pain.

Additionally, task-related fMRI studies reported brain changes in regions involved in pain modulation in chronic low back pain. For example, one study found that when viewing video clips of exercises that may cause back pain, individuals with chronic low back pain showed increased BOLD activity in the dorsomedial prefrontal cortex (DMPFC), anterior insula, and DLPFC compared to healthy controls [97], areas that have been implicated in top-down pain modulation [98]. Another study found that when viewing the back straining video clips, disrupted functional connectivity between the PAG and amygdala were observed in chronic low back pain patients, which is modulated by the level of pain-related fear [99]. Thus, alterations within the descending pain pathways may be related to impaired cognitive and emotional processes that modulates pain and thus, potentially contribute to the development or persistence of chronic low back pain [100, 101].

In resting-state fMRI studies, altered functional connectivity of various brain areas have been reported in chronic low back pain. These include the S1 (i.e., specifically the area that corresponds to the lower back), the region associated with processing the sensory aspect of pain perception [102] as well as the PAG, a key area of pain modulation [103]. Furthermore, changes in networks that may not be directly involved in pain processing have also been observed in chronic low back pain. For example, chronic low back pain patients exhibited aberrant functional connectivity within the default mode network (DMN; a network related to self-referential processes) compared to healthy controls [104-106]. Resting-state connectivity are also found to be altered following a series of exercises that triggers low back pain [102,
demonstrating that impaired brain changes can be influenced by physiological processes. Overall, the current literature has indicated there are widespread brain changes that are largely observed within the regions of the neural pathways in perception and modulation of pain. However, further investigations are required to determine how these brain changes may affect pain, the related cognitive and emotional processes involved in pain modulation and thus, their role in the development, maintenance and presentation of chronic low back pain.

1.3.2 Psychosocial risk factors for chronic low back pain

Chronic low back pain is also influenced by a number of psychosocial factors. Psychosocial factors refer to psychological processes (e.g., cognition and emotion) that interacts with social factors which influence mental states [43, 108]. Studies within community samples have shown a significantly higher prevalence of depression (~13-20%) and anxiety (~8%) in chronic low back pain populations compared to pain-free individuals (~6% and 3.4% respectively) [19, 21, 109]. Not only has depression been shown to be associated with significantly higher levels of pain intensity in individuals with low back pain [110, 111], it increases the risk of chronic low back pain development [109, 112-114]. Furthermore, a number of systematic reviews of cohort studies have found that higher levels of psychological distress [113], fear-avoidance beliefs [113, 115, 116], pain catastrophizing [117], lower levels of perceived health [112, 115] and passive coping strategies [113, 115] were predictors of chronic low back pain.

The interaction between these psychosocial factors and their influence on chronic low back pain has been conceptualised in several key models. One prominent theoretical model is the fear-avoidance model, that suggests the chronicity of pain stems from the beliefs system regarding pain events [118]. This model proposes that when low back pain is perceived as non-
threatening, individuals are more likely to resume or maintain normal function, which promotes recovery. Alternatively, individuals who have an exaggerated view of low back pain being an indicator of tissue damage or severe medical condition (i.e., pain catastrophizing), will often develop pain-related fear. This leads to avoidance behaviours as individuals believe certain movements or activities will cause re-injury or exacerbation of low back pain. These maladaptive pain behaviours increase pain and disability, as well as depression, which ultimately leads to chronic low back pain [118-120]. However, there are limitations to this model as it does not account for coping behaviours or efforts made to restore normal function despite pain and fear-avoidance beliefs [121].

Alternate models, such as the Örebro Behavioral Emotion Regulation Model, propose coping strategies, such as emotion regulation play a significant role in the chronicity of pain by influencing the relationship between pain and depression, with pain catastrophizing as a mediator [122]. This model suggests that when an episode of low back pain occurs, the negative emotions and pain catastrophizing associated with the pain event arises. Individuals respond by activating emotion regulation processes. If effective emotion regulation strategies are employed, it minimises the impact of pain, allowing individuals to maintain normal function and thus, reducing the chances of recurrent low back pain. However, unsuccessful regulation will reinforce pain catastrophizing and elevate levels of negative emotions associated with low back pain. Subsequent low back pain episodes will then produce a heightened negative response, which can eventually develop into persistent pain and depression [122]. Therefore, this model has demonstrated the importance of emotion regulation and pain catastrophizing in chronic low back pain. Although other theoretical models have been proposed, this model takes into account the importance of depression, a risk factor of chronic low back pain, and highlights there are shared mechanisms involved in cognitive control and regulation of pain and emotions. The following section will discuss the
role of various cognitive factors and processes that contribute to chronic low back pain in further detail.

1.4 The role of cognition in chronic low back pain

Cognition refers to processes such as attention, memory, learning, beliefs and perceptions [123, 124]. It plays a significant role in the perception and modulation of pain as it is involved in interpreting the meaning to the pain experience that may be influenced by previous experiences or focus of attention [43, 125]. Previous studies have demonstrated that there is a bidirectional relationship between cognition and pain. Chronic pain has been found to affect cognitive function [124]. Impairments in problem solving, working memory and cognitive flexibility were related to pain intensity in chronic low back pain, independent of depression and anxiety [126, 127]. Moreover, cognitive factors also contribute to pain perception, as well as psychological and physical functioning in chronic low back pain. These factors can be conceptualised into two primary cognitive processes, cognitive content and cognitive coping. Cognitive content refers to the beliefs and perceptions surrounding an individual’s pain condition and potential outcomes, while cognitive coping refers to the cognitive strategies that are used to manage pain, mood and behaviour [128].

Indeed, pain-related cognition such as inappropriate attitudes and beliefs regarding back pain (e.g., back pain reflects injury or tissue damage), maladaptive pain coping strategies and behaviours, such as pain catastrophizing, have been identified a prominent contributors to the development and persistence of chronic low back pain [3, 13, 129, 130]. However, there are still limitations in understanding the role of pain-related cognitions in chronic low back pain. In addition to fear-avoidance, there have been other types of beliefs related to perceived pain controllability that influence chronic low back pain outcomes. According to the implicit theory,
if an attribute is perceived to be controllable that can be changed through effort (*incremental theory*), individuals are more likely to engage in adaptive processes and thus, increases the potential for desired outcomes. Alternatively, if the attribute thought to be fixed or unchangeable (*entity theory*), individuals are more likely to adopt passive coping strategies [131]. Therefore, if low back pain is perceived as a permanent condition with the inevitable progression to long-term disability and physical impairments, it may result in maladaptive coping processes. This has been supported by cross-sectional studies that have shown higher perceived pain controllability in chronic low back pain were associated with reduced pain, disability and depression as well as increased adaptive coping behaviours [132, 133].

Pain-related cognitions influence subsequent cognitive coping processes. While maladaptive cognitive processes such as pain catastrophizing are a predictor of chronic low back pain [117], adaptive emotion regulation processes (e.g., cognitive reappraisal) have not been examined in chronic low back pain. Although, as chronic low back pain groups have reported higher levels of negative emotions [111, 134, 135] and emotional variability [136], ineffective emotion regulation processes are implied. Additionally, comorbid depression has been associated with higher levels of pain intensity and disability in chronic low back pain patients [110, 137]. As negative emotional states has been found to increase pain [63, 138-140], this may suggest that poor emotion regulation indirectly influences pain intensity and disability that is mediated by psychological factors such as negative mood.

The relationship between pain and cognition in chronic low back pain is further supported by MRI studies that observed abnormalities in brain regions underlying both cognitive and pain processes [101, 141]. For example, neuroimaging studies have shown decreased GM volume and cortical thickness in the DLPFC [80-82], which was associated with impaired performance
during a cognitive attention task in chronic low back pain [83]. As the DLPFC is an important hub in the brain that plays a role in various pain-related cognitive processes such as pain modulation [142], emotion regulation [143, 144], pain catastrophizing [145], placebo analgesia [146, 147] and pain controllability [148], alterations in this area may have further implications on the related processes. However, studies investigating the relationship between these brain changes in chronic low back pain and pain-related cognitive processes are limited. Overall, the current literature has shown that while pain-related cognitions are important constructs in chronic low back pain, further investigation into the various types of beliefs and perceptions and their contribution to the development of chronic low back pain is required. Examining the altered neural mechanisms and their influence on pain-related cognitive processes is necessary to establish a more comprehensive understanding of their role in chronic low back pain. The next subsections will expand specifically on the role of beliefs about low back pain and perceived impact of the condition (i.e., subjective well-being), as well as fMRI studies that explore whether brain changes are associated with impaired adaptive (i.e., cognitive reappraisal) and maladaptive (i.e., pain catastrophizing) cognitive processes in chronic low back pain.

1.4.1 Beliefs about low back pain

Beliefs and perceptions have been identified as risk factors in the persistence of low back pain [149, 150]. Beliefs about low back pain refers to an individual’s perception of the cause, consequences and potential recovery of low back pain, which contributes to their interpretation of pain events and thus, coping behaviour [43, 151, 152]. The current literature has established there are different types of pain-related beliefs that influence low back pain outcomes. For example, negative recovery expectations during the acute or subacute phases of low back pain has been linked to prolonged periods of work absences due to the development of chronic low back pain compared to those with positive expectations [153]. Fear-avoidance beliefs have
been associated with persistent pain and disability in chronic low back pain [154]. A systematic review found that elevated levels of fear-avoidance beliefs was predictive of poorer work-related outcomes, such as delayed return to work, in the subacute low back pain, but not during the acute or chronic phases [116]. In contrast, self-efficacy beliefs (i.e., the perceived ability to manage, cope and function with persistent pain) appear to be involved in mediating the relationship between pain and disability in chronic low back pain [155].

While there is some understanding regarding the role of beliefs in back pain, other types such as those related to one’s perception on negative consequences of low back pain have not been well explored. Of particular note is the importance of beliefs regarding the consequences and potential recovery of low back pain (i.e., back beliefs). Several cross-sectional studies have found that negative back beliefs (i.e., the perception that low back pain inevitably results in long-term pain and disability) were associated with higher levels of pain and disability in low back pain [156-158]. There has also been evidence from clinical trials that have demonstrated that correcting misconceptions regarding low back pain through educational booklets is effective in reduced persistent pain and disability [159, 160]. Additionally, a mass media campaign conducted in the state of Victoria in Australia not only resulted in the development of more positive beliefs in both the community and in doctors, the number of claims for work compensation and medical payments for low back pain were also reduced [161, 162]. These studies demonstrated that beliefs about low back pain is a modifiable factor that could be an effective target for potential interventions for chronic low back pain through simple educational programs. However, as there are limited cohort studies in the community-based individuals, little is known about the role of back beliefs in chronic low back pain and whether they are significant contributors to the persistence of low back pain outcomes, particularly pain intensity.
1.4.2 Subjective well-being

The overall state of well-being that represents an individual's physical, mental, social and emotional functioning has also been found to influence chronic low back pain outcomes [163]. In particular, subjective well-being has been identified as a potential risk factor of chronic low back pain. It refers to an individual's cognitive assessments related to life and work satisfaction and emotional responses, including positive and negative affect (e.g., happiness, sadness) to life events that forms a subjective perception of their life, physical and psychological status [164]. This definition indicates that subjective well-being is a multidimensional construct that reflects an individual's self-evaluation of life in relation to health status [165], emotional distress such as depression and anxiety [166], as well as positive aspects of well-being (e.g., vitality) [167]. Indeed, research has shown that chronic low back pain populations not only have lower levels of perceived mental health and quality of life [16, 168], reduced subjective well-being has also correlated with higher levels of pain intensity and disability in low back pain in cross-sectional studies [169, 170]. Furthermore, longitudinal studies have reported that poorer perceived health and depressed mood contributed to the development of chronic low back pain [109, 112], while emotional and psychological distress during acute low back pain predicted persist pain and disability [149, 171]. Lower levels of HRQOL during acute low back pain has also been found to delay recovery [172]. Therefore, these studies have demonstrated diminished well-being plays a significant role in persistent low back pain and disability.

There are three key limitations of previous studies. Firstly, no studies have comprehensively explored subjective well-being as a multidimensional construct that incorporates the various components of subjective well-being including anxiety, depressed mood, positive well-being, self-control, general health and vitality in chronic low back pain. Secondly, while these studies have predominantly examined specific components, particularly the negative aspects of subjective well-being (e.g., psychological and emotional distress), the influence of positive
aspects of subjective well-being has not been investigated in chronic low back pain. Nevertheless, higher levels of positive affect have been found to be related to reduced levels of pain in other chronic pain conditions [173]. Positive affect may be important in promoting well-being [174] and therefore, may provide vital information on resilience in low back pain trajectories. Thirdly, no longitudinal studies have explored the role of subjective well-being using a validated measure that includes the multiple domains of well-being in chronic low back pain.

1.4.3 Cognitive reappraisal

Cognitive reappraisal is an adaptive emotion regulation process that involves the reinterpretation of a situation or stimulus, such as pain, to alter its emotional significance [175]. Previous studies in healthy controls have demonstrated that cognitive reappraisal is effective in reducing negative emotions [176, 177], nociceptive pain intensity and unpleasantness [178-180] and has also been linked to better subjective well-being [176, 181]. Investigations of cognitive reappraisal in chronic pain are limited; however, some studies have observed a negative correlation between the use of cognitive reappraisal (measured by self-report measures) with negative affect in various chronic pain conditions, although no significant relationships were apparent with pain outcomes [182-184]. These studies suggest that while cognitive reappraisal may not have a direct relationship with pain, it may have an indirect influence through modulating negative affect [185]; however, this has not been explored in chronic low back pain.

While cognitive reappraisal may be important in chronic low back pain, less is known on potential underlying mechanisms. There has been evidence that has demonstrated that the brain circuitry involved in cognition is disrupted in chronic pain [186, 187], which may also be
associated with impaired cognitive processes, such as cognitive reappraisal. For example, chronic low back pain groups have exhibited decreased GM volume and altered functional connectivity in key regions associated with cognitive reappraisal including the amygdala [188, 189] and mPFC in chronic low back pain [190, 191]. However, there has not been any studies that have investigated how these brain changes may affect individuals with chronic low back pain and their capacity to engage in cognitive reappraisal.

1.4.4 Pain catastrophizing

In contrast, maladaptive cognitive processes, such as pain catastrophizing (i.e., the exaggerated negative emotional and cognitive response to pain [192, 193]), is detrimental to pain and disability outcomes in chronic low back pain [17, 117, 194]. This misinterpretation of pain events, not only heightens the pain experience, but also leads to increased maladaptive behaviours that delay recovery [118]. Indeed, cross-sectional studies have shown that pain catastrophizing was associated with higher pain intensity and disability in chronic low back pain populations [17, 195, 196]. Longitudinal studies have found that not only is pain catastrophizing a strong predictor for persistent disability in patients with acute and chronic low back pain [197], but it also mediates the relationship between recovery expectations during acute low back pain with disability and work limitations after 3 months [198]. Furthermore, a systematic review of cohort studies found that higher levels of pain catastrophizing in patients with acute, subacute and chronic low back pain were related to ongoing pain and disability at follow-up timepoints, demonstrating it contributes to the persisting low back pain outcomes [117].

The relationship between pain catastrophizing and pain is further supported by fMRI studies. A recent systematic review found that pain catastrophizing negatively correlated with GM
volume in areas related to pain perception and modulation including the S1, S2, insula, ACC, thalamus and DLPFC in chronic pain patients [199]. Additionally, neuroimaging studies found that pain catastrophizing was associated with increased resting-state functional connectivity within the DMN in chronic temporomandibular disorder and migraine patients [200, 201]. As the DMN is commonly linked to self-referential processes [95, 202, 203], increased activity has been thought to reflect the repetitive thoughts from catastrophizing in chronic pain [201]. While studies have observed altered functional connectivity in the DMN in chronic low back pain groups [105, 191, 204], its association with pain catastrophizing has not been explored. Therefore, investigating the relationship between the DMN and pain catastrophizing may provide a better understanding of the brain networks involved in maladaptive coping strategies in chronic low back pain.

1.5 Gaps in our knowledge

There is a growing body of evidence that has established the importance of cognitive factors in the development of chronic low back pain. However, the current literature highlights there are still limitations in our understanding in pain-related cognition in chronic low back pain. For instance, cross-sectional studies have established that pain-related cognition such as negative back beliefs are associated with higher levels of pain intensity and disability. However, the role of pain-related cognition in persistent low back pain outcomes is not well known. In addition, components of subjective well-being have been shown to influence low back pain outcomes; although, limited studies have explored the influence of the multiple dimensions of subjective well-being, such as anxiety, depression, positive well-being, self-control, general health and vitality, on chronic low back pain outcomes. Therefore, further investigations using cohort studies are necessary to determine how back beliefs and subjective well-being may contribute to the progression of chronic low back pain.
Neuroimaging studies have demonstrated that there are brain abnormalities in chronic low back pain populations [79]; however, our understanding of their relationship with pain-related cognitive processes remain limited. Indeed, there has been evidence to show brain regions involved in emotion regulation processes are compromised in chronic low back pain, although, how these brain changes may be associated with cognitive reappraisal processes has not been explored. In contrast, while studies have demonstrated individuals with chronic low back pain report higher levels of pain catastrophizing, further investigation into the underlying neural processes is required. The use of neuroimaging techniques such as magnetic resonance imaging (MRI) have become an increasing popular method to examine the structural and functional properties of the brain and therefore, will be used to identify the relevant brain regions and networks that could further our understanding of underlying mechanisms involved in pain-related cognition in chronic low back pain in this thesis.

1.6 Aims and overview of thesis

Therefore, this thesis will investigate the role of cognitive factors and underlying neurobiological processes associated with the development and persistence of chronic low back pain with two overarching aims. These include:

1. To explore the role of pain-related cognition in low back pain outcomes using cohort study designs;
2. To understand brain regions and networks involved in pain-related cognitive processes in chronic low back pain using fMRI.

The aims of this thesis will be addressed by performing a systematic review and 4 experimental studies presented in the following chapters:
Chapter 2 is a published paper that systematically reviewed the evidence of brain changes observed in chronic low back pain populations in studies using MRI and fMRI. This review examines changes in structural properties within the brain as well as functional abnormalities during tasks, events and resting-state. We also explored how the reported brain changes may be associated with emotional and cognitive processes (Aim 2).

The first empirical study is presented in Chapter 3. This is a published paper that investigates the relationship between beliefs about back pain and low back pain intensity in a community-based cohort over 2 years (Aim 1).

In Chapter 4, a published paper explores the relationship between subjective well-being and its subdomains and low back pain intensity and disability in a community-based cohort of women (Aim 1).

Chapter 5 presents a submitted manuscript of a study that investigates brain activity during an emotion regulation task in individuals with chronic low back pain. This study examines the differences in BOLD response and functional connectivity in the brain during cognitive reappraisal in response to negative emotional stimuli in individuals with chronic low back pain and healthy controls (Aim 2).

In Chapter 6, the final empirical study (submitted), explores the changes in the DMN during resting-state in individuals with chronic low back pain compared with healthy controls. The
relationship between altered functional connectivity in the DMN observed in the chronic low back pain group and pain catastrophizing is also examined (Aim 2).

Finally, the thesis concludes in Chapter 7 with a summary of the empirical studies and a discussion of the potential implications. The strengths and limitations, as well as directions for future research are also outlined.
Chapter 2
The relationship between brain changes, and emotion and cognition in chronic low back pain

Manuscript


2.1 Preamble to systematic review

In the introduction of this thesis, the importance of cognitive and emotional factors and the underlying neural processes in the pain experience, all of which have been shown to be disrupted in chronic low back pain, was considered [101]. A previous systematic review of MRI and fMRI studies across various chronic musculoskeletal pain conditions identified structural and functional changes with common alterations within regions implicated in pain-related cognitive and emotional processes, regardless of diagnosis [187]. This suggests that the observed neural alterations in chronic pain may be mediated by or the result of changes in cognition and mood. In another systematic review specific to chronic low back pain, widespread structural and functional abnormalities were also identified [79]. However, that review reported the overall changes but did not include an in-depth discussion surrounding the potential implications of these changes on cognition and emotion or provide a qualitative assessment of the included studies.
This chapter, therefore, presents a systematic review that aims to examine the structural and functional changes within the brain in chronic low back pain groups in studies that used MRI or fMRI. The correlational relationship between the observed brain changes in chronic low back pain with cognitive and emotional self-report measures (e.g., depression, catastrophizing) as well as performance of behavioural task (completed outside of fMRI scan) are examined. Specific to this review, a discussion of the implications of the brain changes on cognition and emotion, and its potential contribution to the development of chronic low back pain is also included. This review includes a comprehensive search with the inclusion of additional studies than the previous review [79] and the risk of bias for is assessed for each study.
The Relationship Between Structural and Functional Brain Changes and Altered Emotion and Cognition in Chronic Low Back Pain Brain Changes

A Systematic Review of MRI and fMRI Studies

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Objectives: Chronic low back pain (CLBP) is a major health issue, yet its underlying mechanisms remain unknown. Studies have demonstrated the importance of emotion and cognition in chronic pain; however, the relevant brain physiology in magnetic resonance imaging (MRI) studies are unclear in CLBP populations. Therefore, this review aimed to identify MRI brain changes and examine their potential relationship with emotional and cognitive processes in CLBP.

Methods: A systematic search was conducted in 5 databases. Studies that recruited adult, CLBP populations, and used brain MRI protocols were included.

Results: In total, 55 studies met the inclusion criteria. Of the structural MRI studies, 10 of 15 studies found decreased gray matter and 7 of 8 studies found white matter changes in CLBP groups compared with controls. Fourteen resting-state functional MRI studies all reported differences between CLBP and control groups in the default mode network. Interestingly, only 3 of 10 functional MRI studies observed significant differences during noxious stimulation between CLBP and control groups, whereas 13 of 16 studies observed significant brain activation differences in CLBP groups during various external tasks. Finally, there were 3 studies that observed a degree of recovery in functional connectivity following intervention.

Discussion: The brain changes in CLBP groups were mainly observed in areas and networks important in emotion and cognition, rather than those typically associated with nociception. This supports the understanding that emotional and cognitive processes may be the core contributor to the CLBP experience; however, future studies need to explore these processes further.

Key Words: chronic low back pain, fMRI, MRI, emotion, cognition, brain

Low back pain (LBP) is the leading cause of disability worldwide.1 Reports have shown that LBP is accountable for 10.7% of years lived with disability (YLD) (83.1 million YLD) globally2 with significant economic costs.3,4 Although the majority of LBP cases tend to resolve within the first 6 weeks,5–10% of individuals develop chronic low back pain (CLBP).3,6–8 However, 85% of these cases do not have a specific physiological cause (ie, referred to as nonspecific),9,10 making the development of effective treatments and pathways to recovery extremely challenging. Although multidisciplinary pain treatment programs are effective in pain relief in CLBP, the effects seen in studies have been small and short-term.10,11 Despite the lack of clear pathology in nonspecific CLBP, the absence of a physiological cause supports the notion that pain is not a purely sensory-dependent process.12 Pain is a multifaceted subjective construct.13 The prominent theoretical model of pain, known as the Neuromatrix Theory of pain, was developed to conceptualize the complexity of pain. It identified 3 main dimensions: sensory, emotional, and cognitive components.13 Recent pain studies using magnetic resonance imaging (MRI) techniques have identified a network of brain regions, collectively referred to as the pain matrix14 that are in conjunction with the 3 dimensions of pain. The sensory component has been associated with the primary and secondary somatosensory cortices of the brain.15 The emotional component included the cingulate cortex, insula, and areas of the limbic system which influences the perceived unpleasantness of pain stimuli.14,16 For instance, studies have demonstrated that induced negative mood can increase the unpleasantness of a pain stimulus but not the intensity.15,17–20 Finally, the cognitive aspect of pain showed activation in the frontal and parietal regions of the brain.16,21 It is involved in the degree of attention on stimuli, and interprets the meaning of the overall pain experience.16,21 For example, diverting attention away from noxious stimuli by engaging in an attention-demanding task can result in reduced pain intensity.22,23 The widespread activation in the pain...
matrix across these domains clearly suggests that emotional and cognitive factors play a fundamental role in how pain is experienced.²¹

Cross-sectional studies have shown cognitive deficits in individuals with CLBP, independent of depression and anxiety, include delayed information processing,²⁶ impaired memory,²⁵ decision-making,²⁶ as well as poorer cognitive function in neuropsychological tasks.²⁷ Studies have also shown that individuals with CLBP have shown disrupted emotional processes as they have a significantly higher prevalence of mood disorders such as depression than the general population (ie, pain-free individuals).²⁸²⁹ Therefore, this suggests that CLBP is linked to changes in emotional and cognitive function; however, the underlying neuroanatomy and brain function associated in these relationships are not well understood. This is however, an important area of inquiry as the development and maintenance of persistent pain may be associated with changes in brain regions that make up the pain matrix. Indeed, the consequences of this change, whether the cause or the result of persistent pain, alter the experience of pain and the related cognitive and emotional functions.²¹³⁰

Recent reviews have examined cognitive modulation on overall pain perception,³¹ identified MRI brain activations³² as well as brain alterations in various chronic pain conditions.³³ A review also examined the brain changes specifically in CLBP groups³⁴; however, their findings largely focused identified general changes with an absence of the discussion regarding the implications on emotional and cognitive processes and a lack of integration of the qualitative assessment of the studies. Therefore, the aim of this review was to examine the evidence for the structural and functional changes in the brain and identify how these changes may be associated with emotional and cognitive processes in CLBP. It also included assessment for risk of bias.

METHODS

Search Strategy

A computerized search was conducted up to the August 11, 2016 using the databases Medline, PsycINFO, Cinahl, Embase, and Scopus. The following key search terms used in title and abstracts (* = truncated, ADJ1 = retrieves words that are within 1 word of each other): (magnetic resonance imaging [Mesh] OR functional ADJ1 [MRI* or magnetic resonance imaging]) AND (brain [Mesh] OR brain*) AND (back pain [explode]).

Study Selection

Studies were included if they met the following criteria: (1) population consisted of human patients; (2) adult sample only (age above 18 y of age); (3) included individuals with CLBP patients (where the duration is clearly identified as > 3 mo); (4) used brain MRI techniques; (5) peer-reviewed original research with full-text available (reviews, systematic reviews, and meta-analyses were excluded); and (6) published in English. Studies were excluded if they did not meet all the inclusion criteria. In the first phase, all studies were evaluated for eligibility based on the title and abstract. In the second phase, full-text articles of potential eligible studies were retrieved and further screened.

Data Extraction

Study information on author, year, study design, definition of CLBP, sample size, mean (SD) age, percentage of females, analysis method (Table 1), as well as stimulus or task event, follow-up periods (in cohort studies only), main findings, and conclusions were extracted from all eligible studies (Tables 2–5).

Assessment of Risk of Bias

Two reviewers (S.K.N and S.M.H) independently assessed the methodological quality of the selected studies using an adapted scoring system of the Lienvese criteria.³⁰ The Lienvese criteria consists of 15 items that were scored either positive (1) or negative (0) (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CJP/A453). Results were then compared and where reviewers disagreed and consensus could not be achieved, a third reviewer (D.M.U) gave final judgement. The results of this assessment were used to determine the risk of bias which was assessed using a tool adapted from the Cochrane Collaboration for cohort studies.³¹ This risk of bias assessment was based on 4 items for cross-sectional studies and 5 items for cohort studies. Each item was rated as “low,” “moderate,” or “high” based on specific item scores from the Lienvese criteria (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/CJP/A453) and these contributed to an overall assessment of the risk of bias for each study; low (all items rated low), low-moderate (1 item rated moderate), moderate (2 items rated moderate), or high (> 2 items rated moderate or any of the items rated high).

RESULTS

Study Selection

The literature search yielded a total of 1003 papers from the 5 databases. After the removal of duplicates, there were 715 unique articles remaining. After the first phase of screening based on title and abstracts, 633 articles were excluded with a further 27 articles excluded when screened using full-text based on the inclusion criteria. During the second screening phase, articles were excluded if full-texts could not be found, or if they were conference abstracts. After the 2 screening phases, 55 papers were included. The process of study selection is represented in a PRISMA flowchart³² in Figure 1.

Study Characteristics

The study characteristics of the yielded papers are presented in Table 1. The group size of CLBP patients ranged from 8 to 111. All studies consisted of both males and females, except 1 study that only recruited females.⁴⁵ Two studies also had controls groups that were all males that were compared with CLBP groups with individuals of both sexes.⁵⁰⁵⁸ The mean age of CLBP groups were 47.1 years of age. Two studies did not report mean age.⁵¹⁸³

There were 46 studies that compared CLBP patients with healthy controls, whereas 4 studies compared the effects of treatments within-CLBP groups⁸⁸,⁵⁰,⁵⁷,⁷⁷ and 1 study compared subacute back pain (SBP) with CLBP.⁵⁸ There were 6 studies that explored within-CLBP group differences including 3 studies that compared CLBP patients that exhibit pain behaviors with those who did not,⁵⁴⁶⁵,⁶⁶ 2 studies that compared disabled and non-disabled CLBP patients⁴⁵,⁴⁹ and 1 study that compared neuropathic and non-neuropathic CLBP groups.³⁵ Finally, there were 2 longitudinal studies that followed CLBP and SBP²⁴ over the course of 1 year and compared back pain recovery outcomes (ie, groups that recovered from back pain and those who had persistent back pain).

Most CLBP patients were selected based on self-reported LBP every day or almost every day that ranged from at least 3 months to 10 years with pain intensity rating of at least > 2 of
### TABLE 1. Study Characteristics of Selected Studies

<table>
<thead>
<tr>
<th>References</th>
<th>Study Methods</th>
<th>Definition of CLBP</th>
<th>CLBP</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apkarian et al(^{35})</td>
<td>Structural</td>
<td>Diagnosed according to IASP criteria by clinician, had pain &gt; 1 y localized to the lumbarosacral region including buttocks and thighs, with or without pain radiating to the leg</td>
<td>Neuropathic</td>
<td>—</td>
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<tr>
<td></td>
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<td>No flow: 7 (28.6)</td>
<td>43.3 ± 12.4</td>
<td>7 (28.6)</td>
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<td>Fast: 4 (100) Non-Nu</td>
<td>43.3 ± 8.2</td>
<td>4 (100)</td>
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<tr>
<td>Baliki et al(^{36})</td>
<td>Event-related</td>
<td>Clinically diagnosed with CBP</td>
<td>—</td>
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<tr>
<td>Baliki et al(^{37})</td>
<td>Event-related, Treatment</td>
<td>Same as Baliki et al(^{36})</td>
<td>—</td>
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<tr>
<td></td>
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<td>CBP fulfilled IASP criteria; reported pain &gt; 3 mo with pain intensity &gt; 30/100</td>
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<td></td>
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<td>Group 1 13 (92.3)</td>
<td>49.2 ± 17.2</td>
<td>11 (54.5)</td>
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<tr>
<td>Baliki et al(^{38})</td>
<td>Event-related, resting-state, event-related</td>
<td>Clinically diagnosed by clinician, had pain intensity &gt; 40/100 and duration &gt; 1 y</td>
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<tr>
<td>Baliki et al(^{39})</td>
<td>Structural</td>
<td>Diagnosed according to IASP by clinician</td>
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<tr>
<td>Baliki et al(^{40})</td>
<td>Structural, event-related</td>
<td>SBP: diagnosed by clinician for back pain with pain intensity &gt; 40/100 and duration &lt; 16 wk. Recovered (SBPr) when 20% reduced pain intensity at follow-up</td>
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<tr>
<td>Baliki et al(^{41})</td>
<td>Resting-state</td>
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<tr>
<td>Baliki et al(^{42})</td>
<td>Structural, event-related</td>
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<tr>
<td>Baliki et al(^{43})</td>
<td>Resting-state</td>
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<tr>
<td>Balenzuela et al(^{44})</td>
<td>Resting-state</td>
<td>Recruited from Baliki et al(^{36})</td>
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<tr>
<td>Barke et al(^{45})</td>
<td>Event-related</td>
<td>Nonspecific LBP for &gt; 6 mo and pain intensity &gt; 5/10 over the previous 4 wk</td>
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<tr>
<td>Berger et al(^{46})</td>
<td>Resting-state, event-related</td>
<td>LBP for &gt; 1 y with no other pain comorbidities</td>
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<tr>
<td>Buckalew et al(^{47})</td>
<td>Structural</td>
<td>LBP least moderate intensity every day or almost every day &gt; 3 mo</td>
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<tr>
<td>Buckalew et al(^{48})</td>
<td>Structural, resting-state</td>
<td>Reported CLBP every day or almost every day for ≥ 3 mo of at least moderate pain</td>
<td>—</td>
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<td></td>
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<td>Disabling: 8 (50)</td>
<td>74.1 ± 6.4</td>
<td>—</td>
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<td></td>
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<td>Nondisabling: 8 (25)</td>
<td>75.1 ± 7.3</td>
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<tr>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Buckalew et al⁴⁹</td>
<td>Structural</td>
<td>Self-reported LBP every day or almost every day for ≥ 3 mo of at least moderate intensity Disabling: significant disruption to daily activities or being bed bound during some days of ≥ 6 wk in the past 6 mo. Nondisabling: pain that had limited function for &lt; 6 wk over the past 6 mo</td>
<td>Disabled: 8 (50) Age: 74.1 ± 6.4</td>
<td>8 (50) Age: 82.3 ± 1.7</td>
</tr>
<tr>
<td>Callan et al⁵⁰</td>
<td>Event-related</td>
<td>Diagnosed by physician with LBP for &gt; 6 mo</td>
<td>13 (69.2) Age: 51.8 ± 1.9</td>
<td>13 (69.2) Age: 48.7 ± 2.37</td>
</tr>
<tr>
<td>Čeko et al⁵¹</td>
<td>Structural</td>
<td>CLBP with intensity of &gt; 4/10 for &gt; 1 y</td>
<td>14 (NA) Age: 46.7 ± 1.8</td>
<td>— —</td>
</tr>
<tr>
<td>Dolman et al⁵²</td>
<td>Structural</td>
<td>CLBP of ≥ 3/10 pain intensity for at least 6 mo with significant discogenic component to their pain syndrome, confirmed by clinical evaluation and lumbar MRI (excluded purely nonspecific or myofascial causes)</td>
<td>14 (64.3) Age: 46.9 ± 1.8</td>
<td>14 (64.3) Age: 45.9 ± 1.8</td>
</tr>
<tr>
<td>Foss et al⁵³</td>
<td>Event-related</td>
<td>Fulfilled IASP criteria with unrelenting pain for &gt; 1 y (did not distinguish various etiologies)</td>
<td>11 (81.8) Age: 37 (NA)</td>
<td>23 (65.2) Age: 34 (NA)</td>
</tr>
<tr>
<td>Fritz et al⁵⁴</td>
<td>Structural</td>
<td>Experienced continuous back pain for &gt; 3 mo and have not recovered at time of study</td>
<td>111 (70.3) Age: 53.12 ± 11.8</td>
<td>432 (42.8) Age: 48.9 ± 14.0</td>
</tr>
<tr>
<td>Giesecke et al⁵⁵</td>
<td>Event-related</td>
<td>Diagnosed with idiopathic CLBP for &gt; 12 mo (excluded evidence of fracture or malignancy, inflammatory joint disease)</td>
<td>11 (72.7) Age: 44 ± 13</td>
<td>11 (36.3) Age: 41 ± 7</td>
</tr>
<tr>
<td>Hashmi et al⁵⁶</td>
<td>Treatment</td>
<td>Diagnosed by a clinician with CLBP for &gt; 4/10 pain intensity at baseline for &gt; 1 y (same sample as Hashmi et al⁵⁵)</td>
<td>Overall: 30 (46.7) Age: 51.4 ± 9.08</td>
<td>— —</td>
</tr>
<tr>
<td>Hashmi et al⁵⁷</td>
<td>Treatment</td>
<td>Diagnosed by a clinician with CLBP for &gt; 4/10 pain intensity at baseline for &gt; 1 y (same sample as Hashmi et al⁵⁶)</td>
<td>CBPp: 15 (46.6) Age: 52.6 ± 2.6</td>
<td>— —</td>
</tr>
<tr>
<td>Hashmi et al⁵⁸</td>
<td>Structural, event-related</td>
<td>Diagnosed by clinician according to IASP criteria CLBP: reported pain intensity &gt; 40/100 for &gt; 6 mo SBP: reported single intense episode of back pain of &gt; 40/100 pain intensity for 4-16 wk with no prior back pain for &gt; 1 y according to IASP criteria</td>
<td>CBPd: 15 (46.6) Age: 50.1 ± 2.1</td>
<td>— —</td>
</tr>
<tr>
<td>Ivo et al⁵⁹</td>
<td>Structural</td>
<td>Suffering from CLBP of ≥ 4/10 pain intensity for &gt; 1 y according to IASP criteria</td>
<td>14 (57.1) Age: 54 (NA)</td>
<td>14 (57.1) Age: 54 (NA)</td>
</tr>
<tr>
<td>Kobayashi et al⁶⁰</td>
<td>Event-related</td>
<td>Having idiopathic LBP &gt; 3 mo with pain intensity &gt; 3/10 with no structural abnormalities in lumbar spine</td>
<td>8 (37.5) Age: 33 (NA)</td>
<td>8 (0) Age: 29 (NA)</td>
</tr>
<tr>
<td>Kong et al⁶¹</td>
<td>Structural, resting-state</td>
<td>Diagnosed with nonspecific CLBP for &gt; 6 mo by clinic evaluation with the use of x-ray/MRI where available</td>
<td>18 (66.7) Age: 36.1 ± 9.9</td>
<td>18 (66.7) Age: 37.1 ± 9.2</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>References</th>
<th>Study Methods</th>
<th>Definition of CLBP</th>
<th>CLBP</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kornelsen et al</td>
<td>Resting-state</td>
<td>Diagnosed with CLBP with FBSS by physician</td>
<td>N (45.5)</td>
<td>Age (M ± SD) (y)</td>
</tr>
<tr>
<td>Li et al</td>
<td>Treatment</td>
<td>Reported nonspecific low back pain for &gt; 3 mo and pain intensity of ≥ 5/10</td>
<td>20 (50)</td>
<td>38.1 ± 6.4</td>
</tr>
<tr>
<td>Lloyd et al</td>
<td>Event-related</td>
<td>CLBP for &gt; 6 mo, without sciatica and no structural spinal abnormalities other than degenerative change in no &gt; 3 lumbar disks</td>
<td>WS-H: 30 (46.7)</td>
<td>45 ± 12.2</td>
</tr>
<tr>
<td>Lloyd et al</td>
<td>Event-related</td>
<td>CLBP for &gt; 6 mo without sciatica and no structural spinal abnormalities other than degenerative change in no &gt; 3 lumbar disks</td>
<td>WS-H: 11 (54.5)</td>
<td>44 ± 12.8</td>
</tr>
<tr>
<td>Lloyd et al</td>
<td>Event-related</td>
<td>CLBP for &gt; 6 mo, without sciatica and no structural spinal abnormalities other than degenerative change in no &gt; 3 lumbar disks</td>
<td>WS-H: 13 (46.2)</td>
<td>45 ± 10.2</td>
</tr>
<tr>
<td>Lloyd et al</td>
<td>Event-related</td>
<td>CLBP and radicular pain with ongoing pain intensity of &gt; 3/10 of &gt; 6 mo with discogenic component to their syndrome confirmed by lumbar MRI</td>
<td>16 (69)</td>
<td>47.4 ± 7.4</td>
</tr>
<tr>
<td>Loggia et al</td>
<td>Resting-state</td>
<td>CLBP and radicular pain with ongoing pain intensity of &gt; 3/10 of &gt; 6 mo with discogenic component to their syndrome confirmed by lumbar MRI</td>
<td>12 (NA)</td>
<td>43.9 ± 12.9</td>
</tr>
<tr>
<td>Luchtmann et al</td>
<td>Structural</td>
<td>Experiencing LBP &gt; 3 mo and diagnosed with an isolated LDH at either L4-5 or L5-S1, using spinal MRI</td>
<td>12 (50)</td>
<td>43.9 ± 12.9</td>
</tr>
<tr>
<td>Luchtmann et al</td>
<td>Structural</td>
<td>Experiencing LBP &gt; 3 mo and diagnosed with an isolated LDH at either L4-5 or L5-S1, using spinal MRI</td>
<td>12 (50)</td>
<td>43.9 ± 12.9</td>
</tr>
<tr>
<td>Mao et al</td>
<td>Structural</td>
<td>Diagnosed with CLBP according to IASP criteria</td>
<td>30 (66.7)</td>
<td>51.6 ± 8.6</td>
</tr>
<tr>
<td>Mao et al</td>
<td>Event-related</td>
<td>Diagnosed with CLBP according to the IASP criteria</td>
<td>36 (58.3)</td>
<td>50.3 ± 10.6</td>
</tr>
<tr>
<td>Mutso et al</td>
<td>Event-related</td>
<td>CBP: pain intensity &gt; 40/100 for &gt; 10 y</td>
<td>SBP: 32 (50)</td>
<td>40.8 ± 11</td>
</tr>
<tr>
<td>Petre et al</td>
<td>Structural, event-related</td>
<td>SBP: back pain last 4-12 wk with no prior back pain for &gt; 1 y, Recovered (SBP) when 20% reduced pain intensity at follow-up</td>
<td>SBP: 32 (43.8)</td>
<td>45.1 ± 1.3</td>
</tr>
</tbody>
</table>

(Continued)
10, or were diagnosed according to the International Association for the Study of Pain (IASP) criteria by a clinician. There were 19 studies that also targeted specific types of LBP: 12 studies recruited nonspecific CLBP,45,55,60,61,63–66,74,81,86,89 two studies with failed back surgery syndrome,62,77 and 3 studies with a discogenic component.52,67,87

### Risk of Bias

The risk of bias results are presented in Tables 2–5. Of the 55 studies included in this review, 32 studies and the cross-sectional component of a cohort study (59%) had a low to moderate risk of bias and 22 studies and the cohort component of another study (40.9%) had a high risk of bias.

### TABLE 1. (continued)

<table>
<thead>
<tr>
<th>References</th>
<th>Study Methods</th>
<th>Definition of CLBP</th>
<th>N (% of Females)</th>
<th>Age (M ± SD) (y)</th>
<th>N (% of Females)</th>
<th>Age (M ± SD) (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pijnenburg et al54</td>
<td>Resting-state</td>
<td>Nonspecific and disabling LBP for &gt; 6 mo</td>
<td>17 (64.7)</td>
<td>33.3 ± 7.9</td>
<td>17 (70.6)</td>
<td>31.8 ± 8.2</td>
</tr>
<tr>
<td>Schmidt-Wilcke et al53</td>
<td>Structural</td>
<td>Seven weeks of pain from onset and pain persisted &gt; 1 mo beyond course of acute disease</td>
<td>18 (50)</td>
<td>50.4 ± 6.8</td>
<td>18 (50)</td>
<td>49.9 ± 8.7</td>
</tr>
<tr>
<td>Seminowicz et al75</td>
<td>Structural, event-related</td>
<td>CLBP patients with pain intensity of &gt; 4/10 for &gt; 1 y</td>
<td>18 (55.6)</td>
<td>46 ± 10.6</td>
<td>16 (50)</td>
<td>40 ± 13.2</td>
</tr>
<tr>
<td>Stancak et al77</td>
<td>Event-related</td>
<td>Patients scheduled to receive spinal cord stimulation for intractable neuropathic back pain after failed back surgery</td>
<td>8 (37.5)</td>
<td>48 (NA)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tagliazucchi et al78</td>
<td>Resting-state</td>
<td>Participants taken from Baliki et al53</td>
<td>12 (NA)</td>
<td>51.2 (NA)</td>
<td>20 (NA)</td>
<td>38.4 (NA)</td>
</tr>
<tr>
<td>Tagliazucchi et al79</td>
<td>Resting-state</td>
<td>Participants taken from Baliki et al53</td>
<td>12 (NA)</td>
<td>51.2 (NA)</td>
<td>20 (NA)</td>
<td>38.4 (NA)</td>
</tr>
<tr>
<td>Ung et al80</td>
<td>Structural</td>
<td>Axial LBP without radicular symptoms persisting for &gt; 6 mo</td>
<td>47 (46.8)</td>
<td>37.7 ± 7.8</td>
<td>47 (46.8)</td>
<td>37.3 ± 12.2</td>
</tr>
<tr>
<td>Vachon-Presseau et al81</td>
<td>Event-related</td>
<td>Reported idiopathic CLBP for &gt; 6 mo</td>
<td>21 (52.4)</td>
<td>36 (NA)</td>
<td>21 (52.4)</td>
<td>36 (NA)</td>
</tr>
<tr>
<td>Vachon-Presseau et al82</td>
<td>Event-related</td>
<td>Reported CLBP for &gt; 6 mo</td>
<td>21 (52.4)</td>
<td>36 (NA)</td>
<td>21 (52.4)</td>
<td>36 (NA)</td>
</tr>
<tr>
<td>Vachon-Presseau et al83</td>
<td>Event-related</td>
<td>Experiencing LBP for &gt; 6 mo</td>
<td>21 (47.6)</td>
<td>NA</td>
<td>20 (50)</td>
<td>NA</td>
</tr>
<tr>
<td>Vachon-Presseau et al84</td>
<td>Event-related</td>
<td>Experiencing back pain symptoms for &gt; 6 mo</td>
<td>14 (50)</td>
<td>36 ± 10.90</td>
<td>16 (43.75)</td>
<td>36 ± 10.9</td>
</tr>
<tr>
<td>Vachon-Presseau et al85</td>
<td>Structural, event-related</td>
<td>SBP: diagnosed by a clinician with back pain between 4–16 wk with pain intensity &gt; 40/100, Recovered (SBPr) when 20% reduced pain intensity at follow-up of 1 y</td>
<td>1 y follow-up: 69 (49.3)</td>
<td>43.1 ± 10.4</td>
<td>1 y follow-up: 20 (45)</td>
<td>37.4 ± 7.5</td>
</tr>
<tr>
<td>Vrana et al86</td>
<td>Event-related</td>
<td>Experiencing nonspecific LBP for &gt; 6 mo</td>
<td>15 (26.7)</td>
<td>44.2 ± 11.3</td>
<td>14 (64.3)</td>
<td>33.6 ± 12.6</td>
</tr>
<tr>
<td>Wasan et al87</td>
<td>Event-related</td>
<td>Reported ongoing pain intensity of &gt; 3/10 of &gt; 6 mo with discogenic component to their syndrome confirmed by lumbar MRI</td>
<td>16 (69)</td>
<td>47.4 ± 7.4</td>
<td>16 (69)</td>
<td>46.7 ± 6.5</td>
</tr>
<tr>
<td>Younger et al88</td>
<td>Treatment</td>
<td>Had chronic, moderate-to-severe, nonradicular low back pain who had not responses to other nonopiod treatments</td>
<td>10 (60)</td>
<td>47 ± 11</td>
<td>9 (0)</td>
<td>30 ± 10</td>
</tr>
<tr>
<td>Yu et al89</td>
<td>Resting-state</td>
<td>Nonspecific CLBP for &gt; 6 mo by clinic evaluation with the use of x-ray/MRI where available</td>
<td>18 (66.7)</td>
<td>36.1 ± 9.9</td>
<td>18 (66.7)</td>
<td>37.1 ± 9.2</td>
</tr>
</tbody>
</table>

CBP indicates chronic back pain; CLBP, chronic low back pain; FBSS, failed back surgery syndrome; IASP, International Association for the Study of Pain; LBP, low back pain; LDH, lumbar disk herniation; MRI, magnetic resonance imaging; NA, not available or reported; non-Nu, non-neuropathic groups; SBP, subacute back pain; SBPp, persistent subacute back pain; SBPr, recovered subacute back pain; WS-H, high pain behavior (according to Waddell signs); WS-L, no or low pain behavior (according to Waddell signs).
<table>
<thead>
<tr>
<th>References</th>
<th>Brain Analysis Methods and Behavioral Measures</th>
<th>Main Findings (CLBP Compared With Control Groups*)</th>
<th>Risk of Bias</th>
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<tbody>
<tr>
<td>Apkarian et al35</td>
<td>Whole-brain and regional GM volume: VBM</td>
<td>↓ 5%-11% GM volume and global GM density</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>Pain: SF-MPQ</td>
<td>↓ GM in bilateral DLPFC, and right thalamus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depression: BDI</td>
<td>Positive correlation between lateral ventricle size and change in ventricle size, with negative affect dimension of SF-MPQ.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety: BAI</td>
<td>Neuropathic vs. non-neuropathic CBP: no significant differences in GM volume between nuCBP and non-nuCBP groups affect dimension of SF-MPQ predicted DLPFC GM density in CLBP but the opposite effect observed between nuCBP and non-nuCBP groups</td>
<td></td>
</tr>
<tr>
<td>Baliki et al41</td>
<td>Whole-brain and regional GM density: VBM</td>
<td>↓ Global GM volume</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>Depression: BDI</td>
<td>↓ GM in bilateral posterior insula, S2, precentral and postcentral regions, hippocampus, and temporal lobes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety: BAI</td>
<td>No significant correlations between GM density and pain duration, intensity, depression, and anxiety scores</td>
<td></td>
</tr>
<tr>
<td>Buckalew et al47</td>
<td>Regional GM and WM density: VBM neuropsychological testing: digit span, digit symbol substitution, letter-number sequencing, trail making.</td>
<td>No differences in percent global GM or WM, prefrontal GM or thalamic volume between CLBP and HC</td>
<td>LM</td>
</tr>
<tr>
<td></td>
<td>Depression: geriatric depression screen</td>
<td>↓ WM in cingulate superior to the middle CC of left hemisphere</td>
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<td></td>
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<td>CLBP performed worse on forward digit span task (attention-demanding task).</td>
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<td></td>
<td></td>
<td>No significant relationships between forward digit span task and brain volumes</td>
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</tr>
<tr>
<td>Buckalew et al48</td>
<td>WM: DTI neuropsychological testing: repeatable battery for the assessment of neuropsychological status, trail making test A and B, letter-number sequencing</td>
<td>CLBP disabling compared with CLBP nondisabling</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>Depression: geriatric depression screen</td>
<td>↓ WM in left hemisphere</td>
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<tr>
<td></td>
<td></td>
<td>No significant differences in whole-brain cortical thickness</td>
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<td></td>
<td></td>
<td>↑ cortical thickness in right rostral middle frontal gyrus.</td>
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<td></td>
<td></td>
<td>Significant clusters became nonsignificant after controlling for age.</td>
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<tr>
<td></td>
<td></td>
<td>Significant different HADS scores between CLBP and HC.</td>
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<tr>
<td></td>
<td></td>
<td>No significant relationships between HADS scores and cortical thickness in ROI and whole-brain analyses</td>
<td></td>
</tr>
<tr>
<td>Buckalew et al49</td>
<td>WMH localization and segmentation</td>
<td>CLBP disabling compared with CLBP nondisabling and HC</td>
<td>M</td>
</tr>
<tr>
<td>Dolman et al52</td>
<td>GM: cortical thickness and VBM</td>
<td>↑ WMH in left hemisphere</td>
<td>LM</td>
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<tr>
<td></td>
<td>Depression and Anxiety: HADS</td>
<td>No significant differences in whole-brain cortical thickness</td>
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<td></td>
<td>↑ cortical thickness in right rostral middle frontal gyrus.</td>
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<tr>
<td></td>
<td></td>
<td>Significant clusters became nonsignificant after controlling for age.</td>
<td></td>
</tr>
<tr>
<td>Fritz et al54</td>
<td>GM volume: VBM</td>
<td>↑ VLPFC, DLPFC, ventral and dorsal mPFC, and anterior insula.</td>
<td>LM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative correlation between pain intensity and GM volume in VLPFC, DLPFC, and ACC</td>
<td></td>
</tr>
<tr>
<td>Ivo et al59</td>
<td>Regional GM and WM volume: VBM</td>
<td>↑ Global GM and WM volume</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>depression: BDI</td>
<td>↑ GM in DLPFC, thalamus, middle cingulate cortex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety: BAI</td>
<td>CLBP had significantly higher BDI and BAI scores greater than HC group.</td>
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<tr>
<td></td>
<td></td>
<td>Regional brain analyses: no significant correlations between anxiety and depression scores, and brain regions (in DLPFC, middle cingulate cortex, thalamus) in CLBP group.</td>
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<tr>
<td></td>
<td></td>
<td>Whole-brain analyses: no correlation between BDI scores and brain region. Significant negative correlation between BAI scores and anterior cingulate and left lingual gyrus</td>
<td></td>
</tr>
<tr>
<td>Kong et al61</td>
<td>GM volume: cortical thickness and VBM</td>
<td>No differences in total GM</td>
<td>M</td>
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<tr>
<td></td>
<td></td>
<td>↑ cortical thickness in bilateral SI</td>
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<tr>
<td></td>
<td></td>
<td>↑ GM in top third of bilateral postcentrum gyrus.</td>
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<tr>
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<td></td>
<td>No differences when comparing whole volume, middle and bottom third of the postcentrum gyrus bilaterally</td>
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</tbody>
</table>

(Continued)
# Table 2 (continued)

<table>
<thead>
<tr>
<th>References</th>
<th>Brain Analysis Methods and Behavioral Measures</th>
<th>Main Findings (CLBP Compared With Control Groups*)</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luchtmann et al⁶⁸</td>
<td>GM and WM volumes: VBM</td>
<td>↑ GM in right dorsal ACC, left precuneal cortex, left fusiform gyrus, and right brainstem</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ GM in right ALPFC, right temporal lobe, left premotor cortex, right CN, and right cerebellum</td>
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<tr>
<td></td>
<td></td>
<td>↑ WM volume in anterior limb of left internal capsule</td>
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<tr>
<td></td>
<td></td>
<td>Whole-brain analysis</td>
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<tr>
<td></td>
<td></td>
<td>↑ Left precentral and postcentral cortices, bilateral cuneal, and left precuneal cortices.</td>
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<tr>
<td></td>
<td>GM volume: VBM and ROI analyses</td>
<td>↑ GM in bilateral putamen and accumbens, right pallidum, right caudate nucleus, and left amygdala</td>
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</tr>
<tr>
<td></td>
<td>cognition: montreal cognitive assessment</td>
<td>↑ GM in left postcentral gyrus, left precuneus, and bilateral cuneal cortex.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>depression: HAMD</td>
<td>Significantly higher depression and anxiety scores in CLBP group than HC. CLBP group had lower montreal cognitive assessment scores than HCs.</td>
<td></td>
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<tr>
<td></td>
<td>Anxiety: HAMA</td>
<td>No significant correlations between GM abnormalities and psychometric variables in CLBP group</td>
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<td></td>
<td></td>
<td>↑ GM in bilateral basal ganglia, and left posterior thalamus</td>
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<td></td>
<td></td>
<td>↑ GM in brainstem, DLPFC and somatosensory cortex.</td>
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<tr>
<td></td>
<td></td>
<td>Negative correlation between GM in brainstem and left somatosensory cortex, with pain intensity. Positive correlation between pain intensity and GM in left thalamus and putamen</td>
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<tr>
<td>Schmidt-Wilcke et al⁷³</td>
<td>GM volume: VBM</td>
<td>SVM analyses</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ GM in right cerebellum, regions of temporal lobe (bilateral middle temporal gyrus and left occipitaltemporal lobe), left S1 and S2, left M1, right calcarine sulcus, and right DLPFC</td>
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<td>↑ GM in right amygdala, left medial orbital gyrus, and right cuneus.</td>
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<td></td>
<td>VBM analyses</td>
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<td></td>
<td></td>
<td>↑ Left M1 and S1/S2</td>
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<td></td>
<td>↑ Right middle occipital lobe</td>
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<tr>
<td></td>
<td></td>
<td>SVM classifier characterized a pattern of regional GM density that distinguished CLBP from HC with 76% accuracy</td>
<td></td>
</tr>
<tr>
<td>Ung et al⁸⁰</td>
<td>GM density patterns: VBM and SVM</td>
<td></td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ GM in right cerebellum, regions of temporal lobe (bilateral middle temporal gyrus and left occipitaltemporal lobe), left S1 and S2, left M1, right calcarine sulcus, and right DLPFC</td>
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<td>↑ GM in right amygdala, left medial orbital gyrus, and right cuneus.</td>
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<td>VBM analyses</td>
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<td>↑ Left M1 and S1/S2</td>
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<td>↑ Right middle occipital lobe</td>
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<td>SVM classifier characterized a pattern of regional GM density that distinguished CLBP from HC with 76% accuracy</td>
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<tr>
<td>Longitudinal studies</td>
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<tr>
<td>Baliki et al⁴²</td>
<td>Followed-up SBP group:</td>
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<td>H</td>
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<tr>
<td></td>
<td>SBPp vs. SBBr</td>
<td>Follow-up vs. baseline (within SBPp group):</td>
<td></td>
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<tr>
<td></td>
<td>whole-brain GM volume and regional GM density:</td>
<td>↑ global GM volume</td>
<td></td>
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<tr>
<td></td>
<td>VBM</td>
<td>↑ GM density bilateral striatum and insula, and left sensorimotor cortex in whole-brain analyses</td>
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</tr>
<tr>
<td></td>
<td>pain: SF-MPQ</td>
<td>↑ GM in right NAc and right insula in ROI analyses.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mood: PANAS</td>
<td>No significant differences over time in SBPp group. Higher affect dimension of SF-MPQ score in SBPp than SBPr at baseline.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>depression: BDI</td>
<td>At follow-up, SBPp showed decreased scores in all measures except BDI and PANAS positive scores</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WM: DTI</td>
<td>No significant differences in left insula WM</td>
<td>CS: M</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posttreatment CLBP patient compared with HC.</td>
<td>CH: H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posttreatment CLBP patients had ↑ FA in left insula WM, compared with pretreatment patients.</td>
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<tr>
<td></td>
<td></td>
<td>No significant differences observed in WM in right insula (or in any other regions of the brain).</td>
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<tr>
<td></td>
<td></td>
<td>FA values in insula posttreatment negatively correlated with reduced pain intensity</td>
<td></td>
</tr>
<tr>
<td>Čeko et al⁵¹</td>
<td>CLBP pretreatment vs. 6 mo posttreatment (spine surgery or zygaphysical [facet] joint block)</td>
<td>No significant differences in left insula WM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WM: DTI</td>
<td>Posttreatment CLBP patients had ↑ FA in left insula WM, compared with pretreatment patients.</td>
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<td>No significant differences observed in WM in right insula (or in any other regions of the brain).</td>
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<td></td>
<td></td>
<td>FA values in insula posttreatment negatively correlated with reduced pain intensity</td>
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<tr>
<td></td>
<td></td>
<td>Postsurgery, compared with presurgery</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>CLBP pretreatment vs. 4 wk posttreatment</td>
<td>↑ Right basal ganglia (pallidum and putamen)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(microsurgical lumbar discectomy)</td>
<td>↑ Left hippocampus</td>
<td></td>
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<tr>
<td></td>
<td>GM volume: VBM</td>
<td>GM volume changes in hippocampus correlated with preoperative pain intensity (but not duration of chronic pain)</td>
<td></td>
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</tbody>
</table>

(Continued)
TABLE 2. (continued)

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<tr>
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<tr>
<td>Seminowicz et al76</td>
<td>CLBP pretreatment vs. 6 mo posttreatment (spine surgery or zygapophyscal [facet] joint block).</td>
<td>No differences in global GM, WM. Pretreatment, compared with HC</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td>GM and WM volume: cortical thickness</td>
<td>↑ GM in left DLPFC, bilateral anterior insula/frontal operculum, left mid/posterior insula, left S1, left medial temporal lobe, and right anterior cingulate cortex. Posttreatment, compared with pretreatment ↑ cortical thickness left DLPFC. Recovery of cortical thickness in left DLPFC and S2/ posterior insula correlated with reduced pain and improved physical disability. Increased thickness in M1 was associated with reduced physical disability. Increased thickness in right anterior insula was associated with reduced pain</td>
<td></td>
</tr>
<tr>
<td>Vachon-Presseau et al85</td>
<td>Followed-up SBP group: SBPp vs. SPBr (3 y) WM: DTI</td>
<td>Denser WM connections were observed in the corticolumbic network in the SBPp group SBPp consistently had ↑ WM connections in the dorsal mPFC-amygdala-NAC module over the SBPp groups and the HC group. Other WM networks in the ventral mPFC-amygdala and OFC-amygdala-hippocampus networks did not differ between SBPp and SBPr. Predisposed corticolimbic WM connections increased likelihood of transition to CLBP</td>
<td>H</td>
</tr>
<tr>
<td>Younger et al88</td>
<td>CLBP pretreatment vs. 1 mo posttreatment (daily oral morphine) GM volume: TBM</td>
<td>Posttreatment vs. pretreatment ↑ GM in right hippocampus, bilateral rostroventral pons, left medial orbital gyrus ↑ GM in left inferior frontal gyrus, dorsal posterior cingulate, right hypothalamus, bilateral mid-cingulate, bilateral ventral posterior cingulate, right caudal pons, and dorsal anterior cingulate. Higher dosage correlated with volumetric decrease in right amygdala. Higher dosage correlated with volumetric increase in right hypothalamus, left inferior frontal gyrus, right ventral posterior cingulate, and right caudal pons</td>
<td>M</td>
</tr>
</tbody>
</table>

*Unless otherwise specified.

ACC indicates anterior cingulate cortex; ALPFC, anterolateral prefrontal cortex; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CBP, chronic back pain; CC, corpus callosum; CH, cohort component; CLBP, chronic low back pain; CN, caudate nucleus; CX, cross-sectional component; DLPFC, dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter; H, high risk of bias; HADS, Hospital Anxiety and Depression Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Rating Scale for Depression; HC, healthy controls; L, low risk of bias; LM, low-moderate risk of bias; M, moderate risk of bias; M1, primary motor cortex; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; Nu, neuropathic group; OFC, orbital frontal cortex; PANAS, positive and negative affect schedule; PPC, posterior parietal cortex; ROI, region of interest; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SBPp, persistent subacute back pain; SBPr, recovered subacute back pain; SCC, splenium of corpus callosum; SF-MPQ, Short Form McGill Pain Questionnaire; SVM, support vector machine analysis; TBM, tensor-based morphometry; VBM, voxel-based morphometry; VLPFC, ventrolateral prefrontal cortex; WM, white matter; WMH, white matter hyperintensities.

Analysis of the risk of bias assessments revealed that 98.2% of studies achieved low risk of bias scores on the selection of participants (Cochrane criteria item 3) and 61.5% of cohort studies obtained a low score for adequate follow-up procedures (Cochrane criteria item 6) (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/CJP/A453). The majority of studies obtained a moderate risk of bias score in the “assessment of exposure” (76.4%; Cochrane criteria item 2) and the “assessment of outcome” (80.1%; Cochrane criteria item 5). A total of 16 studies obtained a high risk of bias score for statistical adjustment for potential confounding variables (Cochrane criteria item 4). There were only 13 (23.6%) cohort studies and 4 (7.3%) intervention-based studies. However, there was considerable consistency in the evidence for our findings, particularly from noxious stimulation and resting-state studies, despite the various cohorts and methodologies used.

MRI Structural Changes

Gray Matter (GM)

There were 15 studies that examined changes in structural GM with 3 studies that had low-moderate risk of bias,67,74,80 6 studies that had a moderate risk of bias,75,76,80,81 and 6 studies that had a high risk of bias.77,78,82–84 The findings of these studies are presented in Table 2. In terms of global GM volume, 5 studies (2 with low-moderate, 1 moderate, and 2 high risk of bias) did not observe any significant differences between CLBP and healthy controls.72,77,78,80 whereas 3 other studies (2 moderate and 1 high risk of bias) found reduced global GM in CLBP patients compared with controls.35,41,59 There were 5 studies with a low to moderate risk of bias that observed decreased regional GM volumes in areas including
<table>
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<tr>
<td>Balenzuela et al44</td>
<td>Modular connectivity</td>
<td>Modular reorganization in frontal and temporal regions, sensorimotor cortex, basal ganglia, and ACC</td>
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<tr>
<td></td>
<td></td>
<td>↑ FC in caudate nucleus and ACC</td>
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<tr>
<td>Baliki et al40</td>
<td>Resting-state fMRI (low, mid, and high-frequency BOLD oscillations)</td>
<td>↑ High-frequency BOLD oscillation within mPFC and parts of the DMN</td>
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<tr>
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<td>CBP showed (spectral analysis) increased power for high- frequency BOLD oscillations in mPFC, PCC, lateral parietal cortex</td>
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<tr>
<td>Baliki et al43</td>
<td>Resting-state depression: BDI-II</td>
<td>↑ High-frequency oscillations in DMN regions, especially mPFC, and precuneus</td>
<td>H</td>
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<tr>
<td></td>
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<td>↓ mPFC and its FC to other areas of DMN, especially the precuneus</td>
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<td>↑ FC between mPFC with other parts of the DMN was directly related to ↑ FC between mPFC and bilateral insula</td>
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<td>↑ correlation of the DMN, specifically the mPFC with insular cortex.</td>
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<td>No significant relationships between BDI-II and functional parameters</td>
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<tr>
<td>Berger et al46</td>
<td>Modular connectivity of NAc during resting-state</td>
<td>NAc module: ↑ 20%-30% FC between NAc and subcortical regions including the hippocampus and amygdala</td>
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<td>↓ 15%-20% FC between NAc and frontal regions</td>
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<td>NAc and frontal regions correlated more to reward behavior than connectivity between NAc and subcortical structures.</td>
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<td>CBP patients’ brains resembled highly impulsive patients, whereas HC resembled intermediately impulsive</td>
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<td>Buckalew et al38</td>
<td>Resting-state neuropsychological testing: repeatable battery for the assessment of neuropsychological status, trail making test A and B, letter-number sequencing</td>
<td>CLBP disabling compared with CLBP nondisabling</td>
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<td></td>
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<td>↑ right mPFC</td>
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<td>↑ left lateral PFC, Positive correlation between trail making test A (motor speed) and left lateral prefrontal cortical activation at rest</td>
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<tr>
<td>Čeko et al51</td>
<td>Resting-state of cognitive network and DMN longitudinal (6-month follow-up)</td>
<td>Pretreatment compared with HC</td>
<td>CS: M</td>
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<td></td>
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<td>↑ FC between left anterior mid insula and bilateral anterior insula/frontal operculum, bilateral DLPFC, bilateral VLPFC/frontal pole, left SMA/anterior mid-cingulate cortex, PCC/precuneus, left premotor cortex, left PPC, bilateral S1/M1, bilateral temporal, and visual regions</td>
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<td>↑ DLPFC Posttreatment compared with pretreatment (CLBP): ↑ FC between left anterior mid insula and left frontal operculum/anterior insula, right DLPFC, left VLPFC, right SMA/mPFC, PCC/precuneus, right temporal and visual regions</td>
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<td>↑ FC between DLPFC and posterior mid-cingulate cortex, bilateral S1/M1, right premotor cortex, right PPC, left cerebellum, left temporal, bilateral fusiform, bilateral visual</td>
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<td>↑ connectivity of insula to DLPFC and other TPN and TNN areas were related to treatment-related pain reduction. Partial recovery in bilateral insula connectivity (TPN and TNN areas) and left DLPFC connectivity (to TPN areas) posttreatment</td>
<td></td>
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<tr>
<td>Kong et al41</td>
<td>FC in resting-state before and after pain-inducing exercise manoeuvres</td>
<td>CLBP at baseline (before manoeuvrs) vs. HC:</td>
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<td>↑ FC in left fusiform gyrus, occipital gyrus, right PCC, and inferior parietal gyrus</td>
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<td>↑ FC in right S1 and M1, CLBP after manoeuvrs vs. HC:</td>
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<td>↑ FC in left superior frontal gyrus. After vs. before manoeuvrs (within-CLBP groups):</td>
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<td>↑ bilateral S1 and M1, left superior frontal cortex</td>
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<td>Right inferior parietal lobule, cuneus, middle occipital gyrus. Positive correlation between FC and LBP rating changes at left insula, precuneus, amygdala, and fusiform negative correlation between FC and LBP rating changes at S1.</td>
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TABLE 3. (continued)

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<tr>
<td>Kornelsen et al62</td>
<td>Resting-state</td>
<td>Positive correlations between FC changes and LBP rating changes at left insula and amygdala</td>
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<td>↑ Left angular gyrus, right middle, and inferior frontal gyri, left cingulate gyrus, right inferior frontal gyrus extended into right insula, right DLPFC extending into the anterior insula, left precentral gyrus, and right inferior parietal lobule</td>
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<td></td>
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<td>↑ Right medial frontal gyrus, right precuneus, left supramarginal parietal gyrus, bilateral temporal lobes, left posterior cingulate, and bilateral cerebellum</td>
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<tr>
<td>Loggia et al67</td>
<td>FC in resting-state (ASL) before and after clinical maneuvers or thermal stimulations</td>
<td>↑ DMN connectivity to pgACC, left inferior parietal lobule, right insula. CLBP after maneuvers vs. HC</td>
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<td>↑ FC in DMN-mPFC (including pgACC). Baseline pain positively correlated with connectivity strength between DMN-right insula. Baseline pain negatively correlated with connectivity between DMN-pgACC. Clinical pain at baseline and greater ↑ in maneuver-induced pain was associated with ↑ DMN-right insula connectivity</td>
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<tr>
<td>Pijnenburg et al74</td>
<td>Resting-state</td>
<td>↑ Right middle frontal gyrus, right superior frontal gyrus, and lobule VI of vermis</td>
<td>LM</td>
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<td>↑ Left SMA, left precentral gyrus, lobule IV and V of left cerebellum. In conjunction with performance in STSTS task: CLBP required more time to perform STSTS task</td>
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<td>↑ FC at rest in precentral gyrus and lobule IV and V of left cerebellum was associated with ↑ duration for STSTS task in both HC and CLBP</td>
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<tr>
<td>Tagliazucchi et al78</td>
<td>Spontaneous activity of eight resting-state networks</td>
<td>↑ Orbital part of the middle prefrontal cortex and bilateral angular gyrus</td>
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<td>↑ activity in middle prefrontal and angular gyri correlated with insular cortex</td>
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<td>Tagliazucchi et al79</td>
<td>Resting BOLD event triggered averages</td>
<td>↑ Orbital part of the middle frontal cortex, and thalamus</td>
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<td>Wasan et al87</td>
<td>FC in resting-state (ASL) before and after clinical maneuvers and thermal stimulations. Catastrophizing: PCS</td>
<td>↑ ACC After vs. before maneuvers (within-CLBP groups)</td>
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<td></td>
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<td>↑ Bilateral mPFC, bilateral DLPFC, superior parietal lobules, S1, S2, and M1. Differences in CLBP vs. differences in HC</td>
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<td>↑ Left S1, M1, and superior parietal lobule</td>
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<td>↑ activity in mPFC and insular cortices were associated with higher pain intensity. CLBP had significantly higher PCS scores</td>
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<tr>
<td>Yu et al89</td>
<td>FC in resting-state before and after pain-inducing exercise maneuvers in CLBP vs. HC (only scanned once)</td>
<td>↑ FC between PAG and vmPFC/rACC</td>
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<td>↑ Superior temporal gyrus, and precentral gyrus. After maneuvers, CLBP vs. HC</td>
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<td>↑ FC between PAG and vmPFC/rACC</td>
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<td></td>
<td></td>
<td>↑ Lingual gyrus, superior temporal gyrus, precentral gyrus, dorsal cingulate cortex, posterior insula</td>
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<td>CLBP, after vs. before maneuvers: no significant differences. Negative correlations between pain intensity and PAG-vmpFC/rACC in CLBP after pain-inducing maneuvers. Negative correlation between duration of CLBP and PAG-insula and PAG-amygdala FC before pain-inducing maneuvers</td>
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*Unless otherwise specified.

ACC indicates anterior cingulate cortex; ASL, arterial spin labeling; BDI, Beck Depression Inventory; BOLD, blood-oxygen-level dependent; CH, cohort component; CLBP, chronic low back pain; CS, cross-sectional component; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; FC, functional connectivity; fMRI, functional magnetic resonance imaging; H, high risk of bias; HC, healthy controls; LBP, low back pain; L, low risk of bias; LM, low-moderate risk of bias; M, moderate risk of bias; M1, primary motor cortex; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; Nu, neuropathic group; PAG, periaqueductal gray; PCC, posterior cingulate cortex; PCS, Pain Catastrophizing Scale; PFC, prefrontal cortex; pgACC, pregenual anterior cingulate cortex; PPC, posterior parietal cortex; rACC, rostral anterior cingulate cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SMA, supplementary motor area; STSTS, sit-to-stand-to-sit; TNN, task-negative network; TPN, task-positive network; vmPFC, ventrolateral prefrontal cortex; vmpFC, ventral medial prefrontal cortex.
TABLE 4. Main Findings and Risk of Bias Assessment of fMRI Studies in Event-related fMRI Studies in CLBP Populations

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<tr>
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<tr>
<td>Pain stimulation Baliki et al\textsuperscript{39}</td>
<td>Fixed thermal pain stimulation (baseline: 38°C; peak temps: 47°C, 49°C, 51°C) for 3 durations ranging from 12 to 30 s vs. visual rating task</td>
<td>No significant brain activity differences. Both groups showed activations in thalamus, insula, and S2. ↑ NAc-mPFC connectivity, which was stronger in those with more severe back pain. During visual rating task, no significant phasic change was observed in NAc signal in either group. Tonic phases during painful stimulation correlated negatively with stimulus duration and, following stimulus cessation, correlated negatively with stimulus pain in HC and positively with CBP. No significant differences in mean pain ratings between CLBP and HC groups.</td>
<td>M</td>
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<tr>
<td>Lloyd et al\textsuperscript{64}</td>
<td>CLBP with WS-H vs. CLBP with WS-L vs. HC. Adjusted electrical pain stimulation to highest pain they could withstand (alternating 14 s of painful stimulation and 14 s of rest)</td>
<td>↑ Left inferior parietal cortex ↑ Somatosensory (2 different regions along postcentral gyrus in SI). Used patterns of activity to correctly classified 92.3% of CLBP and 92.3% in HC. No significant difference between stimulation intensity between CLBP and HC group.</td>
<td>H</td>
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</table>
| Giesecke et al\textsuperscript{55} | Fixed mechanical pain stimuli: starting at 0.5 kg/cm\textsuperscript{2} and increasing 0.5 kg/cm\textsuperscript{2} intervals. Adjusted mechanical pain stimuli: 36 stimulations delivered at 20 s intervals at random order | CLBP vs. HC at equal pressure (at 2 kg) ↑ Contralateral SI and S2, inferior parietal lobule, cerebellum, ipsilateral S2. Equal pain intensities (CLBP and HC groups) ↑ Contralateral SI and S2, contralateral inferior parietal lobule, ACC, posterior insula and ipsilateral S2, cerebellum in both CLBP and HC groups (but greater magnitude in CLBP groups) CLBP had ↑ pain sensitivity than HC CLBP showed greater increased magnitude of activation in equal pain condition when compared with equal pressure conditions. At equal pressure, CLBP rated higher pain than HC. At equal pain intensity, pain pressure was lower in the CLBP than the HC group When VAS = 3 ↑ right insula, bilateral PCC, primary motor cortices, right PMA and right SMA (HC showed right PMA only). When VAS = 5 ↑ activation in right PMA and right thalamus. Both groups had activation in right insula, bilateral PCC, right PFC, right SMA (larger clusters in CLBP). CLBP had lower pain thresholds and larger unpleasantness at VAS = 3 and 5. No significant differences in the amplitude of BOLD signals but CLBP showed differences in the size of activation clusters No differences between WS-H and HC No differences between WS-H and HC. ↑ Left superior parietal lobe, left extrastriate visual cortex, including fusiform gyrus ↑ activation and right thalamus. Both groups had activation in right insula, bilateral PCC, right PFC, right SMA (larger clusters in CLBP). CLBP had lower pain thresholds and larger unpleasantness at VAS = 3 and 5. No significant differences in the amplitude of BOLD signals but CLBP showed differences in the size of activation clusters No differences between WS-H and HC No differences between WS-H and HC. ↑ Left superior parietal lobe, left extrastriate visual cortex, including fusiform gyrus ↑ Right posterior (retrosplenial) cingulate, extrastriate cortex, left inferior parietal lobule, extending to superior parietal lobule. No significant differences between mean lumbar stimulation tolerance threshold between WS-L, WS-H, and HC groups. WS-H group had significantly higher scores for the catastrophizing subscale of the Pain Coping Strategies Questionnaire and depression subscale of HADS but not the other measures than the WS-L group. Significant negative correlation between the magnitude of the BOLD responses and catastrophizing subscale of Pain Coping Strategies Questionnaire in the WS-L group. ↑ Right amygdala/parahippocampal gyrus, bilateral temporal pole, cerebellum Noxious thermal vs. warm stimuli (within WS-H group) ↑ Bilateral inferior frontal gyrus ↑ Noxious thermal vs. warm stimuli (within WS-L group) ↑ Bilateral inferior frontal gyrus ↑ Noxious thermal vs. warm stimuli (within WS-L group) (Continued)
### TABLE 4. (continued)

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<td>Stancak et al(^{77})</td>
<td>SCS (electrical stimuli) vs. heat pain vs. simultaneous SCS and heat pain in CLBP group only.</td>
<td>Painful heat stimulation from 43 to 46-49°C for 36 s and returning to baseline (32°C) for 36 s rest period</td>
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<td>Vachon-Presseau et al(^{82})</td>
<td>Adjusted thermal pain stimulation at pain intensity of 75/100, adjusted warm stimulation (control) and baseline at 38°C.</td>
<td>CBP and HC activity (nonsignificant)</td>
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<tr>
<td>Vachon-Presseau et al(^{81})</td>
<td>Adjusted thermal pain stimulation at pain intensity of 75/100, adjusted warm stimulation (control) and baseline at 38°C.</td>
<td>Thermal vs. warm conditions in CBP and HC (nonsignificant)</td>
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<tr>
<td>Vachon-Presseau et al(^{84})</td>
<td>Adjusted thermal pain stimulation at pain intensity of 75/100, adjusted warm stimulation (control) and baseline at 38°C.</td>
<td>Activation in both CBP and HC groups (nonsignificant)</td>
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<td>Task-related studies</td>
<td>Spontaneous pain-rating task (CLBP only) and thermal stimulation in HC</td>
<td>Spontaneous pain ratings (CBP only): sustained high pain resulted in ↑ activity in mPFC (including rostral anterior cingulate).</td>
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<tr>
<td>Baliki et al(^{40})</td>
<td>Simple visual attention task depression: BDI Anxiety: BAI</td>
<td>↑ mPFC during task. No differences in task performance between CLBP and HC. mPFC activity was negatively correlated with the task.</td>
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<td>Barke et al45</td>
<td>Viewing images of aversive movement, neutral movements, general fear-inducing images, neutral images, and spider images in CLBP (low and high fear-avoidance), HC and spider phobic participants</td>
<td>Positive correlation between high-frequency oscillations in mPFC BOLD time course and with pain ratings but not visual ratings No fear-related activations were found in high or low fear-avoidance CLBP patients when viewing aversive movement images. No differences between high and low fear-avoidance CLBP patients or high fear-avoidant CLBP patients and HC. Normal fear-related activations were present in high fear-avoidant CLBP patients when viewing the general fear-inducing images</td>
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<tr>
<td>Berger et al46</td>
<td>Gambling task</td>
<td>No significant differences in FC during gambling task CBP were more impulsive on gambling task than HC</td>
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<tr>
<td>Foss et al53</td>
<td>Spontaneous pain-rating task in CLBP vs. acute thermal pain stimulation vs. imaged back pain</td>
<td>CLBP exhibited significantly different fractal properties during spontaneous back pain compared with thermal and imagined pain</td>
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<tr>
<td>Lloyd et al66</td>
<td>Pain anticipation of pain-inducing leg raise maneuver (green light visual cue = 100% leg raise; yellow = 50%; red = 0%) in CLBP with WS-H vs. CLBP with WS-L Catastrophizing: PCS Beliefs: FABQ Depression and Anxiety: HADS</td>
<td>Red cue vs. at rest (within WS-H group): ↑ anterior intraparietal sulcus, extending into posterior supramarginal gyrus, superior parietal lobe, superior lateral occipital cortex, sensorimotor cortex, extending into posterior cingulate gyrus, SMA. Yellow cue vs. red cue (within WS-L group) ↑ posterior supramarginal gyrus, extending into angular gyrus WS-H vs. WS-L during red cue: ↑ precentral and posterior cingulate gyrus, superior parietal lobe, extending into S1 and occipital pole WS-H reported higher anxiety, depression, catastrophizing, and fear-avoidance beliefs than WS-L. Positive covariance between anxiety subscale of the HADS and the BOLD responses in right insula, right frontal pole, pregenual ACC, and paracingulate gyrus between the WS-H and WS-L groups in response to the green vs. yellow cue conditions. Positive covariance between the ruminative subscale of PCS and the BOLD response in the left superior parietal lobe/prefrontal cortex, extending to superior division of the lateral occipital cortex bilaterally and intracalcarine cortex between the WS-H and WS-L groups in green vs. yellow cue conditions. Ruminative subscale of PCS also positively covaried with group differences in right prefrontal cortex, left inferior parietal lobe and left hippocampus in response to the green visual cue as well as the right premotor and sensorimotor cortices, posterior division of right supramarginal gyrus and cuneal cortex ↑ Right DLPFC, dorsal ACC, bilateral superior parietal cortex, bilateral precentral cortex, left postcentral cortex, paracingulate cortex, bilateral precuneus, left amygdala. Negative correlation between back pain intensity and activation of right PFC during MSIT in CLBP. Response accuracy was worse in CLBP when task was complex (interference trials)</td>
<td>H</td>
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<tr>
<td>Mao et al71</td>
<td>MSIT</td>
<td>↑ FC of NAc-mPFC predicted pain persistence ↑ FC between NAc with basal ganglia at baseline and follow-up ↑ FC between NAc with insula at follow-up and over time (ie, SBPp follow-up &gt; SBPp baseline) ↑ FC between NAc and mPFC at baseline and follow-up</td>
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<tr>
<td>Vachon-Presseau et al83</td>
<td>Response to images of noxious agent applied to right hand and foot, and facial expressions of pain, and thermal pain stimulation</td>
<td>No differences between in vicarious brain activity. Positive correlation in right insula activity with patients’ expressiveness and perceived pain intensity in images</td>
<td>H</td>
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<tr>
<td>Vrana et al86</td>
<td>Motor imagery task (presented video clips showing everyday activities)</td>
<td>↑ Left SMA, and right superior temporal sulcus. No significant differences in STAI between CLBP and HC groups</td>
<td>M</td>
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<tr>
<td>Longitudinal studies Baliki et al42</td>
<td>Followed-up SBP group: SBPp vs. SBPr (1 y). Spontaneous back pain-rating task Pain: SF-MPQ</td>
<td>↑ FC of NAc-mPFC predicted pain persistence ↑ FC between NAc with basal ganglia at baseline and follow-up ↑ FC between NAc with insula at follow-up and over time (ie, SBPp follow-up &gt; SBPp baseline) ↑ FC between NAc and mPFC at baseline and follow-up</td>
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<th>Main Findings (CLBP Compared With Control Groups*)</th>
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<td>Hashmi et al⁵⁸</td>
<td>SBP vs. HC vs. CBP followed-up SBP: SBPp vs. SBPr (1 y). Spontaneous back pain rating vs. control visual rating task mood: PANAS depression: BDI</td>
<td>SBPp had negative correlations of insula with DLPFC and posterior cingulate † FC in insula, DLPFC and precuneus positively correlated with insula GM density and negatively with pain intensity. Higher affect dimension of SF-MPQ score in SBPp than SBPr at baseline. At follow-up, SBPr showed decreased scores in all measures except BDI and PANAS positive scores. The number of positive NAc links correlated with affect dimension of SF-MPQ at baseline and follow-up</td>
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<td>Petre et al⁷³</td>
<td>Smokers vs. nonsmokers in SBP vs. CBP vs. HC followed-up SBP: SBPp vs. SBPr (1 y)</td>
<td>SBPp consistently had ↑ FC in dorsal mPFC-amygdala-NAc network compared with other networks and over 56 wk following-up 3 y: SBPp vs. SBPr (1 y).</td>
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<td>Seminowicz et al⁷⁶</td>
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<td>Vachon-Presseau et al⁴⁵</td>
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*Unless otherwise specified.

ACC indicates anterior cingulate cortex; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BOLD, blood-oxygen-level dependent; CBP, chronic back pain; CH, cohort component; CLBP, chronic low back pain; CS, cross-sectional component; DLPFC, dorsal lateral prefrontal cortex; DMN, default mode network; FABQ, Fear-Avoidance Beliefs Questionnaire; FC, functional connectivity; IMRI, functional magnetic resonance imaging; HADS, Hospital Anxiety and Depression Scale; H, high risk of bias; HC, healthy controls; HG, hippocampal gyrus; L, low risk of bias; LM, low-moderate risk of bias; M, moderate risk of bias; M1, primary motor cortex; MPFC, medial prefrontal cortex; MPQ, McGill Pain Questionnaire; MSIT, multisource interference task; NAc, nucleus accumbens; OFC, orbital frontal cortex; PANAS, Positive and Negative Affect Schedule; PCC, posterior cingulate cortex; PCS, Pain Catastrophizing Scale; PFC, prefrontal cortex; PMA, premotor area; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SBP, subacute back pain; SBPp, persistent subacute back pain; SBPr, recovered subacute back pain; SCS, spinal cord stimulation; SF-MPQ, Short Form McGill Pain Questionnaire; SMA, supplementary motor area; STAI, State-Trait Anxiety Inventory; temps, temperatures; VAS, visual analog scale; WS-H, high pain behavior (according to Waddell signs); WS-L, no or low pain behavior (according to Waddell signs).
TABLE 5. Main Findings and Risk of Bias Assessment of Intervention fMRI Studies in CLBP Populations

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<td>Baliki et al38</td>
<td>Spontaneous pain-rating task and visual task before and after 2 wk of treatment (5% lidocaine patches) in CBP</td>
<td>Before treatment (pain—visual task) ↑ mPFC, rostral ACC, superior frontal gyrus, NAc, inferior temporal gyrus, PCC. After treatment vs. before ↑ Middle temporal cortex. Significant decrease in pain after treatment mPFC and rostral ACC at level of genu encoded pain intensity in CBP</td>
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<td>Hashmi et al56</td>
<td>Spontaneous pain-rating task and visual task before and after 6 h, and 2 wk of treatment (5% lidocaine patches treatment vs. placebo) in CBP only</td>
<td>No group differences in pain intensity, sensory, or affective qualities of pain or pain-related brain activation. Spontaneous pain ratings correlated with activity in mPFC, extending from medial frontal pole to genual ACC. Treated CBP showed significantly greater decrease in pain compared with untreated CBP group 50% of overall patients (both lidocaine and placebo) reported &gt; 50% decrease in pain = placebo effect</td>
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<td>Hashmi et al57</td>
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<td>Li et al63</td>
<td>Resting-state before and after 4 wk after treatment (acupuncture) in CLBP and HC groups</td>
<td>CLBP before treatment vs. HC ↓ DLPFC, mPFC, ACC, precuneus. After vs. before, treatment ↑ DLPFC, mPFC, ACC, precuneus. Reductions in clinical pain which correlated with increases in DMN connectivity</td>
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ACC indicates anterior cingulate cortex; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CBP, chronic back pain; CBPd, decreasing CBP; CBPp, persistent CBP; CLBP, chronic low back pain; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; fMRI, functional magnetic resonance imaging; H, high risk of bias; HC, healthy controls; L, low risk of bias; LM, low-moderate risk of bias; M, moderate risk of bias; mPFC, medial prefrontal cortex; MPQ, McGill Pain Questionnaire; NAc, nucleus accumbens; PCC, posterior cingulate cortex.

FIGURE 1. PRISMA flowchart showing systematic study selection.
the dorsolateral prefrontal cortex (DLPFC),59,75,76 insula,41,54 temporal lobes,41 cuneus,70 thalamus,35 medial prefrontal cortex (mPFC),54 posterior cingulate cortex (PCC),47 as well as the precentral and postcentral regions,69,70 in CLBP groups compared with controls. Five high risk of bias studies observed similar findings with decreased GM in the DLPFC,59,75,76 insula,6 temporal lobe,69,75,76 cuneus,80 thalamus,59 and precentral and postcentral regions.69 On the contrary, 2 studies observed increased GM volume in the DLPFC, temporal lobe,40 and the thalamus,52 although these studies were of high risk of bias. Furthermore, mixed results in the cingulate cortex76,68,76 and S1,75,76,80 were observed in a number of high risk of bias studies. Furthermore, within-group comparisons in 1 study did not find any significant GM volume differences between neuropathic and non-neuropathic CLBP groups.55

There were 4 longitudinal studies (2 moderate and 2 high risk of bias) that observed GM changes over time. The 2 moderate risk of bias studies found increased GM in areas including the basal ganglia,69 inferior frontal gyrus, caudal pons, and the cingulate cortex,88 as well as decreased GM in the hippocampus,69,88 posteroventral pons, and medial orbital gyrus88 in CLBP patients following treatment. Of the high risk of bias studies, 1 found increased GM in the DLPFC following treatment in CLBP patients.76 The other study observed significant decreased global as well as regional GM volume in the striatum, insula, S1, and the primary motor cortex (M1) as subacute back pain persisted (SBPp) after 1 year.42 Overall, 10 of the 15 studies, including 2 low-moderate risk of bias studies, found decreased global or regional GM in CLBP groups. These findings show that there are specific regions that consistently show decreased GM volumes, despite the risk of bias assessments. The longitudinal studies also demonstrate a degree of recovery in GM volume following treatment.

White Matter (WM)

There were a total of 8 studies that explored changes in structural WM (Table 2) where 1 study had low-moderate risk of bias, 51 one study had moderate risk of bias,69 5 studies had high risk of bias,69,70,72,82 and 1 study with a cross-sectional and cohort component was of moderate and high risk of bias, respectively.51 Of these studies, 2 studies (1 moderate and 1 high risk of bias) did not find any significant differences in global WM between CLBP patients and controls,51,76 whereas Ivo et al.69 (high risk of bias) found significantly reduced global WM in the CLBP group. Although 1 study with moderate risk of bias found no significant differences in regional WM in the left insula,51,76 2 studies (1 low-moderate and 1 high risk of bias) found decreased WM volume in cingulate superior to middle corpus callosum,47 and anterior limb of the internal capsule.68 Furthermore, 2 studies (1 moderate and 1 high risk of bias) compared within-CLBP groups in those who were disabled and those who were not disabled by their LBP. They found that the disabled CLBP group had reduced WM integrity in the splenium of the corpus callosum as well as increased WM hyperintensities in the left hemisphere, including the anterior thalamic radiation, lower cingulate, inferior longitudinal fasciculus, and superior longitudinal fasciculus compared with the nondisabled CLBP group.49

Finally, 2 longitudinal studies found that CLBP patients exhibited increase in WM integrity in the left insula following treatment51 and denser WM connections in the dorsal mPFC-amygdala-nucleus accumbens (NAc) network in SBP groups increased the likelihood of developing persistent back pain54 but these studies had high risk of bias. Overall, 7 of the 8 studies found changes in WM properties in CLBP groups compared with controls. However, these results should be approached with caution as various methodologies have been used with 6 of the studies, as well as the cohort component of another study, obtaining high risk of bias assessments.

Resting-state Studies

A total of 14 studies examined functional connectivity during resting-state in CLBP groups, predominantly in the default mode network (DMN). Of these studies, 1 study had low-moderate risk of bias,72 6 studies had moderate risk of bias,40,46,61,62,67,89 6 studies that had high risk of bias,43,44,48,79,78,87 and 1 study, with a cross-sectional and cohort component, was of moderate and high risk of bias, respectively.51 Their results are presented in Table 3. There were 6 studies with low to moderate risk of bias that showed increased brain activity in CLBP groups within various DMN areas including the superior, middle, and inferior regions of the frontal gyrus,42,74 cingulate cortex, inferior parietal gyrus,61,62 precentral gyrus,74,89 angular gyrus,62 mPFC,40 as well as increased DMN functional connectivity to the insula, pregenual anterior cingulate cortex (ACC), and inferior parietal lobule67 compared with controls. Increased activity in the angular gyrus,78 orbital region of the middle frontal cortex,73 and the mPFC54 in CLBP groups was also observed in high risk of bias studies. On the contrary, 2 moderate risk of bias studies observed decreased brain activity in the cingulate cortex,62 and precentral gyrus,74 whereas 2 high risk of bias found decreased ACC activity79 and reduced mPFC connectivity to posterior areas of the DMN.43 In addition, 3 studies (1 low-moderate and 2 moderate risk of bias) found decreased DMN brain activity in CLBP groups areas including the S1 and M1,61 supramarginal parietal gyrus, temporal lobes,62 and the supplementary motor area (SMA)43 compared with controls. Furthermore, within-CLBP group comparisons found increased mPFC and decreased lateral prefrontal cortex in the disabled CLBP group compared nondisabled CLBP group in a high risk of bias study.48

Two studies explored the resting-state modular network connectivity (ie, the integrated connectivity of neurons that define the DMN) and found that CLBP patients differed to controls. One study with moderate risk of bias, found that CLBP patients had increased connectivity between the NAc and subcortical regions, whereas controls had more between the NAc and frontal cortical areas.46 Changes in the resting-state connectivity were observed in the frontal and temporal regions, the sensorimotor cortex, basal ganglia and ACC, resulting in a change in the overall network in a high risk of bias study.44

Three moderate risk of bias studies61,67,89 and 1 high risk of bias study89 compared resting brain activity before and after clinical pain-inducing maneuvers. Compared with controls, the moderate risk of bias studies found CLBP groups showed decreased functional connectivity in the superior frontal gyrus,51 and between the DMN and mPFC,67 as well as increased superior temporal gyrus, precentral gyrus, dorsal cingulate cortex, and posterior insula activity89 after the maneuvers. Furthermore, although Yu et al.69 did not find any significant differences before and after the maneuvers, Kong et al.61 observed decreased activity in the inferior parietal lobule, cuneus, and middle occipital gyrus, as well as increased activity in S1, M1, and superior frontal cortex. Increased activation in the S1 and M1 was also observed in a study with high risk of bias.57

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Therefore, of the 14 resting-state studies, 8 studies, including 5 with low to moderate risk of bias, observed increased activity or connectivity in areas within the DMN in CLBP groups.

**Event-related Studies**

**Noxious Stimulation Studies**

Ten studies explored differences in nociceptive pain processing in CLBP groups, using noxious thermal, electrical, and mechanical stimulation. The results are presented in Table 4. Six of the 10 studies, including 1 low-risk of bias study, 6 moderate risk of bias studies, and 1 high risk of bias study, did not observe significant differences in brain activity between CLBP groups (including CLBP with high pain behaviors based on Waddell sign, WS-H in 1 study) and control groups during noxious stimulation. However, the 5 studies with low to moderate risk of bias observed activation in common areas including the thalamus, insula, S1, S2, parietal operculum, mid-cingulate cortex, and M1, as well as increased activity in the inferior temporal cortex. Similar results were observed in the high risk of bias study in the thalamus, insula, and the S1. Only 3 studies (1 low-moderate risk and 2 high risk of bias) observed significantly greater activation in the SMA, insula, PCC, and inferior parietal cortex, in CLBP groups, and superior parietal lobe only in CLBP patients that exhibited low pain behaviors (WS-L; based on Waddell sign) during noxious stimulation compared with controls. Similarly, 6 of these studies did not find any significant differences in reported pain ratings or thresholds between CLBP and control groups in both fixed and adjusted analyses. Another 2 studies found that the pain threshold for CLBP groups was significantly lower than the control groups.

Moreover, within-CLBP group differences were compared in 2 studies with low-moderate risk of bias. They found that, compared with the CLBP WS-L group, CLBP patients WS-H had decreased activity in the posterior retrosplenial cingulate cortex and inferior parietal cortex during noxious stimulation as well as increased activity in the inferior frontal gyrus, superior mid-temporal gyrus, and amygdala during noxious stimulation (compared with warm stimuli). Importantly, both studies also reported no significant differences in pain threshold between WS-H and WS-L groups, suggesting that the differences in brain activity may be related to the observed pain behaviors (ie, Waddell signs) in CLBP. Finally, 1 high risk of bias study observed that there was increased activity in the inferior temporal cortex and cerebellar cortex in CLBP patients during simultaneous spinal cord and heat nociception stimulation compared with when each stimulation occurred alone. Overall, 6 of the 10 studies, 5 of which were of low to moderate risk of bias, did not find significant differences, between CLBP and healthy controls; however, identified several consistent areas that activated following nociceptors, despite their risk of bias.

**Task-related Studies**

There was a total of 16 studies (9 moderate and 7 high risk of bias) that looked at brain processes during various external tasks in CLBP patients (Table 4). Seven of these studies examined brain activity while participants were continuously rating the spontaneous fluctuations of their back pain (ie, back pain in the absence of an external stimuli) with 3 moderate risk of bias studies and 4 high risk of bias studies. Of the cross-sectional moderate risk of bias studies, they found that CLBP patients had activation in the mPFC and when compared with SBP patients, exhibited increased mPFC and amygdala and decreased insula and thalamus activity during the spontaneous pain-rating task. Furthermore, a high risk of bias study showed that CLBP patients experiencing spontaneous back pain exhibit significantly distinct fractal properties compared with during thermal noxious stimuli as well as imagined pain in controls. A longitudinal study with moderate risk of bias observed that increased activation in the amygdala, and basal ganglia when SBP persisted after a year (SBPp). There were 3 other longitudinal studies, that found increased NAc connectivity to the basal ganglia and mPFC but decreased connectivity to the insula in SBP compared with SBP patients who recovered (SBPp) groups; however, all had high risk of bias.

Of the 16 task-related studies, there were only 3 studies that examined brain activity during cognitive tasks. One of the studies (moderate risk of bias) used a monetary gambling task but did not observe any significant brain activity differences between the CLBP and control groups. The other 2 studies (1 moderate and 1 high risk of bias) used an attention task, the multisource inference task. They showed that CLBP groups had decreased activation in the DLPFC, amygdala, dorsal anterior, and paracingulate cortex, superior parietal cortex, precuneus, and the precentral and postcentral cortices compared with controls. There were 2 studies with moderate risk of bias that explored the brain activity during a simple visual task. They found that CLBP groups demonstrated increased activity in areas within the DMN including the mPFC and hippocampus compared with controls. Interestingly, the longitudinal component of the Muto et al study showed that the SBP group had decreased hippocampal connectivity to mPFC and cingulate cortex compared with SBPp group. Finally, there were 4 studies (2 moderate and 2 high risk of bias) that used other various tasks. Two studies (1 moderate and 1 high risk of bias) did not observe apparent differences between CLBP and control groups when viewing pain-evoking images. The third study, with moderate risk of bias, used a motor imagery task and found CLBP patients exhibited decreased activity in the SMA and superior temporal sulcus compared with controls. Finally, a study using a pain anticipation task found increased activation in the precentral gyrus, PCC and superior parietal lobe in CLBP with pain behaviors (WS-H) compared with CLBP without (WS-L), although it had a high risk of bias. Overall, 13 of the 16 studies, including 9 moderate risk of bias studies, demonstrated significant differences in brain activity during various external tasks in CLBP groups.

**Intervention Studies**

There were 4 studies that examined the effects of various treatments on brain activity in CLBP patients with 1 study with low-moderate risk of bias, 2 studies with moderate risk of bias, and 1 study with high risk of bias (Table 5). Of the moderate risk of bias studies, 1 study showed that the functional connectivity between mPFC and the insula predicted the probability of a placebo response; whereas the other study did not report any significant differences in brain activity before and after the use of lidocaine. Instead, they reported a 50% placebo effect in the overall participant group, regardless of the intervention type. Increased activity in the middle temporal cortex was found in a low-moderate risk of bias study after an intervention. Finally, the high risk of bias study observed increased connectivity in CLBP groups in various regions of the cingulate cortex following intervention. Overall 3 of the 4
identified studies, regardless of their risk of bias but including the low-moderate risk of bias study, showed changes in connectivity that might suggest recovery in CLBP individuals with the various interventions examined.

**Relationship Between Brain Changes, and Emotional and Cognitive Measures**

Across the 58 selected studies in this review, 15 explored the correlational relationships between brain changes, and emotional, cognitive and behavioral measures. These include 8 MRI studies examining structural brain changes and volumes, including 2 low-moderate risk of bias studies, 3 moderate risk of bias studies, and 3 high risk of bias studies. Of these 8 studies, 4 did not find any significant relationships with depression and anxiety measures, whereas another study only observed significant negative correlations between anxiety and anterior cingulate and left lingual gyrus GM density but no significant correlations with depression. Another 2 studies did not find any significant associations between GM volumes and neuropsychological assessment tests. One study observed a significant negative correlation between affect dimension of the short form of the McGill Pain Questionnaire (SF-MPQ) with DLPFC GM density, and also predicted DLPFC GM change in both neuropathic and non-neuropathic CLBP group. Furthermore, the lateral ventricle size and change in lateral ventricle size showed a positive correlation with the affective dimension of the SF-MPQ.

Two of the 15 studies, both of high risk of bias, explored the relationship between resting-state, and emotional and cognitive measures. One study did not find any significant correlations between functional connectivity and depression. The other study observed a positive correlation between the performances in Trail Making test A and the left lateral prefrontal cortex activity.

Another 2 of the 15 studies, with a low-moderate risk of bias studies explored the relationship brain activation during noxious stimulation and between emotional and cognitive measures in a CLBP group with high pain behaviors (WS-H) compared with another with low pain behaviors (WS-L). One study found there was a significant negative correlation between the magnitude of the blood-oxygen-level dependent (BOLD) response and the catastrophizing in the WS-H group. The other study found a correlation between the percentage of change in BOLD responses with the anxiety and catastrophizing scores in the WS-H group but no significant relationships in the WS-L group.

The remaining 4 of the 15 studies, utilized task-related functional MRI (fMRI) studies. Two of the studies (moderate risk of bias), using simple visual tasks, did not observe any significant relationships between brain activity and depression or anxiety. A high risk of bias study looking at spontaneous back pain fluctuations found a significant positive correlation between the number of NAc connections with the affect dimension of the SF-MPQ in SBPp groups. The fourth study with high risk of bias used a pain anticipation task and found anxiety and rumination scores positively covaried with the BOLD responses in multiple brain areas when comparing the green versus yellow cue conditions, green versus red cue conditions as well as in response to the green cue. Finally, 1 intervention study (moderate risk of bias) observed a positive correlation between the affect dimension of the SF-MPQ and the brain connectivity between the dorsomedial prefrontal cortex and anterior insula.

**DISCUSSION**

**Overall Findings**

This review aimed to examine MRI evidence of structural and functional brain changes observed in individuals with CLBP and identify how these changes may be associated with emotional and cognitive processes in CLBP. We found that there were widespread brain changes in CLBP groups compared with healthy, pain-free controls, although this was not present in all studies. These alterations were seen across both structural and fMRI protocols. Structural MRI studies generally showed decreased GM volume compared with controls. There was some evidence of reduced WM structures in CLBP individuals; however, there were only a limited number of studies. In fMRI studies, individuals with CLBP did not show significant differences in brain activation during noxious stimulation, although, they did have lower pain thresholds compared with controls. Furthermore, as the brain activity during spontaneous back pain did not activate the areas of the pain matrix typically seen in noxious pain, it supports the notion that chronic pain may not be caused by nociceptive process. Instead, CLBP groups exhibited altered functional connectivity during resting-state, particularly in the DMN, as well as during various attention tasks. There have only been 3 studies explicitly looking at cognitive function, specifically in attention and decision-making in external tasks, whereas 15 studies examined the correlational relationship between the brain changes observed and emotional, cognitive, and behavioral measures in CLBP. Furthermore, 56% of the selected studies reported low to moderate risk of bias based on stringent criteria, indicating relatively sound studies. Taken together, this review therefore demonstrates widespread brain changes in both structural and fMRI studies; however, there is a lack of fMRI studies specifically examining the emotional and cognitive processes that are associated with CLBP, even though they have been shown to be important in the chronic pain experience.

**Beyond Nociception: Chronic Nociception**

Research has clearly established that pain is comprised sensory, emotional, and cognitive components. Despite this review highlighting extensive brain changes in CLBP, significant differences during noxious stimulation were not generally observed between CLBP and healthy control groups. These contrasting findings suggest that sensory pain processes in nociception remain intact in CLBP patients. Interestingly, brain activity during spontaneous fluctuations of back pain did not exhibit activation of typically identified pain matrix areas. Instead, there were several studies that observed increased activity in the mPTC, an area involved in emotional processes, such as processing negative emotions, reappraisal, self-referential thoughts, as well as the self-regulation of emotions that influences pain perception of acute noxious stimuli. Furthermore, a direct comparison between nociceptive and spontaneous pain showed distinct networks with no overlap in brain regions that showed nociceptive pain was associated with insula activity, whereas spontaneous back pain correlated with the mPTC. Taken together, this might suggest that the spontaneous pain experienced in CLBP may be driven by emotional processes. Indeed, recent research has demonstrated behavioral, emotional, and cognitive deficits in CLBP. However, there has been an absence of studies exploring the underlying brain physiology that may explain the altered emotional and cognitive processes.
Implications on Understanding Mechanisms Underpinning Emotional and Cognitive Processes in CLBP

There are limited studies in the current literature that have used MRI techniques to explore the specific emotional and cognitive processes that may be affected in CLBP; however, this review may indicate some of the potential networks involved. Here, we suggest that CLBP may be associated with disrupted functional connectivity in the DMN. The DMN refers to a network of brain areas, consisting primarily of the mPFC, precuneus PCC, and the inferior parietal lobule, that are active during resting-state (ie, when an individual is not engaged in any externally focused tasks). This network typically deactivates as individuals shift their cognitive resources to externally focused tasks or their environment. Although previously thought to be a passive network, recent studies have shown that the DMN is involved in various internal or self-referential thought processes such as recalling episodic or semantic information, personal introspection, planning for the future, as well as the cognitive assessment and regulation of emotions (ie, appraisal and reappraisal). Self-regulation of emotions is an important process in the perception of noxious pain as well as coping and managing the negative effect of pain.

Therefore, altered DMN connectivity may reflect impaired self-regulation processes necessary to cope with CLBP.

Indeed, the findings from this review support a previous study by Woo et al, who observed a distinct network, including the mPFC, involved in self-regulation processes that influence nociceptive pain perception. Specifically, Woo and colleagues propose that there is an “evaluation” functional network that interacts with the pain matrix to produce the overall pain experience. Taken together with the findings of the current review, the DMN may be involved in the evaluative network that becomes impaired in CLBP (depicted in Fig. 2).

The disruption of connectivity in the DMN may also interrupt the function of other interconnected networks, including the cognitive networks involved in externally focused tasks. There were task-related studies from this review that found inefficient deactivation of the DMN, as well as reduced activation of the network involved in executive function during attention tasks. Interestingly, a recent study observed the opposite effect during resting-state with increased connectivity between subregions of the amygdala and the central executive network but reduced amygdala-DMN connectivity in CLBP. The increased central executive network connectivity at rest also correlated with pain catastrophizing, whereas the DMN did not show significant associations with catastrophizing, depression, or anxiety. Taken together, this may reflect the inability to engage in the appropriate mental resources and networks during internal and external processes in CLBP. However, the current literature in this review presented mixed findings where there was no consistency in the relationship between the observed brain changes, and emotional and cognitive processes assessed through task performance and self-report measures. For example, some studies found that CLBP groups showed altered brain connectivity, although, there were no differences in task performance differences, whereas others showed task performance differences but no functional brain changes compared with controls. We also reported contrasting findings where a number of studies who have found significant correlations between structural GM density, functional connectivity during tasks, and BOLD responses during noxious stimulation with various negative affect and catastrophizing measures. Although, other studies did not find any significant associations in structural brain volumes, resting-state, or tasks with behavioral measures. Overall, these findings demonstrate our understanding of the implications of brain changes on emotional and cognitive processes in CLBP remains unclear. Therefore, the relationship between cognitive function and brain activity as well as the degree of interaction between the DMN and other cognitive networks needs to be determined.

Theoretical Implications on Neuromatrix of Pain

This review may have some implications on the theoretical understanding of the Neuromatrix Theory of pain and the related pain matrix areas involved. As spontaneous back pain and acute nociceptive pain exhibit different patterns of brain activity, it may indicate that the sensation of pain is not exclusively produced by activation of the pain matrix. In addition, other studies have demonstrated that other nonpainful sensory stimuli can also produce a pain matrix response, suggesting the pain matrix is not exclusively for pain. Instead, there may

![FIGURE 2. Chronic low back pain is associated with the activation of common regions of the default mode network (black) rather than the pain matrix areas involved in nociception (white). ACC indicates anterior cingulate cortex; IPL, inferior parietal lobule; mPFC, medial prefrontal cortex; MTL, medial temporal lobe (including hippocampus); PCC, posterior cingulate cortex.](www.clinicalpain.com)
be another distinct evaluative network, in addition to the pain matrix that has the ability to produce the pain experience which demonstrates that the brain regions in pain may be more extensive than previously thought. Furthermore, although spontaneous back pain in CLBP may not be a nociceptive process, it may be possible for sensory input to influence the CLBP experience. Sustained postural activity, such as prolonged sitting, has been found to exacerbate some types of CLBP. However, further research would be required to understand how sensory processes may contribute to the CLBP experience. Therefore, the pain matrix may interact with the evaluative network that influence both the inputs and outputs of pain processes and it is important to further explore the role of this network in CLBP.

Limitations

One of the major limitations of the current literature was the absence of studies exploring specific emotional and cognitive processes that may be contribute to or influence CLBP, despite their importance in pain. Furthermore, although the current evidence does support the involvement of emotional and cognitive processes, it is likely that there is also large interindividual variability in terms of their contribution. Between individuals, emotional and cognitive processes may differ according to age, sex, and psychosocial factors. For example, studies have shown that normal aging results in changes in the structural and functional properties of the brain that are associated with changes in cognition. In addition, neuroimaging studies have indeed found that interindividual factors are associated with differences in brain activity during the perception of pain, although, these studies have largely investigated healthy populations. However, other studies have reported individual differences within chronic pain groups, in terms of pain coping strategies, subjective mood, perceived health, and emotional processing in self-report measures. Thus, it is likely that differences in the findings presented here may be impacted by interindividual variability within and between study samples.

In addition, there is substantial variability in the different MRI methodologies used in the studies presented within this review. For instance, new equipment and techniques for data acquisition have been introduced over time in addition to changes in data analyses approaches. This has led to differences in how data have been acquired or analyzed across the studies presented here. For example, acquiring scans on a 1.5 T MRI scanners compared with 3 T scanners may include differences in sensitivity, signal-to-noise ratios as well as spatial and spectral resolution. Furthermore, the type of data analyses used (ie, whole-brain and region of interest) may impact the reported results. For instance, whole-brain analysis allows an exploratory approach that can identify new regions involved in a certain process. However, it may be at risk of type I errors due to the increased number of multiple comparisons and thus, corrections. Alternatively, region of interest analysis is often a hypothesis-driven approach and has a smaller number of comparisons, and therefore increased statistical power, yet it may not detect potentially new areas involved outside the regions of interest. Although comparing the various imaging parameters and data analyses are beyond the scope of this review, it is important to note their potential influence in the results presented within this review.

Finally, while our review presents a body of work linking CLBP to structural and functional brain changes, the causality between the 2 cannot be clearly determined. As the majority of the studies were cross-sectional designs, data are only collected at a single timepoint and therefore, difficult to determine the order of events (ie, CLBP or brain changes). The majority of the longitudinal studies in this review predominantly examined the effects preintervention and postintervention in CLBP groups. Only 5 studies were observational studies that explored brain changes over time, however, they were all in SBP samples. Therefore, these studies demonstrated that there were brain changes associated with the chronicity of preexisting pain. However, it remains unclear whether there are underlying structural and functional brain abnormalities apparent before the onset of pain and thus, contribute to its development.

Other limitations include that the tasks used in the fMRI studies of this review were generally simple tasks. The lack of differentiation between CLBP and control groups in task performance may be due to the simplicity of the task given, as 1 study found performance declined in individuals with CLBP as the task became more complex, although, further investigations are needed. The definition of CLBP also varied between the selected studies. It is important to distinguish differences in duration and cause of CLBP as it may influence brain changes differently; however, these differences were not clearly established in the studies included in this review. Finally, to assess risk of bias we used a tool adapted from the Cochrane collaboration which applies a stringent scoring system (ie, studies needed to obtain a “low” assessment for all criteria to be considered low risk) and as a result the majority of selected studies in this review were rated moderate to high risk of bias.

Future Studies

There are several avenues future research can pursue to further our understanding of the brain in CLBP. Studies need to investigate the specific emotional and cognitive processes affected in CLBP, particularly during complex tasks that target functions associated with the DMN, such as self-regulation of emotion. These studies should also investigate how brain changes may affect the various aspects of pain (ie, pain intensity vs. pain unpleasantness) as well as the ability to shift to the appropriate neural networks from resting-state to externally driven tasks. Future research should also investigate the potential interindividuality, as well as specifically explore the impact of age, sex, and biopsychosocial factors on cognitive and emotional processes that may influence CLBP using neuroimaging techniques. Longitudinal studies will also help establish the causal relationship between brain changes and CLBP to determine if psychological interventions are possible as an effective treatment. Developing effective coping strategies may result in better self-regulation processes to cope with persistent pain. In addition, these results of studies can be further validated by recruiting a larger sample size, particularly in fMRI studies to increase statistical power.

Furthermore, the relationship between structural and functional brain changes needs to be clarified as changes in neuroanatomic structures may not necessarily correlate with brain function. This review showed that individuals with CLBP had decreased GM volume in pain matrix regions; however, the functional brain activity during noxious stimuli remained relatively comparable with the controls. Decreased GM may be a consequence of frequent nociceptive input.
as reduced GM has been associated with pain duration and recovery of GM volume was observed following effective pain relief. Although, the components of GM is comprised not only neurons but also includes astrocytes, glial cells, interstitial space, and vasculature. Therefore, decreased GM but normal functional connectivity in the pain matrix may reflect shrinkage of the various brain tissue components, rather than neuronal atrophy, hence future studies need to explore this relationship.

CONCLUSIONS
This study has systematically reviewed the literature demonstrating that there are widespread structural and functional brain changes in individuals with CLBP. Interestingly, brain activity during spontaneous back pain and altered functional network connectivity were consistently identified in brain areas associated with emotional processing and self-regulation, rather than the pain matrix regions involved in nociception. The activation of these areas may suggest there is another distinct evaluative network responsible for emotional and cognitive function that contributes to the overall experience of pain, which may be the network responsible for facilitating CLBP. Pain has proven to be a complex process and further research, particularly in the specific emotional and cognitive processes, is necessary to understand CLBP.

REFERENCES


Chapter 3
Negative beliefs are associated with persistent low back pain

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3.1 Preamble to empirical paper

Pain-related cognition, such as back beliefs (i.e., perceptions related to the consequences and potential recovery of low back pain), has been associated with poor low back pain outcomes [156-158]. Previous studies have shown that following a mass media campaign promoting accurate information about the course, appropriate management and potential consequences of low back pain, back beliefs of the general population shifted to be more positive. There was also an overall reduction in reported disability and claims for workers compensation and medical payments for low back pain [161, 162]. This demonstrates that back beliefs are a modifiable factor that may encourage adaptive behaviours and subsequently reduce the chronicity of pain. However, our understanding of the role of beliefs about back pain in the development and/or persistence of low back pain is still limited.

This chapter presents a 2-year cohort study that aims to examine the relationship between back beliefs and low back pain intensity in a community-based sample. This study examines the association between back beliefs reported at baseline, with pain outcomes across 4 groups,
including those who reported 1) no, 2) developing, 3) resolving and 4) persistent high pain intensity over a 2-year period. The Back Beliefs Questionnaire (BBQ) is used to assess beliefs about consequences of low back pain [205] and the pain subscale of the Chronic Pain Grade Questionnaire (CPG) measures pain intensity at the baseline and follow-up time points (see Appendix A). Comparisons between the 4 pain groups on participant characteristics and the percentage of negative responses to specific back beliefs statements is also included as a secondary aim.
Negative beliefs about low back pain are associated with persistent high intensity low back pain

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ABSTRACT

While previous cross-sectional studies have found that negative beliefs about low back pain are associated with pain intensity, the relationship between back beliefs and persistent low back pain is not well understood. This cohort study aimed to examine the role of back beliefs in persistent low back pain in community-based individuals. A hundred and ninety-two participants from a previous musculoskeletal health study were invited to take part in a two-year follow-up study. Beliefs about back pain were assessed by the Back Beliefs Questionnaire (BBQ) at baseline and low back pain intensity was measured by the Chronic Pain Grade Questionnaire at baseline and follow-up. Of the 150 respondents (78.1%), 16 (10.7%) reported persistent high intensity low back pain, 12 (8.0%) developed high intensity low back pain, in 16 (10.7%) their high intensity low back pain resolved and 106 (70.7%) experienced no high intensity low back pain. While participants were generally positive about low back pain (BBQ mean (SD) = 30.2 (6.4)), those with persistent high intensity pain reported greater negativity (BBQ mean (SD) = 22.6 (4.9)). Negative beliefs about back pain were associated with persistent high intensity low back pain after adjusting for confounders (M (SE) = 23.5 (1.6) vs. >30.1 (1.7), \( p < .001 \)). This study found negative back beliefs were associated with persistent high intensity low back pain over 2 years in community-based individuals. While further longitudinal studies are required, these findings suggest that targeting beliefs in programs designed to treat and prevent persistent high intensity low back pain may be important.

Introduction

Low back pain is the leading cause of disability worldwide, with the Global Burden of Disease 2010 study reporting low back pain to have contributed 83 million years lived with disability (Hoy et al., 2014). While most cases of low back pain resolve within several weeks, 23\%\ of the population develop persistent pain, with 11–12\%\ being significantly disabled by their low back pain (Balagué, Mannion, Pellisé, & Cedraschi, 2012). Evidence-based
treatment for chronic low back pain are limited, and the effect sizes of analgesic treatments are reported to be small (Machado, Kamper, Herbert, Maher, & McAuley, 2009). Thus, there has been a focus on identifying modifiable risk factors associated with persistent low back pain to assist in informing prevention strategies. A recent systematic review has highlighted the importance of psychological risk factors, such as depression, psychological distress and beliefs in the development of persistent low back pain (Ramond et al., 2011). In particular, there is increasing evidence that an individual’s beliefs about low back pain play a role in low back pain and disability (Fritz & George, 2002; Main, Foster, & Buchbinder, 2010; Wertli, Rasmussen-Bar, Weiser, Bachmann, & Brunner, 2014).

An individual’s beliefs about back pain have been defined as their general belief regarding the inevitable future consequences of having low back pain (back beliefs), such as treatment outcomes, the progression of low back pain and extent of impairment or disability (Symonds, Burton, Tillotson, & Main, 1996). Individuals with negative back beliefs tend to believe that treatments are ineffective, low back pain becomes progressively worse and full recovery is unlikely (Symonds, Burton, Tillotson, & Main, 1995). Cross-sectional studies have found that negative back beliefs are significantly associated with high pain intensity (Bostick, Schopflocher, & Gross, 2013; Urquhart et al., 2008), increased work absence and reduced work productivity (Mannion et al., 2009), and delayed recovery and pain relief (Elfering, Mannion, Jacobshagen, Tamcan, & Müller, 2009). However, only two cohort studies have examined the role of back beliefs in persistent low back pain and have reported conflicting results; with one study of 264 individuals with low back pain showing back beliefs did not predict persistent high levels of pain (Elfering et al., 2009), while another study of 1833 population-based individuals reported negative back beliefs to be a risk factor in developing persistent pain (Elfering, Müller, Rolli Salathé, Tamcan, & Mannion, 2015). The disparity in these findings may be due to the different study cohorts examined in these studies, with the Elfering et al. (2009) study consisting of 63% of individuals with acute low back pain and only 21.6% with a chronic condition. In addition, the study by Elfering et al. (2015) had a larger sample which may have provided more statistical power to detect a significant association. Moreover, the results of a public health campaign conducted in Australia showed a significant positive shift in beliefs in the general population, as well as a reduction in the number of claims for compensation, the rate of days compensated and medical payments for low back pain over three years (Buchbinder, Jolley, & Wyatt, 2001), while the health campaign conducted in Canada did not yield any significant shifts in back beliefs (Gross et al., 2010). Thus, the role of negative back beliefs in persistent low back pain remains unclear. The main aim of this study is to examine whether negative beliefs about low back pain are associated with persistent low back pain in a community-based cohort. A secondary aim of this study is to compare the participant characteristics and beliefs between four different pain groups – those who experienced no pain, developing, resolving, and persistent high back pain intensity.

**Materials and methods**

**Study population**

There were a total of 192 participants recruited at baseline during 2008 and 2009. Participants were initially recruited by research assistants to take part in a study that examined the relationship between pain, obesity and musculoskeletal health through advertisements in local media and weight loss clinics in Melbourne, Australia. Participants were not required to
have low back pain for inclusion in the study. The exclusion criteria included malignancy, significant systemic condition or inability to understand English. Participants were invited by letter to complete a follow-up study in 2011 and 150 participants (78.1%) participated by completing and returning the study questionnaires. Informed consent was obtained from all participants. This study was approved by the Alfred Health and Monash University Human Research Ethics Committee.

**Data collection**

Demographic information, including age, gender, weight and height were obtained from all participants at baseline and follow-up. Body mass index (BMI; kg/m\(^2\)) was calculated from the weight and height data. Mental well-being was determined by the Short Form 36 (SF-36), where lower scores indicate poorer mental health (McHorney, Ware, Lu, & Sherbourne, 1994).

**Pain intensity data**

The Chronic Pain Grade Questionnaire (CPG) was used to examine low back pain intensity at baseline and follow-up. The CPG has been shown to be a reliable and valid tool in both population-based low back pain studies (Smith et al., 1997; Von Korff, Ormel, Keefe, & Dworkin, 1992), and longitudinal pain studies (Elliott, Smith, Smith, & Chambers, 2000). It consists of three items that produce a score of 0–100 for pain intensity. Based on the CPG grading system, a score of 0 indicates no pain, 1–49 refers to low pain intensity and 50–100 refers to high pain intensity.

Participants were divided into four groups based on their CPG pain intensity scores at baseline and follow-up: (i) no, (ii) developing, (iii) resolving, and (iv) persistent high intensity pain. Participants with no high intensity pain at both baseline and follow-up were included in the ‘no high intensity pain’ group, those with high intensity pain at follow-up but not at baseline were in the ‘developing high intensity pain’ group, those who had high intensity pain at baseline but not at follow-up were in the ‘resolving high intensity pain’ group, and those with high intensity pain at both baseline and follow-up were included in the ‘persistent high intensity pain’ group.

**Beliefs about back pain**

The Back Beliefs Questionnaire (BBQ) was administered to determine an individual’s beliefs regarding back pain and its consequences at baseline (Symonds et al., 1996). The BBQ has a total of 14 items with five distractors, leaving nine items used to calculate an overall beliefs score. Each item is rated on a five-point Likert scale (‘1 = completely disagree’ to ‘5 = completely agree’) which is then reversed and summed to provide a total score. The possible scores ranged from 9 to 45 with lower values indicating more negative beliefs. The questionnaire has been reported to have good internal consistency (Cronbach = .7) and test–retest reliability (ICC = .87; Symonds et al., 1995). Studies in Australia (Buchbinder et al., 2001) and Canada (Bostick et al., 2013; Gross et al., 2006) implemented the BBQ in the general adult populations and reported the mean scores of 26.5 (95% CI: 26.1, 26.8), 26.4 (SD: 6.4) and 26.1 (SD: 6.6), respectively.
**Statistical analyses**

Descriptive statistics were reported for the characteristics of the participants in each of the four pain intensity groups, including their demographics, beliefs about back pain and pain intensity. One-way analysis of variance (ANOVA), χ² tests and Kruskal–Wallis tests (if ANOVA assumptions were violated) were used to determine characteristic differences between the four groups. To examine the relationship between beliefs and high intensity low back pain, estimated marginal means were calculated adjusting for age, gender, BMI and mental health. All analyses were performed using the IBM SPSS Statistics (standard version 22.0). A statistical test was considered to be significant if the associated p-value was less than .05.

**Results**

**Description of demographic characteristics and study variables**

Of the 192 participants recruited at baseline, 150 participants (78.1%) participated in the two-year follow-up study. The 150 participants had a mean (SD) age of 48.4 (8.5) years, 114 (76.0%) were female and their mean (SD) BMI was 32.4 (8.8) kg/m². The mean (SD) score of the SF-36 Mental was 46.9 (13.6) and the mean (SD) BBQ score was 30.2 (6.4). The 42 participants who were lost to follow-up were not significantly different in age (M (SD) = 44.8 (10.5) vs. 48.4 (8.54), p = .09), or gender (female: 83.3%, p = .3) but had a significantly higher BMI (M (SD) = 36.7 (9.2) vs. 32.4 (8.8), p = .02) than those who completed the follow-up study. Furthermore, the 42 participants did not differ in their SF-36 Mental subscale (M (SD) = 47.2 (10.8) vs. 46.9 (13.6), p = .7) but had a significantly lower mean BBQ score (M (SD) = 28.0 (7.07) vs. 30.2 (6.38), p = .04).

The characteristics of the participants with no, developing, resolving or persistent high intensity pain are shown in Table 1. While 106 participants (70.7%) reported no high

<table>
<thead>
<tr>
<th>High intensity low back pain</th>
<th>No (n = 106)</th>
<th>Developing (n = 12)</th>
<th>Resolving (n = 16)</th>
<th>Persistent (n = 16)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.7 (8.3)</td>
<td>50.9 (6.6)</td>
<td>42.6 (10.6)</td>
<td>50.1 (7.7)</td>
<td>.15</td>
</tr>
<tr>
<td>Gender (n, % female)</td>
<td>79 (74.5)</td>
<td>11 (91.7)</td>
<td>12 (75.0)</td>
<td>12 (75.0)</td>
<td>.32</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.5 (8.5)</td>
<td>37.0 (9.5)</td>
<td>36.5 (7.5)</td>
<td>36.4 (7.9)</td>
<td>.002</td>
</tr>
<tr>
<td>SF-36 Mental score</td>
<td>49.3 (12.3)</td>
<td>42.7 (16.4)</td>
<td>41.8 (14.5)</td>
<td>39.3 (15.3)</td>
<td>.031</td>
</tr>
<tr>
<td>Back Beliefs score</td>
<td>32.0 (5.7)</td>
<td>26.5 (6.7)</td>
<td>28.6 (4.4)</td>
<td>22.6 (4.9)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain intensity</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17.6 (15.0)</td>
<td>18.1 (15.4)</td>
</tr>
<tr>
<td></td>
<td>34.2 (14.9)</td>
<td>65.0 (10.8)</td>
</tr>
<tr>
<td></td>
<td>57.9 (8.4)</td>
<td>26.9 (15.1)</td>
</tr>
<tr>
<td></td>
<td>67.3 (11.5)</td>
<td>62.3 (11.1)</td>
</tr>
</tbody>
</table>

*Mean (SD) unless otherwise indicated.
*p-Value calculated for differences between participants with no, developing, resolving and persistent high intensity back pain using Kruskal–Wallis unless otherwise indicated.
5Age: 24 cases missing.
*p-Value calculated for differences between participants with no, developing, resolving and persistent high intensity back pain using χ² test.
*BMI: 24 cases missing.
SF-36 mental score: 2 cases missing.
*p-Value calculated for differences between participants with no, developing, resolving and persistent high intensity back pain using ANOVA.
intensity pain at baseline or follow-up, 12 participants (8.0%) reported the development of high intensity pain, 16 participants (10.7%) reported their high intensity pain had resolved and 16 participants (10.7%) reported persistent high intensity pain.

**Comparison of participant characteristics**

There were no differences in the age ($p = .2$) or proportion of females across the four groups ($p = .6$), although there were significant differences in the BMI ($p = .002$), with the post-hoc test showing that the no pain group had a significantly lower BMI than the persistent pain group ($p = .049$). There were also significant overall differences in the SF-36 Mental subscale ($p = .03$), but no post-hoc differences between the four groups ($p > .05$).

**Relationship between back beliefs and back pain**

At baseline, those who had persistent high intensity back pain had lower scores on the BBQ than the no pain ($p < .001$) and developing high pain intensity groups ($p = .02$) but not the resolving pain group ($p = .3$). At baseline, the participants with persistent high intensity back pain reported significantly higher levels of pain intensity compared to the no pain.

![Figure 1. Total Back Beliefs score (mean, 95% confidence intervals) adjusted for age, gender, body mass index and mental health for different pain groups, ($p < .001$) in the no, developing, resolving and persistent high pain intensity groups.](image-url)
(p < .001) and developing high pain intensity groups (p = .02), but not the resolving pain group (p = 1.0). The persistent high pain intensity group also reported higher levels of pain intensity at follow-up than the no pain (p < .001) and resolving high pain intensity groups (p = .001) but not the developing high pain intensity group (p = 1.0).

The estimated marginal means showed that negative back beliefs were significantly associated with persistent high intensity back pain, when adjusted for age, gender and BMI compared to the resolving high intensity pain and no high intensity pain (M (SE) = 23.4 (1.5), vs. M (SE) > 30.0 (1.7), p < .001). This relationship persisted when mental health was added to the estimated marginal means model (M (SE) = 23.5 (1.6), vs. >30.1 (1.7), p < .001). Post-hoc analyses revealed that the participants with persistent high intensity back pain had significantly lower mean Back Beliefs than the no pain (p < .001) and the resolving pain group (p = .004), but not the developing pain group (p = .17) (Figure 1).

Table 2 presents the participants' responses to the nine statements from the BBQ. Participants with persistent high intensity back pain generally had a greater percentage of negative responses for five statements compared to the other three pain groups. This was the case for the following three statements regarding the course of low back pain: ‘back trouble means periods of pain for the rest of one’s life’, ‘once you have had back trouble there is always a weakness’ and ‘later in life back trouble gets progressively worse’ and the remaining two statements which refer to their ability to work (i.e. ‘back trouble will eventually stop you from working’ and ‘back trouble means long periods of time off from work’). However, the persistent high intensity pain group did not have a significantly greater percentage of negative responses for statements related to interventions or coping strategies (i.e. ‘there is no real treatment for back trouble’ or ‘back trouble needs to be rested’), or the potential severity of back pain (i.e. ‘back trouble makes everything in life worse’ or ‘back trouble may mean you end up in a wheelchair’).

Table 2. Percentage of participants that responded negatively to statements about back pain from the Back Beliefs Questionnaire in the no, developing, resolving and persistent high intensity low back pain groups.

<table>
<thead>
<tr>
<th>Back Beliefs Questionnaire statements</th>
<th>Participants with negative beliefs about back paina, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 106)</td>
<td>Developing (n = 12)</td>
</tr>
<tr>
<td>There is no real treatment for back trouble</td>
<td>8 (7.6)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Back trouble will eventually stop you from working</td>
<td>13 (12.3)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Back trouble means periods of pain for the rest of one’s life</td>
<td>22 (20.8)</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>Back trouble makes everything in life worse</td>
<td>43 (40.6)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Back trouble may mean you end up in a wheelchair</td>
<td>5 (4.7)</td>
<td>1 (8.33)</td>
</tr>
<tr>
<td>Back trouble means long periods of time off from work</td>
<td>6 (5.7)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Once you have had back trouble there is always a weakness</td>
<td>39 (36.8)</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td>Back trouble must be rested</td>
<td>27 (25.5)</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Later in life back trouble gets progressively worse</td>
<td>29 (27.4)</td>
<td>4 (33.3)</td>
</tr>
</tbody>
</table>

aSelected agree or completely agree, which is a score of 4 and 5 respectively.
b*p-Value calculated for differences between participants with no, developing, resolving and persistent high intensity back pain using χ² test.
Discussion

This study found that approximately 10% of community-based individuals have persistent high intensity pain over two years and that negative beliefs about low back pain are associated with persistent high intensity low back pain in a community-based cohort. While further studies are needed, these results suggest that strategies targeting negative beliefs about low back pain, such as cognitive behavioural techniques, may assist in preventing the development of persistent high intensity low back pain.

Our finding that negative beliefs are associated with persistent low back pain of high intensity is novel. These results are consistent with previous cross-sectional studies that found that negative back beliefs are associated with high intensity low back pain in the general population (Bostick et al., 2013) and community-based women (Urquhart et al., 2008), as well as a population-based longitudinal study that found negative back beliefs predicted persistent shoulder, neck and back pain (Elfering et al., 2015), although persistent high pain intensity was not explored in this study. In contrast, a population-based longitudinal study by Elfering et al. (2009) did not find back beliefs, measured by the BBQ, to be a predictor of high pain intensity over the course of a year. Discrepancies between the Elfering et al. (2009) study and the current study may be due to the definition of low back pain and the instrument used to measure pain intensity; the Elfering et al. (2009) study used a single item unvalidated question to measure pain intensity weekly over the span of one year, while our study examined persistent high intensity pain over a two-year period using the CPG, a validated measure of pain intensity in low back pain populations (Elliott et al., 2000). Moreover, studies that have focused on fear-avoidance beliefs have not tended to find a relationship between beliefs and pain intensity (Boersma & Linton, 2005; Swinkels-Meewisse, Roelofs, Verbeek, Oostendorp, & Vlaeyen, 2006). This may not be surprising, as the fear-avoidance beliefs investigate the beliefs around avoiding pain-related behaviours, while the back beliefs examine general beliefs regarding the inevitable future outcomes and consequences of having low back pain.

This study also found that individuals in the persistent high intensity pain group had a significantly higher percentage of negative responses to the majority of the statements in the Back Beliefs Questionnaire. However, there were four statements, ‘there is no real treatment for back trouble’, ‘back trouble may mean you end up in a wheelchair’, ‘back trouble makes everything worse’ and ‘back trouble must be rested’, in which individuals in the persistent high intensity pain group did not have greater percentage of negative responses compared to those in the other three pain groups. Although speculative, this finding may reflect that the effect of previous public health campaigns which recommended that individuals stay active and reduce prolonged periods of rest during an episode of low back pain and resulted in a positive shift in individual’s beliefs about back pain (Buchbinder et al., 2001; Gross et al., 2010).

Our finding that there is a relationship between negative back beliefs and persistent high intensity low back pain over 2 years highlights the potential importance of back beliefs in the future management of low back pain. Public health campaigns in Australia (Buchbinder et al., 2001), Scotland (Waddell, O’Connor, Boorman, & Torsney, 2007), and Norway (Werner, Ihlebaek, Laerum, Wormgoor, & Indahl, 2008) observed shifts towards positive beliefs about low back pain following educational interventions. Moreover, clinical trials have found that introducing an informational booklet, providing accurate information about
low back pain to correct misbeliefs about low back pain have been effective in reducing persistent low back pain (Coudeyre et al., 2007). Taken together with our study, this suggests that targeting back pain beliefs in those with back pain is feasible and important for reducing back-related disability and for recovery of low back pain patients.

This study need to be considered in context of its limitations. While there was a modest sample size within each pain group, we were still able to identify a relationship between beliefs and persistent high intensity low back pain. These findings provide an indication of the importance of back beliefs in low back pain, however, future studies with larger numbers of participants are required. The mean BMI of our four pain intensity groups ranged from 30.5 to 37.0 kg/m², with 64.7% of participants classified in the overweight or obese category. While this may influence the generalisability of our results, 62.8% of Australians are reported to be overweight or obese (Australian Bureau of Statistics, 2013), indicating our participants are still representative of the Australian population. Given our cohort included mostly women, it was not possible to examine gender differences in beliefs and pain intensity. Strengths of this study included the recruitment of a community-based cohort that were not selected for low back pain and the use of validated questionnaires to measure both beliefs about low back pain and pain intensity.

The results of this study showed that negative beliefs about low back pain are associated with persistent high intensity low back pain in community-based individuals. While further studies are needed, these results suggest that strategies targeting negative beliefs about low back pain, such as cognitive behavioural techniques or educational programs, may be relevant in preventing the development of persistent low back pain of high intensity.

Conflict of interest

No potential conflict of interest was reported by the authors.

Funding

S.N. is a recipient of an Australian Postgraduate Award and Y.W., A.E.W. and D.U. are recipients of National Health and Medical Research Council Career Development Fellowships (Clinical Level 1 #1065464, Clinical Level 2 #1063574 and Clinical Level 1 #1011975, respectively). B.F. is supported by a National Health and Medical Research Council Early Career Fellowship (#1070073).

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References


Chapter 4
Poor subjective well-being is associated with persistent pain intensity and disability

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4.1 Preamble to empirical paper

As outlined in Chapter 1, pain-related cognitive content (i.e., the beliefs and perceptions surrounding low back pain and impact on potential outcomes) play a significant role in the development and persistence of low back pain. The previous chapter demonstrated the beliefs regarding the consequences of low back pain, was associated with persistent, high pain intensity. An individual’s perception of their health and well-being may also be a contributor to low back pain outcomes. Specifically, subjective well-being refers to an individual’s cognitive assessments and emotional responses to life events. This is a multidimensional construct that represents the subjective perception of their life, physical and psychological status [164]. Components of subjective well-being measured as poorer perceived mental health and health-related quality of life (HRQOL) are associated with higher levels of low back pain intensity and disability [169, 170], as well as the development of chronic low back pain [149, 171, 172]. However, a comprehensive examination of the various aspects of subjective well-being and their contribution to the progression of low back pain outcomes is not well explored.
This cohort study aims to investigate the association between subjective well-being, including its subdomains, and low back pain intensity and disability in community-based women. The Psychological and General Well-Being Index (PGWB) is used to assess overall subjective well-being and its 6 subdomains, including anxiety, depressed mood, positive well-being, self-control, general health and vitality. Pain intensity and disability is measured using the Chronic Pain Grade Scale (CPG). Similar to the previous chapter, participants are categorised into no, developing, resolving and persistent high pain intensity based on the pain intensity subscale of the CPG. This is also performed for disability to produce 4 disability groups. The association between the pain and disability groups and level of well-being, as well as its subdomains is examined.
Poor general health and lower levels of vitality are associated with persistent, high-intensity low back pain and disability in community-based women: A prospective cohort study

Sin Ki Ng, Flavia M. Cicuttini, Susan R. Davis, Robin Bell, Roslin Botler, Bernadette M. Fitzgibbon, Donna M. Urquhart

Abstract

While low back pain significantly impacts an individual’s well-being, our understanding of the role of well-being in the natural history of low back pain is limited. This cohort study aimed to investigate the association between psychological and general well-being and the development and progression of low back pain and disability in community-based women over a 2-year period. 506 women recruited from a research database were invited to participate. Overall psychological and general well-being and its subdomains were assessed at baseline using the Psychological General Well-Being Index (PGWB). The intensity of and degree of disability arising from low back pain were examined using the Chronic Pain Grade Questionnaire at baseline and at 2-year follow-up. Participants were categorized as having no, developing, resolving, or persistent high-intensity pain and disability. 444 participants (87.8%) completed the study. Women with persistent high-intensity pain had lower PGWB scores at baseline than those with no high-intensity pain at follow-up, after adjusting for confounders (M(SE) = 69.9(2.55) vs 80.1(2.63), p < 0.005). Furthermore, women with persistent high disability scores had lower well-being scores than those without persistent high disability scores (M(SE) = 69.1(3.49) vs. 81.2(0.802), p = 0.001). Moreover, lower scores in the well-being subdomains of general health and vitality were associated with persistent high pain intensity and disability (all p < 0.007). In summary, lower levels of general health and vitality were associated with persistent high-intensity low back pain and disability, suggesting that improving these aspects of well-being has the potential to reduce high levels of chronic low back pain and disability in community-based women.

1. Introduction

According to the 2010 Global Burden of Disease study, low back pain (LBP) is the leading cause of disability worldwide and has accounted for approximately 83 million years lived with disability [1]. It poses a significant economic burden due to medical treatment costs [2], as well as indirect costs resulting from work absenteeism and reduced work productivity [3]. LBP also impacts psychological and general well-being, which is defined as the quality of life experienced by each individual, based on numerous factors, from basic health, to the quality of primary and family relationships, to intellectual fulfilment and emotional satisfaction [4].

Previous studies have shown that individuals with chronic LBP report significantly poorer self-perceived psychological [5] and health-related quality of life [6–8] compared with pain-free groups. Moreover, our cross-sectional study showed that lower psychological and general well-being was associated with both low and high levels of pain intensity and disability in community-based individuals [9]. The association between well-being and disability in LBP has also been investigated, with inconsistencies in the results reported and at best, only weak associations observed [10,11]. Furthermore, the role of an individual’s self-perception of their psychological and general well-being in the development and persistence of LBP is not well understood, highlighting the need for longitudinal studies that examine the contribution of well-being.

While cohort studies have investigated the role of psychological and
general well-being as a risk factor for development and recovery outcomes in LBP, these studies have predominantly focused on specific aspects of well-being. For example, there is evidence to suggest that psychological distress [12–14], depressed mood [15,16], as well as lower perceived health [15] and reduced health-related quality of life [17] contribute to the development of persistent LBP and disability. However, no cohort studies have comprehensively explored the role of both psychological and general well-being and in doing so, the contribution of both positive and negative aspects of well-being. Furthermore, previous studies have not used a validated measure to assess both psychological and general well-being and its subdomains, nor have they been examined longitudinally in community-based women, despite poorer women being at a higher risk of developing LBP and experiencing a poorer prognosis compared to men [14,18,19]. Therefore, the aim of this study was to establish whether psychological and general well-being and its related subdomains, assessed by a validated measure, are associated with the development and/or progression of low back pain intensity and disability in community-based women over a 2-year period.

2. Methods

2.1. Study population

Participants were recruited from a previous cross-sectional study investigating androgen levels in 1423 community-based women [20]. These participants were initially recruited between April 2002 and August 2003 from a database derived from random sampling of the electoral roll of the Australian state of Victoria. Full details of the participant recruitment have been described in a previous study [20]. Of the 1423 participants, 754 agreed to being contacted for future research and were invited to participate in the current study in 2006. A total of 542 participants, who agreed to being involved in the present study, were sent the information sheet, consent form, and study questionnaires. 506 participants returned the questionnaire for the baseline study. Participants were invited to complete a follow-up study in 2008, with 444 (87.8%) participants returning the study questionnaire. All participants provided written informed consent. All procedures were conducted in accordance with the Declaration of Helsinki and the study was approved by the Monash University Human Research Ethics Committee.

2.2. Questionnaires

Demographic information, including age, gender, weight, and height, were obtained from participants at baseline and follow-up. Body mass index (BMI; kg/m²) was calculated from self-reported weight and height.

The study questionnaires at both baseline and follow-up included the Chronic Pain Grade Questionnaire (CPG), a seven item questionnaire, used to determine pain intensity and disability over the previous 6 months [21]. The CPG has been shown to be a reliable and valid questionnaire in both population-based low back pain studies [22] and detecting changes in chronic pain severity over time in longitudinal studies [23]. The CPG has 3 items that measure pain intensity and the sum of these items results in a pain intensity score between 0 and 100, with higher scores indicating higher pain intensity. There are 3 items that measure disability, which is used to produce a disability score between 0 and 100, with higher scores indicating higher levels of disability. There is also a single self-report item that indicates the number of days individuals were restricted due to their back pain. The disability score and the number of days is converted to points which are summed to produce an overall disability point score. According to the CPG scoring system, a score of 0 indicates no pain or disability, 1–49 indicates low pain intensity or disability, while 50–100 indicates high intensity pain or disability.

Participants were divided into groups based on whether they had no or low pain intensity (i.e., score of 0–49) or high pain intensity (i.e., score of 50–100) at baseline and follow-up. The following four groups were then formed: i) no, ii) developing, iii) resolving, and iv) persistent high intensity pain. Those who did not report high intensity pain at baseline and follow-up were in the “no pain” group. Participants who did not have high intensity pain at baseline but developed high intensity pain at follow-up were in the “developing pain” group, while those who initially had high intensity pain but did not experience high intensity pain at follow-up were in the “resolving pain” group. Finally, the participants that had reported high intensity pain at baseline and follow-up were in the “persistent pain” group. Similar to the pain intensity groups, participants were divided into no, developing, resolving, and persistent high disability groups based on their disability scores.

The Psychological General Well-Being Index (PGWB), a validated measure of subjective psychological general well-being in the preceding 4 weeks [4,24], was measured at the baseline. The PGWB has 22 items, with each item rated on a six-point Likert scale, which assessed six subdomains, each defined with 3–5 items that include: anxiety (score of 0–25), depressed mood (0–15), positive well-being (0–20), self-control (0–15), general health (0–15), and vitality (0–20). The scores of the subdomains are summed to create a total PGWB score between 0 and 110. Higher scores indicate greater psychological and general well-being.

2.3. Statistical analyses

Descriptive statistics for age, BMI, psychological and general well-being, pain intensity and disability scores were tabulated for the different high intensity pain and disability groups. As the assumptions for one-way analysis of variance (ANOVA) were violated, the Kruskal-Wallis test was used to compare the differences in the demographic variables between the pain intensity and disability groups. Results were considered statistically significant when p was less than 0.05. Estimated marginal means were calculated to determine the association between psychological and general well-being and both low back pain intensity and disability, after adjusting for age and BMI. In the analyses involving estimated marginal means, Bonferroni adjustments were performed to account for multiple comparisons so that a p-value of < 0.007 was considered statistically significant. The IBM SPSS Statistics (standard version 23.0) was used to perform all analyses.

3. Results

Of the 506 participants recruited at baseline, the cohort had a baseline mean (SD) age of 56.8 (12.5) years and BMI of 27.3 (5.67) kg/m². The baseline CPG pain intensity and disability mean (SD) scores were 25.5 (22.3) and 13.9 (20.5) respectively. There was a total of 444 (87.8%) participants who completed the 2-year follow-up study.

The 62 participants who were lost to follow-up were not significantly different to the participants that completed follow-up with respect to age (p = 0.12), BMI (p = 0.25), pain intensity (p = 0.20) or disability (p = 0.14) at baseline. In addition, they did not differ in terms of the median baseline PGWB total score (p = 0.22) or any of the subdomains (p > 0.05), although they had significantly lower vitality scores (p = 0.037).

Of the participants who completed the follow up study, 334 participants (75.2%) had no high intensity pain at baseline or follow-up, 33 (7.43%) developed high intensity pain, 38 (8.56%) had resolving high intensity pain, and 37 (8.34%) reported persistent high intensity pain (Table 1). There were no significant differences between the groups in age (p = 0.069). There were significant differences in BMI (p = 0.002), with the persistent high intensity pain group having a higher BMI compared with the no high intensity pain group (‘persistent’ group: M (SD) = 30.4 (5.37) vs. ‘no pain’ group: M (SD) = 27.0 (5.70), p = 0.001) (See Table 1).
Table 1
Association between psychological and general well-being and no, developing, resolving and persistent high intensity pain.

<table>
<thead>
<tr>
<th>High intensity pain</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n = 334)</td>
<td>Developing (n = 33)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.1 (11.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.0 (5.70)</td>
</tr>
<tr>
<td>CPG pain intensity score: Baseline</td>
<td>17.2 (15.5)</td>
</tr>
<tr>
<td>CPG pain intensity score: Overall PGWB (baseline):</td>
<td>81.5 (15.2)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>18.6 (4.25)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>12.9 (2.17)</td>
</tr>
<tr>
<td>Positive well-being</td>
<td>13.5 (3.45)</td>
</tr>
<tr>
<td>Self-control</td>
<td>12.5 (2.44)</td>
</tr>
<tr>
<td>General health</td>
<td>11.1 (2.64)</td>
</tr>
<tr>
<td>Vitality</td>
<td>13.1 (3.68)</td>
</tr>
</tbody>
</table>

BMI = body mass index; CPG = Chronic Pain Grade Questionnaire; PGWB = Psychological general well-being index.
* Groups were compared using the Kruskall-Wallis test.

3.1. Association between psychological general well-being and no, developing, resolving and persistent high intensity pain

The characteristics of the pain intensity groups are shown in Table 1. Overall, the persistent high intensity pain group consistently had lower scores in overall well-being and the subdomains of the PGWB than the other pain groups. The estimated marginal means showed a significant association between lower overall psychological and general well-being and high intensity pain after adjusting for age and BMI (p < 0.001). The persistent high intensity pain group had a lower total PGWB score compared with the no pain intensity group (M(SE) = 69.9 (2.55) vs. > 80.1 (2.63), p < 0.005) (see Fig. 1A). Furthermore, with respect to the PGWB subdomains, there were significant differences between the pain intensity groups in general health and vitality (all p < 0.007). Specifically, lower general health was significantly associated with persistent high intensity pain when compared with no and developing high intensity pain groups (all p < 0.007) and lower vitality was associated with persistent high intensity pain compared to the other 3 pain groups (all p < 0.007) (see Fig. 1B).

3.2. Association between psychological general well-being and no, developing, resolving and persistent high disability

The characteristics of the disability groups are shown in Table 2. Of the 506 women, 373 (84.0%) reported no disability, 26 (5.26%) developed high disability, 21 (4.73%) had resolving disability, and 22 (4.95%) had persistent high disability. Although there were no significant differences in age (p = 0.24), there were significant differences in BMI (p = 0.001), where the persistent high disability group had higher BMI than the no (p < 0.001), developing (p = 0.001), and resolving (p = 0.01) disability groups.

There was a significant association between the total PGWB score and low back disability after adjusting for age and BMI (p = 0.001). Specifically, there was a lower total PGWB score in the persistent high disability group compared to the no disability group (M(SE) = 69.1 (3.49) vs. 81.2 (0.802), p = 0.001) (see Fig. 2A). Additionally, there were significant differences in the general health and vitality subdomains, with the persistent high disability group having significantly lower general health compared to the no and developing high disability groups (all p < 0.007), as well as lower vitality compared to the no and resolving high disability groups (all p < 0.007). Finally, there was a trend observed in the positive well-being subdomain (p = 0.009), with the persistent high disability group having lower positive well-being than the no disability group (p = 0.009) (see Fig. 2B).

4. Discussion

This cohort study showed that lower general well-being, particularly in the health-related subdomains of general health and vitality, are associated with persistent high intensity low back pain and disability over 2 years in community-based women. These results highlight the importance of an individual’s general well-being in persistent pain and disability and suggests that targeting this domain may be important in the prevention and management of chronic low back pain.

This study is the first to show that general well-being plays a significant role in persistent, high levels of low back pain and disability in community-based women. In contrast, previous mixed gender, cohort studies have focused on examining psychological domains and found that increased psychological distress contributes to the persistence of pain and disability in low back pain patients and the general population [12-14,25]. Our results extend the findings of our previous cross-sectional study [9], which found high intensity pain was associated with general well-being, particularly anxiety, depression, positive well-being, general health and vitality, while high disability was related to lower positive well-being, general health and vitality. Taken together, these findings suggest that multiple aspects of well-being may be associated with pain and disability, with the health domains of general health and vitality possibly driving the persistence of LBP outcomes. Specifically, lower general health refers to an individual having significant concerns of illness, bodily disorder, aches and pains as well as fears regarding their overall health, while low vitality refers to lack of energy or feeling dull, tired and exhausted. By examining a community-based population of women, who are known to have a higher risk of developing LBP and poorer prognoses than men [14,18,19], our results highlight the interconnectedness of general well-being and chronic pain for women living in the community and the need to address these important health issues in a unified way.

In this study, we did not find a statistically significant association between psychological domains and persistent, high levels of pain and disability. However, we observed a consistent pattern of lower scores on psychological domains, such as anxiety and depression, in the persistent high intensity pain and disability groups compared with one or more of the other groups. This suggests that psychological domains may be associated with persistent high levels of pain and disability, however future studies examining this association in larger cohorts are warranted.

Individuals with chronic, disabling low back pain are responsible for the majority of the socioeconomic burden of low back pain. Given we found that poor general well-being is clearly associated with chronic pain and disability in individuals with LBP, these findings have the potential to inform future novel approaches to both assessment and management. First, our findings suggest that the assessment of well-
Fig. 1. A) Overall Psychological General Well-Being Index score for different high intensity pain groups, * \( p < 0.05 \) (unadjusted), ** \( p < 0.007 \) (these values remained significant after Bonferroni adjustment); B) Psychological General Well-Being Index subdomain scores for different high intensity pain groups, * \( p < 0.05 \) (unadjusted), ** \( p < 0.007 \) (these values remained significant after Bonferroni adjustment).

Table 2
Association between psychological and general well-being and no, developing, resolving and persistent high disability.

<table>
<thead>
<tr>
<th></th>
<th>No (n = 373)</th>
<th>Developing (n = 26)</th>
<th>Resolving (n = 21)</th>
<th>Persistent (n = 22)</th>
<th>( p )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.9 (12.1)</td>
<td>56.5 (15.8)</td>
<td>55.5 (12.0)</td>
<td>61.9 (10.8)</td>
<td>0.238</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 (5.75)</td>
<td>26.1 (4.04)</td>
<td>26.7 (4.15)</td>
<td>33.0 (5.93)</td>
<td>0.001</td>
</tr>
<tr>
<td>CPG disability score:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.28 (12.3)</td>
<td>22.1 (16.5)</td>
<td>60.3 (14.1)</td>
<td>69.8 (14.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Overall PGWB (baseline):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>18.7 (4.31)</td>
<td>17.4 (4.36)</td>
<td>17.6 (4.91)</td>
<td>17.2 (5.20)</td>
<td>0.194</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>12.9 (2.18)</td>
<td>12.0 (2.79)</td>
<td>12.7 (3.16)</td>
<td>11.7 (3.47)</td>
<td>0.154</td>
</tr>
<tr>
<td>Positive well-being</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-control</td>
<td>13.4 (3.51)</td>
<td>11.8 (3.40)</td>
<td>12.6 (3.51)</td>
<td>11.5 (4.00)</td>
<td>0.013</td>
</tr>
<tr>
<td>General health</td>
<td>12.4 (2.43)</td>
<td>11.6 (3.19)</td>
<td>12.0 (2.77)</td>
<td>11.6 (3.07)</td>
<td>0.461</td>
</tr>
<tr>
<td>Vitality</td>
<td>10.7 (2.68)</td>
<td>10.4 (1.96)</td>
<td>8.76 (2.21)</td>
<td>6.68 (3.18)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

BMI = body mass index; CPG = Chronic Pain Grade Questionnaire; PGWB = Psychological general well-being index.

* Groups were compared using the Kruskall-Wallis test.
being could be a valuable component of a comprehensive, initial assessment for individuals who present with low back pain, with the aim of identifying individuals at high risk of developing persistent pain and disability and addressing their low well-being within the framework of their rehabilitation program. Our results may also inform the development of holistic, multidimensional programs that address lower general well-being as a part of LBP management. While preventing negative affect is currently an important target for intervention [26,27], our results highlight the importance of examining other aspects of well-being such as general health and vitality. Furthermore, an individual’s capacity to regulate their emotions has been found to promote subjective health [28] and well-being [29], thus highlighting the potential for emotion regulation strategies to assist in improving overall well-being in rehabilitation programs.

This study has several limitations. While the size of the pain intensity and disability groups were small and unequally distributed, we were able to find significant differences between these groups. While it is possible that selection bias may have affected our results, we recruited subjects from a database established though random sampling from a state electoral roll and the participant characteristics of the women in the current study were similar to that of the original study.

Moreover, while previous studies have shown that the association between pain and disability and aspects of well-being such as psychological distress [13] are bi-directional, we assessed psychological and general well-being at baseline, and pain and disability at both baseline and 2-year follow-up, allowing us to investigate the influence of psychological and general well-being on LBP outcomes. While this study cannot imply causality, it highlights that general well-being is important to consider in persistent LBP and disability. Strengths of our study included the use of a cohort study design with 88% of participants followed up over 2 years, and the measurement of pain, disability and well-being using multidimensional, validated questionnaires, which allowed a comprehensive evaluation of the variables within one study. Moreover, this study examined a community-based population of women which allows our results to be widely generalizable.

This study showed that lower general health and vitality were associated with persistent high intensity low back pain and disability in community-based women. These findings suggest that strategies aimed at improving these aspects of well-being may reduce persistent high levels of both low back pain and disability.

![Figure 2](image)

**Figure 2.** A) Overall Psychological General Well-Being Index score for the different high disability groups, *p < 0.05 (unadjusted), **p < 0.007 (these values remained significant after Bonferroni adjustment); B) Psychological General Well-Being Index subdomain scores for different high disability groups, *p < 0.05 (unadjusted), **p < 0.007 (these values remained significant after Bonferroni adjustment).
Contributors

Sin Ki Ng was involved data analysis, interpretation of the data as well as the preparation of the manuscript.

Flavia M Cicuttini was involved data analysis, interpretation of the data as well as the preparation of the manuscript.

Susan R Davis was involved in the design of the experiment and management of data collection.

Robin Bell was involved in the design of the experiment and management of data collection.

Roslin Bottero was involved in the collection and entry at the baseline and follow-up time points.

Bernadette M Fitzgibbon was involved data analysis, interpretation of the data as well as the preparation of the manuscript.

Donna M Urquhart was involved data analysis, interpretation of the data as well as the preparation of the manuscript.

All listed authors significantly contributed to the development of this study. All authors saw and approved the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

Sin Ki Ng is a recipient of an Australian Postgraduate Award.

Donna M Urquhart and Bernadette M Fitzgibbon are recipients of a National Health and Medical Research Council (NHMRC) Career Development Fellowship (Clinical Level 1 #1011975) and a NHMRC Early Career Fellowship (#1070073) respectively.

Susan R Davis is a NHMRC Senior Principal Research Fellow (#1135843).

This study was funded by the Monash University Strategic Grant Scheme and Physiotherapy Research Foundation (Continence and Women’s Health Grant).

Ethical approval

Any aspect of the work covered in this manuscript that has involved human patients has been performed with the ethical approval of all relevant bodies. This study was approved by the institutional ethics committees.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this submission.

Researchers interested in specific approaches to the analysis of the data reported in this paper may apply to use the data in partnership with the data custodians.

References


Chapter 5
Cognitive reappraisal in chronic low back pain: An fMRI study

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5.1 Preamble to empirical paper

In Chapter 2, the systematic review demonstrated that there are structural and functional brain changes in multiple regions that have been associated with cognition and emotion in chronic low back pain; however, studies examining the relationship of these changes with cognition and emotion are limited. Indeed, while 16 task-related fMRI studies were identified in the review, 7 studies examined brain activity during spontaneous fluctuations of back pain in chronic low back pain patients. Another 3 studies explored brain activations in response to images or videos of activities that evoke low back pain; although, only 3 specifically explored functional connectivity during tasks examining cognitive function. This highlights the need for further investigations in order to establish how these brain changes relate to the pain-related cognitive or emotional processes that may contribute to the development of chronic low back pain.

Of particular importance to chronic low back pain may be emotion regulation; a coping mechanism for high levels of negative emotions including aversive stimuli such as pain. In fact, adaptive emotion regulation strategies, such as cognitive reappraisal, have been shown to be
effective in reducing pain as well as pain-related negative affect in healthy, pain-free individuals [178-180]. However, there are no studies that have investigated the effects of cognitive reappraisal in chronic low back pain, indicating that there is limited understanding of whether these processes as well as the underlying neural processes are impaired in this group.

The current chapter presents an exploratory fMRI study exploring neural activity during an emotion regulation task requiring cognitive reappraisal in chronic low back pain. As covered in Chapter 1 (section 1.3.1.2 MRI evidence of structural and functional brain changes in chronic low back pain), fMRI is a non-invasive neuroimaging method that indirectly measures activations in the brain through BOLD signals. These BOLD signals are an indirect measure of neural activity that involves detecting changes in the ratio of oxygenated to deoxygenated blood, an indicator of increased brain activation. Therefore, the following study explores the differences in brain activity as well as functional connectivity (i.e., the temporal correlation of brain activity between various regions) during the cognitive reappraisal task in individuals with chronic low back pain compared to healthy controls.
Neural activity during reappraisal in chronic low back pain: A preliminary BOLD-fMRI and functional connectivity study

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Manuscript category: Original article

Sources of Funding: DMU and BMF are recipients of a National Health and Medical Research Council (NHMRC) Career Development Fellowship (Clinical Level 2 #1142809) and an NHMRC Early Career Fellowship (#1070073) respectively. PBF was supported by a Practitioner Fellowship grant from National Health and Medical Research Council (NHMRC) (1078567). PGE is supported by a Future Fellowship from the Australian Research Council (ARC) (FT160100077). SLR holds a Senior Research Fellowship from National Health and Medical Research Council (NHMRC) (1154651).

Conflict of interest: PBF has received equipment for research from Medtronic, MagVenture A/S and Brainsway Ltd. He is on scientific advisory boards for Bionomics Ltd and LivaNova and is a founder of TMS Clinics Australia. There are no other potential conflicts of interest.
Significance (up to 80 words): This preliminary study is the first to demonstrate decreased functional connectivity during an emotion regulation task in individuals with chronic low back pain compared to healthy controls. This contributes to the literature in furthering our understanding of the role of cognitive and emotional processes in chronic pain, which may have implications in future development of treatment and management programs for chronic low back pain.
Abstract

**Background:** Chronic pain groups often report higher levels of negative emotions, suggesting reduced ability to regulate emotions effectively. However, little is known of the underlying neural cognitive mechanisms. Therefore, the aim of this study was to explore brain activity and functional connectivity during cognitive reappraisal in chronic low back pain (cLBP).

**Methods:** This study recruited 24 female participants; 12 with cLBP and 12 healthy controls. Participants completed an emotion regulation task that involved cognitive reappraisal of negative images during functional magnetic imaging (fMRI). The negative affect following each image and perceived success of the task were reported. Region of interest and seed-to-voxel analyses were conducted using key regions involved in cognitive reappraisal (i.e., amygdalae and dorsomedial prefrontal cortex) as seed regions.

**Results:** During the task, there were no group differences in the behavioural measures in blood oxygen level-dependent (BOLD) brain activation in the seed regions. Functional connectivity analysis showed reduced coupling between the amygdalae and dorsolateral prefrontal cortex, orbitofrontal cortex and inferior parietal cortex in the cLBP group compared to controls. Connectivity between the amygdala and inferior parietal cortex positively correlated with the percent of reduced negative affect during reappraisal in the cLBP group.

**Conclusion:** These preliminary findings demonstrate that individuals with cLBP exhibit similar emotion regulation abilities to healthy controls at the behavioural and BOLD level. However, altered functional connectivity observed in the cLBP group may reduce effective cognitive reappraisal. These results provide evidence for the potential clinical impact of network changes in CLBP.
Introduction
Current models of pain highlight that cognition and emotion are prominent domains that contribute to the development and maintenance of chronic pain (Bushnell, Čeko, & Low, 2013; Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Lumley et al., 2011). Indeed, chronic pain is often associated with elevated negative emotional states which are considered to be both a driver as well as a clinical consequence of the condition (Holmes, Christelis, & Arnold, 2012). One cognitive process that may be essential in moderating these negative emotional states is emotion regulation (Hamilton, Karoly, & Kitzman, 2004; Koechlin, Coakley, Schechter, Werner, & Kossowsky, 2018; Solberg Nes, Roach, & Segerstrom, 2009; Van Damme & Kindermans, 2015). Emotion regulation refers to the ability to alter the magnitude or duration of an emotion (Gross, 1998), which may be important in alleviating pain-related symptoms and minimising the vulnerability to developing chronic pain (Koechlin et al., 2018). Despite the potential clinical importance of emotion regulation in chronic pain, our understanding of its role and underlying neurobiology remains unclear.

Cognitive reappraisal, one such emotion regulation strategy, refers to the reinterpretation of a situation or stimulus to decrease its emotional significance (Gross, 2002). It is not only believed to be more effective in reducing negative emotions compared to other strategies, such as suppression (i.e., the inhibition of current emotions) (Gross & John, 2003; McRae et al., 2010), but it has also been found to modulate noxious pain and the related negative affect in healthy populations (Hampton, Hadjistavropoulos, Gagnon, Williams, & Clark, 2015; Woo, Roy, Buhle, & Wager, 2015).

Cognitive reappraisal appears to be involved in mediating psychological and emotional factors in chronic pain, suggesting it is an important secondary process that modulates risk factors (Koechlin et al., 2018). However, the current literature has predominantly been based on self-report measures, and limited studies have examined emotion regulation capabilities at the behavioural and neural level in chronic pain populations.

Understanding the neural processes in cognitive reappraisal is important to identify the relevant brain regions and networks that can be used for the development of targeted therapies.
Investigation of brain function in chronic pain has already demonstrated that brain activity and circuitry is disrupted in chronic pain (Bushnell et al., 2013; Malfliet et al., 2017), potentially affecting processes such as cognitive reappraisal. In chronic low back pain (cLBP), for instance, decreased gray matter volume and altered functional connectivity has been identified in key regions associated with cognitive reappraisal, such as the amygdala (Jiang et al., 2016; Mao & Yang, 2015) and medial prefrontal cortex (Baliki et al., 2006; Baliki, Mansour, Baria, & Apkarian, 2014; Yuan et al., 2017). However, it remains unknown whether these brain alterations linked to chronic pain may affect cognitive reappraisal.

Therefore, the aim of this exploratory study was to investigate the behavioural and neural differences during a task examining cognitive reappraisal of negative emotion in a cLBP group compared to healthy controls using functional magnetic resonance imaging (fMRI). This study used region of interest (ROI) and seed-to-voxel analyses to compare functional activity and connectivity during a cognitive reappraisal task. The bilateral amygdalae were used as ROIs as previous studies found deactivation of the bilateral amygdalae reflected successful cognitive reappraisal (Buhle et al., 2014; Kanske, Heissler, Schönfelder, Bongers, & Wessa, 2011). The dorsomedial prefrontal cortex (DMPFC) was also selected as an ROI as it has been identified as a part of the network involved in cognitive reappraisal (Kanske et al., 2011; McRae et al., 2010; Phan et al., 2005) but also altered in cLBP populations (Baliki et al., 2014; Yuan et al., 2017). We hypothesised the cLBP group would have a poorer performance in reappraising negative emotional stimuli as well as reduced bilateral amygdalae deactivation and altered functional connectivity within the brain during the cognitive reappraisal task compared to healthy controls.
Methods

Study population
This study recruited a total of 24 participants comprised of 12 healthy volunteers and 12 individuals with cLBP from the community. All participants were female, right-handed (Edinburgh Handedness Inventory (Oldfield, 1971), $M = 83\%$) and did not have a current or history of psychiatric illness, excluding depression and anxiety following onset of cLBP (assessed by the Mini international Neuropsychiatry Interview (MINI) (Sheehan et al., 1998)). The inclusion of only females was to control for any potential gender differences during the reappraisal in the task (Domes et al., 2010; McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008). The participants in the cLBP group had experienced non-specific low back pain for more than 3 months, with moderate to severe low back pain (>21% on the Oswestry Disability Index (Fairbank & Pynsent, 2000)). The healthy participants were excluded if they reported current or a history of any chronic pain conditions (i.e., pain that persisted for more than 3 months).

Procedure
All potential participants were screened for eligibility through a phone screen. Eligible participants attended a 2-hour session at the Monash Biomedical Imaging facility (MBI, Clayton, Victoria). During this session, participants completed the Beck’s Depression Inventory II (BDI-II) (Beck, Steer, & Brown, 1996) and short-form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987) as well as a training session for the emotion regulation task.

The BDI-II is a 21-item self-report measure of depression. Each item refers to different aspects of depression with 4 possible options (0-3) indicating the level of severity. Total scores range between 0-63, with scores between 0 to 13 indicating minimal range, 14 to 19 indicating mild depression, 20 to 28 indicating moderate depression and 29 to 63 indicating severe depression (Beck et al., 1996).
BDI-II has been shown to have good reliability and validity in chronic pain (Harris & D’Eon, 2008) and healthy populations (Wang & Gorenstein, 2013).

The SF-MPQ is a measure of pain that consists of 3 components. The first is the Pain Rating Index that comprises of 15 pain-related word descriptors (e.g., throbbing, aching, fearful pain) and rated on a scale from 0-3 (i.e., none, mild, moderate and severe). It has descriptors comprised of 2 subscales, the sensory (11 words) and affective subscales (4). The other 2 components consist of a 10 cm visual analogue scale (VAS) that measures average pain and the present pain intensity (PPI) item that indicates current level of pain (Melzack, 1987). In this study, as the healthy control group did not report any low back pain, only the cLBP group completed this questionnaire.

Emotion regulation task

All participants completed an emotion regulation task, adapted from Ochsner et al. (2004) and Erk et al. (2010), during an fMRI scan. Participants viewed a series of negative and neutral images and were required to either view them and respond naturally (i.e., Look condition), or reappraise the images to reduce negative emotions by imagining events from a third person perspective (Decrease condition). Following each image, participants reported the strength of their negative affect on a scale of 0 to 8, with 0 representing low and 8 indicating high negative affect. Participants were provided full instructions of the task and given an opportunity to ask questions to ensure they understood the task and completed a full practice block (i.e., 36 trials) prior to the fMRI scan.

The images presented were selected from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008) based on their normative ratings in valence (1 = unpleasant/negative, 5 = neutral, 9 = pleasant/positive) and arousal (1 = calm, 9 = excited). The negative images had a mean valence rating of 2.40 (SD = 0.57) and arousal rating of 5.74 (0.75) while neutral images had a valence rating of 5.16 (0.39) and arousal rating of 3.41 (0.79). Independent t-tests comparing the negative and neutral images showed significant differences in valence ($t(70) = -24.08, p < .001$) and arousal ($t(70) = 12.81, p < .001$) ratings.
The task consisted of two blocks, with 36 trials in each block. At the beginning of each trial, an instructional cue was shown for 2 seconds (i.e., Look or Decrease), followed by one of the selected negative or neutral image that was presented for 10 seconds (Fig. 1). A rectangular bar appeared above a scale numbered 0 to 8. The bar started at 0 and expanded from left to right towards the number 8 and participants pressed a button when the bar reached the number that represented their level of negative affect. Participants were given a 4 second rest period before the next trial. After the completion of the fMRI, participants reviewed all the negative images during decrease trials and rated their level of perceived success in reducing their negative affect on a scale of 0 to 10. The strength of negative affect reported after the Decrease-Negative and Look-Negative trials were used to calculate the percent of reduced negative affect due to cognitive reappraisal based on a formula from a previous study (Campbell-Sills et al., 2011): [(Mean rating during Decrease-Negative – Mean rating during Look-Negative)/Mean rating during Look-Negative] x -100, with higher percentages indicated greater reduction in negative affect due to cognitive reappraisal.

fMRI Data Acquisition

Structural and functional data were acquired on a Siemens Magnetom Skyra 3 Tesla MRI scanner with a 32 channel receive-only phased-array head coil (Siemens, Erlangen, Germany). High resolution magnetisation prepared rapid acquisition gradient echo (MP2RAGE) T1-weighted structural data were acquired (208 sagittal slices, repetition time (TR) = 1540ms, echo time (TE) = 2.55ms, flip angle = 9°, acquisition matrix = 256 x 256, FoV = 256mm, 1mm isotropic voxels). Whole-brain echo-planar images (EPIs) were acquired for the task-related functional data (axial; TR = 2570ms, TE = 30ms, flip angle = 90°, acquisition matrix = 64 x 64, FoV = 192mm, slice thickness = 3.0mm)

fMRI data preprocessing and analyses

All data were preprocessed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) implemented on MATLAB R2017b (MathWorks, Sherborn, MA,
USA). The anatomical image was segmented into white matter (WM), gray matter (GM) and cerebral spinal fluid (CSF). All functional images were slice time corrected and realigned to correct for motion where a mean image was produced for each participant. The mean images were coregistered to the respective anatomical image, which was then normalised to the Montreal Neurological Institute (MNI) T1 template (resampled to 2 x 2 x 2mm voxels). These parameters were applied to the realigned EPIs and then smoothed using an 8mm FWHM Gaussian kernel.

BOLD activation

The preprocessed images were entered into a first-level fixed effects analysis using the general linear model. The 10-second duration of when images were shown for each task condition (Decrease-Negative, Look-Negative, Decrease-Neutral and Look-Neutral) and the 4-second rest period were modelled as boxcar regressors. The six motion parameters obtained from realignment was regressed out as a covariate of no interest. All regressors were convolved with the canonical hemodynamic response function (HRF). A high pass filter set at 128 seconds was applied to remove low-frequency noise. These models were then used to create contrasts for emotion regulation (Decrease-Negative > Look-Negative) and emotional processing (Look-Negative > Look-Neutral) for each participant.

The first-level contrasts were entered into a second-level random effects analysis for group comparison using a full factorial 2 x 2 ANOVA design with the group and task conditions (Decrease-Negative > Look-Negative and Look-Negative > Look-Neutral) as factors in a priori regions of interest (ROI) analysis.

Using the Marsbar toolbox (http://marsbar.sourceforge.net), three 10mm spheres were created for the left (-18, -3, -15) and right (30, -3, -15) amygdala as well as the DMPFC (9, 30, 39) using the coordinates from a meta-analysis in cognitive reappraisal (Buhle et al., 2014). The time series of the blood-oxygenated level dependent (BOLD) activity for each of the regions of interest were extracted. Significance was set at $p < .001$ uncorrected at the peak level and $p < .05$ family-wise error (FWE).
corrected at the cluster level. Partial eta squared ($\eta^2_p$) was calculated to determine the effect sizes for group and task effects.

Functional connectivity

Functional connectivity was assessed using the generalized psychophysiological interaction (gPPI) method in the Conn toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) using MATLAB. The gPPI analyses has been found to be more sensitive and powerful in detecting functional connectivity differences than standard PPI (Cisler, Bush, & Steele, 2014; McLaren, Ries, Xu, & Johnson, 2012). In addition to the preprocessing procedures described previously, the functional data were denoised according to the CompCor method (Behzadi, Restom, Liau, & Liu, 2007) implemented within the Conn toolbox to remove physiological noise. This involved regressing out outliers identified during ART from head motion as well as signals from the WM and CSF.

The gPPI method is used to estimate the changes in functional connectivity between seed regions and the rest of the brain (physiological factor) during a specific task (psychological factor). The time course of BOLD activity in the bilateral amygdalae and DMPFC (defined above) were extracted as the physiological factor and the Decrease-Negative > Look-Negative contrast was defined as the psychological factor. The interaction term was calculated from the product of the ROI time course and the contrast between the conditions.

The gPPI analyses were conducted for each ROI and entered into a one-sample $t$-test to examine functional connectivity for each group separately and then into a two-sample $t$-test for group comparisons. The beta estimates from the gPPI were extracted for further correlational analyses with the behavioural measures using SPSS version 23. The significances threshold was set at $p < .001$ uncorrected at the voxel level and $p < .05$ FWE-corrected at the cluster level. All significant clusters were labelled using the Brodmann’s Area (BA) and Automated Anatomical Labeling (AAL) atlases defined within MRICro (Rorden & Brett, 2000). Cohen’s $d$ was calculated to establish the effect sizes of the group differences.
Results

Behavioural data

There were no significant differences in age or years of education, although BDI scores were significantly higher in those with cLBP compared to healthy controls (Table 1). There were no significant group differences in the percent of reduced negative affect (M ± SE: cLBP = 14.71 ± 5.86 vs healthy controls = 28.38 ± 5.43, Cohen’s d = 0.73) and the perceived level of success (M ± SE: cLBP = 5.72 ± 2.18 vs healthy controls = 6.97 ± 1.39, Cohen’s d = 0.21) during cognitive reappraisal (Fig. 2A and 2B). No significant between group differences in the strength of negative affect were observed in the Decrease-Negative (Cohen’s d = 0.64), Look-Negative (Cohen’s d = 0.03), Decrease-Neutral condition (Cohen’s d = 0.03) and Look-Neutral (Cohen’s d = 0.34) conditions. There was a significant reduction in reported strength of negative affect during the Decrease-Negative condition compared to the Look-Negative condition within the cLBP and healthy control groups (cLBP: t(11) = -2.38, p = 0.037, Controls: t(11) = -4.87, p < 0.001). There was a significantly higher strength of affect in the Look-Neutral condition compared to the Decrease-Neutral in the healthy control group (t(11) = -3.06, p = 0.011) but this was not observed in the cLBP group (Fig. 2C).

Region of interest – BOLD activation

No significant main group effects were observed in the left (F(1,22) = 0.53, p = .473, ηp² = .024) or right amygdala (F(1,22) = 2.14, p = .16, ηp² = .089). There were main task effects with increased activation of the right amygdala during the emotional processing (Look-Negative > Look-Neutral) compared to the cognitive reappraisal (F(1,22) = 9.35, p = .006, ηp² = .298). A similar trend was also observed in the left amygdala (F(1,22) = 3.66, p = .069, ηp² = .143) however, did not reach statistical significance (see Fig. 3). No significant group F(1, 22) = 0.13, p = 0.73, ηp² = 0.006) or task F(1, 22) = 0.13, p = 0.73, ηp² = 0.006) effects were observed in the DMPFC. There were no significant group x task interaction effects observed in any of the seed regions (right amygdala: F(1, 22) = 0.31, p = 0.59,
Cognitive reappraisal in chronic low back pain

\[ \eta_p^2 = 0.01; \text{left amygdala: } F(1,22) = 0.15, p = 0.70, \eta_p^2 = 0.007; \text{DMPFC: } F(1,22) = 0.002, p = 0.97, \eta_p^2 < 0.001. \]

Functional connectivity

In the healthy control group, the gPPI analysis showed significant coupling between the left amygdala and right orbitofrontal cortex and left inferior frontal gyrus (pars orbitalis) as well as between the DMPFC and the right posterior cingulate gyrus (Table 2). No significant relationships were observed with the right amygdala in the healthy control group or between the three seed regions and the rest of the brain in the cLBP group.

Between-group comparisons showed the healthy control group had stronger functional coupling between the right amygdala and the right dorsolateral prefrontal cortex (DLPFC) as well as between the left amygdala and the right orbitofrontal cortex (OFC) and left inferior parietal cortex (IPL) (see Table 3 and Fig. 4). In the cLBP group, Spearman’s rho correlation analysis showed that the connectivity values between the left amygdala and IPL was positively related with the percent of reduced negative affect \((r = 0.81, p = 0.001, \text{see Fig. 5})\). No other significant correlations were observed in the cLBP group.

Discussion

This preliminary study investigated behavioural and neural properties associated with cognitive reappraisal in cLBP compared with healthy controls. There were no significant differences in behavioural measures including the level of negative affect reported after each trial across the 4 task conditions, as well as percent of reduced negative affect and the perceived level of success during cognitive reappraisal between the cLBP and healthy control groups. The BOLD analysis showed significant deactivation in the right amygdala and a trend in the left amygdala during reappraisal across both groups, however, no significant group differences were observed. In the functional
connectivity analysis, the cLBP group had reduced coactivation between the right amygdala and dorsolateral prefrontal cortex (DLPFC) as well as between the left amygdala and orbitofrontal cortex (OFC) and the inferior parietal cortex (IPL) than the healthy control group. Finally, there was a significant positive correlation between the connectivity between the left amygdala and IPL and greater reduction of negative affect during cognitive reappraisal in the cLBP group. Overall, the behavioural and BOLD activation results were not expected, however, the functional connectivity results supported the proposed hypothesis.

Behavioural results

Similar levels of negative affect were reported across the 4 different task conditions in both groups. The percent of reduced negative affect and perceived success during the cognitive reappraisal task did not differ between groups. These findings might suggest that the cLBP and healthy control groups were successful in downregulating their emotional response to negative stimuli at the behavioural level. However, these results should be interpreted with caution as there were large between-group effect sizes, suggesting there may be limitations due to small sample size.

BOLD analysis

The BOLD analysis showed no group differences across the three seed regions with small to moderate effect. Significant task effects where decreased activity during reappraisal across the overall sample were observed in the right amygdala and a trend in the left amygdala. This was consistent with previous studies reflecting reduction in negative emotional response during reappraisal (Buhle et al., 2014; Dörfel et al., 2014; Eippert et al., 2007; Frank et al., 2014; Golkar et al., 2012; Kanske et al., 2011; Kompus, Hugdahl, Ohman, Marklund, & Nyberg, 2009).

Taken together with the behavioural results, these findings may demonstrate that individuals with cLBP have the capacity to engage in effective cognitive reappraisal. However, this only reflects behaviour within a control setting where participants were specifically instructed on the type of emotion regulation strategy used and thus, does not consider the type of emotion regulation
strategies that are used spontaneously or habitually. For example, previous studies found that individuals with mood conditions demonstrated similar levels of performance in reappraisal to healthy controls when provided with specific instructions. Instead, during spontaneous emotion regulation (i.e., when no instructions were given), they reported greater use of maladaptive strategies, such as suppression or rumination, which was also related to sustained negative emotions (Ehring, Tuschen-Caffier, Schnülle, Fischer, & Gross, 2010; Quigley & Dobson, 2014). Furthermore, different strategies are employed depending on the context (Szasz, Coman, Curtiss, Carpenter, & Hofmann, 2018). Therefore, it is possible that emotion regulation strategies are domain specific and individuals with cLBP may have adopted ineffective strategies in response to pain-related events, although this may not necessarily translate to other aspects of their lives.

Functional connectivity

While group differences in BOLD activity were not observed in our sample, reduced functional connectivity between the amygdalae and prefrontal regions, including the DLPFC and OFC as well as with the IPL were apparent in the cLBP group when compared with controls. As these prefrontal and parietal cortical regions are commonly active during cognitive reappraisal (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Erk et al., 2010; Golkar et al., 2012), our findings may reflect disruption in brain regions involved in emotional regulation in cLBP. Interestingly, there were no significant group differences observed with the DMPFC seed, suggesting not all regions involved in reappraisal are affected in cLBP.

Furthermore, only the connectivity between the left amygdala and IPL significantly correlated with the percent of reduced negative affect. Previous studies have demonstrated an association of the IPL with perspective taking (Arora et al., 2015; Ruby & Decety, 2003). Therefore, this might reflect reduced ability to engage in effective cognitive reappraisal, such as distancing, where changing perspective is required in the cLBP group. Despite this, it is possible that the functional connectivity differences observed with the DLPFC and OFC may reflect other cognitive processes involved in
reappraisal that was not measured in this study. For instance, the DLPFC has been active during different types of emotion regulation strategies, as well as negative and neutral stimuli, and therefore, has broadly been associated with cognitive load in response to the attentional demands of the task (Golkar et al., 2012; Kohn et al., 2014).

Future directions and implications

The overall findings contribute to the growing body of evidence that has observed cortical and subcortical reorganisation in cLBP populations. The differences observed in this study were predominantly in regions that have been linked to cognitive reappraisal, which could potentially serve as targets for intervention. Non-invasive brain stimulation such as transcranial direct current stimulation (tDCS) have demonstrated that targeting brain regions such as the DLPFC may promote self-regulation in both emotional and pain processes (Kelley, Gallucci, Riva, Romero Lauro, & Schmeichel, 2019; Seminowicz & Moayedi, 2017). For example, a previous study found that stimulating the DLPFC using tDCS can modulate reappraisal processes (Feeser, Prehn, Kazzer, Mungee, & Bajbouj, 2014). Another study reported that using cognitive-behavioural therapy to change pain-related cognition in a chronic pain group was effective in increasing GM volume in areas including the DLPFC, which was associated with reduced pain catastrophizing (Seminowicz et al., 2013). Hence, these studies demonstrate there are different types of interventions that could potentially be used to reverse maladaptive neuroplastic changes that may have occurred during the development or persistent of pain. It could also improve the behavioural aspect of cognitive reappraisal, whereby individuals may be taught to use adaptive emotion regulation strategies in response to pain-related negative affect and thus, reducing their vulnerability to persisting pain.

While this was a preliminary study, the study utilised a small sample size and therefore interpretation of the findings is limited. Future studies should recruit a larger sample to increase statistical power and explore co-variates such as age and sex as well as secondary psychological factors such as depressed mood. While there were significant differences in depressed mood
(measured by BDI-II) in the sample of this study, the mean scores of the cLBP participants were still within the minimal range, indicating low levels of depressed mood. However, future studies could investigate whether depression could also impact cognitive reappraisal in cLBP. As this is a cross-sectional study, causality cannot be determined. Longitudinal studies will be needed to determine if underlying deficits in the emotion regulation brain networks contribute to the development of cLBP, while exploring effective connectivity in emotion regulation could contribute to a more comprehensive understanding of the networks involved. It is also important to note that gPPI analyses measure relative connectivity values between regions where direction of connectivity cannot be determined, hence, advanced connectivity analyses may allow a more comprehensive understanding of the networks involved and affected during reappraisal in cLBP. This study only explored cognitive reappraisal for emotion regulation. Comparing the different types of emotion regulation strategies and the habitual coping strategies, particularly those in response to events related to the cLBP would be valuable in establishing the role of emotion regulation in cLBP.

Conclusion

Overall, this preliminary study demonstrated that individuals with cLBP reported effective emotion regulation at the behavioural level compared to healthy pain-free controls. While there were no group differences in the BOLD activity within the amygdala, the cLBP group exhibited altered functional connectivity during cognitive reappraisal. Specifically, the cLBP group showed reduced coupling between the amygdalae and the DLPFC, OFC and IPL compared to controls. Moreover, greater connectivity between the amygdala and IPL positively correlated with the percent of reduced negative affect during reappraisal in the cLBP group. These findings suggest that the underlying brain changes observed in cLBP may affect cognitive processes such as emotion regulation which has the potential to be used as treatment targets in future studies.
Author contributions: We declare that all listed authors significantly contributed to the development of this study. Prof Enticott and Prof Rossell were involved in the design of the experiment and management of data collection. Dr Maller and Dr Kirkovski were involved in data analysis and interpretation of the data. A/Prof Urquhart, Prof Cicuttini and Prof Fitzgerald contributed to the development of the study and supervision of data collection. Dr Fitzgibbon and Ms Ng was involved data collection, data analysis, interpretation of the data and the preparation of this manuscript. All authors have read and approved the submission of this manuscript.
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Cognitive reappraisal in chronic low back pain


Cognitive reappraisal in chronic low back pain


Table 1. Demographic characteristics of the chronic low back pain and healthy control groups (M (SD)).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Chronic low back pain</th>
<th>Healthy controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.5 (10.59)</td>
<td>30.25 (5.22)</td>
<td>0.085</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.45 (2.71)</td>
<td>18.27 (2.73)</td>
<td>0.142</td>
</tr>
<tr>
<td>BDI-II</td>
<td>13.00 (9.05)</td>
<td>3.18 (2.64)</td>
<td>0.003</td>
</tr>
<tr>
<td>ODI</td>
<td>45.17 (12.58)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SF-MPQ Pain rating</td>
<td>17.08 (6.01)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SF-MPQ VAS</td>
<td>54.29 (19.43)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SF-MPQ PPI</td>
<td>2.50 (0.52)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

BDI-II = Beck’s Depression Index II (maximum score of 63); ODI = Oswestry Disability Index (maximum score of 100); SF-MPQ = short-form McGill Pain Questionnaire; VAS = Visual analogue scale (maximum score of 100); PPI = Present Pain Index (maximum score of 5); SF-MPQ Pain rating (maximum score of 100).
Table 2. Functional connectivity analyses during cognitive reappraisal (Decrease-Negative > Look-Negative) in the healthy control group.

<table>
<thead>
<tr>
<th>Seed</th>
<th>Region</th>
<th>Cluster</th>
<th>Peak, t</th>
<th>MNI coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Amygdala</td>
<td>R orbitofrontal cortex (BA 11)</td>
<td>85</td>
<td>6.09</td>
<td>22, 62, -10</td>
</tr>
<tr>
<td></td>
<td>L inferior frontal gyrus (pars orbitalis) (BA 47)</td>
<td>78</td>
<td>7.29</td>
<td>-48, 42, -8</td>
</tr>
<tr>
<td>DMFPC</td>
<td>R posterior cingulate gyrus (BA 23)</td>
<td>51</td>
<td>6.14</td>
<td>2, -12, 40</td>
</tr>
</tbody>
</table>

DMFPC = dorsomedial prefrontal cortex; MNI = Montreal Neurological Institute.

p < 0.001 uncorrected at voxel level, p < 0.05 FWE-corrected at cluster level.
Table 3. Functional connectivity analyses showed significant differences during cognitive reappraisal (Decrease-Negative > Look-Negative) between groups (healthy controls > cLBP).

<table>
<thead>
<tr>
<th>Seed</th>
<th>Region</th>
<th>Cluster</th>
<th>Peak, t</th>
<th>MNI coordinates</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Amygdala</td>
<td>R dorsolateral prefrontal cortex (BA 46)</td>
<td>127</td>
<td>6.49</td>
<td>30 22 38</td>
<td>2.65</td>
</tr>
<tr>
<td>L Amygdala</td>
<td>R orbitofrontal cortex (BA 11)</td>
<td>113</td>
<td>5.41</td>
<td>24 58 -12</td>
<td>2.21</td>
</tr>
<tr>
<td></td>
<td>L inferior parietal cortex (BA 40)</td>
<td>65</td>
<td>4.64</td>
<td>-48 -44 58</td>
<td>1.89</td>
</tr>
</tbody>
</table>

cLBP = chronic low back pain; $d = $Cohen’s $d$; MNI = Montreal Neurological Institute. $p < 0.001$ uncorrected at voxel level, $p < 0.05$ FWE-corrected at cluster level.
Cognitive reappraisal in chronic low back pain

Fig. 1. An example of a trial of the emotion regulation task.
Cognitive reappraisal in chronic low back pain

2a) Overall perceived success of cognitive reappraisal (M ± SE) during Decrease-Negative trials,
2b) Percent of reduced negative affect (M ± SE) during cognitive reappraisal, 2c) Average strength of
negative affect (M ± SE) for the Decrease-Negative, Look-Negative, Decrease-Neutral and Look-
Neutral trials in the chronic low back pain (cLBP) and healthy control groups.

* p < .05
Cognitive reappraisal in chronic low back pain

Fig. 3. Region of interest (ROI) analysis in the left (-18, -3, -15) and right (30, -3, -15) amygdala. BOLD activation ($M \pm SE$) was observed during emotional processing (Pro) and reappraisal (Reapp). * $p < .05$
Fig. 4. Functional connectivity analyses showed significant differences between right amygdala and dorsolateral prefrontal cortex, as well as between the left amygdala and right orbitofrontal cortex, and left inferior parietal cortex during cognitive reappraisal (Decrease-Negative > Look-Negative) between groups (healthy controls > cLBP).
Fig. 5. Spearman’s rho of functional connectivity of the left amygdala and inferior parietal cortex (IPL) with percent of reduced negative affect in the chronic low back pain group.
Chapter 6
Default mode network connectivity and pain catastrophizing in chronic low back pain

Manuscript


6.1 Preamble to empirical paper

The previous chapter presented a study that demonstrated disrupted functional connectivity during cognitive reappraisal of negative stimuli in individuals with chronic low back pain. In addition to task-related studies, fMRI can also be used to measure spontaneous brain activity during resting-state (i.e., when individuals are not involved in any task) [206]. Assessment of resting-state neural activity can inform our understanding on large-scale brain networks. Large-scale brain networks refer to various brain regions that function together, indicated by synchronised patterns of brain activity (i.e., functional connectivity). This is important because complex processes, such as cognition, are attributed to dynamic interactions of the various brain regions within these networks [207] and thus, disruptions in these networks can lead to cognitive dysfunction [208]. While there are a number of brain networks relevant to pain, based on the findings of our systematic review, this chapter specifically explores the integrity of and the potential functional significance of the default mode network (DMN) in chronic low back pain.
The DMN was initially defined as the collective brain regions that are active when individuals are not engaged in external tasks [209, 210]. Further examinations have also established the DMN is associated with internal processes such as mentalizing, personal introspection, autobiographic or episodic memory recall and mind wandering [95, 202, 203, 211]. Disrupted DMN connectivity has been observed in several chronic pain disorders [204, 212] as well as disorders that are commonly comorbid with chronic pain, such as depression [213-215] and anxiety [216]. In addition, DMN alterations have been associated with specific clinical symptoms. In depression, for instance, functional abnormalities in the DMN was associated with rumination [217, 218], a process referring to repetitive, negative thoughts focused on the emotional distress as well as the potential causes and consequences of their condition [219]. Of specific relevance to this thesis, alterations in DMN connectivity have shown to have significant correlations with increased pain catastrophizing in chronic pain conditions [200, 201], demonstrating it may be linked to maladaptive cognitive processes. Therefore, the following study investigates the disruptions of DMN connectivity and how it may be related to pain catastrophizing, including its related subscales, rumination, magnification and helplessness, in chronic low back pain. This study is the analysis of resting-state data obtained from the same sample as the study presented in Chapter 5.
Examining resting-state functional connectivity in key hubs of the default mode network in chronic low back pain

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Sources of Funding
This study was supported by the Monash Platform Access Grant. DMU and BMF are recipients of a National Health and Medical Research Council (NHMRC) Career Development Fellowship (Clinical Level 2 #1142809) and an NHMRC Early Career Fellowship (#1070073) respectively. PBF was supported by a Practitioner Fellowship grant from National Health and Medical Research Council (NHMRC) (1078567). PGE is supported by a Future Fellowship from the Australian Research Council (ARC) (FT160100077). SLR holds a Senior Research Fellowship from National Health and Medical Research Council (NHMRC) (1154651).

Conflict of interest
PBF has received equipment for research from Medtronic, MagVenture A/S and Brainsway Ltd. He is on scientific advisory boards for Bionomics Ltd and LivaNova and is a founder of TMS Clinics Australia. There are no other potential conflicts of interest.
Abstract

Objective: Disruptions with the brain have been observed within the default mode network (DMN) in chronic low back pain (CLBP). In order to understand how these disruptions may be related to CLBP, it is important to establish the extent in which this network may be affected. While studies using seed-based analysis have found disrupted functional connectivity in the medial prefrontal cortex (mPFC), a major hub of the DMN, limited studies have investigated other equally important hubs, such as the posterior cingulate cortex (PCC) in CLBP.

Methods: This preliminary study comprised 12 individuals with CLBP and 12 healthy controls. All participants completed a functional magnetic resonance imaging (fMRI) scan during resting-state. The mPFC and PCC were used as seeds to assess functional connectivity.

Results: Both groups displayed similar patterns of DMN connectivity, however, group comparisons showed that CLBP group had reduced connectivity between the mPFC and superior temporal gyrus and cerebellum, as well as between the PCC and angular gyrus compared to healthy controls. We also conducted an exploratory analysis investigating whether the functional significance of the altered mPFC and PCC connectivity was related to pain catastrophizing in CLBP, but no significant results were observed.

Discussion: This study provides evidence that there are disruptions in both the mPFC and PCC connectivity in CLBP, although its functional role requires further investigation.

Keywords: Chronic low back pain; default mode network; resting-state; pain catastrophizing; fMRI.
Introduction

Chronic low back pain (CLBP) is a debilitating health condition (1) that is often associated with emotional and cognitive deficits (2, 3). Recent neuroimaging studies have demonstrated structural and functional reorganisation of the brain that is associated with CLBP outcomes (4-6). For example, there is evidence that has shown reduced regional gray matter volume was related to higher levels of pain intensity (7), while alterations in functional connectivity have been associated with the development of CLBP (8, 9). Therefore, identifying the underlying neural mechanisms could further our understanding of how neural changes may contribute to CLBP.

While the affected brain regions and networks in CLBP are widespread, the current literature suggests that brain activity during resting-state is often disrupted, particularly the default mode network (DMN) (4, 5). The DMN consists of brain regions including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, middle temporal gyrus, middle frontal gyrus and inferior parietal lobule (10-12), that are active at rest (i.e., when not engaged in an external task). It is therefore often associated with internal or self-referential processes such as mentalizing, autobiographic or episodic memory recall and mind wandering, demonstrating it is involved in introspective processes (10, 12-14).

Previous neuroimaging studies using a seed-based approach have reported altered functional connectivity within the DMN during resting-state in CLBP. These studies have identified reduced connectivity in the mPFC, a key region involved in the communication and integration (i.e., hub) of the DMN, with other DMN regions such as the precuneus, as well as increased connectivity to areas outside of the DMN, such as the insula and anterior cingulate cortex (15, 16). Thus, they found disruptions both within the DMN as well as its projections to areas outside of the network in CLBP. However, these seed-based studies have predominantly focused on the mPFC in CLBP. Limited
studies have explored how functional connectivity may be altered in other major hubs of the DMN in CLBP, such as the PCC.

Furthermore, the functional significance of DMN disruptions is not fully understood in CLBP. There is evidence to suggest it may be related to pain catastrophizing (i.e., exaggerated negative emotional and cognitive response to pain-related events (17, 18)) in other chronic pain conditions. For example, neuroimaging studies using the seed-based approach demonstrated that altered connectivity from the PCC to the dorsolateral prefrontal cortex (DLPFC) were related to pain catastrophizing in chronic migraine patients (19), while increased mPFC connectivity to other regions of the DMN in chronic temporomandibular disorder patients correlated with rumination (a subdomain of pain catastrophizing) (20). In CLBP, only one study has investigated the relationship between the DMN with pain catastrophizing. This study investigated connectivity from subregions of the amygdala to two specific regions of the DMN, the mPFC and the PCC. While reduced connectivity was observed between these areas, it was not related to pain catastrophizing (21). Thus, the relationship between changes in DMN connectivity and pain catastrophizing in CLBP remains unclear.

In this study, we examined the differences in functional connectivity of two key hubs of the DMN, namely the mPFC and PCC, in CLBP compared to healthy controls, using a seed-to-voxel approach. We also conducted an exploratory analysis to examine whether altered functional connectivity with the mPFC and PCC may be related to pain catastrophizing. We hypothesized that the CLBP group would exhibit altered functional connectivity with both mPFC and PCC seeds, which would correlate with higher levels of pain catastrophizing.
Methods

Participants

A total of 24 participants were recruited for this study, 12 individuals with CLBP and 12 healthy controls. All participants were female and right-handed (measured by the Edinburgh Handedness Inventory) (22). This study only recruited females to control for any potential gender differences in the DMN (23, 24). Participants were screened using the Mini international Neuropsychiatry Interview (MINI) (25) and were excluded if they had current or a history of any psychiatric conditions (with the exception of depression and anxiety following the onset of CLBP). Participants in the CLBP group were included if they reported having >3 months of moderate to severe non-specific LBP (>21% on the Oswestry Disability Index, (26)). Participants in the healthy control group were pain-free and did not have a history of any chronic pain conditions (i.e., pain that persisted for more than 3 months).

Procedure

Participants for this study were recruited as a part of a larger study. All eligible participants attended one 2-hour session at the Monash Biomedical Imaging centre (MBI, Clayton, Victoria), where they completed a structural and functional MRI scan. This included resting-state acquisition (approximately 6 minutes) where participants were instructed to keep their eyes open and allow their mind to wander. They also completed a series of questionnaires, including the Pain Catastrophizing Scale (PCS) and the Beck Depression Inventory II (BDI-II).

The PCS (27) is a self-report measure that consists of 13 items that assesses the thoughts and feelings of individuals during pain. Participants respond to each item on a 5-point Likert scale (0 = not at all to 4 = all the time). The PCS contains 3 subscales, rumination, magnification and helplessness. It has shown strong reliability and validity in community-based chronic pain and pain-free samples (28).
The BDI-II (29) is a self-report measure of depression. It consists of 21 items referring to various aspects of depression and participants are required to provide a response on a scale of 0 to 3, indicating the level of severity. Total scores range between 0 to 63, with higher scores indicating more severe depression. The BDI-II has been shown to have good reliability and validity in chronic pain (30) and healthy populations (31).

Data acquisition

Structural and functional data were acquired on a Magnetom Skyra 3 Tesla MRI scanner with a 32 channel receive-only phased-array head coil (Siemens, Erlangen, Germany). High resolution magnetisation prepared rapid acquisition gradient echo (MP2RAGE) T1-weighted structural data were acquired using the following parameters: 208 sagittal slices, repetition time (TR) = 1540ms, echo time (TE) = 2.55ms, flip angle = 9°, acquisition matrix = 256 x 256, FoV = 256mm, 1mm isotropic voxels. Whole-brain echo-planar images (EPIs) were acquired for the resting-state data (TR = 2570ms, TE = 30ms, flip angle = 90°, acquisition matrix = 64 x 64, FoV = 192mm, slice thickness = 3.0mm).

Data preprocessing and functional connectivity analysis

All data were preprocessed and analysed through the Conn toolbox in MATLAB 2017a (MathWorks, Sherborn, MA, USA). Resting-state data preprocessing steps included removal of the first 4 volumes, slice time correction, motion correction, co-registration of structural to functional image, segmentation of the structural image into white matter (WM), gray matter (GM) and cerebral spinal fluid (CSF), normalization of the structural and functional images into MNI space and functional images were smoothed at 8mm FWHM Gaussian kernel. The preprocessed data were band-pass filtered at 0.008 to 0.09 Hz and denoised according to the CompCor method (32) to remove physiological noise.
Seed-to-voxel analysis was conducted to assess resting-state functional connectivity of the DMN. This involves extracting the times series of a region of interest (ROI) as seeds and the correlation with the time course with the other voxels of the brain is calculated to determine functional connectivity with other regions. As the mPFC (x, y, z = 4, 42, 3) and PCC (-8, -56, 39) are core hubs of the DMN, they were used as seeds in this study. The co-ordinates of the seed regions were obtained from meta-analysis (33). A 10mm sphere was created for each seed using the Marsbar toolbox (34).

First-level analysis involved extracting the time series from the seed regions and correlated with the rest of the voxels in the brain during resting-state for each individual and transformed into Fisher-transformed correlation coefficients. At the second-level analysis, one-sample t-tests were conducted to examine the CLBP and healthy controls separately and then independent t-tests were conducted to compare group differences for each seed. Significance was set at $p < 0.05$ FWE-corrected at the cluster level. All brain regions were labelled using Automated Anatomical Labeling (AAL) atlases defined within MRICro (35).

**Correlational analyses**

The connectivity values of the significant clusters observed in between group comparisons differences were extracted and the values were entered into a Spearman rho with the overall PCS and its subscale scores. Correlations were considered to be significant when $p < 0.05$. 
Results

Behavioural Results

There were no significant group differences in age. As expected, there were significant differences between the CLBP and healthy control groups in the overall PCS score as well as the Magnification and Helplessness subscales, although not in the Rumination subscale. The CLBP group also reported significantly higher BDI-II scores compared to the healthy controls.

Functional connectivity

Within-group connectivity

With the PCC as the seed, the CLBP group showed functional connectivity to the right superior frontal gyrus, left precuneus, bilateral angular gyri, right middle temporal gyrus, left inferior temporal gyrus and regions of the cerebellum. The healthy control group also demonstrated similar connectivity, with regions including the left middle frontal gyrus, left precuneus, bilateral angular gyri, bilateral middle temporal gyri and cerebellum, as well as the bilateral parahippocampal gyri (see Table 2, Figure 1).

Both CLBP and healthy control groups showed functional connectivity between the mPFC seed with the left anterior and middle cingulate areas, right angular gyrus, and right middle temporal gyrus. In addition, the CLBP group also showed connectivity to the left angular gyrus, brainstem, cerebellum and left parahippocampal gyrus. Connectivity to the right superior temporal pole, left inferior frontorbital gyrus, left middle occipital gyrus, left transverse temporal gyrus, right parahippocampal gyrus and left middle temporal gyrus were also observed in healthy control group (Table 3, Figure 2).
Between-group connectivity

Group comparisons showed the CLBP group had decreased functional connectivity between the mPFC and the left superior temporal gyrus and the cerebellum, as well as between the PCC and angular gyrus (Table 4, Figure 3) compared to healthy controls. The CLBP group did not show significant clusters of increased functional connectivity to other regions of the brain compared with healthy controls.

Exploratory analysis with the Pain Catastrophizing Scale

The analyses using Spearman rho showed there were no significant correlations observed between the significant clusters of the group differences and the overall PCS scores (left temporal gyrus: $r = .37, p = .23$; cerebellum (lobule VI): $r = -0.10, p = .75$; cerebellum (lobule IV, V): $r = 0.15, p = .63$; angular gyrus: $r = -0.37, p = 0.23$) or the rumination (left temporal gyrus: $r = .28, p = .37$; cerebellum (lobule VI): $r = -0.04, p = 0.91$; cerebellum (lobule IV, V): $r = 0.10, p = .75$; angular gyrus: $r = -0.32, p = .31$), magnification (Left temporal gyrus: $r = 0.38, p = .23$; cerebellum (lobule VI): $r = -0.15, p = .64$; cerebellum (lobule IV, V): $r = 0.11, p = .74$; angular gyrus: $r = -0.19, p = .55$), or helplessness (Left temporal gyrus: $r = 0.40, p = .20$; cerebellum (lobule VI): $r = -0.25, p = .43$; cerebellum (lobule IV, V): $r = 0.15, p = .64$; angular gyrus: $r = -0.25, p = .44$) subscale scores in the CLBP group.

Correlation with depression

As depression is highly comorbid with CLBP (36-38), and has also been shown to disrupt DMN connectivity (39-41), we ran a secondary exploratory analysis using Spearman rho to examine whether the observed differences in DMN connectivity between groups was related to scores on the BDI. We observed no significant correlations between the significant clusters and the BDI-II scores (left temporal gyrus: $r = 0.09, p = .80$; cerebellum (lobule VI): $r = 0.21, p = .51$; cerebellum: $r = -0.29, p = .36$; angular gyrus: $r = -0.43, p = .17$).
Discussion

This study used seed-based analyses to examine functional connectivity in CLBP from two key hubs of the DMN, the mPFC and PCC. The CLBP demonstrated reduced functional connectivity (i.e., lower strength of coactivation) between the mPFC and the left superior temporal gyrus and regions of the cerebellum, as well as between the PCC and angular gyrus when compared to healthy controls. In line with the existing literature that have observed disruptions within the DMN (15, 16, 42), these findings add further evidence to show altered connectivity is not only apparent in the mPFC but in PCC as well in CLBP.

Specifically, our findings demonstrate both the mPFC and PCC seeds show altered connectivity with different areas of the brain. This may suggest that while these two hubs function together as a part of the DMN, they exhibit distinct changes in connectivity in CLBP, which may have implications on subsequent neural processes, such as internal spontaneous thought processes. For example, studies have shown connectivity between the mPFC and superior temporal gyrus were associated with attention away from a task (43) as well as stimulus-independent thoughts (13), potentially reflecting increased mind wandering. Furthermore, decreased functional connectivity in the cerebellum (lobule IV and V), regions implicated in the sensorimotor network, during resting-state has been observed in non-specific CLBP patients compared with healthy controls (44). As the mPFC may be an important region in linking the DMN to other networks in CLBP (45), altered connectivity between the mPFC and the cerebellum may have implications on the interaction with other networks, such as the sensorimotor networks. Our results also showed reduced connectivity between the PCC and the angular gyrus, which is also another core region of the DMN (10). Within the DMN, the angular gyrus is considered a cross-modal hub as it is implicated in both the integration of information within the network, as well as processes related to attention, memory, and cognition (46). Our findings may then reflect that information processed within the DMN may be compromised. Overall, our results
therefore suggest that altered connectivity of the mPFC and PCC may impact CLBP differently and should be taken into consideration in future studies.

However, the functional significance of these disruptions remains unclear. An exploratory analysis was therefore conducted to examine whether altered functional connectivity in the mPFC and PCC in the CLBP group were related to pain catastrophizing. Our findings did not support such a relationship which is consistent with previous studies that reported similar findings in CLBP (21) and other chronic pain conditions (47, 48). However, this is in contrast to other studies finding significant correlations between altered DMN connectivity and pain catastrophizing in patients with chronic migraine and temporomandibular disorder (19, 20). It may be that these inconsistencies are due to the differences between chronic pain conditions as CLBP is a heterogeneous pain condition (49). Therefore, it is possible that pain catastrophizing in CLBP is being underpinned by other neural networks. Indeed, one study found increased amygdala-central executive network (CEN) connectivity was related to pain catastrophizing in CLBP (21). As the CEN has been associated with cognitive processes involved in attention and working memory (50, 51), increased activity is thought to reflect the negative cognitive bias from pain catastrophizing (21).

There are alternative processes that may be associated with changes in the DMN. For instance, one study found that altered DMN connectivity during resting-state was associated with clinical outcomes including pain duration, interference and severity in CLBP (45). Further to this, increased activity of the mPFC has also been associated with spontaneous fluctuations of low back pain in CLBP populations (15, 52), supporting the notion that the DMN areas such as the mPFC may be related to pain outcomes in CLBP rather than cognitive processes such as pain catastrophizing.
We also explored whether disrupted DMN connectivity was linked to depression scores, as suggested in previous studies of patients with major depression (39-41). Our results did not yield any significant associations with depression scores on the BDI-II, which was in line with previous studies in CLBP (16, 21). Of note, as the mean BDI-II score of the CLBP group in this study was not clinically significant ($M = 13$, i.e., within minimal range), so our findings may suggest that low levels of depressive symptoms do not affect the DMN in CLBP. Together, the absence of a relationship between BDI-II scores and our groups differences suggests our findings are associated with CLBP specifically, rather than secondary emotional factors such as depression. However, it should be noted that we did not have the data to explore other processes that may influence the DMN, such as anxiety. Not only are high levels of anxiety often reported in CLBP populations (37, 38), it has also been associated with disrupted DMN activity (53, 54), and therefore, should be considered in future studies.

It is also worth noting that there was high inter-individual variability in the clinical features of CLBP within our sample, which was likely to impact on underlying neural networks. For instance, one study identified a subgroup of CLBP patients that reported low levels of emotional and cognitive deficits including low pain catastrophizing (55). In contrast, another subgroup was identified that had significantly prominent cognitive and emotional impairments (55). Together, this highlights the heterogeneity in CLBP presentation, which is anticipated to have differential impact on neural mechanisms. Our behavioural data supports this variability with PCS scores ranging from 8 to 33 as well as BDI-II scores between 2 to 26 in the CLBP group. This suggests that those with CLBP may have different psychological profiles and, thus, there may be larger variability in brain connectivity within the population. However, we were unable to explore this further due to sample size.
There are a number of other considerations that should be taken into account when interpreting the results of this study. Our sample size was relatively small, and therefore, the participants were not matched for age and only consisted of females, which reduced the generalizability of our findings. Future studies with a larger sample will be needed to explore whether there are different subgroups in CLBP population. As this was a cross-sectional study, the causality for the DMN disruptions observed in the CLBP group cannot be determined. Additionally, we only investigated one possible cognitive process (i.e., pain catastrophizing) that may be related to the DMN and did not account for other potential spontaneous thought processes that may occur during resting-state such as mind wandering, daydreaming or creative thinking (56). While little is known about how these processes are affected in the context of pain, one study demonstrated that increased DMN activity during nociceptive pain may represent diversion of attention away from pain stimuli and reflect internal processes such as mind wandering (57). However, as this study was conducted in healthy controls, future studies should explore this further in chronic pain conditions. Despite the limitations of the study, our pain group all reported the same chronic pain condition and consisted of females, eliminating any potential sex differences.

Overall, this study provides evidence that demonstrate disrupted connectivity in the major hubs of the DMN, specifically in the mPFC and PCC, in individuals with CLBP compared to healthy controls. However, our data does not support a relationship of altered DMN connectivity being related to pain catastrophizing in the CLBP. While there is a growing body of evidence demonstrating this network has been implicated in CLBP, the functional significance of DMN changes in chronic pain requires further investigation.
References


Table 1. Demographic characteristics and behavioural measures in chronic low back pain and healthy control groups (M (SD))

<table>
<thead>
<tr>
<th></th>
<th>Chronic low back pain</th>
<th>Healthy controls</th>
<th>p-value</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.5 (10.6)</td>
<td>30.3 (5.22)</td>
<td>0.085</td>
<td>0.74</td>
</tr>
<tr>
<td>PCS</td>
<td>20.3 (8.99)</td>
<td>10.2 (10.9)</td>
<td>0.021</td>
<td>1.01</td>
</tr>
<tr>
<td>PCS Rumination</td>
<td>7.08 (3.70)</td>
<td>4.75 (4.88)</td>
<td>0.20</td>
<td>0.54</td>
</tr>
<tr>
<td>PCS Magnification</td>
<td>4.42 (2.81)</td>
<td>1.58 (1.88)</td>
<td>0.009</td>
<td>1.19</td>
</tr>
<tr>
<td>PCS Helplessness</td>
<td>8.83 (3.83)</td>
<td>3.83 (4.78)</td>
<td>0.010</td>
<td>1.15</td>
</tr>
<tr>
<td>BDI-II</td>
<td>13.0 (9.05)</td>
<td>3.18 (2.60)</td>
<td>0.003</td>
<td>1.47</td>
</tr>
</tbody>
</table>

BDI-II = Beck Depression Inventory II (maximum score of 63); PCS = Pain Catastrophizing Scale (maximum score of 52).
PCS Rumination (maximum score of 16); PCS Magnification (maximum score of 12); PCS Helplessness (maximum score of 24).
Table 2. Significant clusters during resting-state with posterior cingulate cortex as the seed.

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster size</th>
<th>Peak, t</th>
<th>MNI Coordinates</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>Chronic low back pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Superior frontal gyrus</td>
<td>8465</td>
<td>8.44</td>
<td>18</td>
</tr>
<tr>
<td>L Precuneus</td>
<td>6173</td>
<td>15.9</td>
<td>-10</td>
</tr>
<tr>
<td>L Angular gyrus</td>
<td>2361</td>
<td>12.7</td>
<td>-42</td>
</tr>
<tr>
<td>R Angular gyrus</td>
<td>1729</td>
<td>9.21</td>
<td>42</td>
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<tr>
<td>R Middle temporal gyrus</td>
<td>972</td>
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<td>62</td>
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<tr>
<td>L Inferior temporal gyrus</td>
<td>933</td>
<td>6.55</td>
<td>-62</td>
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<tr>
<td>R Cerebellum (Lobule IX)</td>
<td>454</td>
<td>6.87</td>
<td>10</td>
</tr>
<tr>
<td>R Cerebellum (Crus II)</td>
<td>284</td>
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<td><strong>Healthy controls</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>L Middle frontal gyrus</td>
<td>10692</td>
<td>9.89</td>
<td>-26</td>
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<tr>
<td>L Precuneus</td>
<td>5989</td>
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<td>L Angular gyrus</td>
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<td>-54</td>
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<td>L Middle temporal gyrus</td>
<td>2603</td>
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<tr>
<td>R Middle temporal gyrus</td>
<td>2130</td>
<td>7.54</td>
<td>64</td>
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<td>R Angular gyrus</td>
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<tr>
<td>L Parahippocampal gyrus</td>
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<td>-22</td>
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<td>R Parahippocampal gyrus</td>
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Table 3. Significant clusters during resting-state with medial prefrontal cortex as the seed.

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster size</th>
<th>Peak, t</th>
<th>MNI Coordinates</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>x    y    z</td>
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<tr>
<td>Chronic low back pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Anterior cingulate gyrus</td>
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<td>21.2</td>
<td>0    38   6</td>
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<tr>
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<td>4245</td>
<td>9.00</td>
<td>0    -18  36</td>
</tr>
<tr>
<td>R Angular gyrus</td>
<td>1430</td>
<td>7.78</td>
<td>48   -46  32</td>
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<tr>
<td>L Angular gyrus</td>
<td>516</td>
<td>5.63</td>
<td>-50  -72  40</td>
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<td>435</td>
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Table 4. Significant clusters of difference between the chronic low back pain and healthy control group (healthy controls > chronic low back pain).

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<tr>
<td>Posterior cingulate cortex</td>
<td>L Angular gyrus</td>
<td>114</td>
<td>5.28</td>
<td>-54 -66 38</td>
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</tbody>
</table>
**Figure Legend**

Figure 1. Significant clusters during resting-state with the posterior cingulate cortex as the seed, in the chronic low back pain and healthy control groups.

Figure 2. Significant clusters during resting-state with the medial prefrontal cortex as the seed, in the chronic low back pain and healthy control groups.

Figure 3. Significant group differences observed in the posterior cingulate cortex and medial prefrontal cortex seeds (healthy controls > chronic low back pain)
Chapter 7
General Discussion

This thesis investigated the role of pain-related cognition on low back pain outcomes and the underlying neural mechanisms associated with cognitive processes in chronic low back pain. This chapter will present a summary of the main findings from the systematic review and 4 empirical studies, followed by a discussion of the potential implications of the research. The strengths and limitations of this thesis, as well as the future directions for research are also presented.

7.1 Summary of main findings

7.1.1 Structural and functional brain changes may be associated with altered emotion and cognition in chronic low back pain

The systematic review that was performed to examine the evidence for brain changes in chronic low back pain using MRI protocols showed a number of structural and functional abnormalities (Chapter 2). Structural alterations were seen in chronic low back pain groups, with reduced GM volumes in regions involved in the perception and modulation of pain, such as the S1, insula, thalamus, dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex (mPFC). The resting-state fMRI studies, assessing the pattern of brain activity in the absence of a task, observed disruptions in functional connectivity, particularly within the default mode network (DMN); a brain network implicated in self-referential processes such as mind wandering. Event-related fMRI studies exploring the brain activations (measured as BOLD responses) during experimentally induced noxious stimuli showed that individuals with chronic low back pain had lower pain thresholds; however, no significant differences in brain activity were observed, suggesting that nociceptive pain processes may be remain relatively intact.
Interestingly, there were a number of studies that examined the BOLD responses that corresponded with spontaneous fluctuations of low back pain. They observed that during the acute phase of low back pain, pain fluctuations were associated with brain activity in regions typically involved in nociceptive pain processes, such as the insula and thalamus. In contrast, the pain experienced in chronic low back pain activated regions related to emotion and self-referential processes, such as the amygdala and mPFC. This may indicate that there may be distinct neural mechanisms that underpin acute and chronic pain. Brain activity during cognitive tasks was also examined, although, there were limited number of studies, suggesting the need for further work in this area. This review also explored the relationships between the structural and functional brain changes with cognitive and emotional processes, assessed through self-report measures and task performance (completed outside of scanner). The findings showed there were variability within the results as some studies reported that GM volume, task-related functional connectivity and BOLD responses during noxious stimulation, correlated with pain-related negative affect and catastrophizing, while others did not.

This is a comprehensive systematic review that examined the structural and functional brain changes in chronic low back pain. The results of this review demonstrated that there are widespread alterations in brain regions involved in sensory, cognitive and emotional processes in chronic low back pain, which is in line with previous systematic reviews in other chronic pain conditions [186, 187]. There was evidence to suggest that while acute low back pain is associated with nociception, emotional processes may be driving factors of chronic low back pain. However, as there were limited studies that explored how the structural and functional alterations in the brain relates to cognitive and emotional processes, the functional significance of these changes and its influence on chronic low back pain outcomes is unclear.
7.1.2 Negative back beliefs were associated with persistent, high intensity back pain

The role of back beliefs in low back pain were examined in a 2-year community-based cohort study (Chapter 3). Participants were categorised based on their pain intensity scores at baseline and follow-up time points into no, developing, resolving, and persistent high pain intensity groups. Our results demonstrated that negative back beliefs were associated with persistent high pain but not in the no and resolving high pain group. This relationship remained significant when the model was adjusted for age, gender, body mass index (BMI), and mental health. Secondary analyses comparing the 4 pain groups showed no group differences in age, or the proportion of females were observed, although the persistent high pain group had higher levels of BMI than the no high pain group. The persistent high pain group also held more negative beliefs, particularly in response to statements (from the Back Beliefs Questionnaire, BBQ) related to the course of low back pain (i.e., low back pain gets progressively worse) and ability to return to work (i.e., low back pain results in long periods of time off work). Overall, these findings demonstrate that maladaptive cognitions, such as negative back beliefs contribute to the persistence of low back pain.

Negative back beliefs represent the view that low back pain impairs the integrity of the back that inevitably results in long-term pain and disability. Therefore, these results suggest that when low back pain is viewed as a persistent health condition, it reflects lower levels of perceived pain controllability. In accordance with the implicit theory of pain (outlined in Chapter 1), these beliefs may lead to passive coping behaviours that further exacerbates pain and contribute to the development of chronic low back pain. Overall, this study provided evidence that, in addition to fear-avoidance and self-efficacy beliefs, perceptions related to potential consequences of low back pain have repercussions on pain outcomes. As population-based education and media campaigns have been shown to be successful in improving back
beliefs [159, 161], targeting back beliefs, particularly at the community-level for groups or individuals could potentially reduce persistent pain and promote recovery of low back pain.

7.1.3 Poor subjective well-being was associated with persistent, high levels of low back pain and disability

The influence of subjective well-being, and its subdomains, on the progression of low back pain intensity and disability in community-based women over 2 years were investigated (Chapter 4). Similar to the previous study in Chapter 3, participants were categorised into no, developing, resolving, and persistent high pain groups. The results showed that the persistent high pain group reported significantly lower levels of overall subjective well-being than the no and developing high pain group, after adjusting for age and BMI. Examination of the subdomains demonstrated that the persistent high pain group had poorer perceptions of their general health compared to the no high pain and developing high pain groups, as well as reduced vitality compared to the other 3 pain groups. Depressed mood and positive well-being were also lower in the persistent high pain intensity group compared to the no high pain group. Participants were then categorised according to the disability scores into no, developing, resolving, and persistent high disability. Analysis demonstrated that the persistent high disability group had significantly lower overall subjective well-being compared with the no disability group, which remained significant when adjusted for age and BMI. In terms of the subdomains, the persistent high disability group showed reduced general health compared to the no disability and developing disability groups, as well as lower levels of vitality than the no disability and resolving disability groups.

This study demonstrated that an individual’s self-evaluation of their well-being, particularly subdomains related to health, contribute to persistent high pain and disability. As general
health refers to concerns regarding illness, pain and fears related to their health status, it may suggest that those who perceive low back pain to be a significant health burden (i.e., threatening condition) are more likely to develop chronic low back pain. This view could potentially contribute to pain catastrophizing (i.e., the exaggerated view that low back pain is a severe medical condition), which results in increased pain-related fear and maladaptive pain behaviours, as suggested in the fear-avoidance model. Furthermore, vitality refers to the presence of energy and lack of fatigue that is indicative of physical and psychological health [220]. It has been proposed that vitality (i.e., positive energy) is a key process that assists in regulating with negative emotions and coping with life problems. In turn, effective emotion regulation and adaptive coping behaviours reduces the impact of emotional and life stressors and thus, preserving vitality [221]. Considering this, lower levels of vitality may be the result of ineffective coping processes in response to low back pain which, consequently, contributes to persistent pain and disability. While current psychosocial interventions focus on reducing negative aspects of subjective well-being, such as depressive symptoms [222], these results may suggest that improving other aspects, such as perceived health may be important in minimising the progression of chronic low back pain. Therefore, coping strategies, such as adaptive emotion regulation processes that are found to promote subjective well-being [181, 223], could be incorporated in future interventions.

7.1.4 *Altered neural activity reduced effective cognitive reappraisal in chronic low back pain*

The underlying neural processes (i.e., BOLD response and functional connectivity) involved in cognitive reappraisal were investigated in individuals with chronic low back pain compared with healthy controls using fMRI (Chapter 5). The bilateral amygdalae and the dorsomedial prefrontal cortex (DMPFC) were used as regions of interest (ROIs) based on coordinates from a meta-analysis on cognitive reappraisal [143]. There were no significant group differences
observed in the behavioural results; that is, self-report ratings of reduced negative affect and perceived task success during cognitive reappraisal were equal in the chronic low back pain and the healthy control group. Indeed, no group differences were observed in the BOLD analysis, with the data across the both groups showing significant deactivation in the right amygdala. However, when exploring the functional connectivity of the ROIs during the task, the chronic low back pain group, in contrast to the healthy controls, showed decreased connectivity between the right amygdala and DLPFC, as well as between the left amygdala and the orbitofrontal cortex (OFC), and inferior parietal lobule (IPL). As these brain regions are active during cognitive reappraisal [143], disrupted connectivity may suggest impaired emotion regulation processes. Supporting this notion, a subsequent correlational analysis showed that the decreased connectivity between the left amygdala and IPL was associated with smaller reductions of negative affect from reappraisal in the chronic low back pain group.

This is the first study to present evidence for impaired brain mechanisms in cognitive reappraisal in chronic low back pain. It is well established that the brain changes in chronic low back pain disrupts the neural pathways typically involved in the perception and modulation of nociceptive pain (e.g., from experimentally induced noxious stimulation) [79]. Thus, this study adds to the literature by demonstrating that the functional alterations in the brain also affects cognitive processes that may potentially contribute to the development and maintenance of chronic low back pain. Intriguingly, while the disrupted functional connectivity may compromise effective emotion regulation, differences in the behavioural responses and BOLD activity were not observed. This may suggest that individuals with chronic low back pain are capable of engaging in adaptive coping processes in response to negative emotional stimuli, however, this was presented within a controlled environment where the type of emotion regulation strategy used were specifically instructed. As the type of emotion regulation
employed can be context-specific [224], it is not known if these strategies are used in response to pain and emotional distress associated with chronic low back pain.

7.1.5 Disrupted resting-state functional connectivity in key hubs of the default mode network in chronic low back pain

The functional connectivity of two key hubs of the DMN, the mPFC and posterior cingulate cortex (PCC), during resting-state (i.e., in an absence of a task) were examined in individuals with chronic low back pain and healthy controls. In addition, the relationship between the observed differences in the DMN and pain catastrophizing were also explored in chronic low back pain. The results showed that there was reduced functional connectivity between the mPFC and the left superior temporal gyrus and regions of the cerebellum, as well as between the PCC and angular gyrus in the chronic low back pain group compared to healthy controls. This is consistent with previous studies that observed disruptions within the DMN [106, 191, 204] and furthers the current literature by demonstrating that both the key hubs of the DMN, exhibited altered connectivity. Further correlational analysis examining the relationship between the altered DMN connectivity and pain catastrophizing, as well as its subscales, rumination, magnification, and helplessness, in the chronic low back pain group reported no significant relationships. Interestingly, the chronic low back pain group showed significantly higher levels of pain catastrophizing, magnification and helplessness compared to healthy controls.

These findings provide evidence of disruptions in the key hubs of the DMN in chronic low back pain, however, its functional significance was not related to pain catastrophizing. The altered connectivity may impact other processes associated with DMN function, such as mind wandering [95, 211]. Engaging in mind wandering during pain, represents the ability to
disengage from pain stimuli [225]; hence, disruptions in the DMN may reflect sustained attention and hypervigilance of pain, which is related to pain-related fear and anxiety, as well as maladaptive avoidance behaviours [121]. Furthermore, as hubs of networks play an important role in network communication and integration [226], aberrant DMN connectivity may affect its interaction with other networks. It has been suggested that the DMN is a key network a part of the ‘pain connectome’. The pain connectome is the dynamic interactions between various networks that represents the sensorimotor, cognitive and emotional aspects of pain [98]. Therefore, impairments in the DMN may alter its interaction with the other networks within the pain connectome and thus, influence the way pain is perceived and processed in chronic low back pain.

7.1.6 Summary of overall findings

Overall, this body of work aimed to further our understanding of the factors associated with chronic low back pain based on the biopsychosocial model, specifically relationship between cognition (psychological) and neurobiological processes (biological). The key findings of this thesis have been summarised in Figure 1. The significance of the findings from this thesis were two-fold. First, the work in this thesis provided supporting evidence for the significance of cognition in chronic low back pain. Pain-related cognitions (i.e., beliefs and subjective well-being perception; Chapters 3 and 4) were involved in the development of persistent pain and disability outcomes while maladaptive cognitive processes (i.e., pain catastrophizing; Chapter 6) were associated with chronic low back pain. Thus, demonstrating that cognition influences the development and clinical presentation of chronic low back pain patients, likely contributing to the heterogeneity within the low back pain population. Second, the fMRI findings from the thesis supported the relationship between altered cognition in chronic low back pain and changes in brain structure and function. The findings from the systematic review and the study presented in Chapter 6, demonstrated that networks involved in cognition and emotion, such
as the default mode network, are impaired in chronic low back pain, rather than the pain pathways typically involved in nociceptive processes (i.e., in response to noxious stimulation). Further to this, Chapter 5 provided evidence of disruptions in functional connectivity associated with impaired adaptive cognitive coping processes (i.e., cognitive reappraisal) in chronic low back pain. Therefore, these findings have demonstrated that the interaction between cognition and brain mechanisms contributes to or is involved in driving the chronic low back pain experience.
Figure 1. Diagram of key findings identified in this thesis

Cognitive factors
- Negative back beliefs: Risk factors for persistent high pain intensity (Chapter 3)
- Reduced subjective well-being: Risk factors for persistent high pain intensity and disability (Chapter 4)
- Increased pain catastrophizing: (Chapter 6)
- Cognitive reappraisal: Disrupted functional connectivity reduced effective cognitive reappraisal (Chapter 5)

Brain networks
- Widespread structural and functional abnormalities in cognitive and emotional networks (Chapter 2)
- Disrupted default mode network connectivity (Chapter 6)
- Altered connectivity in network involved in cognitive reappraisal

Chronic low back pain
7.2 Implications

The findings from this thesis have contributed to our understanding of the role of pain-related cognition and brain mechanisms involved in chronic low back pain. There are 3 important implications that can be drawn from the evidence. First, this thesis has identified additional modifiable cognitive risk factors as well as altered neural processes associated with cognitive processes that contribute to low back pain outcomes. Second, the cognitive risk factors and the underlying brain mechanisms may assist in the classification of low back pain patients into subgroups that allows novel approaches to personalise treatment for patients. Third, the findings from the studies have highlighted important cognitive and neurobiological processes that can be used as potential targets of interventions for chronic low back pain.

7.2.1 Understanding cognition in chronic low back pain: Modifiable cognitive risk factors and altered brain mechanisms

7.2.1.1 Identifying modifiable cognitive risk factors for persistent low back pain and disability

Cognition is known to play a significant role in the development of chronic low back pain. While the current literature has already documented several risk factors for low back pain [113, 130, 227], the findings from this thesis have identified important cognitive risk factors for high levels of persistent low back pain intensity and disability, potentially contributing to the transition from acute to chronic low back pain. The cohort study in Chapter 3 demonstrated that maladaptive back beliefs, particularly those related to the course of low back pain and ability to return to work, were associated with persistent high pain. This suggests there are specific types of back beliefs that make a more significant contribution to persistent high pain. Furthermore, the cohort study presented in Chapter 4 provided evidence that showed poor subjective well-being was associated with persistent high pain and disability, particularly perceptions related to low general health and vitality. These findings highlight the importance
of the perception on health and well-being in the progression of low back pain and disability. Overall, these findings demonstrated that back beliefs and subjective well-being are modifiable cognitive risk factors for persistent low back pain and disability, which can be used to identify individuals who may be vulnerable to developing persistent pain. As both back beliefs and subjective well-being are modifiable factors (i.e., factors that can be adjusted or changed that alters the progression of chronic low back pain [228]), they may also be used as potential targets for interventions.

7.2.1.2 Integrating brain mechanisms and cognition

The relationship between neurobiological and cognitive processes in the experience of pain has been well established in neuroimaging studies within healthy populations [124, 229]. For example, expectations of pain events influences pain perception as well as the related brain activity [230, 231] while pain during a cognitive task can alter functional connectivity in the associated network [232]. Although there has been a growing body of evidence that has observed maladaptive reorganisation within brain networks underpinning pain perception, cognition and emotion in chronic low back pain, there are limited studies that have specifically investigated the relationship between these brain changes and cognitive processes. The systematic review presented in Chapter 2 reported that of the 55 studies that were included, only 3 investigated the relationship of abnormal brain activity and cognitive function during fMRI. Although, there were 15 studies (included in the review) that had examined the correlational relationship between structural or functional brain changes with self-report measures (e.g., depression or catastrophizing) and performance of behavioural task (completed outside of fMRI scan); however, this approach is not informative of the patterns of brain activity or functional connectivity during specific cognitive processes. Thus, our understanding of the mechanistic role of cognition in the brain and its influenced on chronic low back pain remains limited.
Indeed, the neuroimaging study in Chapter 5 is novel, in that it demonstrated that altered functional connectivity reduced effective cognitive reappraisal in chronic low back pain, establishing a relationship between the neurobiological and cognitive processes. Interestingly, there were no significant group differences in task performance, suggesting that changes within the brain may not always directly influence behaviour. It has been argued that changes in the pattern of functional connectivity within brain networks during a cognitive process can be due to other factors that is not related to cognition; thus, demonstrating there is a complex relationship between neural activity in the brain and cognition [233, 234]. Nevertheless, this highlights the importance taking an integrative approach that considers both neurobiological and cognitive processes in order to develop our understanding of the various risk factors for the progression of chronic low back pain.

7.2.2 Subgroups of chronic low back pain patients

A further implication of this thesis is the emergence of subgroups within the low back pain population. Within-group variability has been observed in the groups of the cohort studies presented in Chapters 3 and 4. Specifically, the resolving groups exhibited positive back beliefs and high levels of subjective well-being, despite having high levels of pain intensity or disability, compared to the persistent groups. There has been one previous study that classified chronic low back pain patients according to various psychological factors, including beliefs related to fear-avoidance and self-efficacy [235]. Another previous study identified subgroups based on subjective well-being, which was indicated by levels of depression, anxiety, emotional distress, and perceived control of life [236]. However, both studies were cross-sectional and therefore cannot provide robust evidence that these subgroups have potential clinical implications. As the findings of this thesis are from cohort studies, they suggest that back beliefs and subjective
well-being may inform the classification of patients and the progression of low back pain. It also highlights the importance of assessing different types of back beliefs, such as those related to life, home and work duties, and measuring the multiple subdomains of subjective well-being that extends beyond the negative aspects such as depression, anxiety (i.e., emotional distress), to other subdomains such as general health and vitality.

In addition to psychosocial factors, the findings from the systematic review (Chapter 2) and the neuroimaging studies in Chapters 5 and 6 may allude to the possibility that the brain changes observed in chronic low back pain may be used to classify patients into subgroups. For example, the study presented in Chapter 5 found an association between decreased functional connectivity between the amygdala and IPL and reduced effective reappraisal. This shows there is within-group variability which could potentially have clinical significance. It may be possible that those with reduced amygdala-IPL connectivity may reflect individuals who may have an increased risk of developing mood disorders. However, due to the limitations of the study (outlined in respective chapter), this implication remains speculative. Furthermore, it has been suggested that understanding the various neurobiological abnormalities can be used as a method of subgrouping or “clustering” variability within populations [237]. An example of this can be seen in depression as it is also known to be a heterogeneous condition [238]. Previous fMRI studies have reported that patients with depression not only exhibit aberrant functional connectivity during cognitive tasks and resting-state [214, 239, 240], but these abnormalities can be used to identify subtypes or ‘biotypes’ within the population [241, 242]. For example, an fMRI study demonstrated that distinct patterns of altered functional connectivity during resting-state identified 4 biotypes of depression which was associated with specific profiles of clinical symptoms that differed in the levels of anxiety, anhedonia and fatigue [241]. Another study found that the specific biotypes was with differences in treatment response to selective serotonin-reuptake inhibitor (SSRI) [242]. Therefore, this demonstrates that alterations in
neurobiological processes can be used to stratify patients into functional subgroups that not only explains clinical symptoms, it is also predictive of treatment response. Similar work in chronic low back pain has recently emerged, with one study that found specific pain characteristics corresponded with distinct patterns of neural activity [243]. Therefore, this study, along with the findings from this thesis suggest that neurobiological processes may be used to distinguish subgroups within chronic low back pain populations.

7.2.3 Potential targets for intervention

7.2.3.1 Psychosocial interventions

The evidence presented in this thesis demonstrates that cognitive factors, such as back beliefs and subjective well-being, contribute to the persistence of low back pain and disability, and therefore, may serve as potential targets for interventions. For example, an individual who presents with negative back beliefs may be guided through specific psychosocial interventions targeted at pain education to correct misconceptions about low back pain and in turn, reduce the potential for the development of persistent pain [244]. As individuals may differ in the types of beliefs related to low back pain, it highlights the need to assess beliefs that may influence low back pain outcomes. As indicated in the results in Chapter 3, this may include targeting beliefs related to consequences of low back pain in patients who present with high back pain intensity. This may involve an in-depth clinical assessment to determine a patient’s perception and anticipated consequences of exercises and daily activities [245]. Hence, appropriate pain education to improve maladaptive beliefs allows for a reconceptualization of pain whereby the perceived threat of pain is reduced [31, 246]. When this is implemented prior to exercise therapy, it may be beneficial to recovery outcomes as the pain from movements is no longer perceived as harmful [247]. Indeed, a recent RCT demonstrated that providing appropriate pain education combined with targeted training in motor control was more
effective in reducing pain, disability, mental and physical functioning as well as maladaptive pain cognitions compared to when general back pain education with standard exercise therapy were prescribed [248]. Another potential method of reducing chronicity of low back pain may be to maintain positive beliefs (e.g., remaining active, pain can be managed effectively) within the community as a preventative measure. This may be achieved through media campaigns that have previously shown to be successful in improving beliefs about low back pain (i.e., back beliefs as measured by the BBQ) in the general population as well as clinicians [161]. The information that is provided during consultations with clinicians and healthcare professionals have also shown to have a strong impact on patients’ beliefs [249]. Informing patients that the back needs to be protected or the pain is related to structural pathology are more likely to have a negative influence on the beliefs in patients [250]. Therefore, providing appropriate pain education targeting beliefs related to consequences and potential outcomes of low back pain to clinicians may ensure they convey the correct information to patients. This promotes positive back beliefs in patients and thus, may reduce persistent low back pain.

Selecting appropriate interventions for an individual may include the assessment of their overall levels of subjective well-being, in addition to their low back pain. For example, individuals with poor subjective well-being, specifically in anxiety and depression may require a psychological approach to target these subdomains of well-being. In contrast, patients who present with lower levels of perceived health, may need to improve aspects of their lives aimed to promote health. There are lifestyle factors, such as smoking [251, 252], higher BMI [253], poorer sleep quality and duration [254-256], and lower levels of physical activity [257], that not only influence subjective well-being, but are also risk factors for chronic low back pain. Previous studies have shown that targeting these factors may improve low back pain outcomes of pain and disability. For example, smoking cessation was associated with reduced chronicity of pain, while exercise interventions improved disability [258, 259] in chronic low back pain.
Together, they may enhance overall subjective well-being which in turn, minimises persistent low back pain and disability. Overall, back beliefs and subjective well-being may be effective targets for interventions in chronic low back pain, however, randomised controlled trials (RCTs) are required before these can be implemented into treatment strategies.

7.2.3.2 Non-invasive brain stimulation

Given that the studies of this thesis (Chapters 2, 5 and 6) have provided supporting evidence of maladaptive changes throughout the brain in chronic low back pain, potential methods for intervention may include the use of non-invasive brain stimulation (NIBS) techniques; describing methods capable of modulating aberrant brain activity through the scalp via magnetic and electrical stimulation. Of particular relevance is transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Specifically, TMS involves applying an electromagnetic coil to the scalp. An electric current is delivered through the coil, generating a magnetic field that induces action potentials (i.e., activating neurons) in the brain, altering neural activity [260]. In contrast, tDCS involves passing a weak electric current through electrodes placed on the surface of the scalp that corresponds to the brain regions of interest. Stimulation via positive electrodes (i.e., anode) is generally considered to increase neuronal excitability while negative electrode (i.e., cathode) decrease neuronal excitability [261]. These methods have been used to modulate brain activity in various chronic pain disorders [262-265], and could potentially revert the maladaptive brain changes in chronic low back pain.

Currently, there have been several studies that explored the effects of NIBS, predominantly in the motor cortex (M1), in chronic low back pain. Stimulation of the M1 using TMS and tDCS have reduced pain [266], which was found to be more effective than physical therapy in chronic
low back pain [267]. However, other studies found that stimulation of the M1 using tDCS did not have any significant effects on pain outcomes in chronic low back pain [268, 269]. In addition to the M1, a recent tDCS study used the dorsal anterior cingulate cortex (dACC) as the target region instead, and found reduction in emotional aspect of pain (i.e., depressive symptoms), but not pain intensity in chronic low back pain [270], demonstrating that different targets may affect different pain outcomes. It is possible that these inconsistencies are due to the heterogeneity within the chronic low back pain population as well as the variability in the protocols and study designs of the NIBS studies. Future research may, therefore, wish to explore the effects of NIBS on various targets depending on driving factors, clinical presentation, or potentially biotypes in chronic low back pain patients. For instance, patients who exhibit significant movement and motor control impairments are more likely to experience beneficial effects from M1 stimulation. In comparison, targeting regions associated with emotion and cognition may be more appropriate in patients who present with significant cognitive or emotional symptoms. Studies have found that stimulation of the dACC reduced pain-related negative affect while the DLPFC has shown to be an effective NIBS target for depression [271], a risk factor of chronic low back pain, and has also to improve cognitive processes [272], including cognitive reappraisal [273]. Therefore, these alternative areas may be potential targets for NIBS for the subgroup of patients who have emotional and cognitive processes driving their chronic low back pain.

Interestingly, the use of NIBS in conjunction with other types of interventions have also been explored in chronic low back pain. One study found that stimulating the M1 using tDCS, followed by exercise therapy significantly reduced pain and improved psychological well-being, compared to the patients received sham-tDCS (i.e., placebo) [274]. These findings may suggest that there is an additive effect on pain outcomes when NIBS techniques are combined with a behavioural intervention. However, similar results were not observed when M1 stimulation
preceded cognitive behavioural management programs [268]. The discrepancies between these two studies may be due to combination of the target region and the type of intervention that were selected. As tDCS alters neuronal excitability in a specific brain area, it has been suggested that it is important to select appropriate behavioural interventions that activate the same neural circuits [275]. Given the M1 is responsible for movement and motor control, stimulation of this area is complementary with exercise interventions. In contrast, cognitive behavioural interventions do not generally involve brain activity in the M1, and thus, the effects of tDCS were not be beneficial in this case. While further research is required, NIBS presents a new avenue for chronic low back pain treatment that can be personalised based on the clinical presentations of patients. Furthermore, rather than using NIBS as a stand-alone intervention, it could be incorporated with multidisciplinary programs, given the appropriate targets are selected, to increase the efficacy of treatments.

7.3 Strengths and Limitations

7.3.1 Strengths of thesis

This thesis presented a strong body of research that provided a comprehensive examination of pain-related cognitive factors and underlying neurobiological processes in chronic low back pain. The systematic review conducted an exhaustive search that resulted in a total of 55 eligible studies. The risk of bias was also assessed that informed the quality of studies that were included in the review. In the studies presented in Chapters 3 and 4, prospective cohort study designs were used, which allows the examination of risk factors on long-term outcomes of both low back pain intensity and disability over the course of 2 years. The inclusion of community-based cohorts enhances the generalisability of our findings to the general population. Validated self-reported measures were also used to assess pain intensity, disability, back beliefs and subjective well-being, providing valid and reliable measures for the intended outcomes. The
statistical data analyses used in these studies involved multivariable analyses, which included adjustment to account for potential confounders.

The task paradigm used in the neuroimaging study (Chapter 5) was adapted from previous fMRI studies that have demonstrated that this task is an appropriate measure for cognitive reappraisal [143, 276, 277]. The task also used images taken from the International Affective Picture System (IAPS), that have been validated based on their level of valence and arousal [278]. This ensures that the images elicit the intended negative emotional responses. Moreover, the studies of Chapters 4 to 6 consisted of only female samples. This not only eliminates potential sex differences, but these findings are specific to the female population, who have a higher risk of developing chronic low back pain compared to males [279]. Despite the strengths of this thesis, there are several limitations that should be considered.

7.3.2 Consideration of heterogeneity in chronic low back pain

The presented studies did not account for the heterogeneity in terms of clinical presentation and symptoms within the chronic low back pain population and therefore, may include potential within-group variability. In the systematic review (Chapter 2), the inclusion criteria for chronic low back pain was defined by having pain for more than 3 months. As a result, the studies in the review consisted of mixed populations as the inclusion criteria for participants varied between studies. While the criteria for some studies were solely based on self-report measures (i.e., patients reporting pain for > 3 months), other studies had various requirements including clinical diagnosis of non-specific chronic low back pain, lumbar disc herniations, failed back surgery syndrome (FBSS), or had a discogenic component assessed by lumbar MRI. The reported findings of the systematic review did not distinguish between these groups.
In the cohort studies in Chapters 3 and 4, the participants were categorised into groups based on their reported levels of pain and disability; although, other potential risk factors that may influence prognosis of low back pain, such as depression or pain catastrophizing, were not considered when subgrouping the participants. Additional information regarding other potential causes of low back pain were not acquired from the community-based samples. While low back pain was present, it is unknown whether the pain may be associated with specific causes, such as axial spondyloarthritis, or may be a secondary symptom due to other diseases including inflammatory bowel disease, or rheumatoid arthritis [32]. Similarly, the chronic low back pain participants in the neuroimaging studies (Chapters 5 and 6) were included based on pain duration of more than 3 months with moderate to severe level of disability. Therefore, various pain types and characteristics (e.g., neuropathic pain, level of central sensitisation) that affect brain processes differently [80, 280] may be present. Furthermore, these studies did not control for cognitive and emotional factors, such as the level of depression, which are known to also affect the neural processes in cognitive reappraisal [276] as well as functional connectivity in the DMN [213-215]. Therefore, this suggests that there may be large variability within the chronic low back pain samples of this thesis.

7.3.3 Sample considerations

While the cohort studies in Chapters 3 and 4 had adequate overall samples, the subgroups were largely disproportionate with 70 to 84% of participants in the no pain or disability groups. The unequal groups sizes may reduce statistical power [281] and the small sample groups may increase the risk of type II errors [282]. This may be due to the method in which participants were categorised. As the cut-off scores of the CPG were used (i.e., score of < 50 vs ≥ 50) [283], the percentage of change in pain intensity and disability scores were not considered. It is possible that individuals categorised in the various groups that does not necessarily reflect the accurate progression of pain. For example, an individual who reported a pain intensity score of
51 at the baseline and 48 at the follow-up timepoint would have been classified into the resolving pain group, despite minimal changes to their level of pain intensity. In contrast, an individual who may have reported 60 and 20 at the baseline and follow-up respectively, is more likely to reflect significant pain resolution. While the results reported significant relationships despite the modest group sizes, it should also be noted that the strength of association, such as the risk ratio, was not explored. Therefore, the findings of the studies cannot be used to determine whether beliefs about low back pain and subjective well-being were risk factors of persistent high pain intensity and disability.

There are limitations related to the sample size, age and sex in the neuroimaging studies (Chapters 5 and 6), which may influence the interpretation and generalisability of the results. The studies consisted of 24 participants, 12 with chronic low back pain and 12 healthy controls. While these were preliminary studies, the small sample reduces statistical power [284]. Additionally, the participants with chronic low back pain were relatively young with a mean age of 36.5 that ranged between 24 to 54 years of age. The variability in age may have confounding effects on the reported results which could manifest in at least two ways. First, age has been found to influence the clinical profile of chronic low back pain patients [285, 286]. For example, a study found that younger adults (aged between 21 to 44) with chronic low back pain reported less disability, but exhibited higher levels of depressed symptoms, compared to older adults (aged 45 to 64) [287]. Second, age-related differences have been found to affect structural GM and WM volumes [288, 289] as well as functional connectivity in the brain [290], regardless of chronic low back pain. Specific to this thesis, evidence has shown that cognitive reappraisal activated different areas of the brain in older adults compared to the younger adults [291, 292]. Age has also shown to affect functional connectivity in the DMN during resting-state [293, 294], which may influence the results of the study in Chapter 6. Furthermore, the included sample also only consisted of females. Given there has been
evidence from fMRI studies that have observed sex differences during cognitive reappraisal [295, 296] and resting-state functional connectivity [297], this limits the generalisability of the findings from this thesis to males with chronic low back pain.

7.3.4 Pain catastrophizing measure

The study presented in Chapter 6 investigated the potential functional significance of disrupted DMN connectivity by assessing its relationship to pain catastrophising. However, there may be limitations with the use of the PCS itself because it is a self-report measure and does not indicate the level of pain catastrophizing that may have occurred during the study. Participants may have been engaged in other self-referential thoughts related to mind wandering, mentalizing or future planning [95] during the time of the fMRI scan. This may possibly explain the lack of associations with the patterns of DMN activity and pain catastrophizing. Indeed, there are questionnaires such as the Amsterdam Resting-State Questionnaire [298], and New York Cognition Questionnaire [299], that can be administered retrospectively that provides an insight to the thought processes that occurred during resting-state; although, there are currently no validated measures for pain-related thoughts. To account for this, one recent study in fibromyalgia patients gave participants statements taken from the PCS and were instructed to reflect on how each statement related to their pain experiences. They found that catastrophic thoughts were related to increased activity in the PCC, suggesting increased DMN activity occurred specifically when engaged in catastrophic thoughts [300]. Therefore, this may provide a better method that could be used to measure for pain catastrophizing in order to clarify whether it is related to disrupted DMN functional connectivity in chronic low back pain.
7.4 Future directions

A number of important areas for future research have been highlighted by this thesis. As the study in Chapter 3 reported that back beliefs were associated with pain outcomes, they can be used to inform future interventions and treatments. A previous study has found that overall work cover claims related to low back pain reduced following a mass media campaign that aimed to correct misconceptions about low back pain [161]. Taken together, these findings suggest that to address persistent pain, future media campaigns could target specific statements about back beliefs related to the course of low back pain and return to work. Moreover, our findings suggest that clinical trials that aim to address persistent low back pain symptoms need to focus on recruiting individuals with high levels of pain that display negative back beliefs using appropriate pain education to determine if targeting back beliefs specifically are effective in improving low back pain outcomes.

This thesis demonstrated that poor subjective well-being and its subdomains are risk factors for persistent low back pain and disability. This is novel, as previous studies, including systematic reviews, have largely considered subjective well-being to be an outcome measure [301, 302]. While subdomains such as anxiety and depression have been examined as predictors of low back pain in systematic reviews [113]; the other subdomains including positive well-being, self-control, general health and vitality have received little attention. An initial step for future research is the need for a comprehensive systematic review to be conducted that examines the current evidence for subjective well-being and its subdomains on low back pain outcomes. With growing evidence for the importance of subjective well-being, further avenues of future research may include conducting an RCT to determine whether improving subjective well-being, particularly in aspects related to general health and vitality, can reduce an individual’s vulnerability to developing persistent low back pain and disability.
In relation to the neuroimaging studies, future studies should recruit larger samples to increase statistical power. This also allows for further investigation into the effects of potential covariates such as age, sex and secondary psychological factors such as depressed mood on brain mechanisms in chronic low back pain. Additionally, the evidence from this thesis (Chapters 2, 5, 6) has established that the changes in brain areas and networks in chronic low back pain are widespread. However, there remains a substantial gap in evidence linking these brain changes to the cognitive, emotional, and behavioural processes that contributes to chronic low back pain and therefore, should be considered in future studies. This may include investigating the neural processes involved in the habitual coping strategies used in response to events related to low back pain. There are different types of emotion regulation, including antecedent-focused (i.e., modifying the situation, attention or cognitive perception to change the emotional response such as cognitive reappraisal) and response-focused strategies (i.e., modulating the expression of emotions as well as physiological and behavioural response such as crying) [303], which has been found to influence chronic pain outcomes differently [185]. Furthermore, the emotion regulation task may use negative autobiographic memories to elicit negative emotional response related to low back pain to examine emotion regulation of personal experiences [304, 305]. Another avenue for future research may include determining the role of DMN connectivity in chronic low back pain as its functional significance remains unclear. This may include establishing how the disrupted connectivity may influence mind wandering and attention to pain, as well as its interaction with other networks of the pain connectome. Therefore, identifying the altered patterns of brain activity and its effects on cognition and emotion can further our understanding of the role the brain plays in chronic low back pain.
Further understanding of the brain mechanisms that contribute to chronic low back pain may be used to develop potential brain biomarkers. A biomarker refers to a characteristic that is an objective measure that is used to indicate normal biological or pathogenic processes, as well as response to an intervention [306]. Therefore, a brain biomarker refers to distinct structural and functional brain characteristics that could potentially be used as a diagnostic tool, categorise pain subgroups, predict the development of chronic low back pain and response to treatment [307, 308]. This can be achieved by using multivariate pattern analysis (MVPA). MVPA is a type of machine learning where an algorithm is applied to a large data set and identifies distinct signature patterns of subgroups within the population [309]. These neural signatures can be used to distinguish chronic low back pain patients from healthy controls. For example, a previous study using MVPA established distinct patterns of GM density throughout the brain in individuals with chronic low back pain compared to healthy controls, despite having similar total GM volume [310]. More importantly, it can potentially be used as a predictive tool that identifies individuals who may be vulnerable to transitioning from acute to persistent pain [311]. Longitudinal neuroimaging studies have found that increased functional connectivity between the mPFC and NAc, as well as smaller volumes within the amygdala and hippocampus during subacute low back pain predicted the development of chronic low back pain [312, 313]. Thus, these structural and functional brain changes can potentially be used one method to identify individuals who may require early interventions to prevent chronicity of pain.

Furthermore, brain biomarkers may also be developed to determine an individual’s likely response to a treatment. By comparing structural and functional characteristics of the brain in individuals who are responders of a given treatment to non-responders, a neural signature can be established that can be used to predict response to treatment in other patients [307]. This may be a potential avenue that assists in personalising treatment for individual patients. Therefore, identifying the various brain changes may contribute to the development of
potential biomarkers that serves as an objective measure than can inform prognosis and treatment for chronic low back pain.

This thesis has already included discussion surrounding the classification of chronic low back pain patients based on cognitive factors or neurobiological processes. However, it has been suggested that adopting a biopsychosocial approach may be more effective [314, 315]. Indeed, there has already been previous attempts have been made to categorise non-specific chronic low back pain, however, there are limitations to the current approach as they have not been informative in clinical practice [316]. This may be due to the fact that they have predominantly been assessed based on factors that are restricted within one domain of the biopsychosocial model, such as biomechanical factors related to movement and motor control impairments [317], nociceptive characteristics such as pain sensitivity [318, 319], pain characteristics [31], and psychological factors [235]. Therefore, integrating biological risk factors, such as biomechanical function of the spine, genetic composition and CNS mechanisms (i.e., central sensitisation, brain function or biomarkers), along with psychosocial factors and pain characteristics could potentially improve the classification of non-specific chronic low back pain, as well as inform potential approach for treatments.

### 7.5 Conclusion

This thesis has demonstrated that pain-related cognition and underlying neural processes are important factors that contribute to chronic low back pain. This thesis included a comprehensive systematic review that not only highlighted the brain changes observed in chronic low back pain, but incorporated a discussion of how these brain changes may be related to cognitive and emotional processes that may be involved in the development of chronic low back pain was also incorporated. The findings of this thesis identified important modifiable
cognitive risk factors, specifically negative back beliefs and poor subjective well-being, that contribute to persistent pain intensity and disability. This thesis presented the first neuroimaging study that showed the impaired brain functional connectivity reduced effective cognitive reappraisal in chronic low back pain. In addition, the findings of this thesis demonstrated that two key hubs of the DMN were shown to be disrupted in chronic low back pain, however, further studies need to explore its functional significance. Overall, these studies contribute to our understanding of the role of pain-related cognition and the underlying brain mechanisms in chronic low back pain, and therefore, has implications for the classification and the development of interventions for chronic low back pain.
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Appendix A

Questionnaires

The following questionnaires were used in this thesis to assess the primary measures of each study. This section includes:

- **Chronic Pain Grade Questionnaire (CPG):** Measured level of low back pain intensity and disability in Chapters 3 and 4,

- **Back Beliefs Questionnaire (BBQ):** Measured beliefs related to the consequences of low back pain (i.e., back beliefs) in Chapter 3,

- **Psychological General Well-Being Index (PGWB):** Measured subjective well-being in Chapter 4,

- **Pain Catastrophizing Scale (PCS):** Measured pain catastrophizing in Chapter 6.
# PAIN INTENSITY

We are interested to know more about the intensity of your back pain. The following questionnaire is the **Chronic Back Pain Grade Questionnaire** which assesses pain intensity.

For the following questions with a scale of 0-10, please place a cross in **ONE** box only. Please complete this questionnaire even if you do NOT experience back pain.

**Question R4.**

**A.** How would you rate your back pain on a 0-10 scale at the present time, that is right now, where 0 is 'no pain' and 10 is 'pain as bad as could be'?

<table>
<thead>
<tr>
<th>No Pain</th>
<th>Pain as bad as could be</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

**B.** In the past 6 months, how intense was your worst pain rated on a 0-10 scale where 0 is 'no pain' and 10 is 'pain as bad as could be'?

<table>
<thead>
<tr>
<th>No Pain</th>
<th>Pain as bad as could be</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

**C.** In the past 6 months, on the average, how intense was your pain rated on a 0-10 scale where 0 is 'no pain' and 10 is 'pain as bad as could be'? (That is, your usual pain at times you were experiencing pain.)

<table>
<thead>
<tr>
<th>No Pain</th>
<th>Pain as bad as could be</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

**D.** About how many days in the last 6 months have you been kept from your usual activities (work, school or housework) because of back pain?

<table>
<thead>
<tr>
<th>Disability Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

**E.** In the past 6 months, how much has back pain interfered with your daily activities rated on a 0-10 scale where 0 is 'no interference' and 10 is 'unable to carry on any activities'?

<table>
<thead>
<tr>
<th>Interference</th>
<th>Unable to carry on any activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

**F.** In the past 6 months, how much has back pain changed your ability to take part in recreational, social and family activities where 0 is ‘no change’ and 10 is ‘extreme change’?

<table>
<thead>
<tr>
<th>No Change</th>
<th>Extreme change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>

**G.** In the past 6 months, how much has back pain changed your ability to work (including housework) where 0 is ‘no change’ and 10 is ‘extreme change’?

<table>
<thead>
<tr>
<th>No Change</th>
<th>Extreme change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4 5 6 7 8 9 10</td>
</tr>
</tbody>
</table>
**Question R5.**

This is the Back Beliefs Questionnaire. We are interested in finding out what people think about back trouble. Please indicate your general view towards back trouble, even if you have never had any. Please read each of the following statements and indicate whether you agree or disagree with each statement on a scale of 1 to 5, where 1 is completely disagree and 5 is completely agree.

<table>
<thead>
<tr>
<th>Beliefs</th>
<th>Completely disagree</th>
<th>Completely agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. There is no real treatment for back trouble</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>B. Back trouble will eventually stop you from working</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>C. Back trouble means periods of pain for the rest of one's life</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>D. Doctors cannot do anything for back trouble</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>E. A bad back should be exercised</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>F. Back trouble makes everything in life worse</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>G. Surgery is the most effective way to treat back trouble</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>H. Back trouble may mean you end up in a wheelchair</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>I. Alternative treatments are the answer to back trouble</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>J. Back trouble means long periods of time off from work</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>K. Medication is the only way of relieving back trouble</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>L. Once you have had back trouble there is always a weakness</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>M. Back trouble must be rested</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
<tr>
<td>N. Later in life back trouble gets progressively worse</td>
<td>□ 1 □ 2 □ 3 □ 4 □ 5</td>
<td></td>
</tr>
</tbody>
</table>
A Study of Women's Health
Emotional and Psychological Wellbeing

50. We are interested in knowing about your feelings about your health, your outlook on life and changes in your emotional and psychological wellbeing. The following set of questions concern these issues.

These questions are from the Psychological General Well-being (PGWB) Index (permission to use this index was obtained).

Listed below are a number of statements concerning how you feel and how things have been going with you during the past month(s).

Please read each statement carefully and indicate the answer which best applies to you by marking it with an X.

A. How have you been feeling in general during the past month?

☐ In excellent spirits
☐ In very good spirits
☐ In good spirits mostly
☐ I have been up and down in spirits a lot
☐ In low spirits mostly
☐ In very low spirits

B. How often were you bothered by any illness, bodily disorder, aches or pains during the past month?

☐ Every day
☐ Almost every day
☐ About half of the time
☐ Now and then, but less than half of the time
☐ Rarely
☐ None of the time

C. Did you feel depressed during the past month?

☐ Yes - to the point that I felt like taking my life
☐ Yes – to the point that I did not care about anything
☐ Yes very depressed almost every day
☐ Yes quite depressed several times
☐ Yes a little depressed now and then
☐ No never felt depressed at all
A Study of Women's Health
Emotional and Psychological Wellbeing

D. Have you been in firm control of your behaviour, thoughts, emotions, or feelings during the past month?
- Yes, definitely so
- Yes, for the most part
- Generally so
- Not too well
- No, and am somewhat disturbed
- No, and am very disturbed

E. Have you been bothered by nervousness or your "nerves" during the past month?
- Extremely so – to the point where I could not work or take care of things
- Very much so
- Quite a bit
- Some – enough to bother me
- A little
- Not at all

F. How much energy, pep, or vitality did you have or feel during the past month?
- Very full of energy – lots of pep
- Fairly energetic most of the time
- My energy level varied quite a bit
- Generally low in energy or pep
- Very low in energy or pep most of the time
- No energy or pep at all – I felt drained, sapped

G. I felt downhearted and blue during the past month.
- None of the time
- A little of the time
- Some of the time
- A good bit of the time
- Most of the time
- All of the time

H. Were you generally tense or did you feel any tension during the past month?
- Yes – extremely tense, most or all of the time
- Yes – very tense most of the time
- Not generally tense, but did feel fairly tense several times
- I felt a little tense a few times
- My general tension level was quite low
- I never felt tense or any tensions at all
A Study of Women's Health
Emotional and Psychological Wellbeing

I. How happy, satisfied, or pleased have you been with your personal life during the past month?

☐ Extremely happy – could not have been more satisfied or pleased
☐ Very happy most of the time
☐ Generally satisfied – pleased
☐ Sometimes fairly happy, sometimes fairly unhappy
☐ Generally dissatisfied, unhappy
☐ Very dissatisfied or unhappy most of the time

J. Did you feel healthy enough to carry out the things you like to do or had to during the past month?

☐ Yes – definitely so
☐ For the most part
☐ Health problems limited me in some important ways
☐ I was only healthy enough to take care of myself
☐ I needed some help in taking care of myself
☐ I needed someone to help me with most or all of the things I had to do

K. Have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile during the past month?

☐ Extremely so – to the point I have just about given up
☐ Very much so
☐ Quite a bit
☐ Some – enough to bother me
☐ A little bit
☐ Not at all

L. I woke up feeling fresh and rested during the past month

☐ None of the time
☐ A little of the time
☐ Some of the time
☐ A good bit of the time
☐ Most of the time
☐ All of the time

M. Have you been concerned, worried or had any fears about your health during the past month?

☐ Extremely so
☐ Very much so
☐ Quite a bit
☐ Some, but not a lot
☐ Practically never
☐ Not at all
A Study of Women's Health
Emotional and Psychological Wellbeing

N. Have you had any reason to wonder if you were losing your mind, or losing control over the way you act, talk, think, feel or of your memory during the past month?

☐ Not at all
☐ Only a bit
☐ Some – but not enough to be concerned or worried about
☐ Some and I have been a little concerned
☐ Some and I am quite concerned
☐ Yes, very much so and I am very concerned

O. My daily life was full of things that were interesting to me during the past month.

☐ None of the time
☐ A little of the time
☐ Some of the time
☐ A good bit of the time
☐ Most of the time
☐ All of the time

P. Did you feel active, vigorous, or dull, sluggish during the past month?

☐ Very active, vigorous every day
☐ Mostly active, vigorous – never really dull, sluggish
☐ Fairly active, vigorous – seldom dull, sluggish
☐ Fairly dull, sluggish – seldom active, vigorous
☐ Mostly dull, sluggish – never really active, vigorous
☐ Very dull, sluggish every day

Q. Have you been anxious, worried or upset during the past month?

☐ Extremely so – to the point of being sick or almost sick
☐ Very much so
☐ Quite a bit
☐ Some – enough to bother me
☐ A little bit
☐ Not at all

R. I was emotionally stable and sure of myself during the past month.

☐ None of the time
☐ A little of the time
☐ Some of the time
☐ A good bit of the time
☐ Most of the time
☐ All of the time
A Study of Women's Health
Emotional and Psychological Wellbeing

S. Did you feel relaxed, at ease or high strung, tight or keyed-up during the past month?
- □ Felt relaxed and at ease the whole month
- □ Felt relaxed and at ease most of the time
- □ Generally felt relaxed but at times felt fairly high strung
- □ Generally felt high strung but at times felt fairly relaxed
- □ Felt high strung, tight, or keyed-up most of the time
- □ Felt high strung, tight, or keyed-up the whole time

T. I felt cheerful, light hearted during the past month
- □ None of the time
- □ A little of the time
- □ Some of the time
- □ A good bit of the time
- □ Most of the time
- □ All of the time

U. I felt tired, worn out, used up, or exhausted during the past month.
- □ None of the time
- □ A little of the time
- □ Some of the time
- □ A good bit of the time
- □ Most of the time
- □ All of the time

V. Have you been under or felt you were under any strain, stress or pressure during the past month?
- □ Yes almost more than I could bear or stand
- □ Yes quite a bit of pressure
- □ Yes some – more than usual
- □ Yes some – but about usual
- □ Yes a little
- □ Not at all
Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all  1 – to a slight degree  2 – to a moderate degree  3 – to a great degree  4 – all the time

When I’m in pain …

1. I worry all the time about whether the pain will end.
2. I feel I can’t go on.
3. It’s terrible and I think it’s never going to get any better.
4. It’s awful and I feel that it overwhelms me.
5. I feel I can’t stand it anymore.
6. I become afraid that the pain will get worse.
7. I keep thinking of other painful events.
8. I anxiously want the pain to go away.
9. I can’t seem to keep it out of my mind.
10. I keep thinking about how much it hurts.
11. I keep thinking about how badly I want the pain to stop.
12. There’s nothing I can do to reduce the intensity of the pain.
13. I wonder whether something serious may happen.

...Total

OBJECTIVES: Chronic low back pain (CLBP) is a major health issue, yet its underlying mechanisms remain unknown. Studies have demonstrated the importance of emotion and cognition in chronic pain, however, the relevant brain physiology in magnetic resonance imaging (MRI) studies are unclear in CLBP populations. Therefore, this review aimed to identify MRI brain changes and examine their potential relationship with emotional and cognitive processes in CLBP.

METHOD: A systematic search was conducted in 5 databases. Studies that recruited adult, chronic low back pain populations, and used brain MRI protocols were included.

RESULTS: Fifty-five studies met the inclusion criteria. Of the structural MRI studies, 10 of 15 studies found decreased gray matter and 7 of 8 studies found white matter changes in CLBP groups compared to controls. Fourteen resting-state functional MRI (fMRI) studies all reported differences between CLBP and control groups in the default mode network. Interestingly, only 3 of 10 fMRI studies observed significant differences during noxious stimulation between CLBP and control groups, while 13 of 16 studies observed significant brain activation differences in
CLBP groups during various external tasks. Finally, there were 3 studies that observed a degree of recovery in functional connectivity following intervention.

**DISCUSSION:** The brain changes in CLBP groups were mainly observed in areas and networks important in emotion and cognition, rather than those typically associated with nociception. This supports the understanding that emotional and cognitive processes may be the core contributor to the CLBP experience, however, future studies need to explore these processes further.
Cognition and emotion are essential in pain, specifically, cognitive factors such as pain-related beliefs influence their perception of pain and thus, their coping behaviours. As pain is an emotional experience, emotion regulation is an important process for pain management, particularly when the pain is chronic. However, our understanding of how these processes contribute to chronic low back pain (CLBP) remain limited. Beliefs about back pain have been associated with chronic low back pain outcomes, although limited longitudinal studies that have explored it may contribute to the persistence of low back pain. Furthermore, while studies have identified brain changes regions associated with cognitive and emotional processes, no studies have explored how these brain changes may affect processes such as emotion regulation using neuroimaging measures in CLBP. Therefore, the current research aimed to explore the role of beliefs about back pain (Study 1) as well as determine whether emotion regulation is impaired in individuals with CLBP (Study 2). Therefore, the current research aimed to examine the role of back beliefs (Study 1) as well as explore the underlying brain networks during emotion regulation in individuals with CLBP (Study 2).

Study 1 was a cohort study where 150 participants were involved in a 2-year follow-up study. Beliefs about back pain were assessed by the Back Beliefs Questionnaire (BBQ) at baseline and low back pain intensity was measured by the Chronic Pain Grade Questionnaire at baseline and follow-up. Results showed that greater negative beliefs were associated with persistent high intensity low back pain after adjusting for confounders ($M$ (SE) = 23.5 (1.6) vs. $> 30.1$ (1.7), $p < 0.001$). Study 2 aimed to investigate functional brain activity during an emotion regulation
task in non-specific CLBP using functional magnetic resonance imaging (fMRI). Participants are presented a series negative and neutral images and instructed to either view them passively or reappraise their negative emotions. Preliminary results for Study 2 will be presented at the conference.

Cognition and emotion are essential components in producing pain experiences, however, our understanding of how these processes may be associated with or contribute to chronic low back pain (CLBP) remain limited. The current study explored the neural activity involved in emotion regulation in adults with CLBP using functional magnetic resonance imaging (fMRI). Participants with CLBP (n = 10) and healthy controls (n = 10) completed an emotion regulation task during an fMRI scan. The task involved the presentation of negative and neutral images and participants were instructed to either view them passively (“look” condition) or reappraise their negative emotions (“decrease” condition). A rating of their negative affect on a scale of 0 to 8 was given following each image and their level of perceived success in down-regulating negative images during the decrease condition were also reported. Preliminary fMRI analysis has shown that the healthy control group had significantly increased BOLD activation in the right middle frontal gyrus and middle temporal gyrus compared to the CLBP group during the decrease condition when viewing negative images. No significant differences were observed in the other conditions. As the middle frontal and temporal gyri have previously been associated with effective emotion regulation, this might suggest that the reduced activation of these areas in the CLBP group observed in this study has implications on their ability to regulate negative emotions. Further analysis incorporating the level of negative affect and perceived success of regulation will be presented at the conference.
Negative beliefs about low back pain are associated with persistent high intensity low back pain.

**Background and aims:** While previous cross-sectional studies have found that negative beliefs about low back pain (LBP) are associated with pain intensity, the relationship between back beliefs and persistent LBP is not well understood. This cohort study aimed to examine the role of back beliefs in persistent LBP in community-based individuals.

**Methods:** A hundred and ninety-two participants from a previous musculoskeletal health study were invited to take part in a two-year follow-up study. Beliefs about back pain were assessed by the Back Beliefs Questionnaire (BBQ) at baseline and low back pain intensity was measured by the Chronic Pain Grade Questionnaire at baseline and follow-up.

**Results:** Of the 150 respondents (78.1%), 16 (10.7%) reported persistent high intensity LBP, 12 (8.0%) developed high intensity LBP, in 16 (10.7%) their high intensity LBP resolved and 106 (70.7%) experienced no high intensity LBP. While participants were generally positive about LBP (BBQ mean (SD) = 30.2 (6.4)), those with persistent high intensity pain reported greater negativity (BBQ mean (SD) = 22.6 (4.9)). Negative beliefs about back pain were associated with persistent high intensity LBP after adjusting for confounders (M (SE) = 23.5 (1.6) vs. >30.1 (1.7), p < .001).

**Conclusion:** This study found negative back beliefs were associated with persistent high intensity LBP over two years in community-based individuals. While further longitudinal studies are required, these findings suggest that targeting beliefs in programs designed to treat and prevent persistent high intensity LBP may be important.
Australian Pain Society, Sydney, Australia, 2018.


*Received Best Rapid Communication Award

**Background:** Emotion and cognition are key components involved in producing pain experiences. Chronic low back pain (CLBP) has been linked to increased negative emotional states, suggesting that emotional processing and regulation may be important in modulating the emotional aspect of pain. However, limited studies have investigated these processes. Therefore, the aim of the current study was to explore the neural activity involved in emotional processing and regulation in adults with CLBP using functional magnetic resonance imaging (fMRI). It was predicted that the CLBP group would have altered neural activity during an emotion regulation task compared to healthy controls.

**Methods:** Participants with CLBP (n = 10, M\(_{age}\) (SD) = 34.4 (9.50)) and healthy controls (n = 10, M\(_{age}\) (SD) = 30.1 (5.45)) were recruited for this study. Individuals with CLBP were included if they had pain for more than 3 months while controls did not have a history of chronic pain or psychiatric conditions. All participants completed an emotion regulation task during an fMRI scan. The task involved the presentation of a series of negative and neutral images and participants were instructed to either view them passively (“look” condition) or reappraise their negative emotions (“decrease” condition). When negative images were shown, the look condition examined negative emotional processing while the decrease condition assessed the down-regulation of negative emotions. Following each image, participants indicated a rating of their negative affect on a scale of 0 to 8. Their level of perceived success in down-regulating negative images during the decrease condition were also reported. The
fMRI analyses compared the BOLD activations of each condition between the CLBP and control groups.

**Results:** Preliminary fMRI analysis has shown that there were no significant differences between CLBP and control groups when viewing negative images (look-negative condition). However, healthy control group had significantly increased BOLD activation in the right middle frontal gyrus [28, 30, 38] ($p_{uncorr} = .002$) and middle temporal gyrus [50, 0, -32] ($p_{uncorr} = .029$) compared to the CLBP group when reappraising the negative images (decrease-negative condition) when viewing negative images. No significant differences were observed in the look and decrease conditions during the neutral images.

**Conclusion:** These results demonstrate that emotional processing of negative stimuli may be comparable to controls in CLBP. However, reduced activation of middle frontal and temporal gyri, areas associated with effective emotion regulation, may suggest individuals with CLBP may require increased neural effort in order to perform equivalent to healthy controls in the emotion regulation task.
Appendix C
Additional Publications

This section includes additional papers that were published during candidature that were not
directly relevant to this thesis. The following manuscripts are included:

Che X, Cash R., Ng SK, Fitzgerald P, & Fitzgibbon BM. (2018). A systematic review of the
processes underlying the main and the buffering effect of social support on the experience of

Roebuck GS, Fitzgerald PB, Urquhart DM, Ng SK, Cicuttini FM, Fitzgibbon BM. (2018). The
psychology of ultra-marathon runners: A systematic review. Psychology of Sport and Exercise,
37, 43-58.
A Systematic Review of the Processes Underlying the Main and the Buffering Effect of Social Support on the Experience of Pain

Xianwei Che, MSc, Robin Cash, PhD, Sin Ki Ng, MSc, Paul Fitzgerald, PhD, and Bernadette M. Fitzgibbon, PhD

Objective: This review aimed to explore the processes that underlie the main and the buffering effect of social support on decreased pain experience.

Materials and Methods: The systematic review was conducted according to the PRISMA guidelines. Online databases of PubMed and PsycINFO were searched for peer-reviewed articles using keywords (“social support,” OR “interpersonal,” OR “social presence,” OR “spouse,” OR “couple,” OR “marriage”) AND “pain”). Articles were included if they examined the cognitive or behavioral processes linking social support to any aspects of reduced pain experience.

Results: The database search identified 38 studies, of which 33 were cognitive-behavioral studies and 5 were neurobiological. Cognitive-behavioral studies generated a total of 57 findings of the analgesic influence of social support. This effect was further categorized as social support decreasing the adverse influence of pain-related stress (28/44 findings), reappraising pain-related stress (7/9 findings), and facilitating coping attempts (24/9 findings). Of the 5 neurobiological studies, the influence of social support on pain reduction was associated with reduced neural and physiological stress systems in response to painful stimuli.

Discussion: This review presents evidence that the stress-buffering effect is more often able to account for the relationship between social support and pain experience. Moreover, findings suggest the critical significance of stress appraisal and attenuated stress systems in linking social support to aspects of reduced pain experience. Findings implicate the role of integrating perceived support and intimacy in support-oriented interventional trials for chronic pain.

Key Words: social support, pain, stress, main effect, buffering effect

(Pain is defined as an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage. Pain is therefore not defined by a noxious stimulus alone but is shaped by a variety of factors including cognition such as beliefs and attention, as well as affective factors such as mood. In a recent proposed update, the definition of pain was suggested to further include a social component. This was done to reflect the influence of one’s social environment on pain, such as its effect over the cognitive and affective components of pain. The proposed inclusion of a social dimension in part reflects the growing number of studies looking into the social modulation of pain, of which social support is one key factor.

Social support refers to the perception or experience that one is loved and cared for by others. Social support thus encapsulates both “perceived” and “received” social support. Perceived social support refers to the perception that supportive resources would be available should they be needed, whereas received social support means the reported exchange of supportive resources. A number of studies have reported that social support is associated with decreased pain experience in clinical settings. In experimental settings, the overwhelming body of research has shown that social support is associated with less pain and greater pain tolerance, regardless of whether the support comes from interacting with support providers or simply reminding individuals experiencing pain of their social connections. However, there is also evidence suggesting that social support can increase or provide no influence on pain, suggesting that further clarity about how social support impacts on pain and under what circumstances is needed.

Recently, increasing evidence suggests the effectiveness of support-assisted pain management therapies (eg, spouse-assisted coping skills training). However, optimizing these approaches is highly limited by our knowledge of the processes translating social support to pain reduction. To date, several behavioral models have been proposed to explain the association of social support and pain experience, especially in the context of chronic pain. The operant model posits that positive responses of social partners (eg, reassurance, positive concerns) can serve as reinforcement of pain behaviors. The communal coping model of pain catastrophizing claims that pain catastrophizers tend to engage in more pain behaviors to attract social support, which in turn may serve to trigger or maintain exaggerated pain expression. Another perspective, the intimacy model, argues that communication of pain may serve to enhance intimacy between couples. According to the first 2 models, however, social support as a type of positive response would increase pain expression. Meanwhile, although the intimacy
model suggests decreased pain in the context of social support, it is more limited in verbal support and romantic couples. Therefore, it remain unclear the cognitive and behavioral variables linking a general overview of social support to decreased pain experience. This is particularly pertinent for the design of support-assisted therapies for chronic pain.

To address this issue, we systematically reviewed evidence surrounding social support and decreased pain experience by drawing on certain theoretical accounts from the general health literature. In particular, we examined evidence for current theories that aim to delineate the cognitive and behavioral mechanisms behind the analgesic influence of social support. Specifically, the “main-effect” hypothesis suggests that social support has an overall beneficial effect on pain experience, irrespective of any influences of stress. Meanwhile, the “buffering-effect” hypothesis suggests that social support may decrease pain experience by effectively reducing the influence of stress. This may involve reevaluating the threatening quality or perceived ability to cope with stress (“stress appraisal” process), or positively modulating an individual’s coping attempts (“response regulation” process). These 2 hypotheses are therefore primarily differentiated by whether or not social support modulates pain directly or indirectly via the influence of stress.

Although the main and the buffering effect may not be mutually exclusive in their effects on pain experience, this literature review aims to examine the potential mechanisms that explain each of these models and summarize the strength of evidence in favor of each. To provide a more general review of diverse pain conditions, the review covers both experimental induced pain in healthy individuals (but see Montoya et al 29) and people with chronic pain. Moreover, as chronic pain includes more than pain ratings, broader pain experiences were reviewed which included not only pain ratings but other pain experiences, for example, functional disability, depressed mood.41 Exploring the relative merits of these proposals bears practical importance as each has direct implications for the design of support-assisted pain management therapy.39

MATERIALS AND METHODS

This review was conducted according to the PRISMA guidelines for systematic reviews.32,44 The study selection process is depicted in Figure 1.

Definition of Variables and Effects

To date, there has no consensus on the operational definition of “social support.” In this review, we defined social support through measures of “social integration” (the number of social roles a person holds, frequency of interaction with members of their social network, and the interconnectedness of relationships between network members), and through “social function” (informational, instrumental, and emotional support).44,45 Pain is defined as a sensory and emotional experience. Here a broad concept of “pain experience” was used, which was defined as a multidimensional phenomenon including physical (eg, intensity, duration, disability) and psychosocial suffering (eg, unpleasantness, negative mood, psychological, and social functioning). We chose this broader definition as pain intensity ratings alone do not capture the dimensionality of pain experience and, perhaps, the domains in which social support has an impact. “Stress” was defined as undesirable changes in daily life that require substantial behavioral readjustment.46,47 For individuals with pain, stress events included physical suffering, functional limitations, financial burden, social isolation, and critical remarks/response from their significant others, as well as other negative life events, all of which have been shown to influence pain experience.48-50 The purpose was not to provide a comprehensive typology of stress, but rather to represent those functions for review. We also defined cognitive-behavioral processes linking support to pain as variables related to perception of pain (eg, perceived threat of pain) and behavioral response to pain (eg, health care utilization). In addition, we examined neurobiological studies that delineate the activations of central and/or autonomic nervous systems in the context of support and pain.

Study results on the analgesic influence of social support were sorted according to whether it supported the main-effect or buffering-effect hypothesis. Specifically, we categorized data to support the main-effect hypothesis where social support is linked to decreased pain experience in the absence of any statistical interaction/moderation or mediation effect with stress, stress appraisal, or stress coping variable. In contrast, we categorized data to support the buffering-effect hypothesis where social support was associated with reduced pain experience. Alternatively, where the data supported a mediation model where social support is linked to decreased stress that in turn reduces pain experience.51,52

Literature Search

We conducted a systematic search of the online database of PubMed and PsycINFO for peer-reviewed articles. Title and abstract were searched with (“social support,” OR “interpersonal,” OR “social presence,” OR “spouse,” OR “couple,” OR “marriage,” AND “pain”).51,52

Eligibility Criteria

Eligibility was defined according to 5 a priori criteria: (1) studies were included if they assessed social support from human beings and excluded if they looked into support from
other species or objects; two studies were included if they assessed the experience related to physical pain and excluded if they investigated other types of pain (eg, social-exclusion pain); three studies were included if they reported protective effect and excluded if they reported adverse or no influence of social support on pain experience; four studies were included if they investigated cognitive and behavioral variable or neurobiological mechanisms that might link social support to pain experience, and were excluded if they only reported the benefits of support without examining the underlying mediator and mechanism; five studies were included if they were published in English peer-reviewed journal from 1980 to 2016 and were in full-text. As per PRISMA guidelines, this time frame was chosen to include studies most likely to directly address the theories are investigating.

Quality Assessment
We used the assessment criteria developed by Campbell et al. The assessment criteria has been used to review the influence of social support on chronic pain. The criteria was developed by combining the guidance on quality assessment with a number of review articles in the area of chronic pain. The combined criteria cover research objective, participant recruitment, data analysis, and so on. For cohort studies, the criteria also evaluate the attrition rate, and the follow-up time period (see the checklist at Supplementary Material S1, Supplemental Digital Content 1, http://links.lww.com/CJP/A510). Two reviewers (X.C., S.K.N.) separately assessed each study using these criteria to avoid potential bias. Any discrepancies were subsequently resolved at a consensus meeting.

Data Collection Procedure
Data extraction followed a priori developed data extraction forms based on modified PICOS-criteria. Specifically, extracted data included (1) number of participants and their clinical characteristics (sample); (2) type of social support; (3) cognitive and behavioral variables underlying the main versus the buffering effect (cognitive and behavioral mediators), or pain induction technique in neurobiological studies; (4) pain experience and (5) findings.

Studies were classified as either cognitive-behavioral or neurobiological studies. With regard to cognitive-behavioral studies, this review examined whether social support was related to decreased pain experience through modulating the influence of stress, appraisal of stress and coping resources, or coping attempts. With respect to neurobiological studies, it reported on the neural and physiological mechanisms that are associated with pain reduction in the context of social support.

Effect Size
We also reviewed the magnitude of the analgesic influence of social support where possible. Effect size was calculated in studies using analysis of variance. In cases where path analysis (including mediation) was performed, the path coefficient was calculated from the independent variable to the mediator and dependent variable. Standardized or unstandardized coefficients were also extracted from studies using multiple regression analysis.

RESULTS

Study Selection
The electronic database search delivered 5400 results (Fig. 1). We removed 1199 duplicates and screened 4201 remaining studies. Of these, 3869 studies were discarded as they did not meet the eligibility criteria after reviewing the title and abstract. The remaining 332 studies were full-text assessed and 294 did not meet the eligibility criteria and were consequently discarded. This systematic review thus contains 38 studies (33 cognitive-behavioral studies and 5 neurobiological studies).

Cognitive-behavioral Studies Examining the Main Effect Versus the Buffering Effect
All of the included 33 cognitive-behavioral studies examined both the main and the buffering effect, in which they assessed pain as well as pain-related stress (Table 1). Some studies examined >1 type of support, stress, or pain experience, and reported evidence in favor of both the main and buffering effect in a single study. Consequently, the number of findings, rather than the number of studies, was tallied to assess evidence in favor of these 2 effects. In total, 57 findings were reported in 33 studies, of which 37 (65%) supported the buffering effect. Of those, 28 findings showed the benefits of support on pain experience by reducing the adverse influence of pain-related stress ("Stress" sections in Table 1); 7 findings showed this effect by decreasing the threatening quality of stress or increasing perceived ability to cope with stress ("Stress appraisal" section in Table 1); and 2 reported this effect by facilitating stress coping ("Active coping" section in Table 1). Moreover, 20 findings (35%) supported the main effect without any interaction with stress ("Effect" section in Table 1).

Moreover, we also considered the findings according to whether they were a "cross-sectional" or "cohort" study (Table 1). Among the buffering-effect findings, 29/37 (78%) were cross-sectional (ie, data were collected at a specific timepoint), whereas 8 of them (22%) were cohort findings (ie, data were collected at intervals through a period of time). Moreover, of the main-effect findings, 15/20 (75%) were cross-sectional and 5/20 (25%) were cohort.

Quality Assessment Analysis
Reviewer agreement on the quality assessment was 92.7%. The authors who developed this assessment tool used a score of 73 to separate studies of low quality from others within their investigations. This was performed to assign approximately same number of studies in each quality categories. Similarly, we chose to use a quality score of 77, which was close to 73 and was able to approximately split the included studies equally. Moreover, next scores in our data set (70 or 80) would result in too less (ie, 3) or too many (ie, 14) studies in the low-quality group. Specifically, studies with a score below 77 were classified as "low quality" (n = 11), a score between 77 and 84 as "medium quality" (n = 10), and a score above 84 as "high quality" (n = 12). Nearly all the included studies (94% or above) reported clear research objective, population parameters, and appropriate sample size. Most studies (73% or above) offered sufficient assessment of variables (eg, measures are validated or measures at least 2 dimensions), recruitment procedure, and strong statistics. However, only 67% of the studies reported inclusion/exclusion criteria and only 33% of studies provided evidence of the ratio of recruitment versus participation. In the cohort studies, only 29% provided the attrition rate, 57% reported an attrition rate smaller than 20%, and 71% had a follow-up period longer than 6 months.

Of the 37 findings supporting the buffering effect 26 (70%) showed medium to high quality. Among the main-effect
### TABLE 1. Behavioral Studies Examining the Main Effect Versus the Buffering Effect

<table>
<thead>
<tr>
<th>References</th>
<th>Sample</th>
<th>Type of Social Support</th>
<th>Cognitive/Behavioral Variable</th>
<th>Pain Experience</th>
<th>Findings</th>
<th>Study Design (CS/CH)</th>
<th>Quality</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress (physical suffering)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown et al17</td>
<td>Patients with RA (N = 233)</td>
<td>Emotional support</td>
<td>Pain</td>
<td>Depression</td>
<td>1. The negative correlation of emotional support and depression was strengthened when pain was included.</td>
<td>CS CH</td>
<td>Medium</td>
<td>Buffering</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Moderating effect of emotional support was not found over a 6-month period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revenson et al22</td>
<td>Patients with RA (N = 101)</td>
<td>Received positive support</td>
<td>Pain severity</td>
<td>Depression</td>
<td>1. Received positive support predicted reduced depression without interacting with pain severity.</td>
<td>CS High</td>
<td>Low</td>
<td>Main</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Penninx et al40</td>
<td>Older people without chronic disease</td>
<td>Presence of a partner; close social relationships; diffuse social relationships; emotional support</td>
<td>Arthritis</td>
<td>Psychological functioning; depressive symptoms</td>
<td>1. Presence of a partner had direct, favorable effect on psychological functioning without interacting with arthritis. 2. Close social relationships had direct, favorable effect on psychological functioning without interacting with arthritis. 3. Having diffuse social relationships interacted with arthritis pain to predict depressive symptoms in severe arthritis 4. Emotional support interacted with arthritis pain to predict depressive symptoms in severe arthritis</td>
<td>CS CH</td>
<td>Low</td>
<td>Buffering</td>
</tr>
<tr>
<td></td>
<td>(N = 719); with mild arthritis (N = 612); with severe arthritis (N = 359)</td>
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<td></td>
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</tr>
<tr>
<td>Feldman et al35</td>
<td>Patients with reflex sympathetic dystrophy syndrome (N = 109)</td>
<td>Perceived social support</td>
<td>Pain</td>
<td>Depressed mood</td>
<td>1. Previous day’ support interacted with previous day’ pain to predict present day’ depressed mood</td>
<td>CH Low</td>
<td>Low</td>
<td>Buffering</td>
</tr>
<tr>
<td>Telfair and Gardner34</td>
<td>Adolescents with sickle cell disease (N = 79)</td>
<td>Group satisfaction</td>
<td>Pain</td>
<td>Psychological well-being (anxiety; depression) Depression</td>
<td>1. Group satisfaction interacted with high pain to predict high psychological well-being</td>
<td>CS Medium</td>
<td>Low</td>
<td>Buffering</td>
</tr>
<tr>
<td>Riemersma et al30</td>
<td>Patients with RA (N = 197)</td>
<td>Positive support</td>
<td>Pain</td>
<td>Depression symptoms</td>
<td>1. Positive support predicted reduced depression without interacting with pain</td>
<td>CS High</td>
<td>Low</td>
<td>Main</td>
</tr>
<tr>
<td>Cano et al18</td>
<td>Chronic musculoskeletal pain patients (N = 110)</td>
<td>Marital satisfaction</td>
<td>Pain</td>
<td>Depression symptoms</td>
<td>1. Marital satisfaction predicted reduced depressive symptoms without interaction with pain</td>
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<td>CS CH</td>
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<td>Affleck et al10</td>
<td>Patients with RA (N = 129)</td>
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<td>1. Positive support predicted reduced depression without interacting with physical function</td>
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<td>Kerns et al14</td>
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<td>Cano et al18</td>
<td>Chronic musculoskeletal pain patients (N = 110)</td>
<td>Marital satisfaction</td>
<td>Negative spousal response</td>
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<td>1. Marital satisfaction predicted reduced depressive symptoms without interaction with negative spousal response</td>
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<td>Raichle et al76</td>
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<td>Rosen et al77</td>
<td>Patients with provoked vestibulodynia (N = 175 couples)</td>
<td>Dyadic adjustment</td>
<td>Spousal negative response</td>
<td>Sexual satisfaction</td>
<td>1. Dyadic adjustment mediated the adverse impact of negative spousal response on sexual satisfaction</td>
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<td>DeLongis et al78</td>
<td>Married couples (N = 75)</td>
<td>Emotional support</td>
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<td>Symptoms (headache; backache; flu; sore throat; mood)</td>
<td>1. Emotional support was negatively related to hassle-next day symptoms association.</td>
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<td>Weinberger et al79</td>
<td>Patients with osteoarthritis (N = 439)</td>
<td>Social support</td>
<td>Negative life events</td>
<td>Functional status (psychological disability; physical disability; pain)</td>
<td>1. Social support had direct, favorable effect on functional status, without interaction with daily hassle</td>
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<td>Affleck et al80</td>
<td>Patients with RA (N = 74)</td>
<td>Social support</td>
<td>Negative life events</td>
<td>Mood disturbance</td>
<td>1. Social support interacted with daily stressor to predict next day mood disturbance</td>
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<td>Alonso and Coe81</td>
<td>Healthy women (N = 184)</td>
<td>Access to support providers</td>
<td>Distress (anxiety; depression)</td>
<td>Menstrual pain</td>
<td>1. Access to support providers interacted with distress to predict menstrual pain</td>
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<td>Pekkarinen et al82</td>
<td>Female geriatric nurses (N = 975)</td>
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<td>1. Social support interacted with physical workload to predict musculoskeletal symptoms</td>
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<td>Waltz et al83</td>
<td>Clinical pain patients (N = 234)</td>
<td>Emotional support; social interaction</td>
<td>Psychological functioning (reduced RA helplessness; sense of mastery; self-esteem, etc.)</td>
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<td>1. Psychological functioning mediated the protective influence of emotional support on pain</td>
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<td>Kerns et al84</td>
<td>Chronic pain patients (N = 234)</td>
<td>Pain-related support</td>
<td>Low self-appraised problem-solving competence</td>
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<td>1. Pain-related support interacted with low problem-solving competence to predict depressive symptoms</td>
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(Continued)
findings, 12/20 (60%) showed medium to high quality. Specifically, of the cross-sectional findings which reported the buffering effect (29/37), 20/29 (69%) were identified as medium to high quality. However, only 8 findings were from cohort studies which showed the buffering effect, and 6 of them (75%) showed medium to high quality. In the 20 findings showing the main effect, 15 of them (75%) were cross-sectional. But more than half (8/15, 53%) of them showed low quality. Only 5 findings were cohort studies, and all of them identified as medium to high quality. Full descriptions of study quality are detailed in the following sections. Details of quality assessment can be found at Supplementary Material S1 (Supplemental Digital Content 1, http://links.lww.com/CJP/A510).

The cognitive-behavioral studies focused on different aspects of stress that social support has beneficial effects on, that is, the overall adverse influence of stress, or a specific aspect (and potentially those that inform the former) including stress appraisal, and stress coping. Accordingly, studies were organized based on these stress categories.

### Whether Social Support Buffers Stress to Reduce Pain

People with chronic pain experience a variety of stress events that impact on their quality of life in different ways. People with chronic pain experience a variety of stress events that impact on their quality of life in different ways. People with chronic pain experience a variety of stress events that impact on their quality of life in different ways.

First, physical suffering means the severity and frequency of painful episodes as well as related unpleasantness. Physical suffering causes stress for individuals with chronic pain and is associated with increased functional impairment and depression. In this review, we identified 21 findings which examined, among patients with chronic pain, whether social support was able to decrease the adverse impact of physical suffering on other aspects of pain experience. Among them

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<td>Holtzman and DeLongis16</td>
<td>Patients with RA (N = 69)</td>
<td>Morning satisfaction with spousal response</td>
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<td>Evening pain intensity</td>
<td>1. Morning satisfaction with spousal response interacted with morning pain catastrophizing to predict evening negative effect. 2. Morning satisfaction with spousal response decreased evening pain intensity without interaction with morning pain catastrophizing</td>
<td>CS CS</td>
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<td>Vlaeyen et al8</td>
<td>Healthy participants (N = 149)</td>
<td>Social presence</td>
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<td>Pain intensity; facial expression of pain</td>
<td>1. Perceived threat mediated the inhibitory effect of social presence on pain intensity. 2. Perceived threat mediated the inhibitory effect of social presence on pain intensity; facial expression of pain</td>
<td>CS CS</td>
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<td>Corley et al85</td>
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<td>Global relationship satisfaction; situational relationship satisfaction after 2-minute interaction</td>
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<td>1. Global relationship satisfaction predicted less pain without interacting with threat manipulation. 2. Situational relationship satisfaction predicted less pain in the low threat condition</td>
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<td>Manne and Zautra49</td>
<td>Women with RA (N = 103)</td>
<td>Spousal support</td>
<td>Coping with RA (information seeking; cognitive restructuring)</td>
<td>Psychological adjustment</td>
<td>1. Adaptive coping mediated the positive relationship between spousal support and better psychological adjustment</td>
<td>CS CS</td>
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<td>Holtzman et al11</td>
<td>Patients with RA (N = 73)</td>
<td>Morning satisfaction with social support</td>
<td>Morning coping with RA (stoic distancing)</td>
<td>Evening pain severity</td>
<td>1. Morning satisfaction with social support interacted with increased stoic distancing to predict reduced evening pain severity</td>
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<td>López-Martínez et al20</td>
<td>Chronic pain patient (N = 117)</td>
<td>Perceived social support</td>
<td>Active coping with pain</td>
<td>Depressed mood; pain intensity</td>
<td>1. Perceived social support was related to reduced depressed mood without interacting with active coping response. 2. Perceived social support was related to reduced pain intensity without interacting with active coping response</td>
<td>CS CS</td>
<td>High</td>
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**Buffering means the buffering effect and main means the main effect.**

**CH indicates cohort study; CS, cross-section study; RA, rheumatoid arthritis.**
8/21 (38%) showed that social support interacted with physical suffering to predict decreased depression,17,19,40,63,69 and emotional well-being.64,66 Another 4 findings (19%) showed a mediation role of social support, whereby the adverse influence of physical suffering was reduced on depression,65,68 and quality of life.67 Moreover, 3 findings (14%) showed in mediation models that social support resulted in decreased physical suffering, which was in turn associated with reduced functional impairment and depression.20 Further, among the 15 findings (71%) of buffering effect 10 (67%) showed medium to high quality. However, 6 findings (29%) showed a main effect where social support was linked to reduced depression18,50,62 and greater psychological functioning (mastery, self-efficacy, and self-esteem),40 without the interaction with pain severity. However, 3 of these (50%) reported low quality with inadequate description of inclusion/exclusion criteria, small sample size, insufficient assessment of variables, or no participation rate.

Functional disability is defined as the difficulty in performing an activity, for example, household activity and social activity.87 It is a significant source of stress for people with chronic pain that is associated with greater emotional distress (anxiety and depression).50 Eight findings were identified, which examined among patients with chronic pain whether or not social support can decrease the influence of functional disability on other pain experience. Three findings (38%) showed that social support interacted with functional disability to predict decreased emotional distress.70,72,73 All above findings were showed to be of good quality. In addition, 5 findings (62%) reported the main effect, in which social support was negatively related to emotional distress, without interacting with functional disability.18,50,71,73,74 The main effect of support was often observed in long-term emotional distress (≥13 y),73 and most of them (3/5) showed good quality.

Moreover, close others of patients with chronic pain sometimes respond to the displays of pain and suffering in negative ways, for example, expressing irritation or anger.87 Although ignoring pain expression is sometimes associated with better pain-related outcomes, this is typically perceived as a negative response that may make the individuals with pain feel more depressed.74,75 In total, we identified 7 findings which examined whether social support can buffer the influence of close other’s negative response on pain experience in people with chronic pain. Five of these (71%) showed the buffering effect, in which social support decreased the adverse influence of negative responses on depression, or on sexual satisfaction in another study, either with an interaction,50,62,74 or a mediation effect.75,77 Moreover, 3 of these 5 findings (60%) showed good quality. However, another 2 findings (29%) showed the main effect in which social support was predictive of decreased depression without interacting with negative spousal response.18,76

In addition, some studies examined whether social support can buffer the influence of other negative life events. Negative life events are undesirable life activities to which individuals need to substantially adjust their behavior.47 These have been reported to aggravate physical symptoms and mood disturbance in both chronic pain,86 and healthy populations.88 Negative life events may take the form of specific distress, for example, workload52; or cover multiple life domains.28 Findings are inconsistent when negative life events are nonspecific. Three findings (38%, 38%) showed that social support was able to interact with negative life events to predict decreased physical suffering or mood disturbance.76,80 But another 3 findings (38%, 38%) only observed the main effect of support without significant interaction with negative life events.83,79 Moreover, the 6 findings were reported both in people with chronic pain,79,80 and in healthy populations who sometimes experienced symptoms like headache, backache, and shoulder pain.78 All these 6 findings were showed to be of good quality. However, the buffering effect was consistently reported when specific negative life events were measured. Two findings (28%, 24%) showed that social support interacted with emotional distress (anxiety and depression) or physical workload to predict less pain.81,82 Moreover, these findings included healthy participants experiencing menstrual pain,81 or some musculoskeletal symptoms.82 But only one of them showed good quality.82 The other study showed inadequate description of inclusion/exclusion criteria, inadequate report on demographics and the strength of effect, and no participation rate.83

**Whether Social Support Changes Stress Appraisal to Reduce Pain**

Here we identified 7 findings (78%) which showed that social support could help individuals with pain perceive the pain or related stress as less threatening or become more confident to cope with (“Stress appraisal” section in Table 1). Moreover, 5 findings were shown to be of good quality. Two findings have shown an interaction effect between social support and a stress appraisal variable in the prediction of decreased emotional well-being. Specifically, in pain patients who reported low social support, perceived incompetence to solve problem or high pain catastrophizing (helplessness, rumination, magnification) was associated with more depressive symptoms and higher negative effect. But these associations were decreased significantly in pain patients with high level of social support.66,84

Another 2 findings showed with mediation models that emotional support and social interaction could decrease pain severity through psychological functioning in people with chronic pain. Higher emotional support or social interaction was associated with higher psychological functioning (self-esteem, sense of mastery), which in turn linked with lower pain severity.83 In addition, an experimental study induced cold pain in which social presence (a female observer) helped healthy participants perceive cold pain as less threatening, which then resulted to lower pain intensity and less facial expression of pain despite the female observer was a stranger and had minimum verbal exchange with the participants.83 A recent experimental study also found that situational relationship satisfaction after 2-minute couple interaction was associated with lower induced cold pain when pain was perceived as threatening. But global relationship satisfaction was related to less pain irrespective of the level of threat.85 Another study also found the main effect of support in patient group, that morning satisfaction with spouse was related to less evening pain irrespective of morning pain catastrophizing.86

**Whether Social Support Promotes Coping Strategies to Reduce Pain**

Four findings were on the topic of whether social support modulates pain experience through active coping response, and all of them were conducted in patients with chronic pain (“Active coping” section in Table 1). In one finding, on mornings when patients were satisfied with social support, increased use of distancing (diverting attention away from pain) was associated with decreased evening pain severity.81 This finding was categorized as low quality as
there was inadequate description of recruitment procedure
and strength of effect (effect size). However, another finding
showed quality results with mediation models whereby
spousal support resulted to better psychological adjustment
to arthritis pain through active coping responses, namely
information seeking and cognitive reappraisal.49 These 2
coping strategies describe the effort to search for advice
about the illness and make it less distressing.88
In contrast, a more recent finding showed with good
quality that social support does not facilitate active coping
responses to reduce pain intensity. In this study, perceived
social support was related to decreased pain intensity and depressed
mood without the interaction with active pain coping.30 This
study detailed multiple active coping responses, for example,
engaging in physical therapy, clearing mind of bothersome
thoughts, participating in leisure activities, distracting attention
from the pain, etc.30 Moreover, these sets of coping response
could predict decreased depressed mood but not pain intensity.20

**Effect Size**
Only a small proportion of studies provided available
data to calculate effect size, whereas other studies provided
the coefficient of social support variables (Supplementary
llw.com/CJP/AS110). Across the statistical models, social
support had a small impact on pain experience in both the main20,71) and the buffering model.68,75,82

**Neurobiological Studies Examining the Influence of Social Support on Pain**
Four neurobiological studies have induced pain in healthy participants,24,28,30,90 and in 1 study in people with
chronic pain.26 Four studies have investigated the neural
mechanisms of social support related to pain experience
(Table 2). In 1 study, participants with a diagnosis of fibro-
myalgia reported lower pain sensitivity and pain ratings to
tactile stimulation when they were accompanied by their sig-
ificant other compared with when they were alone. This
study further found that primary somatosensory cortex
activity in response to painful elbow stimulation (a tender
point), measured using magnetoencephalography, was lower
when the significant other was present.26
In another study, married females underwent func-
tional magnetic resonance imaging during the threat of
electrical stimuli in 3 conditions: holding their husband’s
hand, holding a male stranger’s hand and no hand-holding.
Results showed that spousal and stranger hand-holding
produced lower bodily arousal and brain activation in
threat-related regions (ventral anterior cingulate cortex;
supramarginal gyrus) relative to no hand-holding. More-
over, marital quality affected brain activation to electric
stimuli during spousal hand-holding whereby higher marital
quality predicted lower threat-related neural activation in
anterior insula (AI), and hypothalamus.30
In another study, female participants in a long-term
romantic relationship were subject to thermal pain during
functional magnetic resonance imaging scanning whereas
they were shown pictures of their partner or control images
(stranger, object).28 Viewing partner pictures relative to
control pictures produced less pain ratings, lower activation
of pain-related regions (AI, dorsal anterior cingulate cortex
d[ACC]) but higher activation in safety-related region
(ventromedial prefrontal cortex [VMPFC]). Further, greater
activation of VMPFC in response to partner pictures
was related to lower pain ratings as well as pain-related
brain activation. Interestingly, greater VMPFC response to
partner pictures covaried with longer length of relationship
and greater perceived partner support.

In addition, reward-related neural processing is reported
to underlie pain reduction.30 In this study, viewing pictures
of romantic partner relative to acquaintance produced lower
thermal pain ratings in healthy participants. Imaging data
further showed decreased pain-related activation (insula,
thalamus), but increased activation of reward regions (OFCC)
in the viewing of romantic partner relative to acquaintance’s
picture. Moreover, pain relief during viewing pictures of
romantic partner was also associated with increased reward
activation (caudate nucleus, nucleus accumbens, OFCC), but
with decreased pain-related activation (dACC, AI). This
pattern of neural response was not observed in a distraction
task which also produced pain relief.

Social support was also found to reduce neuroendocrine
and/or autonomic response to pain in 2 studies. Roberts et al.24
examined healthy participants’ experience to cold pain in 1 of
the 3 conditions: verbal social support, neutral nonsupport,
alone. Compared with participants in neutral nonsupport and
alone conditions, participants in the verbal support condition
reported less pain, less task difficulty and tension, as well as
lower blood pressure, heart rate, and cortisol response. Fur-
ther analysis showed that perceived social support during cold
pain was negatively associated with pain intensity, unpleas-
anteness, and cortisol response.

**DISCUSSION**
Inspired by the evidence of support-assisted pain man-
gagement therapies, the current review specifically explored
the processes underlying the main and the buffering effect
of social support on pain experience. Our review presented evi-
dence supporting both the main and the buffering effect.
However, the buffering effect is more often able to explain
findings in studies that were deemed to be of higher quality.
In this context, our results suggest that social support is asso-
ciated with decreased pain experience through managing
stress, namely, physical suffering, functional disability,
stressful response of close other, and other negative life events.
Findings further show potential processes associated with the
buffering effect, that is, stress appraisal and coping. In this
section, we first discuss why the buffering effect can more
often describe the influence of support on pain reduction in
comparison to the main effect. Then, cognitive, behavioral,
and neurobiological processes are detailed that may underlie
this buffering effect. Finally, we present a social-buffering
model of pain reduction that binds together evidence across
behavioral, neuroimaging, and physiological research fields.

The Buffering Effect Describes More Often the Influence of Social Support on Decreased Pain
The majority of our findings (37/57, 65%) show that the
interaction of support and stress is likely associated with
aspects of reduced pain experience.19,78 This finding is more
often observed in cross-sectional studies (29/37, 78%) with
good quality (20/29, 69%).90 There is also evidence (20/57,
35%) showing the main effect of social support.50,79
Although most of these findings (15/20, 75%) are cross-
sectional, they were found to be of low quality.40,71 Our
findings therefore suggest that in most of the cases social
support may help patients cope with negative life events
and manage pain experience.
### TABLE 2. Neurobiological Studies Investigated the Effect of Social Support on Pain

<table>
<thead>
<tr>
<th>References</th>
<th>Sample</th>
<th>Type of Social Support</th>
<th>Pain Induction Technique</th>
<th>Pain Experience</th>
<th>Findings</th>
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</table>
| Montoya et al\(^26\) | Fibromyalgia patients (N = 18); migraine patients (N = 18)            | Presence of significant others; patient alone          | Tactile stimulation      | Pain sensitivity; pain rating; brain activity measured by magnetoencephalography   | 1. Pain sensitivity and pain ratings were reduced in the presence of significant others compared with alone situation in fibromyalgia patients.  
2. Primary somatosensory cortex activity elicited by elbow stimulation was also reduced in fibromyalgia patients in the presence of their significant others compared with alone condition |
| Coan et al\(^90\) | Married women (N = 16)                                                | Holding husband’s hand; holding stranger’s hand; no hand-holding | Electric stimuli         | Rating of unpleasantness and body arousal; brain activation measured by fMRI       | 1. Spousal hand-holding revealed reduced unpleasantness than stranger and no hand-holding.  
2. Spousal and stranger hand-holding revealed reduced body arousal than no hand-holding.  
3. Higher marital quality predicted less threat-related neural activation in spousal hand-holding (AI, hypothalamus) |
| Younger et al\(^30\) | Healthy people in new romantic relationship (N = 15)                  | Viewing picture of romantic partner; viewing picture of familiar acquaintance; a distracting task | Thermal pain             | Pain rating; brain activation measured by fMRI   | 1. Viewing pictures of romantic partner relative to acquaintance reduced self-reported pain.  
2. Viewing pictures of romantic partner relative to acquaintance increased reward neural activation (OFC); decreased pain-related activation (insula, thalamus).  
3. Pain relief was associated with increased reward neural activation (caudate head, nucleus accumbens, OFC); but with decreased pain-related activation (AI) in viewing pictures of romantic partner |
| Eisenberger et al\(^28\) | Female participants in long-term romantic relationship (N = 21)       | Picture of romantic partner; picture of stranger; picture of object | Heat stimulations        | Pain rating; brain activation measured by fMRI       | 1. Viewing partner pictures led to reduced pain-related brain activation (dACC, AI) and increased safety-related brain activation (VMPFC).  
2. Greater VMPFC response to partner pictures was related to decreased pain ratings and attenuated pain-related brain activation (dACC, AI).  
3. Greater VMPFC response to partner pictures covaried with longer relationship lengths and greater perceived partner support |
| Roberts et al\(^24\)   | Healthy female undergraduates (N = 76)                                | Verbal social support; neutral nonsupport; alone        | Cold pressor task        | Pain rating; physiological response (blood pressure, heart rate, cortisol); tension and task difficulty  | 1. Social support condition attenuated blood pressure, heart rate, and cortisol reactivity, as well as reduced pain ratings, task difficulty, and tension compared with neutral nonsupport and alone conditions |

AI indicates anterior insula; dACC, dorsal anterior cingulate cortex; fMRI, functional magnetic resonance imaging; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; vACC, ventral anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex.
These results may be further explained by the fact that the buffering-effect hypothesis emphasizes more cognitive and behavioral changes that are critical in pain reduction. Compared with the main effect, which only suggests the sense of stability or predictability related to support, the buffering effect conceptualizes broader cognitive and behavioral processes including appraisal of life situations and coping resources, inhibition of maladaptive and/or facilitation of adaptive responses to life situations.46,47 The buffering-effect model thus recognizes that a broader range of cognitive and behavioral changes facilitated by supportive resources may help individuals with pain better cope with life situations and therefore manage pain experience. For instance, studies have shown that social support can help people with chronic pain redefine the situation they are in, distract attention from this illness; decrease thinking one cannot do anything to cope with pain, and reduce restrictions on social activities.11,20,24 Therefore, the buffering-effect hypothesis might be a more flexible theoretical account.

However, one should be careful to prefer the buffering over the main-effect perspective in the explanation of the benefits of support on pain experience. In this systematic review, we did not provide effect size for each study due to the diversity of study designs and statistics provided, that is, correlation, group contrast, regression, mediation model. Available data suggest that the analgesic influence of social support is small in supporting one of both of the 2 models. Although relatively less supported by the literature, the main effect is still implicated in a number of studies. Moreover, some studies even showed both the main and the buffering effect in a single study.46,78 It suggests that the 2 theoretical accounts may be not mutually exclusive. Indeed the main and the buffering effect may depend on the type of measure of support.39 A structural measure of support (eg, the number of close relationships) may influence health outcomes through the main effect, whereas a functional measure (eg, emotional support) may exert its impact mainly through the buffering effect on stress.40 We therefore suggest, in the context of pain experience, that the buffering effect is more often able to account for the impact of social support on pain experience than the main effect.

We have noted some factors that may bias the evidence in favor or against these 2 theoretical accounts. The accurate assessment of buffering effect requires that the choice of measures of stress is appropriate. As reviewed earlier, a wide variety of stressors (> 50 items) ranging from family, work, to outdoor activity, and economic situation have been described,78,79 for many of which a single type of social support is small in supporting of both of the 2 models. Although relatively less supported by the literature, the main effect is still implicated in a number of studies. Moreover, some studies even showed both the main and the buffering effect in a single study.46,78 It suggests that the 2 theoretical accounts may be not mutually exclusive. Indeed the main and the buffering effect may depend on the type of measure of support.39 A structural measure of support (eg, the number of close relationships) may influence health outcomes through the main effect, whereas a functional measure (eg, emotional support) may exert its impact mainly through the buffering effect on stress.40 We therefore suggest, in the context of pain experience, that the buffering effect is more often able to account for the impact of social support on pain experience than the main effect.

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In summary, the buffering effect is a more flexible theoretical account in the context of pain research, and thus may more often explain the influence of social support on pain experience. However, this does not mean that the main effect is inappropriate as of the lack of effect size. We have also discussed the potential factors that may result in the preference of one perspective over another in support and pain research. In the following section, we discuss which cognitive or behavioral mediators might underlie the buffering effect of support on pain experience.

The Buffering Effect on Pain Experience is Associated With Stress Appraisal and Coping

Our review also examines aspects through which the buffering effect may account for the association between social support and pain experience. When supportive resources are available, the reduction of pain experience is associated with decreased perceived threat of pain,5,85 decreased pain helplessness,63 reduced pain catastrophizing, and perceived incompetence of problem solving,6,86 as well as by increased perceived mastery and self-esteem.83 These findings were found to be of medium to high quality. They support the stress appraisal process as being one of the mediators of the buffering effect.39

Social support may help appraise a potential stressor in more benign ways.45 Literature surrounding support and threat has shown that social support helps individuals “calm down” when experiencing a potential stressor.91 For example, individuals demonstrate lower body arousal and perceived tension in the experience of painful stimuli when they hold their partner’s hand or receive verbal support from confederate.24,90 Moreover, social support is suggested to suppress heart rate increase and threat-related theta oscillation to upcoming painful stimulation, which in turn associated with pain reduction.72 The findings therefore suggest that social support assists to perceiving pain and related stress as less threatening which in turn reduces pain. This argument is further corroborated by findings that social support fostered reinterpretation of uncomfortable feelings as neutral or comfortable sensations and produced higher tolerance to cold pain.22,23

In addition, social support may enhance the perceived ability to cope with imposed demands. In one study, verbal social support from confederate reduced task difficulty in the experience of cold pain.24 Another study showed that emotional support is associated with increased self-efficacy in the adjustment to diabetes.93 In this review, findings show that social support is positively associated with perceived mastery and self-esteem in the experience of chronic pain. These psychological mediators further act to decrease pain severity.53 Moreover, findings show that social support is able to buffer the adverse influence of perceived incompetence and helplessness on pain experience.66,84 These findings indicate that supportive resources contribute to the reduction of pain experience through bolstering perceived ability to cope with pain and related stress.

We also discuss evidence of the response regulation process of the buffering hypothesis. This line of research focuses on behavioral changes (action) to cope with pain, whereas stress appraisal specifically entails cognitive changes (perception) associated with social support. Specifically, 2 studies indicated that social support is associated with lower pain intensity and higher psychological adjustment by increased use of information seeking regarding treatments, cognitive reappraisal (ie, thinking of pain in more benign ways), and stoic distancing (ie, distracting attention away from pain).11,49 Other studies similarly showed that social support-assisted coping attempts (reinterpretation, distraction) and increased pain tolerance.22,23
These studies suggest that pain experience was reduced via social support and its influence on coping responses. However, a more recent study indicated that the level of social support is associated with decreased pain intensity and depressed mood, independent of any interaction with coping response. This discrepancy might be due to the manner in which coping responses were categorized. Although López-Martínez et al. used similar coping response criteria as former studies (eg, distracting attention from pain), they included broader categories of coping response (eg, engaging in physical therapy and leisure activities) and treated them as a single variable in the examination of buffering effect. It is likely that social support is not related to each of these coping strategies during the specific period of testing. Overall these findings provide evidence that stress coping may link social support to decreased pain experience, at least when supportive resources are able to prime a particular coping attempt.

**Neurobiological Mechanisms Mediating the Process of Stress Appraisal**

There is some preliminary neuroimaging evidence of mechanisms that may underlie the benefits of support on pain relief. In these studies, social support was manipulated in different ways: the presence of significant other; holding hand of significant other, and viewing pictures of significant other. In general, social support was associated with the reduction of pain rating, along with decreased threat-related and pain-related brain activation, for example, insula, anterior cingulate cortex (ACC), and hypothalamus. This is in line with an earlier behavioral observation, which showed that social presence decreased pain by suppressing perceived threat of pain. Moreover, a recent study showed that images of a significant other (individuals from whom the participants perceive most support on a daily basis) represent prepared safety cues to inhibit fear-learning process. This finding provides more evidence that social support could signal safety to suppress the threatening nature of pain.

The benefits of social support on pain have also been shown through physiological measures. An impending stressor can increase the response of the sympathetic nervous system and hypothalamus-pituitary-adrenal axis, which result to increases in heart rate, blood pressure, and cortisol level (see review in Muscatell and Eisenberger). Social support has been shown to suppress these physiological systems in the experience of a stressor. For example, lower level of blood pressure, heart rate, skin conductance, and cortisol response are observed when verbal social support or social presence is provided during the experience of thermal pain. These findings make sense given the threatening nature of painful stimuli and suggest that social support reduces the activation of physiological stress systems in response to pain stimuli.

**MODEL AND SUMMARY OF FINDINGS**

The evidence presented across behavioral-cognitive, neuroimaging, and physiological research lends significant support to the social-buffering model of pain reduction (Fig. 2). Evidence in favor of the buffering effect has been more often reported in social support and pain research. Although based on a relatively small number of studies, social support seems to prime safety-related brain activation (ie, VMPFC) when individuals are experiencing pain. This positive experience may assist with managing the threatening quality of pain and related stress (perceived threat, body arousal, and tension), and/or with perceived ability to cope with them (perceived mastery, self-esteem, and perceived competence). This stress appraisal process is also associated with decreased neural (ACC, AI, hypothalamus) and physiological (heart rate, skin conductance, blood pressure, cortisol) stress systems that are involved in the experience of threat and pain. This pattern of decreased cognitive-behavioral and neurobiological response to pain-related stress may in turn result in decreased pain experience.

It is worthwhile to note that social support may be associated with different stress appraisal processes, that is, perceived threat versus perceived coping ability, in acute and chronic pain. Pain-related cognitive patterns seem to be more strongly established in patients with chronic pain compared with transient pain evoked in healthy individuals. Moreover, these patterns of cognition include both decreased perceived threat of pain and increased perceived coping ability. Our review shows that, in people with chronic pain, social support is associated with both reduced perceived threat and increased perceived coping ability that can decrease pain. With regard to acute pain, the literature suggests that social support primarily inhibits perceived threat of pain. Therefore, this model may differ in acute versus chronic pain in how supportive resources can initiate the stress appraisal process.

Another limitation of this model is the difference in the nature of study designs. Studies in people with chronic pain almost exclusively examine potential associations between social support and pain, whereas experimental studies allow...
Manipulation of experimental conditions to generate stronger conclusions. However, there is a lack of experimental studies that could potentially generate stronger evidence in people with chronic pain. Only a single study was identified in which pain was experimentally induced in fibromyalgia patients. Nonetheless, consistent with findings in healthy individuals, social support reduced pain sensitivity, and threat-related and pain-related brain activation in the primary somatosensory cortex.26

With regard to neurobiological mechanisms, the most consistent findings across studies are shown in Figure 2. However, one study provides an alternative explanation whereby social support could reduce pain via the activation of reward-related neural pathways (eg, caudate, nucleus accumbens, OFC).32 Moreover, these brain areas are shown to have high densities of opioid receptors that have analgesic effects.113,114 Findings in this study are likely complementary to others28,30,90 as they focus on different brain areas that are involved in different mechanisms of analgesia. Moreover, differences in the nature of the romantic relationship might account for the inconsistency. Younger et al30 recruited participants in the early stage of romantic relationship (first 9 months); whereas participants in the other 2 studies were in a long-term romantic relationship. One study suggests that long-term romantic relationship not only maintains the reward value from new love, but also involves neural systems implicated in attachment.113

Another notion is that the influence of social support on pain may be at least partially mediated by attentional distraction. Social support, regardless of whether in the form of social presence or picture imagery, could distract attention from painful stimuli and consequently reduce pain-related brain activation. This is difficult to rule out in some early studies that did not include a control condition.26 However, more recent studies which include additional control conditions such as a distraction task and stranger control and further detailed the influence of social support on pain experience.28,30,90 It has also been proposed that the benefits of support might be related to the attachment style of individuals with pain.114 Attachment style is associated with how the individual with pain interprets supportive resources. For example, some people prefer closeness but fear abandonment (attachment anxiety), whereas others find it difficult to trust and rely on others (attachment avoidance).115 This difference may then modulate the influences of social support and related neural and physiological response.110,114

LIMITATIONS AND FUTURE DIRECTIONS
There are several limitations of this review. First, we were unable to examine the different types of social support, for example, emotional support (eg, love, caring), informational support (eg, advice, feedback), instrumental support (eg, materials, actions). The present review aimed to provide a general overview of the influence of support rather than to disentangle subtypes of social support. It was also not possible to definitively assign the reviewed supportive resources into either group as several covered multiple types of support, for example, social presence, positive support. Future studies could be designed to explore the role of different subtypes of social support in the experience of pain. Further, there are only a small number of studies that examine the neurobiological mechanisms of the buffering effect. This limits the conclusions that can be drawn at this stage and more studies are warranted. Moreover, the type of pain may influence results. Chronic pain was reported in the behavioral correlational studies, whereas acute pain was induced in the neurobiological studies. We then extended the evidence of neural mechanisms derived from acute pain to
explain the buffering effect in people with chronic pain. It is worthwhile to examine whether acute and chronic pain activate similar neural processes while supportive resources are available. Lastly, as pain itself is a stressor, it is somewhat artificial to dichotomize the presence of pain-related threat as a binary phenomenon. In this review, pain-related stress was mixed across binary and continuous variables. Future studies could consistently define and measure pain-related stress as a continuous variable.

CONCLUSIONS AND IMPLICATIONS

The benefits of social support on pain experience have been described in a large number of studies. Theoretical models suggest that social support is associated with decreased pain through its main effect or the buffering influence on stress. Findings in the present review suggest that the buffering effect can more often describe the benefits of social support on pain experience. The evidence suggests that pain reduction is partially mediated by the process of support buffering the adverse influence of stress, through processes such as stress appraisal and active coping. Moreover, social support may serve as a safety signal to modulate the perception of threat, and thereby suppress the activation of neural and physiological stress systems in response to pain.

Findings from this review also offer suggestions for support-assisted pain management therapies. Recent guidelines for prescribing opioids for chronic pain suggested potential risks (ie, opioid use disorder), and recommended cognitive-behavioral therapy (CBT) for chronic pain. CBT has been shown to result in significant improvements in physical suffering and mood in chronic pain conditions. As a modified CBT, support (usually spousal)-assisted coping skills training has included training components like communication skills, behavioral rehearsal, and mutual goal-setting. Findings from initial trials suggest the potential of support therapies in decreasing pain and disability. Building on this, our review suggests the critical significance of perceived support and attachment. These psychological processes have been shown to buffer threat response and improve coping ability. Future trials could therefore further develop upon the role of support and attachment in therapeutic interventions, including the enhancement of support relationships and their dynamics.

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Clin J Pain  Volume 34, Number 11, November 2018
Main and Buffering Effect of Social Support

Che et al


The psychology of ultra-marathon runners: A systematic review

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ARTICLE INFO

Keywords:
Ultra-runner
Ultra-endurance
Distance runner
Personality
Mood
Cognition

ABSTRACT

Objectives: An ‘ultra-marathon’ is a footrace over a distance > 42.2 km. There is considerable interest in the psychological characteristics of ultra-marathon runners (‘ultra-runners’) and the psychological effects of running an ultra-marathon. This review aimed to summarise the existing literature concerning the psychology of ultra-runners.

Design: A systematic review was performed. Studies were included if they investigated ultra-runners’ personality traits, mood, cognitive processes, cognitive function, pain perception, motivations, phenomenology, psychopathology or response to sports psychology interventions.

Method: Four databases (PubMed, Scopus, Web of Science and PsycINFO) were searched electronically up until December 2017.

Results: Fifty-one studies met the inclusion criteria. A few conclusions regarding the psychology of ultra-runners may be drawn from these studies. First, the acute mood effects of ultra-running appear to include an increase in fatigue and a decrease in vigour and tension. Secondly, the most important factor motivating ultra-runners to engage in their sport appears to be the opportunity to achieve personal goals. Finally, ultra-running seems to be associated with a psychological drive to explore physical and mental limits.

Conclusion: Although the existing literature sheds some light on ultra-runners’ mood states, motivations and phenomenology, further high-quality studies investigating the psychology of these remarkable athletes are needed.

1. Introduction

An ‘ultra-marathon’ is a footrace over a distance longer than the marathon distance of 42.2 km (26.2 mi). Ultra-marathons can be distance-limited or time-limited. In a distance-limited race, the aim is to run a certain distance in the shortest time. Common distances for distance-limited ultra-marathons include 50 km (31.1 mi), 80.5 km (50 mi), 100 km (62.1 mi) and 161 km (100 mi). In a time-limited race, the aim is to run the longest distance within a given time. Common times for time-limited ultra-marathons include 6 h, 12 h, 24 h and 48 h. Some ultra-marathons involve multiple running stages held over consecutive days. The total distance run in these multi-stage races can be extremely long. In the world’s longest ultra-marathon, the Self-Transcendence 3100 Mile Race, competitors run 4989 km (3100 mi) over a maximum of 52 days, which represents a minimum daily running distance of 95.9 km (59.6 mi), or over two marathons (http://3100.srichinmoyraces.org). Ultra-marathons can be run on any surface and are often held in remote wilderness settings. They fall within the broader category of ‘ultra-endurance’ events. These are most commonly defined as endurance events with a duration of more than 6 h (Wortley & Islas, 2011), although this definition actually excludes some of the shorter ultra-marathons, such as 50-km races, which are normally completed in under 6 h.

Since ultra-marathon running (or ‘ultra-running’) became an organised sport in the 1970s and 1980s, there has been considerable interest in the psychological effects of ultra-running and the psychological characteristics of ultra-runners. Much of this interest stems from the unique demands that ultra-running and other ultra-endurance sports place on participants. Ultra-runners must sustain endurance exercise for extremely long periods of time. The psychological effects of such prolonged endurance exercise and the psychological attributes of the athletes who successfully engage in it are of obvious interest to sport psychologists and exercise scientists. Questions that have been
investigated by researchers include what motivates ultra-runners to engage in such an arduous sport (Doppelmayr & Molkentin, 2004; Hanson, Madaras, Dicke, & Buckworth, 2015; Hashimoto, Hagura, Kuriyama, & Nishiyama, 2006; Krouse, Ransdell, Lucas, & Pritchard, 2011), whether ultra-running is associated with any personality traits (Folkins & Wieselberg-Bell, 1981; Freund et al., 2013; Hughes, Case, Stumptfe, & Evans, 2003; McCutcheon & Yoakum, 1983), what effects running an ultra-marathon has on mood and cognitive function (Doppelmayr, Finkenagel, & Doppelmayr, 2005; Graham et al., 2012; Hurdiel et al., 2015; Lucas, Anson, Palmer, Hellemans, & Cotter, 2009; Tharion, McMenemy, Terry, & Rauch, 1990; Tharion, Strowman, & Rauch, 1988; Wollseifen et al., 2016), whether ultra-runners have abnormal pain tolerance (Freund et al., 2013) and whether ultra-running is associated with psychopathsologies such as eating disorders and exercise dependence (Allegre, Therme, & Griffiths, 2007; Lantz, Rhea, & Mesnier, 2004; Pierce, McGowan, & Lynn, 1993; Szabo, De La Vega, Ruiz-Barquin, & Rivera, 2013).

Although there is a significant scientific literature investigating the psychology of ultra-runners, no attempt has yet been made to synthesise the findings from individual studies and to draw some general conclusions regarding these unique athletes. Indeed, no published review of this literature exists. The aim of this review is to provide a critical summary of the literature, to indicate what is currently known about ultra-runners’ psychology and to highlight gaps in the literature and directions for future research.

2. Methods
2.1. Protocol and eligibility criteria
A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The methods used in the review were specified in advance and documented in a protocol, which is available online as part of the supplementary electronic materials. Studies were included in the review if they were reported in a peer-reviewed journal article written in English and had as one of their main purposes the investigation of ultra-runners’ (i) personality traits, (ii) mood or emotions, (iii) cognitive processes during races, (iv) cognitive function, (v) pain perception, (vi) motivations for engaging in ultra-running, (vii) phenomenology or subjective experience of ultra-running, (viii) psychopathological traits or symptoms or (ix) response to sports psychology interventions. With respect to pain perception, studies that involved the measurement of pain-related psychophysiological parameters such as pain threshold or pain tolerance were included in the review. Studies that investigated only the experience of muscle pain by ultra-runners during or after races were not included, however (see, e.g., Nieman et al., 2005). Studies that investigated the experience of thermal sensations, nausea or perceived exertion by ultra-runners during or after races were also treated as not falling within the inclusion criteria (see, e.g., Brown & Connolly, 2015; Clemente-Suarez, 2015; Joslin et al., 2014; Stumptfe & Hoffman, 2015). An ‘ultra-runner’ was defined as a person who, at the time of the study, had previously completed or was registered to compete in an event that involved running more than 42.2 km (26.2 mi). This definition included competitors in ‘walk/run’ events, which are races in which participants are permitted to either walk or run.

2.2. Information sources and search strategy
Relevant articles were identified by electronically searching the PubMed, Scopus, Web of Science and PsycINFO databases. The databases were searched on 1 December 2017 using the following search string (appropriately adapted for each database): ultra-marathon OR ultramarathon OR “ultra marathon” OR ultra-runner OR ultrarunner OR “ultra runner” OR ultra-distance OR ultradistance OR “ultra distance” OR ultra-endurance OR ultraendurance OR “ultra endurance” OR ultra-marathoner OR ultramarathoner OR “ultra marathoner” OR ultra-marathons OR ultramarathons OR “ultra marathons” OR ultra-runners OR ultrarunners OR “ultra runners” OR ultra-marathons OR ultramarathons OR “ultra marathoners”. In PubMed and Web of Science, all search fields were searched. In Scopus and PsycINFO, the ‘Title’, ‘Abstract’ and ‘Keywords’ or ‘Key Concepts’ search fields were searched. There was no restriction in the searches on publication date or document type. Eligibility assessment was performed in an unblinded, standardised manner by two reviewers (GR and SN) acting independently. The reviewers reviewed the title and abstract of each search record to assess whether the record was potentially eligible for inclusion in the review. They then reviewed the full-text of any article that was deemed to be potentially eligible for inclusion and determined whether the article met the inclusion criteria. Disagreements between the reviewers were resolved by their meeting to discuss the article and reaching a consensus as to its inclusion or exclusion.

3. Results
3.1. Study selection
The searches produced a total of 3444 records. After removal of duplicates, there were 1506 unique records. Of these, 1384 were discarded following review of their title and abstract. The full-text of the remaining 122 articles was reviewed in detail and it was determined that 42 of these articles met the inclusion criteria. A further nine articles that met the inclusion criteria were identified by checking the references of these articles and checking their forward citations on Google Scholar. Thus, 51 articles, and the studies reported by these articles, were included in the review. A flowchart summarising the study selection process is depicted in Fig. 1.

3.2. Study characteristics
For each of the included studies, the study population, methods and relevant findings are summarised in Table 1. The studies are divided into 10 sub-categories in Table 1. Nine of these sub-categories correspond to the nine areas of research identified in the inclusion criteria. The final sub-category contains studies that fell within one of these areas of research but were ‘case studies’ in the sense that they involved only a single participant. The number of studies in each of the sub-categories is as follows: (i) ultra-runners’ personality traits — 9 studies, (ii) ultra-runners’ mood or emotions — 11 studies, (iii) ultra-runners’ cognitive processes during races — 1 study, (iv) ultra-runners’ cognitive function — 9 studies, (v) ultra-runners’ pain perception — 2 studies, (vi) ultra-runners’ motivations for engaging in ultra-running — 6 studies, (vii) ultra-runners’ phenomenology — 7 studies, (viii) ultra-runners’ psychopathological traits or symptoms — 7 studies, (ix) ultra-runners’ response to sports psychology interventions — 1 study and (x) case studies — 5 studies. Seven studies fell within more than one sub-category — these are marked with an asterisk (*) in Table 1. As Table 1 shows, the studies included in the review are methodologically very diverse. Thirty-nine of the studies are quantitative studies, eight are qualitative studies and four employ a mix of quantitative and qualitative methods. The quantitative studies include cross-sectional studies, uncontrolled pretest-posttest studies (where the relevant ‘intervention’ is running an ultra-marathon), controlled pretest-posttest studies and interrupted time series studies. Because of this methodological diversity and the impossibility of using a single quality assessment tool or even a small number of such tools to assess the methodological quality of all of the included studies, a risk of bias assessment was not performed as part of this systematic review.

3.2.1. Ultra-runners’ personality traits
Nine studies investigated the personality traits possessed by ultra-
runners (Acevedo, Dzewaltowski, Gill, & Noble, 1992; Folkins & Wieselberg-Bell, 1981; Freund et al., 2013; Hashimoto et al., 2006; Hughes, Case, Stuempfe, Evans, & Personality profiles of Iditasport ultra-marathon participants, 2003; Krouse et al., 2011; McCutcheon & Yoakum, 1983; Rauch, Tharion, Strowman, & Shukitt, 1988; Teranishi Martinez & Scott, 2016). These studies used a wide range of psychometric instruments, including the Adjective Checklist, Multiple Affect Adjective Checklist (MAACL), Philosophies of Human Nature Scale, Self-Motivation Inventory, State-Trait Anxiety Inventory, Commitment to Running Scale (CRS), Sport Orientation Questionnaire (SOQ), Trait Sport-Confidence Inventory (TSCI), NEO-Five Factor Inventory, Sensation Seeking Scale (SSS), Myers-Briggs Type Indicator, Perception of Success Questionnaire, Temperament and Character Inventory, General Self-Efficacy Scale and Ten-Item Personality Inventory. Seven studies found that ultra-running was associated with certain personality traits. Compared with the general population, ultra-runners have been reported to be more self-motivated (Rauch et al., 1988), more extraverted, open and experience-seeking and less disinhibited (Hughes et al., 2003), more introverted (Hashimoto et al., 2006) and more self-transcendent and less cooperative and reward-dependent (Freund et al., 2013). Compared with other runners, they have been reported to be more neurotic (Teranishi Martinez & Scott, 2016). Acevedo et al. (1992) compared a sample of ultra-runners to the norm groups for the SOQ, TSCI and CRS, which consisted of a population of undergraduate students enrolled in non-competitive physical activity skills classes (Gill & Deeter, 1988), a population of high school, university and professional athletes from various sports (Vealey, 1986) and a population of runners of varying levels of experience and ability (Carmack & Martens, 1979), respectively. Compared with these norm groups, ultra-runners were more competitive and goal-oriented but less win-oriented, more confident and more committed to running. Krouse et al. (2011) examined the goal orientations of a cohort of female ultra-runners and found that they were considerably higher in task orientation than ego orientation (with respect to ultra-running). The remaining two studies in this sub-category did not find any significant differences between ultra-runners and the general population with respect to personality traits (Folkins & Wieselberg-Bell, 1981; McCutcheon & Yoakum, 1983).

3.2.2. Ultra-runners’ mood or emotions
Eleven studies investigated ultra-runners’ mood states or emotions (Anglem, Lucas, Rose, & Cotter, 2008; Graham et al., 2012; Hoffman & Hoffman, 2008; Lane & Wilson, 2011; Micklewright et al., 2009;
### Table 1
Summary of the study populations, methods and relevant findings of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methods</th>
<th>Relevant findings</th>
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<tr>
<td><strong>i. Ultra-runners’ personality traits</strong></td>
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<tr>
<td>Polkims &amp; Wieselberg-Bell, 1981*</td>
<td>46 competitors in a 161-km (100-mi) UM (4 ♀, 42 ♂)</td>
<td>Participants completed the AQL and MAQL.</td>
<td>• The mean scores on both instruments were within the normal range.</td>
</tr>
<tr>
<td>McCutcheon &amp; Yoakum, 1983</td>
<td>50 URs, 8 DRs and 58 HCs (all ♂)</td>
<td>Participants completed the SMI and four subscales of the PHINS.</td>
<td>• There were no significant differences between the three groups on either instrument.</td>
</tr>
<tr>
<td>Rauch et al., 1988*</td>
<td>44 competitors in an 80.5-km (50-mi) UM (2 ♀, 42 ♂)</td>
<td>Participants completed the SMI and Form X-2 of the STAI.</td>
<td>• There were also no differences between faster and slower runners in the UR group.</td>
</tr>
<tr>
<td>Azevedo et al., 1992*</td>
<td>112 competitors in one of two 161-km (100-mi) UM (26 ♀, 86 ♂)</td>
<td>Participants completed the SOQ, TSCI and CRS and a questionnaire assessing their goals.</td>
<td>• Participants’ SMI scores were higher than those reported for a norm group of undergraduate college students but similar to those reported for other athletes.</td>
</tr>
<tr>
<td>Hughes et al., 2003</td>
<td>66 competitors in a 161-km (100-mi) multi-disciplinary race over 3 years (18 ♀, 48 ♂), including 35 URs</td>
<td>Participants completed Form S of the NEO-FFI and Form V of the SSS.</td>
<td>• Participants were more extraverted and open than the norm group for the NEO-FFI.</td>
</tr>
<tr>
<td>Hashimoto et al., 2006*</td>
<td>52 competitors in either a 100-km (62.1-mi) UM or a 24-h UM (12 ♀, 40 ♂)</td>
<td>Participants completed the Japanese version of the MBTI.</td>
<td>• Participants were more experience-seeking but less disinhibited than the norm group for the SSS.</td>
</tr>
<tr>
<td>Krouse et al., 2011*</td>
<td>344 URs (all ♀)</td>
<td>Participants completed the PSQ.</td>
<td>• The ISFJ type was the most common personality type among participants.</td>
</tr>
<tr>
<td>Freund et al., 2013*</td>
<td>22 participants: 11 competitors in a 64-d, 4487-km (2788-mi) UM and 11 matched HCs (all ♂)</td>
<td>Participants completed the German versions of the TCI and GSES.</td>
<td>• The ISFJ and INFJ types and introversion were all significantly more common among participants than in the normative population for the Japanese version of the MBTI.</td>
</tr>
<tr>
<td>Teranishi Martinez &amp; Scott, 2016</td>
<td>189 participants (132 ♀, 57 ♂): 68 URs, 38 MRs, 62 DRs (5 km to HM), 17 DIs (&lt; 5 km), 2 non-runners and 2 other participants</td>
<td>Participants completed the TIPI, FPS, a measure of well-being and a questionnaire assessing the frequency with which they ran in natural and non-natural environments.</td>
<td>• Participants were more extraverted and open than the norm group for the NEO-FFI.</td>
</tr>
<tr>
<td><strong>ii. Ultra-runners’ mood or emotions</strong></td>
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<td></td>
</tr>
<tr>
<td>Rauch et al., 1988*</td>
<td>44 competitors in an 80.5-km (50-mi) UM (2 ♀, 42 ♂)</td>
<td>Participants completed the POMS before and after the race.</td>
<td>• Participants exhibited the ‘iceberg’ profile of mood states before the race.</td>
</tr>
<tr>
<td>Tharion et al., 1988</td>
<td>56 competitors in either an 80.5-km (50-mi) UM or a 161-km (100-mi) UM (all ♀)</td>
<td>Participants completed the POMS before and after the races.</td>
<td>• Fatigue increased and vigour and tension decreased during the race.</td>
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Table 1 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methods</th>
<th>Relevant findings</th>
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<tbody>
<tr>
<td>Thorin et al., 1990</td>
<td>14 competitors in a 161-km (100-mi) UM (all ♂)</td>
<td>Participants completed the POMS before, immediately after and 1 week, 1 month and 3 months after the race.</td>
<td>• Fatigue increased during the race but returned to pre-race levels by 1 week after the race.</td>
</tr>
<tr>
<td>Anglem et al., 2008</td>
<td>60 competitors in a 411-km (255-mi), 5-day multi-disciplinary adventure race (19 ♂, 41 ♀)</td>
<td>Participants completed the BRUMS daily during the race and serially in the fortnight following the race.</td>
<td>• Fatigue increased and vigour and tension decreased during the race. All three scales returned to baseline by 2 weeks after the race.</td>
</tr>
<tr>
<td>Hoffman &amp; Hoffman, 2008</td>
<td>48 participants (24 ♂, 24 ♀): 16 URs, 16 regular moderate exercisers and 16 non-exercisers</td>
<td>Participants completed the POMS before and after a short session of aerobic exercise.</td>
<td>• Depression, anger and confusion were generally low but depression was modestly elevated on the third day after the race.</td>
</tr>
<tr>
<td>Micklewright et al., 2009</td>
<td>8 competitors in a 73.4-km (45.6-mi) UM (1 ♂, 7 ♀)</td>
<td>Participants completed a shortened version of the POMS before and immediately after the race.</td>
<td>• Fatigue and confusion increased and vigour decreased during the race.</td>
</tr>
<tr>
<td>Lane &amp; Wilson, 2011</td>
<td>34 competitors in a 282-km (175-mi), 6-day UM (8 ♂, 24 ♀)</td>
<td>Participants completed the EmIS and BRUMS before the race and also completed the BRUMS and items from the UMACL before and after each stage of the race.</td>
<td>• Fatigue increased and vigour decreased during each stage of the race except the final stage.</td>
</tr>
<tr>
<td>Nicolas et al., 2011</td>
<td>14 competitors in a 24-h UM (all ♂)</td>
<td>Participants completed the French version of the RESTQ-Sport immediately before and after the race and serially in the month following the race.</td>
<td>• High trait emotional intelligence was associated with higher calmness and happiness and lower anger, confusion, depression, fatigue and tension during the race.</td>
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<tr>
<td>Graham et al., 2012</td>
<td>11 competitors in a 7-day, 241-km (150-mi) UM (all ♂)</td>
<td>Participants completed the BRUMS each day during the race.</td>
<td>• Fatigue increased and vigour decreased over the first 6 days of the race.</td>
</tr>
<tr>
<td>Wollfefflein et al., 2016*</td>
<td>11 URs (5 ♂, 6 ♀)</td>
<td>Participants completed a 6-h running session, with EEG performed and mood assessed using the MoodMeter® computer program and flow state assessed using the FFS-2 before the session and hourly during the session.</td>
<td>• Both improved on the final day of the race but not to pre-race levels.</td>
</tr>
<tr>
<td>Longman et al., 2017</td>
<td>66 competitors in a 160.1-km (102.6-mi) UM (all ♂ and all heterosexual)</td>
<td>Participants reported valence and arousal ratings in response to sexually provocative images and positive- and negative-valence IAPS images before and after the race.</td>
<td>• Depression, tension and confusion increased over the first 6 days but returned to pre-race levels on the final day.</td>
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### Table 1 (continued)

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| **iii. Ultra-runners’ cognitive processes during races**<br> Acevedo et al., 1992* | 112 competitors in one of two 161-km (100-mi) UM (26 ♀, 86 ♂) | Participants completed a questionnaire assessing their cognitive processes during races and cognitive strategies during training and racing. | • In response to a forced-choice question, about 50% of participants reported experiencing mainly internally focused thoughts during races and 50% reported experiencing mainly externally focused thoughts.  
• In response to an open question, however, approximately 75% of the thoughts described were externally focused.  
• A variety of cognitive strategies were used during training and racing, including visualisation, reading pre-race paraphernalia, setting goals, self-talk and thought control. |
| **iv. Ultra-runners’ cognitive function**<br> Glace et al., 2002 | 19 competitors in a 161-km (100-mi) UM (1 ♀, 18 ♂) | Participants were monitored during the race for MSC and their dietary intake before and during the race was also monitored. | • 10 participants reported MSC, which included light-headedness and confusion.  
• Participants who developed MSC had a greater intake of total calories, carbohydrates and fluid during the race than those who did not and also completed shorter training runs.  
• Cognitive performance decreased over the course of the race but not in a linear fashion.  
• It decreased over the course of day 1, then increased and peaked at a level above baseline on the morning of day 2, decreased again over the course of day 2, reached its lowest level on the morning of day 3 and then increased in the last testing session.  
• Response time and error rate for simple tasks were stable across the race.  
• Response time for complex tasks was 16% higher after the race but the change was not significant.  
• Error rate for complex tasks was stable across the race.  
• Response time for complex tasks improved as participants exercised at higher intensities.  
• Cognitive performance was significantly reduced after the race.  
• Mean (± SD) sleep duration during the race was 12 ± (± 17) minutes.  
• There was no correlation between post-race cognitive performance and sleep duration or finishing time.  
• Faster runners in the race outperformed slower runners in various ways.  
• They were more accurate on the inhibitory control task in trials requiring motor inhibition.  
• They also had shorter response times in the dual-task paradigm in trials where a prospective memory cue with a positive or negative emotional valence was given.  
• Cognitive performance was stable across the whole 6 h. |
| Doppelmayr et al., 2005 | 2 competitors in a 216-km (134-mi) UM (both ♀) | Participants performed tests of cognitive performance before the race and then at regular intervals during the race. | |
| Lucas et al., 2009 | 9 competitors in a 411-km (255-mi), 5-day, multi-disciplinary adventure race | Participants were administered the Stroop test before, during and after the race, with some testing occurring while they performed a cycling stress test at various intensities. | |
| Hurdel et al., 2015 | 17 competitors in a 166-km (104-mi) UM (1 ♀, 16 ♂) | Participants completed a test of cognitive performance before and after the race and their sleep duration during the race was measured. | |
| Cons et al., 2015 | 30 competitors in an 80-km (49.7-mi) UM (all ♂) | Participants performed two tasks assessing cognitive performance before the race: an inhibitory control task and a dual-task paradigm incorporating a working memory task and a prospective memory task. | |
| Wolbeiffen et al., 2016* | 11 URs (5 ♀, 6 ♂) | Participants completed a 6-h running session and their cognitive performance was assessed using an adapted version of the ‘Chalkboard Challenge’ brain game before the session and hourly during the session. | |
| Tonacci et al., 2016 | 149 participants (23 ♀, 126 ♂): 53 competitors in a 332.5-km (206.6-mi) mountain UM, 43 non-UR athletes and 53 HCs | The UR participants’ olfactory function was measured before, during and after the race and the olfactory function of the non-UR athletes and HCs was measured at rest. | • The UR participants’ olfactory function decreased significantly from pre-race to post-race.  
• Mid-race olfactory function was weakly correlated with mid-race total body water and post-race olfactory function was correlated with sleep duration during the race.  
• The UR participants’ pre-race olfactory function was similar to that of the non-UR athletes and HCs. |
Participants' executive function was assessed using the colour-word interference task of the Stroop test before and after the race.

The change in executive function was positively correlated with participants' heart rate responses to an orthostatic challenge post-race.

Olfactory function decreased significantly over the course of the race.

Total sleep duration was positively correlated with the change in olfactory function.

COWAT scores increased from pre-race to post-race.

TMT scores did not significantly change from pre-race to post-race.

Faster runners (but not slower runners) experienced a modest reduction in pressure pain sensitivity after the race.

There was no relationship between pain pressure sensitivity and overall pain level after the race.

The URs displayed higher pain tolerance than the HCs on the CPT.

Mean (± SD) immersion time was 180 s (± 0 s) for the URs compared to 96 s (± 58 s) for the HCs.

Pain intensity rating at 180 s was correlated with scores on various TCI and GSES scales.

Nature, 'personal goal achievement' and 'life meaning' were the most commonly cited motivations for the adventure URs.

Personal goal achievement, 'nature' and 'self-esteem' were the most commonly cited motivations for the non-adventure URs.

Competition was more commonly cited by the MRs than the other two groups.

'To feel sense of achievement', 'to provide challenge', 'to push beyond current capability', 'to socialise with other runners' and 'to meet people' were the most commonly cited motivations for continuing ultra-running.

Personal goal achievement', 'general health orientation' and 'self-esteem were the most important motivations.

'Competition' was the least important.

'Intrinsic achievement' and 'commitment' were the most important motivational factors.

'Exploration and competitiveness' was the least important.

'Personal goal achievement', 'general health orientation' and 'self-esteem were the most important motivations for the URs.

'Recognition' and 'competition' were the least important for them.

'Life meaning' was more important and 'weight concern' and 'general health orientation' less important for the URs compared to the other groups.

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Table 1 (continued)

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</table>
| Ferrer et al., 2015          | 9 competitors in either a 24-h or a 48-h UM (4 ♀, 5 ♂) | Participants completed the MOMS.                                       | - General health orientation and personal goal achievement were the most motivations.  
|                              |                                          |                                                                         | - Age was positively associated with physical motivations.                         
|                              |                                          |                                                                         | - Physical motivations were negatively associated with mean running speed but positively associated with total distance covered during the 24-h race. |
| vii. Ultra-runners’ phenomenology |                                          |                                                                         |                                                                                  |
| Hanold, 2010                 | 8 elite URs (all ♀)                      | Semi-structured interviews were conducted with participants.            | - Participants expressed the view that no single ideal ultra-running body exists.  
|                              |                                          |                                                                         | - Ultra-running assisted some participants to view their bodies more positively. |
|                              |                                          |                                                                         | - Participants distinguished between two types of pain: ‘good pain’ and ‘bad pain’. |
| Crust et al., 2010           | 12 participants in a 100-km (62.1-mi) walk/run event (7 ♀, 5 ♂) | Participants were interviewed several times during the event and finishers subsequently participated in a focus group. | - Participants identified the ability to maintain a sense of perspective, tenacity, total commitment to one’s goals, challenge-seeking, a sense of humour and objectivity as attributes of the mentally tough event participant.  
|                              |                                          |                                                                         | - Participants encountered numerous stressors during the race.                   
|                              |                                          |                                                                         | - Coping strategies included making small goals, treating the race as a mental or physical battle, careful monitoring of pace, nutrition and hydration and seeking social support. |
| Holt et al., 2014            | 6 competitors in a 125-km (77.7-mi) UM (1 ♀, 5 ♂) | Participants were interviewed before and during the race and wrote a summary of their experiences and participated in a focus group after the race. | - Participants encountered numerous stressors during the race.                   
|                              |                                          |                                                                         |                                                                                 |
| Simpson et al., 2014         | 26 URs (7 ♀, 19 ♂)                      | Phenomenological interviews were conducted with participants.           | - There were five themes that characterised participants’ experiences of participating in UMs: community, preparation and strategy, management, discovery and personal achievement.  
|                              |                                          |                                                                         | - Themes relating to mental toughness that emerged from participants’ responses included perseverance/persistence, overcoming adversity, perspective, life experience, psychological skills use and camaraderie in the ultra-running community. |
| Jaeschke et al., 2016        | 12 URs (3 ♀, 9 ♂)                       | Semi-structured interviews were conducted with participants.            |                                                                                  |
| Philippe et al., 2016        | 10 competitors in either a 65-km (40-mi), 97-km (60-mi) or 173-km (107-mi) UM (2 ♀, 8 ♂) who withdrew from their respective races | Self-confrontation interviews were conducted with participants after their race. | - Seven sequences of experience were representative of participant experiences: (1) feeling pain; (2) putting meaning to those feelings; (3) adjusting running style; (4) attempting to overcome the problem; (5) other runners’ influence; (6) assessing the situation; and (7) deciding to withdraw.  
|                              |                                          |                                                                         | - Finishers had fewer sequences in SVP and more sequences in SVL compared with non-finishers. |
| Rochat et al., 2017          | 13 competitors in either a 65-km (40-mi), 97-km (60-mi) or 173-km (107-mi) UM (4 ♀, 9 ♂) (EI participants) and 28 competitors in various UMs ranging in length from 50km (31 mi) to 170km (106 mi) ('Blog participants') | EIIs were conducted with the EI participants after their races and blog posts by the blog participants about their races were obtained and five sets of data were combined and analysed, with participants’ sequences of experience during the races categorised into one of three ‘vitality states’: SVP, SVL or SVR. | - Finishers were more likely to experience a transition from SVL to SVP than non-finishers. |
|                              |                                          |                                                                         | - SVP was more common from the second quarter of the races onwards and SVL more common from the third quarter of the races onwards. |
| viii. Ultra-runners’ psychopathological traits or symptoms |                                          |                                                                         |                                                                                  |
| Polkarev & Wieselberg Bell, 1981 | 46 competitors in a 163-km (100-mi) UM (4 ♀, 42 ♂) | Participants completed the MMPI.                                       | - Mean scores on all MMPI scales were within the normal range.                   
|                              |                                          |                                                                         | - Finishers had more deviant scores than non-finishers on various scales, however, including the psychopathic deviant, hysteria, schizophrenia and hypochondriasis scales. |
|                              |                                          |                                                                         | - A weighted combination of MMPI scales predicted finishing status with 79% accuracy. |

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</table>
| Weight & Noakes, 1987          | 150 participants (all ♀): 15 URs, 85 MRs, 25 cross-country runners and 25 HCs | Participants completed the EAT-26 and EDI. | • 14% of runner participants had EAT-26 scores indicating at-risk status for an eating disorder but only 4% also reported a history of low body mass and amenorrhoea.  
• 20% of the UR group were at risk of developing an eating disorder and had a history of low body mass and amenorrhoea.  
• The UR group had higher EAT-26 scores than the other three groups.  
• There were no significant differences between the groups on the EDI.  
• The URs and MRs had higher NAS scores than the other two groups and the URs had higher scores than the MRs.  
• NAS scores were positively correlated with average weekly training distance.  
• EAT-26 score was positively correlated with ExIS score and score on the injury tolerance scale of the BAS.  
• ExIS score was positively correlated with score on the injury tolerance scale of the BAS.  
• Female participants with high ExIS scores were more likely to report disordered eating behaviours than male participants and female participants with low or moderate ExIS scores.  
• Training volume was positively associated with ExIS score and the fat.  
• Knowledge of the FAT was very poor, with 92.5% of participants having never heard of it. |
| Pierce et al., 1993            | 150 DRs (all ♂): 61 URs, 32 MRs, 24 5-km runners and 33 recreational runners | Participants completed the NAS. | • 3.2% of participants were at risk for exercise dependence.  
• The strongest positive predictor of EDS-R score was engaging in exercise in the city in an unstructured space and the strongest negative predictors were increasing age and BMI.  
• 17% of the URs and 8.8% of the university athletes were at risk for exercise addiction.  
• Training volume was positively associated with EAI score for the university athletes but not the URs.  
• 32% of participants reported disordered eating behaviours and 5.2% met the criteria for a clinical eating disorder.  
• 44.1% of participants were at risk of the FAT.  
• Knowledge of the FAT was very poor, with 92.5% of participants having never heard of it. |
| Lantz et al., 2004             | 87 competitors in either an 80.5-km (50-mi) UM or 161-km (100-mi) UM (14 ♀, 73 ♂) | Participants completed the EAT-26, ExIS and BAS. | • 32% of participants reported disordered eating behaviours and 5.2% met the criteria for a clinical eating disorder.  
• 44.1% of participants were at risk of the FAT.  
• Knowledge of the FAT was very poor, with 92.5% of participants having never heard of it. |
| Allegre et al., 2007           | 95 competitors in a 100-km (62.1-mi) UM (9 ♀, 86 ♂) | Participants completed the French version of the EDS-R and a questionnaire assessing their physical activity habits. | • 3.2% of participants were at risk for exercise dependence.  
• The strongest positive predictor of EDS-R score was engaging in exercise in the city in an unstructured space and the strongest negative predictors were increasing age and BMI.  
• 17% of the URs and 8.8% of the university athletes were at risk for exercise addiction.  
• Training volume was positively associated with EAI score for the university athletes but not the URs.  
• 32% of participants reported disordered eating behaviours and 5.2% met the criteria for a clinical eating disorder.  
• 44.1% of participants were at risk of the FAT.  
• Knowledge of the FAT was very poor, with 92.5% of participants having never heard of it. |
| Szabo et al., 2013             | 242 participants (76 ♀, 164 ♂): 95 elite URs and 147 university athletes | Participants completed the Spanish version of the EAI. | • 32% of participants reported disordered eating behaviours and 5.2% met the criteria for a clinical eating disorder.  
• 44.1% of participants were at risk of the FAT.  
• Knowledge of the FAT was very poor, with 92.5% of participants having never heard of it. |
| Folcher et al., 2015           | 306 competitors in an 89-km (55.3-mi) UM (all ♀) | Participants completed the LEAF-Q and FAST and a questionnaire assessing knowledge of the FAT. | • 32% of participants reported disordered eating behaviours and 5.2% met the criteria for a clinical eating disorder.  
• 44.1% of participants were at risk of the FAT.  
• Knowledge of the FAT was very poor, with 92.5% of participants having never heard of it. |
| McCormick et al., 2018         | 29 competitors in a 97-km (60-mi) UM (4 ♀, 25 ♂) | Participants were randomised to a group that received a motivational self-talk intervention or a control group and also completed measures of self-efficacy, perceived control, performance expectations and motivation before the intervention and before the race. | • The motivational self-talk intervention did not affect pre-race self-efficacy, perceived control, performance expectations or motivation.  
• There was no difference in race performance between the intervention group and the control group.  
• Most participants in the intervention group found the intervention helpful and continued to use it in races and training 6 months after the race.  
• There were no significant differences in pre-run, intra-run and post-run levels of depression, anxiety and hostility.  
• The participant’s motivations were initially mostly intrinsic and related to his need to develop feelings of competence but they became more extrinsic as he became the focus of media attention during the run.  
• The participant experienced both associative and dissociative thoughts during the run.  
• Associative thinking was associated with superior running performance. |
| x. Case studies                |            |                                                   |                                                                                                                                                  |
| Joesting, 1981                 | 1 UR who completed an 80.5-km (50-mi) solo run (♀) | The study participant completed the ‘Today’ form of the MAACL before, during and after the run. | • The participant’s motivations were initially mostly intrinsic and related to his need to develop feelings of competence but they became more extrinsic as he became the focus of media attention during the run.  
• The participant experienced both associative and dissociative thoughts during the run.  
• Associative thinking was associated with superior running performance. |
<p>| Bull, 1988                     | 1 UR who completed a 20-day, 800-km (497-mi) run (♂) | The investigator gave a qualitative description of the study participant’s motivations for undertaking the run and his cognitive processes during the run. |                                                                                                                                                  |</p>
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<tr>
<td>Bull, 1989</td>
<td>1 UR who completed a 20-day, 800-km (497-mi) run (♂)</td>
<td>The investigator gave a qualitative description of a sports psychology</td>
<td>• The intervention consisted of four phases: (a) establishing rapport; (b) forming</td>
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<td>consulting intervention provided by him to the study participant before and during the run.</td>
<td>a psychological profile of the participant; (c) developing an appropriate mental training</td>
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<td>program; and (d) ongoing evaluation of the participant's progress and crisis</td>
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<td>intervention.</td>
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<td>• The participant's mood state decreased and her pain levels increased over the</td>
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<td>course of the race.</td>
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<td>• Pain levels accounted for 90% of the variance of mood state.</td>
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<td>• All POMS-BI scales showed changes post-race and all except the clear-headed-confused</td>
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<td>scale returned to baseline within 1 month after race.</td>
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<td>• 70.6% of the thoughts described by the participant during the race were</td>
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<td>associative and 29.4% dissociative.</td>
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<td>• Total EmRecQ score was higher during the race than after it.</td>
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<td>• RPE was positively correlated with EmRecQ score and negatively correlated with</td>
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<td>TMD on the POMS.</td>
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<td>Kirkby, 1996</td>
<td>1 competitor in a 48-h UM (♀)</td>
<td>The study participant rated her mood state and pain intensity levels and</td>
<td>• The participant identified as assisting her to complete the run fell into four</td>
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<td>described her thoughts every 35 min during the race and completed the</td>
<td>categories: motivation, group cohesiveness, self-awareness and mental stamina.</td>
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<td>POMS-BI serially before and after the race.</td>
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<td>scale returned to baseline within 1 month after race.</td>
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<td>Johnson et al., 2016</td>
<td>1 UR who completed a 3641-km (2262-mi), transcontinental run (♀)</td>
<td>The study participant completed the POMS and EmRecQ and reported her RPE</td>
<td>• The participant identified as assisting her to complete the run fell into four</td>
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<td>before, during and after the run and also participated in a narrative</td>
<td>categories: motivation, group cohesiveness, self-awareness and mental stamina.</td>
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<td>interview 9 months after the run.</td>
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**Abbreviations:** ACL, Adjective Checklist; BAS, Body Alienation Scale; BRUMS, Brunel Mood Scale; COWAT, Controlled Oral Word Association Test; CPT, Cold Pressor Test; CRS, Commitment to Running Scale; DR, distance runner; EAI, Exercise Addition Inventory; EAT-26, Eating Attitudes Test-26; EDIS-R, Exercise Dependence Scale-Revised; EEG, electroencephalography; EI, enactive interview; EmIS, Emotional Intelligence Scale; EmRecQ, Emotional Recovery Questionnaire; ExIS, Exercise Identity Scale; FAST, Female Athlete Screening Tool; FAT, female athlete triad; FFS, Flow State Scale; LEAF-Q, Low Energy Availability in Females Questionnaire; GI, gastrointestinal; GSES, General Self-Efficacy Scale; HC, healthy control; HMR, half-marathon runner; International Affective Picture System, IAPS; MAACL, Multiple Affect Adjective Checklist; MBTI, Myers-Briggs Type Indicator; MFQ-SF, Multidimensional Fatigue Symptom Inventory - Short Form; MMPI, Minnesota Multiphasic Personality Inventory; MMS, Motivations of Marathoners Scale; MR, marathon runner; MSC, mental status changes; NAS, Negative Addiction Scale; NEO-FFI, NEO-Five Factor Inventory; PHNS, Philosophies of Human Nature Scale; POMS, Profile of Mood States; POMS-BI, the bipolar form of the POMS; PSQ, Perception of Success Questionnaire; RESTQ-Sport, Recovery—Stress Questionnaire for Athletes; RPE, rating of perceived exertion; SD, standard deviation; SLSS, Self-Loathing Subscale; SMI, Self-Motivation Inventory; SOQ, Sport Orientation Questionnaire; SSS, Sensation Seeking Scale; STAI, State-Trait Anxiety Inventory; SVL, state of vitality loss; SVP, state of vitality preservation; SVR, state of vitality revival; TCI, Temperament and Character Inventory; TIPI, Ten-Item Personality Inventory; TMD, Total Mood Disturbance; TMT, Trail Making Test; TSCI, Trait Sport-Confidence Inventory; UM, ultra-marathon; UMACL, UWIST Mood Adjective Checklist; UR, ultra-runner.
Athletes (RESTQ-Sport), Flow State Scale and MoodMeter (2009; Rauch et al., 1988; Tharion et al., 1990, 1988). The POMS and Emotional Intelligence Scale, UWIST Mood Adjective Checklist measure six mood states: anger, confusion, depression, fatigue, tension and vigour. The remaining studies in this sub-category used the Mood States (POMS) (McNair, Lorr, & Droppleman, 1971) or the Brunel Mood Scale (BRUMS) (Terry, Lane, Lane, & Keohane, 1999), which is derived from the POMS (Anglem et al., 2008; Graham et al., 2012; Hoffman & Hoffman, 2008; Lane & Wilson, 2011; Micklewright et al., 2009; Rauch et al., 1988; Tharion et al., 1990, 1988). The POMS and BRUMS measure six mood states: anger, confusion, depression, fatigue, tension and vigour. The remaining studies in this sub-category used the Emotional Intelligence Scale, UWIST Mood Adjective Checklist (UMACL), French version of the Recovery–Stress Questionnaire for Athletes (RESTQ-Sport), Flow State Scale and MoodMeter computer program (Lane & Wilson, 2011; Nicolas et al., 2011; Wollseifen et al., 2016). The results of the studies utilising the POMS or BRUMS display a high level of consistency. Seven studies found that running an ultra-marathon (or a stage of a multi-stage ultra-marathon) was associated with an increase in fatigue and a decrease in vigour (Anglem et al., 2008; Graham et al., 2012; Lane & Wilson, 2011; Micklewright et al., 2009; Rauch et al., 1988; Tharion et al., 1990, 1988). Four of these studies found that tension was also significantly reduced after an ultra-marathon (Anglem et al., 2008; Rauch et al., 1988; Tharion et al., 1990, 1988).

Three studies monitored participants' mood states serially in the period of time following an ultra-marathon (Anglem et al., 2008; Nicolas et al., 2011; Tharion et al., 1990). Each of these studies found that between one week and one month was required for complete resolution of the mood alterations caused by ultra-running, including the changes in fatigue, vigour and tension. Two studies identified variables that were associated with the mood changes that occurred during or after an ultra-marathon. Lane and Wilson (2011) found that trait emotional intelligence predicted scores on multiple scales of the POMS and UMACL during a multi-stage ultra-marathon. Micklewright et al. (2009) found that the discrepancy between a runner's predicted finishing time and their actual finishing time was related to post-race Total Mood Disturbance (TMD), confusion and vigour on the POMS. The other studies in this sub-category examined a range of questions. Wollseifen et al. (2016) assessed the mood states and 'flow state' of a group of ultra-runners hourly during a 6-h running session. They found that perceived psychological relaxation and flow state increased during the first hour of running but decreased thereafter. Hoffman and Hoffman (2008) administered the POMS to a group of ultra-runners, a group of regular moderate exercisers and a group of non-exercisers prior to and after a session of aerobic exercise. They found that TMD decreased after the session for all three groups but the size of the effect was approximately double for the ultra-runners and regular moderate exercisers compared with the non-exercisers. In the final study in this sub-category, by Longman et al. (2017), competitors in a 161.5-km (102.6-mi) ultra-marathon reported arousal levels in response to sexually provocative images before and after the race and the ratings were found to be significantly lower after the race.

3.2.3. Ultra-runners’ cognitive processes during races

One study investigated ultra-runners’ cognitive processes during races (Acevedo et al., 1992). This study drew upon the distinction first proposed by Morgan and Pollock (1977) between ‘associative’ cognitive processes, in which attention is focussed on internal sensations experienced during running, such as sensations arising from the lower limbs or sensations associated with respiration, and ‘disassociative’ cognitive processes, in which attention is focussed away from these sensations. Approximately 50% of the ultra-runners who took part in the study reported experiencing mainly internally focussed thoughts during races while 50% reported experiencing mainly externally focussed thoughts. About 75% of the thoughts described in response to an open-ended question about cognitive processes during races were externally focussed, however. Participants reported using a variety of cognitive strategies during training and racing, including visualisation, reading pre-race paraphernalia, setting goals, self-talk and thought control.

3.2.4. Ultra-runners’ cognitive function

Nine studies examined ultra-runners’ cognitive function (Cona et al., 2015; Doppelmayr et al., 2005; Glace, Murphy, & McHugh, 2002; Hurdiel et al., 2015; Lucas et al., 2009; Martínez-Navarro et al., 2016; Tonacci et al., 2017, 2016; Wollseifen et al., 2016). These studies assessed various domains of cognitive function, including attention, working memory, information processing speed, verbal fluency and executive function. Six studies utilised formal tests of cognitive function (Doppelmayr et al., 2005; Hurdiel et al., 2015; Lucas et al., 2009; Martínez-Navarro et al., 2016; Tonacci et al., 2017; Wollseifen et al., 2016). Two of these studies found that cognitive function was reduced after an ultra-marathon (Doppelmayr et al., 2005; Hurdiel et al., 2015) while four studies either failed to find any statistically significant differences between pre-race and post-race cognitive function or found that cognitive function was improved post-race (Lucas et al., 2009; Martínez-Navarro et al., 2016; Tonacci et al., 2017; Wollseifen et al., 2016). Two studies treated impaired olfactory function as a ‘biomarker’ of cognitive impairment and investigated the effect of running an ultra-marathon on olfactory function (Tonacci et al., 2016, 2017). Both of these studies found that olfactory function was reduced after an ultra-marathon. One study investigated whether competitors in a 161-km (100-mi) ultra-marathon experienced any changes in their mental status such as confusion or disorientation during the race (Glace et al., 2002). Ten of the 19 participants reported mental status changes, with most changes occurring after 88 km (54.7 mi). In the final study in this sub-category, the cognitive function of a group of competitors in an 80-km (49.7-mi) ultra-marathon was assessed prior to the race using an inhibitory control task and a dual-task paradigm that incorporated a working memory task and a prospective memory task (Cona et al., 2015). It was found that faster runners in the race outperformed slower runners on these tests. In particular, faster runners were more accurate on the inhibitory control task in trials requiring motor inhibition and had shorter response times in the dual-task paradigm in trials where a prospective memory cue with a positive or negative emotional valence was given.

3.2.5. Ultra-runners’ pain perception

Two studies investigated ultra-runners’ pain perception (Freund et al., 2013; Hoffman, Lee, Zhao, & Tsodikov, 2007). In the first study, competitors in a 161-km (100-mi) race underwent a test of pressure pain sensitivity before and after the race and evidence was found for a modest exercise-induced analgesic effect following the race but only in the faster runners (Hoffman et al., 2007). In the other study, the pain tolerance of a group of competitors in a 64-day, 4487-km (2788-mi) ultra-marathon and a group of age- and gender-matched controls was measured prior to the race using the cold pressor test (Freund et al., 2013). The ultra-runners displayed considerably higher cold pain tolerance than the controls. None of the ultra-runners withdrew their hand from the water (which was cooled to < 2 °C) during the 3-min test while the mean immersion time for the control group was 96 s.

3.2.6. Ultra-runners’ motivations for engaging in ultra-running

Six studies explored ultra-runners’ motivations for engaging in ultra-running (Doppelmayr & Molkenthin, 2004; Ferrer, Baumann, Brandenberger, Kyle J. Ellis, & Otis, 2015; Hanson et al., 2015; Hashimoto et al., 2006; Krouse et al., 2011; Kruger & Saayman, 2013). Five of these studies used the Motivations of Marathoners Scales (MOMS) developed by Masters, Ogles, and Jolton (1993) or a system for classifying ultra-runners while four studies either failed to treat impaired olfactory function as a ‘biomarker’ of cognitive impairment and investigate the effect of running an ultra-marathon on olfactory function (Tonacci et al., 2016, 2017). Both of these studies found that olfactory function was reduced after an ultra-marathon. One study investigated whether competitors in a 161-km (100-mi) ultra-marathon experienced any changes in their mental status such as confusion or disorientation during the race (Glace et al., 2002). Ten of the 19 participants reported mental status changes, with most changes occurring after 88 km (54.7 mi). In the final study in this sub-category, the cognitive function of a group of competitors in an 80-km (49.7-mi) ultra-marathon was assessed prior to the race using an inhibitory control task and a dual-task paradigm that incorporated a working memory task and a prospective memory task (Cona et al., 2015). It was found that faster runners in the race outperformed slower runners on these tests. In particular, faster runners were more accurate on the inhibitory control task in trials requiring motor inhibition and had shorter response times in the dual-task paradigm in trials where a prospective memory cue with a positive or negative emotional valence was given.

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motivation for engaging in ultra-running was to achieve personal goals or to feel a sense of achievement (Doppelmayr & Molkenthin, 2004; Hanson et al., 2015; Hashimoto et al., 2006; Krouse et al., 2011; Kruger & Saayman, 2013). Health-related reasons were the most or second-most common or important motivation in three studies (Ferrer et al., 2015; Hanson et al., 2015; Krouse et al., 2011) and self-esteem reasons were the third-most common or important motivation in three studies (Doppelmayr & Molkenthin, 2004; Hanson et al., 2015; Krouse et al., 2011). By contrast, competing with other ultra-runners was the least or second-least important motivation in four studies (Ferrer et al., 2015; Hanson et al., 2015; Krouse et al., 2011; Kruger & Saayman, 2013). Ferrer et al. (2015) examined whether there is a relationship between motivations for ultra-running and race performance and found that health- and weight-related motivations were negatively associated with mean running speed but positively associated with total distance covered during a 24-h ultra-marathon.

3.2.7. Ultra-runners’ phenomenology

Seven studies investigated how ultra-runners themselves describe their experiences of ultra-running (Crust, Nesti, & Bond, 2010; Hanold, 2010; Holt, Lee, Kim, & Klein, 2014; Jaeschke, Sachs, & Dieffenbach, 2016; Philippe, Rochat, Vauthier, & Hauw, 2016; Rochat, Hauw, Antonini Philippe, Crettaz von Roten, & Seifert, 2017; Simpson, Post, Young, & Jensen, 2014). In all of these studies, data were collected by interviewing ultra-runners about their experiences of a particular ultra-marathon or their ultra-running experiences generally. In some studies, data were collected from additional sources such as focus groups or written materials produced by participants. In five studies, data analysis consisted of the investigators identifying themes emerging from participants’ responses (Crust et al., 2010; Hanold, 2010; Holt et al., 2014; Jaeschke et al., 2016; Simpson et al., 2014). There is considerable overlap in the themes identified in these studies. First, in three studies, participants commented that ultra-running was for them associated with a drive to explore their physical and mental limits (Crust et al., 2010; Hanold, 2010; Simpson et al., 2014). This drive was described by a participant in the study by Simpson et al. (2014) as follows: [Ultra-running is] definitely about proving to myself, testing myself, looking for the edges, for the limits and knowing that in these races I’m not just pushing myself on limits like speed, like when you do marathons. With these you are pushing and it’s ‘can I do it at all?’, ‘what can go wrong?,’, ‘what’s going to break?,’ ‘how am I going to deal with that?’ So pushing things until something breaks is definitely part of it. Secondly, participants in three studies commented on the camaraderie that exists within the ultra-running community and the support that runners provide to each other during races (Holt et al., 2014; Jaeschke et al., 2016; Simpson et al., 2014). Thirdly, participants in three studies noted that, in the ultra-running community, a runner is usually regarded as having been successful if they finish a race (Hanold, 2010; Holt et al., 2014; Simpson et al., 2014). Finishing is viewed as very important but, except among elite runners, finishing time and finishing position are considered relatively unimportant. Finally, in three studies, participants expressed the view that pain is a normal part of ultra-running and that pain arising during running is only concerning if it disrupts their experiences of ultra-running (Crust, Nesti, & Bond, 2010; Hanold, 2010; Simpson et al., 2014), with participants in two studies commenting that pain arising during running is only concerning if it disrupts their experiences of ultra-running (Crust, Nesti, & Bond, 2010; Hanold, 2010; Simpson et al., 2014). This drive was described by a participant in the study by Simpson et al. 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intervention helpful and continued to use motivational self-talk in training and races six months after the race.

3.2.10. Case studies

Four of the included studies were case studies. Two of these studies relate to a 20-day, 800-km (497-mi) solo run undertaken by an ultra-runner through inhospitable terrain in the Western United States (Bull, 1988, 1989). The investigator for both studies was a sports psychologist who provided a sports psychology intervention to the runner prior to and during the run. One study is a qualitative description of the intervention provided to the runner, including the mental training program developed for him (Bull, 1989). The other study (Bull, 1988) is a description of the runner’s motivations for undertaking the run and his cognitive processes during the run. His motivations were initially primarily intrinsic but became more extrinsic as the race progressed and he became the subject of media attention. He experienced both associative and dissociative thoughts during the run, with associative thinking reportedly associated with superior running performance. Another study involved an ultra-runner who completed the MAACL before, during and after an 80.5-km (50-mi) run (Joesting, 1981). There were no significant alterations in her mood during or after the run. In the fourth case study, an ultra-runner rated her mood state and pain intensity levels and described her thoughts every 35 min during a 48-h ultra-marathon (Kirby, 1996). It was found that her mood state decreased and her pain levels increased over the course of the race, with pain levels accounting for 90% of the variance of mood state. 70.6% of the thoughts she described were associative and 29.4% were dissociative. In the final case study, the participant, who undertook a 3641-km (2262-mi) transcontinental run, completed the POMS and Emotional Recovery Questionnaire (EmRecQ), a measure of positive mood states, and reported her rating of perceived exertion (RPE) (Borg, 1982) before, during and after the run (Johnson, Kentá, Ivarsson, Almyreñ, & Karlsson, 2016). An association between RPE and mood state was found, with RPE positively correlated with total EmRecQ score and negatively correlated with TMD on the POMS.

4. Discussion

As the results of this review demonstrate, there is a significant body of research into the psychology of ultra-runners. The field is developing rapidly, with over half of the studies included in the review dating from 2010 or later. In general, the results of the included studies display little consistency. For example, the findings of the studies investigating ultra-runners’ personality traits are heterogeneous and there is conflicting evidence with respect to some traits such as self-motivation and extraversion (Hashimoto et al., 2006; Hughes et al., 2003; McCutcheon & Yoakum, 1983; Rauch et al., 1988). Similarly, the results of studies investigating the effects of ultra-running on cognitive function are mixed and it remains unclear whether ultra-running acutely causes an impairment in cognitive function (Doppelmayr et al., 2005; Hurdiel et al., 2010; Masters & Ogles, 1995; Ogles & Masters, 2000, 2003).

There are three areas where it appears possible to draw conclusions, however. First, the acute effects of ultra-running on mood have been reasonably well studied and these effects appear to include an increase in fatigue and a decrease in vigour and tension. This profile of affective changes is similar to that reported in marathon runners following a race (Hassmén & Blomstrand, 1991) but differs from the positive mood changes that follow shorter sessions of aerobic exercise (Reed & Ones, 2006). It is unsurprising that very prolonged endurance exercise results in increased fatigue and decreased vigour. The effect of ultra-running on tension is more interesting and various explanations have been proposed for it, including explanations based on the anxious effect of aerobic exercise generally (Rauch et al., 1988) and explanations based on the resolution of pre-race anxieties relating to performance and the possibility of injury (Thorun et al., 1996). A consensus also appears to be developing within the literature regarding the duration of the mood changes caused by ultra-running, with all of the studies that examined this question finding that between one week and one month was required for these changes to resolve.

Secondly, studies investigating ultra-runners’ motivations for engaging in their sport have nearly universally found that the most important motivating factor is the opportunity to achieve personal goals. This appears to differentiate ultra-runners from marathoners, as marathoners’ motivations for running are more mixed, with most studies finding that self-esteem reasons and health-related reasons are at least as important for them as personal goal achievement (Havenar & Lochbaum, 2007; Masters & Ogles, 1995; Ogles & Masters, 2000, 2003). One possible explanation for this difference is that ultra-marathons vary widely in distance and ultra-runners are therefore able to select races that will be very challenging for them to complete. In this way, ultra-running offers runners the opportunity to set themselves extremely challenging task-oriented goals. The same opportunity does not exist in marathon running where the race distance is fixed (although runners can of course set goals with respect to finishing time or finishing position).

Finally, a relatively consistent body of findings is emerging from phenomenological studies of ultra-runners. One of the most interesting findings to arise from these studies is the observation that ultra-runners tend to be people who experience a strong drive to explore their physical and mental limits. It is possible that this drive represents a distinct personality trait associated with ultra-running and possibly other ultra-endurance sports. The question of whether such a ‘limits-exploring’ trait exists and if so how to characterise and measure it does not yet appear to have received any attention from personality psychologists.

There are a number of limitations of the included studies that should be mentioned here. First, many of the studies had very small samples. Twenty studies involved a sample of 19 participants or fewer. Only one of these studies included a power calculation (Micklewright et al., 2009) and at least some of them may have been under-powered with respect to the effects they were investigating. The issue of under-powering is a pervasive one in psychological research generally (Maxwell, 2004; Szucs & Ioannidis, 2017).

Secondly, some of the included studies used psychometric instruments that were not well suited to answering the questions that the studies sought to investigate. For instance, of the nine studies investigating ultra-runners’ personality traits, only two studies used inventories based on the five-factor model (FFM) of personality (Hughes et al., 2003; Teranishi Martinez & Scott, 2016), despite this model having achieved something close to consensus among personality researchers (Allen, Greenlees, & Jones, 2013). One study used the Myers-Briggs Type Indicator, a type-based inventory whose psychometric validity has been questioned (Pittenger, 2005). If, as is to be hoped, future research in this area makes greater use of FFM inventories, it will be interesting to note whether ultra-runners have a similar personality profile to regular exercise participants, with increased extraversion and conscientiousness and reduced neuroticism (Rhodes & Smith, 2006), or some other personality profile.

Thirdly, some of the included studies drew upon normative data that was of limited relevance or applicability. Demographic studies of ultra-runners indicate that they are predominantly male, are older than other distance runners, with a mean age of around 45 years, and tend to be well educated and to work in white-collar professions (Hoffman & Fogard, 2012; Hoffman, Chen, & Krishnan, 2014). As Hughes et al. (2003) have observed, this means that some normative data has limited relevance to ultra-runners. For instance, their finding that ultra-runners participating in a 161-km multi-disciplinary race were less disinhibited than the general population may have been an artefact arising from the difference in age between the runners and the norm group for the SSS, as disinhibition decreases with age. The study by Acevedo et al. (1992) provides an example of the weak use of normative data. In this study, a group of ultra-runners was administered the SOQ and the runners’
responses were compared to those of a norm group consisting of college students enrolled in non-competitive physical activity classes. The runners were found to be more competitive and goal-oriented but less win-oriented than this norm group. There are several different norm groups for the SOG, however, and if Acevedo and colleagues had compared the runners to a norm group consisting of college students enrolled in competitive physical activity skills classes, they would have found that the runners were less competitive than this group, although the findings with respect to goal-orientation and win-orientation would have remained (Gill & Deeter, 1988). This suggests that their conclusion that ultra-runners are more competitive than ‘other athletes’ is, at the very least, an over-simplification.

Fourthly, the included studies generally reported little information about the performance levels of the ultra-Runners who participated in the studies. Some studies reported information about participants’ running history or training habits but few included data relating to anthropometric parameters such as body fat percentage or physiological parameters such as maximum oxygen uptake (VO₂max). Factors that have been found to predict ultra-marathon performance include training volume and intensity (Knechtle, Knechtle, Rosemann, & Lepers, 2010; Tanda & Knechtle, 2015), best marathon time (Knechtle, Knechtle, Rosemann, & Lepers, 2011a), skinfold thickness (Knechtle, Knechtle, Rosemann, & Senn, 2011b), VO₂max (Davies & Thompson, 1979; Fornasier et al., 2017) and peak treadmill velocity during the VO₂max test (Noakes, Myburgh, & Schall, 1990). The lack of information about performance levels is regrettable because ultra-runners of different performance levels may differ in important ways. In this regard, a system for classifying the performance level of distance runners, including ultra-runners, similar to the system proposed by De Pauw et al. (2013) for cyclists, would be valuable. Such a system would likely draw upon anthropometric and physiological parameters and the use of it would therefore require pre-experimental testing to measure these parameters. Finally, most of the included studies were uncontrolled. This limitation is particularly relevant to the studies investigating the effects of ultra-running on mood and cognitive function. Without a control group, it is difficult to know whether effects that were detected were due to the running element of an ultra-marathon or some other element of the race. An example of an important non-running element of an ultra-marathon is sleep deprivation. Completing an ultra-marathon often requires runners to endure significant sleep deprivation, which is known to impact on both mood and cognitive function (Alhola & Polo-Kantola, 2007; Bahanon, Trainer, Feldner, & Blumensath, 2010). In order to disentangle the effects of prolonged running from those of sleep deprivation, studies would need to include a control group that experienced any sleep deprivation that the ultra-runner participants were required to undergo but did not perform any running. Future research in this area should ideally involve large samples, utilise appropriate psychometric instruments, compare ultra-runners to relevant normative populations, include information about the performance level of the ultra-runners studied and, particularly if a causal relationship is being investigated, make use of control groups. There are a number of promising avenues for future research. First, although it has not been particularly fruitful to date, research into ultra-runners’ personality traits should continue. Such research could potentially have applications in the field of public health. Ultra-runners perform an extraordinary amount of physical exercise. Knechtle (2012) estimates that the average weekly training distance of male ultra-runners is 85.0 km, nearly double that of male recreational marathoners (Rüst et al., 2012). Although the health impacts of ultra-endurance training remain controversial (Hoffman & Krishnan, 2014; Lee, Morrison, Lissemore, Hefthron, & Krahn, 2016), investigating the personality traits of ultra-runners could shed light on the psychological factors that contribute to a person’s physical activity levels. Such knowledge could be relevant to efforts to design interventions to improve physical activity levels, which is a global public health priority (Kohl et al., 2012). Secondly, the finding of Freund et al. (2013) that ultra-runners have considerably higher pain tolerance than non-running controls warrants further research into ultra-runners’ pain perception. Abnormally high pain tolerance may partially explain ultra-runners’ ability to persist with endurance exercise for extremely long periods of time. Questions for future investigators include what physiological and psychological factors underlie ultra-runners’ enhanced pain tolerance, how their pain tolerance compares to that of other athletes and whether elevated pain tolerance is an inherited trait or the result of ultra-endurance training. Finally, the finding of Cona et al. (2015) that inhibitory control and working and prospective memory skills are predictive of ultra-running ability is intriguing and merits further attention. This finding forms part of a recent line of research in which a relationship between cognitive performance and athletic performance has been reported (Martin et al., 2016; Vestberg, Gustafson, Maurex, Ingvar, & Petrovic, 2012). Future studies should clarify the exact nature of the cognitive advantages associated with ultra-running ability and should compare these with the advantages that have been found to be predictive of ability in other sports. They should also investigate why faster runners possess these advantages and whether it is due to some form of cognitive skills transfer, as has been hypothesised for athletes in general (Jacobson & Mattheus, 2014).

5. Conclusion

Research into the psychology of ultra-runners is a rapidly developing area within sports psychology. The existing literature sheds some light on the mood effects of ultra-running, the motivations of ultra-runners for engaging in their sport and the phenomenology of ultra-running. There is much that remains to be learned, however. A number of promising avenues for future research exist. These include further exploration of ultra-runners’ personality traits and pursuing recent findings that ultra-runners have abnormally high pain tolerance and that cognitive performance in various domains is associated with ultra-running ability. Given how little is known regarding these remarkable athletes, it is likely that they will continue to attract the attention of sport psychologists, exercise scientists and other researchers for some time to come.

Disclosure statement

Paul B. Fitzgerald has received equipment for research from MagVenture A/S, Medtronic Ltd, Cervel Neurotech and Brainway Ltd and funding for research from Neuronetics and Cervel Neurotech. He is on the scientific advisory board for Biometics Ltd.

Funding

Paul B. Fitzgerald is supported by National Health and Medical Research Council Practitioner Fellowship [APP1078567]. Donna M. Urquhart is supported by an NHMRC Career Development Fellowship [APP1011975]. Sin Ki Ng is a recipient of an Australian Postgraduate Award. Bernadette M. Fitzgibbon is supported by an NHMRC Early Career Fellowship [APP1070073].

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.psychosport.2018.04.004.

References

