

Examining the Role and Neurophysiological Mechanisms of Social Support in Pain Experience

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ABSTRACT

Pain is a highly subjective experience determined not only by sensation but also by an individual's psychological state and social environment. Indeed, previous research has identified the key role of cognitive and emotional factors in pain perception and the neurobiological mechanisms that may underpin these processes. More recently, a growing body of research has indicated the significance of social factors contributing to pain perception, particularly social support demonstrating a protective influence on pain. If social support is influential in modulating the experience of pain, social support may be fundamental for therapeutic strategies in the management of pain. However, optimizing social support strategies is limited by our understanding of the social contexts in which social support has an analgesic influence, the magnitude of the effect, and the neurophysiological mechanisms through which social support may have an effect on pain.

The focus of this thesis was to investigate the role of social support in pain experience and the neurophysiological mechanisms that may facilitate this effect. This was addressed through a total of five manuscripts including two review articles and three experimental studies.

Through a systematic review and meta-analysis, the first manuscript identified the social contexts within which social support may reduce pain. The results of this investigation identified that social support may have the most protective effect on pain when it is clearly communicated (e.g. via verbal support). The results further indicated the particular importance of intimate relationships in pain reduction through touching or visual representation of an intimate other. This study also quantified the effects of social support on pain-related physiological arousal whereby conclusions were highly limited by the small number of studies in this space.

In the second study, I undertook a systematic review to investigate the potential psychological and behavioural processes as well as neurobiological mechanisms underpinning the influence of social support on pain reduction. This review aimed to address whether evidence best supports the main or the buffering effect of social support on pain experience. The results indicated that social support may reduce pain through a buffering effect on the threat of pain, in which social support may modulate stress appraisal and attenuate neurobiological stress systems.

In study three, the buffering effect of social support was directly examined in the context of the threat of pain. An experimental protocol was used to introduce continuous threat of pain leading up to painful stimulation during which participants held the hand of a significant other, a stranger, or not at all. Electroencephalogram (EEG) and electrocardiogram (ECG) were used to evaluate neural and physiological threat of pain. The results demonstrated reduced neural (i.e. frontal theta power, 4-8 Hz) and autonomic (i.e. heart rate) response to the threat of pain under the social support (significant other) condition, which were further associated with subsequent pain reduction. In addition, neural changes in theta power were source localized to the insular cortex and the anterior cingulate cortex, regions commonly observed in the processing of threat and pain.

Study four investigated the effects of social support on the neural dynamics and parasympathetic activity to prolonged pain using EEG and ECG. A dynamic pain protocol was used to induce tonic pain perception during which visual representation of an intimate other or a stranger was provided. The results indicated reduced pain perception in the context of an intimate other, which was associated with increased frontocentral alpha activity and decreased central gamma activity. The ECG data demonstrated increased high-frequency heart-rate variability in the intimate other condition. Findings of this investigation may indicate the role of social support in modulating the gating and integration of nociception.

The medial prefrontal cortex (mPFC) is thought to play a key role in the analgesic influence of social support. Study five investigated the causal role of the mPFC in orchestrating the behavioural and brain connectivity effects of social support on pain. Across sessions the activity in the mPFC was increased or decreased (or no change as in the Sham condition) by facilitatory intermittent Theta Burst Stimulation (iTBS) or suppressive continuous TBS (cTBS) respectively. The findings suggested that iTBS over the mPFC has the capacity to causally modulate pain perception and network configuration in a context-dependent manner. Specifically, visual representation of stranger increased pain and connectivity between central regions and frontoparietal regions. In contrast, visual representation of an intimate other increased connectivity only between frontal and occipital regions and did not modulate pain perception. This study also identified neuroplastic changes as evaluated by TMS-EEG and the association with social modulation of pain.

The combined results of this thesis suggest: (1) the effects of social support on pain are context-dependent; (2) social support may reduce pain by modifying stress appraisal and neurobiological stress systems prior to pain onset; (3) social support may modulate the gating and integration of nociceptive information; (4) the mPFC may play a causal role in mediating the influence of social support on pain. Together, this series of studies are an important contribution to understanding and neural mechanisms underpinning the impact of social support on pain which may have therapeutic implications.

LIST OF PUBLICATIONS

Published Manuscripts Directly Relevant to this Thesis

Che, X., Cash, R., Chung, S., Fitzgerald, P., & Fitzgibbon B. (2018). Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *92*, 437-452.

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Qiao, L., Xu, L., **Che, X.**, Zhang, L., Li, Y., Xue, G., Chen, A. (2018). The motivation-based promotion of proactive control: the role of salience network. *Frontiers in Human Neuroscience, 12*, e328.

Zhang, Y., Luo, X., **Che, X.**, Duan, W. (2016). Self-compassion buffers the effect of examination stress on negative affect in college students. *Frontiers in Psychology, 7*, e1802.

Li, B., Cheng, G., Zhang, D., Wei, D., Qiao, L., Wang, X. & **Che, X.** (2016). Emotional type modulates regional brain responses to infant faces in nulliparous women. *Plos One, 11*, e0166860.

Che, X., Luo, X., Tong, D., Fitzgibbon, B., & Yang, J. (2015). Habitual suppression relates to difficulty in regulating emotion with cognitive reappraisal. *Biological Psychology, 112*, 20-26.

Oral Presentations

Che, X., Cash, R., Fitzgerald, P., & Fitzgibbon B. The social regulation of pain: autonomic and neurophysiological changes associated with perceived threat. *Australasian Society for Social & Affective Neuroscience (AS4SAN)*, Melbourne, Australia, 2017.

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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 (3) original papers published/accepted in peer reviewed journals and two (2) unpublished publications. The core theme of the thesis is to investigate the role and neurophysiological mechanisms of social support in pain experience. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Central Clinical School under the supervision of Dr Bernadette Fitzgibbon, Dr Robin Cash, and Professor Paul Fitzgerald.

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:

Project design (in consultation with my supervisors and co-authors); review of appropriate literature; securing ethics approval; recruitment of participants; data collection; conducting data analysis; writing of papers. Supervisors and co-authors provided input into completed manuscript drafts.

Thesis Chapter	Publication Title	Publication Status	Nature and % of Candidate's Contribution	Co-Author Names, Nature and % of Contribution	Co-Authors Monash Student?
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2	Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis	Published Neuroscience and Biobehavioral Reviews	80%. Manuscript conceptualisation, review of relevant literature, data analysis, manuscript preparation.	1) Dr Bernadette Fitzgibbon. Review of manuscript, supervisory input (10%). 2) Dr Robin Cash. Review of manuscript, supervisory input (5%). 3) Prof Paul B. Fitzgerald. Review of manuscript, supervisory input (3%). 4) Dr Sung Wook Chung. Screening of included studies, review of manuscript (2%).	No (all co-authors)
3	A Systematic Review of the Processes Underlying the Main and the Buffering Effect of Social Support on the Experience of Pain	Published Clinical Journal of Pain	80%. Manuscript conceptualisation, review of relevant literature, manuscript preparation.	1) Dr Bernadette Fitzgibbon. Review of manuscript, supervisory input (10%). 2) Dr Robin Cash. Review of manuscript, supervisory input (5%). 3) Prof Paul B. Fitzgerald. Review of manuscript,	No No No

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4	The social regulation of pain: autonomic and neurophysiological changes associated with perceived threat	Published Journal of Pain	80%. Study conceptualisation and protocol design, securing of ethical approval, participant recruitment and testing, data collection and analysis, manuscript preparation	1) Dr Bernadette Fitzgibbon. Review of manuscript, supervisory input (10%). 2) Dr Robin Cash. Review of manuscript, supervisory input (6%). 3) Prof Paul B. Fitzgerald. Review of manuscript, supervisory input (4%).	No (all co-authors)
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				3) Prof Paul B. Fitzgerald. Review of manuscript, supervisory input (4%).	
6	The Medial Prefrontal Cortex as a Flexible Hub Mediating Behavioral as well as Local and Distributed Neural Effects of Social Support on Pain: a Theta Burst Stimulation and TMS-EEG Study	Under review NeuroImage	80%. As above	1) Dr Bernadette Fitzgibbon. Review of manuscript, supervisory input (8%). 2) Dr Robin Cash. Review of manuscript, supervisory input (6%). 3) Prof Paul B. Fitzgerald. Review of manuscript, supervisory input (2%). 4) Dr Neil Bailey. Technical assistance (2%). 5) Dr Sung Wook Chung. Technical assistance (2%).	No (all co-authors)

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

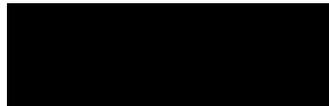
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The undersigned hereby certifies that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author, I have consulted with the responsible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

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Date: 10/03/2019

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GLOSSARY OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
CBT	Cognitive-behavioural Therapies
CPT	Cold Pressor Test
cTBS	Continuous Theta Burst Stimulation
ECG	Electrocardiogram
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
HF-HRV	High-frequency HRV Heart Rate Variability
HRV	Heart Rate Variability
IASP	International Association for the Study of Pain
iTBS	Intermittent Theta Burst Stimulation
LEPs	Laser-evoked Potentials
MEG	Magnetoencephalography
mPFC	Medial Prefrontal Cortex
NCF	Nucleus Cuneiformis
OFC	Orbital Frontal Cortex
PAG	Periaqueductal Grey
PB	Parabrachial Nucleus
PNS	Parasympathetic Nervous System
RVM	Ventromedial Medulla
S1	Primary Somatosensory Cortex
S2	Secondary Somatosensory Cortex
SNA	Social Network Analysis
SNS	Sympathetic Nervous System

TEPs	TMS-evoked Potentials
TBS	Theta Burst Stimulation
TMS	Transcranial Magnetic Stimulation
VMPFC	Ventromedial Prefrontal Cortex

CHAPTER ONE

General Introduction and Thesis Overview

This chapter provides an overview on pain mechanisms and pain modulation. This chapter will focus on the influence of social support on pain. It will also review neuroscience methods to investigate how social support may impact pain, as relevant to the thesis, and briefly summarises the potential of this knowledge to clinical practice. A critical review of the field is provided in chapters 2 to 5.

1.1. Pain and Pain Mechanisms

The International Association for the Study of Pain (IASP) defines pain as *“an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”* (IASP, 1994). Thus, to experience pain does not require nociception or injury, nor does the magnitude of an insult equate to an individual perceived pain. Rather, pain is multi-dimensional, whereby a sensory component provides information on the intensity, location, and duration of the stimulus, and an affective component drives the unpleasant or aversive feeling of pain (Haggard et al., 2013; Melzack and Casey, 1968). Pain is therefore a subjective experience, differing between individuals as a result of a complex and dynamic interaction between ‘bottom-up’ signalling and ‘top-down’ modulation as a result of environmental influence, psychosocial factors and neurobiological circuits (Ploner et al., 2017).

There are different functional meanings for acute versus chronic pain. Acute pain is caused by external or internal injury and has a distinct warning function. It drives protective behaviours to

avoid bodily injury and therefore is of particular importance for survival and evolution. In contrast, chronic pain, usually defined as lasting longer than 3 months (IASP, 1994; Loeser, 2001), is not only lacking obvious behavioural benefits but also heavily impairs quality of life (Hodges and Tucker, 2011). The fact that chronic pain has a major adverse impact on human well-being has driven numerous studies to investigate the neural mechanisms of pain with the prospect to develop more effective treatments (Mouraux and Iannetti, 2018).

Advances in neuroimaging techniques revolutionized our understanding of the central nervous representation of pain (for a review see Derbyshire, 2000; Martucci et al., 2014; Morton et al., 2016; Mouraux and Iannetti, 2018; Tracey, 2008). The 'neuromatrix' perspective (Melzack, 1999), commonly referred to as the 'pain matrix' (Tracey and Mantyh, 2007), indicates that painful stimuli activate a distributed brain network including the primary (S1) and secondary (S2) somatosensory cortex, thalamus, insular cortex, as well as the anterior cingulate cortex (ACC) and prefrontal cortex (Apkarian et al., 2005; Peyron et al., 1999; Tracey et al., 2000). This theoretical perspective suggests that the 'pain matrix' is pain-specific, i.e. mediating pain experience itself (Ploghaus et al., 1999). Moreover, some studies have indicated that brain structures constituting the 'pain matrix' may have a distinct role in mediating different components of pain (Ingvar and Hsieh, 1999). For example, the sensory component is thought to be independently and specifically represented in the S1 and S2, while the affective aspect of pain is represented in medial brain structures such as the ACC (Albe-Fessard et al., 1985; Avenanti et al., 2005). However, brain regions implicated in the 'pain matrix' are not solely activated by painful stimuli, but also by non-painful stimuli, such as auditory and tactile stimuli (for a review, see Legrain et al., 2011). Thus, other adaptations have been proposed to explain the central modulation of pain, including the 'interoception' and the 'salience network' perspective.

The 'interoception' perspective views pain as a homeostatic emotion (Craig, 2002, 2003a, b).

Homeostasis of the human body is described as a dynamic and ongoing process in order to maintain

an optimal balance in the physiological condition of the body (Cannon, 1939; Craig, 2003a). In this view, pain is both a distinct sensation and a motivation that requires a behavioural response, akin to other sensations such as temperature, itch, hunger and thirst (Craig, 2003a). Moreover, pain and these body sensations are suggested to be mediated by a recently discovered lamina I ‘spinothalamocortical’ pathway (Craig, 2002, 2003a). Specifically, the small-diameter primary afferent fibres (e.g. A δ and C fibre) that carry the information of the physiological status of the body (e.g. nociceptors, thermoreceptors) terminate on projection neurons in lamina I of the spinal dorsal horn. Modality specific lamina I neurons then project to the brainstem sites (e.g. the parabrachial nucleus, PB, the periaqueductal gray, PAG), which provide the central afferent pathway for homeostasis. In primates, lamina I neurons also project to the thalamus, which relays information to both the insular cortex to represent interoception, and to the ACC and orbital frontal cortex (OFC) to produce behavioural drive (Craig, 2003a, b). This argument provides a rational explanation for the association between pain, temperature, itch and other feelings from the body.

Another more recent theoretical perspective argues that brain regions in the ‘pain matrix’ may form part of a ‘salience network’ which is involved in detecting, orienting attention to, and reacting to salient sensory events (Cauda et al., 2012; Legrain et al., 2011; Seeley et al., 2007). A key concept in this argument is the ‘salience’ of a given stimulus, generally defined as its ability to stand out from the surrounding stimuli (Yantis, 2008). From a neural network perspective, the ACC and insular cortex are suggested to be the key nodes of the ‘salience network’ (Seeley et al., 2007). Similar to the homeostatic perspective, the salience system acts regardless of whether a salient stimulus is conveyed through nociceptive pathways. However, this does not mean that the salience system does not contribute to the experience of pain, but rather highlights the significance of the nociceptive system in detecting and reacting to salient changes (Legrain et al., 2011).

There is also evidence surrounding neural mechanisms in chronic pain and possible differences with acute pain. People with chronic pain have undergone both structural and functional brain changes, most consistently in the insula and prefrontal cortex (Baliki et al., 2008; Geha et al., 2008; Rodriguez-Raecke et al., 2009). Interestingly, one study demonstrated that fluctuations of spontaneous pain in chronic pain patients were uniquely associated with increased activity in the mPFC, whereby experimentally-induced thermal pain was strongly associated with increased insula activity. This study indicated the role of the mPFC in differentiating fluctuations of spontaneous pain from experimentally-induced pain in people with chronic pain (Baliki et al., 2006).

Overall, these mechanistic investigations have improved our understanding of how the brain represents pain perception and drives protective behavioral responses. These studies have also provided the groundwork for mechanistic explorations supporting top-down pain modulation. Studies have begun to reveal a cerebral network mediating top-down pain modulation, i.e. the descending pain modulatory system, which commonly includes the frontal cortex, ACC, insular cortex, amygdala, hypothalamus, PAG, nucleus cuneiformis (NCF), and rostral ventromedial medulla (RVM) (Tracey and Mantyh, 2007). This descending pain system is suggested to mediate the modulation of pain by a variety of psychosocial factors (for a review see Bushnell et al., 2013).

1.2. Pain Modulation

It is well accepted that pain is a highly subjective experience and varies across individuals and contexts. Indeed, a direct correlation between the intensity of noxious stimuli and pain perception is not always apparent, suggesting that the experience of pain is influenced by contextual processes in the top-down modulation of pain (Ossipov et al., 2010). Among other influential factors, literature to date has revealed the influence of attention (Ploner et al., 2010; Tracey et al., 2002), emotion (Hampton et al., 2015; Lapate et al., 2012), as well as beliefs and expectations (Wager et al., 2004;

Wiech et al., 2006) in modulating pain perception. Understanding these contextual factors may shed a light on the role of social support in pain which can prime positive affect (Younger et al., 2010) and may distract attention from pain (Montoya et al., 2004). Moreover, while there is now greater understanding of the factors that contribute to variability of pain experience, in both acute and chronic contexts, mechanisms implicated in the risk or resilience factors to pain remain to be determined (Bushnell et al., 2013; Ossipov et al., 2014).

1.2.1. Attentional Modulation of Pain

Numerous studies have demonstrated the role of cognition in pain perception, in particular attention (Brooks et al., 2002; Dunckley et al., 2007; Frankenstein et al., 2001; Kong et al., 2013; Seminowicz et al., 2004). In general, paying attention to pain increases pain perception whilst distraction reduces pain. In studies using neuroimaging techniques, research suggests that the descending pain modulatory system, especially the PAG, mediates these attentional effects on pain (Bantick et al., 2002; Petrovic et al., 2000; Tracey et al., 2002; Valet et al., 2004). For example, distraction away from pain can increase PAG activity and reduce pain perception compared to attending to pain (Tracey et al., 2002). Further, distraction increases the top-down gating influence of cingulo-frontal cortex on PAG and posterior thalamus activity (Valet et al., 2004). These studies together provide mechanistic evidence on how attention could affect pain.

1.2.2. Emotional Modulation of Pain

It is well-established that pain may lead to negative mood and emotion. Conversely, there is also evidence that negative mood and emotion can exacerbate pain experience (Loggia et al., 2008; Wiech and Tracey, 2009). It is thought that emotional modulation of pain alters the perceived unpleasantness of pain (Loggia et al., 2008; Villemure et al., 2003). This is contrast to the attentional effects whereby pain intensity appears to be affected more consistently (Loggia et al., 2008; Royl et

al., 2011; Villemure et al., 2003). However, it is acknowledged that research protocols used in attention and emotion may not be able to completely isolate one from the other (Bushnell et al., 2013). One study was designed to dissociate the emotional and attentional circuits in the modulation of pain, which found ACC and the insular cortex to be associated with the emotional and attentional effects on pain respectively (Villemure and Bushnell, 2009). In addition to the induction of emotion, some studies have also demonstrated the efficacy of emotion regulation strategies (e.g. reappraisal, emotion suppression) in pain reduction (Hampton et al., 2015; Lapate et al., 2012), suggesting behavioural interventions targeting emotional processes to have an effect on pain.

1.2.3. Beliefs and Expectations' Influence on Pain

Pain experience can also be modulated by pain-related cognitions such as beliefs and expectations towards pain. A prime example of how beliefs and expectations influence pain can be seen in the so-called "placebo" (or expectation) effect, in which the mere belief that one is receiving an effective treatment can induce pain relief (Amanzio and Benedetti, 1999; Benedetti et al., 1999; Price et al., 1999). Advances in placebo research have revealed the descending pathway via brainstem structures that may mediate the placebo analgesia (Petrovic et al., 2002; Wager et al., 2004; Zubieta et al., 2005). For example, administration of the opioid antagonist naloxone decreased placebo analgesia and activity in the descending pain modulatory system including the hypothalamus, PAG, RVM, which demonstrated the role of the descending pathway in placebo analgesia (Eippert et al., 2009a). Further evidence has extended the descending pain modulatory system to the spinal level in which decreased spinal cord responses were observed in placebo analgesia (Eippert et al., 2009b).

Perceived controllability is another relevant pain-related belief which refers to the extent to which one believes that pain is under control (Salomons et al., 2004). Perceived controllability has been shown to reduce pain (Wiech et al., 2006) and increase the ability to cope with pain (Jensen and Karoly, 1991; Jensen et al., 2001). There is evidence that perceived controllability may reduce pain-

evoked activations in the ACC, insular cortex, and the somatosensory cortex (Salomons et al., 2004). The analgesic influence of perceived controllability was further shown to rely on the functioning of the prefrontal cortex in changing the threatening quality of pain (Salomons et al., 2007; Wiech et al., 2006). Together, this body of research suggests pain-specific cognitions, such as beliefs and expectations of pain, influence the activity of pain-related brain regions and the experience of pain.

1.3. Social Support and Pain

The effects of social relationships on our physiological and psychological well-being has long been observed clinically (Uchino, 2006; Uchino et al., 1996). A body of research is beginning to emerge providing experimental evidence for the role of social factors in pain modulation (Krahé et al., 2013). Indeed, the growing recognition of the importance of social factors is reflected in the recent re-definition of pain proposed to include a social component, arguing that *“social environments determine exposure to pain, thoughts, and feelings when in pain, communication of distress to others, and others’ experience and responses”* (Williams and Craig, 2016).

Among these social factors the role social support in pain experience has received the most attention (Brown et al., 2003; Goldstein et al., 2016; Roberts et al., 2015). Social support generally refers to the perception or experience that one is loved and cared for by others (Wills, 1991), although there is some debate around its definition. It is commonly accepted that social support encapsulates both ‘perceived’ and ‘received’ support, in which perceived support refers to the perception that supportive resources would be available should they be needed whereas received support means the reported exchange of supportive resources (Dunkel-Schetter and Bennett, 1990; Uchino, 2009). Based on the supportive resources, social support is also believed to have multiple types, including informational, socioemotional, and instrumental support (House, 1983; Turner, 1983).

The effects of social support on pain perception have been mixed. Brown and colleagues provided the first line of evidence that verbal communication with a friend or even a stranger reduced experimental pain (Brown et al., 2003). A series of studies then demonstrated an analgesic influence of social support in the context of touching (Goldstein et al., 2016; Master et al., 2009) or viewing (Eisenberger et al., 2011; Master et al., 2009) a significant other. However, there is also evidence showing that social support may have no effect (Modić Stanke and Ivanec, 2010) or even an adverse impact (Gallant and Hadjistavropoulos, 2017; Karmann et al., 2014; Vervoort et al., 2011) on pain.

Notably, however, different variations of social support have been manipulated across these studies, such as social presence, verbal support, social touch, and mental representation of social support. In the cases of social presence, the social partner is physically present without any verbal or physical contact with the participant (Edwards et al., 2017). In the studies of verbal support or social touch, the social partner verbally interacts with (Roberts et al., 2015) or holds the hand of the participant (Master et al., 2009). In the cases of mental representation of social support, participants view an image of a social partner without the social partner being physically present (Eisenberger et al., 2011). Perhaps, different types of social support, as well as other considerations such as the specific relationship and relationship quality, impact on whether or not social support has an effect on pain.

In order to address the discrepancy in the literature to date, Krahé and colleagues systematically reviewed evidence surrounding the influence of social support on experimental pain (Krahé et al., 2013). The authors found that the effects of social support on pain were largely influenced by the degree to which participants could perceive the social partner as helpful and the pre-existing social relationships. In general, social support is able to reduce pain when it is explicitly expressed (e.g. verbal communication, social touch) by a significant other (e.g. a romantic partner) (Krahé et al., 2013). However, given that this is a burgeoning field, the results of this analysis were limited by the

number of studies. Personality factors were also found to modulate the impact of social support on pain, notably pain catastrophizing (Sullivan et al., 2004), adult attachment style (Krahé et al., 2015), and the motivation to help by the social partner (Kindt et al., 2018a; Kindt et al., 2018b).

Beyond the experimental evidence, several behavioural models were proposed to explain the association of social support and pain experience in chronic pain conditions. The operant model suggests that positive responses from social partners (e.g. reassure positive concerns) reinforce pain behaviours (Fordyce, 1977). The intimacy model posits that communication of pain may serve to enhance intimacy between couples (Cano and Williams, 2010). In another model, the communal coping model of pain catastrophizing, pain behaviours serve to attract social support, which in turn triggers or maintains exaggerated pain expression (Sullivan et al., 2001).

1.4. Neural and Physiological Techniques in Social Support and Pain

In contrast to the growing literature on the 'behavioural effects' of social support on pain, there has been less investigation into the potential 'mechanisms' underpinning the analgesic influence of social support. In this section, I will review the neural and physiological effects of social support on pain, based on the method applied.

1.4.1. *Functional Magnetic Resonance Imaging (fMRI)*

Functional Magnetic Resonance Imaging measures brain activity by detecting changes associated with blood flow. It has excellent spatial resolution especially for deep brain structures but has relatively poor temporal resolution. There have been two studies providing mechanistic evidence on how social support influences pain (Eisenberger et al., 2011; Younger et al., 2010). In one study, viewing images of a romantic partner relative to an acquaintance resulted in less pain in healthy participants. Moreover, reduced pain was associated with decreased pain-related activation (ACC,

insular cortex) but with increased reward activation (caudate nucleus, nucleus accumbens, OFC) in the romantic partner relative to the acquaintance condition (Younger et al., 2010). In another study, viewing images of a romantic partner relative to control images produced less pain perception, lower activation in pain-related regions (ACC, insular cortex) but higher activation in a safety-related region (ventromedial prefrontal cortex, VMPFC). Further, greater activation in the VMPFC was associated with lower pain ratings and pain-related brain activation when viewing a romantic partner relative to control images (Eisenberger et al., 2011). Therefore, the findings from these two studies suggest a mechanism in which social support may prime feelings of attachment and/or reward to reduce pain perception and brain response.

1.4.2. Magnetoencephalography (MEG)

Magnetoencephalography measures brain activity by recording magnetic fields produced by electrical activity of neurons. It has excellent temporal resolution and good spatial resolution. One study has used MEG in the investigation of social support effects on pain. In this study, participants with a diagnosis of fibromyalgia, a chronic pain disorder defined by widespread pain and tenderness, reported less pain in response to thermal stimuli when they were accompanied by a romantic partner compared to when they were alone. MEG data further showed reduced amplitude of somatosensory evoked fields elicited by elbow stimulation in the presence of a romantic partner. The authors suggested that decreased pain and somatosensory activity may be related to social support buffering the threat of pain or distracting attention away from pain (Montoya et al., 2004).

1.4.3 Laser-evoked Potentials (LEPs)

LEPs measure evoked brain responses time-locked to transient, noxious thermal stimulation. Two types of LEPs are commonly observed in responding to noxious stimuli. The first is an early negative deflection, termed as N1, which is believed to reflect early sensory processing preceding the

conscious experience (Lee et al., 2009). The second type of LEPs comprises a biphasic complex, termed as N2–P2, which may underlie the conscious experience of the sensory processing captured by N1 (Lee et al., 2009). Using LEPs, one study found that the presence of a romantic partner compared to the absence affected N2 and P2 local peak amplitudes, but this effect was modulated by attachment style (Krahé et al., 2015).

1.4.4. Assessments of the Autonomic Nervous System

In addition to the central nervous activity, there is also evidence on the autonomic mechanisms associated with the influence of social support on pain (McClelland and McCubbin, 2008; Roberts et al., 2015). As discussed earlier, pain is suggested to be mediated by a ‘spinothalamocortical’ pathway (Craig, 2002, 2003a). This circuit has also been found to regulate the balance of the sympathetic (‘SNS’) and parasympathetic (‘PNS’) nervous system in pain (for a review, see Cortelli et al., 2013). SNS activity in the context of social support and pain has been evaluated using heart rate (Sambo et al., 2010), blood pressure (McClelland and McCubbin, 2008), skin response (Platow et al., 2007), and cortisol levels (Roberts et al., 2015). Although some studies indicated that social support reduced sympathetic arousal to pain (Roberts et al., 2015; Sambo et al., 2010), the number of studies is highly limited and the evidence is to a large extent confounded by social contexts (McClelland and McCubbin, 2008; Roberts et al., 2015).

In contrast, no study has evaluated the PNS response in the social modulation of pain. The PNS is suggested to be associated with the regulatory control over sympathetic arousal (Thayer et al., 2009). The PNS response may therefore provide a means by which social support can increase physiological control over pain-related arousal. Heart rate variability (HRV), which is the physiological variation in time intervals between heartbeats, has been widely used to evaluate the balance between the SNS and PNS activity (Cardiology, 1996). A large body of evidence

demonstrates that a high HRV may represent an important index of an effective sympathovagal balance and of cardiac health (Bootsma et al., 1994; Thayer et al., 2010). There are different ways to measure HRV, ranging from time-domain to frequency-domain measures (Cardiology, 1996), among which high-frequency HRV (HF-HRV) is suggested to be strongly associated with cardiac vagal tone (i.e. parasympathetic tone) (Koenig et al., 2014).

1.5. Promising Neurophysiological Methods to Better Understand the Connection between Social Support and Pain

Electroencephalography (EEG), Transcranial Magnetic Stimulation (TMS), and TMS-EEG are promising and complimentary neurophysiological methods to better understanding how social support acts to influence pain.

1.5.1. Electroencephalography (EEG)

EEG provides a measure of rhythmic fluctuations in electrical activity produced by large populations of neurons (Buzsáki, 2004; Buzsáki and Draguhn, 2004; Le Van Quyen and Bragin, 2007). EEG has excellent temporal resolution (i.e. in the millisecond range), which is highly valuable for detecting transient changes in brain state. Oscillatory frequencies are conventionally divided into delta (<4 Hz), theta (4 – 7 Hz), alpha (8 – 12 Hz), beta (13 – 30 Hz) and gamma (>30 Hz) bands (Buzsaki, 2006; Hirsch and Brenner, 2011). In addition to rhythmic oscillation, EEG also provides means for evaluating neural coupling over distance and across frequencies (Sauseng and Klimesch, 2008). Neurons in the human brain are to a large extent interconnected, whereby the whole brain can be seen as a huge network consisting of millions of sub-networks ranging from micro-level to large-scale connections (Varela et al., 2001). It is widely accepted that human behaviour arises from the

communication between neurons within and between neural networks (Fuster, 1997; Varela et al., 2001).

To the best of our knowledge, no study has investigated the oscillatory mechanisms associated with social modulation of pain. But there are many studies investigating neural oscillations in the context of pain (Chang et al., 2002; Hauck et al., 2015; Nickel et al., 2017). Although the frequency dynamics of pain are not entirely understood (Ploner et al., 2017), most of the studies found decreased activity in alpha band (sometimes extending to beta band) but increased activity in gamma band (Nickel et al., 2017; Peng et al., 2014; Schulz et al., 2015; Tiemann et al., 2010; Zhang et al., 2012). Changes in alpha and gamma activity are thought to underlie nociceptive attention and subjective experience of pain respectively (Hauck et al., 2015; Nickel et al., 2017; Peng et al., 2014). A line of evidence also found increased delta activity in pain (Chang et al., 2002; Hauck et al., 2015; Huber et al., 2006; Le Pera et al., 2000), but its functional relevance in pain remains to be determined. In terms of EEG connectivity, only one study has explored phase synchronization in response to painful stimuli and found increased theta range connectivity between central and parietal regions (Taesler and Rose, 2016).

In the field of social support, one study found that viewing images of a romantic partner was associated with higher delta activity compared to images of an unknown person or a known and appreciated person. The authors indicated delta activity to be associated with feelings of attachment or love (Başar et al., 2008). Additionally, one study has looked at EEG connectivity in the context of social touch and pain by simultaneously recording EEG in both individuals in a romantic relationship. Social touch by a romantic partner decreased pain perception but increased alpha band coherence between the couples. Alpha band coupling between couples was suggested to be associated with the integration of information from tactile, visual, and nociceptive inputs (Goldstein et al., 2018).

1.5.2. Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) is a non-invasive approach which can modulate brain activity and thereby provide unique causal insights into brain-behaviour relationships. Specifically, TMS can generate weak electric currents via rapid changes in magnetic field and trigger depolarization of the neurons under the coil (Siebner and Rothwell, 2003; Wagner et al., 2007). When TMS is applied repetitively (repetitive TMS, rTMS), the excitability of stimulated cortical region can be altered (Maeda et al., 2000). Theta Burst Stimulation (TBS) is one of the most established rTMS protocols and has the capacity to modulate neural excitability (Chung et al., 2017; Huang et al., 2005; Ni et al., 2014). TBS delivers pulses in bursts of three at high frequency (50 Hz) with an inter-burst interval at low frequency (5 Hz) for a total of 600 pulses. TBS can be used to increase or decrease cortical excitability depending on whether intermittent (iTBS, a 2s train of TBS repeated every 10s) or continuous (cTBS, 20 or 40 s of TBS without any interruption) stimulation, respectively, is employed (Huang et al., 2005). Thus, TBS provides a means to modulate brain activity and explore the effects and mechanisms of social support on pain but has not been used for this purpose to date.

In addition, changes in neural activity induced by TBS can be measured using single-pulse TMS and concurrent EEG (TMS-EEG) (Cash et al., 2017; Chung et al., 2017). EEG responses induced by a single-pulse TMS can be illustrated with waveforms and topographic representation of TMS-evoked potentials (TEPs) (Rogasch et al., 2014). TEPs are suggested to reflect the shifts in the inhibition-excitation balance in cortical circuits following a single TMS pulse (Du et al., 2018; Rogasch and Fitzgerald, 2013). TEPs following stimulation of the motor cortex and non-motor context (e.g. prefrontal cortex) consist of a series of negative and positive peaks (Chung et al., 2017; Mäki and Ilmoniemi, 2010; Rogasch and Fitzgerald, 2013). Among these peaks, N100 is considered to be the most robust TEP component with the greatest signal-to-noise ratio (Cash et al., 2017; Noda et al., 2016) and to be most reliably modulated by TBS (Chung et al., 2017; Chung et al., 2018b). Although the physiological origin and functional significance of N100 component has not been fully elucidated,

several studies have suggested the N100 component to be linked to cortical inhibitory processes (Bender et al., 2005; Bonnard et al., 2009; Chung et al., 2017; Farzan et al., 2013; Rogasch et al., 2012, 2015).

1.6. The Clinical Importance of Understanding the Influence of Social Support on Pain

While it is not the focus of this PhD, understanding the effects and mechanisms of social support on pain is important for improving the application of social support strategies in the management of pain. Indeed, a number of cognitive-behavioural therapies (CBT) have included a significant other (mostly the spouse/partner) in the management of chronic pain and these studies have demonstrated add-on effects of social support (Abbasi et al., 2012; Keefe et al., 2004; Keefe et al., 1996, 1999; Martire et al., 2003; Martire et al., 2008; Radojevic et al., 1992). Better understanding in which contexts social support has an analgesic influence and the potential mechanisms will allow for optimising social support strategies in pain management.

1.7. Summary of the Literature

The role of social support in pain experience is a growing area of research. Overall, the literature suggests a potential role of social support strategies in the management of pain. Indeed, some interventional trials have demonstrated the effectiveness of social support-assisted therapies for the management of chronic pain (Abbasi et al., 2012; Keefe et al., 1996, 1999). However, studies have demonstrated mixed effects of social support and it has not been fully elucidated in which contexts social support has a protective effect on pain and the magnitude of this effect. Moreover, research is still in the early stage to understand the neural and physiological mechanisms through which social

support influences pain. Overall, the utilization of social support strategies in pain management is challenged by limitations in the current research evidence.

1.8. Aims and Overview of Chapters

The overall aim of this thesis is to examine the role of social support in pain experience and neurophysiological mechanisms. This was addressed through a total of two review articles and three experimental studies (Chapter 2 to Chapter 6, three published and two under review).

In chapter 1, a brief introduction and overview of the thesis are provided.

Chapter 2 contains a published systematic review and meta-analysis (Neuroscience & Biobehavioral Review) which characterized the contexts in which social support has an analgesic effect and quantified the magnitude of the effect.

Chapter 3 contains a published systematic review (Clinical Journal of Pain) which assessed the potential psychological and behavioural processes as well as neurobiological mechanisms associated with the effect of social support on pain reduction.

Chapter 4 contains the first published empirical paper (Journal of Pain), which explicitly manipulated the perceived threat of pain to examine whether or not social support can reduce pain through a buffering effect on the neurophysiological markers of threat of pain.

Chapter 5, currently under review, investigated the changes in neural oscillations and parasympathetic activity that may be associated with the influence of social support on prolonged pain.

Chapter 6, currently under review, describes the use of TBS to the medial prefrontal cortex and TMS-EEG to investigate neural plasticity and brain connectivity changes that may mediate the influence of social support on pain.

Chapter 7 contains the summary of the study chapters and the implications of the results. In addition, limitations and future directions are included in this section. The thesis closes with a brief conclusion.

CHAPTER TWO

Effects and Social Context

Manuscript

Che X., Cash R., Chung S.W., Fitzgerald P., & Fitzgibbon B.M. (2018). Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Review*, *92*, 437-452.

Preamble to systematic review and meta-analysis

Social support can have mixed effects on pain experience (Brown et al., 2003; Gallant and Hadjistavropoulos, 2017; Goldstein et al., 2016; Karmann et al., 2014; Modić Stanke and Ivanec, 2010). A previous systematic review highlighted the contribution of potential covariates in the social modulation of pain, such as the perceived intention of the social partner and the pre-existing social relationships (Krahé et al., 2013). However, no study has characterized the magnitude of the influence of social support. Moreover, a number of relevant additional studies have been published since the 2013 systematic review (Edwards et al., 2017; Goldstein et al., 2016; Roberts et al., 2015; Shaygan et al., 2017). In addition, how social support may influence pain-related physiological arousal has not previously been systematically assessed.

This chapter systematically characterises the contexts in which social support has an analgesic effect and quantifies the magnitude of the effect using a meta-analysis. We also provide a detailed examination of the role of social relationships in the social modulation of pain. In addition to pain

experience, this chapter also demonstrates the influence of social support on pain-related physiological arousal. The presence of publication bias is also considered.



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Review article

Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis

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ABSTRACT

Social support is demonstrated to have mixed effects on both pain and related physiological arousal. In this study, a meta-analysis was conducted to characterise these effects. A total of 2416 studies were identified in a systematic search, among which 21 were eligible for the quantitative review. The mere presence of another person was not sufficient to modulate pain perception. However, the presence of a stranger was identified to decrease pain-related arousal (SMD = -0.31), and the presence of a significant other increased facial expression of pain (SMD = 0.21). We further found verbal support to decrease pain (SMD = -0.69) and arousal (SMD = -0.99), and we demonstrated moderate to large analgesic effects of intimate relationships through touching (SMD = -0.95) and viewing (SMD = -0.60) of a romantic partner. Finally, we presented evidence of publication bias for pain-related arousal but not for behavioural pain outcomes. Together, our findings suggest that the impact of social support on pain is context-dependent with the verbal communication of support and intimate relationships being of particular importance.

1. Introduction

Under the right conditions, having supportive relationships with others provides benefits to the individual (Cohen and Wills, 1985; Uchino, 2006). These benefits may arise through the forms of receiving supportive resources from others (e.g. emotional, economical, informational) and the perception that supportive resources are available should they be needed (Dunkel-Schetter and Bennett, 1990; Uchino, 2009). In the context of pain research, social support may be associated with the reduction of pain (Brown et al., 2003; Eisenberger et al., 2011) and related physiological arousal (Roberts et al., 2015; Sambo et al., 2010). For instance, holding the hand of a significant other or providing social support without actual presence (i.e. primed support) can reduce the intensity and/or unpleasantness of pain and heart rate increase evoked by painful stimuli (Che et al., 2017; Master et al., 2009).

In contrast, social support also has the potential to increase pain experience (Hurter et al., 2014; McClelland and McCubbin, 2008). Indeed, pain behaviours are in some instances suggested to be used to trigger sympathy or attention (Williams, 2002), and/or to avoid social responsibilities (Glenton, 2003). A recent review highlighted the contribution of potential covariates in the social modulation of pain. Specifically, social support in general decreases pain when it is clearly communicated (e.g. verbal support, 'social support variations'), or in

cases where it is provided by a significant other (e.g. romantic partner, 'social relationships') (Krahé et al., 2013). However, no study has characterised the magnitude of the influence of social support nor the modulating impact of potential covariates. Moreover, since the last systematic review (Krahé et al., 2013) there have been a number of additional studies published in this area (Edwards et al., 2017; Gallant and Hadjistavropoulos, 2017; Goldstein et al., 2016; Karmann et al., 2014; Roberts et al., 2015), with some of these studies also examining pain-related arousal which has not previously been assessed in a systematic review.

A growing body of research indicates the effectiveness of support-assisted therapies for the management of chronic pain (e.g., spouse-assisted coping skills training) (Keefe et al., 1996, 1999). However, in order to optimise these approaches, a better understanding of the context(s) in which social support has an analgesic effect is necessary. To this end, a meta-analysis was conducted to quantify the influence of social support on pain. Studies were limited to those that provided a no-support baseline condition relative to stranger or close other support. This helps to control the variability induced by baseline conditions (e.g. a stranger condition) and clarify the role of pre-existing social connections. Moreover, we quantified physiological changes evoked by painful stimuli in the context of social support. Physiological arousal is closely associated with health outcomes (Cohen and Wills, 1985;

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Uchino, 2006), and it may suggest ways in which social support modulates pain experience (Goldstein et al., 2017). This meta-analysis may help to summarise and quantify the complex and multivariate influence of social support on experimental pain and is intended to help direct future research and assist in the optimisation of treatment strategies.

2. Methods

2.1. Protocol and registration

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2009). The protocol was registered in the database of International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42017076667).

2.2. Search strategy

A comprehensive electronic literature search was performed in PubMed, PsycINFO, The Cochrane Library and EMBASE to the end of August 2017. The keywords used for the search were ‘pain’ AND (‘interpersonal’ OR ‘social support’ OR ‘social presence’ OR ‘social interaction’ OR ‘social modulation’ OR ‘social context’ OR ‘attachment’ OR ‘social influence’ OR ‘social touch’ OR ‘empathy’). Full search records can be found in *Supplementary Material S1*.

Two reviewers (XC and SC) independently assessed the titles and abstracts of the initial search results against the inclusion criteria (see Table 1). Full-text versions were examined in instances where it was unclear from the summary data alone whether a particular study met inclusion criteria. Full-text articles of potentially eligible studies were then screened. Discrepancies between the reviewers were solved by consensus. Reference lists of full-text potentially eligible studies were also checked for missing studies.

2.3. Selection criteria

The same inclusion and exclusion criteria were used for the systematic review and meta-analysis, as outlined in Table 1. Specifically, studies were included if they matched all five *a priori* criteria: studies were included if (1) pain was induced in experimental settings (e.g. cold pain) but were excluded if they used clinical procedure or clinical pain

Table 1
Inclusion and exclusion criteria.

	Inclusion	Exclusion
Interventions	Experimentally induced pain	Clinical procedure Clinical pain assessment
Comparisons	Presence and absence of social support	No control condition of social support
Outcomes	Behavioural pain outcomes: Pain intensity Pain unpleasantness Facial expression of pain Pain threshold Pain tolerance Physiological studies were included if they also reported behavioural pain outcomes	No behavioural pain outcome
Data reported	Data that enables analysis and estimation of effect size	Unpublished data Data without Mean Data without SD/SEM Data without N
Publication type	Peer-reviewed journal Written in English	Review article Case report Grey literature Non-English article

SD-standard deviation; SEM-standard error of mean; N-sample size.

assessment; (2) both the presence and absence of social support were manipulated (regardless of a within- or between-group design), but were excluded if there was no baseline condition of support; (3) behavioural pain outcomes were reported, but were excluded if they did not report any behavioural pain measure; (4) sufficient data were available to compute effect size using Hedge’s adjusted *g* (i.e. mean, standard deviation (SD), and sample size) but were excluded if data were not available; (5) the article was published in peer-reviewed journals and written in English.

2.4. Outcome measures

Based on the literature on social support and pain, behavioural pain measures included pain intensity, pain unpleasantness, facial expression of pain, pain threshold, and pain tolerance. Physiological outcomes included heart rate, blood pressure (both diastolic and systolic), skin response, and cortisol levels.

2.5. Data extraction

The mean, SD, and sample size were extracted for the outcome measures in each experimental condition or group (i.e. support, no-support). In cases where numerical values were not available, data were extracted directly from relevant figures using Plot Digitizer software (Huwaldt, 2010). We also contacted the corresponding authors for additional data when they were not directly available from the article.

In accordance with meta-analyses in pain research (Boerner et al., 2014; Thompson et al., 2016), data were averaged in certain instances using the formula from the Cochrane Handbook for Systematic Reviews of Interventions (Formula 1, *m* = mean; *n* = sample size; SD = standard deviation) (Higgins and Green, 2011). Specifically, data were averaged: (1) when a study applied more than one type of pain-induction technique (Edwards et al., 2017; Montoya et al., 2004); (2) when painful stimuli were applied to different sites of the body (Montoya et al., 2004); (3) when a particular pain outcome (e.g. pain intensity) was assessed with more than one measurement (Edwards et al., 2017; Roberts et al., 2015); or (4) when results were reported in different genders (Edwards et al., 2017; Jackson et al., 2005; McClelland and McCubbin, 2008). Moreover, in cases where painful stimuli were delivered at different intensity levels (Eisenberger et al., 2011; Kleck et al., 1976), data of the highest intensity were extracted because it was most likely to reliably evoke pain. In addition, if a study assessed pain outcomes in different time points, data were extracted from the last time point (Brown et al., 2003; Sullivan et al., 2004). This was done as most of the included studies assessed pain at the end of painful stimulation. Finally, data from the first paper were extracted when the same dataset was reported in multiple papers (Goldstein et al., 2017).

Formula 1:

$$Mean = \frac{n1 * m1 + n2 * m2}{n1 + n2}$$

SD

$$= \sqrt{\frac{(n1-1)*SD1^2 + (n2-1)*SD2^2 + \frac{n1*n2}{n1+n2}*(m1^2 + m2^2 - 2*m1*m2)}{n1 + n2 - 1}}$$

2.6. Methodological study appraisal

We adapted the assessment tool developed by Lautenbacher et al. (2017), to assess the quality of psychophysical studies on experimental pain among healthy controls. This tool was developed based on the pain literature (e.g. Tesarz et al., 2012) and the Newcastle-Ottawa Scale (Wells et al., 2010). This assessment tool includes six items and was used to examine age effect on pain perception. We therefore adapted

this tool to our dataset by replacing one of the items with social support blinding. Specifically, the items were: (1) reported blinding processes of study purpose to participants; (2) similar gender distribution across all condition/group; (3) specification of stimulus location; (4) specification of physical type of stimulus; (5) report on psychophysical method of threshold determination; and (6) the extent to which the study population represents the true population. Two reviewers (XC and SC) independently assessed each study and discrepancies were addressed by consensus. More details of this assessment tool can be found in *Supplementary Material S2*.

2.7. Meta-analysis

2.7.1. Calculating effect sizes

Continuous outcome measures were used in the meta-analysis. Extracted data were entered into the MIX 2.0 computer program (Bax, 2011), which allows for the calculation of statistical significance of differences between means with 95% confidence intervals (CIs). The standardised mean difference (SMD) calculated using Hedge's adjusted g was estimated for the effect size. Hedge's adjusted g is similar to Cohen's d but it adjusts for the small sample bias (Hedges and Olkin, 1985). For SMDs, values of 0.2 were considered small, 0.5 as medium and 0.8 as large (Cohen, 1988). It is noted that an SMD below 0.2 (with $p \leq 0.05$) was only considered as trivial. In cases where standard error (SE) values were reported, SD values were estimated using the formula $SD = SE * \sqrt{n}$ (n = sample size) (Higgins and Green, 2011).

It is noted that the SMD method does not account for the differences in the scale directions. In this case, pain threshold and pain tolerance have opposite directions compared to other behavioural pain measures. Based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011), we thus multiplied the mean values of pain threshold and pain tolerance by -1 to correct for the difference in scale direction.

2.7.2. Subgroup analyses

In the subgroup analyses, we examined the main effect and the interaction effect between social support variations and social relationships.

There were four variations of social support based on the included studies: social presence, verbal support, social touch, and primed support. In the cases of social presence, the social partner was physically present without any verbal communication or eye contact with the participant (Edwards et al., 2017). In the studies of verbal support the social partner verbally interacted with the participant. In some studies, the social partner verbally encouraged the participant to engage in the pain task (Brown et al., 2003; Roberts et al., 2015), while in another study the social partner answered the questions of the participant in an empathetic fashion (Jackson et al., 2005). In the condition of social touch, the social partner held the hand of the participant without verbal communication (Master et al., 2009). In the cases of primed support, the social partner was not physically present. Social support was manipulated through viewing an image of the social partner (Eisenberger et al., 2011), or verbally interacting with the social partner before the pain task (Platow et al., 2007).

We further distinguished between different types of social relationships (Krahé et al., 2013), based on whether the social partner was a stranger, a parent, a friend, or a romantic partner of the participant. According to the history of social interactions, social relationships were categorised as 'close other' (i.e. romantic partner, parent, friend), and 'stranger'.

In the supplementary analysis, we also investigated the gender difference as some studies have shown that the social modulation of pain was most prominent in female pain recipients (Chambers et al., 2002; Jackson et al., 2005; McClelland and McCubbin, 2008). Data of two genders were thus analysed separately from relevant studies.

2.7.3. Test of heterogeneity

In systematic reviews and meta-analyses, conclusions are less clear when the results vary across studies. A statistical test of heterogeneity is therefore commonly reported to establish whether studies are consistent (Higgins et al., 2003). In line with other meta-analyses in experimental pain (Kim et al., 2017; Thompson et al., 2016), heterogeneity between studies was evaluated using the I^2 statistics in this study. I^2 measures the percentage of total variance across included studies that is due to heterogeneity. It is expressed as $I^2 = 100\% \times (Q - df) / Q$, where df is the degree of freedom, and Q is computed by summing the squared deviations of each study's estimate from the overall meta-analytic estimate (Higgins et al., 2003). I^2 ranges from 0% to 100%, with 0% indicating no observed heterogeneity, and $> 50\%$ representing moderate heterogeneity. Moreover, Galbraith plots were included to assess and illustrate the extent of heterogeneity between studies. These plots indicate the proportion of studies whose results are positioned within two standard errors of the effect estimates (i.e. meta-analytic estimate divided by its standard error). If at least 95% of the included studies lie within two standard errors of the population effect, the effect is interpreted as being consistent across studies (Thompson, 1994). As of the variations in important study characteristics (e.g. pain modality, support variations, pain outcomes), we anticipated heterogeneity among studies and thus random-effect models were employed. A random-effect model allows for statistical control of heterogeneity and permits generalisation of results beyond those included in the meta-analysis.

2.7.4. Publication bias

Publication bias may adversely affect the reliability of the conclusions of a meta-analysis. A number of methods were therefore employed to examine publication bias. The selectivity funnel plot is a straightforward method to visually inspect publication bias (Light and Pillemer, 1984). This provides a graphical representation of effect estimates against sample size, which is computed as the standard error of the effect estimates. Results from small studies will be positioned at the bottom of the graph, with the spread narrowing among larger studies (Sterne et al., 2011). In the absence of bias, the scatter will resemble a symmetrical inverted funnel. However, the funnel plot provides only an informal illustration, which should be further examined by more objective statistics (Egger et al., 1997). Egger's regression test and the Begg-Mazumdar Kendall τ are most commonly used. Egger's regression test uses a linear regression approach to measure publication bias. It is expressed as Standardized Effect Size = $a + b \times$ Inverse Standard Error, where intercept 'a' provides a measure of publication bias (Egger et al., 1997). The Begg-Mazumdar test is based on correlating the standardized effect estimates with the variance of the effect estimates using a rank correlation test (i.e. Kendall's tau) (Begg and Mazumdar, 1994). In addition, a Bayesian approach was used to detect and mitigate the effects of publication bias. This approach assigns weights to a set of four models under different publication bias assumptions and averages the results from these models. It can yield the posterior distribution of a mitigated test statistic which can be used to make inferences about the existence of an effect (Guan and Vandekerckhove, 2016).

3. Results

3.1. Selection of studies and characteristics

Online database searches identified a total of 2416 records (Fig. 1). After duplicates were removed, 1836 studies remained. Initial screening of the title and abstract was performed against the inclusion and exclusion criteria. After excluding 1788 records from the initial screening, full-text versions of 48 studies were screened for eligibility. A total of 21 studies were included in the systematic review and meta-analysis, among which 21 were appropriate for behavioural outcome analysis and 6 for physiological outcome analysis.

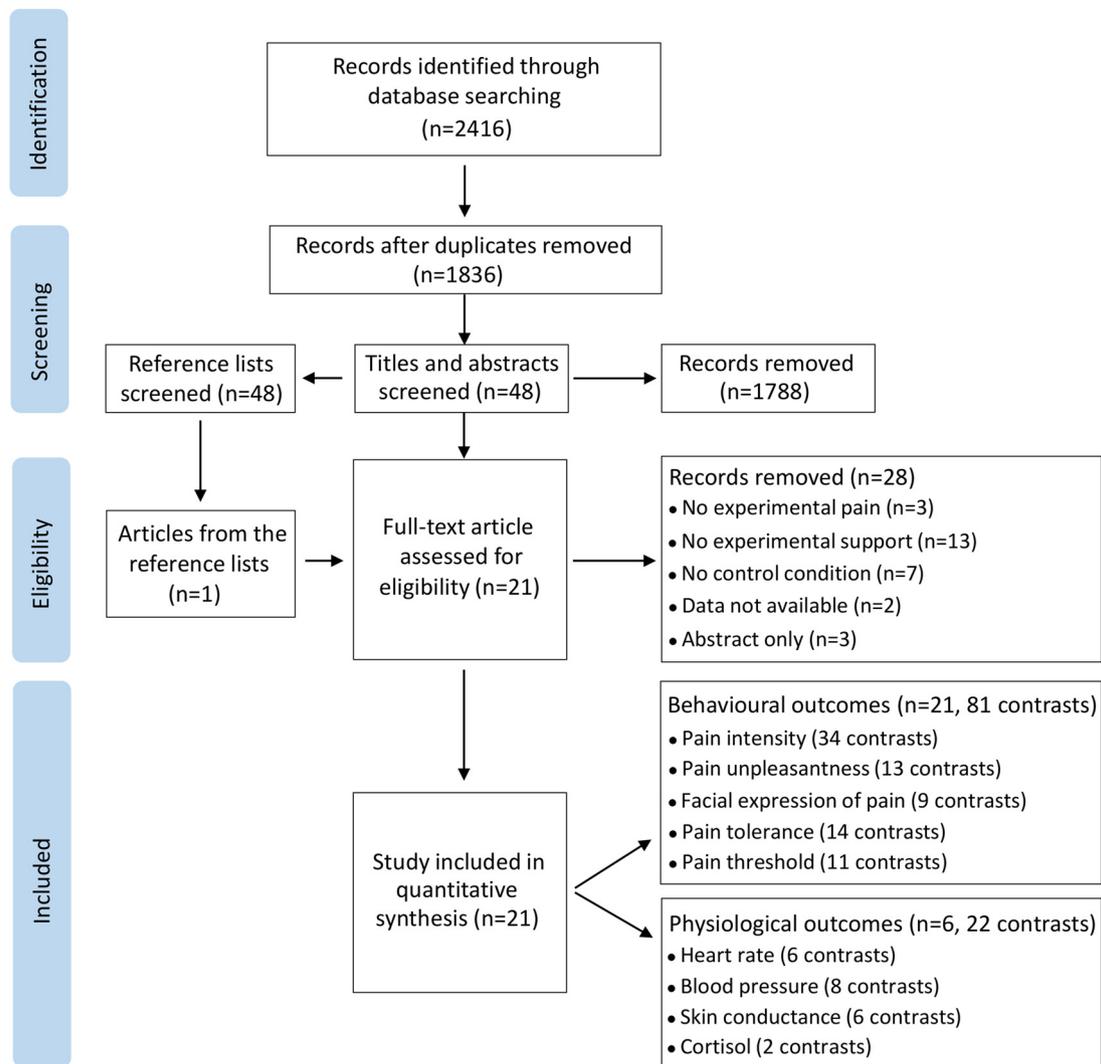


Fig. 1. Flow diagram of selected studies (n = number of articles).

Selected studies included both within-group (i.e. participants underwent both social support and no-support manipulation, e.g. Eisenberger et al., 2011), and between-group (i.e. participants underwent either a social support or a no-support manipulation, e.g. Brown et al., 2003) designs. A total of 81 contrasts were identified for behavioural pain assessment. All participants (n = 1379) reported behavioural pain measures, among which 830 were females. Participants were mostly health adults except for fibromyalgia and migraine patients in one study (Montoya et al., 2004), and child-parent dyads in another (Vervoort et al., 2011). The experimental pain was induced by a variety of methods including thermal (both cold and heat), pressure, electrical, and laser stimuli. It is noted that most of the studies examined social presence (62 contrasts), while relatively fewer studies investigated verbal support (6 contrasts), social touch (5 contrasts), or primed support (8 contrasts). All the studies demonstrated accepted qualities of 4 as suggested by Lautenbacher et al. (2017) (Table 2). Moreover, 22 contrasts of physiological arousal were identified which were conducted among 348 healthy adults (180 females).

3.2. Behavioural pain outcomes

Table 2 summarises the characteristics of the studies that examined the effects of social support on behavioural and physiological pain outcomes. Studies were separated into different datasets that included multiple experiments, and/or contrasts, and/or outcome measures.

3.2.1. Effects of social support on behavioural pain outcomes

We first pooled data extracted from all experiments, contrasts, and behavioural outcomes (i.e. intensity, unpleasantness, facial expression of pain, tolerance, and threshold). Overall, social support showed no effect on behavioural pain with a pooled SMD of -0.10 (95% CI: [-0.16, -0.03], $p = 0.003$) (Fig. 2). Moreover, there was no effect of social support on each behavioural pain measures (with no SMD ≥ 0.2 , and $p \leq 0.05$).

3.2.2. Publication bias in studies examining behavioural outcomes

Galbraith plot indicated heterogeneity in the dataset of behavioural outcomes, with more than 5% of the dots beyond two standard errors of the population effect (Fig. 3A). The test of heterogeneity was significant ($Q = 124.60$, $p = 0.001$, $I^2 = 35.79\%$). There was a slight asymmetry in the shape of the selectivity funnel plot (Fig. 3B), with each line in the funnel representing various levels of significance (0.01, 0.05, and 0.1). Begg's test ($\tau = -0.15$, $p = 0.07$) and Egger's regression test ($t = -0.72$, $p = 0.08$) indicated no evidence of publication bias (Fig. 3C). In addition, the Bayesian analysis yielded similar effect size (-0.09) compared to the estimated effect size (-0.10) (Fig. 3D). These combined analyses suggested a minimal possibility of publication bias in the dataset of behavioural outcomes.

3.2.3. Subgroup analyses on behavioural outcomes

A series of subgroup analyses were performed to examine the main

Table 2
Characteristics of included studies.

Study	Sample	Gender ratio	Age (range)	Pain modality	Conditions and contrasts	Behavioural outcomes	Physiological outcomes	Quality score
Borsook and MacDonald (2010)	Healthy participants (N = 45)	16M:29F	(18-30)	Pressure pain	1. Stranger positive interaction vs. no interaction (pre-post design)	1. Intensity 2. Unpleasantness		5.5
Brown et al. (2003)	Healthy participants (N = 101)	52M:49F	(17-21)	Cold pain	1. Random interaction vs. alone 2. Active support vs. alone 3. Social presence vs. alone	1. Intensity 1. Intensity 1. Intensity		5
Edwards et al. (2017)	Experiment 1: Healthy participants (N = 48) Experiment 2: Healthy participants (N = 48) Experiment 3: Healthy participants (N = 48)	24M:24F 24M:24F 24M:24F	M: 26.62 ± 8.14; F: 22.75 ± 3.54 M: 24.21 ± 7.6; F: 19.67 ± 2.35 M: 25.42 ± 5.11; F: 23.92 ± 4.23	Cold pain; Pressure pain Cold pain; Pressure pain Cold pain; Pressure pain	1. Friend presence vs. alone 2. Stranger presence vs. alone 3. Male friend presence vs. alone 4. Female friend presence vs. alone 5. Partner presence vs. alone 6. Friend presence vs. alone	1. Intensity 2. Tolerance 3. Threshold 1. Intensity 2. Tolerance 3. Threshold 1. Intensity 2. Tolerance 3. Threshold 1. Intensity 2. Tolerance 3. Threshold		4 4 4
Eisenberger et al. (2011)	Healthy participants (N = 17)	0M:17F	23.4 ± 3.8	Heat pain	1. Partner image-viewing vs. object image-viewing 2. Stranger image-viewing vs. object image-viewing	1. Unpleasantness 1. Unpleasantness		4
Fishman et al. (1995)	Healthy participants (N = 60)	30M:30F	–	Cold pain	1. Stranger social touch vs. alone	1. Intensity	1. HR 2(1). SBP 2(2). DBP	4
Gallant and Hadjistavropoulos (2017)	Healthy participants (N = 97)	42M:55F	(60-89)	Heat pain	1. Family member presence vs. alone 2. Stranger presence vs. alone	1. Intensity 2. Unpleasantness 3. Facial expression 4. Tolerance 5. Threshold 1. Intensity 2. Unpleasantness 3. Facial 4. Tolerance 5. Threshold		4.5
Goldstein et al. (2016) ^a	Healthy participants (N = 23)	0M:23F	(19-40)	Heat pain	1. Stranger hand-holding vs. alone 2. Partner hand-holding vs. alone 3. Partner presence vs. alone	1. Intensity 1. Intensity 1. Intensity		4.5
Jackson et al. (2005) ^a	Healthy participants (N = 88)	33M:55F	(18-47)	Cold pain	1. Transaction with empathetic stranger vs. coping alone	1. Intensity 2. Tolerance		4.5
Karmann et al. (2014)	Healthy participants (N = 126)	63M:63F	39.9 ± 13.5	Heat pain	1. Partner presence vs. alone 2. Stranger presence vs. alone	1. Intensity 2. Facial 1. Intensity 2. Facial		6
Kleck et al. (1976)	Experiment 1: Healthy participants (N = 20) Experiment 2: Healthy male participants (N = 40)	20M:0F 40M:0F	– –	Electrical shock Electrical shock	1. Stranger observer vs. alone 2. Stranger observer vs. alone	1. Intensity 2. Facial 1. Intensity 2. Facial	1. SCR 1. SCR	4 4.5
Krahé et al. (2015)	Healthy participants (N = 39)	0M:39F	25.87 ± 5.17	Laser pain	1. Partner presence (participant focus) vs. alone 2. Partner presence (other focus) vs. alone	1. Intensity 1. Intensity		5.5

(continued on next page)

Table 2 (continued)

Study	Sample	Gender ratio	Age (range)	Pain modality	Conditions and contrasts	Behavioural outcomes	Physiological outcomes	Quality score
Master et al. (2009)	Healthy participants (N = 25)	0M:25F	–	Heat pain	1. Partner hand-holding vs. object hand-holding 2. Stranger hand-holding vs. object hand-holding 3. Partner image-viewing vs. object image-viewing 4. Stranger image-viewing vs. object image-viewing	1. Unpleasantness 1. Unpleasantness 1. Unpleasantness 1. Unpleasantness		4
McClelland and McCubbin (2008)	Healthy participants (N = 68)	36M:32F	19.97 ± 2.75	Cold pain	1. Friend presence vs. alone	1. Intensity 2. Tolerance	1. HR 2(1). SBP 2(2). DBP	4
Modić Stanke and Ivanec (2010)	Healthy participants (N = 43)	0M:43F	(19-33)	Heat pain	1. Stranger presence at 0.5 m vs. alone 2. Stranger presence at 1.5 m vs. alone	1. Intensity 2. Unpleasantness 3. Tolerance 4. Threshold 1. Intensity 2. Unpleasantness 3. Tolerance 4. Threshold		5.5
Montoya et al. (2004)	Fibromyalgia patients (FIB) (N = 16); Migraine patients (MIG) (N = 16)	FIB : – MIG : –	FIB : (36-68) MIG : (36-68)	Thermal pain (hot and cold)	1. Partner presence vs. alone	1. Intensity ^b 2. Threshold ^c		4.5
Platow et al. (2007)	Healthy participants (N = 54)	32M:22F	(18-35)	Cold pain	1. In-group stranger reassurance vs. no-reassurance 2. Out-group stranger reassurance vs. no-reassurance	1. Tolerance 1. Tolerance	1. SCR 1. SCR	5
Roberts et al. (2015)	Healthy participants (N = 76)	0M:76F	(18-21)	Cold pain	1. Stranger verbal support vs. alone 2. Stranger presence vs. alone	1. Intensity 2. Unpleasantness 1. Intensity 2. Unpleasantness	1. HR 2(1). SBP 2(2). DBP 3. Cortisol ^d 1. HR 2(1). SBP 2(2). DBP 3. Cortisol	5
Sambo et al. (2010)	Healthy participants (N = 30)	10M:20F	29.1 ± 7.3	Heat pain	1. High-empathy stranger presence vs. alone 2. Low-empathy stranger presence vs. alone	1. Intensity 1. Intensity	1. HR 2. SCR 1. HR 2. SCR	4.5
Sullivan et al. (2004)	Healthy participants (N = 64)	26M:38F	(17-30)	Cold pain	1. Stranger presence vs. alone	1. Intensity ^e 2. Facial ^f		5
Vervoort et al. (2011)	Healthy children and parents (N = 38)	16M:22F	14.5 ± 2.52	Cold pain	1. Believed parent observation vs. alone	1. Intensity 2. Facial		5
Vlaeyen et al. (2009)	Healthy participants (N = 149)	61M:88F	M: 33.3 ± 9.3; F: 29.6 ± 11.3	Cold pain	1. Stranger presence vs. alone	1. Intensity ^g 2. Facial ^g		5.5

M-male; F-female; HR-heart rate; DBP-diastolic blood pressure; SBP-systolic blood pressure; SCR-skin conductance response; FIB-fibromyalgia; MIG-migraine.

^a data were not available in experiment 2.

^b data were extracted from neutral image condition.

^c data were averaged across people with fibromyalgia and migraine.

^d data were extracted from the time point right after pain.

^e data were averaged across high and low catastrophizers.

^f data were the total pain behaviours.

^g data were averaged across threat and no-threat conditions.

and the interaction effect of social support variations and social relationships on behavioural pain.

3.2.3.1. Social presence. Overall, social presence showed no effect on behavioural outcomes (SMD = -0.06, 95% CI: [-0.11, -0.004], $p = 0.03$). Similarly, no effect was observed on each behavioural pain

measure (with no SMD ≥ 0.2 , and $p \leq 0.05$) (see *Supplementary Material S3*).

Further analysis revealed that close other presence increased facial expression of pain with a small effect size (SMD = 0.21, 95% CI: [0.03, 0.38], $p = 0.02$). It was demonstrated to have no effect on other behavioural pain measures (with no SMD ≥ 0.2 , and $p \leq 0.05$) (Fig. 4A).

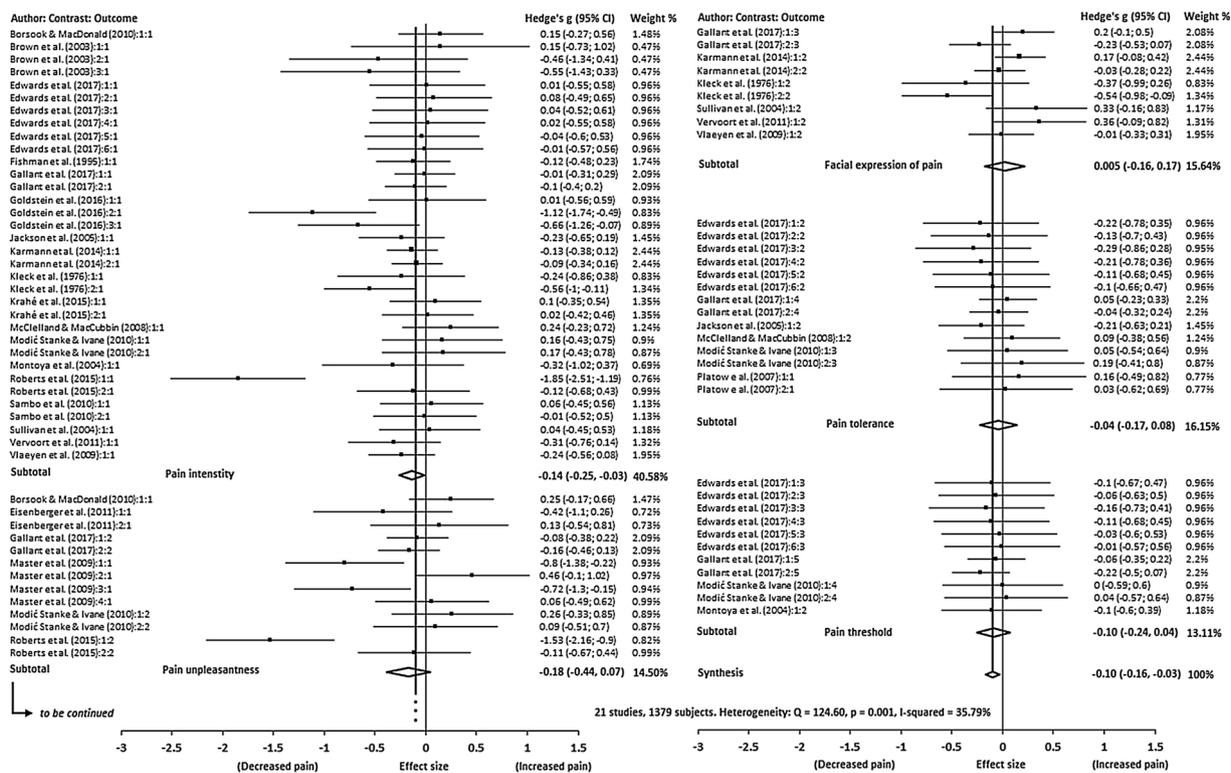


Fig. 2. Forest plot of the Hedge's adjusted g analysis for pooled effects of social support on behavioural pain outcomes.

There was no effect of stranger presence on behavioural pain, either in the pooled analysis (SMD = -0.09, 95% CI: [-0.17, -0.02], $p = 0.01$), or in the analyses of separate behavioural measures (with no SMD ≥ 0.2 , and $p \leq 0.05$) (Fig. 4B).

3.2.3.2. Verbal support. Overall, verbal support decreased behavioural pain with a medium effect size (SMD = -0.69, 95% CI: [-1.30, -0.08], $p = 0.03$). However, verbal support showed no effect on separate measures of pain intensity or pain tolerance (with no SMD ≥ 0.2 , and $p \leq 0.05$) (Fig. 5A).

Moreover, stranger verbal support resulted in a decrease in behavioural pain with a large effect size (SMD = -0.92, 95% CI: [-1.71, -0.13], $p = 0.02$). Similarly, this effect was not observed on pain intensity or pain tolerance separately (with no SMD ≥ 0.2 , and $p \leq 0.05$) (Fig. 5B).

No study has exclusively examined the effect of verbal support by a close other on behavioural pain ratings. Brown and colleagues examined verbal support from a friend but data were averaged across friend and stranger verbal support (Brown et al., 2003).

3.2.3.3. Social touch. Results showed no effect of social touch on behavioural pain, either in the pooled analysis (SMD = -0.30, 95% CI: [-0.80, -0.21], $p = 0.25$), or in the analyses of different behavioural measures (with no SMD ≥ 0.2 , and $p \leq 0.05$) (Fig. 6A).

We did observe decreased behavioural pain in close other (all from romantic partner) social touch with a large effect size (SMD = -0.95, 95% CI: [-1.37, -0.52], $p = 0.00001$). However, stranger social touch showed no effect on behavioural pain outcomes (SMD = 0.07, 95% CI: [-0.27, 0.41], $p = 0.70$) (Fig. 6B).

3.2.3.4. Primed support. Overall, primed support demonstrated no effect on behavioural pain outcomes (SMD = -0.01, 95% CI: [-0.25, 0.22], $p = 0.91$). Similarly, no effect was observed on separate pain measures (with no SMD ≥ 0.2 , and $p \leq 0.05$) (Fig. 7A).

Further analysis showed decreased behavioural pain in primed support from a close other (all from romantic partner image-viewing)

with a medium effect size (SMD = -0.60, 95% CI: [-1.04, -0.16], $p = 0.008$). But primed support from a stranger demonstrated no effect on behavioural pain (SMD = 0.15, 95% CI: [-0.06, 0.36], $p = 0.17$) (Fig. 7B).

3.2.3.5. Gender effect. Among the studies that reported findings for each gender, the majority examined the effect of social presence, but we pooled data from all variations of support. In male participants, social support showed no effect on the overall pain experience (SMD = -0.13, 95% CI: [-0.29, 0.03], $p = 0.12$), or on the separate pain measures (with no SMD ≥ 0.2 , and $p \leq 0.05$). Similarly, no significant effect was observed among female participants in either the pooled analysis (SMD = -0.05, 95% CI: [-0.21, 0.11], $p = 0.53$) or the separate analyses of measures (with no SMD ≥ 0.2 , and $p \leq 0.05$) (see Supplementary Material S4).

3.3. Physiological outcomes

3.3.1. Effects of social support on physiological outcomes

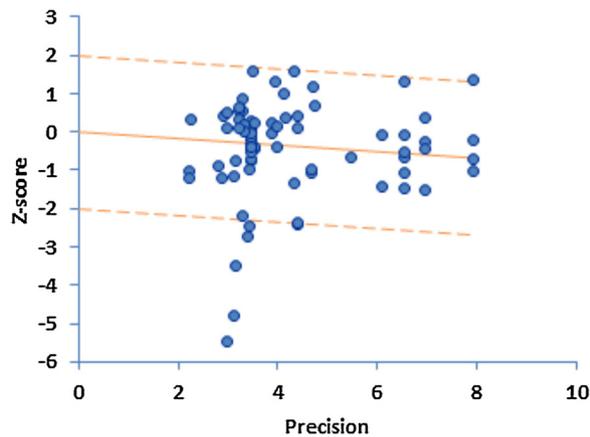
As shown in Fig. 1, physiological measures included heart rate (4 studies, 6 contrasts), blood pressure (3 studies, 8 contrasts), skin conductance (3 studies, 6 contrasts), and cortisol level (1 study, 2 contrasts). As each measure reflects certain aspects of physiological arousal, they were pooled together to investigate overall pain-related arousal.

Overall, social support decreased physiological response to painful stimulation with a small effect size (SMD = -0.25, 95% CI: [-0.44, -0.06], $p = 0.008$). Further analyses showed that this effect was only observed in skin response (SMD = -0.28, 95% CI: [-0.51, -0.05], $p = 0.01$), but not in other physiological measures (with no SMD ≥ 0.2 , and $p \leq 0.05$) (Fig. 8).

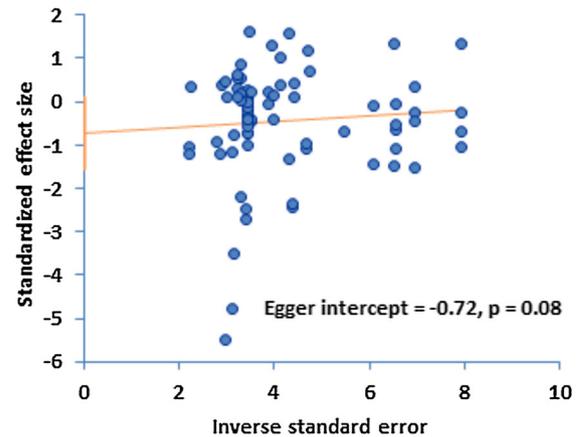
3.3.2. Publication bias in studies examining physiological outcomes

Galbraith plot suggested heterogeneity in the pooled dataset of the physiological outcomes, in which more than 5% of the points were beyond two standard errors of the population effect (Fig. 9A). The test

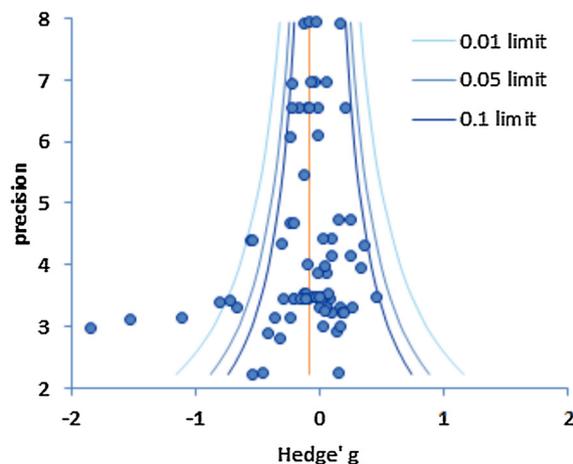
A. Galbraith plot



C. Regression plot



B. Selectivity funnel plot



D. Bayesian triplot

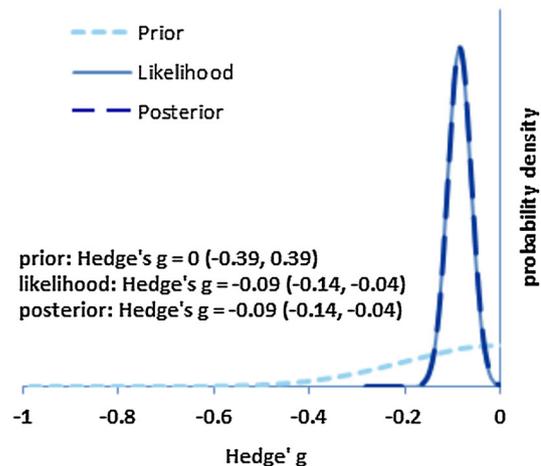


Fig. 3. Series of tests for heterogeneity and publication bias for the effects of social support on behavioural pain outcomes. (A) Galbraith plot suggested heterogeneity with more than 5% of the data beyond two standard errors of the population effect. (B) Selectivity funnel plot indicated slight publication bias with a few studies showing asymmetry towards decreased pain. (C) Regression plot suggested no publication bias with the intercept showing small deviation from 0 ($p > 0.05$). (D) Bayesian triplot indicated no publication bias with the likelihood effect size (-0.09) comparable as the estimated effect size (-0.10).

of heterogeneity was also significant ($Q = 63.14$, $p = 0.001$, $I^2 = 66.74\%$). There was an asymmetry in the shape of the selectivity funnel plot (Fig. 9B). Begg's test ($\tau = -0.32$, $p = 0.03$) and Egger's regression test ($t = -3.25$, $p = 0.05$) indicated evidence of publication bias (Fig. 9C). Moreover, the Bayesian analysis yielded a smaller effect size (-0.20) compared to the original outcome (-0.25) (Fig. 9D). Therefore, these combined analyses suggested the possibility of publication bias in physiological outcomes.

3.3.3. Subgroup analyses on physiological outcomes

3.3.3.1. Social presence. There was no effect of social presence on pooled physiological outcomes (SMD = -0.12, 95% CI: [-0.34, 0.10], $p = 0.29$), however, it was shown to decrease skin response with a small effect size (SMD = -0.38, 95% CI: [-0.64, -0.12], $p = 0.004$) (Fig. 10A).

Further analyses demonstrated that stranger presence decreased physiological outcomes (SMD = -0.31, 95% CI: [-0.48, -0.13], $p = 0.0004$), while close other presence (a friend) increased physiological responses (SMD = 0.44, 95% CI: [0.16, 0.71], $p = 0.002$), both with small effect sizes (Fig. 10B).

3.3.3.2. Verbal support. Verbal support decreased physiological

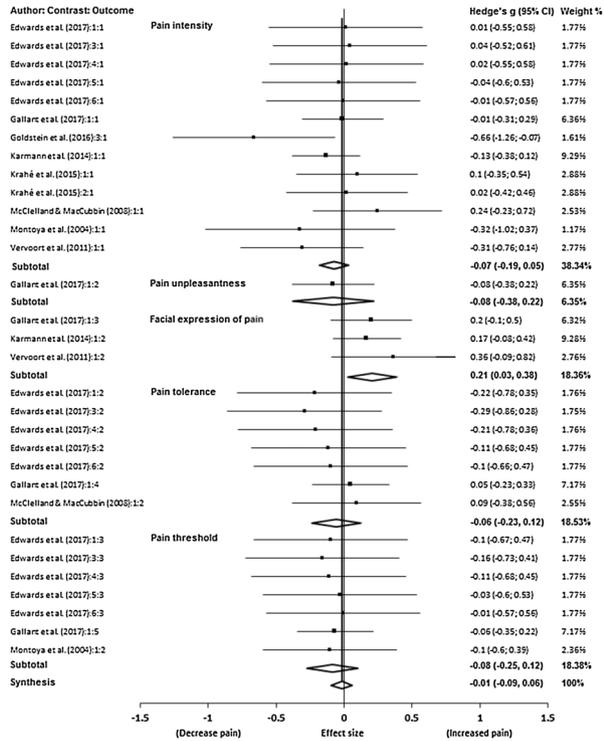
responses from one study with a large effect size (SMD = -0.99, 95% CI: [-1.29, -0.69], $p = 0.00001$) (Fig. 11A).

3.3.3.3. Social touch. Social touch was shown to have no effect on physiological responses from one study (SMD = -0.09, 95% CI: [-0.30, 0.11], $p = 0.37$) (Fig. 11B).

4. Discussion

The present study aimed to quantify the influence of social support on pain and related physiological arousal. Built on the literature to date, we further examined two covariates, i.e. social support variations and social relationships, which have been largely reported to modulate social support effect on pain. Our data demonstrated that social presence alone did not affect pain perception. However, the presence of a significant other resulted in an increase of facial expression of pain, and the presence of a stranger was associated with decreased physiological arousal. Meanwhile, verbal support, mainly from a stranger, decreased pain and arousal. We also demonstrated an analgesic effect of intimate relationships occurred in response to touching and viewing a romantic other. Finally, we found evidence of publication bias for pain-related arousal but not for behavioural pain outcomes.

A. Close other presence: pain outcomes



B. Stranger presence: pain outcomes

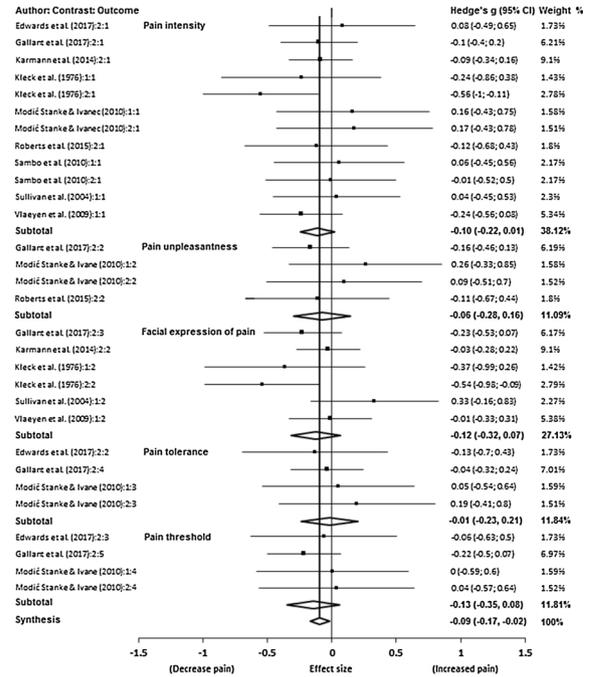


Fig. 4. Forest plot of the Hedge's adjusted g analysis for the influence of social presence on behavioural pain outcomes.

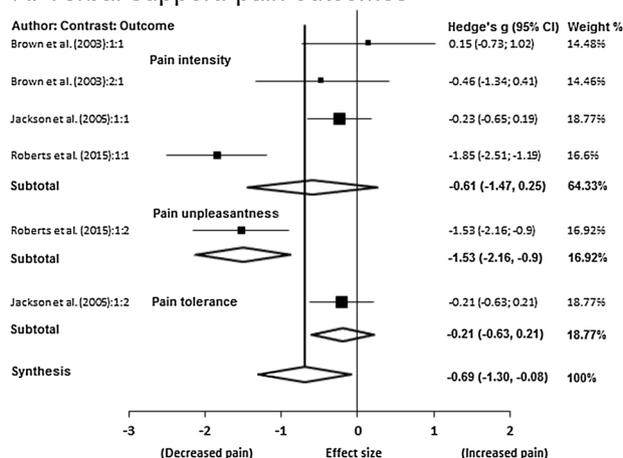
4.1. Social presence

We found significant distinctions in the effects of close other presence and stranger presence. Results are therefore discussed separately. Our results demonstrate that pain ratings (i.e. intensity, unpleasantness) and pain sensitivity (i.e. threshold, tolerance) did not vary as a function of the presence of a close other (Fig. 4A). These findings suggest that the mere presence of a significant other has no influence on pain perception. However, close other presence did increase facial expression of pain (Fig. 4A). Moreover, this result was consistently observed across various close relationships (i.e. parent, romantic partner, and family member) and age groups (i.e. children, young adult, and old adult) (Gallant and Hadjistavropoulos, 2017; Karmann et al., 2014; Vervoort et al., 2011, 2008). The facial expression of pain is a powerful means of communicating painful feelings which can easily capture the attention of the significant other, and would be expected to attract

necessary support for the pain sufferer (Botvinick et al., 2005; Eritz and Hadjistavropoulos, 2011). In this regard, heightened facial display of pain may serve as a trigger for empathy and social support from significant others, and thus bears evolutionary significance (Williams, 2002).

We also found increased physiological responses to pain in the presence of a friend (Fig. 10B). This finding is consistent with the heightened facial expression of pain (Gallant and Hadjistavropoulos, 2017; Karmann et al., 2014; Vervoort et al., 2011, 2008). McClelland and McCubbin (2008) suggested that in the presence of a significant other, the pain recipient may increase physiological arousal to elicit desirable social responses. Their results indicated that the increase in arousal occurred in the absence of visual interactions with the social partner, which can otherwise play a critical role in eliciting an empathetic response (Williams, 2002). On the other hand, this finding is contradictory to evidence that physical presence of a friend can

A. Verbal support: pain outcomes



B. Stranger verbal support: pain outcomes

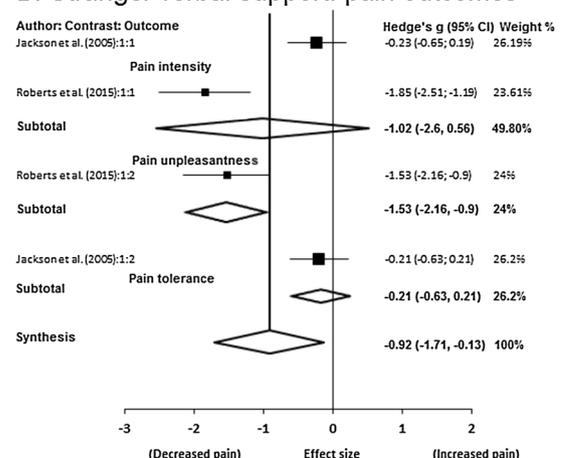


Fig. 5. Forest plot of the Hedge's adjusted g analysis for the effects of verbal support on behavioural pain outcomes.

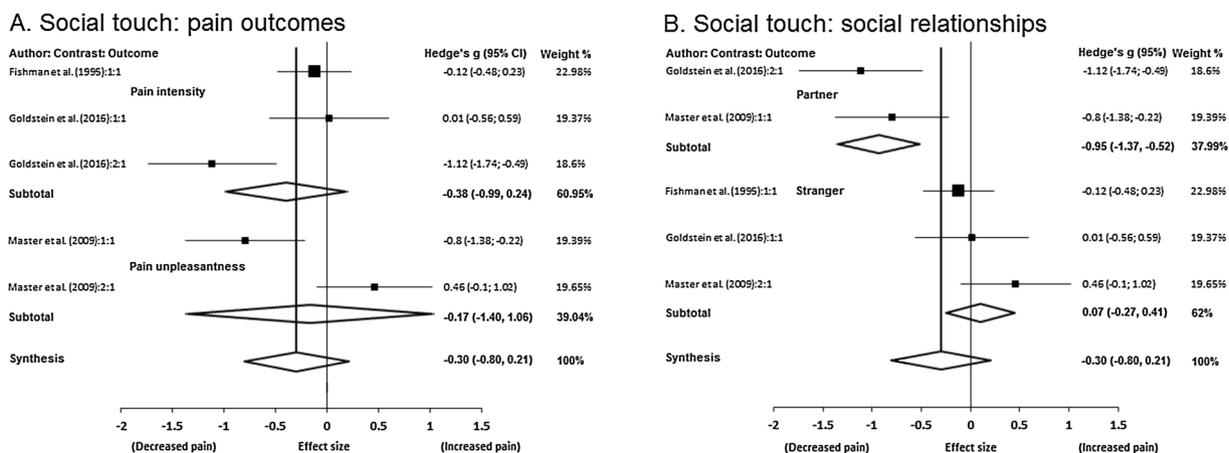


Fig. 6. Forest plot of the Hedge's adjusted g analysis for the influence of social touch on behavioural pain outcomes.

suppress physiological arousal to psychosocial stressors, for example, an arithmetic task or public speech (Fontana et al., 1999). It is possible that stress type plays a role in this discordance. Inserting hand into iced water for two minutes composes a direct threat to the body in which individuals may need help from the significant other (McClelland and McCubbin, 2008). Meanwhile, individuals may be less aroused and more capable of coping with a moderate social-evaluative threat with the presence of a close other (Fontana et al., 1999).

Our results demonstrate that the presence of a stranger did not influence pain perception or expression (Fig. 4B). Some studies have shown that the presence of a stranger is associated with decreased pain (Edwards et al., 2017; Gallant and Hadjistavropoulos, 2017; Karmann et al., 2014; Kleck et al., 1976). It has been proposed that individuals tend to display and report less pain to an unfamiliar other as pain expression could be 'inappropriate' and may indicate 'vulnerability' (Brody, 2000; Craig, 2009; Underwood et al., 1992). Moreover, individuals are reluctant to show excessive pain as they may not receive desirable responses from an unpredictable stranger (Gallant and Hadjistavropoulos, 2017; Williams, 2002). However, another line of research has demonstrated no impact of stranger presence on pain (Modić Stanke and Ivanec, 2010; Roberts et al., 2015). The authors argued that stranger presence is not sufficient to communicate social support (Roberts et al., 2015), and that decreased pain perception or display could be the outcome of socially desirable behaviour that was minimised in their protocol (Modić Stanke and Ivanec, 2010). Nevertheless, these findings are not mutually exclusive and they suggest the need for controlling social desirability bias in support and pain research.

In addition, other social and temperament factors may also play a

role in the social presence effect of pain. There is evidence that stranger presence may signal 'safety' in the reduction of pain and related threat. But this effect was only observed in a high threatening context (Vlaeyen et al., 2009). Further evidence has suggested that the effects of stranger presence can be determined by attachment style. Specifically, individuals with high attachment avoidance reported more pain in the presence of a stranger than in absence (Sambo et al., 2010). Avoidant individuals tend to mistrust social relationships (Bowlby, 1969; Feeney and Noller, 1990; Main, 2000). Their preference for independence may be associated with increased anxiety in the presence of a total stranger, which may in turn increase pain perception (Sambo et al., 2010). Moreover, pain catastrophising may modulate the influence of social support. In the presence of a stranger, high pain catastrophisers expressed more pain and used fewer coping strategies that might minimise pain (Sullivan et al., 2004). These findings highlight the complexities of stranger presence in pain perception and display.

Interestingly, physiological responses were reduced in the context of stranger presence (Fig. 10B), in contrast to the presence of a close other which tended to increase arousal. Stranger presence has been repeatedly reported to decrease physiological arousal to painful stimuli (Kleck et al., 1976; Sambo et al., 2010), as well as to other psychosocial stressors (Fontana et al., 1999; Lepore, 1995; Lepore et al., 1993). However, it is interesting to find that decreased arousal did not necessarily translate into pain reduction. One possibility is the lack of perceived support in the presence of a stranger (Roberts et al., 2015). Indeed, the effect of social support on pain is modulated by the extent to which the participant could perceive the social partner as helpful (Krahé et al., 2013). Therefore, knowing that someone is present is sufficient to buffer physiological arousal; but pain reduction relies on

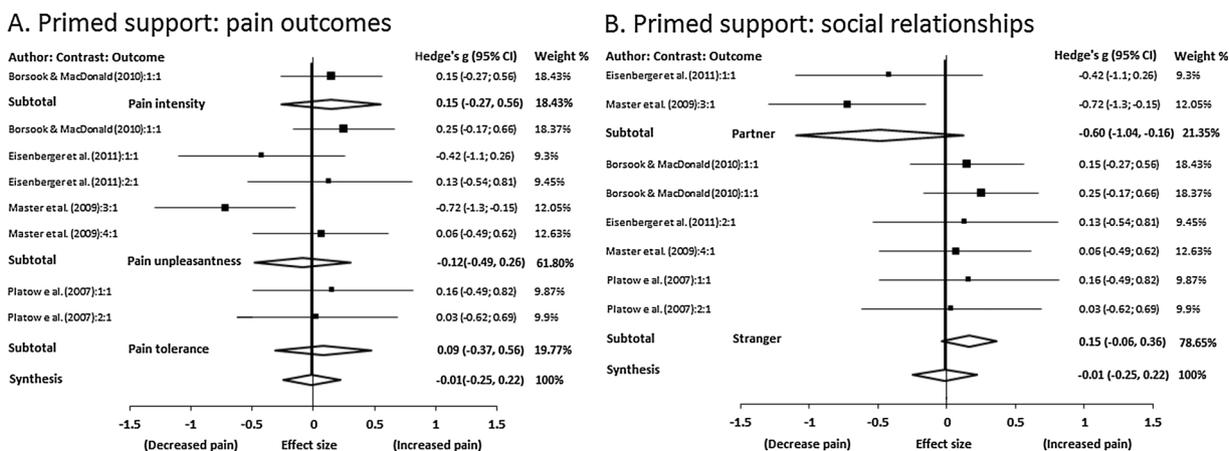


Fig. 7. Forest plot of the Hedge's adjusted g analysis for the effects of primed support on behavioural pain outcomes.

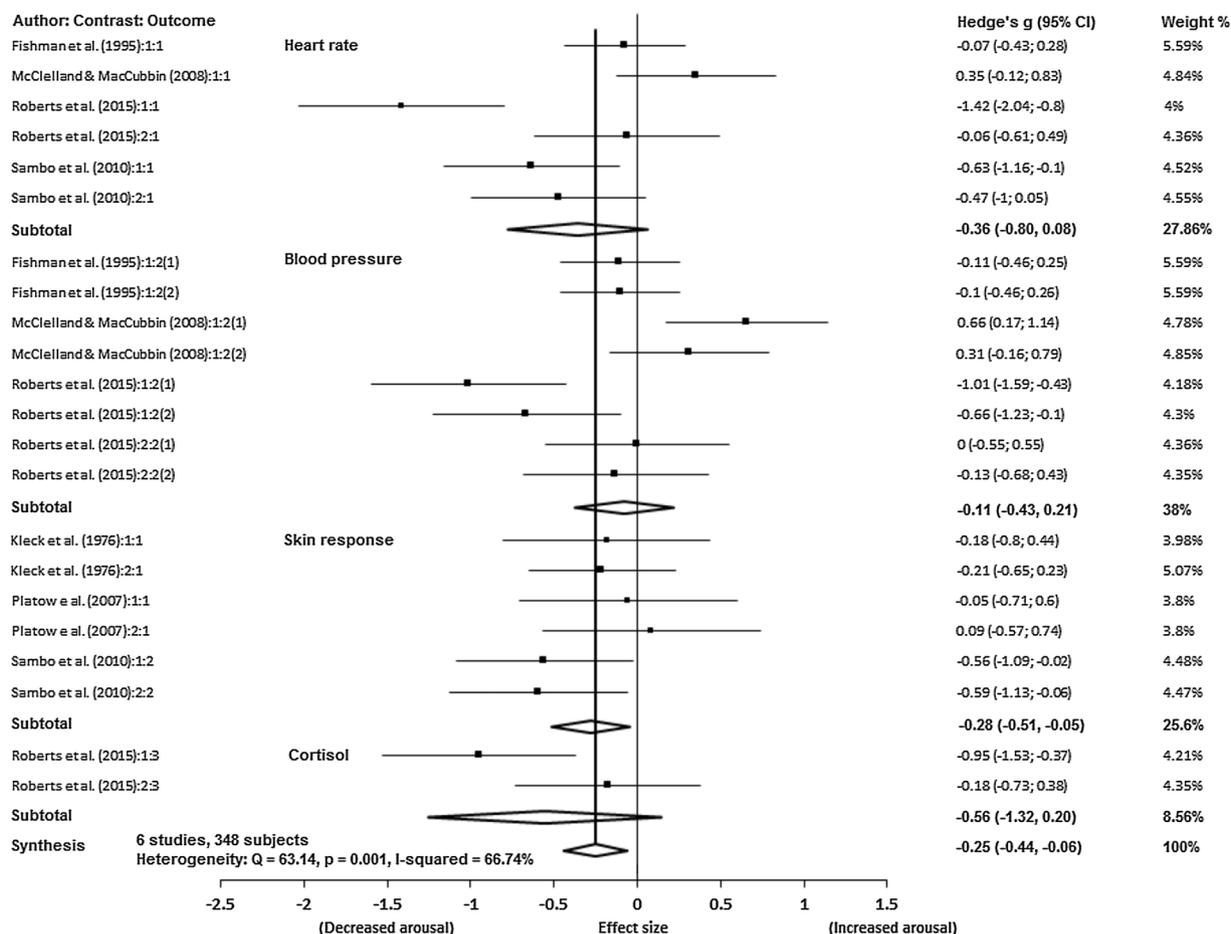


Fig. 8. Forest plot of the Hedge's adjusted g analysis for pooled effects of social support on physiological outcomes.

not only the physical presence but also the level of perceived support from the social partner.

4.2. Verbal support

In contrast to social presence, our data showed that verbal support decreased overall pain experience (Fig. 5A). In a systematic review, Krahé et al. (2013) suggested an analgesic influence of verbal communication when it is positive and structured (i.e. pre-determined verbal elements and interactions) (Brown et al., 2003; Chambers et al., 2002; Jackson, 2007; Roberts et al., 2015). However, uninstructed (i.e. not pre-determinant, random) verbal communications were related to increased pain (Brown et al., 2003). Here the majority of the data centred on positive and structured verbal support. Our results thus corroborate the findings of the systematic review (Krahé et al., 2013). Interestingly, most of the data were derived from verbal support from a stranger which reduced pain with a large effect size (SMD = -0.92) (Fig. 5B). Moreover, this effect was most prominent among females (Jackson et al., 2005; Roberts et al., 2015). Findings together suggest that verbal support, at least from a stranger, can communicate support and reduce pain, especially in female pain recipients.

Our results also suggest that verbal support may buffer physiological arousal in the reduction of pain (Fig. 11A). Although this finding is only based on one study, it did assess multiple physiological responses. Nevertheless, more studies are required in this area. Moreover, these results are consistent with recent evidence which emphasises the significance of intimacy and emotion regulation (Cano and Williams, 2010). Specifically, verbal communication and validations may serve to increase intimacy and/or healthy emotion regulation, which may in turn result in a decrease in pain and perceived threat (Corley et al.,

2016; Leong et al., 2015). Moreover, the stress-buffering effect of verbal support is enhanced by oxytocin (Heinrichs et al., 2003), a neuropeptide that promotes intimacy and social interaction (Carter, 1998; McCarthy and Altemus, 1997; Uvnäs-Moberg, 1998). Overall, our findings suggest that the analgesic effects of verbal support may be modulated by availability or levels of oxytocin that buffers physiological arousal to pain.

It is noted that studies categorised under verbal support may provide somewhat different forms of support. In some studies, the social partner verbally encouraged the participant to engage in the pain task (Brown et al., 2003; Roberts et al., 2015), while in another study the social partner was not allowed to initiate any interaction but answer the questions of the participant in an empathetic fashion (Jackson et al., 2005). These types of social interaction may result in varied perceived social support by the one in pain and therefore have different effects on pain experience. Here we averaged them for the purpose of a meta-analysis. Future studies are warranted to investigate the effects of different aspects of verbal support.

4.3. Social touch

Social touch did not influence overall pain ratings (i.e. intensity, unpleasantness) (Fig. 6A). However, the effects of social touch were strongly influenced by pre-existing social connectedness. Analgesic effects of social touch were evident with touch by a romantic partner but not by a stranger (Fig. 6B). Although based on a small number of studies, these findings highlight the importance of intimacy in communicating support and reducing pain. Indeed, human touch communicates distinct emotions (Hertenstein et al., 2006). Holding the hand of a romantic partner is suggested to promote intimacy between couples

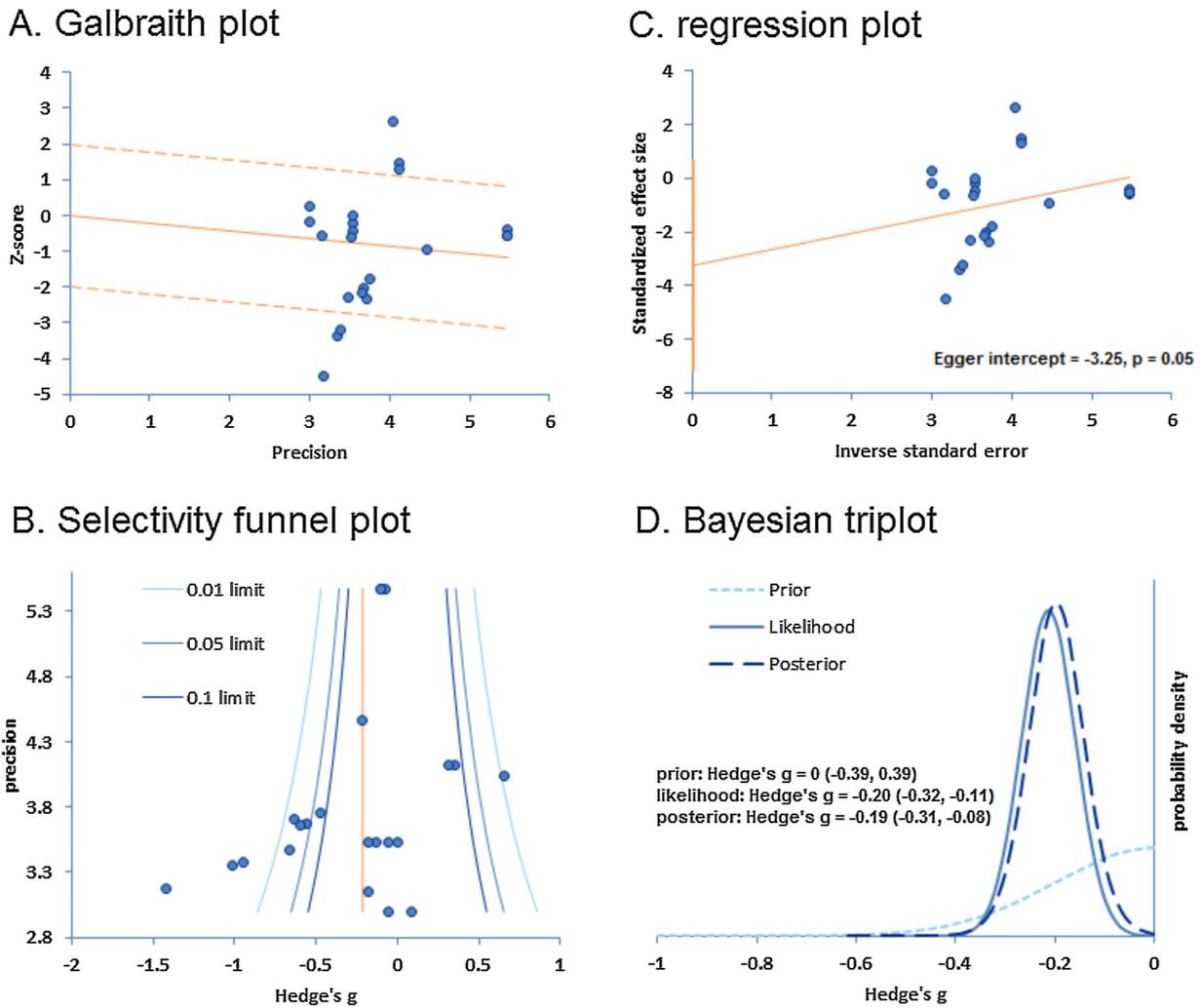


Fig. 9. Series of tests for heterogeneity and publication bias for the influence of social support on physiological outcomes. (A) Galbraith plot suggested heterogeneity with more than 5% of the data beyond two standard errors of the population effect. (B) Selectivity funnel plot indicated publication bias with studies showing asymmetry around the estimated effect. (C) Regression plot suggested publication bias with the intercept deviated from 0 ($p = 0.05$). (D) Bayesian triplot indicated publication bias with the likelihood effect size (-0.20) smaller than the estimated effect size (-0.25).

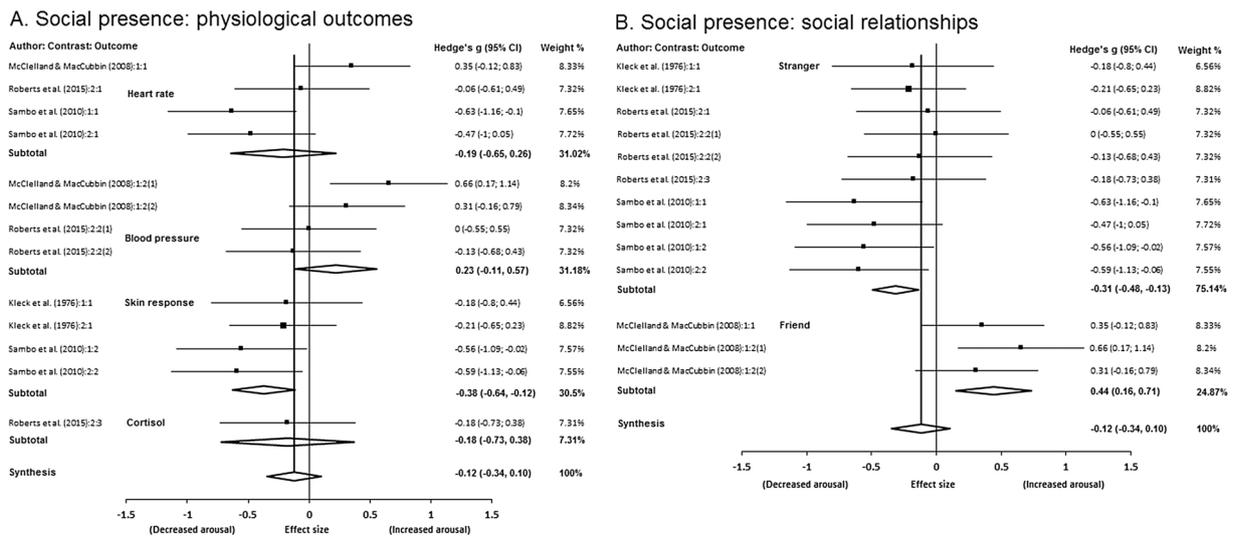
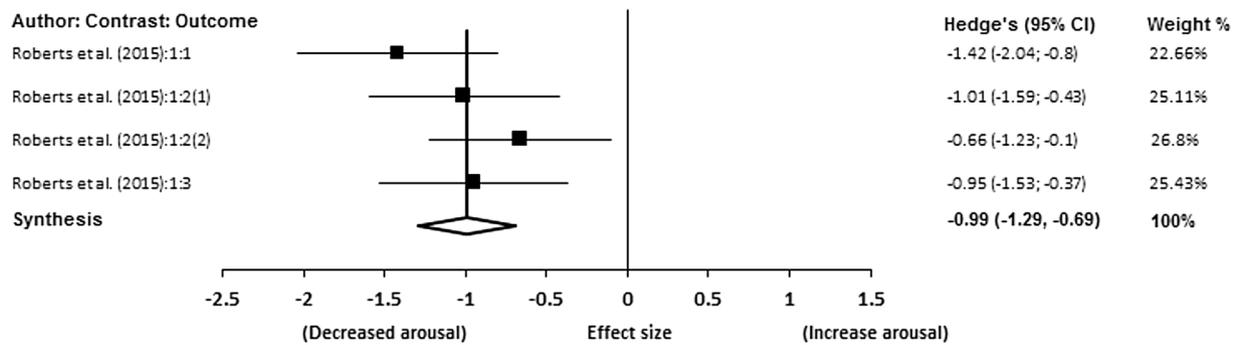


Fig. 10. Forest plot of the Hedge's adjusted g analysis for the effects of social presence on physiological outcomes.

A. Verbal support



B. Social touch

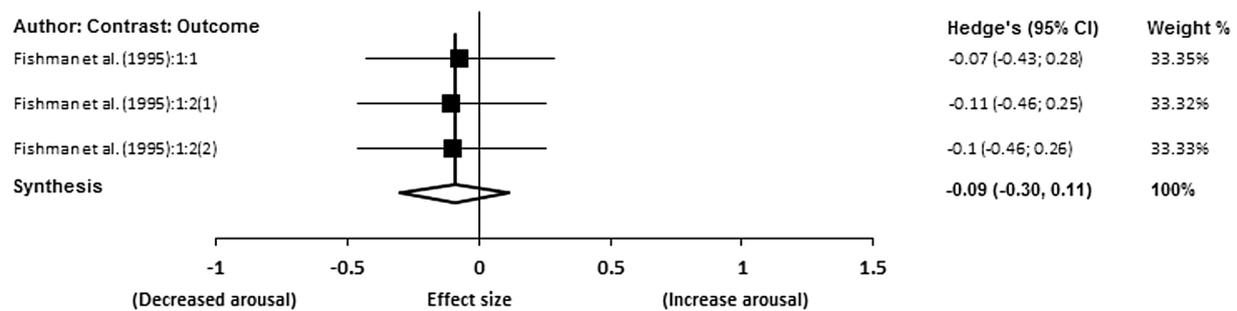


Fig. 11. Forest plot of the Hedge's adjusted *g* analysis for the influence of verbal support and social touch on physiological outcomes.

(Goldstein et al., 2016, 2017; Master et al., 2009). On the contrary, holding hand by a stranger may be somewhat socially uncomfortable for both partners and thus associated with mixed results (Krahé et al., 2013).

Recent advances in neurobiological research have enriched our understanding of the mechanisms behind social touch. Although physiological arousal to pain was decreased by stranger touch (Fishman et al., 1995), the effect size was small and did not reach significance (Fig. 11B). Meanwhile, social touch by the romantic partner attenuated bodily arousal and threat-related brain activation (e.g. ventral anterior cingulate cortex) to painful stimuli (Coan et al., 2017, 2006). Close other hand-holding is also associated with decreased heart rate and threat-related theta oscillation in high threatening contexts (Che et al., 2017). These findings together indicate the role of intimate social touch in buffering neural and physiological threatening responses to pain. Moreover, intimate social touch has been shown to increase the inter-partner coupling of respiration and heart rate during pain, which was suggested to promote the communication of emotions (Goldstein et al., 2017). Therefore, social touch from a significant other may be associated with neurophysiological processes supporting emotional interaction, stress control, and pain reduction.

4.4. Primed support

In a similar manner to social touch, our data also demonstrated no changes in overall pain by primed support (e.g. image-viewing) (Fig. 7A). However, viewing images of a romantic partner was associated with pain relief in healthy individuals (Fig. 7B). Moreover, this finding has been extended into people with chronic pain, in which images of a loved one were rated the most pleasant and were associated with the greatest pain reduction (Shaygan et al., 2017). These studies suggest that the effects of primed support, where present, are strongly determined by relationship quality. Functional imaging studies have

explored the neural correlates of this effect. One study found that the analgesic effect of partner image-viewing was associated with reward-related neural activation (e.g. orbitofrontal cortex) (Younger et al., 2010). Moreover, partner images may be interpreted as safety stimuli (e.g. ventromedial prefrontal cortex) that in turn decrease pain and threat response (Eisenberger and Cole, 2012; Eisenberger et al., 2011). This argument has been corroborated by recent studies in which social support images could serve as prepared safety stimuli to attenuate conditioned fear response (i.e. skin response) (Hornstein and Eisenberger, 2017; Hornstein et al., 2016, 2017). Therefore, viewing an image of a significant other may prime safety or attachment feelings which have analgesic effects.

It is noted that partner hand-holding and image-viewing both decreased pain. Unlike the presence of a social partner, our results support that holding the hand or viewing images of an intimate partner can provide social support to an individual in pain. This is proposed to occur through an increase in attachment and emotional interactions (Eisenberger et al., 2011; Goldstein et al., 2017). However, limited conclusions can be made here as the findings are based on two studies under each category, which clearly indicates the need for more studies to determine the consistency of effects. Moreover, these two variants of support may rely on different mechanisms to decrease pain. Initial evidence suggests a mechanism of emotional communication and stress buffering in the context of intimate social touch (Che et al., 2017; Goldstein et al., 2017). A more recent study found that intimate social touch increased brain-to-brain coupling of alpha power mainly over the central cortical regions between romantic couples. The authors proposed that this may result from sensory integration from tactile, visual, and nociceptive inputs (Goldstein et al., 2018). In contrast, intimate image-viewing is thought to prime attachment feelings involved in the prefrontal cortex (Eisenberger et al., 2011; Younger et al., 2010). It would be interesting for future studies to directly compare and contrast the effects of these two types of social support during pain.

Personal and interpersonal variables may modulate the receipt and provision of social support in the influence on pain. Some characteristics of the support recipients, e.g. attachment style and pain catastrophising, have been demonstrated to modulate the social presence effect on pain (Sambo et al., 2010; Sullivan et al., 2004). However, it remains unknown whether other related characteristics also play a role in the social modulation of pain. There is evidence that individuals who are more prone to rely on others, or lower in neuroticism, tend to benefit more from social support (Park et al., 2013). Moreover, characteristics of the social partner may also influence the provision of support. For example, individuals with higher dispositional empathy may be more willing to provide social support to others (Trobst et al., 1994). Future investigations should therefore explore the characteristics of both the individual providing support and the person experiencing pain.

4.5. Publication bias

The presence of publication bias can affect the results of a meta-analysis. We therefore used several methods to test publication bias in this study. There was no clear evidence of publication bias in the behavioural dataset, although we observed a trend towards significance (Fig. 3). This is probably due to the ‘true heterogeneity’ (Sterne et al., 2011), in which a few studies (i.e. potential outliers) reported relatively larger analgesic effects of verbal support (Roberts et al., 2015) and partner hand-holding (Goldstein et al., 2016) among most of the studies of social presence. It suggests the different effects of social support variants and the need for more studies evaluating verbal support and intimate hand-holding. However, we did observe a possibility of publication bias in the physiological dataset (Fig. 9). It is possible that potential variables were confounding the results, e.g. sample sizes in each study, and the total number of studies. Moreover, publications from languages other than English were omitted here which might contribute to publication bias.

4.6. Limitations

Some limitations should be considered when interpreting the results of this study. Sample sizes varied in different analyses and they were small in certain subgroup analyses, e.g. close other social touch. This could influence the effect size and statistical significance. Further, the control condition in some studies may be different from the experimental condition in terms of multisensory integration beyond the proposed difference in social support, e.g. no touch versus social touch (Krahé et al., 2013). Moreover, some studies have suggested a gender difference in the social support effect of pain (Chambers et al., 2002; Jackson et al., 2005). Here we did not find an overall effect of gender on the social presence effect (see *Supplementary Material S2*). Due to the limited data, we did not statistically examine the gender differences in other types of social support. However, the analgesic influence of partner hand-holding (Fig. 6B), partner image-viewing (Fig. 7B), and stranger verbal support (Fig. 5B) was behaviourally more prominent in females. Future research is therefore warranted investigating gender effects in social support and pain. Some studies have also suggested other possible covariates beyond the support variations and relationship quality, e.g. attachment style (Krahé et al., 2015), and pain catastrophising (Sullivan et al., 2004). We did not exclusively quantify these covariates as of the limited data. In addition, neural imaging studies were not reviewed quantitatively due to the limited number of studies.

4.7. Future directions

Results of this study also provide insights for future studies. Oxytocin is suggested to increase the stress-buffering effect of verbal support (Heinrichs et al., 2003). However, no study has exclusively examined the role of oxytocin in the analgesic influence of social

support, despite oxytocin being linked to both analgesia (González-Hernández et al., 2014; Paloyelis et al., 2016) and to social support (Heinrichs et al., 2003) independently. Moreover, while social touch is associated with higher level of oxytocin (Holt-Lunstad et al., 2008; Light et al., 2005), it remains to be determined if this effect is common across other forms of social support. Further research is needed to investigate the role of oxytocin and other stress hormones in support and pain research, e.g. glucocorticoids (Wittig et al., 2016), and epinephrine (Wirtz et al., 2006). Finally, two recent studies have assessed the inter-partner coupling of neural and physiological responses that may be involved in communicating emotions and reducing pain (Goldstein et al., 2018, 2017). These studies extend the current investigations to concurrent recordings of both partners in the social modulation of pain. However, more studies are needed to validate and extend these interesting findings.

5. Conclusions and implications

Social support has been documented to modulate pain and related arousal for several decades. In this study, we systematically quantified these effects and possible covariates. The mere presence of another person, although it may impact physiological arousal, was not found to be sufficient to reduce pain. However, we did identify social support to decrease pain when it is more clearly expressed, e.g. verbal communication, hand-holding. Our findings also highlight the significance of intimate relationships in pain reduction. Together, we provide comprehensive findings in which the context of social support can modulate pain as well as the magnitude and possible mechanisms underlying this effect.

Our results may also provide insights for the support therapies for chronic pain management (Abbasi et al., 2012; Keefe et al., 2004, 1996, 1999). Verbal support showed a medium effect size and it would be particularly effective at highlighting the positive and structured interactions between couples (Krahé et al., 2013) as well as verbal validations from the partner (Leong et al., 2015). Verbal interactions characterised by encouragement, reinterpretation, and emotional validation could be involved in training programs. Moreover, our results support that spousal intimacy could be an area of therapeutic focus (Eisenberger et al., 2011), potentially through mutual activities between couples. It may also important to clearly express intimacy in support therapies through nonverbal interactions, e.g. touch. Beyond pain research, our results also suggest a protective influence of social support on threat response, i.e. pain (Che et al., 2018), which therefore has an implication in coping with traumatic experiences (Richmond et al., 2018).

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Conflicts of interest

There are no other conflicts.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2018.07.005>.

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CHAPTER THREE

Potential Processes and Mechanisms

Manuscript

Che X., Cash R., Ng S.K., Fitzgerald P., & Fitzgibbon B.M. (2018). A systematic review of the processes underlying the main and the buffering effect of social support on the experience of pain. *Clinical Journal of Pain*, 34, 1061-1076.

Preamble to systematic review

The previous chapter provides a quantitative review of the social contexts and effect size in the social modulation of pain. However, the processes and mechanisms that link social support to pain reduction remain unknown. In a recent systematic review, Bernardes et al. (2017) argued that pain-related social support needs to be investigated within the scope of stress and coping process as social support has been shown to buffer the detrimental effects of stress on health outcomes.

This chapter aims to explore potential processes and mechanisms associated with social support effects on pain by systematically assessing the literature suggesting it holds a protective effect. Given the diversity of the literature (e.g. experimental versus clinical), a broad concept of “pain experience” is used which includes both physical (e.g. intensity, duration, disability) and psychosocial suffering (e.g. unpleasantness, negative mood, psychological, and social functioning). The literature is assessed in the context of the main and the buffering effect hypothesis, two primary models within general health literature to explain the association of social support and health outcomes. This chapter also provides a detailed examination of cognitive processes, behavioural responses, as

well as neural and physiological activities derived from pain research both in experimental and clinical settings.

A Systematic Review of the Processes Underlying the Main and the Buffering Effect of Social Support on the Experience of Pain

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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 (2/4 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
(*Clin J Pain* 2018;34:1061–1076)

Pain is by definition an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage.¹ 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.^{2–5} In a recent proposed update, the definition of pain was suggested to further include a social component.⁶ 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.^{7,8} 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.^{9–12}

Social support refers to the perception or experience that one is loved and cared for by others.¹³ 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.^{14–16} A number of studies have reported that social support is associated with decreased pain experience in clinical settings.^{17–20} 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,^{9,12,21–24} the presence of others,^{5,25–27} or simply reminding individuals experiencing pain of their social connections.^{12,28–30} However, there is also evidence suggesting that social support can increase^{31,32} or provide no influence on pain,^{10,33} 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).^{34,35} 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.³⁶ 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.³⁷ Another perspective, the intimacy model, argues that communication of pain may serve to enhance intimacy between couples.³⁸ According to the first 2 models, however, social support as a type of positive response would increase pain expression. Meanwhile, although the intimacy

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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 processes 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).³⁹ 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,⁴⁰ 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 al²⁶) 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.^{42,43} 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 by definition 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,

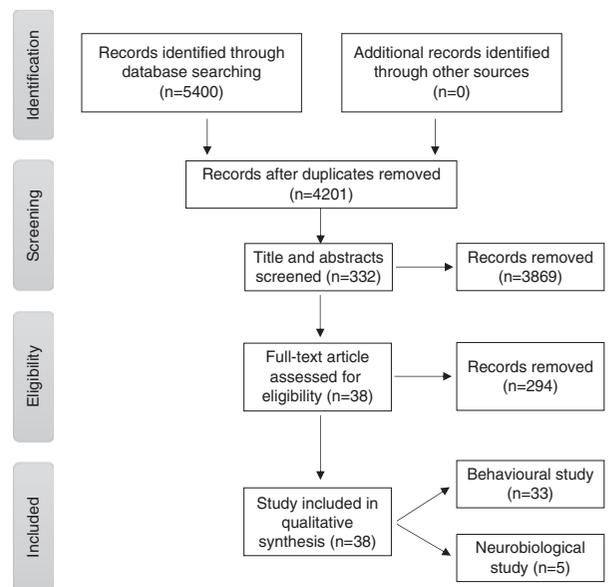


FIGURE 1. Flow diagram of selected studies (n = number of articles).

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 was associated with reduced 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 showed a protective effect on pain experience through the influence on stress. Specifically, where the data supported an interaction/moderation model whereby the support×stress interaction term is related to decreased pain experience. Alternatively, where the data supported a mediation model where social support is linked to decreased stress that in turn reduces pain experience.^{5,20}

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 objects⁵³; (2) studies were included if they assessed the experience related to physical pain and excluded if they investigated other types of pain (eg, social-exclusion pain⁵⁴); (3) studies were included if they reported protective effect and excluded if they reported adverse or no influence of social support on pain experience^{55,56}; (4) 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^{9,12}; (5) 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.⁵⁷ The assessment criteria has been used to review the influence of social support on chronic pain.^{57,58} The criteria was developed by combining the guidance on quality assessment with a number of review articles in the area of chronic pain.⁵⁹⁻⁶¹ 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.⁴² 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.⁴⁰ 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.⁵⁷ 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

References	Sample	Type of Social Support	Cognitive/Behavioral Variable	Pain Experience	Findings	Study Design (CS/CH)	Quality	Effect
<i>Stress (physical suffering)</i>								
Brown et al ¹⁷	Patients with RA (N = 233)	Emotional support	Pain	Depression	1. The negative correlation of emotional support and depression was strengthened when pain was included. 2. Moderating effect of emotional support was not found over a 6-month period	CS CH	Medium Medium	Buffering Main
Revenson et al ⁶²	Patients with RA (N = 101)	Received positive support	Pain severity	Depression	1. Received positive support predicted reduced depression without interacting with pain severity	CS	High	Main
Penninx et al ⁴⁰	Older people without chronic disease (N = 719); with mild arthritis (N = 612); with severe arthritis (N = 359)	Presence of a partner; close social relationships; diffuse social relationships; emotional support	Arthritis	Psychological functioning; depressive symptoms	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	CS CS CS CS	Low Low Low Low	Main Main Buffering Buffering
Feldman et al ⁶³	Patients with reflex sympathetic dystrophy syndrome (N = 109)	Perceived social support	Pain	Depressed mood	1. Previous day' support interacted with previous day' pain to predict present day' depressed mood	CH	Low	Buffering
Telfair and Gardner ⁶⁴	Adolescents with sickle cell disease (N = 79)	Group satisfaction	Pain	Psychological well-being (anxiety; depression)	1. Group satisfaction interacted with high pain to predict high psychological well-being	CS	Medium	Buffering
Riemsma et al ⁵⁰	Patients with RA (N = 197)	Positive support	Pain	Depression	1. Positive support predicted reduced depression without interacting with pain	CS	High	Main
Cano et al ¹⁸	Chronic musculoskeletal pain patients (N = 110)	Marital satisfaction	Pain	Depressive symptoms	1. Marital satisfaction predicted reduced depressive symptoms without interaction with pain	CS	Low	Main
Ferreira and Sherman ⁶⁵	Older adults with osteoarthritis (N = 73)	Perceived social support	Pain	Depressive symptoms	1. Perceived social support mediated the impact of pain on depressive symptoms	CS	High	Buffering
Holtzman and DeLongis ⁶⁶	Patients with RA (N = 69)	Morning satisfaction with spousal response	Morning pain severity	Evening pain catastrophizing	1. Morning satisfaction with spousal response interacted with morning pain severity to predict evening pain catastrophizing	CS	Low	Buffering
López-Martínez et al ²⁰	Chronic pain patient (N = 117)	Perceived social support	Pain intensity	Depressed mood; functional impairment; functional status	1. Decreased pain intensity mediated the relationship between perceived social support and decreased depression. 2. Decreased pain intensity mediated the relationship between perceived social support and decreased functional impairment. 3. Decreased pain intensity mediated the relationship between perceived social support and increased functional status	CS CS CS	High High High	Buffering Buffering Buffering

(Continued)

TABLE 1. (continued)

References	Sample	Type of Social Support	Cognitive/Behavioral Variable	Pain Experience	Findings	Study Design (CS/CH)	Quality	Effect
Morgan et al ⁶⁷	Cancer patients with pain (N = 177 dyads)	Partner support	Pain	Quality of life	1. Partner support mediated the negative impact of pain on quality of life	CS	Medium	Buffering
Sturgeon et al ⁶⁸	Chronic pain patients (N = 675)	Satisfaction with social roles	Pain intensity	Depression and anger	1. Satisfaction with social roles mediated the negative impact of pain intensity on depression. 2. Satisfaction with social roles mediated the negative impact of pain intensity on anger	CS CS	Medium Medium	Buffering Buffering
Lee et al ¹⁹	Chronic arthritis pain patients (N = 299)	Tangible social support	Arthritis pain	Depressive symptoms	1. Tangible social support interacted with arthritis pain to predict less depressive symptoms	CH	Low	Buffering
Park et al ⁶⁹	Older adults	Social support	Pain intensity	Depressive symptoms	1. Social support interacted with pain intensity to predict depressive symptoms	CS	—	Buffering
<i>Stress (functional disability)</i>								
Affleck et al ⁷⁰	Patients with RA (N = 129)	Satisfaction with support	Functional disability	Psychosocial adjustment to illness	1. The positive relation between support satisfaction and psychosocial adjustment was increased when disability was included	CS	Medium	Buffering
Fitzpatrick et al ⁷¹	Patients with RA (N = 158)	Social relationship	Disability	Psychological well-being (depression; self-esteem)	1. Social relationship had direct, favorable effect on psychological well-being without interacting with disability	CS	Low	Main
Goldberg et al ⁷²	Male chronic pain patients (N = 105)	Spousal support	Pain-related interference	Depression	1. Spousal support interacted with pain-related interference to predict depression	CS	High	Buffering
Riemsma et al ⁵⁰	Patients with RA (N = 197)	Positive support	Physical function	Depression	1. Positive support predicted reduced depression without interacting with physical function	CS	High	Main
Cano et al ¹⁸	Chronic musculoskeletal pain patients (N = 110)	Marital satisfaction	Physical disability	Depressive symptoms	1. Marital satisfaction predicted reduced depressive symptoms without interacting with physical disability	CS	Low	Main
Strating et al ⁷³	Patients with RA (N = 129)	Emotional support satisfaction; satisfaction with social companionship	Impairment-disability	Distress	1. Emotional support satisfaction predicted reduced distress without interaction with impairment-disability in short-term RA. 2. Satisfaction with social companionship predicted reduced distress by interacting with impairment-disability in short-term RA. 3. This interaction disappeared in long-term RA	CH CH CH	Medium Medium Medium	Main Buffering Main
<i>Stress (stressful response of close other)</i>								
Kerns et al ⁷⁴	Chronic pain patients (N = 106)	Marital satisfaction	Spousal punishing response	Depressive symptoms	1. Marital satisfaction interacted with higher spousal punishing response to predict lower depressive symptoms	CS	Low	Buffering
Revenson et al ⁶²	Patients with RA (N = 101)	Received positive support	Stressful response	Depression	1. Received positive support interacted with high stressful response to predict reduced depression	CS	High	Buffering
Cano et al ⁷⁵	Chronic pain patients (N = 165)	Marital satisfaction	Negative spousal response	Depressive symptom	1. Marital satisfaction mediated the positive relationship between negative spousal response and depressive symptom	CS	Low	Buffering

(Continued)

TABLE 1. (continued)

References	Sample	Type of Social Support	Cognitive/Behavioral Variable	Pain Experience	Findings	Study Design (CS/CH)	Quality	Effect
Riemsma et al ⁵⁰	Patients with RA (N = 197)	Positive support	Stressful response	Depression	1. Positive support interacted with stressful response to predict depression	CS	High	Buffering
Cano et al ¹⁸	Chronic musculoskeletal pain patients (N = 110)	Marital satisfaction	Negative spousal response	Depressive symptoms	1. Marital satisfaction predicted reduced depressive symptoms without interaction with negative spousal response	CS	Low	Main
Raichle et al ⁷⁶	Chronic pain patients (N = 94)	Marital satisfaction	Negative spousal response	Depression	1. Marital satisfaction predicted reduced depression directly, without interacting with spousal negative response	CS	High	Main
Rosen et al ⁷⁷	Patients with provoked vestibulodynia (N = 175 couples)	Dyadic adjustment	Spousal negative response	Sexual satisfaction	1. Dyadic adjustment mediated the adverse impact of negative spousal response on sexual satisfaction	CS	High	Buffering
<i>Stress (other negative life events)</i>								
DeLongis et al ⁷⁸	Married couples (N = 75)	Emotional support	Negative life events	Symptoms (headache; backache; flu; sore throat); mood	1. Emotional support was negatively related to hassle-next day symptoms association. 2. Emotional support was negatively related to hassle-same day mood association. 3. Emotional support was not related to hassle-same day symptoms association. 4. Emotional support was not related to hassle-next day mood association.	CH CH CH CH	High High High High	Buffering Buffering Main Main
Weinberger et al ⁷⁹	Patients with osteoarthritis (N = 439)	Social support	Negative life events	Functional status (psychological disability; physical disability; pain)	1. Social support had direct, favorable effect on functional status, without interaction with daily hassle	CS	High	Main
Affleck et al ⁸⁰	Patients with RA (N = 74)	Social support	Negative life events	Mood disturbance	1. Social support interacted with daily stressor to predict next day mood disturbance	CH	Medium	Buffering
Alonso and Coe ⁸¹	Healthy women (N = 184)	Access to support providers	Distress (anxiety; depression)	Menstrual pain	1. Access to support providers interacted with distress to predict menstrual pain	CS	Low	Buffering
Pekkarinen et al ⁸²	Female geriatric nurses (N = 975)	Social support	Physical workload	Musculoskeletal symptoms	1. Social support interacted with physical workload to predict musculoskeletal symptoms	CS	Medium	Buffering
<i>Stress appraisal (perceived threat/coping ability)</i>								
Waltz et al ⁸³	Clinical pain patients (N = 234)	Emotional support; social interaction	Psychological functioning (reduced RA helplessness; sense of mastery; self-esteem, etc.)	Pain	1. Psychological functioning mediated the protective influence of emotional support on pain 2. Psychological functioning mediated the protective influence of social interaction on pain	CH CH	High High	Buffering Buffering
Kerns et al ⁸⁴	Chronic pain patients (N = 234)	Pain-related support	Low self-appraised problem-solving competence	Depressive symptoms	1. Pain-related support interacted with low problem-solving competence to predict depressive symptoms	CS	High	Buffering

(Continued)

TABLE 1. (continued)

References	Sample	Type of Social Support	Cognitive/Behavioral Variable	Pain Experience	Findings	Study Design (CS/CH)	Quality	Effect
Holtzman and DeLongis ⁶⁶	Patients with RA (N = 69)	Morning satisfaction with spousal response	Morning pain catastrophizing	Evening negative affect; evening pain intensity	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	CS CS	Low Low	Buffering Main
Vlaeyen et al ⁵	Healthy participants (N = 149)	Social presence	Perceived threat of cold pain	Pain intensity; facial expression of pain	1. Perceived threat mediated the inhibitory effect of social presence on pain intensity. 2. Perceived threat mediated the inhibitory effect of social presence on facial expression of pain	CS CS	Medium Medium	Buffering Buffering
Corley et al ⁸⁵	Healthy couples (N = 134 dyads)	Global relationship satisfaction; situational relationship satisfaction after 2-minute interaction	Threat manipulation of cold pain	Pain intensity	1. Global relationship satisfaction predicted less pain without interacting with threat manipulation. 2. Situational relationship satisfaction predicted less pain in the low threat condition	CS CS	Low Low	Main Buffering
<i>Active coping</i> Manne and Zautra ⁴⁹	Women with RA (N = 103)	Spousal support	Coping with RA (information seeking; cognitive restructuring)	Psychological adjustment	1. Adaptive coping mediated the positive relationship between spousal support and better psychological adjustment	CS	High	Buffering
Holtzman et al ¹¹	Patients with RA (N = 73)	Morning satisfaction with social support	Morning coping with RA (stoic distancing)	Evening pain severity	1. Morning satisfaction with social support interacted with increased stoic distancing to predict reduced evening pain severity	CS	Low	Buffering
López-Martínez et al ²⁰	Chronic pain patient (N = 117)	Perceived social support	Active coping with pain	Depressed mood; pain intensity	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	CS CS	High High	Main Main

Buffering means the buffering effect and main means the main effect. CH indicates cohort study; CS, cross-section study; RA, rheumatoid arthritis.

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 ways⁵⁰ (“Stress” sections in Table 1).

First, physical suffering means the severity and frequency of painful episodes as well as related unpleasantness.⁸⁶ Physical suffering causes stress for individuals with chronic pain and is associated with increased functional impairment and depression.^{20,40} 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

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 depression^{18,50,62} 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} 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,⁸⁰ and healthy populations.⁴⁸ Negative life events may take the form of specific distress, for example, workload⁸²; or cover multiple life domains.⁷⁸ Findings are inconsistent when negative life events are nonspecific. Three findings (3/8, 38%) showed that social support was able to interact with negative life events to predict decreased physical suffering or mood disturbance.^{78,80} But another 3 findings

(3/8, 38%) only observed the main effect of support without significant interaction with negative life events.^{78,79} 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 (2/8, 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.⁸¹

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.⁵ 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.⁶⁶

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.¹¹ 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.²⁰ 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.⁸⁹ 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 Material S2, Supplemental Digital Content 1, <http://links.lww.com/CJP/A510>). Across the statistical models, social support had a small impact on pain experience in both the main^{20,71}) 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 fibromyalgia reported lower pain sensitivity and pain ratings to tactile stimulation when they were accompanied by their significant 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 functional 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. Moreover, 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.⁹⁰

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 [dACC]) 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 (OFC) 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, OFC), 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 al²⁴ 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. Further analysis showed that perceived social support during cold pain was negatively associated with pain intensity, unpleasantness, and cortisol response.

DISCUSSION

Inspired by the evidence of support-assisted pain management therapies, the current review specifically explored the processes underlying the main and the buffering effect of social support on pain experience. Our review presented evidence 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 associated 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%).^{69,82} 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

References	Sample	Type of Social Support	Pain Induction Technique	Pain Experience	Findings
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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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. 2. Spousal and stranger hand-holding attenuated brain activation in threat-related regions relative to no hand-holding (vACC, PCC, supramarginal gyrus). 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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	<ol style="list-style-type: none"> 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.^{39,47} 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.^{11,20,49} 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 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.^{40,78} 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 also 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 support is not helpful. A direct, protective effect of social support on pain experience was thus observed. Moreover, the conceptualization and measure of social support are also critical. There is evidence suggesting that situational received support is able to buffer the influence of pain-related threat on pain intensity whereby global perceived social support has general analgesic effects irrespective of the level of threat.⁸⁵ However, other studies have shown that the effects of situational received support are inconsistent,¹⁵ but global perceived social support is a more consistent predictor of health outcome.^{15,16,39} It therefore remains an open question whether a particular type of social support is related to decreased pain experience by acting upon one process rather than another.

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,⁸⁵ reduced pain catastrophizing, and perceived incompetence of problem solving,^{66,84} 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 are in turn associated with pain reduction.⁹² 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.⁸³ 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.²⁰ This discrepancy might be due to the manner in which coping responses were categorized. Although López-Martínez et al²⁰ 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^{26,28,30,90} (Table 2).

These studies indicate that the influence of social support on pain is mainly mediated by decreased neural response to threat cues. The neurological response elicited by painful stimuli is thought to embody not only a direct sensory pain response, but in addition a threat response that is registered across other cortical and subcortical regions. For example, the activation of ACC and insula is also known to occur in response to impending threat.⁹⁴ Moreover, it has been suggested that activation of the hypothalamus is related to recruitment of the hypothalamus-pituitary-adrenal axis, which responds to a stressor and releases hormone cortisol for energy mobilization.⁹⁵ Given that activation of these areas is reduced by social support, social support may help to decrease the threatening nature of painful stimuli. This idea is further corroborated by the finding that social support is associated with less bodily arousal to painful stimuli, and that higher marital satisfaction predicts lower activation of insula and hypothalamus in response to painful stimuli.⁹⁰

Similarly, social support may elicit neural responses related to a feeling of "safety" during the experience of pain. Eisenberger et al²⁸ report that viewing an image of one's partner while experiencing pain produces greater activity in the VMPFC, a brain node associated with tracking the safety value of a stimulus.⁹⁶⁻⁹⁸ Greater activity in VMPFC in response to partner's picture is associated with decreased activation of ACC and insula, as well as with longer relationship length and greater perceived partner support. Another study showed that self-reported social support is associated with increased gray matter volume in the posterior cingulate cortex,⁹⁹ a brain region that responds to safety cues along with VMPFC.⁹⁴ These results suggest that social support may signal safety and thereby reduce threat-related neural and autonomic responses.¹⁰⁰⁻¹⁰² This is in line with

an earlier behavioral observation, which showed that social presence decreased pain by suppressing perceived threat of pain.⁵ 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.¹⁰³ 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 Eisenberger⁹⁵). Social support has been shown to suppress these physiological systems in the experience of a stressor.¹⁰⁴⁻¹⁰⁸ 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.^{24,109,110} 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.^{28,100} 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.⁵² Moreover, these patterns of cognition include both decreased perceived threat of pain and increased perceived coping ability.^{66,83} 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.^{24,28} 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

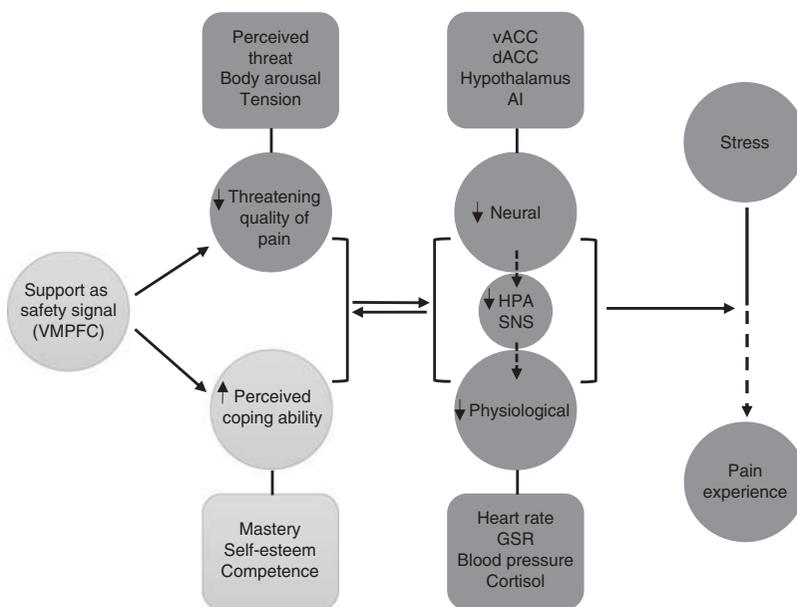


FIGURE 2. Social-buffering model of pain reduction. Social support decreases pain experience through modulating pain-related stress. This effect is associated with the stress appraisal process. Specifically, supportive resources can be interpreted by individuals with pain as safety signals in the VMPFC, which in turn decrease the threatening quality of pain and/or increase perceived ability to cope with pain. Moreover, this stress appraisal process is mediated by decreased neural and physiological stress systems. AI indicates anterior insula; dACC, dorsal anterior cingulate cortex; GSR, galvanic skin response; HPA, hypothalamus-pituitary-adrenal axis; SNS, sympathetic nervous system; vACC, ventral anterior cingulate cortex; VMPFC, ventromedial prefrontal cortex.

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).³⁰ Moreover, these brain areas are shown to have high densities of opioid receptors that have analgesic effects.^{111,112} Findings in this study are likely complementary to others^{28,90} 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 condition, have confirmed 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 interpret 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 stress 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.³⁹ 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 influences 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.¹¹⁶

CBT has been shown to result in significant improvements in physical suffering and mood in chronic pain conditions.^{117–120} As a modified CBT, support (usually spousal)-assisted coping skills training has included training components like communication skills, behavioral rehearsal, and mutual goal-setting.^{34,35,121} 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.^{15,100} 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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Note:

1. There was an error in the text. 'Therefore, it remain unclear the cognitive and behavioural variables linking a general overview of social support to decreased pain experience' should be changed to 'Therefore, the cognitive and behavioural variables linking a general overview of social support to decreased pain experience remain unclear'. *(Page 39, Line 3)*
2. 'Higher emotional support or social interaction' should be changed to 'Higher emotional support or more pleasurable social life activity'. *(Page 45, Line 36)*

CHAPTER FOUR

The Threat of Pain

Manuscript

Che X., Cash R., Fitzgerald P., & Fitzgibbon B.M. (2018). The social regulation of pain: autonomic and neurophysiological changes associated with perceived threat. *Journal of Pain*, 19, 496-505.

Preamble to empirical paper

Chapter 3 indicates that social support may reduce pain by modulating perceived threat of painful stimuli. However, previous studies have simultaneously assessed pain perception and the threat of pain, in which the buffering effect suffers from an indirect manner of examination (Eisenberger et al., 2011; Montoya et al., 2004; Younger et al., 2010).

This chapter aims to directly examine the buffering effect that may underpin the effect of social support on pain reduction. In the published manuscript, a novel experimental protocol is used to introduce 6-second continuous threat of pain leading up to painful stimulation in which the presence of social support is manipulated by holding the hand of a significant other. EEG and heart rate are used to evaluate neural and autonomic changes to the threat of pain. Neural and autonomic responses are analysed in the threat of pain phase and related to subsequent changes in pain perception. EEG source localization is performed to identify possible generators of neuronal oscillations and associate them to evidence from functional imaging.

This chapter significantly extends the literature by providing direct evidence that social support may reduce pain through buffering the autonomic and neurophysiological response to the threatening quality of noxious stimuli before the onset of painful stimuli. Moreover, findings in this chapter further indicate the particular significance of close relationship in reducing pain and related threat, and this effect is beyond a particular type of relationship but rather from a romantic partner, a family member, or a close friend.

Original Report

The Social Regulation of Pain: Autonomic and Neurophysiological Changes Associated With Perceived Threat

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Abstract: The analgesic effect of social support is proposed as a function of social support modulating perceived threat of painful stimuli. In the current study, we directly examined the social buffering effect in the context of the threat of pain. Eighteen healthy participants were subjected to the threat of pain while they held the hand of a close other, a stranger, or not at all. Neural and autonomic responses were recorded using electroencephalogram and heart rate, respectively. Close other hand-holding reduced pain perception. This was accompanied by decreased heart rate and frontal theta oscillation (4–8 Hz) during the threat phase preceding painful stimulation. Interestingly, decreased heart rate and frontal theta in the close other hand-holding condition were uniquely associated with greater pain reduction during subsequent nociceptive stimulation. Neural changes were source-localized to the insular cortex and the rostral-ventral portions of anterior cingulate cortex, regions involved in the processing of threat and pain. Together, our data build upon work to date linking social support to pain by showing autonomic and neurophysiological changes associated with pain reduction.

Perspective: Social support may reduce pain through buffering the autonomic and neurophysiological response to the threatening quality of noxious stimuli. Results implicate that in clinical settings the caregiver could help people with chronic pain reappraise pain and related conditions as less stressful.

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Key words: Social support, pain, stress, heart rate, theta oscillation.

Supportive relationships with others have substantial benefits for individuals.^{11,57} These benefits arise through forms of social support including the structure of one's social relationships (eg, having intimate relationships with others), or the explicit functions performed by others¹⁰ (eg, emotional, economical, informational support). In the context of pain research, literature has largely suggested that social support, in its

various forms, has analgesic effects for pain patients^{7,33,36} as well as in experimental settings with healthy individuals.^{6,17,31,39} Thus, social connectedness may play an important role in the perception of pain.

Preliminary evidence in this area has indicated a “stress-buffering” process in which social support may reduce pain-related threat response that in turn decreases pain.^{25,51,60} For example, one study identified that perceived threat of pain mediated the influences of social support on pain reduction.⁵⁹ Several imaging studies have also suggested that social support may prime safety or reward themes that in turn result in the reduction of pain and related threat response.^{19,62} However, a limitation of current investigations into the buffering effect on pain is the simultaneous assessment of the painful sensation and threat of pain, in which the buffering effect suffers from an indirect manner of examination (eg, Eisenberger et al,¹⁹ and Younger et al⁶²). In addition, where the threat of pain has been specifically addressed, it has been assessed through a self-report dichotomous variable (ie,

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2 The Journal of Pain

yes or no; eg, Corley et al,¹² and Vlaeyen et al⁵⁹). However, the social buffering effect involves not only the subjective, self-reported experience of threat or stress, but (albeit related) neural, cardiovascular, and neuroendocrine dimensions of perceived threat, which are closely associated with health outcomes.⁵⁶

In the current investigation, we build upon the literature of social support and pain to date by using electroencephalogram (EEG) and heart rate measures to assess neural and autonomic changes during the threat of pain and its relationship to pain reduction. To do so, we used a novel manipulation to introduce 6-second continuous threat of pain leading up to painful stimulation. It is important to note that EEG and heart rate offer high temporal resolution. In the present paradigm, this allowed us to reveal the dynamic increase in neural and autonomic response during pain-related threat, and crucially, directly show the buffering effect of social support on threat and pain experience as well as the graded influence of social support depending on the quality of the relationship (ie, close acquaintance vs stranger). Because EEG theta oscillation (4–8 Hz⁸) is suggested as one potential neural correlate of the perception of threatening cues,^{15,43} we hypothesized that social support would reduce theta activity and autonomic heart rate in the threat stage leading up to painful stimulation. Importantly, we anticipated that these changes during the threat of pain would be related to decreased pain ratings after noxious stimulation.

Methods

Subjects

Eighteen healthy adults participated in this study (8 male and 10 female, age range = 18–35 years, mean = 25.2, SD = 5.7). All participants were right-handed, not taking any medication, and had no history or current diagnosis of a neurological or a psychiatric disorder, assessed using the Mini International Neuropsychiatric Interview.⁵³ Involvement in the study required inclusion of a participant's close other (romantic partner, family member, or close friend). All study participants and their close other provided informed consent and the experiment was approved by the Alfred Hospital and Monash University Human Research and Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki.

Experimental Design and Procedure

Noxious electrical stimuli were delivered under 3 conditions: during hand holding of 1) the subjects' close acquaintance ("close other" condition), 2) a stranger ("stranger" condition), and 3) in the absence of hand-holding ("no-holding" condition). The stranger was a staff member who was gender-matched to the close other (a total of 2 staff members only were used for this role). The close other/stranger was only present during the relevant experimental condition and was instructed not to talk or have any eye contact during the recording.

As shown in Fig 1, the experimental task consisted of 30 trials in each condition. Each trial started with the

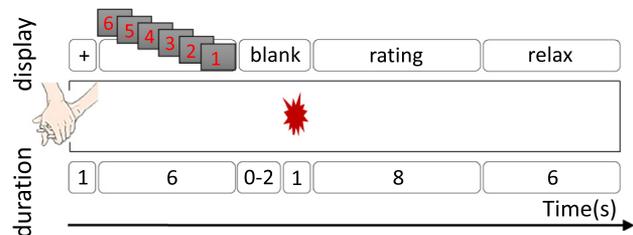


Figure 1. Illustration of the experimental design.

presentation of a fixation cross for 1 second. This was followed by the presentation of numbers in center-screen counting down from 6 to 1, at the rate of 1 number per second. A blank screen was then shown for between 0 to 2 seconds, which was followed by a train of painful stimuli lasting for 1 second. This jittered interval was designed to control for the habituation to the impending stimuli. Immediately after the stimulation participants were asked to rate pain intensity and then pain unpleasantness aroused by the stimuli. Participants gave a verbal rating within 8 seconds (described in *Trial-by-Trial Rating of Painful Sensation*). The participant was allowed to relax for a further 6 seconds before commencement of the subsequent trial. The duration of each condition was approximately 10 minutes. The participant held the hand throughout the condition when relevant. The order of conditions were pseudorandomized and counterbalanced across participants.

Painful Stimuli

Before the start of each condition, individual current levels were determined. Small electrical stimuli were applied to the dorsum of the left little finger (Stimulus Isolator; ADInstruments, Sydney, Australia). Trains of fifty 500- μ s (frequency = 50 Hz, total time = 1 second) stimuli were applied. After each train of stimuli participants gave a verbal pain rating between 0 and 10 (0 = no pain; 10 = worst pain imaginable). The calibration procedure started from a very low current, for which the participants could barely feel the stimulation, then the current was gradually increased. The calibration process was halted when participants rated the intensity as 7.²⁶ We then repeated the current 10 more times to see if it can consistently create a painful feeling of 7 for at least 8 times. If not, the current was increased again until it did elicit a painful rating of 7 for 8 or 10 stimuli. This method of pain calibration has been used in previous studies,^{32,35,52} and was chosen to avoid habituation to perceived threat of pain. The calibration procedure was performed in the absence of the close other or the stranger to avoid any confounding influence.

Trial-by-Trial Rating of Painful Sensation

To assess perceived pain after the offset of each train of stimuli, subjects provided pain intensity and unpleasantness ratings on a numerical scale ranging from 0 to 10 (pain intensity: no pain to worst pain imaginable; pain unpleasantness: not unpleasant to most unpleasant pain

imaginable). To associate decreased neurophysiological threat response with pain relief (ie, a measurement of pain reduction induced by holding the hand of a close other or stranger compared with no-holding), we specifically computed the difference between the mean of pain intensity in no-holding trials and the mean of pain intensity in close other trials^{19,62} (or stranger trials) and then correlated to changes in heart rate and EEG theta activity.

Heart Rate Recording

Heart rate was monitored continuously during each of the 3 conditions using electrocardiogram (PowerLab/4SP; ADInstruments, Sydney, Australia). Three electrodes were administered to the volar surface of bilateral forearms and the calf muscle of the right leg, respectively. Data were recorded with LabChart (version 5.5.6, ADInstruments) in the sampling rate of 1,000 Hz on a separate computer.

EEG Recording

Recordings took place in a sound-attenuated, temperature-controlled, and electrically shielded room. Subjects were seated in a slightly reclined chair with face approximately 50 cm from the computer monitor. Continuous EEG was recorded using a 64-channel Quickcap (Neuroscan Inc, Victoria, Australia) with CPZ as the reference electrode. Vertical electro-oculogram activity was monitored with electrodes attached above and below the left eye, and horizontal electro-oculogram activity was monitored with electrodes located at the outer canthus of both eyes. Data were sampled at 1,000 Hz with impedances below 5 k Ω throughout the testing.

Data Analysis

For the electrocardiogram data, interbeat interval series were derived using Pan-Tompkins algorithm that identifies the peak of the R wave as the fiducial point.⁴⁶ Artifacts were checked visually and edited as necessary according to published guidelines.³ Then interbeat interval series were transformed to beat-per-minute (BPM) series and baseline corrected (–500 to 0 ms, where time 0 represents the onset of the first countdown number) for each trial. Specifically, percent change of BPM was calculated using the Equation 1. This method is believed to control for individual differences in baseline heart rate, and capture the dynamics of event-related heart rate change in a short period.⁴ Percent change of BPM series were then averaged across trials for each participant in each condition, and area under the curve (AUC) was calculated with the linear trapezoidal rule to measure event-related heart rate change during the presentation of countdown numbers (0–6,000 ms).^{34,37} For 2 participants, heart rate recordings were unavailable due to technical issues.

$$\begin{aligned} &\text{Percent change of BPM} \\ &= (\text{BPM at each time point} \\ &\quad - \text{BPM mean} [-500 \text{ to } 0 \text{ ms}]) / \\ &\quad \text{BPM mean} (-500 \text{ to } 0 \text{ ms}) \times 100 \quad (1) \end{aligned}$$

We then examined the correlation between heart rate change and pain relief in the close other (or stranger) compared with the no-holding condition. Because of the dynamic changes of heart rate, we were particularly interested in investigating the specific time windows in which those two would correlate. To this end, a sliding window method was used. The window length was set as 1,000 ms with 50% of overlapping. This was chosen as each countdown number was presented for 1,000 ms. In each window, heart rate reduction was computed as the difference of AUC between the no-holding and the close other (or stranger) condition. Pearson correlations were further computed to assess the relationship of heart rate reduction and pain relief.

Offline EEG data were preprocessed using custom-written scripts that implement functions from EEGLAB (version 13.6.5b; see Delorme and Makeig¹⁶) running under Matlab R2016b (The MathWorks, Inc, Natick, MA). Bad channels were first removed. Data were then filtered (Butterworth filter, band-pass = .5–100 Hz, band-stop = 48–52 Hz), referenced to the average reference, and corrected for stereotyped artifacts including eye blinks, lateral eye movements, muscle, and line noise using the FastICA algorithm.³⁰ Stereotyped artifacts were identified by visual inspection of the spatial and temporal representation of the independent components. Continuous data were then segmented into 7,000-ms nonoverlapping epochs spanning from 1,000 ms before to 6,000 ms after the onset of the first countdown number. Missing channels were interpolated, and epochs were inspected again to remove any anomalous activity in the signal.

Time–frequency representations were calculated with Hanning tapered “mtmconvol” method (7 cycles per time window), as implemented in FieldTrip toolbox.⁴⁵ This method can convolve dynamic EEG time–frequency data with a complex wavelet, and has the advantage that the temporal spread is fully confined to the time window of interest. We calculated power for frequencies ranging from 1 to 100 Hz in the time window of –1,000 to 6,000 ms. Power values were calculated for each trial, and averaged across trials for each subject in each condition. Single-trial baseline corrections were performed with an interval of –500 ms to 0 ms as the baseline.

We further assessed the relationship between power changes and pain relief between conditions. Specifically, power changes were calculated as the difference between no-holding and either close other or stranger conditions. A sliding window method was also adopted for the heart rate analysis, to capture the dynamic relationship between power changes and pain reduction.

Source Localization (Standardized Low Resolution Electromagnetic Tomography Algorithm)

Source localization was further performed to explore the possible generators of neuronal oscillations for which we observed significant differences across conditions. The standardized low resolution electromagnetic tomography

algorithm (sLORETA) is frequently used to estimate possible generators of neuronal oscillations or evoked potentials.⁴⁷ It finds a unique inverse solution for the cortical source of scalp EEGs. Results of sLORETA have been validated using combined EEG-positron emission tomography and EEG-functional magnetic resonance imaging (fMRI) data.^{44,48}

In the current study, time-varying cross-spectra were calculated for single-trial data including baseline (–500 to 0 ms) and test intervals.^{29,42} Here we first limited the test intervals to the time periods in which differences in theta activity were observed between conditions (see the Results section). These steps were further supplemented by analyses in which the test intervals were extended to the entire presentation of countdown numbers (0–6,000 ms). Current source density of theta activity was estimated for cortical voxels. To align the source localization with the time–frequency analysis, event-related changes of the current source density for each time frame within the test interval were calculated as log event-locked deviations from baseline mean.

Statistical Analyses

Repeated measures 2-way analysis of variance (ANOVA) calculations were first performed with SPSS (version 22; IBM Corp, Armonk, NY) on pain intensity and pain unpleasantness to examine the habituation to the noxious stimuli. Pain intensity and pain unpleasantness were split to the first and second half, respectively (15 trials in each half), and condition (close other, stranger, no-holding), and time (first half, second half) were specified as the repeated measure factors. Post hoc t-tests were conducted with a Bonferroni correction with the α level set to .05.

Further, repeated measures 1-way ANOVAs were performed to examine the condition difference in current calibration, pain intensity, pain unpleasantness, and AUC of heart rate change, respectively. Condition (close other, stranger, no-holding) was specified as the repeated measure factor. Post hoc t-tests were conducted with a Bonferroni correction to further explore the significant main effects of condition, and the α level was set to .05.

For time–frequency data, differences between conditions were evaluated using a nonparametric cluster-based permutation test. This method can be used to compare conditions for significant spatiotemporal differences, which provides a straightforward way to solve the multiple comparisons problem.³⁸ In other words, this analysis identifies time periods and electrode clusters in which a given frequency bin differs across conditions. This method was applied to the time window of interest (0–6,000 ms) in all scalp channels. An observed test statistics value was considered in the cluster permutation if it was below the threshold of .05 in at least 2 of the neighboring channels.⁴⁵ Further, 5,000 iterations of trial randomization were carried out for generating the permutation distribution at a given frequency band. A threshold of .025 (2-tailed) was used for evaluating the electrodes that exhibit a significant difference in power. As our a priori hypothesis related to theta activity, statistical analysis was

first carried out in theta band (4–8 Hz). Additional analyses were performed separately in other frequency bands (delta = 1–3 Hz, alpha = 9–12 Hz, beta = 13–30 Hz, gamma = 31–100 Hz).

For sLORETA statistical differences between conditions were calculated as images of voxel-by-voxel t values. The localization of differences in cortical activity was on the basis of the standardized electrical current density and resulted to 3-D t score images. In these images, cortical voxels of significant difference were identified using a nonparametric approach thresholded at .05 determined by 5,000 randomizations.⁴⁷

Results

Behavioral Results

Habituation Analysis

Two-way repeated measure ANOVA revealed a main effect of condition in pain intensity ($F_{2,34} = 6.19$, $P < .05$, partial eta squared $[\eta_p^2] = .27$). There was no main effect of time ($F_{1,17} = .16$, $P = .69$, $\eta_p^2 = .01$), or an interaction effect of Condition \times Time ($F_{2,34} = 2.03$, $P = .15$, $\eta_p^2 = .11$). Similarly, we found a main effect of condition in pain unpleasantness ($F_{2,34} = 5.00$, $P < .05$, $\eta_p^2 = .23$). There was no main effect of time ($F_{1,17} = .14$, $P = .71$, $\eta_p^2 = .01$), or the interaction effect of Condition \times Time ($F_{2,34} = 2.33$, $P = .11$, $\eta_p^2 = .12$). These data together confirmed the absence of habituation. Specific comparisons between conditions are detailed in 1-way ANOVA.

Current Calibration

A repeated measure ANOVA revealed that the main effect of condition was not significant in the current calibration ($F_{2,34} = .43$, $P = .65$, $\eta_p^2 = .03$), confirming that the participants received noxious stimuli of the same current level across 3 conditions (mean = 4.71 mA, SD = 1.56 across conditions).

Pain Intensity

A main effect of condition was found in pain intensity ($F_{2,34} = 6.24$, $P < .05$, $\eta_p^2 = .27$), with post hoc tests showing that pain intensity was lower in close other (95% confidence interval [CI] = –1.75 to –.13, $P < .05$) and stranger condition (95% CI = –1.26 to –.04, $P < .05$) relative to no-holding condition (Fig 2A). Close other and stranger condition revealed no differences in pain intensity (95% CI = –1.02 to .44, $P = .92$).

Pain Unpleasantness

Similarly, we found a main effect of condition in pain unpleasantness ($F_{2,34} = 4.96$, $P < .05$, $\eta_p^2 = .23$). Post hoc tests showed that pain unpleasantness was lower in the close other relative to the no-holding condition (95% CI = –1.51 to –.02, $P < .05$; Fig 2B), but no difference was found in the stranger versus no-holding condition (95% CI = –1.23

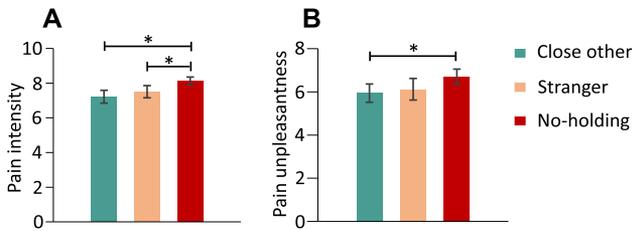


Figure 2. Influence of social support on pain perception. Subjective ratings of (A) pain intensity and (B) pain unpleasantness (mean \pm standard error of the mean). The asterisk represents statistical significance ($P < .05$).

to .06, $P = .10$), or the close other versus stranger condition (95% CI = $-.81$ to $.44$, $P = .99$).

Heart Rate Response and Relationship With Pain

Heart rate increased with the progression of countdown numbers in all conditions, although it appeared to taper off between 4,500 to 6,000 ms (Fig 3A). A main effect of condition was found in the AUC of heart rate change ($F_{2,28} = 3.19$, $P < .05$, $\eta_p^2 = .19$). Post hoc tests showed that close other condition produced less AUC than no-holding condition (95% CI = -7.88 to $-.21$, $P < .05$; Fig 3B), whereas other comparisons did not reach significance. One outlier was detected using GraphPad Prism

(<https://www.graphpad.com>) thresholded at $P < .05$ and consequently removed.

Results also showed that heart rate decrease induced by close other hand-holding was associated with greater pain relief. Pearson correlation revealed that this relationship only reached significance in the late stage of countdown numbers presentation (3,500–6,000 ms; Fig 3C). The results remained consistent when absolute, rather than relative, heart rate measures were used for statistical analysis (see Supplementary Fig 1). In terms of the stranger condition, there was no significant correlation between heart rate reduction and pain relief.

Event-Related Time–Frequency Results and Relation to Pain

The whole-scalp cluster analysis on theta frequency revealed a period (3,300–4,310 ms) during which theta power was significantly decreased in the close other relative to no-holding condition (Fig 4A). The topography of this power decrease had a frontal, slightly right lateralized distribution (significant at AF4, F2, FZ, and FC2). A supplementary analysis showed that there was no difference in any other frequency bands between the close other and no-holding condition.

In terms of the relationship to pain relief (Fig 4B), modulation of theta power was associated with greater pain relief in the late stage of countdown numbers presentation (3,000–5,500 ms).

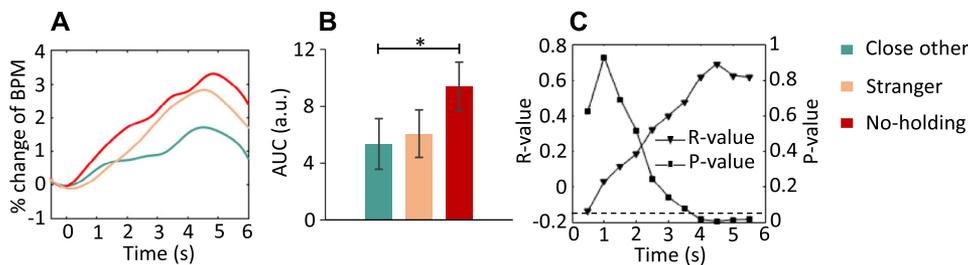


Figure 3. Heart rate change and relationship with pain relief. (A) Shows the event-related dynamic changes of heart rate with the progression of countdown numbers. (B) Shows the AUC of heart rate changes across conditions. Each column and error bar represent the mean and the standard error of the mean. The asterisk represents statistical significance ($P < .05$). (C) Shows the correlation between heart rate (HR) reduction (HR [no-holding condition] – HR [close other condition]) and pain relief (pain intensity [no-holding condition] – pain intensity [close other condition]). a.u., arbitrary unit.

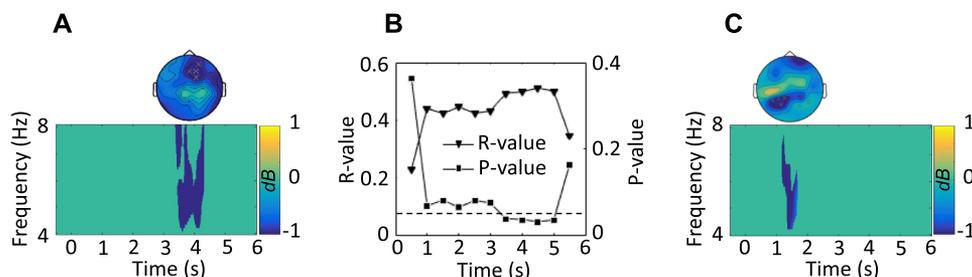


Figure 4. Social support modulates EEG theta activity during threat of pain phase. (A) Time frequency plot showing the reduction in theta power in the close other relative to no-holding condition. Cluster analysis showed that this reduction in theta power reached significance at electrodes AF4, FZ, F2, and FC2 during 3,300 to 4,310 ms after the start of the threat phase. Areas with no significant differences were zeroed out. (B) There was a significant correlation (below the line; $P < .05$) between the reduction in theta power and subjective rating of pain relief in the same close other compared with no-holding condition. (C) Time frequency plot showing the electrodes (P1, P3, P5, PO3) and earlier time period (1,100–1,780 ms) in which theta power was significantly reduced in the stranger relative to no-holding condition.

The nonparametric cluster-based permutation also identified an early period (1,100–1,780 ms) in which theta power was significantly decreased in the stranger relative to no-holding conditions. This power decrease was located over left parieto-occipital regions (P1, P3, P5, and PO3; Fig 4C). No other significant differences were observed in any other frequency bands between the stranger and no-holding condition. Moreover, this spatiotemporal modulation of theta power was not associated with pain relief.

Source Localization

Periods identified by the nonparametric cluster-based permutation as differing significantly between conditions were subjected to source localization procedures. In the time window that theta power difference was observed (3,300–4,310 ms), decreased source localized theta activity was found in the left pregenual anterior cingulate cortex (pgACC; Brodmann area [BA] 24, Montreal Neurological Institute [MNI] coordinates: $X = -5$, $Y = 23$, $Z = 14$, $t = -3.47$, $P < .05$), the bilateral subgenual anterior cingulate cortex (sgACC; BA 25, MNI coordinates: $X = 0$, $Y = 1$, $Z = -5$, $t = -3.55$, $P < .05$), and the right insula (BA 13, MNI coordinates: $X = 45$, $Y = 10$, $Z = -5$, $t = -3.44$, $P < .05$), in the close other relative to no-holding condition (Fig 5).

When the test interval was extended to the whole stage of countdown numbers presentation (0–6,000 ms), decreased activity of the left pgACC (BA 32, MNI coordinates: $X = -5$, $Y = 35$, $Z = 15$, $t = -4.37$) was observed in the close other relative to no-holding condition (see Supplementary Fig 2).

In another time window (1,110–1,780 ms), no brain activation was found at $P < .05$, corrected for multiple

comparisons, in the stranger relative to no-holding condition. No brain activation was found when we extended the test interval to the entire presentation of countdown numbers (0–6,000 ms).

Discussion

Preliminary evidence has indicated a buffering process that may link social support to pain reduction.^{25,59,60} In the current study, we used a novel design to manipulate the threat of pain and characterize the autonomic and neurophysiological changes within the proposed buffering effect. Consistent with most of the literature, our results show that social support alleviated the experience of pain. In addition, our data provide novel evidence of the buffering effect in which social support reduced heart rate and frontal theta oscillations during the threat of pain (ie, before noxious stimulation), and that the magnitude of these changes were related to greater pain reduction. These findings provide evidence that the analgesic influence of social support may be driven by its role in the modulation of the threat of pain.

Previous studies have shown that social support is able to attenuate pain and physiological responses to painful stimuli, including heart rate,^{21,51} blood pressure,^{21,51} skin conductance,^{28,49} and cortisol levels.⁵¹ Building on these findings, our data show that hand-holding with a close acquaintance reduced pain perception (Figs 2A and 2B), and heart rate preceding delivery of painful stimuli that was seen in other conditions (Figs 3A and 3B). We further found that decreased autonomic response to the threat of pain was associated with greater pain reduction in the presence of social support. Therefore, by assessing the threat of pain before painful stimulation our results directly show the social-buffering effect through attenuated autonomic arousal to pain. Moreover, this was only observed in the close other but not in the stranger condition, which further suggests a modulatory influence of relationship quality in the buffering effect.

In addition, an interesting dynamic relationship was observed between the reduction in autonomic and subjective metrics of pain experience by social support (Fig 3C). Specifically, this relationship only reached significance in the late stage of presentation of countdown numbers (approximately 3.3–6 seconds) preceding the delivery of noxious stimuli. A well controlled methodology was used in the pain calibration to determine the intensity of painful stimulation. Countdown numbers were adopted to dynamically manipulate the threat of painful stimuli with the intention that individuals may experience accumulated stress with the impending threat of pain. This is supported by our results, which showed a dynamic increase in heart rate in anticipation of painful stimuli (Fig 3A). Unique to our study design, the buffering influence of social support on the autonomic response could be tracked in the lead up to the delivery of noxious stimuli. Furthermore, the data suggest that this change was not simply due to somatosensory distraction (as suggested by Eisenberger et al¹⁹), because stranger hand-holding did not decrease heart rate, which also created somatosensory distraction. Together, these findings

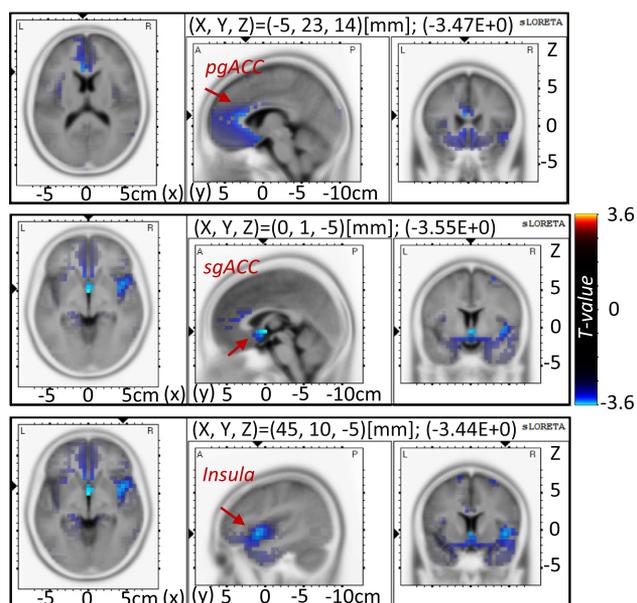


Figure 5. Source localization of EEG theta oscillation in the time window of 3,300 to 4,310 ms in close other versus no-holding condition. Results were shown at $P < .05$, multiple comparison corrected.

suggest that the buffering influence of social support on pain experience may actually increase in value as pain threat increases. Thus, the analgesic effect of social support is associated with downregulating the threatening quality of painful stimuli.

We also showed decreased frontal theta activity during the threat of pain in the presence of close other hand-holding, which provides, to our knowledge, for the first time, the neurophysiological evidence of the social buffering effect in the context of pain. Previous studies have suggested that social support may prime safety or reward-related brain activation (eg, ventromedial prefrontal cortex) in the reduction of pain.^{18,19,62} One EEG study reported that frontal theta is related to the expression of fear,⁴³ whereas other studies suggested that this is associated with the experience of social distress (eg, social exclusion).^{13,58} Therefore, decreased frontal theta in our protocol may represent a lower level of stress aroused by impending painful stimuli. Importantly, decreased frontal theta in the close other condition selectively predicted greater pain reduction when the painful stimulation becomes more threatening (approximately 3–5.5 seconds; Fig 4B). This finding builds upon the behavioral and fMRI evidence in this area, by providing direct evidence for the social buffering hypothesis in which decreased frontal theta activity to the threat of pain is able to predict greater pain reduction.

However, there are other potential, although perhaps inter-related, interpretations. Beyond threat processing, frontal theta oscillation is also implicated in top-down control^{8,23,34} and behavioral adjustment to uncertain or aversive outcomes.^{9,16} In the context of the present results, an alternative explanation is therefore that frontal theta oscillations may also reflect the effort required to regulate the experienced distress. This may explain why heart rate tapers off in the end of stress manipulation when it is otherwise expected to be at its highest.

Finally we provide source localization analysis performed in the theta range to examine the potential neurological mediators generating the buffering effect. This procedure identified event-related changes of the current source density in the theta range that are presumed to account for the effects of social support observed as described previously. Specifically, decreased neural activity was found in the pgACC, sgACC, and insular cortex (anterior as well as posterior parts) in the close other compared with no-holding condition (Fig 5). Although EEG has the advantage of high temporal resolution, the results of EEG source localization are limited in terms of spatial resolution, especially compared with fMRI studies. Nonetheless, the results of EEG beam-forming were highly congruent with regions of neural activity identified in related fMRI works.^{9,19,62}

It is acknowledged that the threat of pain may be highly connected to pain experience.⁵⁰ The current study induced threat of pain before painful stimulation, which was designed to directly examine the social buffering effect. However, this does not mean that they are independent of each other. Our data support this idea by showing high correlations between decreased neurophysiological threat response and pain reduction in the context of

social support. Moreover, it was not our intention to show that heart rate and neural (EEG) activity are fully independent, because they are likely to be at least partially related via the hypothalamic–pituitary–adrenal axis. Instead, the present methodology allowed us to measure each independently and together they tell a story of closely inter-related autonomic and regionally specific neural changes associated with the social modulation of pain.

Close other hand-holding did not show any advantage over stranger hand-holding in decreasing pain or suppressing neurophysiological stress systems. This is different from the literature, which shows the effects of spousal hand-holding on pain reduction compared with stranger hand-holding.^{9,39} This finding could be interpreted to support the evidence that the quality of a relationship modulates the analgesic effects of social support.³¹ Indeed, several studies in this area manipulate social support through romantic relationships, whereas our participants' "close other" included not only romantic partners, but also friends and family members. This was done to be more reflective of the broad levels of social support in daily life, however, these types of relationships may not have the same salience as a romantic partner and may therefore have less of an effect on buffering the threat of pain.

Consistent with the literature,^{9,39} stranger hand-holding did not reduce pain unpleasantness (Fig 2B) or modulate the autonomic response in anticipation of painful stimuli (Fig 3B). However, pain intensity ratings were decreased in the stranger relative to no-holding condition (Fig 2A). This discrepancy in terms of the reduction in pain intensity but not unpleasantness underscores the multidimensional definition of pain experience (ie, somatosensory and affective–motivational dimension⁴⁰), and further research is warranted to explore the modulation of specific dimensions of pain by social support. Our findings suggest that stranger hand-holding does not necessarily provide social support to individuals in distress as it is not able to decrease the unpleasant feelings or physiological arousal. Nonetheless, the data indicate that some qualities of pain experience are reduced by stranger hand-holding and that a different mechanistic basis might underlie this effect.

To further explore this possibility, EEG oscillation was contrasted in the stranger with no hand-holding condition and significantly lower posterior theta was observed (eg, parietal, occipital regions) in the early presentation of countdown numbers (Fig 4C). A number of studies have shown the involvement of posterior theta in the processing of stimuli of high emotional arousal (eg, emotional faces), especially in the early stage of stimulus presentation.^{2,23} Further studies have reported an early increase in posterior theta power during selective processing of threatening cues.^{15,55,63} These studies suggest the critical role of posterior theta in selective attention for emotionally arousing and especially threatening cues. The reduction in posterior theta power in the present study may therefore reflect reduced processing of threatening stimuli, perhaps due to distraction or attentional processes associated with stranger hand-holding.

Beyond the theoretical implications, our findings may also help understand and improve the role of social support in chronic pain patients. Our data may provide evidence in favor of support-assisted pain management therapies, in which the caregiver could help pain patients reappraise pain and related conditions as less stressful.^{1,24,27} Our results further emphasize the significance of relationship quality as well as the quality of social support in pain management. Factors influencing the quality of social support, such as frequent changes in caregivers in a pain management facility, could affect patient's pain outcomes. Moreover, although pain may not always be continuous, the threat of pain may continue between pain flares, and our data suggest that social support is likely to have a more prolonged and meaningful effect on patients' pain experience through modifying the threat of pain. However, it may be the case that our findings using a paradigm of acute pain in healthy participants do not generalize to chronic pain populations. In studies of people with chronic pain, cognitive responses to pain have been reported to be altered in chronic pain conditions compared with healthy individuals (ie, pain is perceived as more painful and threatening).^{14,22} It may be that there is a ceiling effect beyond which social support can cope. Moreover, although our behavioral outcomes assessed the effect of social support on perceived pain, social support may act on other aspects of the chronic pain experience such as functional disability and depression.^{5,61} Further research is therefore required to investigate the relationship and effect of social support in chronic pain patients.

There are several limitations in the study. Despite the significant results reported in this investigation, they are on the basis of a relatively small sample size. The extent to which the findings might therefore generalize to a larger and potentially more diverse sample is not clear and should be investigated in future studies. In addition, hand-holding was used to convey social support in this study. However, social support is a multidimensional

construct that goes beyond physical contact. Indeed, a recent meta-analysis has shown that the influence of social support on pain is modulated by the subject's perception of the intention and capacity of the social partner to provide assistance, as well as the preexisting relationship between them.³¹ Further studies are therefore warranted to investigate the possible effects of social support across different contexts (ie, beyond hand-holding), as well as factors that may affect the influence of social support such as relationship quality. Finally, although we present analysis suggesting that the neural source of EEG activity in our data was congruent with brain regions involved in the processing of threat and pain,^{9,20,41,54} EEG source localization is limited in spatial resolution, particularly in the localization of deeper brain regions.⁴⁷ Future studies could consider examining this protocol with concurrent fMRI and EEG recording.

Overall, this study extends the work of previous studies suggesting that social support may be able to reduce pain through modifying perceived threat of pain.^{19,25,59,60} In this study, we provided a novel manipulation to induce a threat phase before the painful stimulation to directly examine the social buffering effect and the dynamics within this effect. Our findings show that social support decreased threat-related changes in heart rate and reduced frontal theta activity, with the magnitude of these changes associated with greater pain reduction. Furthermore, the social buffering effect was generally stronger and did not subside as the threat of pain increased. Our results thus provide evidence in support of the social buffering effect by showing the neural and physiological dimensions of this effect. Together, this study provides novel insights of the dynamics of the buffering effect of social support on pain.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpain.2017.12.007>.

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Note:

1. There was an error in the text. 'od' should be 'of'. (Page 58, Line 40)

CHAPTER FIVE

Neural Oscillations and Parasympathetic Activity

Manuscript

Che X., Cash R., Fitzgerald P., & Fitzgibbon B.M. Distinct neural dynamics and autonomic activity in response to viewing a romantic other compared to a stranger during pain: An EEG and HRV investigation. Paper under review.

Preamble to empirical paper

Chapter 3 and preliminary fMRI evidence suggest that social support may reduce pain by priming feelings of attachment and/or reward (Eisenberger et al., 2011; Younger et al., 2010). Social support may also modulate the processing of nociceptive information (e.g. ACC, insular cortex) as revealed by fMRI evidence (Eisenberger et al., 2011). However, fMRI has limited temporal resolution and EEG may reveal new information on how social support may modify the gating and integration of nociceptive information. It is also unknown whether social support can act through the parasympathetic system to affect pain, in addition to the autonomous evidence.

This chapter aims to investigate the role of social support in modulating pain perception as well as associated neural dynamics and parasympathetic activity. A tonic pain protocol is introduced which induces prolonged pain during which social support is manipulated by visual representation of an intimate other. Continuous EEG and ECG are recorded during pain delivery to evaluate the dynamics in neural oscillations and HF-HRV respectively.

This chapter extends the literature by demonstrating the role of social support in modulating the gating and integration of nociceptive information as well as in priming regulatory control over bodily arousal to pain.

The organisation of this chapter is in keeping with the requirements for submission to the journal. However, where appropriate, minor formatting changes have been made to improve consistency with other sections of this thesis. The study and related data presented here were from the first session of a three-session data collection protocol presented in chapter six. In this chapter, EEG and ECG data are exclusively looked at to investigate the role of social support in modulating pain perception as well as associated neural dynamics and parasympathetic activity.

Title Page

**Distinct neural dynamics and autonomic activity in response to viewing a romantic other
compared to a stranger during pain: An EEG and HRV investigation**

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Original article

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Significance:

Social support may modulate the gating and integration of nociceptive information.

Abstract

Background: This study was designed to investigate the effects of social support through the visual representation of an intimate other on the subjective experience of pain and measured associated neural and autonomic changes.

Methods: Healthy participants (N = 23) were subjected to cold pain during which they viewed an image of their romantic partner or a stranger. Neural activity and heart rate variability (HRV) were evaluated using electroencephalogram (EEG) and electrocardiography (ECG) respectively.

Results: Compared to the stranger image, viewing a romantic partner was associated with reduced pain intensity ratings and increased perceived support. We also identified distinct neural oscillations in the romantic partner relative to stranger condition, which is characterized by increased frontocentral alpha activity and decreased central gamma activity. The ECG data also demonstrated increased high-frequency HRV in the romantic partner relative to the stranger condition.

Conclusions: Social support from viewing an intimate other is sufficient to reduce pain. This effect may be associated with social support modulating the gating and integration of nociceptive information. Our data further suggest that social support analgesia may also be associated with increased regulatory control over bodily arousal to pain.

Significance:

Social support may modulate the gating and integration of nociceptive information.

Keywords: romantic relationship; social support; pain; alpha oscillation; gamma oscillation; HRV

Introduction

The experience of pain can be reduced by social support (Brown et al., 2003; Master et al., 2009; Goldstein et al., 2016), which refers to received support from others and the perceived availability of supportive resources (Dunkel-Schetter and Bennett, 1990; Uchino et al., 2012). However, simply having supportive resources is not necessarily sufficient to reduce pain (Krahé et al., 2013). Indeed, a recent meta-analysis by our group has demonstrated that the physical presence of a significant other may not in itself reduce pain (Che et al., 2018). Rather, social support tends to have the most effect on pain reduction when the pain recipient perceives the intentions of the social partner as helpful (e.g. view or touch a romantic partner) (Master et al., 2009; Younger et al., 2010; Eisenberger et al., 2011). However, the latter argument is only based on a limited number of studies, and more research is needed to better understand the importance of how social support is delivered, and by whom, in social support analgesia (Che et al., 2018).

There is also a lack of evidence on the mechanisms related to the influence of social support on pain. Painful stimuli carried by afferent C fibre and A δ nociceptors terminate in the dorsal horn, with the information being further transmitted to the thalamus and higher-order brain regions (e.g. anterior cingulate cortex, ACC) (Craig, 2003). This spino-thalamo-cortical circuit also regulates the balance of the sympathetic ('SNS') and parasympathetic ('PNS') nervous system (Cortelli et al., 2013). In social support literature, one proposed mechanism is the capacity of social support to prime feelings of attachment which buffers pain-related responses (e.g. ACC) (Younger et al., 2010; Eisenberger et al., 2011). However, there is no evidence surrounding the dynamic neurophysiological changes related to the social modulation of pain. Research using electroencephalography (EEG) indicates that pain is encoded by suppressed alpha (8-12 Hz) and increased gamma (31-100 Hz) activity. These features are thought to underlie early nociceptive attention and the subsequent subjective experience of pain respectively (Peng et al., 2014; Nickel et al., 2017). At the peripheral level, social support is suggested to buffer sympathetic arousal to pain (Sambo et al., 2010; Roberts et al., 2015; Che et al., 2017). While studies have explored sympathetic arousal, the PNS response

involved in the regulatory control over arousal remains relatively unexplored (Thayer et al., 2009) and may therefore provide a means by which social support can increase physiological control over pain. Heart rate variability (HRV), especially high-frequency HRV (HF-HRV), is thought to reflect bodily control over sympathetic arousal (Thayer et al., 2012; Holzman and Bridgett, 2017).

In this investigation, we aimed to elucidate the effects of intimate social support on pain experience. Using EEG and HRV, we further assessed the neurophysiological and autonomic changes associated with the social modulation of pain. Healthy individuals were subjected to 3-minutes cold pain while viewing an image of a romantic partner or a stranger. This was done to coincide with the functional imaging evidence which also used the image-viewing protocol (Younger et al., 2010; Eisenberger et al., 2011). We hypothesized that a romantic partner image would result in decreased self-reported pain as well as decreased gamma oscillations, and increased alpha activity and HF-HRV. Together, this investigation will provide evidence of the effects of social support on self-report response to pain, as well as information on neural integration processes and bodily arousal that may be associated with these effects.

Methods

Participants

A group of healthy, pain-free, right-handed adults participated in this study (8 males and 15 females, age range: 21-36 years, Mean=26.26, SD=4.24). The sample size was comparable to studies which investigated the neural mechanisms associated with effects of social support on pain (Younger et al., 2010; Eisenberger et al., 2011). Exclusion criteria included use of psychoactive medication, or a history or current diagnosis of a psychiatric disorder, as assessed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan and Lecrubier, 2001). Participation in the study required involvement in a relationship reported as romantic. Participation did not require a pre-requisite measure of relationship quality, although this information was recorded. All study participants provided informed consent and the experiment was approved by the Alfred Hospital and Monash

University Human Research and Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki.

Experimental Design and Procedure

Participants recruited to this study underwent a three-session data collection protocol belonging to a more extensive experiment. The study presented here was from the first session only where EEG and ECG were recorded. Following consent, participants first completed questionnaires before set-up of EEG and ECG. Participants were asked to complete a number of questionnaires, this included the Dyadic Adjustment Scale (DAS) (Spanier, 1976) which is the only one included in this investigation. During 3 minute pain stimulation trials, participants viewed an image of either a stranger or their romantic partner, and rated pain at 20 second intervals.

Dyadic Adjustment in the Relationship

The Dyadic Adjustment Scale (DAS) was the only questionnaire used in this study (Spanier, 1976). DAS is a widely used measure of quality of romantic relationships (Coan et al., 2006). The 32-item DAS consists of four correlated subscales (i.e. Dyadic Consensus, Dyadic Satisfaction, Dyadic Cohesion, and Affectional Expression). The total DAS score is recommended which has a theoretical range of 0 to 151.

Attachment Image

Participants were asked to take a digital image of their romantic partner, consistent with a template image (i.e. the gender matched stranger image), and provide it for the study. Specifically, the image should show a natural smile that comforts them, include only the head and shoulders of the romantic partner and be taken against a plain white background. Images were then edited by the researchers (GNU Image Manipulation Program, GIMP, V2.8,) to have the fixed size (17.5 cm × 17.5 cm), content (from the top of head to shoulders), and matched for luminance using the “auto adjust color levels” function (Parsons et al., 2013). Two images, one male and one female in early adulthood, served as the stranger images.

Tonic Pain Protocol

Prior to, and between experimental trials, participants were required to insert their dominant hand into a bucket of warm water ($40\text{ }^{\circ}\text{C} \pm 0.2\text{ }^{\circ}\text{C}$) for 2 minutes and relax for another 5 minutes. This approach was used to adjust and control baseline hand temperature (Hadjileontiadis, 2015). Next, participants were asked to hold a bottle filled with ice with the dominant hand for 3 minutes (i.e. a single trial). Participants were told to press a button with the non-dominant hand in the keypad to start the trial. The button press started the presentation of an image (Presentation, Version 17.0, Neurobehavioral Systems, Berkeley, CA), which was either their romantic partner or a stranger matched to the partner's gender (Eisenberger et al., 2011). These two conditions were performed separately in a single testing session, and the order of conditions were pseudorandomized and counterbalanced across participants. The 3 minute trial was divided into 20-second blocks (i.e. total 9 blocks per trial) during which the participants viewed the image for 16 seconds and then rated pain intensity within 4 seconds. The participants were asked to rate "pain intensity at the moment" on a scale of 0-10 (0 = no pain; 10 = worst pain imaginable), by pressing the corresponding button on a keypad. At the end of the trial, participants were asked to rate their overall perceived support from the image by pressing the corresponding button (0 = not at all; 10 = extremely high).

Pain Stimulation

In accordance with the work by Hadjileontiadis (2015), participants were asked to hold a 0.5L plastic bottle with iced water ($-1\text{ }^{\circ}\text{C} \pm 0.2\text{ }^{\circ}\text{C}$) with the dominant hand for 3 minutes (Fig. 1a). A pillow was provided on which participants rested their hands to avoid hand movement. Participants were asked to put the volar surface of his/her dominant hand on the surface of the bottle, and not to squeeze or avoid it, to minimize the variability of touching. Different ice bottles were used in different experimental trials for consistency.

EEG Recording

EEG recordings took place in a temperature-controlled, sound-attenuated, and electrically shielded room. Participants were seated in a slightly reclined chair with their faces approximately

0.5m from the computer monitor. A 64 channel Quickcap (NeuroScan Inc., Australia) was used to record continuous EEG with CPZ as the reference electrode. Two electrodes were attached above and below the left eye respectively to monitor Vertical electrooculogram (EOG) activity. Horizontal EOG activity was monitored with electrodes located at the outer canthus of both eyes. Data were sampled at 1000 Hz with impedances below 5 k Ω throughout the testing.

ECG Recording to Assess HRV

Continuous ECG was recorded simultaneously with EEG recording (Chouchoul et al., 2011; Ahn et al., 2016), using the same NeuroScan Acquire system. Two Ag/AgCl electrodes were attached to the left and right wrist of the participant respectively, which shared the reference electrode (i.e. CPZ) with the EEG recording. Data were also sampled at 1000 Hz.

Data Analysis

Offline EEG data were preprocessed using custom-written scripts that implement functions from EEGLAB (version 13.6.5b) (Delorme and Makeig, 2004) running under Matlab R2017b (The MathWorks, Inc.). Data from malfunctioning channels (no more than three) were visually inspected and removed. This number never exceeded three electrodes. Butterworth filters (band-pass: 0.5-100Hz; band-stop notch filter: 48-52 Hz) were then applied to the data (Selesnick and Burrus, 1998). Continuous data were segmented to retain only the image viewing stage (i.e. 16 seconds in each block, in total 9 in each trial). Data were further segmented into 1 second non-overlapping epochs in order to examine the dynamic changes in oscillatory activity (Peng et al., 2014; Schulz et al., 2015). Segmented data were re-referenced to the average signal, and the fast independent component analysis algorithm (FastICA) was employed to remove stereotyped artefacts including eye blinks, lateral eye movements, muscle, and line noise. (Korhonen et al., 2011). Stereotyped artefacts were identified by visual inspection of the temporal and spatial representation of the independent components. Data was interpolated for excluded channels, and epochs were inspected again to remove any anomalous activity.

EEG frequency representations were calculated with Multitaper Method Fast Fourier Transform ('mtmfft'), as implemented in FieldTrip toolbox, in the range of 0-100Hz (Oostenveld et al., 2011). Power spectra were calculated for each epoch, and averaged across epochs for each minute (i.e. first, second, third) in each condition. This was done to investigate the dynamic changes in pain-related oscillations (Peng et al., 2014). Power spectra were also averaged across epochs for the entire 3 minute of pain induction in a separate analysis.

For the ECG data, inter-beat-interval (IBI) series were derived by using the Pan-Tompkins algorithm which identifies the peak of the R wave as the fiducial point (Pan and Tompkins, 1985). Artefacts were checked visually and edited as necessary according to published guidelines (Berntson et al., 1997). Thereafter, IBI series were linearly interpolated to obtain evenly sampled signals and detrended using a highpass filter with the cutoff frequency of 0.02 Hz (Terkelsen et al., 2005; Peng et al., 2015). In order to investigate the dynamic changes in HF-HRV and coincide with the analysis of EEG, IBI series for each minute were subjected to power spectral analysis using discrete Fourier transformation (DeBoer et al., 1987; Akselrod, 1988). HF-HRV was expressed as the relative value of high frequency component (0.15-0.4 Hz) in proportion to the total power minus the very low frequency component (0-0.04 Hz) (Cardiology, 1996). Relative values of HF-HRV are designed to emphasize the controlled and balanced behavior of the sympathetic and parasympathetic branch of the autonomic nervous system (Cardiology, 1996). This measure was also used in a recent study which examined the dynamics of HF-HRV in tonic pain (Peng et al., 2015).

Statistical Analyses

In order to examine social support and time effects on pain, a repeated measures two-way ANOVA was performed in SPSS (version 23; IBM Corp, Armonk, NY). Condition (partner, stranger) and time (9 time points at 20 seconds interval) were specified as the two repeated measures factors. Post-hoc pairwise comparisons were conducted to further explore the significant main and interaction effects, with a Bonferroni correction and α -level set to 0.05.

We also evaluated the difference between conditions of overall perceived support using a paired sample T-test. Bivariate correlation analyses were further performed to investigate the associations between pain intensity changes and perceived support (and relationship quality). Specifically, changes in pain intensity were calculated using area under the curve (AUC) of pain intensity with the linear trapezoidal rule. The AUC approach was employed as it provides a summary measure of the pain dynamics across a specific time window in which overall perceived support (i.e. 3-minute) or neurophysiological (i.e. 1-minute or 3-minute window) data were analyzed.

For EEG data, non-parametric cluster-based permutation tests were performed in order to identify changes in neural oscillatory activity related to the influence of social support on pain. This approach provides a straightforward way to solve the problem of multiple comparisons (Maris and Oostenveld, 2007). This method was applied to the 1 second time windows across all channels. An observed test statistics value was considered in the cluster permutation if it was below the threshold of 0.05 in at least 2 of the neighboring channels (Oostenveld et al., 2011). We performed 5000 iterations of trial randomization for generating the permutation distribution at a given frequency band. A threshold of 0.025 (two-tailed) was then adopted to evaluate the electrodes that exhibit significant difference in power. According to our a priori hypothesis, statistical analyses were firstly carried out in delta (1-3 Hz), alpha (8-12 Hz), and gamma (31-100Hz) band. Additional analyses were performed separately in other frequency bands (i.e. theta: 4-7 Hz; beta: 13-30 Hz).

HF-HRV data were examined to investigate the peripheral changes in the social support influence over pain. In a repeated measures two-way ANOVA, condition (partner, stranger) and time (3 time points at 1 minute interval) were specified as the two repeated measures factors. Post-hoc pairwise comparisons were performed with Bonferroni correction, and the α -level was set to 0.05.

A series of correlation analyses were performed to examine the associations between changes in neurophysiological responses and pain intensity. We also investigated the associations between neurophysiological changes and perceived support (and relationship quality).

Results

Pain Intensity Ratings

As shown in the Fig. 1b, pain intensity demonstrated a pattern of ascending, stabilization, and a desensitization response especially in the control condition. These patterns could be roughly delineated by the 1st, 2nd and 3rd minutes. The ANOVA revealed a significant main effect of condition for pain intensity ($F_{1,22} = 10.71$, $P = 0.003$, $\eta_p^2 = 0.33$). Post-hoc pairwise comparison indicated that pain intensity was lower ($P_{Bonf} = 0.003$) in the romantic partner compared to stranger condition (Fig. 1b). The ANOVA also revealed a main effect of time ($F_{8,176} = 5.21$, $P = 0.016$, $\eta_p^2 = 0.19$). Post-hoc pairwise comparisons showed that, across conditions, pain intensity kept increasing ($P_{Bonf} < 0.05$) till the end of the second minute (20-120 second) compared to the start of pain induction.

-----Please insert Fig. 1 here-----

Overall Perceived Support and Relationship Quality

A paired sample T-test confirmed that overall perceived support was higher in the romantic partner compared to the stranger condition ($t_{22} = 9.22$, $P = 0.0001$) (Fig. 1c). Further analysis showed that higher perceived support was associated with greater pain reduction throughout the course of pain in the romantic partner relative to stranger condition ($P = 0.006$) (Fig. 1d).

Mean relationship quality scores were 116.68 (SD = 10.28). We did not observe an association between partner relationship quality and pain intensity ratings ($P > 0.05$).

EEG Analysis

In the first minute of pain induction, no differences were found between the romantic partner and stranger condition.

In the second minute, when pain sensation has stabilized, cluster-based permutation testing revealed a significant increase of alpha power in the romantic partner relative to stranger condition

(Fig. 2a). The topography of this power increase had a fronto-central, left-lateralized distribution (significant at F5, FC3, FC5 and C3) (Fig. 2b). Alpha power changes did not correlate with the changes in pain intensity or perceived support or relationship quality ($P_s > 0.05$). No difference was found in any other frequency bands.

-----Please insert Fig. 2 here-----

In the third minute of pain induction, characterized by apparent desensitization, cluster analysis identified a significant decrease in gamma power in the romantic partner relative to stranger condition (Fig. 2c). This power decrease was located over the central electrodes (significant at CZ, C2, CP1, and CP2) (Fig. 2d). Separate analyses confirmed that this result was not influenced by the 50 Hz notch filter. The decrease in gamma power was associated with greater pain reduction during the third minute of pain in the romantic partner relative to stranger condition ($P = 0.04$) (Fig. 2e). Gamma changes were not associated with perceived support or relationship quality ($P_s > 0.05$)

The cluster analysis also identified two clusters in the delta band that significantly differed between the romantic partner and stranger condition during the third minute of pain. In one cluster, partner condition showed decreased delta power over the frontal electrodes (significant at AF3, AF4, F3, F1, FZ, F2, and FCZ) (Fig. 3a, 3b). Romantic partner condition also demonstrated reduced delta power over the parietal electrodes (significant at CP5, CP3, CP1, CP2, CP4, CP6, P5, P3, P1, PZ, P2, P6, PO3, and POZ) (Fig. 3c, 3d). Changes in frontal or parietal delta power across conditions were not associated with pain intensity changes or perceived support or relationship quality ($P_s > 0.05$). No further difference was found in other frequency bands.

-----Please insert Fig. 3 here-----

The supplementary cluster analysis revealed no difference in any frequency bands when data were averaged across the entire period of pain induction.

High-frequency Heart Rate Variability

A two-way ANOVA revealed a condition \times time interaction effect in HF-HRV ($F_{2,44} = 3.72$, $P = 0.04$, $\eta_p^2 = 0.15$). To investigate this interaction effect, two one-way ANOVAs were performed across time windows within each condition, and paired T-tests were conducted across conditions for each time window. A significant main effect was found in the romantic partner condition ($F_{2,44} = 4.75$, $P = 0.02$, $\eta_p^2 = 0.18$), with post-hoc pairwise comparisons showing that HF-HRV was significantly higher in the second than the first minute of pain induction ($P_{Bonf} = 0.03$). No significant main effect was observed in the stranger condition ($P > 0.05$). Across conditions, paired T-tests showed a significantly higher HF-HRV in the romantic partner relative to the stranger condition only in the second minute of pain induction ($P_{Bonf} = 0.03$) (Fig. 4). Changes in HF-HRV were not correlated with perceived support or relationship quality ($P_s > 0.05$).

-----Please insert Fig. 4 here-----

Discussion

The present study was designed to characterize the neurophysiological and autonomic mechanisms associated with the effects of social support on pain experience. Consistent with previous evidence (Master et al., 2009; Eisenberger et al., 2011), our behavioral results indicated that pain perception was reduced when viewing an image of a romantic partner. The benefits of social support on pain perception were associated with distinct oscillatory responses between conditions, with the romantic partner image demonstrating higher alpha activity during the apparent pain stabilization stage (2nd minute) followed by lower gamma and delta oscillations in the late desensitization period (3rd minute) of pain induction. Interestingly, a positive relationship was

observed between decreased gamma power and pain reduction in the romantic partner relative to stranger image. Our results also indicated that romantic partner image was associated with higher HF-HRV during tonic pain. Together, this work provides several lines of evidence demonstrating that social support modulates the dynamic neural, autonomic and subjective response to pain.

Initial evidence suggests that social support by viewing or touching an intimate other may have an analgesic influence (Krahé et al., 2013; Che et al., 2018). This argument is based on limited evidence (Master et al., 2009; Younger et al., 2010; Eisenberger et al., 2011) which needs to be further examined. We presented an experimental pain protocol, which is seemingly characterized by an ascending, stabilization, and desensitization phase (Fig. 1b). Moreover, pain was reduced in the social support condition, and this effect was most prominent after the initial increase in pain. Our findings provide further evidence of the analgesic influence of intimate social support, as well as a unique contribution of social support during the ongoing induction of pain.

As expected, the ratings of perceived support were higher in the romantic partner relative to stranger condition (Fig. 1c). Furthermore, pain reduction was greatest in those individuals who reported the greatest level of perceived support (Fig. 1d), further substantiating the moderating influence of social support on pain experience. Surprisingly, relationship quality was found to have no impact on pain perception or on the neurophysiological changes in this study. It may be that perceived support provides a metric that is more directly relevant to moderating pain experience while relationship quality encompasses a more complex constellation of features (e.g. dyadic satisfaction and affectional expression) (Spanier, 1976). Nonetheless, the result was somewhat unexpected as relationship quality (e.g. dyadic satisfaction) was found to buffer brain activations (e.g. insula, hypothalamus) to pain-related threat (Coan et al., 2006). It is possible that social support variants (e.g. hand-holding, visual presentation) may modulate the influence of relationship quality on the neurobiological activation to pain.

We explored the neural changes associated with and potentially mediating the influence of social support on tonic pain. Following an initial increase in perceived pain, the stabilization phase

(2nd minute) displayed significantly higher frontocentral alpha power in the romantic partner compared to stranger condition (Fig. 2a, 2b). Given that pain has been shown to reduce alpha power (Huber et al., 2006; Dowman et al., 2008; Nir et al., 2012; Shao et al., 2012; Gram et al., 2015; Nickel et al., 2017), the increased alpha power in the romantic partner condition is consistent with a reduction in subjective pain at the cortical level. Moreover, pain is proposed to suppress alpha power to open the ‘gate’ and permit the relevant nociceptive inputs to be actively processed in high-order brain areas (Ploner et al., 2006; Jensen and Mazaheri, 2010; Hauck et al., 2015). Decreased alpha is therefore suggested as a mechanism of attention driven by nociceptive inputs (Chang et al., 2002; Ohara et al., 2004; Hauck et al., 2015). Indeed, contralateral alpha power was found to be negatively associated with the stimulus intensity of pain which directly modulated the attention level (Nickel et al., 2017). Moreover, cognitive distraction restored the alpha suppression to pain (Peng et al., 2014). Conversely, increased alpha activity is commonly associated with cortical “deactivation” or inhibition and is sometimes referred to as an ‘idling’ state (Jensen and Mazaheri, 2010; Cash et al., 2017). The present results therefore suggest that alpha power may be also involved in social support modulating the gating of nociceptive transmission.

In addition, the romantic partner condition was associated with reduced central gamma power during the late stage of pain induction (Fig. 2c, 2d). Our data demonstrated that decreased gamma power was correlated with greater pain reduction (Fig 2e). This is in line with previous research which indicated that pain enhances gamma oscillatory activity, primarily over frontal and central regions (Schulz et al., 2015; Nickel et al., 2017). Moreover, these changes were found to be independent of stimulus saliency and the site of noxious stimulation (Schulz et al., 2015; Nickel et al., 2017). Increased gamma activity is therefore thought to represent the integration of nociceptive inputs with higher-order cognitive and affective functions, thus mediating the subjective experience of pain (Zhang et al., 2012; Peng et al., 2014; Hauck et al., 2015). Taken together, higher alpha power in the social support condition may reflect increased gating of nociceptive information, while

reduced central gamma activity may indicate reduced transmission and integration of nociceptive information for cognitive processing, thus modulating the subjective experience of pain.

Several studies have also demonstrated that pain increases delta activity (Le Pera et al., 2000; Chang et al., 2002; Huber et al., 2006; Hauck et al., 2015; Ploner et al., 2017). Similarly, we observed decreased delta activity in the frontal and parietal cortices in the romantic partner relative to the stranger condition during pain induction (Fig 3a-d). Interestingly, one study found that frontal delta power was increased during attachment image-viewing, but this was in the absence of pain induction (Başar et al., 2008). It is possible that the delta increase associated with viewing a romantic partner is offset by the dramatic delta decrease related to lower level of pain. Our results are therefore not necessarily to rule out the possibility of perceived attachment (i.e. increased delta) in the social modulation of tonic pain, but delta changes may rather reflect a combination of both perceived attachment and pain. Future research may therefore wish to isolate the contributions of perceived attachment and pain to delta changes by including more control conditions (e.g. support-no pain condition).

We also observed a more rapid and larger increase in HF-HRV in the romantic partner condition beyond the cortical activation (Fig. 4). During exposure to pain, HF-HRV returns to baseline after an initial decrease, which suggests regulatory control over body arousal (Treister et al., 2012; Peng et al., 2015). Increased HF-HRV in our data is potentially indicative of a higher level of physiological control in response to pain. Our findings therefore extend the evidence of social support-assisted management of sympathetic arousal (Sambo et al., 2010; Roberts et al., 2015), by directly providing evidence of the parasympathetic activity that is associated with the physiological control over pain. Moreover, higher HF-HRV in social support condition is consistent with the increased alpha and decreased gamma activity. Painful stimuli can disrupt the homeostasis of human body mediated by the spino-thalamo-cortical circuit (Craig, 2003), which is associated with increased sympathetic and suppressed parasympathetic activity (Cortelli et al., 2013). Our results therefore provide comprehensive evidence that social support can modulate not only the gating and

integration of nociceptive information in the cortical level, but the regulatory control over bodily arousal in the peripheral level.

Experimental pain protocols, as employed in this study, may improve our understanding of the role of social factors in pain experience, a key component in the biopsychosocial model which views pain as the result of the dynamic interactions among physiologic, psychological, and social factors (Gatchel, 2004; Gatchel et al., 2007). Our findings suggest the impact of a social context on the neurobiological processing of pain. Our data may also provide information on how the types of interactions within relationships may impact upon pain, although more work is needed in this area. The intimacy model, for example, argues that verbal communication between couples may serve to enhance intimacy and adaptive coping responses to pain (Cano and Williams, 2010). Using a non-verbal visual presentation of social support, our results suggest the benefits on decreasing pain and possibly building intimacy (as indicated by increased perceived support). Beyond theoretical implications, this study further informs the therapeutic benefits of social support in the management of pain. Shaygan and colleagues (Shaygan et al., 2016) demonstrated that viewing images of a significant other mitigated pain in chronic pain conditions. Although conducted in a group of healthy people, our findings add to this work suggesting that the analgesic effect seen in Shaygan et al study (Shaygan et al., 2016) could be associated with the modulation of pain processing in the cortical and peripheral level. These results may therefore inform to optimize the partner-assisted pain management strategies which lack empirical evidence surrounding the contexts and mechanisms of the pain-relieving effect of social support (Keefe et al., 1996, 1999; Abbasi et al., 2012).

There are several limitations of the study. We did not require a certain level of quality in the romantic relationship of our participants. This may limit the replications of previous findings among early stage relationships (Younger et al., 2010) or in studies which only included relationships where there was a high level of satisfaction (Coan et al., 2006). Nonetheless, this should have been at least partially captured by our measure of relationship quality and therefore can be included when

comparing studies of this kind. We also did not control for attraction arousal of the two stranger images, which should be recorded in future research. Our study design also induced pain to the dominant hand in this study as opposed to the non-dominant hand in some studies (Younger et al., 2010; Eisenberger et al., 2011), which may further limit comparability to other work. It is also important to note the limitation of translating our findings to clinical groups as we presented findings in healthy participants. As the central nervous system undergoes significant change in chronic pain (Apkarian et al., 2011), neural responses to social support may have a differential effect as seen in this study. Finally, while we presented a sample size comparable to the literature on this topic, it was relatively small with a restricted age range, and we are therefore not able to compare age or sex differences in the analgesic effect of intimate relationship which has been mainly observed in females (Master et al., 2009; Eisenberger et al., 2011).

Future directions to investigate the mechanisms related to the influence of social support on pain could expand on neurophysiological and peripheral responses as were investigated in this study. This includes the assessment of the neuroendocrine responses which may reveal valuable information on the potential mechanisms associated with social support and pain. Social interaction with an intimate other may result in the release of oxytocin (Holt-Lunstad et al., 2008) which has analgesic effects (Paloyelis et al., 2016), given recent evidence that oxytocin may enhance the analgesic influence of social support (Kreuder et al., 2018). Moreover, other candidate hormones may be also considered as of their involvement in the processing of social intimacy and pain (e.g. β -endorphin (Keverne et al., 1989; Pearce et al., 2017), glucocorticoids (Wittig et al., 2016)). In addition, other psychological processes may be also related to the experience of social support and therefore modulate pain experience, for example, the feeling of attachment and attraction (Eisenberger et al., 2011), self-esteem and perceived competence (Che et al., 2018), which were not included in this study.

To conclude, our findings suggest that social support, as provided by visual representation of a romantic partner, is sufficient to significantly reduce neural, autonomic and subjective dimensions

of pain experience. In the context of previous findings, our data suggest that this reduction of subjective pain experience may be associated with the gating and reduced integration of neural signals associated with pain. Our data further suggest that this reduction may also be associated with increased regulatory control over bodily arousal to pain. Together these findings enhance our understanding of the neural and autonomic factors associated with the analgesic effects of social support.

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Author Contributions:

XC, RC, and BF contributed to the experimental design, data collection and analysis, and manuscript preparation. PF contributed to experimental design and manuscript preparation.

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Figure legends:

Fig. 1. Pain delivery, rating and overall perceived support. (a) Experimental set-up, showing pain stimulus (ice-filled water bottle) and pain intensity rating using a key-pad. (b) Dynamic changes in pain intensity during painful stimulation. Data points indicate group mean pain intensity. Each one minute interval is shaded separately. (c) The partner condition showed higher overall perceived support. (d) Higher perceived support was associated with greater pain reduction in the partner condition ($n = 23$). PT and ST denote the partner and stranger image-viewing condition respectively. Error bars represent standard error of the mean (SEM). *** denotes $P < 0.001$.

Fig. 2. Neural oscillatory activity during the stabilization (2nd minute) and desensitization (3rd minute) phase of pain. (a) Frequency spectrum indicating that alpha power was significantly greater in the partner compared to stranger image-viewing condition during pain stabilization. (b) The increase in alpha power reached significance at fronto-central electrodes F5, FC3, FC5 and C3. (c) Frequency spectrum showing that gamma power was significantly lower in the partner compared to stranger image-viewing condition during pain desensitization. (d) The decrease in gamma power reached significant at electrodes CZ, C2, CP1, and CP2. (e) Reduced gamma power from the significant channels was associated with greater pain reduction in the partner condition ($n = 23$). PT and ST denote the partner and stranger image-viewing condition respectively. The shaded area represents the SEM. X indicates $P < 0.05$.

Fig. 3. Partner image-viewing decreases delta oscillations in the pain desensitization phase (3rd minute). (a) – (b) Decrease in delta power at frontal electrodes AF3, AF4, F3, F1, FZ, F2, and FCZ. (c) – (d) Decrease in delta power at posterior electrodes CP5, CP3, CP1, CP2, CP4, CP6, P5, P3, P1, PZ, P2, P6, PO3, and POZ. The shaded area represent the SEM. X indicates $P < 0.05$.

Fig. 4. Changes in the high-frequency heart rate variability across the pain induction. Error bars represent the SEMs. n.u. denotes the normalized units. * denotes $P < 0.05$.

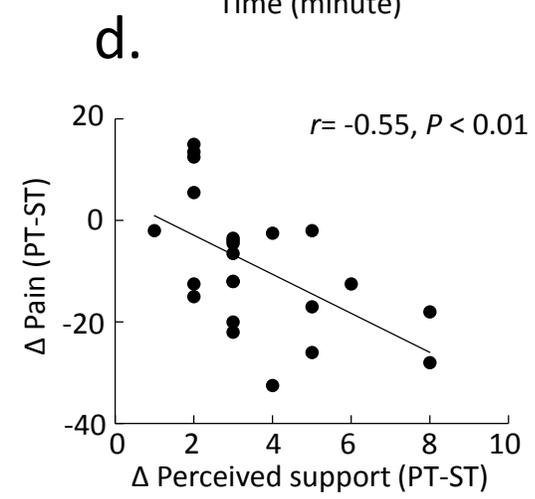
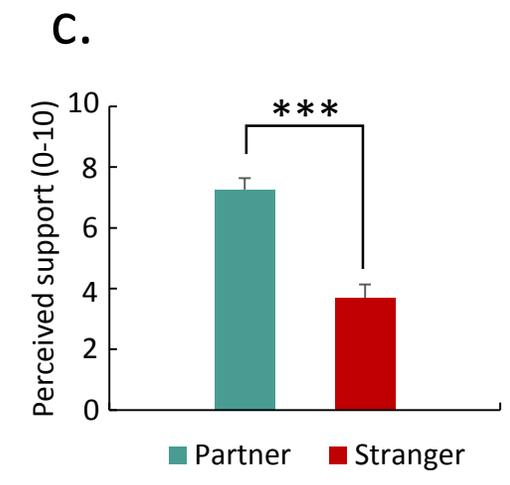
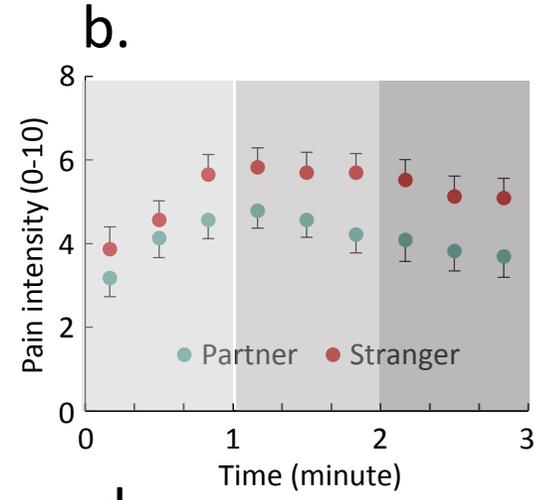
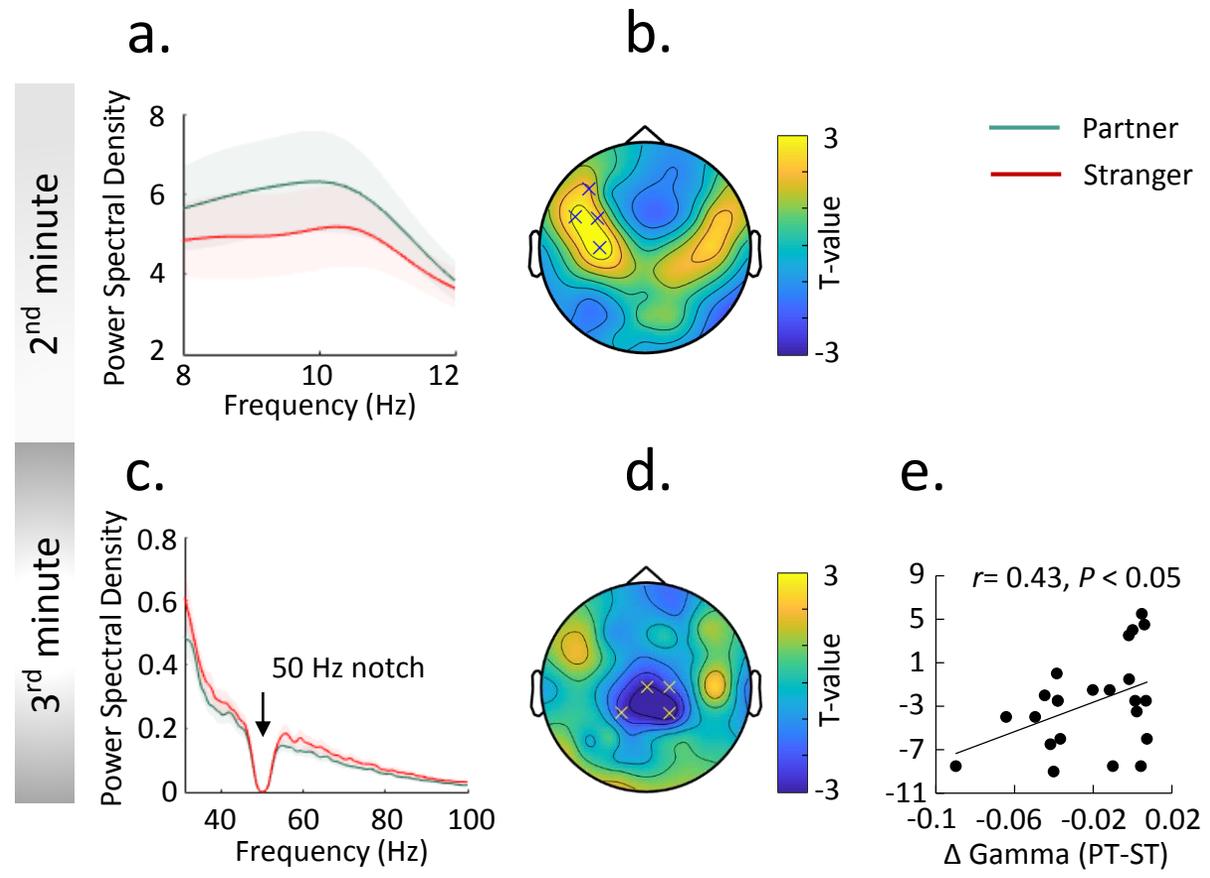


Fig. 2



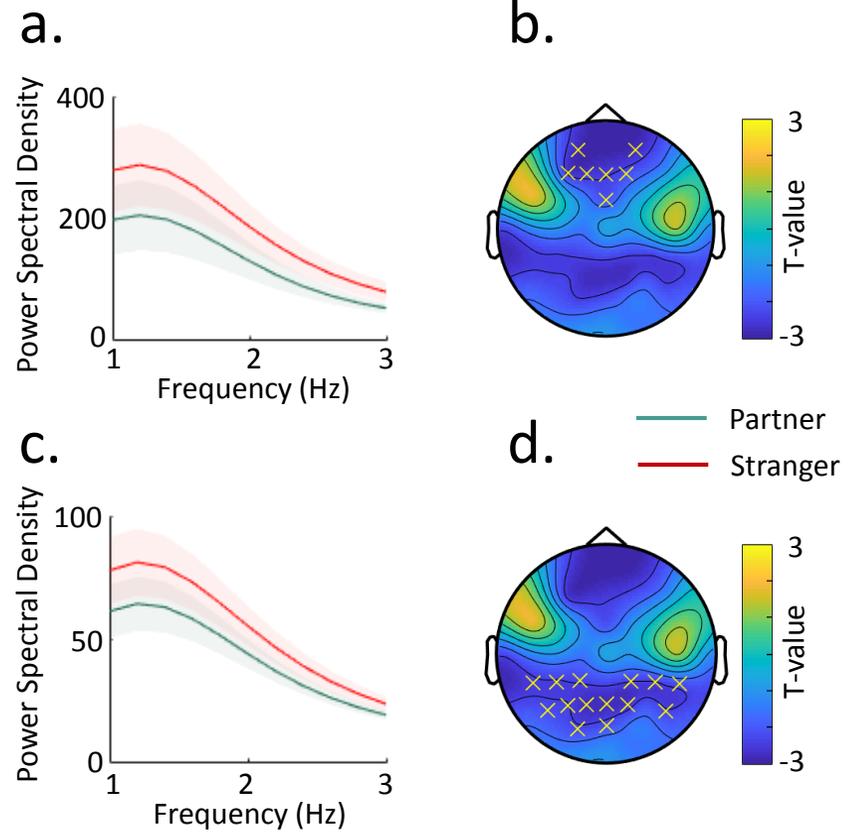
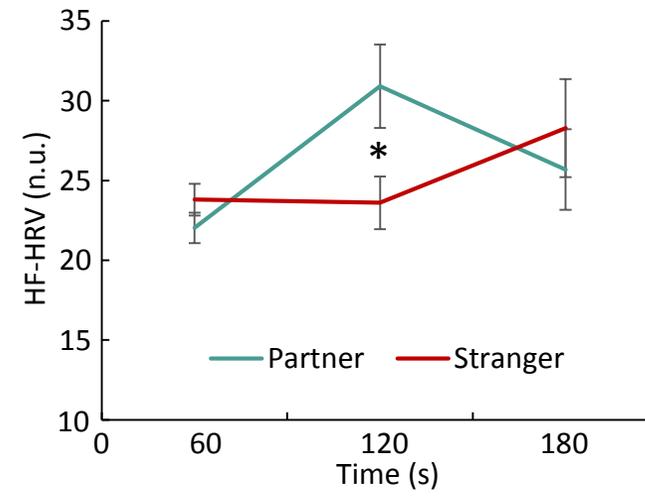


Fig. 4



CHAPTER SIX

Neural Plasticity and Connectivity

Manuscript

Che X., Cash R., Chung S., Bailey N., Fitzgerald P., & Fitzgibbon B.M. The medial prefrontal cortex as a flexible hub mediating behavioural as well as local and distributed neural effects of social support on pain: a theta burst stimulation and TMS-EEG Study. Paper under review.

Preamble to empirical paper

Preliminary evidence suggests a key role of the medial prefrontal cortex (mPFC) in the analgesic influence of social support (Eisenberger et al., 2011; Younger et al., 2010). This is suggested to be related to the role of the mPFC in signalling safety (Delgado et al., 2006; Phelps et al., 2004; Quirk et al., 2006). However, to date a causal influence of the mPFC in facilitating the processing of social support and its impact on pain has not been demonstrated. Further, Chapter 5 demonstrates a role of social support in modulating neural oscillations supporting the processing of nociceptive information, but the brain-wide dynamics that may underpin the influence of social support on pain remain unknown.

In this chapter, TMS was used to investigate the causal role of the mPFC in orchestrating the behavioural and brain connectivity effects of social support on pain. Activity of the mPFC is either increased or decreased (or no change) across sessions using different TBS protocols. Pain perception and EEG connectivity are evaluated before and after the delivery of TBS. Using TMS-EEG, we further

aim to explore the neural plasticity changes over the prefrontal cortex and its association with social modulation of pain.

This chapter demonstrates the role of the mPFC in causally modulating pain perception and network configuration dependent on social support contexts.

The organisation of this chapter is in keeping with the requirements for submission to the journal. However, where appropriate, minor formatting changes have been made to improve consistency with other sections of this thesis.

Title Page

The Medial Prefrontal Cortex as a Flexible Hub Mediating Behavioral as well as Local and Distributed Neural Effects of Social Support on Pain: a Theta Burst Stimulation and TMS-EEG Study

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Abstract

Increasing evidence points to an analgesic influence of social support, in which the medial prefrontal cortex (mPFC) is thought to play a key role. Transcranial Magnetic Stimulation (TMS) has the capacity to causally modulate brain activity. This study was designed to investigate the potential role of mPFC in orchestrating the behavioral and neural effects of social support on pain. Twenty-three healthy participants underwent a three-session cross-over, single-blinded, sham-controlled protocol in which they received Theta Burst Stimulation (TBS) (facilitatory intermittent TBS, suppressive continuous TBS, or Sham) delivered to the mPFC. In each session, participants underwent cold pain while viewing an image of a romantic partner or a stranger. Effects of TBS to the mPFC were assessed using a measure of pain perception, neural activity and network connectivity using electroencephalography (EEG) and TMS-EEG. In the stranger condition, pain experience increased following iTBS. This was associated with increased connectivity between central regions and fronto-parietal regions. In contrast, in the romantic partner condition, iTBS increased connectivity only between frontal and occipital regions and did not modulate pain experience. In line with recent studies, neither cTBS nor Sham stimulation elicited neural or behavioral changes. Together these findings suggest that the mPFC has the capacity to causally modulate pain-related information integration and network configuration in a context-dependent manner.

Keywords: social support; pain; theta burst stimulation; TMS-EEG; connectivity

1. Introduction

Pain experience is modulated by a variety of social contexts in daily life (for review see Krahé et al., 2013). Emerging evidence has suggested an analgesic influence of social support (Che et al., 2017; Goldstein et al., 2016), which commonly refers to received support from others and the perceived availability of supportive resources (Dunkel-Schetter and Bennett, 1990). However, recent systematic reviews, including one meta-analysis from our group, have demonstrated that this effect is not universal and highlighted the role of contextual factors (Che et al., 2018; Krahé et al., 2013). Indeed, social support from a significant other can prime intimacy and reduce pain, but the presence of another person in general may not have an overall effect (for a review see Che et al., 2018).

Advancing our understanding of the role of social support in pain therefore requires improved knowledge of the mechanisms that mediate the impact of social support on pain. Initial evidence suggests a role of social support in priming feelings of attachment, as supported by increased brain activity (blood-oxygen-level dependent imaging, BOLD) in the medial prefrontal cortex (mPFC) (Eisenberger et al., 2011; Younger et al., 2010). This is consistent with the proposed role of the mPFC in processing social intimacy (Gamond and Cattaneo, 2016; Gamond et al., 2017). Moreover, the mPFC is a key node of the default mode network (DMN), which is associated with self-report perceived social support (Che et al., 2014) and mind wandering away from pain (Kucyi et al., 2013). However, given methodological limitations of the techniques used, this initial evidence was unable to assess the causal relationships of the mPFC in facilitating the processing of social support and its impact on pain. Moreover, the brain-wide dynamics that may underpin the influence of social support on pain remain unknown.

Transcranial Magnetic Stimulation (TMS) is a non-invasive approach which can modulate brain activity, and thereby provide unique insights into brain-behavior relationships. Theta Burst Stimulation (TBS) is one of the most established repetitive TMS protocols and has the capacity to modulate neural excitability (Huang et al., 2005; Ni et al., 2014) and network connectivity (Iwabuchi et al., 2017; Rastogi et al., 2017). More specifically, TBS can increase or decrease cortical excitability

depending on whether intermittent (iTBS) or continuous (cTBS) stimulation, respectively, is employed (Huang et al., 2005). Thus, TBS provides a means to causally modulate the mPFC and its associated networks and explore the role of this brain region in the effects of social support on pain. In addition, changes in neural activity induced by TBS can be measured using single-pulse TMS and concurrent electroencephalography (TMS-EEG) (Cash et al., 2017; Chung et al., 2017). Of note, recent studies suggest that iTBS may be more effective than cTBS in modulating brain activity when applied to the prefrontal cortex (Berlim et al., 2017; Chung et al., 2017).

Changes in EEG activity and connectivity following TBS may help to reveal regional and network-based neural mechanisms that mediate the influence of social support on pain. Although the frequency dynamics of the experience of pain are not entirely understood (Ploner et al., 2017), with each of the bands implicated (e.g. for alpha see Furman et al., 2018), most of the studies link subjective pain ratings with increased gamma activity (31-100 Hz) in central and frontal cortex (Nickel et al., 2017; Schulz et al., 2015; Zhang et al., 2012). To our knowledge, only one EEG study has explored phase synchronization in response to painful stimuli, which found increased theta range (4-7 Hz) connectivity between central and parietal regions (Taesler and Rose, 2016). Additionally, only one study has looked at EEG connectivity in the context of social influence on pain, in which increased alpha band (8-12 Hz) connectivity was suggested to underlie the effects of social touch on pain reduction (Goldstein et al., 2018).

This study was designed to investigate the role of the mPFC in mediating the effects of social support on pain. Participants underwent a three-session cross-over, single-blinded, sham-controlled protocol in which they received either iTBS, cTBS, or Sham stimulation. A pain task was performed before and after TBS during which participants were subjected to cold pain while viewing an image of either a romantic partner or a stranger (Eisenberger et al., 2011). We hypothesized that iTBS would increase neural activity in the mPFC (assessed using TMS-EEG) and that in the romantic partner condition, iTBS would increase social support related alpha connectivity and reduce pain related gamma power, theta connectivity, and pain sensation. In contrast, we hypothesized no

changes in the stranger condition. We also anticipated less pronounced and potentially opposite changes in the sham and cTBS sessions.

2. Methods

2.1. Participants

Twenty-three healthy right-handed adults participated in this study. Three participants withdrew after the first session. Data from 20 participants were therefore analyzed (see Table 1). Exclusion criteria included a history or current diagnosis of a psychiatric disorder, or use of psychoactive medication, as assessed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan and Lecrubier, 2001). All participants identified as being in a romantic relationship. An informed consent was provided by all participants, and the experiment was approved by the Alfred Hospital and Monash University Human Research and Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki.

2.2. Experimental Design and Procedure

Participants underwent a three-session data collection protocol with each session at least 72 hours apart to avoid any potential carry-over effects (Fig. 1). The experimental procedures were the same in each of the three sessions except for the type of TBS protocol (i.e. iTBS, cTBS or Sham), the order of which was counterbalanced across participants. During the first session participants completed several self-report questionnaires (see Table 1). In each session, participants first underwent a 3-minute pain protocol with EEG recorded to assess neural oscillations and connectivity. In the pain protocol, participants viewed an image of either a stranger or their romantic partner (in total 2 separate trials), and rated pain at 20-second intervals for the three minutes. Next, single-pulse TMS was delivered to the mPFC and cortical responses were recorded using concurrent EEG. Participants then received either iTBS, cTBS or Sham stimulation to the mPFC, which was followed by a repeat of the pain and TMS-EEG protocol described above.

----- Please insert Fig. 1 here -----

2.3. *Social support or Stranger Attachment Image*

Consistent with a template image (i.e. the gender-matched stranger image), a digital image of the romantic partner was taken by the participants and provided for the study. Specifically, the image was requested to be against a plain white background, demonstrating a natural smile and including only the head and shoulders. One of the researchers (XC) then edited the images (GNU Image Manipulation Program, GIMP, V2.8,) to have the fixed size (17.5 cm × 17.5 cm), content (from the top of head to shoulders), and matched for luminance using the “auto adjust color levels” function (Parsons et al., 2013). Two images, one male and one female in early adulthood, served as the stranger images.

2.4. *Pain Protocol*

In order to control baseline hand temperature (Hadjileontiadis, 2015), participants were asked to insert their dominant hand into a bucket of warm water ($40\text{ }^{\circ}\text{C} \pm 0.2\text{ }^{\circ}\text{C}$) for 2 minutes and relax for another 5 minutes prior to and between experimental trials. Participants were then asked to hold a bottle filled with iced water ($-1\text{ }^{\circ}\text{C} \pm 0.2\text{ }^{\circ}\text{C}$) for 3 minutes (i.e. a single trial) with the dominant hand (Hadjileontiadis, 2015). A trial was started by pressing a button with the non-dominant hand in the keypad. The button press started the presentation of an image (Presentation, Version 17.0, Neurobehavioral Systems, Berkeley, CA), which was either their romantic partner or a stranger matched to the partner’s gender (Eisenberger et al., 2011). These two conditions were performed separately in two trials, and the order of conditions was pseudorandomized and counterbalanced across participants. A 3-minute trial was divided into nine 20-second blocks during which the participants viewed the image for 16 seconds and then rated pain intensity within 4 seconds. The participants were asked to rate “pain intensity at the moment” on a scale of 0-10 (0 = no pain; 10 = worst pain imaginable), by pressing the corresponding button on a keypad. At the end

of the trial, participants rated their “overall perceived support” from the image by pressing the corresponding button (0 = not at all; 10 = extremely high). A pillow was provided on which participants rested the back of their hands to avoid hand movement. Participants were told to put the volar surface of the dominant hand on the surface of the bottle, and not to avoid or squeeze it, to minimize the variability of touching. Fresh ice bottles were used for each experimental trial for consistency.

2.5. EEG Recordings

EEG recordings took place in a temperature-controlled, sound-attenuated, and electrically shielded room. Participants were seated in a slightly reclined chair with their faces approximately 0.5m from the computer monitor. A 64-channel EEG cap (NeuroScan Inc., Australia) was used to record continuous EEG with CPZ and FPZ as the reference and ground electrode respectively. Two electrodes were attached above and below the left eye to monitor vertical electrooculogram (EOG) activity. Horizontal EOG activity was monitored with electrodes located at the outer canthus of both eyes. EEG impedances were kept below 5 k Ω throughout the experiment.

For EEG recordings during the pain protocol, EEG signals were filtered (0.05–200 Hz) and sampled at 1,000 Hz. For TMS-EEG recordings, EEG signals were amplified (1,000 \times) and low-pass filtered (DC—2,000 Hz) with a high acquisition rate of 10,000 Hz. As the TMS click sound might contaminate the EEG signals (Nikouline et al., 1999), participants were asked to listen to white noise through intra-auricular earphones (Etymotic Research, ER3-14A, USA) during TMS-EEG recordings (Fuggetta et al., 2005). The sound level was adjusted such that each individual reported that they could no longer hear single-pulse TMS at 110% resting motor threshold (RMT).

2.6. Transcranial Magnetic Stimulation

Both single-pulse TMS and TBS were delivered using a figure-of-eight MagVenture B-65 fluid-cooled coil (MagVenture A/S, Denmark) in a biphasic mode. In the determination of the RMT, stimuli

were applied to the left motor cortex with the coil positioned at 45° angle relative to midline (Chung et al., 2018a; Chung et al., 2018b). The RMT was determined with the EEG cap on, as the minimum stimulus intensity required to elicit at least three out of five motor evoked potentials (MEPs) >0.05 mV in amplitude in the relaxed first dorsal interosseous muscles (Conforto et al., 2004). Prefrontal TMS was then administered, with the coil centred at the F1 electrode. This electrode was selected as it is positioned over the superior frontal gyrus (Koessler et al., 2009), and increased left mPFC activity is associated with social support effects on pain (Eisenberger et al., 2011; Younger et al., 2010). Moreover, the coil was positioned at 90° angle relative to midline (handle pointing left, see Fig. 2a) in order to target the mPFC (Downar et al., 2012; Salomons et al., 2014). The edge of the TMS coil was marked on the EEG cap for consistent re-positioning of the coil within and between sessions (Rogasch et al., 2013). The TMS-evoked potentials (TEPs) were recorded using EEG during single-pulse TMS (105 pulses, 4 s interval \pm 10% jitter) at 110% RMT, delivered before and after TBS. TBS consisted of a burst of 3 pulses given at 50Hz repeated every 5Hz, where (1) iTBS involved a 2s train of TBS repeated every 10s for a total of 192s, (2) cTBS without any break/interruption for a total of 40s, or (3) Sham – the iTBS protocol was administered using a MagVenture Placebo B-65 coil which has a sound level identical to the B-65 coil. TBS was delivered with the intensity of 70% RMT (Goldsworthy et al., 2012), with a total of 600 pulses.

In order to validate the target site, electric field simulations for the cooled B-65 TMS coil (90° angle) were performed using the SimNIBS modelling environment, which utilizes a finite element model of brain current flow based on an MRI derived template head model (Windhoff et al., 2013). Visualization of the electrical fields was performed using the Gmsh mesh generator (Geuzaine and Remacle, 2009).

2.7. EEG Data Analysis

EEG data during the pain protocol were preprocessed offline using custom-written scripts that implement functions from EEGLAB (version 13.6.5b) (Delorme and Makeig, 2004) running under

Matlab R2017b (The MathWorks, Inc.). Data from malfunctioning channels were visually inspected and removed. Butterworth filters (band-pass: 0.5-100Hz; band-stop notch filter: 48-52 Hz) were then applied to the data (Selesnick and Burrus, 1998). Continuous data were segmented to retain only the image viewing stage, i.e. 16 seconds in each block, in total 9 in each three-minute pain stimulation trial. Data were further segmented into 1-second non-overlapping epochs to remove any contaminated data (Peng et al., 2014; Schulz et al., 2015). Segmented data were re-referenced to the average reference, and the fast independent component analysis algorithm (FastICA) was used to remove stereotyped artefacts, e.g. eye blinks, lateral eye movements, muscle, and line noise (Korhonen et al., 2011). Stereotyped artefacts were identified by visual inspection of the temporal and spatial representation of the independent components. Missing channels were then interpolated, and epochs were inspected again to remove any anomalous activity in the signal.

EEG frequency representations were calculated with the Multitaper Method Fast Fourier Transform ('mtmfft'), as implemented in FieldTrip toolbox, in the range of 0.5-100Hz (Oostenveld et al., 2011). Power spectra were calculated for each epoch, and then averaged across epochs in each condition.

EEG connectivity was calculated between each electrode using the debiased estimator of the weighted phase lag index (wPLI) based on the frequency representations obtained above. The wPLI is considered as a conservative measure of phase synchronization, which is suggested to be robust against volume conduction, non-brain related artifacts and common reference artifacts (Vinck et al., 2011). The measure also has good test-retest reliability (Hardmeier et al., 2014). For each frequency, the wPLI provided a value of coherence for each electrode pair. Connectivity values were then averaged in the frequency domains of interest, i.e. theta (4-7 Hz), or alpha (8-12 Hz). Exploratory analyses were also performed in other frequency bands (i.e. delta: 1-3 Hz; beta: 13-30 Hz; gamma: 31-100 Hz).

2.8. TMS-EEG Data Analysis

TMS-EEG data were preprocessed as previously described (Chung et al., 2017). Specifically, data were epoched around the TMS pulses (−1,000 to 1,000 ms), baseline corrected (−500 to −50 ms), and then the large magnetic pulses were removed and interpolated (−5 to 15 ms). Data were down-sampled to 1,000 Hz and epochs containing excessive noise and/or disconnected electrodes were removed during manual inspection. Prior to independent component analysis (ICA) based artifact rejection, the epoched data were concatenated across the two time-points (Pre and Post) to avoid bias in component rejection. Two rounds of FastICA were performed using semi-automated component classification algorithm (Rogasch et al., 2017). The first ICA was performed to remove large TMS-evoked muscle artefacts and decay artefact (Rogasch et al., 2014). All data were band-pass (1–80 Hz) and band-stop filtered (line noise removal, 48–52 Hz), and epochs were visually inspected again to remove any anomalous activity. The second round of ICA was used to remove other non-neural artefacts, e.g. eye blinks, saccadic movement, persistent muscle activity, decay artefact and electrode noises. Removed channels were then interpolated. Finally, data were re-referenced to common average and segregated into original time-point blocks (Pre and Post) and epochs averaged for each condition.

2.9. Source Estimation

Cortical sources of the TEPs were estimated using Brainstorm (Tadel et al., 2011). TMS-EEG data were co-registered with the template brain model (i.e. ICBM 152). The forward model used the Symmetric Boundary Element Method implemented in OpenMEEG software (Gramfort et al., 2010), and the inverse model used the computation of minimum norm estimations (MNEs) with dipole orientations constrained to be normal to the cortex (Lin et al., 2006). Differences in estimation were calculated using absolute subtraction.

2.10. Statistical Analyses

Statistical analyses were performed on the primary outcome measures (self-reported pain ratings, TEPs, EEG power and connectivity).

Pain intensity ratings across 3-minute blocks were summarized by calculating the area under the curve (AUC). The effects of TBS and time as well as their interaction were analyzed using repeated measures two-way ANOVAs in SPSS (version 23; IBM Corp, Armonk, NY). The partner and stranger condition were examined separately. TBS (iTBS, cTBS or Sham) and time (Pre, Post) were specified as the two repeated measures factors. Post-hoc pairwise comparisons were conducted to further explore the significant main and interaction effects, with the α -level set to 0.05 and Bonferroni corrected.

For TEPs, statistical analyses were conducted using cluster-based permutation statistics at a global scalp level (Maris and Oostenveld, 2007). The cluster-based permutation test provides a straightforward way to solve the problem of multiple comparisons across space (EEG channels) and time (Maris and Oostenveld, 2007). Statistics were performed on a priori peak of interest (i.e. N100: 90–130 ms), which is considered to be the most prominent and robust TMS-EEG component for the exploration of TMS induced plasticity changes (Chung et al., 2015; Nikulin et al., 2003). Exploratory analyses were also performed on other peaks: N40 (30–50 ms), P60 (50–80 ms), and P200 (160–240 ms), which have been commonly observed following prefrontal stimulation (Chung et al., 2017; Rogasch et al., 2014). Paired T-tests were first made across time point (Post vs Pre) for each TBS condition ('within-comparison'). Comparisons between TBS conditions ('between-comparison') were then performed using delta score of each TBS condition ($\Delta = \text{Post} - \text{Pre}$). An observed test statistics value was considered in the cluster permutation if it was below the threshold of 0.05 in at least 2 of the neighboring channels (Oostenveld et al., 2011). We performed 5000 iterations of trial randomization for generating the permutation distribution, controlling for multiple comparisons across space ($P < 0.025$; two-tailed test).

For EEG power changes, the same cluster-based permutation statistics were used to identify differences in neural oscillatory activity. This method was applied to each 1-second time window

across all channels. Comparisons were made between Pre- and Post-stimulation for each TBS (iTBS, cTBS or Sham) and image (partner, stranger) condition. According to our a priori hypothesis, statistical analyses were firstly carried out in alpha (8-12 Hz), theta (4-7 Hz) and gamma (31-100Hz) bands. Additional exploratory analyses were performed separately in other frequency bands (i.e. delta: 1-3 Hz; beta: 13-30 Hz).

Connectivity wPLI values were statistically tested using the network-based statistic (NBS) toolbox (Zalesky et al., 2010). The NBS is a non-parametric statistical method which uses cluster analysis to perform null hypothesis testing across networks of values from pairs of potentially connected nodes (Zalesky et al., 2010). It is robust against unequal sample sizes and controls for the family-wise error rate (Zalesky et al., 2010). Paired T-tests were performed to examine significant connectivity changes from Pre- to Post-stimulation for each TBS (iTBS, cTBS, Sham) condition. Statistical comparisons were made using 5000 permutations, with a primary threshold for electrode pairs set at $P < 0.005$ to ensure only robust differences in connectivity between electrode pairs would be compared at the cluster level (Bailey et al., 2018). The secondary threshold for family-wise corrected cluster null hypothesis testing was $P < 0.025$ (two-tailed).

Correlation analysis was performed to examine brain-behaviour relationships between TBS-induced changes in pain ratings and significant TBS-induced changes in EEG power and TEP amplitude.

In the supplementary analysis, a repeated measures two-way ANOVA was performed on overall perceived support to examine the effects of TBS (iTBS, cTBS or Sham) and time (Pre, Post) as well as the interaction effect.

3. Results

The effectiveness of TBS over the mPFC was initially validated before the investigation of outcome measures. Fig. 1b shows the electric field distribution in the cortical grey matter for the cooled B-65 coil. The TMS coil effectively targeted the left prefrontal cortex, with maximum field

strengths occurring around the left mPFC. Moreover, single-pulse TMS over left mPFC resulted in a series of negative and positive peaks including N40, P60, N100 and P200 (*Supplementary Material S1*). Consistent with other TMS-EEG studies in the prefrontal cortex (Chung et al., 2018b; Hill et al., 2017), each peak showed a distinctive pattern in scalp topography and source estimation.

----- Please insert Fig. 2 here -----

3.1. Effects of TBS on Pain Intensity Ratings

In the partner condition, the ANOVA revealed no effect of TBS protocol, time, or their interaction on pain ratings ($P_s > 0.05$), suggesting that pain ratings were the same across stimulation type and time window (Fig. 3a-d). In the stranger condition (Fig. 3e-h), the ANOVA revealed an interaction effect of TBS protocol and time on pain ratings ($F_{2,38} = 3.51$, $P = 0.04$, $\eta_p^2 = 0.16$). Post-hoc tests were performed to investigate this interaction. Two one-way ANOVAs (one for Pre, one for Post) were first performed across TBS conditions, which were followed by three paired T-tests (one for each TBS condition) conducted across time windows. One-way ANOVAs revealed no effect of TBS on pain ratings in either time window ($P_s > 0.05$), suggesting that pain ratings were the same across TBS conditions in both Pre- and Post-stimulation (Fig. 3e-h). Across time windows, paired T-tests showed a significant increase in pain ratings from Pre- to Post-iTBS ($P_{Bonf} = 0.003$) (Fig. 3e and Fig. 3h). No difference was observed in the cTBS (Fig. 3f) or Sham (Fig. 3g) condition ($P_{Bonf} > 0.05$).

----- Please insert Fig. 3 here -----

3.2. Plastic Effects of TBS on TEPs

Cluster-based permutation tests revealed that the amplitude of the primary TEP component of interest, N100, was significantly increased from Pre- to Post-iTBS ($P_{corrected} = 0.011$) (Fig. 4a). Moreover, the topography of this change was mainly distributed around the frontal regions where iTBS was delivered (Fig. 4d *left panel*). In line with recent evidence (Chung et al., 2017), there were no changes in N100 amplitude following cTBS (Fig. 4b) or Sham (Fig. 4c) ($P_{corrected} > 0.05$). Changes in

N100 amplitudes were not associated with increased pain in the stranger condition from Pre- to Post-iTBS ($P > 0.05$).

These findings were supported by secondary analyses in which N100 amplitude Pre- to Post-stimulation was compared across all TBS conditions using permutation tests. Relative to sham, N100 changes from Pre- to Post-stimulation were significantly larger in the iTBS condition ($P_{corrected} = 0.006$). Moreover, changes in N100 were mainly distributed around the fronto-central regions (Fig. 4d, right panel). No difference was found in the iTBS versus cTBS or the cTBS versus Sham comparisons.

----- Please insert Fig. 4 here -----

3.3. Effects of TBS on EEG Oscillations in the Pain Protocol

In the partner condition, cluster-based permutation statistics revealed a significant increase in gamma power from Pre- to Post-iTBS ($P_{corrected} = 0.024$). The topography of this power increase had a fronto-central, right-lateralized distribution (significant at F4, F6, FC4, FC6, and C4) (Fig. 5a). The increase in gamma power was associated with larger N100 amplitude from Pre- to Post-iTBS ($r = -0.49$, $P = 0.03$) (Fig. 5a). No correlation was found between gamma changes and pain rating changes ($P > 0.05$). No difference was found in any other frequency bands.

----- Please insert Fig. 5 here -----

In the stranger condition, we also found increased gamma power from Pre- to Post-iTBS ($P_{corrected} = 0.019$). Increased gamma in the stranger condition was mainly distributed in the left central-parietal regions (significant at T7, C5, C3, CP5, P7, P5 and O1) (Fig. 5b). However, no correlation was found between gamma changes and N100 amplitude or pain ratings changes ($P_s > 0.05$). No difference was found in any other frequency bands.

Following sham stimulation, alpha activity was greater in both the partner and stranger condition. Moreover, in both the partner ($P_{corrected} = 0.006$) and stranger ($P_{corrected} = 0.021$) condition, increased alpha was mainly distributed in the central regions (Fig. 5c, and Fig. 5d).

3.4. Effects of TBS on EEG Connectivity in the Pain Protocol

In the partner condition, we found a significant cluster in the alpha band which indicated higher fronto-occipital alpha connectivity from Pre- to Post-iTBS ($P_{corrected} = 0.019$) (Fig. 6a). In the stranger condition, there was an increase in central-parietal and central-frontal theta connectivity from Pre- to Post-iTBS ($P_{corrected} = 0.003$) (Fig. 6b). No other significant clusters were observed in other frequency domains and no significant clusters were observed in the cTBS or Sham stimulation.

----- Please insert Fig. 6 here -----

3.5. Supplementary Analysis

In the partner condition, the ANOVA revealed a main effect of time on overall perceived support ($F_{1,19} = 6.54$, $P = 0.019$, $\eta_p^2 = 0.26$), with post-hoc test showing that overall perceived support decreased from Pre- to Post-stimulation across TBS conditions ($P_{Bonf} = 0.019$) (Supplementary Material S2). No effect was observed in the stranger condition ($P_s > 0.05$).

4. Discussion

Previous studies have indicated that the mPFC plays a key role in mediating the analgesic effects of social support (Eisenberger et al., 2011; Younger et al., 2010). Using TBS, this study was designed to modulate mPFC activity and related networks mediating pain experience in the presence or absence of visual social support. Our data indicate that while iTBS elicited typical changes in TMS-EEG measures of neural activity at rest, it led to differential effects across social support conditions during pain. Crucially, these data suggest that iTBS differentially influenced network connectivity and behavior across social support conditions. In line with other recent studies, cTBS and Sham stimulation did not elicit prominent changes. In sum, these findings provide novel evidence to support the role of mPFC as a hub mediating the analgesic effects of social support on pain processing.

Firstly, it is important to examine the efficacy of TBS conditions in modulating neural excitability, prior to considering behavioral and other effects. The neuroplastic effects of TBS delivered over non-motor regions such as the mPFC is most commonly quantified using TEPs. TEPs are suggested to reflect the shifts in the inhibition-excitation balance in cortical circuits following a single TMS pulse (Du et al., 2018; Rogasch and Fitzgerald, 2013). In this instance, we focused on N100 amplitude which is considered to be the most robust TEP component with the greatest signal-to-noise ratio (for discussion, see Cash et al., 2017; Noda et al., 2016). Furthermore, prior studies have identified N100 as being the component most reliably modulated by TBS (Chung et al., 2017; Chung et al., 2018a). In agreement with previous studies, N100 amplitude was increased by iTBS (Fig. 4a), however there were no changes with cTBS or Sham stimulation (Fig. 4b-c). The absence of TEP changes with cTBS is in line with recent evidence which also observed more robust effects of iTBS compared to cTBS in modulating activity in prefrontal cortex (Chung et al., 2017; Chung et al., 2018a).

iTBS delivered to the mPFC modulated the influence of social support on pain experience in a context-dependent fashion. Specifically, viewing a stranger was associated with more pain following mPFC-iTBS whereas pain did not increase in the romantic partner condition. This selective and differential influence of mPFC stimulation on pain experience according to social support condition was not evident in the Sham or cTBS conditions. Studies have shown a dual, opposing roles for the mPFC in pain (for a review see Ong et al., 2018), in which mPFC may serve to suppress pain via its connection with the periaqueductal gray (PAG) (An et al., 1998; Kucyi et al., 2013), but induces the persistency and chronification of pain via the corticostriatal projection (Baliki et al., 2012; Vachon-Preseau et al., 2016). Moreover, the mPFC has been found to mediate the selective attention to pain (Peyron et al., 1999), and as a key node of the DMN, it has been associated with rumination about pain (Kucyi et al., 2014). Effectively, our findings may indicate that mPFC-iTBS actually increased pain experience, but that social support was sufficient to buffer this change. The

effects of social support on pain may be further explained by neural and network related changes as described next.

Previous research has established that pain and pain modulation are associated with distinct changes in neural activity, particularly in the gamma band (Peng et al., 2014). Our research supports these findings, showing that modulating mPFC activity using iTBS increased fronto-central gamma activity in the romantic partner condition. Furthermore, these changes correlated with plastic changes in TEP amplitude following iTBS (Fig. 5a). In contrast, the stranger condition was associated with increased central-parietal gamma activity post iTBS (Fig. 5b). Gamma band activity is suggested to encode subjective pain experience (Nickel et al., 2017; Zhang et al., 2012). However, the increase in fronto-central gamma activity in the social support condition may otherwise reflect the role of gamma band activity in other higher-order cognitive processes, such as attention and the episodic memory retrieval (Canolty et al., 2006; Keizer et al., 2010; Marshall et al., 2015). One possibility is that the increase in fronto-central gamma activity following iTBS is related to attentional processing of visual social support and the retrieval of memory related to the romantic partner. The increase in gamma activity proximal to the stimulation site following excitatory stimulation at the prefrontal cortex is consistent with recent findings (Noda et al., 2017), however our data are the first to indicate a relationship between plastic changes in N100 amplitude and gamma activity linked to social support.

In the stranger condition in which pain experience increased following iTBS, gamma activity was increased in central-parietal regions contralateral to the somatic site of pain delivery (Fig. 5b). This finding is consistent with previous studies which indicated gamma band activity in central-parietal cortical regions associated with somatosensory perception and pain integration (Hauck et al., 2015; Ploner et al., 2017; Zhang et al., 2012).

One of the most interesting aspects of our findings relates to the differential effects of mPFC TBS on network connectivity across different social support conditions. Connectivity across distributed neural regions typically manifests across lower frequencies, in particular the theta and

alpha bands (Sauseng et al., 2010; Sauseng and Klimesch, 2008). In the romantic partner condition, iTBS increased alpha band connectivity between frontal regions surrounding the stimulation site and occipital regions involved in visual processing (Fig. 6a). This finding is consistent with previous evidence identifying a specific role of alpha band connectivity in mediating social support analgesia (Goldstein et al., 2018). In particular, social support by touching a romantic partner reduced pain experience, and this effect was associated with increased synchronization of the couple's alpha waves (Goldstein et al., 2018). Beyond this evidence, alpha band coherence is suggested to support complex social interactions, e.g. imitation (Dumas et al., 2010), social coordination (Tognoli et al., 2007). Our finding extends the literature by demonstrating that alpha coupling between frontal and occipital regions may serve to process visually presented social support information.

In contrast, iTBS over the mPFC led to distributed changes in theta connectivity in the stranger condition. Specifically, connectivity was increased between left central regions associated with sensory processing of the pain stimulus, frontal regions near the TBS stimulation site and parietal regions likely involved in the integration of pain-related information (Fig. 6b). Previous evidence has identified a specific role of theta connectivity in relation to pain experience in which painful stimuli increased theta connectivity between central cortex and the parietal and frontal cortices in healthy individuals (Taesler and Rose, 2016). Moreover, we found increased coupling between temporal (as indicated by T7 electrode) and frontal regions, in which the temporal cortex plays a key role in understanding the intention of others (Allison et al., 2000; Pelphrey et al., 2004). In sum, it appears that stimulation of the mPFC using iTBS is able to enhance the neural signatures associated with social support and pain experience in a context-specific fashion. Furthermore, these findings provide evidence that the mPFC has the capacity to orchestrate and modulate distributed effects associated with social support and pain across distributed regions.

In contrast to iTBS, cTBS did not demonstrate any changes in cortical plasticity (Fig. 4b), pain experience (Fig. 3b, Fig. 3f) or neural activity. This is consistent with the literature which suggests that cTBS is less effective in modulating brain activity compared to iTBS (Berlim et al., 2017; Chung et

al., 2017). However, we did observe an increase in alpha power following Sham stimulation independent of the image type (Fig. 5c, Fig. 5d). Pain has been shown to suppress alpha activity which is related to nociceptive attention (Nickel et al., 2017; Peng et al., 2014). Conversely, increased alpha activity is associated with cortical “deactivation” and is sometimes referred to as an ‘idling’ state (Cash et al., 2017; Jensen and Mazaheri, 2010). Increased alpha activity post Sham stimulation therefore may suggest less attention driven by the painful stimuli or the social support information as the participants knew what to expect from Pre- to Post-stimulation.

Findings of the current study improves our understanding of the mechanisms that may mediate the influence of social support on pain. Using TBS, activity of the mPFC was temporarily modulated which allowed the investigation of its causal role in the processing of social support as well as the influence on pain experience. Moreover, TMS-EEG has the capacity to assess neural plasticity changes caused by TBS. Combination of these techniques would supplement in generating stronger conclusions surrounding social support and pain. Furthermore, the current study provides evidence beyond local brain activation, which extends the literature to understand the neural networks and dynamics surrounding the impact of social support on pain. Overall, our findings may help to understand the potential therapeutic influence of social support in the management of pain whereby empirical evidence is limited surrounding the social contexts and mechanisms of the pain-relieving effect of social support (Keefe et al., 1996, 1999).

We acknowledge some limitations with the current study. We only used one image of the romantic partner whereby a consistent reduction in perceived social support across sessions was evident, independent of TBS condition (*Supplementary Material S2*). Habituation to the image may have influenced the capacity to elicit reductions in pain experience in the romantic partner condition following iTBS. Future studies would benefit from using multiple images that have the same valence to the support recipient. Secondly, the TMS coil was positioned based on F1 electrode location. Electrode-based positioning is commonly employed in TMS-EEG research (Cash et al., 2017; Chung et al., 2018b) and similar to the F3 approach used in the treatment of clinical disorders (Beam et al.,

2009). However, it is not as accurate as MRI-guided neuronavigation which was not feasible in the present study. Moreover, we only targeted the left mPFC based on fMRI evidence identifying the left mPFC activation in social support analgesia (Eisenberger et al., 2011; Younger et al., 2010). Future studies would provide interesting evidence by targeting both left and right mPFC.

In conclusion, this study used TBS alongside EEG and TMS-EEG to investigate the mechanisms underlying the influence of social support on pain. Our data demonstrated neural plasticity changes in the mPFC, which was associated with increased pain experience at the subjective and neural level in the context of viewing a stranger. In contrast, social support was associated with distinct neural activity and connectivity that could be modulated by plasticity changes in the mPFC activity. As such, it seems that stimulation of the mPFC can flexibly elicit context-dependent behavioral and brain connectivity changes surrounding social support and pain. Overall, our findings demonstrate the key role of the mPFC in social modulation of pain and potentially as a network hub regulating local and distributed brain activities.

Author contributions:

XC, RC, and BF contributed to the experimental design, data collection and analysis, and manuscript preparation. PF contributed to the experimental design and manuscript preparation. SC and NB contributed to the data analysis and manuscript preparation.

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Figure legends:

Fig. 1. Experimental procedure.

Fig. 2. TMS delivery and electric field modelling of the study. (a) Both single-pulse and TBS were delivered to the F1 electrode in the 10-20 system. (b) Distribution of the induced normalized electric field (norm E) with maximal activation at the left mPFC.

Fig. 3. Pain ratings modulated by different TBS protocols. In the romantic partner condition, (a) – (c) show no effects of iTBS, cTBS, or Sham stimulation on pain ratings across the 3-minute pain task. (d) represents the area-under-curves (AUCs) of pain ratings across the pain task. In the stranger condition, (e) – (g) show the pain ratings across the pain task and (g) represents the AUC of pain dynamics. Stranger condition was associated with more pain from Pre- to Post-iTBS. ** indicates $P < 0.01$.

Fig. 4. Modulation of cortical activity assessed via TEPs following different TBS protocols. Grand average TEP waveforms from the three fronto-central electrodes (FC1, FCZ and FC2) for (a) iTBS, (b) cTBS and (c) Sham conditions. iTBS resulted in a larger N100 amplitude from Pre- to Post-stimulation. (d) Scalp maps represent the comparison between iTBS-induced N100 from Pre- to Post-stimulation (*left panel*), and between iTBS-induced N100 change and Sham-induced N100 change (*right panel*). X indicates $P < 0.05$, * indicates $P < 0.01$.

Fig. 5. Modulation of EEG oscillations by different TBS protocols. (a) iTBS increased fronto-central gamma power in the romantic partner condition (significant at F4, F6, FC4, FC6, and C4) (*left and middle panel*). Increased gamma activity was associated with larger N100 amplitude from Pre- to Post-iTBS (*right panel*). (b) iTBS increased central-parietal gamma power in the stranger condition (significant at T7, C5, C3, CP5, P7, P5 and O1). (c) – (d) show the increased central alpha power in the romantic partner and stranger condition respectively from Pre- to Post-Sham stimulation. Power is expressed as $10 \cdot \log_{10} (\mu V^2/Hz)$. X indicates $P < 0.05$, * indicates $P < 0.01$.

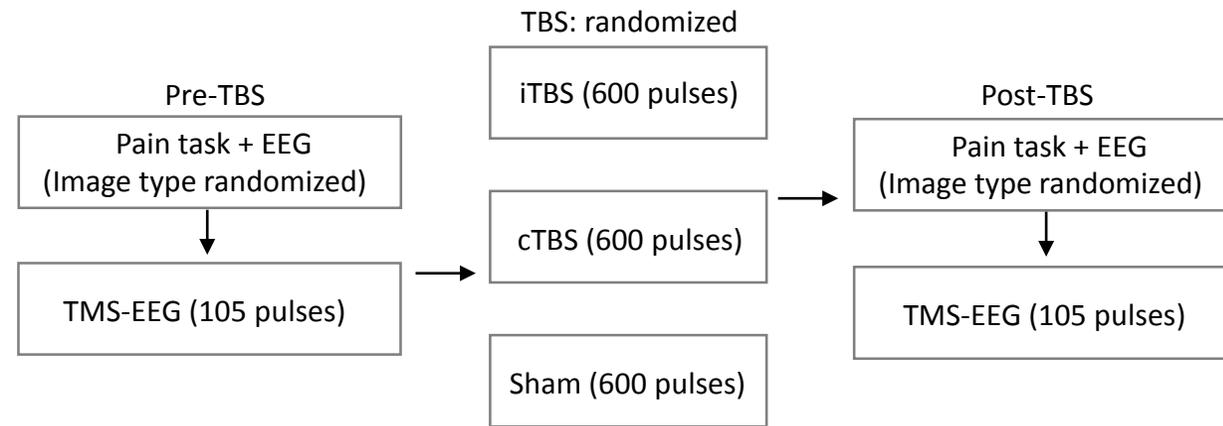
Fig. 6. EEG connectivity modulated by TBS protocols. (a) iTBS increased fronto-occipital alpha connectivity in the romantic partner condition. (b) In the stranger condition, iTBS increased central-

frontal and central-parietal theta connectivity. Large dots highlight the significant electrodes, and the color and thickness of the lines indicate the T statistics.

Table 1. Descriptive characteristics of the sample

	Sample size	Mean	Standard deviation
Gender	8 (M), 12 (F)	-	-
Age	20	26.45	4.54
BDI	20	2.2	2.46
STAY-Y2		36.5	6.47
MSPSS		6.03	0.82
PCS		12.9	9.39
DAS		117.55	10.15
ECR-R: anxiety		2.26	0.82
ECR-R: avoidance		2.13	0.77

M–male; F–female; SD–Standard Deviation; BDI–The Beck Depression Inventory; STAY-Y2–The State-Trait Anxiety Inventory-trait; MSPSS–The Multidimensional Scale of Perceived Social Support; PCS–The Pain Catastrophizing Scale; DAS–Dyadic Adjustment Scale; ECR-R–The Experiences in Close Relationships-Revised



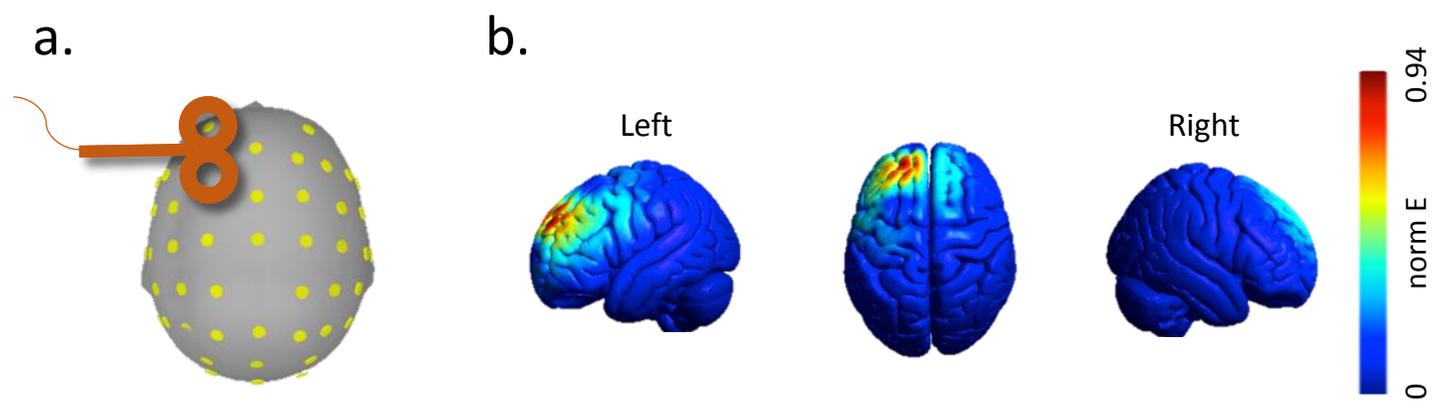


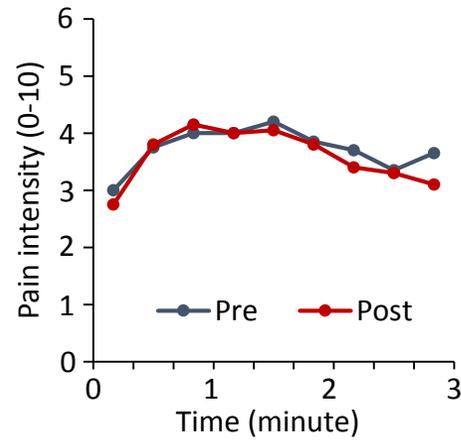
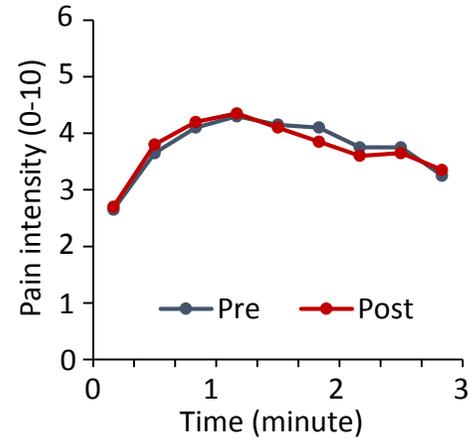
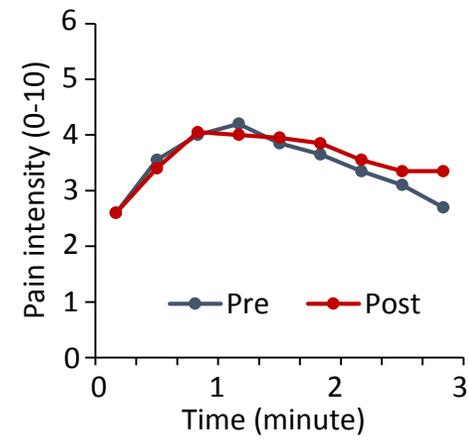
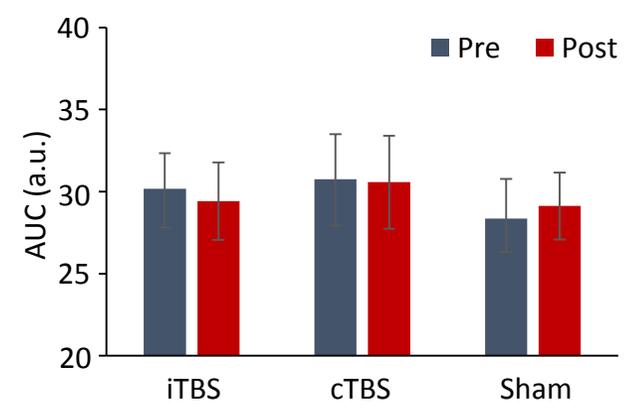
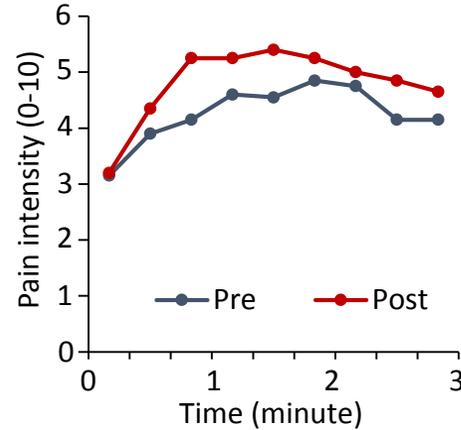
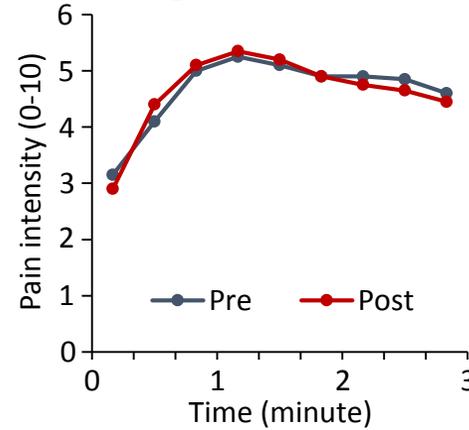
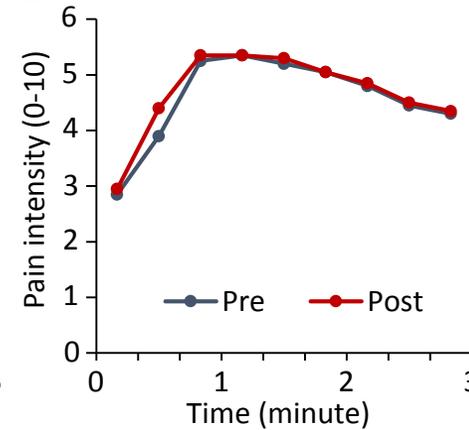
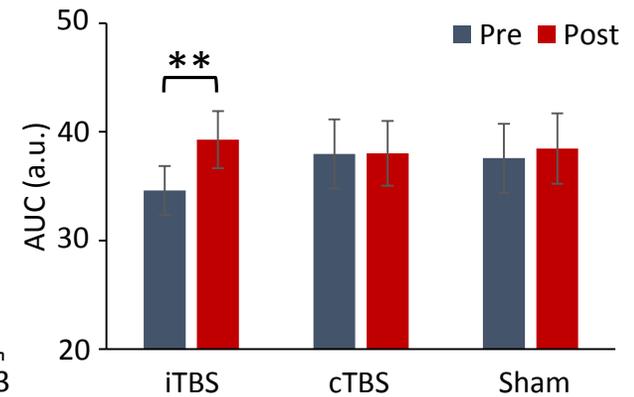
Fig. 3[Click here to download 9. Figure: Fig. 3.pdf](#)**a. Partner: iTBS****b. Partner: cTBS****c. Partner: Sham****d. Partner: AUC****e. Stranger: iTBS****f. Stranger : cTBS****g. Stranger : Sham****h. Stranger : AUC**

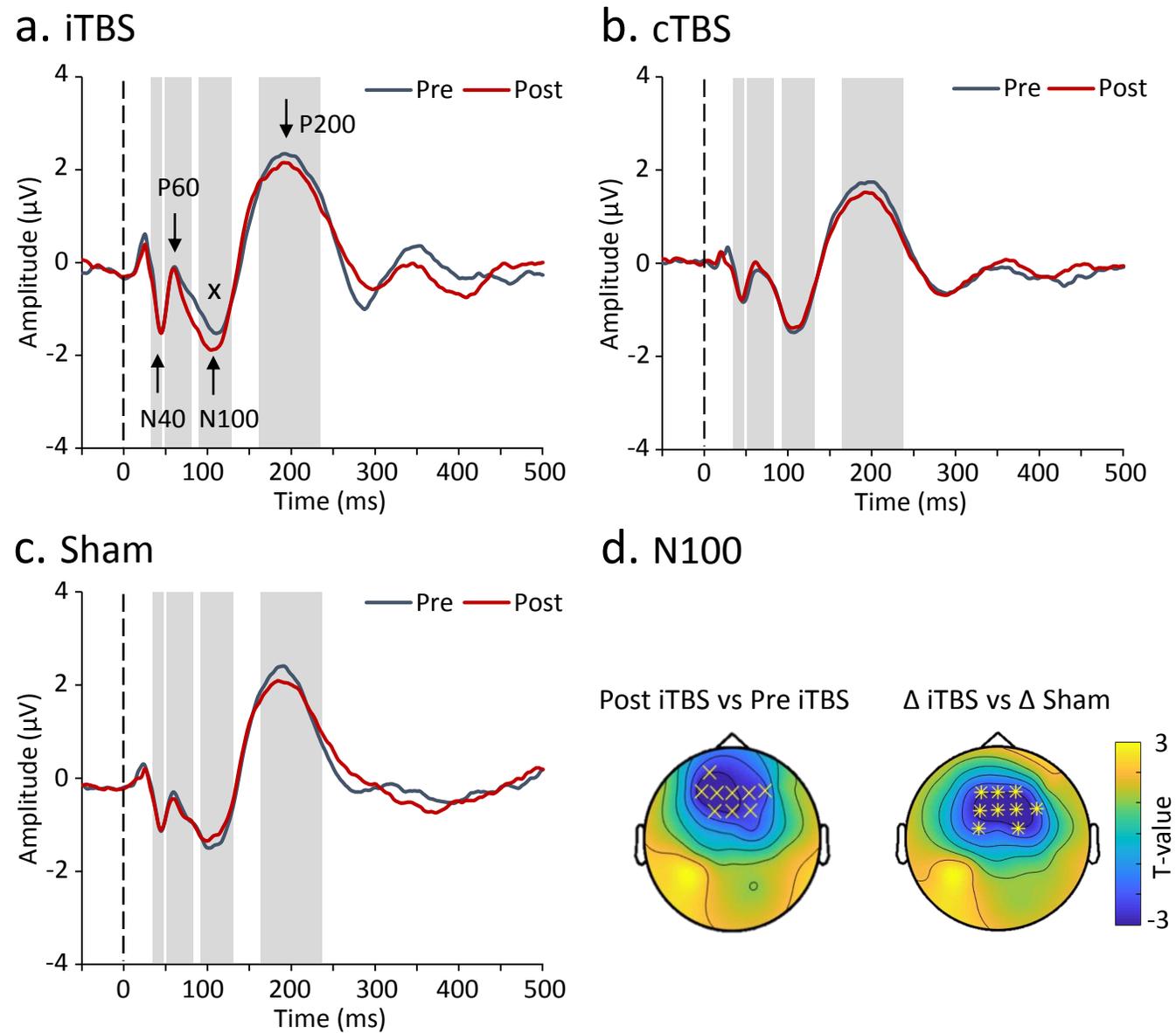
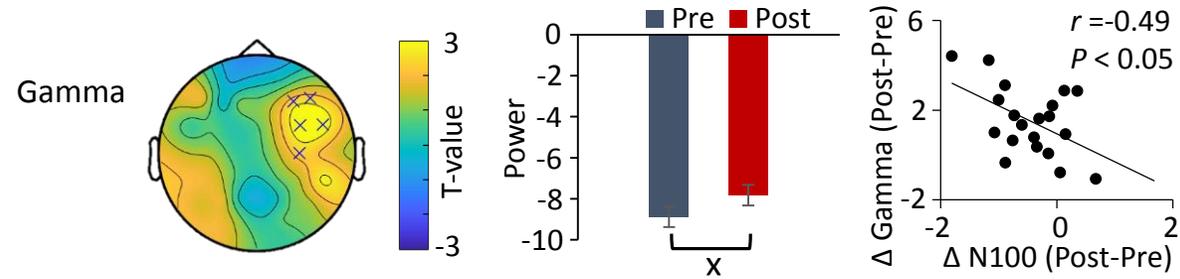
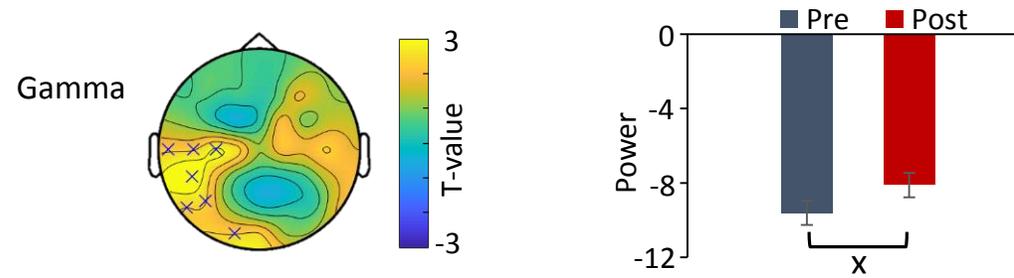
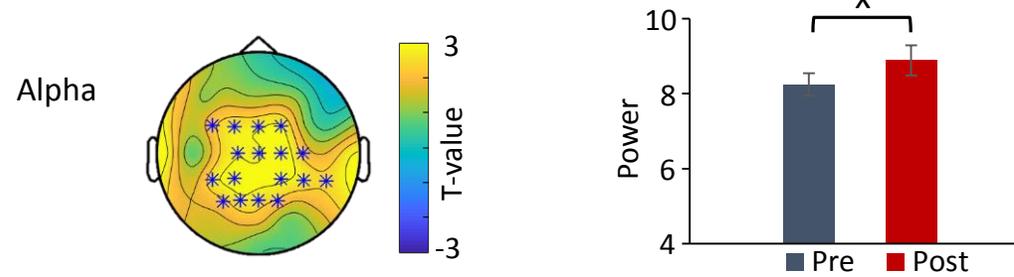
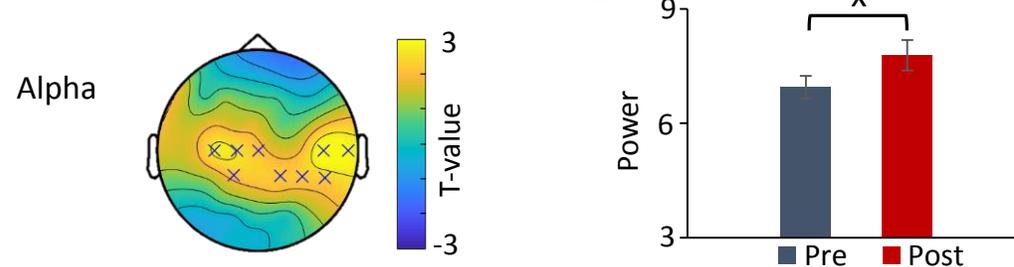
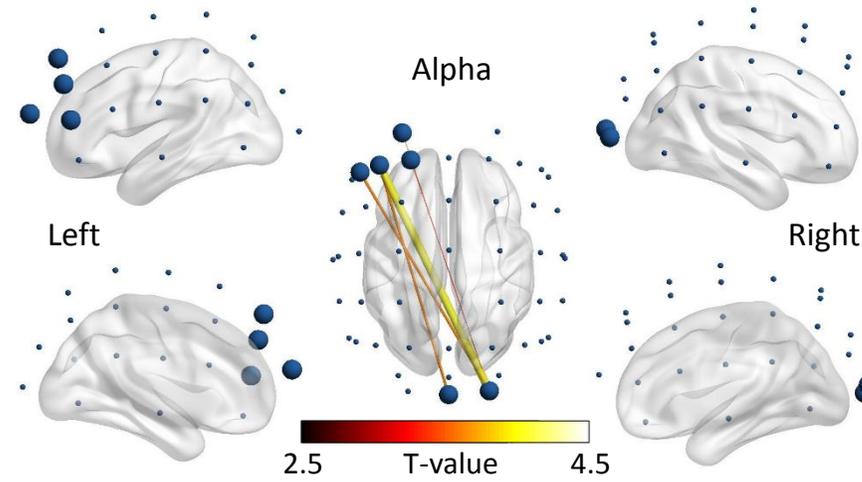
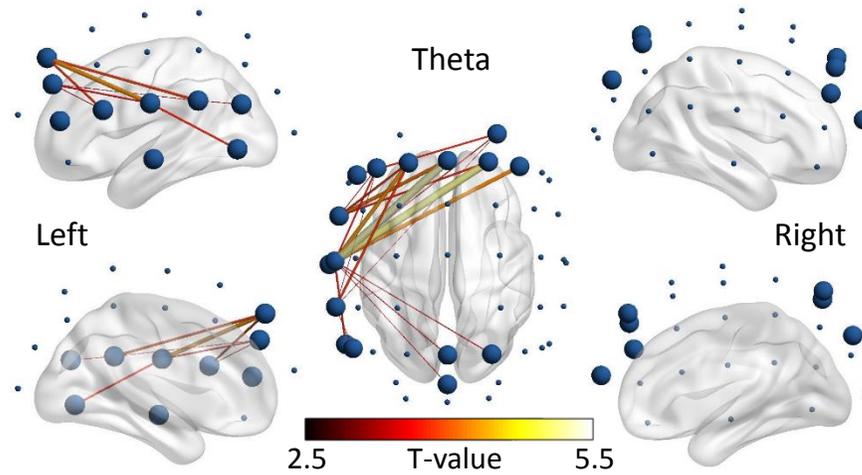
Fig. 4[Click here to download 9. Figure: Fig. 4.pdf](#)

Fig. 5[Click here to download 9. Figure: Fig. 5.pdf](#)**a. Post iTBS vs Pre iTBS : Partner****b. Post iTBS vs Pre iTBS : Stranger****c. Post Sham vs Pre Sham: Partner****d. Post Sham vs Pre Sham: Stranger**

a. Post iTBS vs Pre iTBS : Partner



b. Post iTBS vs Pre iTBS : Stranger



All data and Matlab codes are available upon request from the corresponding author.

CHAPTER SEVEN

General Discussion

This thesis examined the role of social support in pain experience and the underpinning neurophysiological mechanisms. The main findings are summarized below, followed by a discussion of potential implications. Limitations of the research and future directions for the field are also presented.

7.1. Summary of Main Findings

7.1.1. Chapter 2: Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis

Chapter 2 provided a systematic review and meta-analysis investigating the social context in which social support may have an analgesic effect and the magnitude of the effect. The results indicated that the presence of another person without any form of interaction, regardless of a stranger or a significant other, was not sufficient to modulate pain perception (e.g. pain ratings, tolerability, or threshold). However, the presence of a significant other was related to increased facial expression of pain, which was consistently observed across various close relationship pairings (i.e. a parent, romantic partner, and a family member). In contrast, when social support was provided actively, analgesic effects were observed. Specifically, verbal communication of support decreased pain experience. The majority of evidence for this effect were derived from verbal support from a stranger. Moderate to large analgesic effects were also seen in response to social touch or visual representation within intimate relationships. This was not observed from strangers. This review also

provided the first attempt to identify the influence of social support on pain-related physiological arousal. Although social support overall tended to reduce physiological arousal, results were highly limited by the small number of studies in this area. Finally, in an overall assessment of the literature, publication bias for pain-related arousal was observed but not for pain experience.

The primary finding of this investigation is that the effects of social support on pain are context-dependent and differ in magnitude. Not only does the relationship with the person providing support matter, so does the delivery of social support. In particular, social support may have the most analgesic impact when it is clearly communicated (e.g. verbal communication) or explicitly expressed by a significant other (e.g. touch, visual representation). Together with the evidence from a systematic review (Krahé et al., 2013), these findings may address the discrepancy whereby social support shows mixed effects on pain (Brown et al., 2003; Gallant and Hadjistavropoulos, 2017; Karmann et al., 2014; Modić Stanke and Ivanec, 2010; Vervoort et al., 2011). In addition, the findings presented within this chapter on the magnitude of the effects outline potential directions to develop social support strategies in the management of pain (e.g. social touch, verbal communication).

7.1.2. Chapter 3: A systematic review of the processes underlying the main and the buffering effect of social support on the experience of pain

In Chapter 3, we systematically reviewed the psychological and behavioural processes linking social support to pain reduction within two primary models of general health literature, i.e. the main and the buffering effect hypothesis. We also systematically reviewed the neurobiological mechanisms through which social support may reduce pain experience. Overall, the findings indicated that social support may reduce pain through buffering the adverse influence of pain-related stress. Further breakdown of the buffering effect suggested that the social-buffering effect derived from social support reappraising pain-related stress and facilitating coping attempts. This review also summarised the neurobiological evidence which, while few in number, indicated reduced activity

within neural (e.g. ACC, hypothalamus, insular cortex) and physiological (e.g. heart rate, skin response, blood pressure) stress systems to pain in the context of social support. Finally, this review presented an integrated model, i.e. the social-buffering model, which summarised the behavioural and neurobiological literature to account for potential pathways through which social support may have an analgesic influence.

This review is the first to present an integrative perspective of the processes and mechanisms by which social support may reduce pain. Previous studies have demonstrated separate evidence surrounding psychological (Holtzman and DeLongis, 2007; Vlaeyen et al., 2009) and behavioural processes (Holtzman et al., 2004; López-Martínez et al., 2008) as well as neural (Eisenberger et al., 2011; Younger et al., 2010) and physiological responses (Roberts et al., 2015) associated with the analgesic influence of social support.

However, most of the studies included in this review were cross-sectional correlational studies, in which pain experience and the threatening quality of pain were mixed and could be interchanged. Therefore, in combination with Chapter One, this review indicated the need for more investigation into the mechanistic evidence surrounding social support and pain. This leads to the following empirical studies within this thesis to investigate the mechanisms underpinning the influence of social support on pain, with key findings outlined below.

7.1.3. Chapter 4: The social regulation of pain: autonomic and neurophysiological changes associated with perceived threat

Chapter 4 directly investigated the social-buffering hypothesis by introducing threat of pain before the onset of painful stimuli. This was the first study to separate threat of pain from pain experience. Using EEG and ECG, we recorded neural and autonomic response to the threat of pain in a six second period prior to the administration of a painful stimulus. Participants underwent this paradigm either

holding the hand of a significant other, a stranger, or no hand-holding. The behavioural results demonstrated that social support, as manipulated by holding hand of a significant other, decreased pain perception compared to no hand-holding. We also identified that holding hand of a significant other resulted in decreased heart rate and frontal theta activity (4-8 Hz) in the threat-of-pain phase. Using correlation analysis, we found that decreased heart rate and frontal theta activity were associated with less pain perception in the significant other compared with no-holding condition. Significant neural changes in frontal theta activity were further localized to the insular cortex and the rostral-ventral portions of anterior cingulate cortex which were commonly observed in the processing of pain and stress. These findings support the buffering effect whereby attenuated threat response to pain can predict pain reduction in the context of social support. Notably, holding hand of a stranger had no overall effect on pain perception or autonomic response but decreased posterior theta activity compared to no hand-holding.

The study is significant as it directly demonstrates mechanistic processes involved in the buffering effect through which social support may act to reduce pain. Specifically, social support may decrease neural (i.e. frontal theta) and autonomic (i.e. heart rate) threat response to pain which is further associated with pain reduction. The results of this study also indicated the significance of relationship quality in the social modulation of pain as holding hand of a stranger had no overall effect on pain perception or autonomic response.

7.1.4. Chapter 5: Distinct neural dynamics and autonomic activity in response to viewing a romantic other compared to a stranger during pain: An EEG and HRV investigation

Chapter 5 presented a study investigating the neural dynamics and parasympathetic activity associated with the effects of social support on pain. This extended Chapter 4 by providing evidence on how social support may modulate neural oscillations and parasympathetic activity supporting the processing of pain and threat. In this study, social support was manipulated by visual representation

of an intimate other or a stranger while participants underwent cold pain over several minutes. The results indicated that social support reduced pain perception, with the effect being most prominent in the phases when pain experience stabilises and then desensitises. Further, participants reported higher overall perceived support in the social support condition, which was associated with lower pain perception. The neural oscillation data revealed higher frontocentral alpha activity (8-12 Hz) and lower central gamma activity (31-100 Hz) in the social support compared to the stranger condition. A correlation was observed between decreased pain and reduced central gamma activity in the social support condition. In addition, social support was associated with higher HF-HRV compared to the stranger condition.

The results of this study are significant as they demonstrate oscillatory changes supporting the role of social support in modulating the processing of nociceptive information. Previous studies have suggested that social support may buffer pain-related neural systems, such as the ACC and insular cortex (Eisenberger et al., 2011; Younger et al., 2010). Using EEG, this study demonstrated increased alpha but decreased gamma activity in the social support condition, which are thought to underlie early nociceptive attention and the subsequent subjective experience of pain respectively (Nickel et al., 2017; Peng et al., 2014). Social support may therefore buffer the gating and integration of painful information as relevant to the changes in ACC and insular cortex observed in earlier fMRI studies.

The results of this study also identified increased PNS activity in the social support condition. The literature to date has focused on the SNS whereby social support may be able to decrease sympathetic arousal to pain (Roberts et al., 2015; Sambo et al., 2010). This study provided the first line of evidence that social support may increase parasympathetic activity to pain which is believed to be associated with the regulatory control over sympathetic arousal (Thayer et al., 2009). Overall, the neural dynamics and PNS activity add a novel understanding to how social support may reduce pain.

7.1.5. Chapter 6: The medial prefrontal cortex as a flexible hub mediating behavioural as well as local and distributed neural effects of social support on pain: a theta burst stimulation and TMS-EEG Study

Chapter 6 contained a study to explore the causal role of the mPFC in orchestrating the behavioural and neural connectivity effects of social support on pain. The mPFC is thought to process social intimacy (Gamond and Cattaneo, 2016; Gamond et al., 2017) and is positively associated with perceived social support (Che et al., 2014). In this study, state-of-the-art neurophysiological methods were applied to modulate the activity of the mPFC, as well as explore changes in frequency dynamics and neural connectivity. Participants underwent a three-session protocol in which the activity in the mPFC was either increased (iTBS), decreased (cTBS), or not changed (Sham). Pain in the context of social support was manipulated both Pre- and Post-stimulation using the same protocol as Chapter 5. The results indicated that iTBS over the mPFC modulated pain perception and neural connectivity in a context-dependent manner. Specifically, in the stranger condition, iTBS increased pain perception and neural connectivity between central regions and frontoparietal regions from Pre- to Post-stimulation. In contrast, in the social support condition, iTBS did not modulate pain perception and increased connectivity only between frontal and occipital regions from Pre- to Post-stimulation. In line with these changes, iTBS resulted in a larger N100 amplitude around the frontal cortex as an index of neuroplasticity. However, neither cTBS nor Sham stimulation elicited neural or behavioural changes.

Compared to previous studies exploring brain activity supporting social support effects on pain (Eisenberger et al., 2011; Younger et al., 2010), this study directly modulated the activity of the mPFC using TBS. In contrast to the null hypothesis, iTBS produced increased pain perception in the stranger condition, which may be associated with the role of the mPFC in inferring the help motivation of another person (Harmer et al., 2001; Schuwerk et al., 2014). However, iTBS over the mPFC did not reduce pain perception in the social support condition. This study was also able to

provide novel evidence on brain-wide dynamics, whereby increased alpha band connectivity after iTBS may underpin the processing of social support (Goldstein et al., 2018) in the romantic partner condition and increased theta band connectivity may support pain-related information integration in the stranger condition (Taesler and Rose, 2016). Overall, these findings suggest that the mPFC has the capacity to causally modulate the influence of social support on pain perception and associated neural coupling in a context-dependent manner.

In addition, this study indicated a larger N100 amplitude following iTBS, which demonstrated neuroplasticity changes related to social support effects on pain. The N100 may reflect the shifts in the inhibition-excitation balance in cortical circuits (Du et al., 2018; Rogasch and Fitzgerald, 2013), although its specific neurophysiological functioning remains to be established.

7.2. Implications

There are a number of key implications arising from the findings of this thesis. These findings may theoretically improve our understanding of the social context in which social support may have an analgesic influence and the underlying mechanisms. This thesis also introduced novel neurophysiological techniques that may be used to explore the mechanistic evidence surrounding social support and pain. Indeed, the work presented here represents the first application of EEG, TBS and TMS-EEG to investigate neural oscillations, neural connectivity, and neuroplasticity underpinning the influence of social support on pain. While not directly explored in this thesis, the findings from this body of work may help optimise the use of social support strategies in the management of pain by better understanding the contexts and mechanisms of social support in pain.

7.2.1. Understanding the Effects and Mechanisms of Social Support on Pain

This thesis has contributed to understanding the complex influence of social support on pain. The literature to date has suggested mixed effects of social support on pain (Brown et al., 2003; Gallant and Hadjistavropoulos, 2017; Vervoort et al., 2011). Chapter 2 (Study One) explored these effects and demonstrated them to be context-dependent that how support is delivered (i.e. actively or passively) matters as dose who is providing the support. Moreover, this study quantified these effects using a meta-analysis. Overall, social support may have the strongest protective effect on pain when it is clearly expressed through verbal communication or explicitly delivered (e.g. touch, visual representation) by an intimate other. This conclusion is further supported by the empirical studies in the subsequent chapters (Chapter 4 and 5).

The findings from the thesis also improve our understanding of the mechanisms through which social support can decrease pain. Chapter 3 (Study Two) presented an integrated perspective, the social-buffering model of pain reduction, which indicated that social support may reduce pain through modifying the behavioural and neurobiological stress systems. Chapter 4 (Study Three) directly demonstrated the buffering hypothesis in which social support reduced pain by buffering the neural and autonomic responses to the threat of pain. In Chapter 5 (Study Four), social support was found to modulate the gating (i.e. alpha power) and integration (i.e. gamma power) of nociceptive information. Changes in alpha and gamma activity are suggested to be generated from the sensorimotor cortex and prefrontal cortex respectively which encode stimulus intensity and sensory integration of pain (Nickel et al., 2017; Schulz et al., 2015). Therefore, Chapter 5 added further evidence to the social-buffering model in which reduced gating and integration of nociception may be closely related to brain activities encoding pain and threat. In Chapter 5, social support was also associated with increased bodily control over pain-related arousal (i.e. HF-HRV), which is consistent with the attenuated neurobiological stress systems in the social-buffering model. In addition, Chapter 6 (Study Five) demonstrated a causal role of the mPFC in orchestrating neural

networks supporting the processing of social support (i.e. alpha coupling) and pain (i.e. theta coupling). This indicates the relevance of the mPFC in priming feelings of attachment and buffering pain and related threat (Eisenberger and Cole, 2012; Eisenberger et al., 2011). Overall, the results of these series of findings indicate a mechanistic pathway in which social support may suppress neurophysiological response to pain that possibly arising from its priming influence on perceived attachment.

Beyond the social context, findings in this thesis also extend the neural mechanisms of pain. The insular cortex and ACC are suggested to represent interoception and to produce behavioural drive respectively in the 'interoception' perspective (Craig, 2002, 2003a, b). These two regions are also the key nodes of the 'salience network' (Legrain et al., 2011; Seeley et al., 2007). As shown in Chapter 4 (Study Three), our finding demonstrates that ACC and insula activity may be represented as EEG theta oscillation in the context of upcoming painful stimuli. Therefore, this result may add neurophysiological evidence to the pain mechanisms.

7.2.2. Novel Neuroimaging Techniques to Reveal the Mechanistic Evidence

Another implication of this thesis is the use of novel neuroimaging techniques to investigate complex human experiences, in this case how social support may influence pain experience from a mechanistic perspective. Compared to functional imaging and neurophysiological recordings, TBS is capable of modulating brain activity (Chung et al., 2016; Chung et al., 2017; Huang et al., 2005) and therefore provides a window to investigate the brain-behavioural relationships. In Chapter 6 (Study Five), activity of the mPFC was modulated using TBS and the results demonstrated a causal role of the mPFC in mediating the behavioural and network changes related to social support and pain. Furthermore, neuroplasticity changes caused by TBS were assessed using TMS-EEG in this study. By analysing TEPs and TMS-evoked oscillations TMS-EEG can provide valuable information on neuroplasticity changes underpinning behavioural performances (Chung et al., 2018a; Chung et al.,

2018b; Hill et al., 2017). Interestingly, Chapter 6 found a positive relationship between a larger N100 amplitude and frontal gamma activity following iTBS. This finding provides direct evidence that neuroplasticity changes induced by iTBS are associated with brain activity involved in the social modulation of pain. Overall, these techniques advanced our understanding of how the mPFC may mediate the influence of social support on pain. This work extends the previous work using fMRI (Eisenberger et al., 2011; Younger et al., 2010) by causally modulating the activity in the mPFC and measuring changes in neural coupling and neuroplasticity. To our knowledge, this is the first study to use TBS and TMS-EEG in the social modulation of pain and we expect it to lead to future TMS and TMS-EEG studies on this topic due to its ability to provide rich information on causality and neuroplasticity.

Further, this thesis simultaneously assessed neural and autonomic responses which is important to understand the integration of the CNS and ANS as well as their relevance in pain and social support. Chapter 4 (Study Three) indicated attenuated theta activity and a smaller heart rate acceleration evoked by the threat of pain under social support. In Chapter 5 (Study Four), social support decreased the gating (i.e. alpha power) and integration (i.e. gamma power) of painful information but increased bodily control over pain-related arousal (i.e. HF-HRV). Although the direct association between neural and autonomic responses were not found, these studies provided comprehensive evidence on how social support can help manage the neural and physiological systems mediating pain and related threat.

In addition, brain-wide dynamics were evaluated in Chapter 6 (Study Five), which demonstrated network configurations potentially supporting the processing of social support and pain. This is highly novel as it provides a network perspective to account for the social modulation of pain beyond the separate brain activations.

7.2.3. Translational Implications for Social Support Strategies in the Management of Pain

In the past three decades, studies included a spouse in the management of chronic pain (Abbasi et al., 2012; Keefe et al., 2004; Keefe et al., 1996, 1999; Martire et al., 2003; Martire et al., 2007, 2008; Moore and Chaney, 1985; a family member in Radojevic et al., 1992). These programs usually included coping skills training (e.g. distraction, activity-based skills, and cognitive restructuring) and couple skills training aimed to supplement the effects of coping skills. Most of the studies indicated that adding a spouse resulted in less pain and/or increased psychological adjustment to pain (Abbasi et al., 2012; Keefe et al., 2004; Keefe et al., 1996, 1999; Martire et al., 2003; Martire et al., 2008; Radojevic et al., 1992), with a few studies demonstrating no add-on effects of a spouse (Martire et al., 2007; Moore and Chaney, 1985). The findings from this thesis may have implications for improving the integration of a romantic partner, or alternative a close other, in pain management.

A key finding of the thesis was that social support may reduce pain through modifying the neural and physiological stress systems to pain and related threat (Chapter 3 to 5). This finding indicates the critical role of social support in helping people with chronic pain reappraise the threatening quality of pain and the perceived efficacy to cope with pain. Indeed, in the spouse-assisted pain management programs, patients who had increased self-efficacy over the course of the program had significant improvement in pain, physical disability, and psychological adjustment (Keefe et al., 1996). Moreover, the modulating impact of self-efficacy on these outcomes was observed at 6-month and 12-month follow-up (Keefe et al., 1999). Therefore, social support strategies may have better outcomes whereby the support provider can help people with chronic pain feel less threatened by the chronic condition and enhance their perceived competence and efficacy to cope with pain.

Another important finding of the thesis was the significance of intimate relationships in pain reduction (Chapter 2, 5, and 6). An intimate relationship is suggested to increase emotional

communication between the couple (Goldstein et al., 2017) and to prime feelings of attachment and reward (Eisenberger et al., 2011; Younger et al., 2010). Keefe and colleagues (1996, 1999) demonstrated that the efficacy of a spouse-assisted pain management program was largely determined by the changes in marital adjustment over the program, whereby patients showed increased marital satisfaction had much better outcomes than others. Therefore, social support therapies may wish to include an intimate other where possible. Moreover, perceived intimacy could be an area of therapeutic focus in the spouse-assisted pain management programs, potentially through mutual activities and verbal communication and validation (Keefe et al., 1996, 1999). That is, including a focus on improving relationship quality as part of the pain-management program.

The findings from this thesis also indicated the importance of how social support is presented. Specifically, conveying social support in an explicit manner (e.g. through verbal support) may reduce pain. In contrast, the mere presence of a significant other may not be sufficient to reduce pain and may even increase the facial expression of pain. This may be caused by the pain sufferer being unclear of the social partner's intention and ability to help (Krahé et al., 2013), or the presence of a significant other enhancing pain behaviours in order to seek empathy (Williams, 2002). These findings suggest that supportive others in pain management should provide support in a clear manner. It also suggests that the mere presence of a significant other should be avoided, or behaviours and interactions addressed, where it results in increased pain behaviours.

In addition to spouse-assisted programs, this thesis also supports the efficacy of self-help support groups in the management of chronic pain. One study revealed increased functional ability and decreased recourse to health professionals following a self-help support group, which was characterized by participating group outdoor activities, sharing knowledge on the chronic pain condition, and developing mutual support between group members (Subramaniam et al., 1999). Chapter 2 (Study One) indicated verbal support, even from a stranger, can communicate support

and reduce pain perception. Chapter 5 and 6 further suggested the significance of intimate relationship in decreasing pain and nociceptive information integration. These findings collaborate the self-help support groups in promoting verbal communication and building close relationships between group members.

This thesis also suggests the use social support strategies in pain-related procedures. There is evidence that gentle social touch can effectively reduce pain and crying in newborns undergoing a procedure (e.g. heel lance procedure) (Gray et al., 2000; Herrington and Chiodo, 2014). Our results demonstrated moderate to larger effects of social support on pain by social touch. In addition to skin-to-skin touch, our findings also indicate other social support variants, e.g. verbal support, which may be used to manage pain in other age groups (e.g. children, adults) and procedures (e.g. dental procedures).

7.3. Methodological Considerations

There are several important considerations which apply across the empirical studies in this thesis. Awareness of these will be important for future investigations to explore the effects and mechanisms of social support on pain. For limitations specific to individual empirical studies, the reader is directed to the relevant thesis chapters.

7.3.1. EEG Analysis

EEG has been extensively used as a neuroimaging technique. Adequate offline data cleaning steps are essential for the removal of various, often large-amplitude artefacts in EEG data. There are different pipelines to clean EEG data and a semi-automatic pipeline running under MATLAB (The MathWorks Inc, Natick, MA) was used in this thesis. An important limitation of this pipeline is that

components representing artefact must be manually selected for removal by the experimenter, which could potentially lead to a level of subjectivity. We have tried to concatenate the data from different experimental conditions to reduce the subjectivity. There are also fully-automatic cleaning pipelines (Bigdely-Shamlo et al., 2015; Winkler et al., 2011), which in a way can control the subjectivity but the results may be influenced by the embedded algorithm and thresholding. As EEG analysis techniques continue to evolve, it would be essential to develop more objective frameworks for cleaning and analysing EEG data.

7.3.2. Sampling Considerations

All of the empirical studies in this thesis recruited healthy participants from the local universities and neighbourhoods as approved by the Alfred Hospital and Monash University Human Resources and Ethics Committee. This may limit the translation of our findings to chronic pain populations. Both behavioural patterns and the central nervous system undergoes significant change in chronic pain (Apkarian et al., 2011; Lumley et al., 2011). Therefore, behavioural and neural responses to social support in clinical groups may have a differential effect as seen in this thesis. There are several studies investigating the role of social support in chronic pain in experimental settings. One study found that the presence of a romantic partner reduced pain and related somatosensory activity in fibromyalgia (Montoya et al., 2004). Another study demonstrated decreased daily pain in the visual representation of a significant other among people with chronic pain (Shaygan et al., 2017). These studies provide valuable information on the effects and mechanisms of social support in chronic pain and more studies of this are needed.

The sample sizes used in the present studies were also relatively small (N = 18-23). A limitation in Chapter 4 was that a power analysis was not performed. For the studies described in Chapters 5 and 6, we performed a power analysis using G*Power (<http://www.gpower.hhu.de/en.html>). The analyses yielded a sample size of 24, which should provide a power of greater than 95% to identify a

large effect size at an alpha value of 0.05 when using a Repeated Measures ANOVA. Further, the samples in the thesis have a relatively narrow age range, mainly consist of young adults. This may limit the generation of the conclusions to other age ranges, e.g. older adults or children. In addition, the sample sizes did not allow the examination of sex differences in the social modulation of pain. Sex effects may be of note, given research suggesting female pain recipients may benefit from social support more than men (Jackson et al., 2005), as well as biological sex differences which may influence mechanistic processes. Future studies might wish to use a larger sample with wider age range, capable of exploring sex effects.

7.3.3. Social Support Paradigms

It is noted that both social touch and primed social support were manipulated in this thesis, as they both have been demonstrated to have a protective effect on pain experience (Chapter 2, Study One) and are both ecologically valid. However, it is possible that different social support paradigms have different effects, as our systematic and meta-analysis review revealed (Chapter 2). In the work of this thesis, the paradigms differed due to differences in the requirements of the study. For chapters five and six, participants were required to attend for three sessions. Thus, we chose to use primed social support to increase the likelihood we would be able to recruit volunteers. Human touch communicates distinct emotions (Hertenstein et al., 2006) and thus it provides an excellent protocol to investigate distinct relationships. Indeed, social touch by a romantic partner may promote intimacy (Goldstein et al., 2017) while by a stranger may be somewhat socially uncomfortable (Krahé et al., 2013). But it remains to be determined the shared and distinct effects between social touch by a romantic partner and by an acquaintance. It is also noted that no hand-holding was used as a control condition which may differ from social touch in sensory input and attention and thus holding an object would be considered in future studies. In addition, socially desirable effects need to be considered when participants reported pain experience in the presence of a significant other. Similarly, primed social support was found to reduce pain (Chapter 5, Study Four) and this effect was

suggested to arise from its role in priming feelings of attachment (Chapter 6, Study Five) and modulating the transmission and integration of nociceptive information (Chapter 5, Study Four). This paradigm was used in this thesis to be compatible with previous functional imaging studies (Eisenberger et al., 2011; Younger et al., 2010). But this paradigm is slightly different from the proposed spousal pain therapies whereby a spouse is present. Findings from this paradigm indicate the potential benefits of a mental imaginary component in spousal pain coping therapies. These findings also have direct implications for coping with procedure pain, e.g. a dental procedure.

The majority of social support protocols in the literature have targeted on emotional support. Other types of social support, such as the informational and instrumental support, have been less investigated. It is possible that different types of social support may have distinct effects on pain experience (Cohen and Wills, 1985; DeLongis et al., 1988; Lee et al., 2016), and thus a more comprehensive understanding on the impact of multiple forms social support types is needed. We also used different types of close relationships in chapter four. It is possible that different types of close relationships have different effects (Chapter 2) and more research is required into this area.

7.3.4. Relationship Quality

The empirical studies did not require a certain level of relationship quality between the pain recipient and the support provider for eligibility. This may limit the comparability of our findings to other studies which only included early stage romantic relationship (Younger et al., 2010) or highly satisfied relationship (Coan et al., 2006). Nonetheless, we demonstrated significant pain reduction in Chapter 3 and 5. Moreover, we have recorded the relationship quality in the last two empirical studies but found no association between relationship quality and pain or neurophysiological changes. In contrast, we did observe a positive relationship between overall perceived support and pain reduction in Chapter 5. Whilst relationship quality was more general, overall perceived support

was measured during the pain task and specific to the ongoing pain. It is possible that situational (e.g. online social support) and global (e.g. relationship quality) social support has distinct roles in pain experience (Corley et al., 2016). Future studies are needed to further examine the distinct impact of situational and global support on pain.

7.3.5. Pain Induction

It is noted that bottled iced water was used to induce ongoing pain in chapter 5 and chapter 6, compared to previous studies in which cold pressor test (CPT) was used (Brown et al., 2003; Edwards et al., 2017). A recent study demonstrated the effectiveness of bottle iced water in inducing cold pain (Hadjileontiadis, 2015). We chose this method as it can induce ongoing cold pain that is tolerable to the participants for the duration of the experimental conditions. The CPT was problematic in this context as participants may need to withdraw their hand prior to the completion of the condition. However, one limitation of the bottled iced water was condensation on the surface of the bottle. To control for this, we used a fresh bottle before each condition and precisely controlling the timing to take out the bottle from the freezer to minimise condensation.

7.3.6. Potential Additional Modulating Factors

Pain is influenced by a wide range of psychological and social factors that are integrated, along with the sensory input, to create a pain experience. Current evidence has suggested the particular relevance of several personality and social factors in the social modulation of pain, including adult attachment style, pain catastrophizing, and the motivation to help by the social partner. Adult attachment style describes individual differences in representational models of close relationships (Bowlby, 1969). Sambo and colleagues (2010) found that individuals with high attachment avoidance reported more pain in the presence relative to the absence of a stranger. Avoidant individuals tend to mistrust social relationships (Bowlby, 1969; Feeney and Noller, 1990; Main, 2000), thus the

presence of a total stranger may be associated with increased anxiety and pain perception (Sambo et al., 2010). In a following study, avoidant individuals reported more pain and N2 and P2 laser-evoked potentials (LEPs) in the presence relative to the absence of a romantic partner. These findings further corroborated the modulating role of attachment style and suggested mechanistic evidence in which attachment avoidance may modulate the perceived salience of painful stimuli (Krahé et al., 2015).

Another important factor that may influence the impact of social support on pain is pain catastrophizing. Pain catastrophizing is defined as ‘an exaggerated negative mental set brought to bear during actual or anticipated painful experience’ (Sullivan et al., 2001). In the presence of a stranger, high pain catastrophisers express more pain behaviours (e.g. facial displays, vocalizations) and utilise fewer coping strategies that might minimise pain (Sullivan et al., 2004). In contrast, another study found no difference in pain expression among high-catastrophizing children when alone or in the presence of a parent. Instead, low-catastrophizing children expressed more pain in the presence of a parent (Vervoort et al., 2011). Pain catastrophizing may be also relevant to the role of social support in chronic pain conditions. In a group of chronic pain population, pain catastrophizing was found to interact with social support in the prediction of emotional health (Holtzman and DeLongis, 2007). Therefore, while the influence of pain catastrophising has not shown consistent effects, the modulating role of pain catastrophizing warrants further investigations. In addition, there are other pain-related cognitions that may also have an impact, such as helplessness, fear of movement/(re)injury, and sense of mastery (Bunketorp et al., 2006; Waltz et al., 1998).

A line of research indicates motivation of the social partner to help the person in pain to be of particular importance in determining the effects of social support on pain experience. The spouses of people with chronic pain may provide help for autonomous or volitional motives (e.g. enjoyment,

full commitment) or rather for controlled or pressured (e.g. avoiding guilt and criticism) motives (Kindt et al., 2016). Studies have largely indicated that social support may have protective effects on emotional health of people with chronic pain only when the help is out of volitional motives (Kindt et al., 2018a; Kindt et al., 2018b). Moreover, this effect is suggested to be accounted for by the improvements in the need satisfaction of the pain sufferer (Kindt et al., 2015; Kindt et al., 2016). Future studies may wish to further characterise the role of helping motivation in social support effects on pain, and the influence of this on mechanistic findings.

7.4. Future Directions

The present findings provide the initial groundwork for a number of future explorations. In addition to large sample replication studies of those presented here, this also includes evaluating the synchronisation between the pain recipient and the support provider using hypescanning, investigating the role of oxytocin in the social modulation of pain, social network analysis, using TMS and TMS-EEG in social support and pain, and investigating the role of helping motivation of the social partner.

7.4.1. Using Hypescanning to Reveal the Synchronisation between Social Partners

Recent advances in neuroimaging techniques allow to simultaneously monitor the brain or body activity of several persons engaged in an interpersonal mutual exchange ('hypescanning') (Babiloni and Astolfi, 2014; Dumas, 2011; Dumas et al., 2011). Due to its high temporal resolution, EEG has been largely used to evaluate synchronised brain activity using hypescanning systems (Wang et al., 2018). In a recent study, Goldstein and colleagues (2018) found increased between-partner alpha band coupling while individuals held hand of a romantic partner during pain administration. Moreover, increased coupling in this network was associated with less pain and increased

empathetic accuracy of the romantic partner. This study provides the first line of evidence that brain-to-brain coupling is involved in the analgesic influence of social support. In another study, the authors from the same group demonstrated decreased pain and increased heart rate coupling between romantic couples during social touch and pain administration. Beyond pain research, hypescanning has been used in a variety of social interactions, e.g. imitation (Dumas et al., 2010), social coordination (Tognoli et al., 2007). This technique will provide valuable information on how synchronised activity between the pain recipient and the social partner may mediate the effects of social support on pain.

7.4.2. Oxytocin in the Social Modulation of Pain

The hypothalamic peptide oxytocin has been largely linked to positive social interactions (Chen et al., 2011; Holt-Lunstad et al., 2008; Light et al., 2005) and has analgesic effects (González-Hernández et al., 2014; Paloyelis et al., 2016). Further, intranasal administration of oxytocin enhanced the buffering effect of social support on cortisol response to a psychosocial stressor (Heinrichs et al., 2003). Only recently has one study directly explored the role of oxytocin in the analgesic effect of social support (Kreuder et al., 2018). In this study, intranasal administration of oxytocin increased the analgesic effect of social support, which was associated with a stronger decrease in anterior insular, a larger increase in the middle frontal gyrus, and a higher functional coupling between these two regions. This study firstly demonstrates that oxytocin may increase the benefits of social support on pain and that this effect may be mediated by brain activity involved in cognitive control and pain inhibition. Future studies are needed to further reveal how oxytocin can mediate the analgesic influence of social support. In addition, oxytocin may be administered in partner-assisted pain management therapies to potentially increase the benefits of social support.

7.4.3. Social Network Analysis

Social network analysis (SNA) is an emerging technique in sociology which may serve as a valuable tool in the investigation of social support and pain. SNA characterizes networked structures in terms of nodes (e.g. a person within the network) and links (e.g. relationships or interactions) as well as a series of other characteristics (e.g. bridge, centrality) (Otte and Rousseau, 2002). Using SNA, a recent study demonstrated a positive association between pain tolerance of an individual and the pain tolerance of his or her friends. Specifically, for every one second increase in friends' average pain tolerance, the expected pain tolerance of the individual increased by 0.21 second (Engebretsen et al., 2018). Using this technique a variety of questions could be addressed surrounding social support and pain. For example, from which types of social support can a certain pain sufferer benefit the most? How the strength of relationship can affect pain perception? What are the changes in social networks and social relationships as a result of pain? It is expected to see more SNA investigations in social support and pain, providing rich information in the broad impact of an individual's social network. This has the potential to provide novel information outside of the targeted and specific relationship pairings currently used within this field (e.g. romantic other, family etc).

7.5. Conclusions

Social support plays a role in pain experience, however, the influence of social support on pain is context-dependent. The findings presented in this thesis contribute to our understanding of this effect. To our knowledge, this thesis provides the first meta-analysis of the magnitude of effects of different social support contexts, and it provides the first EEG, TBS and TMS-EEG investigation of potential underlying mechanisms. Overall, the findings presented here support that social support generally has a protective effect on pain, particularly when it is clearly expressed by a significant other. In addition, the analgesic influence of social support may be associated with the role of social support in buffering neurophysiological stress systems to pain, impacting on the integration and

gating of pain signals. Finally, we provide a world-first study, directly modulating the activity of the medial prefrontal cortex, and identifying the role of this region in the social-buffering effect through orchestrating the neural networks underpinning social support and pain. It is hoped that this body of work will contribute to the understanding of the effects and potential mechanisms of social support in pain which may ultimately have therapeutic implications and improve the lives of those living with pain.

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APPENDIX A

Supplemental Material for Research Chapters

The following is the supplemental material for the study entitled "*Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis*" which forms Chapter Two of this thesis.

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#5	Add	Search (pain[MeSH Major Topic]) AND "social modulation"[MeSH Major Topic] Filters: Journal Article; Full text; Publication date to 2017/08/31; Humans; English	0	20:48:50
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4. [Affective empathy, cognitive empathy and social attention in children at high risk of criminal behaviour. \[References\].](#)

Supplementary Material S2: Methodological study appraisal

Each criterion was judged as either:

“Successfully fulfilled” (1);

“Partially fulfilled (0.5);

“Not fulfilled” (0).

1. Reported blinding processes of study purpose to participants.

2. Similar gender distribution across all condition/group.

© As long as the support and no-support condition have the same distribution.

3. Specification of stimulus location.

4. Specification of physical type of stimulus.

5. Report on psychophysical method of threshold determination.

© 0.5 was given to studies using cold pain as the temperature was consistent.

6. To which extent the study population represents the true population.

© 0.5 was given to studies having 1 SD of the sample size generated from this meta-analysis (55.16 ± 34.75), which means at least 21 participants.

© 0.5 was given to studies having at least two categories of age range below. For studies that reported mean and SD of age, one SD was used to revert the data.

Early adult: 18-25 years;

Middle adult: 26-60;

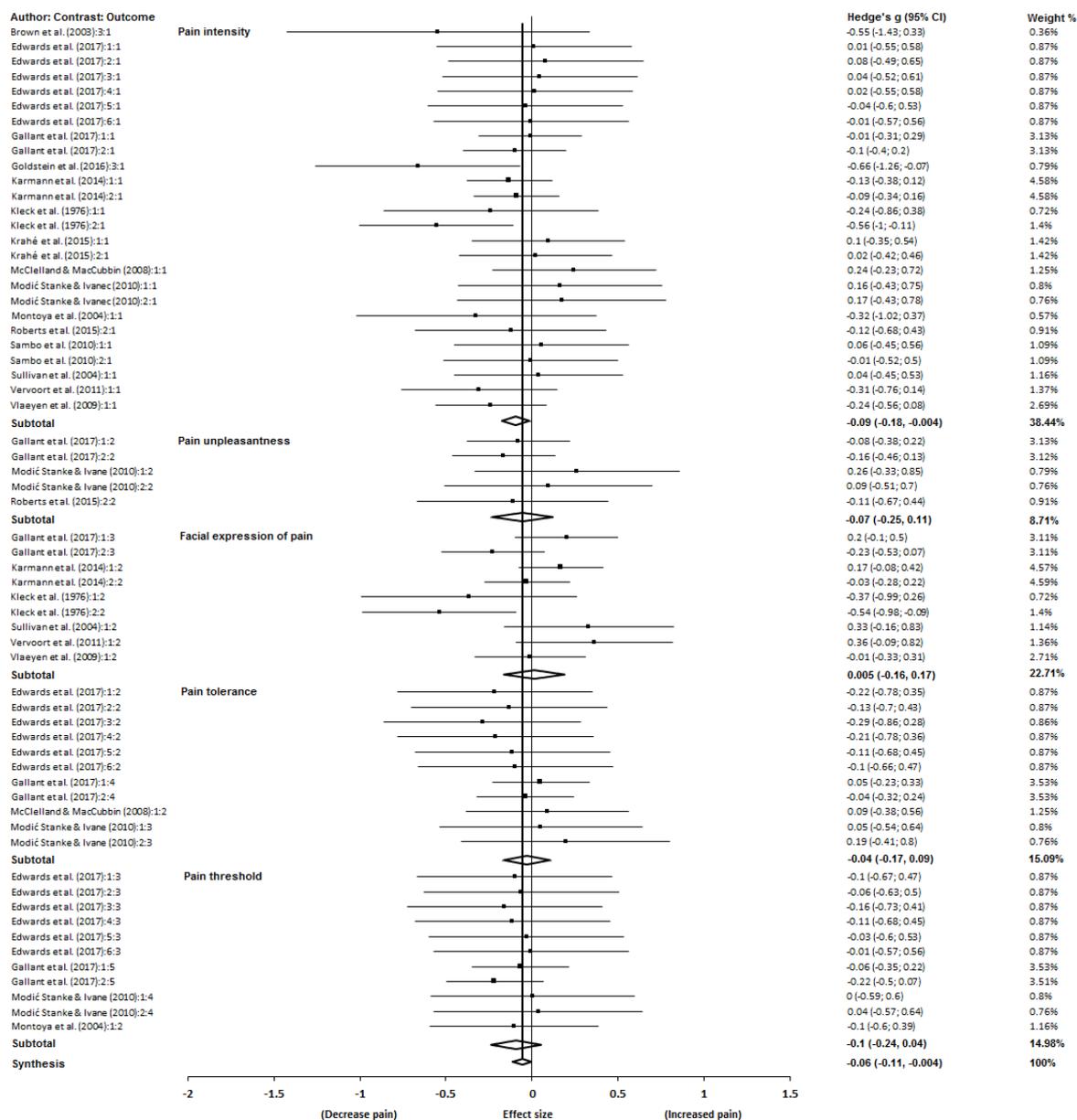
Old adult: 61 and above

Study	Sample	1	2	3	4	5	6	Total score
Borsook & MacDonald (2010)	Healthy participants (N=45)	1	1	1	1	1	0.5	5.5
Brown et al. (2003)	Healthy participants (N=101)	1	1	1	1	0.5	0.5	5
Edwards et al. (2017)	Experiment 1: Healthy participants (N=48)	0	1	1	1	0.5	0.5	4
	Experiment 2: Healthy participants (N=48)	0	1	1	1	0.5	0.5	4
	Experiment 3: Healthy participants (N=48)	0	1	1	1	0.5	0.5	4
Eisenberger et al. (2011)	Healthy participants (N= 17)	0	1	1	1	1	0	4
Fishman et al. (1995)	Healthy participants (N=60)	0	1	1	1	0.5	0.5	4
Gallant et al. (2017)	Healthy participants (N = 97)	0	1	1	1	1	0.5	4.5
Goldstein et al. (2016) ^a	Healthy participants (N= 23)	0	1	1	1	1	0.5	4.5

Jackson et al. (2005) ^a	Healthy participants (N= 88)	0	1	1	1	0.5	1	4.5
Karmann et al. (2014)	Healthy participants (N=126)	1	1	1	1	1	1	6
Kleck et al. (1976)	Experiment 1: Healthy participants (N= 20)	0	1	1	1	1	0	4
	Experiment 2: Healthy male participants (N= 40)	0	1	1	1	1	0.5	4.5
Krahé et al. (2015)	Healthy participants (N= 39)	1	1	1	1	1	0.5	5.5
Master et al. (2009)	Healthy participants (N= 25)	0	1	1	1	1	0	4
McClelland & McCubbin 2008)	Healthy participants (N=68)	0	1	1	1	0.5	0.5	4
Modić et al. (2010)	Healthy participants (N= 43)	1	1	1	1	0.5	1	5.5
Montoya et al. (2004)	Fibromyalgia patients (FIB) (N= 16); Migraine patients (MIG) (N= 16)	0	1	1	1	1	0.5	4.5
Platow et al. (2007)	Healthy participants (N= 54)	1	1	1	1	0	1	5
Roberts et al. (2015)	Healthy participants (N= 76)	1	1	1	1	0.5	0.5	5

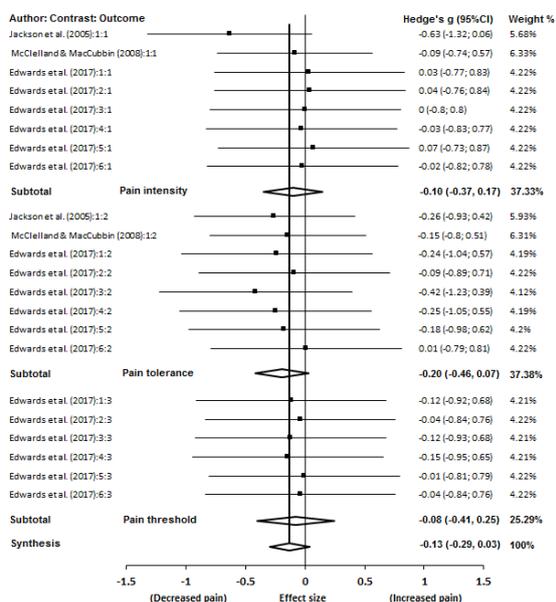
Sambo et al. (2010)	Healthy participants (N= 30)	0	1	1	1	1	0.5	4.5
Sullivan et al. (2004)	Healthy participants (N =64)	1	1	1	1	0.5	0.5	5
Vervoort et al. (2011)	Healthy children and parents (N= 38)	1	1	1	1	0.5	0.5	5
Vlaeyen et al. (2009)	Healthy participants (N= 149)	1	1	1	1	0.5	1	5.5

Supplementary Material S3: Forest plot of the Hedge's adjusted g analysis for social presence on behavioural pain outcomes.

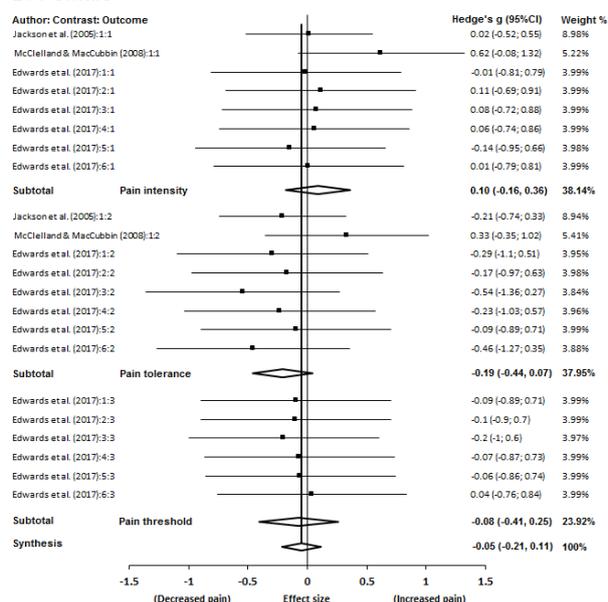


Supplementary Material S4: Forest plot of the Hedge's adjusted g analysis for gender difference in the social support effect on behavioural pain outcomes.

A. Male



B. Female



The following is the supplemental material for the study entitled "*A Systematic Review of the Processes Underlying the Main and the Buffering Effect of Social Support on the Experience of Pain*", which forms Chapter Three of this thesis.

Supplementary Material S1

Quality assessment checklist (CS Cross-section, CH Cohort):

- 1: Does the study have a clear defined research objective? CH/CS
- 2: Does the study clearly describe the recruitment procedure? CH/CS
- 3: Does the study adequately describe the inclusion/exclusion criteria? CH/CS
- 4: Does the study report on the population parameters and demographics? CH/CS
- 5: Does the study report participation rates and provide evidence of comparisons of responders and non-responders to the recruitment? CH/CS
- 6: Does the study include the sufficient assessment of social support and pain experience? Criteria—
Higher quality where measure is validated or measures at least two dimensions. CH/CS
- 7: Does the study adequately report on the strength of effect (e.g. ways of calculating effect size, reporting of confidence intervals)? CH/CS
- 8: Does the study use multivariate analysis? CH/CS
- 9: Is the study sample size appropriate for the analysis used? CH/CS. The number of cases in the final multivariable model was at least 10 times the number of independent variables in the analysis.
- 10: Do the authors report on the limitations of their study? CH/CS
- 11: Does the study report attrition rates and provide evidence of comparisons of responders and non-responders? CH
- 12: Does the study report an attrition rate < 20 %? CH
- 13: Does the study have a follow up time period > 6 months? CH

Quality assessment results:

Reference	Scoring criteria for quality assessment													Score %
	All designs										Cohort			
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Affleck (1988)	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N/A	N/A	N/A	80
Fitzpatrick (1988)	Y	Y	N	Y	N	Y	N	Y	Y	Y	N/A	N/A	N/A	70
Manne (1989)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N/A	N/A	N/A	90
Kerns (1990)	Y	N	N	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	70
Weinberger (1990)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	100
Revenson (1991)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	90
Goldberg (1993)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	90
Penninx (1997)	Y	Y	N	Y	N	N	Y	Y	Y	Y	N/A	N/A	N/A	70
Telfair (1999)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N/A	N/A	N/A	80
Cano (2000)	Y	N	N	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	70
Riemsma (2000)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	100
Alonso (2001)	Y	Y	N	N	N	Y	N	Y	Y	Y	N/A	N/A	N/A	60
Kerns (2002)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	90
Cano (2004)	Y	Y	Y	Y	N	Y	N	Y	N	Y	N/A	N/A	N/A	70
Holtzman (2004)	Y	N	Y	Y	Y	Y	N	Y	Y	N	N/A	N/A	N/A	70
Ferreira (2007)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	90
Holtzman (2007)	Y	Y	Y	Y	N	N	Y	Y	N	Y	N/A	N/A	N/A	70
Lopez-Martinez (2008)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N/A	N/A	N/A	90
Vlaeyen (2009)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N/A	N/A	N/A	80
Morgan (2011)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	80
Raichle (2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	N/A	N/A	100
Pekkarinen (2013)	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	80
Rosen (2013)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	90
Sturgeon (2015)	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N/A	N/A	N/A	80
Corley (2016)	Y	Y	Y	Y	N	N	N	Y	Y	Y	N/A	N/A	N/A	70

Park (2016)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N/A	N/A	N/A	80
DeLongis (1988)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	85
Brown (1989)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N	Y	77
Affleck (1994)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	77
Waltz (1998)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	85
Feldman (1999)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	Y	N	62
Strating (2006)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	77
Lee (2016)	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	Y	69
Overall total %	100	85	67	97	33	76	73	97	94	94	29	57	71	

Y yes, N no, N/A not applicable

Supplementary Material S2

Reference	Findings	Effect	Effect size statistics	Effect size proximity
<i>Stress (physical suffering)</i>				
Brown et al. (1989) [16]	1. The negative correlation of emotional support and depression was strengthened when pain was included.	<i>Buffering</i>	Differences of R ² in multiple regression (<i>Free Statistics Calculators</i>)	0.055 (wave 1 and 2 averaged)
	2. Moderating effect of emotional support was not found over a 6-month period.	<i>Main</i>	Support and pain effect were reported together.	n/a
Revenson et al. (1991) [66]	1. Received positive support predicted reduced depression without interacting with pain severity.	<i>Main</i>	Multiple regression	$\beta = 0.250$
Penninx et al. (1997) [39]	1. Presence of a partner had direct, favourable effect on psychological functioning without interacting with arthritis.	<i>Main</i>	Multiple regression (no disease and severe arthritis averaged)	$\beta = 0.165$
	2. Close social relationships had direct, favourable effect on psychological functioning without interacting with arthritis.	<i>Main</i>	Multiple regression (no disease and severe arthritis averaged)	$\beta = 0.100$
	3. Having diffuse social relationships interacted with arthritis pain to predict depressive symptoms in severe arthritis.	<i>Buffering</i>	Multiple regression (no disease and severe arthritis difference)	$\Delta \beta = 0.100$
	4. Emotional support interacted with arthritis pain to predict depressive symptoms in severe arthritis.	<i>Buffering</i>	Multiple regression (no disease and severe arthritis difference)	$\Delta \beta = 0.008$

Feldman et al. (1999) [59]	1. Previous day' support interacted with previous day' pain to predict present day' depressed mood.	<i>Buffering</i>	Multiple regression	B= 0.02
Telfair and Gardner (1999) [61]	1. Group satisfaction interacted with high pain to predict high psychological wellbeing.	<i>Buffering</i>	ANOVA (common variance was set to 0.5 in <i>WebPower</i>)	0.237
Riemsma et al. (2000) [49]	1. Positive support predicted reduced depression without interacting with pain.	<i>Main</i>	Multiple regression	$\beta = 0.150$
Cano et al. (2004) [17]	1. Marital satisfaction predicted reduced depressive symptoms without interaction with pain.	<i>Main</i>	Multiple regression	$\beta = 0.210$
Ferreira and Sherman (2007) [63]	1. Perceived social support mediated the impact of pain on depressive symptoms.	<i>Buffering</i>	Differences of R^2 in multiple regression (<i>Free Statistics Calculators</i>)	0.147
Holtzman and DeLongis (2007) [62]	1. Morning satisfaction with spousal response interacted with morning pain severity to predict evening pain catastrophizing.	<i>Buffering</i>	Multiple regression	b = 0.030
López-Martínez et al. (2008) [16]	1. Decreased pain intensity mediated the relationship between perceived social support and decreased depression.	<i>Buffering</i>	Path analysis	0.029 (path coefficient)
	2. Decreased pain intensity mediated the relationship between perceived social support and decreased functional impairment.	<i>Buffering</i>	Path analysis	0.031 (path coefficient)
	3. Decreased pain intensity mediated the relationship between perceived	<i>Buffering</i>	Path analysis	0.019 (path coefficient)

	social support and increased functional status.			
Morgan et al. (2011) [65]	1. Partner support mediated the negative impact of pain on quality of life.	<i>Buffering</i>	Path analysis	0.070 (path coefficient)
Sturgeon et al. (2015) [64]	1. Satisfaction with social roles mediated the negative impact of pain intensity on depression.	<i>Buffering</i>	Path analysis	0.114 (path coefficient)
	2. Satisfaction with social roles mediated the negative impact of pain intensity on anger.	<i>Buffering</i>	Path analysis	0.081 (path coefficient)
Lee et al. (2016) [18]	1. Tangible social support interacted with arthritis pain to predict less depressive symptoms.	<i>Buffering</i>	Multiple regression	$\beta = 0.040$
Park et al. (2016) [60]	1. Social support interacted with pain intensity to predict depressive symptoms.	<i>Buffering</i>	Multiple regression	$\beta = 0.040$

Stress (functional disability)

Affleck et al. (1988) [68]	1. The positive relation between support satisfaction and psychosocial adjustment was increased when disability was included.	<i>Buffering</i>	Differences of R ² in multiple regression (<i>Free Statistics Calculators</i>)	0.143
Fitzpatrick et al. (1988) [71]	1. Social relationship had direct, favourable effect on psychological well-being without interacting with disability.	<i>Main</i>	ANOVA (support sum of square divided by total sum of square)	0.202
Goldberg et al. (1993) [69]	1. Spousal support interacted with pain-related interference to predict depression.	<i>Buffering</i>	Multiple regression	$\beta = 0.800$

Riemsma et al. (2000) [49]	1. Positive support predicted reduced depression without interacting with physical function.	<i>Main</i>	Multiple regression	$\beta = 0.140$
Cano et al. (2004) [17]	1. Marital satisfaction predicted reduced depressive symptoms without interacting with physical disability.	<i>Main</i>	Multiple regression	$\beta = 0.210$
Strating et al. (2006) [70]	1. Emotional support satisfaction predicted reduced distress without interaction with impairment-disability in short-term RA.	<i>Main</i>	Multiple regression	$\beta = 0.170$
	2. Satisfaction with social companionship predicted reduced distress by interacting with impairment-disability in short-term RA.	<i>Buffering</i>	Multiple regression	$\beta = 0.220$
	3. This interaction disappeared in long-term RA.	<i>Main</i>	Multiple regression	$\beta = 0.110$

Stress (stressful response of close other)

Kerns et al. (1990) [72]	1. Marital satisfaction interacted with higher spousal punishing response to predict lower depressive symptoms.	<i>Buffering</i>	Multiple regression (only ΔR^2 , no β or separate R^2)	n/a
Revenson et al. (1991) [66]	1. Received positive support interacted with high stressful response to predict reduced depression.	<i>Buffering</i>	Multiple regression (no β)	n/a
Cano et al. (2000) [73]	1. Marital satisfaction mediated the positive relationship between negative spousal response and depressive symptom.	<i>Buffering</i>	Path analysis (gender averaged)	0.120 (path coefficient)

Riemsma et al. (2000) [49]	1. Positive support interacted with stressful response to predict depression.	<i>Buffering</i>	Multiple regression	$\beta = 0.113$
Cano et al. (2004) [17]	1. Marital satisfaction predicted reduced depressive symptoms without interaction with negative spousal response.	<i>Main</i>	Multiple regression	$\beta = 0.210$
Raichle et al. (2011) [75]	1. Marital satisfaction predicted reduced depression directly, without interacting with spousal negative response.	<i>Main</i>	Multiple regression	$\beta = 0.430$
Rosen et al. (2013) [74]	1. Dyadic adjustment mediated the adverse impact of negative spousal response on sexual satisfaction.	<i>Buffering</i>	Path analysis	0.104 (path coefficient)
<i>Stress (other negative life events)</i>				
DeLongis et al. (1988) [78]	1. Emotional support was negatively related to hassle-next day symptoms association.	<i>Buffering</i>	Multiple regression	$\beta = 0.120$
	2. Emotional support was negatively related to hassle-same day mood association.	<i>Buffering</i>	Multiple regression	$\beta = 0.200$
	3. Emotional support was not related to hassle-same day symptoms association.	<i>Main</i>	Multiple regression (no β or separate R^2)	n/a
	4. Emotional support was not related to hassle-next day mood association.	<i>Main</i>	Multiple regression (no β or separate R^2)	n/a
Weinberger et al. (1990) [79]	1. Social support had direct, favourable effect on functional status, without interaction with daily hassle.	<i>Main</i>	Multiple regression (no β or separate R^2)	n/a

Affleck et al. (1994) [76]	1. Social support interacted with daily stressor to predict next-day mood disturbance.	<i>Buffering</i>	Multiple regression	$\beta = 0.410$
Alonso and Coe (2001) [80]	1. Access to support providers interacted with distress to predict menstrual pain.	<i>Buffering</i>	ANOVA (only F and p value)	n/a
Pekkarinen et al. (2013) [77]	1. Social support interacted with physical workload to predict musculoskeletal symptoms.	<i>Buffering</i>	Logistic regression	0.49
<i>Stress appraisal (perceived threat/ coping ability)</i>				
Waltz et al. (1998) [82]	1. Psychological functioning mediated the protective influence of emotional support on pain.	<i>Buffering</i>	Path analysis (no path coefficient)	n/a
	2. Psychological functioning mediated the protective influence of social interaction on pain.	<i>Buffering</i>	Path analysis (no path coefficient)	n/a
Kerns et al. (2002) [81]	1. Pain-related support interacted with low problem-solving competence to predict depressive symptoms.	<i>Buffering</i>	Differences of R ² in multiple regression (<i>Free Statistics Calculators</i>)	0.042
Holtzman and DeLongis (2007) [62]	1. Morning satisfaction with spousal response interacted with morning pain catastrophizing to predict evening negative affect.	<i>Buffering</i>	Multiple regression	b = 0.090
	2. Morning satisfaction with spousal response decreased evening pain intensity without interaction with morning pain catastrophizing.	<i>Main</i>	Multiple regression	b = 0.220
Vlaeyen et al. (2009) [6]	1. Perceived threat mediated the inhibitory effect of social presence on pain intensity.	<i>Buffering</i>	Path analysis	0.098 (path coefficient)
		<i>Buffering</i>	Path analysis	

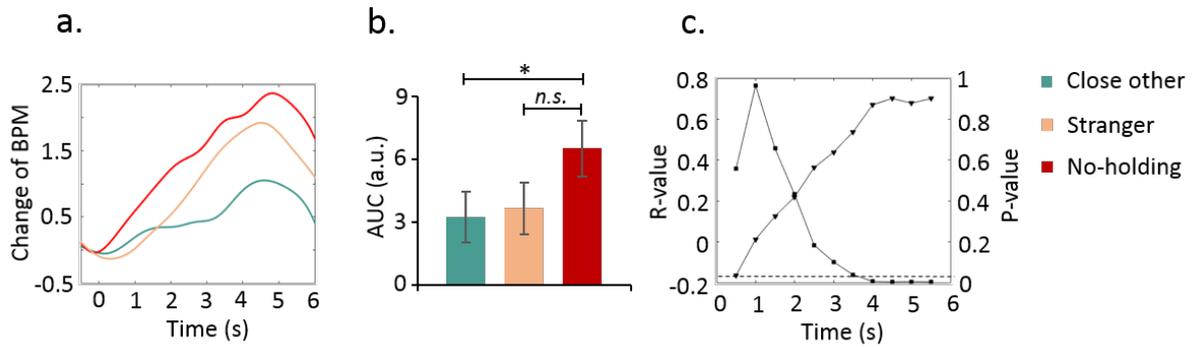
	2. Perceived threat mediated the inhibitory effect of social presence on facial expression of pain.			0.066 (path coefficient)
Corley et al. (2016) [83]	1. Global relationship satisfaction predicted less pain without interacting with threat manipulation.	<i>Main</i>	Quadratic modelling (no effect size)	n/a
	2. Situational relationship satisfaction predicted less pain in the low threat condition.	<i>Buffering</i>	Quadratic modelling (no effect size)	n/a

Active coping

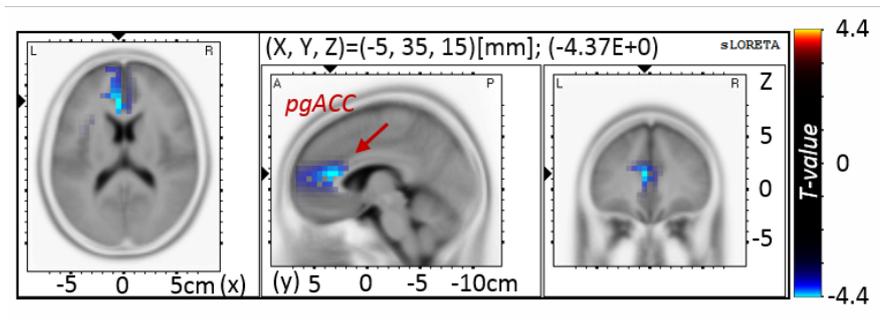
Manne and Zautra (1989) [48]	1. Adaptive coping mediated the positive relationship between spousal support and better psychological adjustment.	<i>Buffering</i>	Path analysis	0.121 (path coefficient)
Holtzman et al. (2004) [10]	1. Morning satisfaction with social support interacted with increased stoic distancing to predict reduced evening pain severity.	<i>Buffering</i>	Multiple regression	$\beta = 0.080$
López-Martínez et al. (2008) [19]	1. Perceived social support was related to reduced depressed mood without interacting with active coping response.	<i>Main</i>	Path analysis	0.120 (path coefficient)
	2. Perceived social support was related to reduced pain intensity without interacting with active coping response.	<i>Main</i>	Path analysis	0.110 (path coefficient)

Note: buffering indicates the buffering effect; main means the main effect. Effect size proximity is shown with the absolute value. β is standardized coefficient, while B and b are unstandardized coefficients. R^2 is the goodness-of-fit measure for the model.

The following is the supplemental material for the study entitled "*The social regulation of pain: autonomic and neurophysiological changes associated with perceived threat*", which forms Chapter Four of this thesis.



Supplementary Material S1. Absolute heart rate changes and relationship with pain relief. (a) Shows the event-related dynamic changes of heart rate with the progression of countdown numbers. (b) Shows the area under the curve (AUC) of heart rate changes across conditions. Each column and error bar represent the mean and the SEM. Asterisk represents statistical significance ($p < 0.05$). n.s means non-significant. (c) Shows the correlation between heart rate reduction ($HR_{(no-holding)} - HR_{(close other)}$) and pain relief ($Pain\ intensity_{(no-holding)} - Pain\ intensity_{(close other)}$).

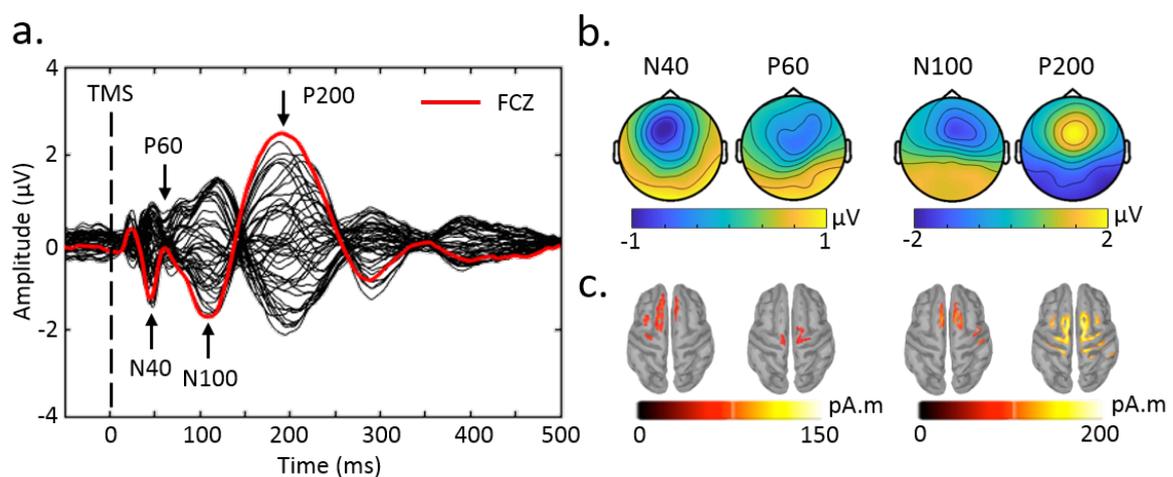


Supplementary Material S2. Source localization of EEG theta oscillation in the entire presentation of countdown numbers (0-6000 ms) in the close other versus no-holding condition.

The following is the supplemental material for the study entitled “*The Medial Prefrontal Cortex as a Flexible Hub Mediating Behavioural as well as Local and Distributed Neural Effects of Social Support on Pain: a Theta Burst Stimulation and TMS-EEG Study*”, which forms Chapter Six of this thesis.

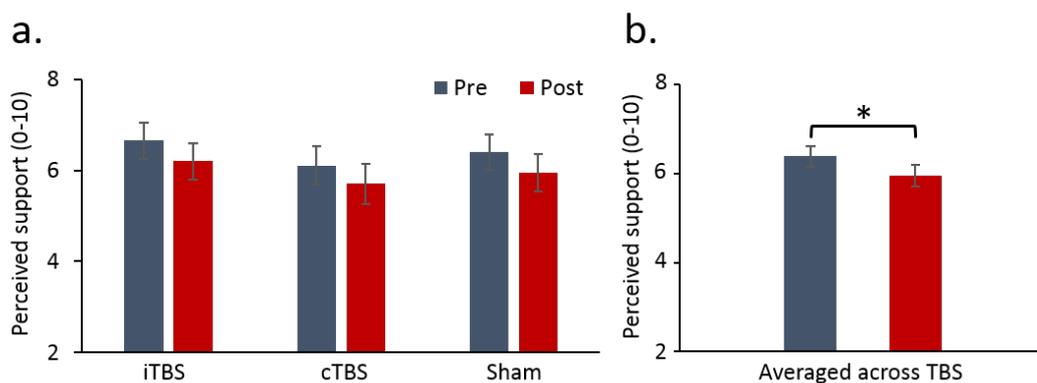
Supplementary Material S1: A series of negative and positive peaks resulted from single-pulse TMS over the mPFC.

(a) Butterfly plot of all electrodes with peaks of interest shown in text. The red line indicates the waveform obtained from the fronto-central electrode FCZ for graphical representation. (b) Voltage distribution and (c) Minimum Norm Estimates (MNEs) of the source level activity at the cortex for each peak.



Supplementary Material S2: Overall perceived support as a function of TBS and time.

(a)- (b) Overall perceived support decreased from Pre- to Post-stimulation across TBS conditions



APPENDIX B

Poster Abstracts

Australian Pain Society, Sydney, Australia, 2018

Che, X., Cash, R., Fitzgerald, P., & Fitzgibbon B. The social regulation of pain: autonomic and neurophysiological changes associated with perceived threat.

Background and Aims:

There is evidence to suggest that social support reduces the intensity of pain. More recent studies have suggested that this effect could be mediated by the social-buffering effect on perceived threat of pain. However, previous studies have ultimately combined painful sensations with perceived threat of pain, which makes it difficult to directly examine this idea. In this study we therefore used a unique study design to tease apart the influence of social support on the threat of pain, as opposed to actual pain, to more directly investigate the social-buffering effect of pain and related autonomic and neural responses.

Methods:

Eighteen healthy participants (8 males and 10 females, age range: 18-35 years, Mean=25.2, *SD*=5.7) were included in the study. Subjects were asked to hold the hand of a close other, or a stranger or not at all while they experienced the threat of pain. This was induced by presenting countdown numbers from 6 to 1 (0-6s) which was followed by a painful stimulus. During this time, neural and autonomic responses were recorded using electroencephalogram (EEG) and heart rate respectively.

Results:

One-way ANOVAs revealed that close other hand-holding reduced pain intensity (95% CI = [-1.75, -.13], $p < .05$) and pain unpleasantness (95% CI = [-1.26, -.04], $p < .05$) compared to no hand-holding. This was accompanied by decreased heart rate (95% CI = [-7.88, -.21], $p < .05$), and frontal theta oscillation (4-8Hz, significant at AF4, F2, FZ, and FC2) ($p < .05$) in the later stage preceding painful stimulation (3-6s in heart rate and 3.3-4.3s in frontal theta respectively) in the close other versus no-holding condition. Interestingly, decreased heart rate and frontal theta were uniquely associated with greater pain reduction in the later stage leading up to painful stimulation (3.5-6s in heart rate and 3-5.5s in frontal theta respectively, $p_s < .05$). Neural changes in close other hand-holding were further source localized to the insular cortex and the rostral-ventral portions of the anterior cingulate cortex, regions involved in the processing of threat and pain.

Conclusions:

The results of the present study demonstrate the analgesic effect of social support. Our data further suggest that this effect could be mediated by the changes in autonomic and neurophysiological responding to the threat of nociceptive stimuli. Overall, our findings present evidence that social support may decrease pain through a buffering effect on the threatening quality of pain.

World Congress on Pain, Boston, USA, 2018

Che, X., Cash, R., Chung, S., Fitzgerald, P., &, Fitzgibbon B. (2018). Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis.

Aim of Investigation:

Under the right conditions, having supportive relationships with others can reduce pain and related physiological arousal. However, some studies have shown no effect or even a negative effect of social support on pain and arousal. A recent systematic review has further suggested possible covariates of this influence, for example, social support variations (e.g. physical presence, social touch), and social relationships (e.g. significant other, stranger). In the current study, a meta-analysis was therefore conducted to quantify the complex and multivariate influence of social support on pain and related arousal.

Methods:

A comprehensive electronic literature search was performed in PubMed, PsycINFO, The Cochrane Library and EMBASE to the end of August 2017. The keywords used for the search were 'pain' AND ('interpersonal' OR 'social support' OR 'social presence' OR 'social interaction' OR 'social modulation' OR 'social context' OR 'attachment' OR 'social influence' OR 'social touch' OR 'empathy'). Two reviewers (XC and SC) independently assessed the search results against the inclusion criteria: (1) pain was induced in experimental settings; and (2) both the presence and absence of social support was manipulated; and (3) behavioural pain outcome was assessed; and (4) data were provided that enable analysis and estimation of effect size; and (5) it was published in a peer-reviewed journal in English. Behavioural pain outcomes included pain intensity, pain unpleasantness, facial expression of pain, pain threshold, and pain tolerance. Physiological outcomes included heart rate, blood pressure (both diastolic and systolic), skin response, and cortisol levels. Data were extracted to calculate

effect size using Hedge's adjusted g (standardised mean difference, SMD). Test of heterogeneity (I^2 statistics), and publication bias (selectivity funnel plot, Begg-Mazumdar Kendall τ , Egger's regression test) were also performed.

Results:

A total of 2416 studies were identified in a systematic search, among which 20 were eligible for the meta-analysis. Our results showed that the mere presence of another person was not sufficient to decrease pain perception (with no $SMD \geq 0.2$, and $p \leq 0.05$). However, the presence of a significant other resulted in an increase of facial expression of pain ($SMD = 0.21$, 95% CI: [0.03, 0.38], $p = 0.02$), and the presence of a stranger decreased physiological arousal ($SMD = -0.31$, 95% CI: [-0.48, -0.13], $p = 0.0004$). Meanwhile, verbal support, mainly from a stranger, decreased both pain ($SMD = -0.69$, 95% CI: [-1.30, -0.08], $p = 0.03$) and arousal ($SMD = -0.99$, 95% CI: [-1.29, -0.69], $p = 0.00001$). Our data also showed the analgesic effect of intimate relationships occurred in response to touching ($SMD = -0.95$, 95% CI: [-1.37, -0.52], $p = 0.00001$), as well as viewing a romantic other ($SMD = -0.60$, 95% CI: [-1.04, -0.16], $p = 0.008$). Finally, we found evidence of publication bias for pain-related arousal ($\tau = -0.32$, $p = 0.03$; Egger's $t = -3.25$, $p = 0.05$), but not for behavioural pain outcomes ($\tau = -0.14$, $p = 0.07$; Egger's $t = -0.72$, $p = 0.08$).

Conclusions:

In this study we systematically quantified the influence of social support on pain and related arousal. Our results suggest that the mere presence of another person, although it may suppress physiological arousal, is not sufficient to reduce pain. However, social support is shown to decrease pain when there is active engagement of social support, e.g. verbal communication, hand-holding. Findings further highlight the significance of intimate relationships in emotion communication and pain reduction. Our results may therefore provide insights for the support therapies.

APPENDIX C

Additional Published Manuscript

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ORIGINAL PAPER



Self-compassion Modulates Heart Rate Variability and Negative Affect to Experimentally Induced Stress

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Abstract

Self-compassion has increasingly been recognized to buffer stress and promote emotional health. However, few studies have examined the influences of self-compassion on physiological stress response. The current study aimed to investigate the impact of self-reported self-compassion on physiological stress response and negative affect induced in a laboratory setting. Healthy male participants ($N = 34$, Asians) were grouped into high ($N = 17$, age: mean = 19.65, $SD = 0.59$) or low ($N = 17$, age: mean = 19.71, $SD = 0.82$) self-compassion groups based on the Self-Compassion Scale. They were subjected to the Trier Social Stress Test, with electrocardiography recorded and negative affect assessed by the Positive and Negative Affect Schedule. Results demonstrated that self-compassionate individuals showed higher vagally mediated heart rate variability (vmHRV) at baseline ($CI = [0.30, 0.91]$, $p = 0.01$). Interestingly, self-compassionate individuals demonstrated higher vmHRV to an acute stressor after an anticipated decrease in vmHRV ($CI = [0.02, 0.67]$, $p = 0.04$). Moreover, self-compassionate individuals reported less negative affect in response to stress ($CI = [-8.29, -0.42]$, $p = 0.03$). Our results demonstrate the role of self-compassion in the flexible adjustment of physiological and psychological responses to stress.

Keywords Self-compassion · Stress · Emotion · Heart rate variability



The Motivation-Based Promotion of Proactive Control: The Role of Salience Network

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It has been shown that reward motivation can facilitate proactive control, a cognitive control mode that is characterized of prior preparation and sustained holding of the goal-relevant information in working memory. However, it remains to be established the neural networks that may be involved in this promotion effect. In this study, participants underwent the AX-Continuous Performance Task (AX-CPT) that measures relative proactive control during functional magnetic resonance imaging (fMRI) scanning. We employed independent component analysis to decompose multiple brain networks and identified the task related network. Results showed that the salience network (SN) was engaged in the AX-CPT protocol. Importantly, our data demonstrated that reward modulated the association between task engagement of SN and proactive control, whereby the positive correlation was particularly observed in the reward condition. Moreover, reward modulated task engagement of the SN in a proactive manner, which may contribute to the behavioral proactive performance. Overall, our data suggest the involvement of SN in the reward facilitation effect of proactive control.

Keywords: dual-mechanism of control, independent component analysis, AX-Continuous Performance Task, salience network, proactive control, reactive control, reward

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RESEARCH ARTICLE

Regional Brain Responses Are Biased Toward Infant Facial Expressions Compared to Adult Facial Expressions in Nulliparous Women

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Abstract

Recent neuroimaging studies suggest that neutral infant faces compared to neutral adult faces elicit greater activity in brain areas associated with face processing, attention, empathic response, reward, and movement. However, whether infant facial expressions evoke larger brain responses than adult facial expressions remains unclear. Here, we performed event-related functional magnetic resonance imaging in nulliparous women while they were presented with images of matched unfamiliar infant and adult facial expressions (happy, neutral, and uncomfortable/sad) in a pseudo-randomized order. We found that the bilateral fusiform and right lingual gyrus were overall more activated during the presentation of infant facial expressions compared to adult facial expressions. Uncomfortable infant faces compared to sad adult faces evoked greater activation in the bilateral fusiform gyrus, precentral gyrus, postcentral gyrus, posterior cingulate cortex-thalamus, and precuneus. Neutral infant faces activated larger brain responses in the left fusiform gyrus compared to neutral adult faces. Happy infant faces compared to happy adult faces elicited larger responses in areas of the brain associated with emotion and reward processing using a more liberal threshold of $p < 0.005$ uncorrected. Furthermore, the level of the test subjects' Interest-In-Infants was positively associated with the intensity of right fusiform gyrus response to infant faces and uncomfortable infant faces compared to sad adult faces. In addition, the Perspective Taking subscale score on the Interpersonal Reactivity Index-Chinese was significantly correlated with precuneus activity during uncomfortable infant faces compared to sad adult faces. Our findings suggest that regional brain areas may bias cognitive and emotional responses to infant facial expressions compared to adult facial expressions among nulliparous women, and this bias may be modulated by individual differences in Interest-In-Infants and perspective taking ability.



Protective Effect of Self-Compassion to Emotional Response among Students with Chronic Academic Stress

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The literature has shown that self-compassion is a protective factor of an individual's emotional response to chronic stress. However, this stress-buffering effect has not been completely analyzed in individuals who report significantly high academic stress. The present study explored the role of self-compassion in a group of undergraduate students who experience chronic academic stress. A total of 208 undergraduate students who were preparing for the Postgraduate Entrance Examination (PEE) were recruited and completed the Self-Compassion Scale, Adolescent Self-Rating Life Event Check List, and Positive and Negative Affect Schedule. Differences analysis confirmed that the participants reported significantly higher academic stress than their peers who were not preparing for PEE. Self-compassion positively related to positive affect but negatively related to negative affect and learning stress. Further analysis showed that self-compassion negatively mediated the relationship between chronic academic stress and negative affect. Findings imply that self-compassion-centered interventions can be developed in the educational context to assist students cope with chronic academic stress.

Keywords: self-compassion, chronic academic stress, stress-buffering effect, emotional response, mediation



Habitual suppression relates to difficulty in regulating emotion with cognitive reappraisal



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ABSTRACT

One common strategy to cope with the difficulties of daily life is suppression. Habitual users of suppression tend to suppress their feelings rather than expressing them. Although this strategy may reduce outward response to emotion, it is not thought to lessen induced negative affect. Moreover, it remains unclear whether people with high suppression scores can reduce negative affect through cognitive reappraisal. In the present study, twenty-nine healthy participants differing in suppression scores were directed to reappraise aversive stimuli during functional magnetic resonance imaging (fMRI). Results showed that higher suppression scores correlated with decreased response of dorsomedial prefrontal cortex (dmPFC) during cognitive reappraisal. Further, high suppression scores related to enhanced negative affect to stimuli with greater negative affect correlating with decreased dmPFC response during cognitive reappraisal. This study suggests that people with high suppression scores experience difficulty in reducing negative affect through cognitive reappraisal and implicates neurobiological processes that may underlie this difficulty.

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