Psychological and neurobiological processes in coping with pain: The role of social interactions

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From the moment we are born, our experiences are fundamentally shaped by our social environment. Early in life, social connections are vital for ensuring survival, and across the lifespan, ample research has indicated that interacting with others can be beneficial for coping with threats to psychological and physiological well-being (Di Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001; Kikusui, Winslow, & Mori, 2006; Uchino, 2006). A prime indicator of actual or potential threat to well-being is pain. Pain is a complex psychological phenomenon which comprises an "unpleasant sensory and emotional experience", integrating sensory, affective and motivational dimensions which alert us to threat and motivate us to seek ways of dealing with this threat (International Association for the Study of Pain, 1994).

Pain is heavily influenced by the environment or context in which it occurs. Affective (e.g., sadness; Bayet, Bushnell, & Schweinhardt, 2014; Yoshino et al., 2010) and cognitive factors (e.g., attention; see Villemure & Bushnell, 2002, for a review) are known to influence pain and have received much research attention in several fields including most recently cognitive neuroscience (see Wiech, Ploner, & Tracey, 2008, and Wiech & Tracey, 2009, for reviews). By contrast, there is a paucity of research on social influences on pain, particularly in experimental psychology and cognitive neuroscience (Decety & Fotopoulou, 2015; Krahé, Springer, Weinman, & Fotopoulou, 2013). Exceptions are placebo studies (reviewed in Colloca, Klinger, Flor, & Bingel, 2013) and studies in chronic pain populations (Leonard, Cano, & Johansen, 2006). Moreover, there has long been evidence from animal studies that social variables affect pain-related behaviours and neural processes (see e.g., Martin, Tuttle, & Mogil, 2014, and also below).

Yet, similar conclusions in humans have proven difficult for a variety of reasons (see Krahé et al., 2013, for a review). First, in relation to candidate mechanisms explored, hypotheses and terminology have been rooted in the research traditions from which they stem, with few studies within each tradition and little integration across different areas. Second, there has been great variability in the research methods employed across studies, from the type of pain examined to the source and type of social variables being studied or manipulated. Not surprisingly, comparisons between studies is difficult and *prima facie* the results appear contradictory with social factors exerting both positive (e.g., Brown, Sheffield, Leary, & Robinson, 2003) and

negative (e.g., Mcclelland & Mccubbin, 2008) effects on pain. Thus, this complexity requires a more in-depth and interdisciplinary consideration of the available literature. A promising development in this respect is the relatively new, interdisciplinary field of social cognitive neuroscience, which offers theoretical and empirical tools to consider the psychological and neurobiological mechanisms that may underlie the social modulation of pain.

Accordingly, this chapter aims to provide an overview of studies available to date which have experimentally examined some of the neurobiological mechanisms underlying the effects of social factors on the experience of pain, both on subjective pain report and on pain-related neural processing. In particular, we focus on the role of social interactions characterised by (inter)personal features (rather than more broad social influences, e.g., group membership) between a person experiencing pain and pain-free individuals. These studies use paradigms in which pain is experimentally induced in healthy volunteers. The role of social factors in the context of clinical or chronic pain is reviewed comprehensively elsewhere (e.g., Cano & Williams, 2010; Leonard et al., 2006) and lies beyond the scope of this chapter. We begin by introducing pain within the field of neuroscience. We then review findings from experimental research into the social modulation of pain, before moving to research which has investigated neurobiological processes underpinning the effects of social interactions on pain. In doing so, we present theoretical frameworks from psychology and neuroscience within which findings have been understood and attempt to create links between these levels of explanation. We conclude with a summary of the main findings and present an outlook for future research.

Pain

Pain is frequently conceptualised as comprising sensory (sometimes termed 'sensory-discriminative') and affective-motivational dimensions (Auvray, Myin, & Spence, 2010; Melzack & Casey, 1968). The sensory dimension of pain is usually (but not always; Loeser & Melzack, 1999) associated with a noxious (harmful) stimulus and is thought to provide the organism with information on the intensity, temporality, and spatial location of noxious stimuli (Haggard, Iannetti, & Longo, 2013; Melzack & Casey, 1968). If triggered by a stimulus, sensory input is relayed to the brain by nociceptive afferent fibres. These include fast-conducting, myelinated Aδ fibres and slow-conducting, unmyelinated C fibres, which are associated with immediate sharp, pricking sensations and subsequent, dull, burning sensations, respectively. The activation of these fibres is associated to a degree with reported pain sensations (e.g.

Iannetti, Zambreanu, Cruccu, & Tracey, 2005), and in this sense the sensory dimension of pain is linked to nociception, "the neural process of encoding noxious stimuli" (International Association for the Study of Pain, 1994). However, nociceptive fibre activation is not sufficient for the conscious experience of pain, which is thought to arise with involvement of the central nervous system, including cortical activity (Haggard et al., 2013).

Further, pain includes an affective-motivational dimension, which is characterised by actual or anticipated feelings of unpleasantness and motivated actions to alleviate these feelings (Auvray et al., 2010). These aspects include pain-related fear and may be especially predictive of factors such as disability related to pain (see also Wiech & Tracey, 2009). The understanding of pain as multidimensional, comprising both discriminatory and emotional components, has been validated by the range and functional specialisation of brain areas associated with pain in neuroimaging studies. Specifically, primary and secondary somatosensory cortices, insular cortex, anterior cingulate cortex (ACC), and prefrontal cortices as well as the thalamus have been most reliably associated with noxious stimulation across studies (see Apkarian, Bushnell, Treede, & Zubieta, 2005). Collectively, these areas have been termed the 'neuromatrix' (Melzack, 1999) or 'pain matrix' (see e.g., Tracey & Mantyh, 2007). However, areas in the 'pain matrix' have also been found to be activated in a range of contexts not related to pain (see Craig, 2009; Medford & Critchley, 2010, for reviews focusing on the ACC and insula) and by stimuli which are not painful, such as auditory and somatosensory stimuli (see Legrain, Iannetti, Plaghki, & Mouraux, 2011). Accordingly, two alternative theoretical perspectives have been developed that have re-conceptualised the functional role of the 'pain matrix' areas as forming part of a neural system processing the entire physiological condition of the body (interoception; see Craig, 2002), or as part of a neural 'salience network' processing possible threats – including, but not restricted to, pain – to the body in its environment (Legrain et al., 2011).

According to the first of these proposals, the fact that pain feels unpleasant and motivates actions to reduce this unpleasantness may distinguish it from exteroceptive modalities, such as vision or hearing. This distinction has been instrumental in a conceptual shift from viewing pain as an exteroceptive modality to understanding it as part of interoception, with the latter being defined as the representation of the physiological condition of the body, or 'how we feel' (Craig, 2002). In this view, pain can be compared to feelings such as thirst and temperature, which alert us to our bodily needs and motivate actions to maintain homeostasis (Craig, 2002). Furthermore, a unique neural pathway from the periphery to the cortex has been proposed for

interoceptive modalities (Craig, 2002; 2003; 2009). In particular, pain and all feelings from the body are processed peripherally and centrally by a recently discovered lamina I spinothalamocortical pathway that projects to the posterior granular and mid-dysgranular regions of the insular cortex (serving as primary interoceptive cortex) via the brainstem parabrachial nucleus and posterior part of the ventromedial thalamic nuclei (Craig, 2003; Craig, 2009). Primary interoceptive signals are thought to be represented in the mid/posterior insula, where they are also integrated with exteroceptive information coming from different brain areas. Moreover, further re-mappings within the anterior insula, the ACC, and the orbitofrontal cortex are thought to consolidate body-state signals with social, motivational, and contextual information to ultimately give rise to the conscious experience of emotions, as well as to prepare the organism for the necessary action in the environment (Craig, 2002; Craig, 2009; Critchley, 2005; Damasio et al., 2000). Importantly for the present chapter, these re-mappings suggest possible neurobiological mechanisms by which not only cognitive, but also social contextual factors can influence the awareness of interoceptive and other multimodal information about one's own body, as we discuss further below.

The second theoretical alternative to the 'pain matrix' idea suggests that these brains areas may instead form part of a general neural 'salience network' (see e.g., Cauda et al., 2012; Garcia-Larrea & Peyron, 2013; Legrain et al., 2011; Medford & Critchley, 2010; Seeley et al., 2007). Salience has various definitions: It can refer to the ability of a stimulus to stand out from other stimuli, the novelty of a stimulus in relation to previous experience, or its threat value (see Legrain et al., 2011; Ronga, Valentini, Mouraux, & Iannetti, 2013). In the context of pain, a common core of these meanings is that salience describes the importance (its weighting in relation to other factors) of a stimulus for indicating potential or actual threat to the body (Legrain et al., 2011) and for influencing responses to such a stimulus accordingly (Garcia-Larrea & Peyron, 2013). Conceptualising the ACC and anterior insula as being part of a 'salience network' may help to understand why these areas are also involved in processing other interoceptive modalities and exteroceptive stimuli which provide information on threat to our body (Craig, 2009; Garcia-Larrea & Peyron, 2013; Medford & Critchley, 2010; Mouraux & Iannetti, 2009). In addition, this 'salience network' may also integrate contextual factors from the (social) environment. For example, enhancing the threat value of impending noxious stimuli by telling participants the noxious stimulation might not be safe on certain parts of skin led to more stimuli being classified as painful, and this integration of contextual information about stimulus salience was reflected by activity in the anterior insula (Wiech et al., 2010).

These two perspectives on the neurobiological basis of pain offer insights into the neural regions involved in processing noxious and painful stimuli and point to mechanisms by which this processing may be modulated by social contextual factors. We now turn to experimental studies examining the effects of social interactions on pain in order to provide a background to the neurobiological studies, which use some of these experimental paradigms.

Experimental research into the effects of social interactions on pain

Experimental studies manipulating social interactions and examining their causal effects on subjective pain report (e.g., pain ratings) and pain behaviours (e.g., facial expressions) have provided accumulating evidence that interacting with others influences the experience of pain (Krahé et al., 2013). In this section, we review key findings to consider some of the psychological mechanisms involved in the social modulation of pain and the theoretical frameworks within which they have been understood. Stemming from research into the benefits of social support for a range of health outcomes, a common feature of the majority of psychological and neuroimaging studies considered below is that they have manipulated social variables designed to signal a potentially supportive – rather than e.g., threatening – intent (though see Karos, Meulders, & Vlaeyen, 2015; Peeters & Vlaeyen, 2011, who manipulated social threat). In line with the view that the provision of care and support is a key function of social interactions within the context of pain, these studies draw on theoretical accounts of how interacting with others may help us cope with pain (notably attachment theory, Bowlby, 1997/1969, and social baseline theory, Coan, 2008, 2011, Coan & Sbarra, 2015). Accordingly, we will review the existing studies within these theoretical traditions below. However, we first need to clarify some important conceptual distinctions in the social variables manipulated by both traditions.

Studying the effects of social priming and social interactions

At the broadest level, studies can be seen to manipulate an aspect of social cognition if they "use any stimuli that can reasonably be identified as belonging to a conspecific" (Chakrabarti, 2013, p. 414). This conceptualisation draws no distinction between virtual (e.g., avatars) or actual social partners, absent or present social partners (as long as absent partners are somehow primed or brought to mind), and static (e.g., facial expressions) or interactive (e.g., verbally, non-verbally communicative) social signals. In social cognitive neuroscience, researchers have

begun to introduce further differentiations, focusing especially on the degree of *interaction* and *engagement* involved in social manipulations (Schilbach et al., 2013). In particular, the interactive nature of a social manipulation has been proposed to depend on whether it requires a 3rd person or 2nd person perspective. A 3rd person perspective includes observation of social stimuli without engaging in direct interaction (e.g., viewing static pictures of faces), while a 2nd person perspective involves dynamic interaction with social stimuli (Schilbach et al., 2013), such as communicating with another person. The latter perspective may be conceptualised to extend to social situations in which there is a *potential* or *possibility* for (inter)action, e.g., another person is physically present but interactions are not purposefully manipulated (a common paradigm in pain research; Krahé et al., 2013, and below). Some researchers have argued that only a 2nd person perspective describes a shared, emotionally engaging, 'truly social' interaction (Schilbach et al., 2013). Although the distinctions between 2nd and 3rd person perspectives have undergone several re-conceptualisations, and 'reciprocity' has been proposed as an alternative to 2nd and 3rd person distinctions (De Bruin, Van Elk, & Newen, 2012; Przyrembel, Smallwood, Pauen, & Singer, 2012), real-life interactions between two or more individuals can unequivocally be classified as having increased ecological validity (Schilbach et al., 2013). We will use the distinction between 2nd and 3rd person perspectives in structuring the results of different research paradigms below.

Effects of unambiguously positive social interactions on the experience of pain

Attachment theory (Bowlby, 1977; Bowlby, 1997/1969) is one of the most influential theories describing the development, nature and adaptive function of close and enduring interpersonal relationships and it has been applied both to pain (see Meredith, Ownsworth, & Strong, 2008; Meredith, 2013) and its modulation by social context (Hurter, Paloyelis, De C. Williams, & Fotopoulou, 2014; Krahé, Drabek, Paloyelis, & Fotopoulou, 2016; Krahé et al., 2015; Sambo, Howard, Kopelman, Williams, & Fotopoulou, 2010; Wilson & Ruben, 2011). The key tenet of attachment theory is that infants are biologically programmed to form a close bond with their primary caregiver early in life to ensure their survival and wellbeing in times of threat. In particular, threats to the internal condition of the body, such as hunger, cold, and pain, are proposed to activate a set of attachment behaviours designed to maintain closeness to the caregiver (Bowlby, 1997/1969). According to attachment theory, the primary way of coping with pain is to seek help and support from the caregiver, also termed 'attachment partner'. If the attachment partner is consistently responsive to the individual's needs, this is an adaptive

strategy for dealing with threats. Building on these principles, social baseline theory (Coan, 2008, 2011, Coan & Sbarra, 2015) proposes that the brain's default expectation is that access to social resources such as support from others will be available, and proximity to others thus allows certain processes such as monitoring threats to be "outsourced", freeing up own resources. Indeed, many studies show that social support reduces stress, including physiological measures such as cortisol (e.g., Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kikusui et al., 2006). Thus, akin to research showing that social support reduces stress and has beneficial effects on other health outcomes (Eisenberger & Cole, 2012; Uchino, 2006), social interactions – in the face of a positive interaction history – may attenuate pain, as we review below.

Indeed, in reviewing the experimental literature into the social modulation of pain, structured and unambiguously positive verbal interactions (2nd person perspective) were found to reduce pain (see Krahé et al., 2013). For example, verbal support from a research confederate present during an icy water (coldpressor) task, such as "You're doing great!" or "Remember you're not alone", attenuated participants' subjective pain ratings as well as physiological markers of stress, such as blood pressure, heart rate, and cortisol reactivity compared to the mere presence of the confederate and a no interaction control condition (Roberts, Klatzkin, & Mechlin, 2015, p. 560). In addition – though without a verbal interaction – holding one's romantic partner's hand (vs. holding a stranger's hand or an object/no hand) reduced pain (Master et al., 2009), with higher trait empathy of the partner associated with greater pain reduction in the person in pain (Goldstein, Shamay-Tsoory, Yellinek, & Weissman-Fogel, 2016). Drawing on these findings, we put forward that clearly positively intentioned social interactions may lead to reductions in pain measures when they signal (relative) safety of painful stimuli or the environment in which they occur (see also Krahé et al., 2013).

Furthermore, social manipulations without a potential for (inter)action (3rd person perspective) also tended to lead to reductions in pain, as we will discuss in greater detail in relation to neurobiological processes below. However, this positive effect was true only when they were interpersonally relevant, e.g., when there was a close pre-existing relationship between the social partners (see e.g., Eisenberger et al., 2011, discussed in greater detail below). Related to this, overall relationship satisfaction as well as having a satisfying interaction with the romantic partner immediately *before* taking part in a coldpressor task alone reduced pain during this task, though only when the task was not perceived to be very threatening (Corley, Cano, Goubert, Vlaeyen, & Wurm, 2016). These studies point to the importance of the relationship between

social interactions partners but also especially emphasise the role of how this relationship is perceived – both in the situation and habitually e.g., depending on personality traits of the person in pain and the general quality of the relationship.

Effects of ambiguous social interactions and the moderating role of personality traits

How aspects of the social relationship are perceived may play a particularly critical role in more ambiguous (usually 2nd person perspective) social interactions, e.g., interactions in which the content is unstructured or of mixed valence, or another person is present but does not communicate with the person in pain. Participants reported less pain in the presence of their partner when their partner had (unbeknownst to them) been instructed to try and take on their perspective compared to when their partner had not received such an instruction (Leong, Cano, Wurm, Lumley, & Corley, 2015). As participants in the perspective-taking condition reported that their partner had been more validating (caring and understanding of their experience) during the task, this might explain these effects. However, it is noteworthy that partner validating *behaviours* during the task, as rated by the research team, did not predict pain; thus, participants' perceptions of the partner rather than the partner's overt behaviours seemed to drive the pain-attenuating effects.

Furthermore, effects of more ambiguous interactions on pain were often found to be shaped by individual differences in personality variables linked to the perceived availability of others to meet one's needs. As postulated by attachment theory, variations in early experiences with the attachment partner give rise to the development of different 'attachment styles' or classifications (see Main, Kaplan, & Cassidy, 1985), which remain relatively stable across the life span (Waters, Merrick, Treboux, Crowell, & Albersheim, 2000) and extend to adult romantic relationships (Hazan & Shaver, 1987). Attachment styles comprise internal working models of relationships, organising and representing how the individual views the self and others (Main et al., 1985). At a neural level, these styles have been linked to functional neuroanatomical differences (Vrticka & Vuilleumier, 2012) and influence sensitivity to the attachment-related neuropeptide oxytocin (Meinlschmidt & Heim, 2007; see also below) as well as functional connectivity between brain networks (Riem et al., 2013).

If individuals feel that their attachment partner is available and responsive when needed, a secure attachment style will develop. In adulthood, securely attached individuals feel

comfortable trusting and depending on their partner and turning to them for support (Hazan & Shaver, 1987). On the other hand, insecure attachment styles develop when early interactions are characterised by unreliable or unresponsive caregiving. In this case, individuals may not perceive their attachment partner to be supportive (Collins & Feeney, 2004) and may not engage in the primary attachment behaviours of seeking support from the attachment partner. Instead, insecurely attached individuals may use secondary coping strategies (see Shaver & Mikulincer, 2002; Mikulincer, Shaver, & Pereg, 2003). Two types of secondary coping strategies, corresponding to two subtypes of insecure attachment, namely anxious and avoidant attachment styles, have been identified. Anxiously attached individuals have experienced unreliable caregiving; hence, they fear abandonment and are extremely motivated to remain close to attachment partners. These individuals employ 'hyperactivating' strategies, which include heightened monitoring of the partner and any possible threats in the environment (Shaver & Mikulincer, 2002; see also links with pain catastrophising e.g. Ciechanowski, Sullivan, Jensen, Romano, & Summers, 2003, and the communal coping model of pain catastrophising; Sullivan et al., 2001). In the context of pain, hyperactivating strategies include exaggerating the threat of pain and ruminating about pain (Wilson & Ruben, 2011). Avoidantly attached individuals, on the other hand, have experienced unresponsive caregiving. They tend not to trust relationship partners and remain independent and distant (Hazan & Shaver, 1987). Avoidant attachment has been associated with holding negative trust memories (Mikulincer, 1998), viewing close others as less supportive (Collins & Feeney, 2004) and not benefiting from emotional support (Mikulincer & Florian, 1997. Correspondingly, they use 'deactivating' strategies (see Shaver & Mikulincer, 2002), which, in the context of pain, include suppressing the magnitude of threat, ignoring pain, and dealing with pain themselves without turning to their attachment partner for help (Wilson & Ruben, 2011). Insecure attachment has been found to be linked to heightened pain in experimental studies (Meredith, 2013) and been proposed to constitute a risk factor for developing chronic pain (Meredith et al., 2008).

Insecure attachment has been found to moderate the effects of social interactions on the experience of pain and may help to explain why social interactions have been found to both attenuate and increase pain. Effects of individual differences in attachment style seem to be particularly apparent when social interactions are more ambiguous. For example, Sambo et al. (2010) and Krahé et al. (2015), discussed in greater detail below, found that for participants with a more avoidant attachment style, the presence of both a stranger and their romantic partner enhanced pain compared to when participants experienced pain on their own. More avoidantly

attached individuals also displayed less pain when they thought their partner was feeling high (vs. low) empathy for them (Hurter et al., 2014). As a proposed function of facial expressions of pain is to solicit social support (see e.g., Williams, 2002), avoidant individuals may suppress pain displays in an attempt to evade social support. Overall, these findings on the moderating role of attachment style indicate the importance of both the habitual and situational perception of the partner's intentions.

Summary

Taken together, the above findings suggest that positively intentioned real or imagined interactions seem to attenuate pain (especially when interpersonally relevant), while the direction of effects especially for more ambiguous interactions seems to depend on individual differences in attachment style. Empathy from the social partner also seems to play a role in these effects. Considering these findings and drawing on attachment theory and principles of predictive coding theory we proposed an integrative framework within which the role of social interactions on pain may be understood (see Krahé et al., 2013, for details; see also Decety & Fotopoulou, 2015). In particular, we put forward that social interactions may influence pain by acting as social, predictive signals of contextual safety or threat, both in regards to noxious stimuli and the social) environment in which they occur. Further, the perception of social interactions themselves (e.g., individual differences in attachment style) was argued to influence these signals. While behavioural findings may be understood within such a framework, it is vital to support them with research offering insights at a different level of explanation, namely studies investigating the neurobiological mechanisms underlying effects of social interactions on pain. Candidate neural regions such as a "salience network" processing threats to the body – involved in weighting the importance of safety and threat and integrating these with social contextual factors – as well as neurobiological pathways related to attachment, such as those involving oxytocin, have already briefly been mentioned and will be explored in more detail in the next section.

Neurobiological mechanisms underlying the effects of social interactions on pain

To date, five studies have used social cognitive neuroscientific methods to explore some of the neurobiological mechanisms underlying the social modulation of pain (Eisenberger et al., 2011; Krahé et al., 2015; Krahé et al., 2016; Younger, Aron, Parke, Chatterjee, & Mackey, 2010) and

threat of pain (Coan, Schaefer, & Davidson, 2006). We will begin by addressing studies using functional magnetic resonance imaging (fMRI) paradigms, most of which have adopted 3rd person perspectives (e.g., priming interactions by viewing photographs of the romantic partner) before moving to psychopharmacological studies (without a social interaction but extensively linked to social affiliative processes) and lastly studies measuring evoked brain potentials using 2nd person approaches (e.g., touch by a social partner).

Attachment safety and reward in fMRI studies

Two studies primed social interactions by presenting pictures of the romantic partner and either an acquaintance (Younger et al., 2010) or a stranger and an object (Eisenberger et al., 2011), while participants received noxious stimuli during functional magnetic resonance imaging (fMRI). Younger et al. (2010) discovered that viewing partner pictures reduced pain ratings relative to seeing pictures of acquaintances who were matched with the partner in terms of length of acquaintance and attractiveness. In line with findings reviewed above, this suggests that the intimacy of the relationship between the social partner and the person in pain, over and above familiarity or attractiveness, might play a role in effects of social interactions on pain. Eisenberger et al. (2011)'s findings support this notion; viewing pictures of the partner reduced pain ratings more than viewing pictures of a stranger or an object, especially on trials inducing high levels of pain.

Regarding the patterns of neural activation associated with their effects, Eisenberger et al. (2011) showed that viewing partner pictures was linked to activation in the ventromedial prefrontal cortex (VMPFC) and that greater activation in this area was associated with decreases in pain-related outcome measures. As the VMPFC has been linked to signalling safety, this study indicates that seeing pictures of loved ones may signal safety at a neural level. Similarly, Coan et al. (2006) reported a decrease in activation in brain regions associated with processing bodily threat when holding the spouse's hand compared to holding a stranger's hand or no hand. In particular, reductions in activity in the anterior insula, superior frontal gyrus, and hypothalamus as a function of spouse hand-holding were evident only when participants reported high relationship satisfaction. Both findings link with behavioural evidence that social support figures (people participants identify to be the most supportive on a daily basis) may serve as 'prepared safety stimuli' (Hornstein, Fanselow, & Eisenberger, 2016), that is, stimuli which signal safety without this association needing to be learnt in the lab, and which for

example inhibit a learned fear response to other stimuli. Hornstein et al. (2016) found that pictures of supportive figures served as such prepared safety stimuli and that effects were not due to familiarity or reward (in contrast to Younger et al., 2010's findings). Together with research reviewed in the previous section (e.g., Master et al., 2009), these studies highlight the role of interpersonal closeness and safety – in short, attachment – in influencing the experience of pain.

Furthermore, Younger et al. (2010) found that viewing pictures of the partner activated reward-related neural regions, such as the caudate head and nucleus accumbens, and that activity in these regions was correlated with pain relief when participants viewed pictures of their partner. This is in accordance with studies demonstrating that viewing photographs of one's own children or the romantic partner is associated with activation in neural reward systems rich in dopamine and oxytocin (e.g., Aron et al., 2005; Bartels & Zeki, 2004), though this association is shaped by individual differences in attachment style: Mothers with a secure attachment style showed greater activation in reward-related regions and the hypothalamus, rich in oxytocin receptors, when seeing pictures of their infants' faces than did insecurely attached mothers (Strathearn, Fonagy, Amico, & Montague, 2009). Reward-related mechanisms, mediated by endogenous neuromodulators, have been widely explored in regards to positive expectations of pain relief (placebo analgesia, see e.g., Atlas & Wager, 2012; Price, Finniss, & Benedetti, 2008; Scott et al., 2007; Tracey, 2010), which can arguably be understood as expectations of the (relative) safety of a noxious stimulus.

Psychopharmacological studies and social salience

Neuromodulators such as dopamine and endogenous opioids may also code social reward and the motivation to affiliate and form social bonds (D'amato & Pavone, 1993; Mccall & Singer, 2012) and modulate the experience of pain during interactions with close others. Evidence from animal research suggests that interacting with siblings – but not unknown conspecifics – reduces pain sensitivity in mice, with effects mediated by endogenous opioids (D'amato & Pavone, 1993). A neuropeptide which interacts with both dopaminergic and opioid systems (Mccall & Singer, 2012) and which is linked closely to attachment in animals (see Insel, 2000) and humans (see Hurlemann & Scheele, 2016, for a recent review) is oxytocin. Oxytocin is synthesised in the hypothalamus and acts both peripherally as a hormone and centrally as a neurotransmitter (Macdonald & Macdonald, 2010). Of direct relevance to threat, oxytocin has

known anxiolytic effects (see Campbell, 2010). In relation to pain, oxytocin has been found to reduce pain behaviours in animal studies (see Rash, Aguirre-Camacho, & Campbell, 2014, for a review), also in interaction with opioid systems (Russo et al., 2012).

Findings from animal studies highlight the importance of studying the pain-modulatory role of oxytocin in humans. The development of a nasal spray which allows safe, non-invasive central administration of oxytocin to the human brain (see Macdonald et al., 2011) has recently made it possible to study the role of oxytocin in humans. It should be noted, however, that criticisms have emerged regarding power issues relating to the level of absorption by this method (Leng & Ludwig, 2016) and the small samples sizes of extant studies (Walum, Waldman, & Young, 2016). In relation to pain, experimental studies have shown that intranasally administered oxytocin (vs. a placebo spray) attenuates subjective pain report and neural responses linked to the perceived salience of threats to the body (Paloyelis et al., 2016) as well as anxiety (Zunhammer, Geis, Busch, Greenlee, & Eichhammer, 2015), although it is unclear how specific these effects are to pain vs. threats more generally. Indeed, oxytocin has been proposed to influence interoceptive processing (see *Pain* section above; Hurlemann & Scheele, 2016), indicating a perhaps more general role of oxytocin in affecting the processing of bodily threats, including pain.

Although there is currently no research directly assessing how oxytocin might be involved in mediating the effects of social interactions on pain in humans, studies into the effects of oxytocin on the perception of social stimuli point to possible mechanisms to be tested in future research. In particular, oxytocin may mediate effects of social interactions on pain is by modulating the perception of social interactions themselves. Oxytocin has been implicated in influencing the salience of social stimuli (see Averbeck, 2010; Shamay-Tsoory & Abu-Akel, 2016) and it has been proposed that oxytocin further enhances the salience of cues that are already salient for a particular individual, "setting in motion a biased search for information that is congruent with people's current chronic interpersonal beliefs and expectations" (Bartz et al., 2010, p. 21373). In this view, the effects of oxytocin depend strongly on individual differences, and indeed it has been widely demonstrated that oxytocin effects are shaped by context and early interpersonal experiences (Bartz, Zaki, Bolger, & Ochsner, 2011). For example, while intranasal oxytocin led to memories of the mother as being more close and caring in individuals low in attachment anxiety, it had the opposite effect in individuals with high attachment anxiety (Bartz et al., 2010). Thus, in the case of more securely (or less

anxiously) attached individuals, oxytocin may enhance the salience of cues linked to close attachment bonds and indeed, oxytocin effects appear to be most beneficial in a positive social context and for individuals with a secure attachment history (see also Shamay-Tsoory & Abu-Akel, 2016). For example, oxytocin reduced stress-related cortical responses only in conjunction with social support (Heinrichs et al., 2003), and only in individuals with no history of early parental separation (Meinlschmidt & Heim, 2007). Together, this suggests that within the context of pain, oxytocin may enhance social representations in line with participants' attachment style and may potentially underlie the moderating effects of attachment style on the experience of pain in a social context. However, this must remain speculative at present, as the interaction between oxytocin and attachment style has not yet been examined within the context of the social modulation of pain.

Electrophysiological studies: Effects of social interactions on early and late stages of pain-related processing

The studies outlined thus far have used fMRI and pharmacological methods to investigate neural mechanisms underlying effects of primed social interactions on pain. In neuroscientific pain research, non-invasive electrophysiological measures, such as electroencephalography (EEG) provide an additional window of insight into the neural mechanisms of pain by mapping specific electrophysiological responses that may be associated with noxious stimuli. A type of event-related potentials, namely laser-evoked potentials (LEPs), has been widely studied (see Bromm & Treede, 1984; Legrain et al., 2011). LEPs are psychophysiological measures of evoked brain responses, 'time-locked' to transient, noxious, thermal stimulation (such as laser pulses) and relate specifically to the activation of Aδ nociceptive fibres (see *Pain* section above). The amplitude and latency of these LEPs indicate the magnitude and speed of neural processing, respectively, and LEP amplitude is correlated with subjective pain report (Iannetti et al., 2005). Evoked potentials such as LEPs are superior to fMRI in their temporal resolution; because they can reflect neural processes occurring milliseconds after a stimulus is presented, it is possible to capture and tease apart different stages of neural processing. In relation to pain, two types of LEPs have been described. The earliest response to a noxious stimulus is denoted by the N1 component, reflecting activation in operculoinsular and primary somatosensory cortices (Garcia-Larrea et al., 2003; Valentini et al., 2012) and which is thought to capture nociception (Lee, Mouraux, & Iannetti, 2009; see also *Pain* section). The second type of LEP is the later N2-P2 complex; its underlying cortical generators primarily comprise

operculoinsular and anterior cingulate cortices (Bromm & Treede, 1984; Garcia-Larrea et al., 2003) and this complex has been proposed to reflect the conscious experience of pain (Lee et al., 2009). LEPs have been shown not to be specific to pain but instead to capture any salient threats to the body in the environment (Legrain et al., 2011) and have the advantage that it is possible to examine at which stage of neural processing manipulations of social interactions may exert their effects.

Recording LEPs while participants' romantic partner was either present or absent during the administration of laser pulses demonstrated that as well as leading to increased pain ratings, the presence of the romantic partner led to greater N2 and P2 amplitudes, i.e. augmented the brain's response to noxious stimulation, in individuals with higher attachment avoidance (Krahé et al., 2015). As discussed above, more avoidantly attached individuals may view and respond to social interactions, including support from others, in a more negative manner. Thus, rather than predicting safety, partner presence may have maintained the salience, i.e. threat value, of the noxious stimuli. Effects of partner presence dependent on attachment style were found for N2 and P2, but not for N1. This finding provides support for theories of interoception that propose that social contextual factors are integrated into the experience of pain within the anterior insula and anterior cingulate cortices and may modulate salience at this level of the neurocognitive hierarchy. There was no evidence for a moderating role of attachment anxiety on the effects of partner presence on pain or LEPs, akin findings by Sambo et al. (2010), who reported that attachment anxiety moderated effects of social interactions on pain only when additional disambiguating features – in their case information on the social partner's perceived level of empathy – were provided.

In a further study, we manipulated an embodied interaction related to social bonding by exploring the effects of affectively pleasant touch, i.e., slow, gentle stroking of the forearm or palm, on the experience of pain and LEPs, and again investigated the moderating role of adult attachment style (Krahé et al., 2016). Affective touch plays an important role in initiating and maintaining social bonds (see e.g., Morrison, Löken, & Olausson, 2010) and can promote feelings of state attachment security (Jakubiak & Feeney, 2016b). At a neurobiological level, slow stroking caresses have been associated with increased endogenous μ-opioid activity (Nummenmaa et al., 2016), and together with evidence from animal studies that touch by conspecifics can activate endogenous analgesic processes mediated by opioid and oxytocinergic mechanisms (Agren, Lundeberg, Uvnäs-Moberg, & Sato, 1995; Kehoe & Blass,

1986) suggests that this form of touch may have pain-attenuating effects. In humans, imagining touch (vs. imagining verbal support) reduced pain experienced alone (Jakubiak & Feeney, 2016a) as did 'embodied' social support manipulations such as holding the hand of the romantic partner (vs. the hand of a stranger or holding an object; Master et al., 2009; see also Goldstein et al., 2016).

In Krahé et al. (2016), a research confederate applied slow, gentle touch (generally perceived to be pleasant), and faster touch (generally perceived to be neutral) to participants' forearm or the palm of their hand immediately before participants received noxious laser pulses while LEPs were recorded. Varying the speed and location of the touch in this way afforded several advantages. First, it allowed us to study the role of the affective quality of the touch (pleasant vs neutral). Second, some of the physiological mechanisms underlying the perception of slow dynamic touch have been characterised. While slow, pleasant touch to the hairy skin of the body is thought to be coded by C tactile (CT) afferent fibres (see e.g., Löken, Wessberg, Morrison, Mcglone, & Olausson, 2009), perceived pleasantness of touch to non-hairy "glabrous" skin – in which CT fibres are absent – may instead be linked to top-down expectations regarding the social meaning of the touch. By manipulating touch location and measuring LEPs, we were able to explore the role of the CT system vs. such higher-order processing in the effects of affectively pleasant touch on early and later pain-related neural responses and subjective pain report. Given the importance of touch in attachment (see above), we expected individual differences in attachment style to shape these effects.

In line with our predictions, we discovered that higher attachment anxiety predicted a greater attenuation in N1 and N2 amplitudes when pleasant (vs. neutral) touch was applied to the forearm, whereas higher attachment avoidance predicted the opposite effect (Krahé et al., 2016). Thus, pleasant touch may dampen neural responses to noxious stimuli for individuals who seek signs of closeness and connection, but may enhance these responses in those who prefer to cope alone. Because these effects were found only in the group of participants who had received touch to the forearm, the earliest effects of affective touch on the neural processing of noxious stimuli (captured by the N1 component) seemed to be mediated by the CT system. As effects on pain ratings – again dependent on attachment style – were also found in the group that received touch to the palm of the hand (indicating that these effects were not dependent on the CT system), the conscious experience of pain may also be influenced by top-down factors concerning the perception of touch by others. Together, the two LEP studies reviewed in this

section indicate that presumed supportive interactions may have beneficial effects in more anxiously attached individuals, especially when the intention of the social partner is clearer, but may be detrimental and enhance neural responses related to processing salient threats to the body in more avoidantly attached individuals.

Summary

This chapter has shown that social interactions play a major role in the modulation of pain, as evidenced at cognitive, behavioural and the neurobiological levels. Research into the neurobiological processes underlying effects of social interactions on pain has put forward several candidate mechanisms. Studies employing functional neuroimaging techniques have proposed mediating processes relating to the rewarding nature of close relationships or their potential to signal attachment safety, possibly relating to dopaminergic and opioid systems, respectively. The degree to which the social modulation of pain relies on either of these mechanisms, or a combination of the two, remains to be specified, and the two may not mutually exclusive. Indeed, a common denominator may be that the rewarding nature of social relationships strengthens and maintains attachment bonds. In addition, neuropeptides involved in pain modulation and the perception of social interactions, notably oxytocin, which acts in conjunction with both dopamine and opioids for several of its functions, may underpin some of the moderating effects of attachment style on the effects of social interactions on pain. Yet, further studies are needed to experimentally test this possibility. Lastly, there is evidence to suggest that social interactions influence pain by modulating processing in a neural salience network, with individual differences in attachment style shaping these neural responses related to weighting safety and threat and integrating these with social contextual factors. In sum, fMRI, pharmacological and EEG studies all point to the importance of attachment and individual differences in attachment style in the social modulation of pain, providing support at a neurobiological level for the importance of social interactions in signalling perceived safety (or threat) in the context of pain. It should be noted, however, that further proposed mechanisms stemming from experimental research in psychology, including the role of perceived empathy on the experience of pain, have not yet been examined using neuroimaging methods and may provide further insights into the how social interactions influence the experience of pain.

Future directions

The advantage of the above psychological and neuroscientific studies is that their laboratory conditions and experimental design allow for rigorous control over the parameters involved. For example, emerging knowledge of the physiological pathways coding slow gentle touch (the CT system) now makes it possible to examine the effects of social touch with greater neurophysiological specificity and allow for more tightly matched control conditions (e.g. touch conditions that do not activate the CT system). This provides an advantage over previous studies which manipulated touch by means of non-controlled hand-holding. However, at the same time laboratory-based studies lack ecological validity. This is particularly acute in regards to pain, as there are important differences between both experimental and clinical pain, and between the social variables that can be operationalised and measured in the lab and naturalistic social conditions. The reality of clinical pain is different both in its physiology but also its psychological and social nature. For example, one may feel unsure as to the origins, or consequences of clinical pain, and a person and their social environment may experience pain differently when it is present for long periods rather than acute in its time course. Similarly, the experience of social support in everyday life may be multifaceted and varied in time. Thus, it is important for some of the above mechanisms to be tested with different methods and in large community or clinical cohorts. For example, observational or diary studies in chronic back pain populations may provide corroborating evidence for the role, type and availability of social support provided.

Conversely, some of the existing insights generated by clinical pain studies may be used to motivate and constrain psychological and neuroscientific studies. A positive and rare example in this direction is the recent experimental research on 'acceptance' (see above), a concept that stems from the clinical literature on pain. Another candidate psychological concept is the role of individual differences in pain catastrophising, which has already been tested in experimental studies (e.g., Sullivan, Adams, & Sullivan, 2004). Of course, an important development in the field is the design and implementation of randomised control trials on different types of social interactions on pain. These may involve support from health care specialists such nurses or dentists in acute pain settings, or certain types of trained supportive (e.g., empathic) actions from social partners. In this vein, some mechanisms put forward in experimental studies in psychology could be investigated using neuroimaging methods: while there is plenty of research into the neural processes underlying empathy *for* pain (see e.g. Lamm, Decety, & Singer, 2010, for a review), the effects of empathy *on* pain-related neural processing requires further study.

In fact, both could be combined to study neurobiological processes in the person giving and receiving support within the same interaction.

Regarding neurobiological pathways, more research regarding the role of oxytocin and also endogenous opioids is needed, especially within the context of manipulated social interactions. Further, neural activation by noxious stimuli has been found not to be pain-specific, but instead reflects processing of salient threats to the body more generally (Legrain et al., 2011). It would therefore be useful to compare effects of social interactions on noxious as well as other threatening stimuli within the same study to be able to examine whether social modulatory effects are specific to pain. Given that social interactions influence a range of health outcomes, yet effects of presumed social support have been more mixed in regards to pain than e.g., stress, this will be a useful avenue to explore.

Future research should further extend some of the interpersonal interactions and mechanisms examined in the current literature to broader social contexts, such as differences in the modulation of pain in in-group versus out-group contexts and also threatening interactions. At a neurobiological level, such an investigation could for example be linked to sex hormones such as testosterone, associated with dominance and pain-modulatory effects of social threat in animals (Langford et al., 2011).

In all the above endeavours, it is critical to consider the evidence which suggests that individual differences in personality traits, especially attachment style, moderate effects of social interactions on pain. Although theoretical perspectives commonly emphasise the beneficial effects of social interactions for pain (e.g., social baseline theory; Coan, 2008), social interactions may be unhelpful in the context of a negative attachment history, i.e., an insecure attachment style. Assessing individuals' attachment style, and generally asking individuals about their preferred types of social interactions during pain (see e.g., Krahé, Paloyelis, Sambo, & Fotopoulou, 2014), is needed to better understand when and why social interactions may be advantageous or counterproductive to the alleviation of pain.

It is certainly a long way from basic experimental research in psychology and neuroscience to explaining the impact of interacting with others on pain in naturalistic situations. However, the goal of the reviewed research and the present chapter was to begin to gain a better understanding of how individuals' pain experiences are shaped by social interactions.

References

Agren, G., Lundeberg, T., Uvnäs-Moberg, K., & Sato, A. (1995). The oxytocin antagonist 1-deamino-2-d-Tyr-(Oet)-4-Thr-8-Orn-oxytocin reverses the increase in the withdrawal response latency to thermal, but not mechanical nociceptive stimuli following oxytocin administration or massage-like stroking in rats. *Neuroscience Letters, 187*, 49-52.

Apkarian, A.V., Bushnell, M.C., Treede, R.-D., & Zubieta, J.-K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain, 9*, 463-463.

Aron, A., Fisher, H., Mashek, D.J., Strong, G., Li, H., & Brown, L.L. (2005). Reward, motivation, and emotion systems associated with early-stage intense romantic love. *Journal of Neurophysiology, 94*, 327-337.

Atlas, L.Y., & Wager, T.D. (2012). How expectations shape pain. *Neuroscience Letters, 520*, 140-148.

Auvray, M., Myin, E., & Spence, C. (2010). The sensory-discriminative and affective-motivational aspects of pain. *Neuroscience & Biobehavioral Reviews, 34*, 214-223.

Averbeck, B.B. (2010). Oxytocin and the salience of social cues. *Proceedings of the National Academy of Sciences, 107*, 9033-9034.

Bartels, A., & Zeki, S. (2004). The neural correlates of romantic and maternal love. *NeuroImage, 21*, 1155 - 1166.

Bartz, J.A., Zaki, J., Bolger, N., & Ochsner, K.N. (2011). Social effects of oxytocin in humans: Context and person matter. *Trends in Cognitive Sciences, 15*, 301-309.

Bartz, J.A., Zaki, J., Ochsner, K.N., Bolger, N., Kolevzon, A., Ludwig, N., & Lydon, J.E. (2010). Effects of oxytocin on recollections of maternal care and closeness. *Proceedings of the National Academy of Sciences, 107*, 21371-21375.

Bayet, S., Bushnell, M., & Schweinhardt, P. (2014). Emotional faces alter pain perception. *European Journal of Pain, 18*, 712-720.

Bowlby, J. (1997/1969). *Attachment and Loss, Vol. 1: Attachment*. London: Random House.

Bromm, B., & Treede, R.D. (1984). Nerve fibre discharges, cerebral potentials and sensations induced by CO2 laser stimulation. *Human Neurobiology, 3*, 33-40.

Brown, J.L., Sheffield, D., Leary, M.R., & Robinson, M.E. (2003). Social support and experimental pain. *Psychosomatic Medicine, 65*, 276-283.

Campbell, A. (2010). Oxytocin and human social behavior. *Personality and Social Psychology Review, 14*, 281-295.

Cano, A., & Williams, A.C.d.C. (2010). Social interaction in pain: Reinforcing pain behaviors or building intimacy? *Pain, 149*, 9-11.

Cauda, F., Torta, D.M.E., Sacco, K., Geda, E., D'Agata, F., Costa, T., . . . Amanzio, M. (2012). Shared "core" areas between the pain and other task-related networks. *PLoS ONE, 7*, e41929.

Chakrabarti, B. (2013). Parameterising ecological validity and integrating individual differences within second-person neuroscience. *Behavioral and Brain Sciences, 36*, 414-415.

Ciechanowski, P., Sullivan, M., Jensen, M., Romano, J., & Summers, H. (2003). The relationship of attachment style to depression, catastrophizing and health care utilization in patients with chronic pain. *Pain, 104*, 627-637.

Coan, J.A. (2008). Toward a neuroscience of attachment. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment: Theory, research, and clinical applications* (2nd ed., pp. 241–265). New York: Guilford Press.

Coan, J.A. (2011). The social regulation of emotion. In J. Decety & J. T. Cacioppo (Eds.), *Handbook of social neuroscience* (pp. 614-623). New York: Oxford University Press.

Coan, J.A., & Sbarra, D.A. (2015). Social Baseline Theory: the social regulation of risk and effort. *Current opinion in psychology, 1*, 87-91.

Coan, J.A., Schaefer, H.S., & Davidson, R.J. (2006). Lending a hand: Social regulation of the neural response to threat. *Psychological Science, 17*, 1032-1039.

Collins, N.L., & Feeney, B.C. (2004). Working models of attachment shape perceptions of social support: Evidence from experimental and observational studies. *Journal of Personality and Social Psychology, 87*, 363–383.

Colloca, L., Klinger, R., Flor, H., & Bingel, U. (2013). Placebo analgesia: Psychological and neurobiological mechanisms. *Pain, 154*, 511-514.

Corley, A.M., Cano, A., Goubert, L., Vlaeyen, J.W., & Wurm, L.H. (2016). Global and Situational Relationship Satisfaction Moderate the Effect of Threat on Pain in Couples. *Pain Medicine*, pnw022.

Craig, A.D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience, 3*, 655-666.

Craig, A.D. (2003). Interoception: The sense of the physiological condition of the body. *Current Opinion in Neurobiology, 13*, 500-505.

Craig, A.D. (2009). How do you feel -- now? The anterior insula and human awareness. *Nature Reviews Neuroscience, 10*, 59-70.

Critchley, H.D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *The Journal of Comparative Neurology, 493*, 154-166.

D'Amato, F.R., & Pavone, F. (1993). Endogenous opioids: A proximate reward mechanism for kin selection? *Behavioral and Neural Biology, 60*, 79-83.

Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., L. B. Ponto, L., Parvizi, J., & Hichwa, R.D. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature neuroscience, 3*, 1049-1056.

De Bruin, L., Van Elk, M., & Newen, A. (2012). Reconceptualizing Second-person Interaction. *Frontiers in Human Neuroscience, 6*.

Decety, J., & Fotopoulou, A. (2015). Why empathy has a beneficial impact on others in medicine: Unifying theories. *Frontiers in Behavioral Neuroscience, 8*.

Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., & Kleijnen, J. (2001). Influence of context effects on health outcomes: A systematic review. *The Lancet, 357*, 757-762.

Eisenberger, N.I., & Cole, S.W. (2012). Social neuroscience and health: neurophysiological mechanisms linking social ties with physical health. *Nature neuroscience, 15*, 669-674.

Eisenberger, N.I., Master, S.L., Inagaki, T.K., Taylor, S.E., Shirinyan, D., Lieberman, M.D., & Naliboff, B.D. (2011). Attachment figures activate a safety signal-related neural region and reduce pain experience. *Proceedings of the National Academy of Sciences, 108*, 11721-11726.

Garcia-Larrea, L., & Peyron, R. (2013). Pain matrices and neuropathic pain matrices: A review. *Pain, 154*, S29-S43.

Goldstein, P., Shamay-Tsoory, S.G., Yellinek, S., & Weissman-Fogel, I. (2016). Empathy Predicts an Experimental Pain Reduction During Touch. *The Journal of Pain*.

Haggard, P., Iannetti, Gian D., & Longo, Matthew R. (2013). Spatial Sensory Organization and Body Representation in Pain Perception. *Current Biology, 23*, R164-R176.

Hazan, C., & Shaver, P. (1987). Love conceptualized as an attachment process. *Journal of Personality and Social Psychology, 52*, 511 - 524.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003). Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry, 54*, 1389-1398.

Hornstein, E.A., Fanselow, M.S., & Eisenberger, N.I. (2016). A Safe Haven: Investigating Social-Support Figures as Prepared Safety Stimuli. *Psychological Science*, 0956797616646580.

Hurlemann, R., & Scheele, D. (2016). Dissecting the role of oxytocin in the formation and loss of social relationships. *Biological Psychiatry, 79*, 185-193.

Hurter, S., Paloyelis, Y., de C. Williams, A.C., & Fotopoulou, A. (2014). Partners' Empathy Increases Pain Ratings: Effects of Perceived Empathy and Attachment Style on Pain Report and Display. *The Journal of Pain, 15*, 934-944.

Iannetti, G.D., Zambreanu, L., Cruccu, G., & Tracey, I. (2005). Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. *Neuroscience, 131*, 199-208.

Insel, T.R. (2000). Toward a Neurobiology of Attachment. *Review of General Psychology, 4*, 176-185.

International Association for the Study of Pain. (1994). Part III: Pain terms, a current list with definitions and notes on usage. In H. Merskey & N. Bogduk (Eds.), *Classification of Chronic Pain* (2nd ed., pp. 209-214). Seattle: IASP Press.

Jakubiak, B.K., & Feeney, B.C. (2016a). Keep in touch: The effects of imagined touch support on stress and exploration. *Journal of Experimental Social Psychology, 65*, 59-67.

Jakubiak, B.K., & Feeney, B.C. (2016b). A Sense of Security: Touch Promotes State Attachment Security. *Social Psychological and Personality Science*, 1948550616646427.

Karos, K., Meulders, A., & Vlaeyen, J.W. (2015). Threatening social context facilitates pain-related fear learning. *The Journal of Pain, 16*, 214-225.

Kehoe, P., & Blass, E.M. (1986). Behaviorally functional opioid systems in infant rats: II. Evidence for pharmacological, physiological, and psychological mediation of pain and stress. *Behavioral Neuroscience, 100*, 624.

Kikusui, T., Winslow, J.T., & Mori, Y. (2006). Social buffering: Relief from stress and anxiety. *Philosophical Transactions of the Royal Society B: Biological Sciences, 361*, 2215-2228.

Krahé, C., Drabek, M.M., Paloyelis, Y., & Fotopoulou, A. (2016). Affective touch and attachment style modulate pain: A laser-evoked potentials study. *Philosophical Transactions of the Royal Society B, 371*, 20160009.

Krahé, C., Paloyelis, Y., Condon, H., Jenkinson, P.M., Williams, S.C.R., & Fotopoulou, A. (2015). Attachment style moderates partner presence effects on pain: a laser-evoked potentials study. *Social Cognitive and Affective Neuroscience, 10*, 1030-1037.

Krahé, C., Paloyelis, Y., Sambo, C.F., & Fotopoulou, A. (2014). I like it when my partner holds my hand: development of the responses and attitudes to support during pain questionnaire (RASP). *Frontiers in Psychology, 5*, 1027.

Krahé, C., Springer, A., Weinman, J.A., & Fotopoulou, A. (2013). The social modulation of pain: Others as predictive signals of salience – A systematic review. *Frontiers in Human Neuroscience, 7*, 386.

Lamm, C., Decety, J., & Singer, T. (2010). Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *NeuroImage, 54*, 2492-2502.

Langford, D.J., Tuttle, A.H., Briscoe, C., Harvey-Lewis, C., Baran, I., Gleeson, P., . . . Mogil, J.S. (2011). Varying Perceived Social Threat Modulates Pain Behavior in Male Mice. *The Journal of Pain, 12*, 125-132.

Lee, M.C., Mouraux, A., & Iannetti, G.D. (2009). Characterizing the cortical activity through which pain emerges from nociception. *The Journal of Neuroscience, 29*, 7909-7916.

Legrain, V., Iannetti, G.D., Plaghki, L., & Mouraux, A. (2011). The pain matrix reloaded: A salience detection system for the body. *Progress in Neurobiology, 93*, 111-124.

Leng, G., & Ludwig, M. (2016). Intranasal oxytocin: myths and delusions. *Biological Psychiatry, 79*, 243-250.

Leonard, M.T., Cano, A., & Johansen, A.B. (2006). Chronic pain in a couples context: A review and integration of theoretical models and empirical evidence. *The Journal of Pain, 7*, 377-390.

Leong, L.E., Cano, A., Wurm, L.H., Lumley, M.A., & Corley, A.M. (2015). A perspective-taking manipulation leads to greater empathy and less pain during the cold pressor task. *The Journal of Pain, 16*, 1176-1185.

Loeser, J.D., & Melzack, R. (1999). Pain: an overview. *The Lancet, 353*, 1607-1609.

Löken, L.S., Wessberg, J., Morrison, I., McGlone, F., & Olausson, H. (2009). Coding of pleasant touch by unmyelinated afferents in humans. *Nature neuroscience, 12*, 547-548.

MacDonald, E., Dadds, M.R., Brennan, J.L., Williams, K., Levy, F., & Cauchi, A.J. (2011). A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. *Psychoneuroendocrinology, 36*, 1114-1126.

MacDonald, K., & MacDonald, T.M. (2010). The Peptide That Binds: A Systematic Review of Oxytocin and its Prosocial Effects in Humans. *Harvard Review of Psychiatry, 18*, 1-21.

Main, M., Kaplan, N., & Cassidy, J. (1985). Security in infancy, childhood, and adulthood: A move to the level of representation. *Monographs of the Society for Research in Child Development, 50*, 66-104.

Martin, L.J., Tuttle, A.H., & Mogil, J.S. (2014). The Interaction Between Pain and Social Behavior in Humans and Rodents. In K. B. Taylor & P. D. Finn (Eds.), *Behavioral Neurobiology of Chronic Pain* (pp. 233-250). Berlin, Heidelberg: Springer Berlin Heidelberg.

Master, S.L., Eisenberger, N.I., Taylor, S.E., Naliboff, B.D., Shirinyan, D., & Lieberman, M.D. (2009). A picture's worth. *Psychological Science, 20*, 1316-1318.

McCall, C., & Singer, T. (2012). The animal and human neuroendocrinology of social cognition, motivation and behavior. *Nature neuroscience, 15*, 681-688.

McClelland, L., & McCubbin, J. (2008). Social influence and pain response in women and men. *Journal of Behavioral Medicine, 31*, 413-420.

Medford, N., & Critchley, H. (2010). Conjoint activity of anterior insular and anterior cingulate cortex: Awareness and response. *Brain Structure and Function, 214*, 535-549.

Meinlschmidt, G., & Heim, C. (2007). Sensitivity to Intranasal Oxytocin in Adult Men with Early Parental Separation. *Biological Psychiatry, 61*, 1109-1111.

Melzack, R. (1999). From the gate to the neuromatrix. *Pain, 82*, S121-S126.

Meredith, P. (2013). A review of the evidence regarding associations between attachment theory and experimentally induced pain. *Current Pain and Headache Reports, 17*, 1-9.

Meredith, P., Ownsworth, T., & Strong, J. (2008). A review of the evidence linking adult attachment theory and chronic pain: Presenting a conceptual model. *Clinical Psychology Review, 28*, 407-429.

Mikulincer, M. (1998). Attachment working models and the sense of trust: An exploration of interaction goals and affect regulation. *Journal of Personality and Social Psychology, 74*, 1209-1224.

Mikulincer, M., & Florian, V. (1997). Are emotional and instrumental supportive interactions beneficial in times of stress? The impact of attachment style. *Anxiety, Stress & Coping, 10*, 109-127.

Mikulincer, M., Shaver, P., & Pereg, D. (2003). Attachment Theory and Affect Regulation: The Dynamics, Development, and Cognitive Consequences of Attachment-Related Strategies. *Motivation and Emotion, 27*, 77-102.

Morrison, I., Löken, L.S., & Olausson, H. (2010). The skin as a social organ. *Experimental brain research, 204*, 305-314.

Mouraux, A., & Iannetti, G.D. (2009). Nociceptive Laser-Evoked Brain Potentials Do Not Reflect Nociceptive-Specific Neural Activity. *Journal of Neurophysiology, 101*, 3258-3269.

Nummenmaa, L., Tuominen, L., Dunbar, R., Hirvonen, J., Manninen, S., Arponen, E., . . . Sams, M. (2016). Social touch modulates endogenous μ-opioid system activity in humans. *NeuroImage, 138*, 242-247.

Paloyelis, Y., Krahé, C., Maltezos, S., Williams, S.C., Howard, M.A., & Fotopoulou, A. (2016). The Analgesic Effect of Oxytocin in Humans: A Double-Blind, Placebo-Controlled Cross-Over Study Using Laser-Evoked Potentials. *Journal of Neuroendocrinology, 28*, 1-10.

Peeters, P.A.M., & Vlaeyen, J.W.S. (2011). Feeling more pain, yet showing less: The influence of social threat on pain. *The Journal of Pain, 12*, 1255-1261.

Price, D.D., Finniss, D.G., & Benedetti, F. (2008). A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought. *Annual Review of Psychology, 59*, 565-590.

Przyrembel, M., Smallwood, J., Pauen, M., & Singer, T. (2012). Illuminating the Dark Matter of Social Neuroscience: Considering the Problem of Social Interaction from Philosophical, Psychological, and Neuroscientific Perspectives. *Frontiers in Human Neuroscience, 6*.

Rash, J.A., Aguirre-Camacho, A., & Campbell, T.S. (2014). Oxytocin and pain: a systematic review and synthesis of findings. *The Clinical Journal of Pain, 30*, 453-462.

Riem, M.M.E., van Ijzendoorn, M.H., Tops, M., Boksem, M.A.S., Rombouts, S.A.R.B., & Bakermans-Kranenburg, M.J. (2013). Oxytocin effects on complex brain networks are moderated by experiences of maternal love withdrawal. *European Neuropsychopharmacology, 23*, 1288-1295.

Roberts, M., Klatzkin, R., & Mechlin, B. (2015). Social Support Attenuates Physiological Stress Responses and Experimental Pain Sensitivity to Cold Pressor Pain. *Annals of Behavioral Medicine*, 1-13.

Ronga, I., Valentini, E., Mouraux, A., & Iannetti, G.D. (2013). Novelty is not enough: laser-evoked potentials are determined by stimulus saliency, not absolute novelty. *Journal of Neurophysiology, 109*, 692-701.

Russo, R., D'Agostino, G., Mattace Raso, G., Avagliano, C., Cristiano, C., Meli, R., & Calignano, A. (2012). Central administration of oxytocin reduces hyperalgesia in mice: Implication for cannabinoid and opioid systems. *Peptides, 38*, 81-88.

Sambo, C.F., Howard, M., Kopelman, M., Williams, S., & Fotopoulou, A. (2010). Knowing you care: Effects of perceived empathy and attachment style on pain perception. *Pain, 151*, 687-693.

Schilbach, L., Timmermans, B., Reddy, V., Costall, A., Bente, G., Schlicht, T., & Vogeley, K. (2013). Toward a second-person neuroscience. *Behavioral and Brain Sciences, 36*, 393–462.

Scott, D.J., Stohler, C.S., Egnatuk, C.M., Wang, H., Koeppe, R.A., & Zubieta, J.-K. (2007). Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron, 55*, 325-336.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., . . . Greicius, M.D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience, 27*, 2349-2356.

Shamay-Tsoory, S.G., & Abu-Akel, A. (2016). The social salience hypothesis of oxytocin. *Biological Psychiatry, 79*, 194-202.

Shaver, P.R., & Mikulincer, M. (2002). Attachment-related psychodynamics. *Attachment & Human Development, 4*, 133-161.

Strathearn, L., Fonagy, P., Amico, J., & Montague, P.R. (2009). Adult attachment predicts maternal brain and oxytocin response to infant cues. *Neuropsychopharmacology, 34*, 2655-2666.

Sullivan, M.J., Thorn, B., Haythornthwaite, J.A., Keefe, F., Martin, M., Bradley, L.A., & Lefebvre, J.C. (2001). Theoretical perspectives on the relation between catastrophizing and pain. *The Clinical Journal of Pain, 17*, 52-64.

Sullivan, M.J.L., Adams, H., & Sullivan, M.E. (2004). Communicative dimensions of pain catastrophizing: Social cueing effects on pain behaviour and coping. *Pain, 107*, 220-226.

Tracey, I. (2010). Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nature Medicine, 16*, 1277-1283.

Tracey, I., & Mantyh, P.W. (2007). The cerebral signature for pain perception and its modulation. *Neuron, 55*, 377-391.

Uchino, B. (2006). Social Support and Health: A Review of Physiological Processes Potentially Underlying Links to Disease Outcomes. *Journal of Behavioral Medicine, 29*, 377-387.

Villemure, C., & Bushnell, M.C. (2002). Cognitive modulation of pain: How do attention and emotion influence pain processing? *Pain, 95*, 195-199.

Vrticka, P., & Vuilleumier, P. (2012). Neuroscience of human social interactions and adult attachment style. *Frontiers in Human Neuroscience, 6*.

Walum, H., Waldman, I.D., & Young, L.J. (2016). Statistical and methodological considerations for the interpretation of intranasal oxytocin studies. *Biological Psychiatry, 79*, 251-257.

Waters, E., Merrick, S., Treboux, D., Crowell, J., & Albersheim, L. (2000). Attachment security in infancy and early adulthood: A twenty-year longitudinal study. *Child Development, 71*, 684-689.

Wiech, K., Lin, C.-s., Brodersen, K.H., Bingel, U., Ploner, M., & Tracey, I. (2010). Anterior insula integrates information about salience into perceptual decisions about pain. *The Journal of Neuroscience, 30*, 16324-16331.

Wiech, K., Ploner, M., & Tracey, I. (2008). Neurocognitive aspects of pain perception. *Trends in Cognitive Sciences, 12*, 306-313.

Wiech, K., & Tracey, I. (2009). The influence of negative emotions on pain: Behavioral effects and neural mechanisms. *NeuroImage, 47*, 987-994.

Williams, A.C.d.C. (2002). Facial expression of pain: An evolutionary account. *Behavioral and Brain Sciences, 25*, 439-455.

Wilson, C.L., & Ruben, M.A. (2011). A pain in her arm: Romantic attachment orientations and the tourniquet task. *Personal Relationships, 18*, 242-265.

Yoshino, A., Okamoto, Y., Onoda, K., Yoshimura, S., Kunisato, Y., Demoto, Y., . . . Yamawaki, S. (2010). Sadness enhances the experience of pain via neural activation in the anterior cingulate cortex and amygdala: An fMRI study. *NeuroImage, 50*, 1194-1201.

Younger, J., Aron, A., Parke, S., Chatterjee, N., & Mackey, S. (2010). Viewing pictures of a romantic partner reduces experimental pain: Involvement of neural reward systems. *PLoS ONE, 5*, e13309.

Zunhammer, M., Geis, S., Busch, V., Greenlee, M.W., & Eichhammer, P. (2015). Effects of intranasal oxytocin on thermal pain in healthy men: a randomized functional magnetic resonance imaging study. *Psychosomatic Medicine, 77*, 156-166.