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# Behavioural and psychophysiological facets of pain perception in healthy and chronic pain populations

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**Abstract**

Chronic pain, such as chronic head pain, represents one of the most disabling neurological and psychosocial conditions worldwide. Beyond a sensory disorder, chronic pain exemplifies a systemic dysregulation spanning neural, affective, and cognitive domains. Neuroimaging evidence demonstrates maladaptive plasticity and altered cortical connectivity, producing persistent central sensitisation and hyperresponsivity to innocuous stimuli (allodynia). Psychologically, anxiety, depression, and catastrophising contribute to hypervigilance and impaired emotional regulation.

This thesis empirically tested an integrative model of pain grounded in cognitive science, embodied cognition, and the biopsychosocial paradigm. Pain is here theorised as a process of dysregulated sense-making, reflecting a breakdown in the integration of interoceptive, affective, and cognitive systems. The project investigated how anticipatory anxiety, affective touch, sensory hypersensitivity, and mindfulness-based regulation interact to shape pain perception and adaptation. Four empirical studies were conducted with healthy participants and patients with chronic pain, primarily chronic migraine, combining psychophysiological, behavioural, self-report, and digital methodologies.

Study 1 (Chapter 2) examined autonomic reactivity (skin conductance response) to pain anticipation of painful stimuli in normal and transient states of anxiety induced by the Straw Breathing Task. Forced respiration effectively induced subjective anxiety without parallel autonomic activation, revealing a cognitive–affective and autonomic dissociation.

Study 2 (Chapter 3) investigated the relationship between affective touch and pain perception, examining both direct and vicarious effects. Chronic migraine patients and healthy participants retained hedonic sensitivity to affective touch, indicating its strength and potential therapeutic role. Conversely, patients exhibited reduced empathy for others' pain, possibly reflecting an avoidance response to external suffering. Overall, pain and affective touch appear as distinct and only weakly related phenomena.

Study 3 (Chapter 4) conceptualised cutaneous allodynia as a dimensional construct operating on a continuum of pain perception and as a potential marker of the transition from latent to overt pain conditions. Psychometric and network analyses revealed that in chronic pain, the embodied system may shift from adaptive flexibility to rigid hypervigilance, increasing pain attention, allodynia-like responses, and emotional distress. Depressive affect emerged as a central node linking pain and emotion, supporting a dimensional model of sensitisation.

Study 4 (Chapter 5) translated these findings into practice through the digital mindfulness intervention (BBMIND), which is addressed to individuals suffering from head pain, aiming to improve the management of chronic pain conditions.

Despite common barriers to digital engagement, participants reported high usability and modest adherence to the program. The intervention enhanced some mindfulness skills and reduced headache frequency, supporting the feasibility of digital mindfulness as a complementary tool in the management of chronic pain.

In conclusion, pain perception emerges as a dynamic, embodied process integrating physiological, emotional, and cognitive dimensions. Affective dysregulation and attentional bias (hypervigilance) appear central to sustaining chronic pain, whereas hedonic perception retains a protective function. Mindfulness-based regulation offers a pathway to restore balance and promote adaptive neuro-affective integration.

**Keywords:** Chronic pain; skin conductance response; affective touch; cutaneous allodynia; mindfulness.

**Riassunto**

Il dolore cronico, come la cefalgia cronica, rappresenta una delle condizioni neurologiche e psicosociali più invalidanti a livello globale. Oltre alla dimensione sensoriale, il dolore cronico costituisce un modello paradigmatico di disregolazione sistemica che coinvolge i domini neurobiologico, affettivo e cognitivo. Le evidenze di neuroimaging documentano fenomeni di plasticità maladattiva e alterazioni della connettività tra sistemi corticali, associate a sensibilizzazione centrale persistente e iperattivazione verso stimoli innocui (allodinia). Sul piano psicologico, ansia, depressione e catastrofismo favoriscono stati di ipervigilanza e una ridotta capacità di regolazione emotiva e di adattamento all'esperienza dolorifica.

In una prospettiva biopsicosociale e incarnata, il dolore cronico è concettualizzato come un processo maladattivo di senso, espressione di una frattura nell'integrazione tra sistemi neurobiologici, affettivi e cognitivi. Il presente progetto di tesi ha testato empiricamente un modello integrativo del dolore fondato sulle scienze cognitive, sulla cognizione incarnata e sul paradigma biopsicosociale, indagando l'interazione tra ansia anticipatoria, tocco affettivo, ipersensibilità sensoriale e l'attitudine mindfulness nella percezione e nell'adattamento al dolore cronico.

Sono stati condotti quattro studi su partecipanti sani e pazienti con dolore cronico, principalmente con emicrania cronica, attraverso metodologie psicofisiologiche, comportamentali, soggettive e digitali.

Lo Studio 1 (Capitolo 2) ha esaminato la risposta autonomica di conduttanza cutanea durante l'anticipazione di stimoli dolorosi in condizioni normali e in stati transitori di ansia indotti dallo Straw Breathing Task. La respirazione forzata ha incrementato l'ansia soggettiva senza corrispondente attivazione fisiologica, rivelando una dissociazione cognitivo–affettiva.

Lo Studio 2 (Capitolo 3) ha analizzato l'interazione tra la percezione del tocco affettivo e del dolore, in forma diretta e vicaria, nella popolazione sana e in pazienti emicranici. Si è mantenuta la sensibilità edonica al tocco affettivo, a indicare la sua forza e il suo potenziale terapeutico. Tuttavia, i pazienti hanno mostrato ridotta empatia per il dolore altrui, forse per meccanismi di evitamento. Complessivamente, il dolore e il tocco effettivo appaiono come fenomeni distinti e poco correlati tra loro.

Lo Studio 3 (Capitolo 4) ha concettualizzato l'allodinia cutanea come costrutto dimensionale operante su un continuum della percezione dolorifica e potenziale indicatore di transizione verso forme croniche conclamate. Le analisi psicometriche e di rete hanno evidenziato nel dolore cronico un passaggio da configurazioni adattive a stati rigidi e ipervigili, caratterizzati da maggiore attenzione selettiva al dolore, risposte simil-allodiniche e distress emotivo. Il dominio affettivo-depressivo è

emerso come nodo centrale tra dolore ed emozione, a sostegno di un modello dimensionale della sensibilizzazione.

Lo Studio 4 (Capitolo 5) ha applicato tali evidenze a un intervento digitale di mindfulness (BBMIND) rivolto a soggetti con cefalgia cronica. Nonostante le consuete difficoltà di adesione digitale, i partecipanti hanno riportato alta usabilità e moderata costanza. L'intervento ha migliorato alcune competenze di mindfulness e ridotto la frequenza cefalalgica, confermandone la fattibilità come strumento complementare di regolazione del dolore.

In conclusione, la percezione del dolore emerge come un processo dinamico e incarnato, in cui le dimensioni fisiologiche, emotive e cognitive interagiscono costantemente. La disregolazione affettiva e i bias attentivi, come l'ipervigilanza a sensazioni dolorifiche, appaiono centrali nel mantenimento della cronicità, mentre la percezione edonica mostra un potenziale ruolo protettivo. La mindfulness si conferma uno strumento integrativo capace di ristabilire un equilibrio adattivo e di potenziare le risorse di autoregolazione.

**Parole chiave:** Dolore cronico; conduttanza cutanea; tocco affettivo; allodinia cutanea; mindfulness.

# 1. INTRODUCTION

## 1.1. Basic principles of nociception and pain perception

Pain is a somatic sensation, a complex, subjective phenomenon, definable as *"an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (Raja et al., 2020).

This revised definition of the original one by IASP (1979) emphasises the subjective component of pain. It is a subjective, multidimensional experience fundamental to survival, recognising and fleeing from dangers and learning to avoid harm in the future. Pain perception involves several mechanisms, including anatomical structures, neurological pathways that involve the central and peripheral nervous systems, psychological factors that affect neural responses, and cognitive processes that integrate sensory and emotional inputs (Lee et al., 2020). Therefore, both in daily life and in the research field, the definition of pain becomes a "*semantic trick*" (Merskey, 1991), a term that attempts to describe a subjective physical experience that can have physical or non-physical causes. Actually, it's not possible to discriminate whether the individual's experience of pain is due to tissue damage or not on the subjective record. People may report pain sensations without tissue damage or any likely pathophysiological cause, such as psychological reasons. Thus, pain is always subjective: we all have a unique understanding of this concept, acquired through our personal experiences of pain. This definition avoids binding pain to the stimulus. It leads to distinguishing between nociception, the neural process of coding noxious stimuli that damage or threaten to damage tissue, and pain, which is always a psychological state, even if it is most often linked to a physical cause (Merskey, 1991; Raja et al., 2020).

The somatosensory system has specific primary sensory neurons, called nociceptors, that are activated by mechanical, chemical, or thermal stimuli capable of causing tissue damage, but not by harmless stimuli such as gentle touch (Sherrington, 1906; Burgess & Perl, 1967). The complexity of defining nociceptors stems from their stimulus thresholds, which determine the capacity to elicit pain upon activation (Weidner et al., 1999). These receptors are widely distributed throughout the body and can be found in the skin, blood vessels, muscles, joints, and visceral organs (Meyer et al., 2006). A and C nerve fibres transduce the nociceptive signal detection by these receptors. Among A fibres, Aβ can also detect innocuous stimuli; they are responsive to non-noxious mechanical inputs from skin, muscles, and joints and generally do not mediate nociceptive signalling (Djouhri et al., 1998; Snider & McMahon, 1998). In fact, activation of large-diameter fibres can attenuate pain perception, a phenomenon commonly experienced when stroking an injured area. Instead, most of the nociceptors arise from Aδ-fiber, thinly myelinated and of medium diameter, convey well-localised pain signals,

and C fibres are unmyelinated and of small diameter, generally more broadly distributed, and are precluded from precise localisation of the stimulus and transmit poorly localised pain signals. These fibres differ in their conduction velocities and are thought to underlie the dual temporal phases of pain perception: Aδ-fibers are implicated in the rapid, sharp sensation known as "*first pain*", whereas C-fibres are associated with the slower, more diffuse "*second pain*" (Julius & Basbaum, 2001). On the contrary, visceral nociception lacks the conventional fast and slow components and presents diffuse, deep, and poorly localised discomfort. It can also rise in the absence of overt tissue injury (Raja et al., 1999; Basbaum, 2000). Among Aδ-fibre nociceptors, the two principal subtypes both respond to intense mechanical stimuli but exhibit different responses to high thermal stimuli and react variably to tissue injury. Many C-fibre nociceptors are polymodal, responding to thermal and mechanical noxious stimuli; most also respond to noxious chemical stimuli, such as acid or capsaicin. Also, the so-called "silent" or "sleeping" nociceptors are responsive only when triggered by tissue injury (Julius & Basbaum, 2001) (see Figure 1.1).

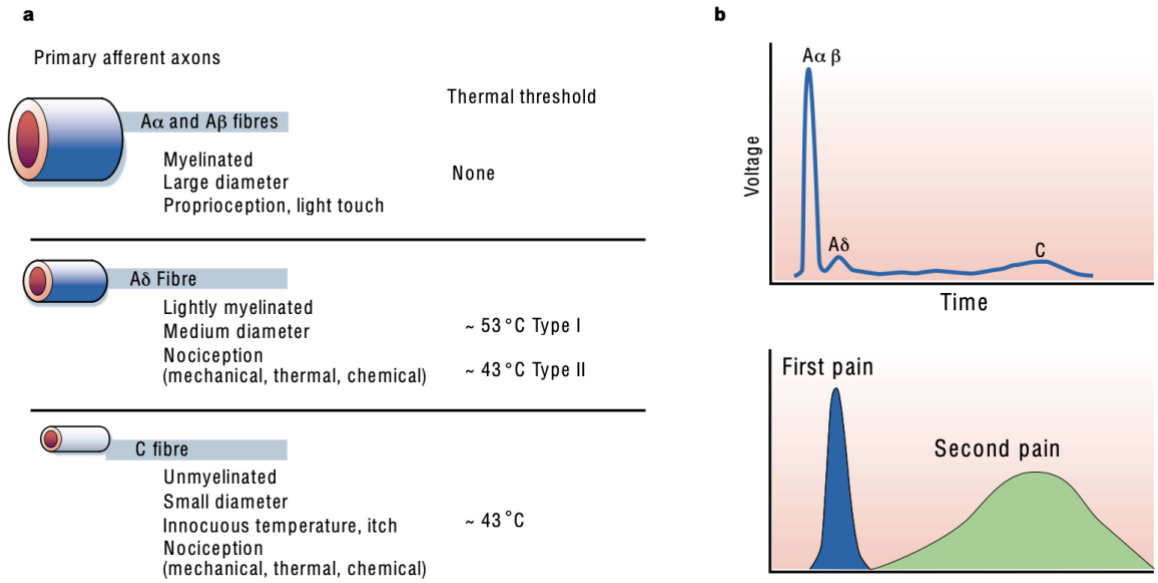


Figure 1.1: (a) Different nociceptors for different types of pain. Small-diameter (A), medium-to-large-diameter (A) myelinated afferent and small-diameter unmyelinated afferent fibres (C) in the peripheral nerves. (b) A or C fibres nociceptors and their different conduction velocities (6–25 and ~1.0 m s–1, respectively) are responsible for the first (fast) and second (slow) pain responses to injury (from Julius & Basbaum, 2001).

A fundamental part of processing painful stimuli occurs in both the peripheral and central nervous systems, even before the signal reaches the brain. Noxious stimuli are converted into electrical

impulses by free, “unencapsulated” nerve endings arising from the axons and terminating within the walls of arterioles and adjacent connective tissues. They may extend their innervation to specific areas of the dermis and epidermis (Dubin & Patapoutian, 2010). Nociceptors exhibit a pseudounipolar morphology that involves a single axon extending from the neuronal soma, which is located in either the dorsal root ganglion or the trigeminal ganglion. This axon subsequently bifurcates into two distinct branches: one projects peripherally to innervate the skin, the other extends centrally to form synapses with second-order neurons in the dorsal horn of the spinal cord, anatomically organised into distinct laminae, or the trigeminal subnucleus caudalis, respectively. This direct axonal pathway between peripheral targets and the spinal cord (or brainstem) facilitates efficient action potential propagation and minimises the likelihood of conduction failure (Dubin & Patapoutian, 2010).

Nociceptive Aδ- and C-fibres primarily terminate in the superficial laminae (I and II), although a smaller proportion extend into deeper regions. In contrast, Aβ-fibers predominantly innervate the deeper laminae (III–VI). Nociceptive-specific neurons are predominantly localised within the superficial laminae and receive input exclusively from Aδ- and C-fibres.

These neurons generate action potentials responding to noxious stimuli detected in peripheral tissues. In contrast, neurons that exclusively receive input from Aβ-fibers are associated with proprioceptive or tactile functions and react only to non-noxious mechanical stimuli.

A third class of neurons, the wide-dynamic-range neurons (D'Mello & Dickenson, 2008), integrates input from all three types of sensory fibres (Aβ, Aδ, and C-fibres). They can respond to all three types of sensory fibres and therefore to mechanical, thermal, and chemical insults. These neurons exhibit graded firing patterns proportional to stimulus intensity and display a progressive increase in action potential output and after-discharges in response to repetitive stimulation. Importantly, wide-dynamic-range neurons frequently receive input from both somatic and visceral sources, a convergence believed to contribute to referred pain phenomena, such as the heart during myocardial ischemia, which may be perceived as somatic pain in distant regions, like the shoulder.

Additionally, the dorsal horn of the spinal cord contains excitatory (glutamatergic) and inhibitory (GABAergic) interneurons, which modulate the activity of nociceptive-specific and wide-dynamic-range neurons, thereby influencing overall nociceptive processing (D'Mello & Dickenson, 2008).

Projection neurons in laminae I and V of the dorsal horn represent the main output pathways from the spinal cord to supraspinal structures. They give rise to several significant ascending tracts, including the spinothalamic and spinoreticulothalamic pathways, which convey nociceptive information to the thalamus and brainstem. The spinothalamic tract is primarily associated with the sensory-discriminative dimension of pain, mediating information about stimulus location and intensity. In contrast, the spinoreticulothalamic pathway is implicated in transmitting more diffusely

localised, affective components of pain. The spinal tract projects to the parabrachial nucleus in the dorsolateral pons, which acts as a critical relay to the amygdala, a limbic structure that encodes the emotional and aversive valence of painful stimuli. The fast connectivity between the parabrachial nucleus and amygdala suggests an essential role in mediating the affective-motivational aspects of pain (Basbaum et al., 2009). Nociceptive information is relayed to various cortical areas, following transmission to the brainstem and thalamic regions.

The experience of pain arises from the activation of a distributed network of cortical areas (Apkarian et al., 2005; Tracey & Mantyh, 2007). This network encompasses areas primarily involved in the sensory-discriminative processing of pain, such as the primary (S1) and secondary somatosensory (S2) cortices, as well as regions implicated in affective processing, including the anterior cingulate cortex (ACC), insular cortex, hypothalamus, and amygdala. Additionally, the prefrontal cortex, basal ganglia, and cerebellum play roles in pain processing (Talbot et al., 1991; Andersson et al., 1997; Bushnell et al., 1999; Coghill et al., 1999; Chen et al., 2002; Strigo et al., 2003).

This distributed network encodes the multidimensional nature of pain, encompassing sensory, affective, and cognitive components, and enables the organism to generate adaptive responses to potentially harmful stimuli (Tracey & Mantyh, 2007). Specifically, the co-activation of mid and anterior regions of the insular cortex and the premotor cortex may reflect a posterior-to-anterior flow of information within the insula, which contributes to transforming sensory events into autonomic responses and creating individual emotional experiences. Moreover, the anterior cingulate cortex is also reliably engaged during the cognitive processing of nociceptive stimuli, alongside the prefrontal and posterior parietal cortices, which are supposed to maintain attention and evaluative processes of anticipation, learning, and cognitive control (Peyron et al., 1999; Peyron et al., 2007; Ploghaus et al., 1999; Sawamoto et al. 2000; Garcia-Larrea & Peyron, 2013). Besides the ascending pain pathways, the nociceptive process also utilises descending modulatory systems that regulate nociceptive transmission at the level of the spinal cord, modulating the intensity and quality of pain signals transmitted to higher brain centres (Basbaum et al., 2009) (see Figure 1.2).

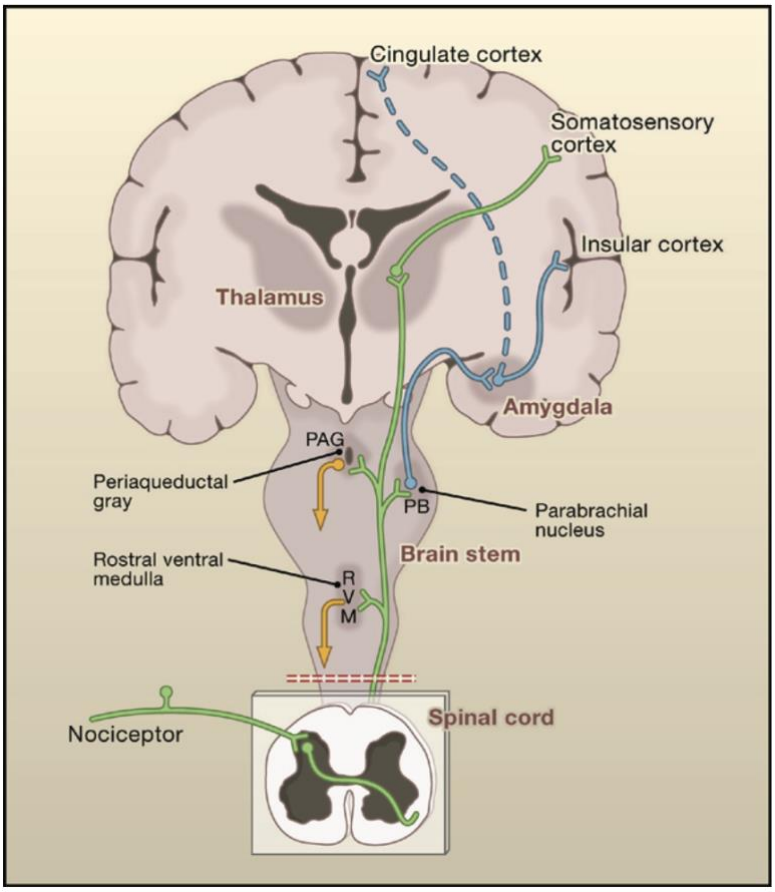


Figure 1.2: Graphic representation of Pain Pathway. Nociceptive signals from primary afferent neurons are relayed to projection neurons located in the dorsal horn of the spinal cord. A portion of these projection neurons transmits sensory-discriminative information, such as pain intensity and spatial characteristics, to the somatosensory cortex via the thalamus. Additional projection pathways target the cingulate and insular cortices via connections in the brainstem (parabrachial nucleus) and the amygdala, thereby contributing to the emotional and affective dimensions of pain. This ascending pain pathway activates neurons in the rostral ventromedial medulla and the periaqueductal grey of the midbrain, which are key components of descending modulatory circuits that influence spinal nociceptive processing (From Basbaum et al., 2009).

## 1.2. The perception and processing of the experience of pain

It is a common tendency to equate *nociception* with the subjective experience of *pain*, even though they are far from synonyms. When tissue injury occurs, peripheral sensory information is transmitted to the somatosensory cortex, culminating in the conscious experience of pain. Moreover, pain is fundamentally unpleasant; it elicits affective responses that enrich the experience with an emotional dimension, making people associate it with the sensation of nociception. Otherwise, nociception refers to unconscious physiological processes, whereas pain is a conscious, subjective phenomenon. Pain may occur without nociceptive input, and nociception may proceed without the

conscious experience of pain. Pain emerges from a dynamic construction of mindful awareness, an integrative activity of brain networks that integrate internal and external perceptual stimuli. Thus, pain should be conceptualised as a complex, consciousness-dependent, somatic, affective, and cognitive experience (Torebjörk, 1974; Torebjörk & Ochoa, 1982; Perl, 2007; Ackerley & Watkins, 2018). Cortical activity is necessary to generate a painful experience, as evidenced by well-documented laser-evoked potentials (LEPs) studies that disentangle the steps involved in the emergence of pain from nociception (Cruccu et al., 2004). Nociceptive stimulation by LEPs triggers an early-latency electrocortical response (N1 wave) that represents neural activity related to ascending nociceptive input. Later neural activity responses (N2 and P2 waves) reflect cortical processes related to the conscious detection of nociceptive input and are linked to the advent of pain, distinctly from nociception (Ohara et al., 2004; Iannetti et al., 2008). The N2 and P2 components are generated by a widespread network of cortical regions, including bilateral operculo-insular areas and the anterior cingulate cortex (García-Larrea et al., 2003). Some areas are more involved in the conscious perception of nociceptive input; others, such as the anterior insula, may be more specifically implicated in the subjective awareness of the stimulus (Craig, 2009).

Notably, when several painful stimuli occur, the amplitude of the P2 response is significantly higher to the initial stimulus than to the following ones. This suggests that the magnitude of the initial P2 response may serve as a predictor of subsequent conscious detection. Additionally, the magnitude of the P2 wave in LEPs is influenced by the level of attention and arousal: distraction and decreased states of arousal can reduce its responsiveness (Beydoun et al., 1993; Legrain et al., 2002; Lee & Iannetti, 2009). Pain experience is a somatic perception of tissue damage, including other aversive somatic sensations such as nausea, fatigue, or dizziness. The involvement of limbic areas leads to emotional distress, such as negative emotional arousal related to the perceived threat.

Furthermore, cognitive functions play a role in attentional focus, interpretation, and attribution of pain experience (Chapman, 2004). Additionally, an injury can disrupt the brain's homeostatic regulation systems, triggering stress and prompting the activation of coping strategies to restore homeostasis, particularly in chronic pain conditions. (Melzack, 1999). These findings suggest that pain is influenced by several factors that make it unique in each individual, as cognitive-affective processing represents one of the most critical substrates of the algesic experience, modulating its overall outcome.

It has been suggested that psychological and autonomic mechanisms are primary modulators of the perception of noxious and innocuous stimuli, wielding a greater impact than the stimulus intensity. Empirical findings on the perception of noxious and innocuous stimuli frequently report variations associated with affective valence, attentional focus, or perceived aversiveness of the stimulus, as well

as cardiovascular responses such as heart rate, and the cognitive process of rating the stimuli, rather than differences in the stimuli themselves. These observations highlight the crucial role of psychological and interoceptive factors in the processing of somatosensory stimuli and support the concept of a salience detection system for sensory perception. Functional MRI studies suggest that neural responses to noxious and innocuous stimuli are highly interrelated, with inter-individual variability in pain sensitivity accounting for a substantial proportion of the observed variations in the BOLD signal associated with these types of stimulation. The cortical areas traditionally associated with pain processing are not exclusively dedicated to nociceptive input. Instead, these regions likely contribute to a broader salience detection network, integrating multisensory, cognitive, affective, and autonomic information across multiple functional domains (Legrain et al., 2011; Powers et al., 2024). It has been demonstrated that beliefs and attention modulate pain. Positive expectations can lead to hypoalgesia, a reduction in the perceived intensity of pain, thus potentially eliciting a placebo response. In contrast, negative expectations may enhance pain perception, resulting in hyperalgesia, a phenomenon associated with the nocebo effect (Kong & Benedetti, 2014). Furthermore, an increased attention to one's pain can amplify the perceived intensity.

The autonomic nervous system (ANS) is activated in response to harmful stimuli; additionally, the experience of pain can influence autonomic responses to noxious stimulation, as cortical regions involved in pain regulation also participate in modulating ANS activity. Top-down psychological mechanisms, including emotional appraisal, implicit and explicit learning processes, and exposure to stress, can modulate the arousal (Berntson et al., 1991; Lee et al., 2020). Experimental manipulation of attention or emotional states has been shown to affect the subjective experience of pain and the associated autonomic responses to nociceptive input: autonomic activity is highly responsive to fluctuations in subjective pain experience. Pain sensitivity is malleable and can quickly increase or decrease over time; therefore, autonomic reactions must also be flexible, able to adapt to both foreseen and actual changes in environmental circumstances. In fact, anticipatory cues of forthcoming painful stimuli have been shown to rapidly modulate autonomic reactivity. The pain appraisal accommodates itself to contextual factors and regulates autonomic response, making them flexible to respond appropriately and effectively.

Therefore, ANS physiological markers, such as skin conductance response, can be assumed to indicate pain in experimental and clinical contexts. Nonetheless, a critical limitation of autonomic signals is that there is no specificity: an increased arousal is elicited not only by pain but also by other emotionally salient and aversive or appetitive events, including pain anticipation, reward or unexpected outcomes, or even as pleasant and unpleasant imagery (Mischkowski et al., 2018).

The sympathetic branch of the autonomic nervous system plays a central role in mediating the affective and physiological responses to tissue injury. It prepares the body for escape or confrontation, thus protecting the organism from danger. The hypothalamus activates the sympathetic nervous system to initiate a coordinated set of responses to maintain homeostasis and promote survival.
Because defensive responses and their associated physiological changes are largely involuntary, we often perceive them as externally imposed rather than internally generated, interpreting and expressing them as subjective feelings rather than recognising them as bodily processes. For instance, in response to a threatening or physiologically arousing event, individuals may report, "It scared me" or "It made me angry," attributing the emotional experience to the external stimulus. As emotional responses reflect a person's state of being within a specific context, the emotional interpretation of events is often shaped by the physiological arousal they elicit. In this framework, autonomic nervous system (ANS) activation constitutes a fundamental component of the psychological experience of injury, contributing to and shaping that experience. It's not surprising that pain research and intervention are becoming more involved in the complex interplay between biological, psychological, and social features (Chapman, 2004).

### 1.3. Chronic pain

The experience of pain results from the interaction between perceptual features, such as location, duration, and intensity of the nociceptive stimulus, and affective-motivational factors, including emotional unpleasantness and distress, which play a crucial protective and adaptive role aimed at protecting and resolving existing or potential body damage or risk to life.
However, under certain conditions, pain may persist well beyond the expected tissue healing time, as it becomes unhinged from the tissue damage and loses its original adaptive or protective function, thereby becoming a chronic pathological condition. The commonly accepted definition of chronic pain as "*persistent or recurrent pain lasting longer than 3 months*" distinguishes it from acute pain that can be clinically useful, however it doesn't give credit to the fact that chronic pain is not the temporal extension of acute one, as they don't incorporate the exact underlying mechanism (Turk & Okifuji, 2002; Barroso & Apkarian, 2021). It can be assumed that chronic pain subtends an abnormal network state. Compared to the typical brain organisation, chronic pain represents a unique neurological condition characterised by widespread alterations in global structural and functional brain connectivity, as well as specific disruptions in localised network interactions. Specifically, regions that are typically highly interconnected and integrative centres exhibit reduced activity and diminished involvement in coordinating and disseminating information.

In contrast, areas that are usually less connected demonstrate increased activity, a measurable indicator of rank-order disruption. The most significantly affected brain regions exhibit a notable dissociation: nonhub areas, such as the precentral and postcentral gyrus in the sensorimotor cortex, increase their connectivity to the rest of the brain, while other regions, as the insula and operculum, which are typically functional brain hubs, are downregulated. Notably, this reorganisation of brain topology is comparable across various chronic pain conditions. For example, this phenomenon is documented in chronic pain as osteoarthritis, chronic regional pain syndrome, subacute back pain and chronic back pain.

Furthermore, greater disruption in this network architecture is consistently associated with higher reported levels of pain intensity. Remarkably, many brain regions are affected by chronic pain. In individuals with chronic pain, the thalamus, a key player in nociception, and the hippocampus, a crucial area involved in memory formation and learning, exhibit increased connectivity with other brain regions compared to healthy individuals. This suggests that brain network disruption in chronic pain also affects brain regions not directly related to pain, such as the ventral tegmental area, nucleus accumbens, and hippocampus. Consequently, even the emotional limbic brain, well recognised for its role in linking nociception and pain perception, can be affected in chronic pain in its interrelation with memory, emotion, and motivation (Mutso et al., 2012; Baliki & Apkarian, 2015; Mansour et al., 2016). The mesocorticolimbic system, a primary dopaminergic pathway in the brain, comprises the ventral tegmental area, which sends dopaminergic projections to various regions. These include the prefrontal cortex via the mesocortical pathway and the nucleus accumbens, amygdala, and hippocampus through the mesolimbic pathway. Collectively, these interconnected regions play a central role in processing reward, motivation, aversion, and value, and are critically involved in regulating learning mechanisms (Wise, 2004; Martikainen et al., 2015; Baliki et al., 2008).

A reduction in grey matter density in the dorsolateral prefrontal cortex and the right thalamus has been detected in chronic back pain (Apkarian et al., 2004; Kim et al., 2008). Additionally, these changes were strongly correlated with duration, pain intensity, and sensory and negative affective features. Recent findings indicate that an individual's capacity for fear extinction learning can predict the magnitude of affective behaviours associated with neuropathic pain. Moreover, this relationship is linked to the degree of neuronal activity alterations within the central nucleus of the amygdala in chronic pain (Ji et al., 2018). There is a close interrelationship between pain, memory, and emotional learning in pain management. Pain, physiologically connoted as having a strong emotional valence, drives adaptive neural mechanisms to minimise future harm by promoting the extinction of pain-inducing behaviours. Conversely, the experience of pain relief reinforces protective behaviours, thereby supporting adaptive responses. The hippocampus is implicated in these pain-related

behavioural processes. The hippocampus exacerbates the anticipatory anxiety of pain in the prediction and evaluation of future pain experiences and in the heightened perception of pain following negative emotional states.

Furthermore, the hippocampal formation plays a critical role in encoding pain-associated memories. In chronic pain, morphological alterations in the hippocampus have been linked to an exaggerated recall of memories associated with painful experiences. Chronic pain sufferers often display impairments in hippocampal-dependent cognitive functions, including deficits in memory performance and classical conditioning tasks. These findings support the conceptualisation of chronic pain as an ongoing learning process, wherein persistent pain becomes recurrently associated with negative affect and aversive emotional states. This persistent association induces plastic changes in neural circuits, leading to the consolidation of maladaptive memory traces. Pain is a significant driver of neural plasticity, contributing to the formation, maintenance, and potential extinction of pain-related memories. The inability to extinguish these pain-related memories, combined with the continuous reinforcement of pain experiences, may contribute to the development and maintenance of a chronic, maladaptive pain state (Barroso & Apkarian, 2021).

Additionally, the affective component of pain involves an early and rapid emotional response, often resembling hypervigilance or fear, which essentially functions as a perception of threat, followed by conscious awareness of these bodily changes that contribute to a pronounced negative subjective experience. The changes in bodily states, particularly those related to visceral responses and autonomic activity, function as "somatic markers" (Damasio, 1994). These affective signals provide evaluative feedback of perceptual experiences and help to determine whether an event poses a potential threat. Essentially, somatic markers are bodily-based representations, or *somatic images*, that inform decision-making and behaviour. The brain processes these markers as images, representing external and internal stimuli or events: this processing mode enhances cognitive efficiency. In pain or tissue injury, somatic markers often manifest as complex patterns of physiological arousal, symbolising a threat to physical integrity and potentially to psychological or social well-being. These somatic images can form intricate associative networks, interacting with other cognitive and emotional representations that can become dysfunctional in chronic pain.

In chronic pain, pain catastrophizing can also occur. It can be defined as an exaggerated negative cognitive and emotional orientation toward actual or anticipated pain experiences. This cognitive style has been linked to increased pain intensity and to both physical and psychological dysfunction across a range of clinical and non-clinical populations (Gatchel et al., 2007). Specifically, catastrophizing combined with feelings of helplessness and a ruminative thinking appears to be a notable feature in sufferers of chronic migraine (Pistoia et al., 2022). Furthermore, when fear-avoidant

beliefs supervene, maladaptive cognitions centred on the fear of experiencing pain lead to the prevention of pain, and frequently exacerbate discomfort and disability, undermining the individual's well-being (Gatchel et al., 2007). Moreover, the sense of self-efficacy and self-mastery—the perceived ability to face and control aversive situations—also play a crucial role in shaping the meaning attributed to pain. Higher levels of perceived control are associated with reduced threat appraisal and lower pain intensity or unpleasantness, ultimately leading to increased pain tolerance. The sense of acquired impotence can arouse negative feelings, frustration and depression (Bandura et al., 1987; Gatchel et al., 2007).

The changes occurring in chronic pain are also underpinned by physiological sensitisation of the peripheral and central nervous systems, which can affect daily life sensory interactions with the world. Central and peripheral are two distinct processes, differing in their underlying molecular mechanisms and clinical presentation, yet they can superficially resemble each other in their effects. Peripheral sensitisation involves a lowered threshold and heightened responsiveness of nociceptors, resulting from the exposure of the peripheral terminals of high-threshold primary sensory neurons to inflammatory mediators and damaged tissue. Consequently, its effects are typically localised to the site of tissue injury. Peripheral sensitisation contributes to the overall sensitisation of the nociceptive system and to primary hyperalgesia, an inflammatory pain hypersensitivity at inflamed sites. However, it remains a nociceptor-driven phenomenon and generally requires the presence of ongoing peripheral pathology to persist. Peripheral sensitisation is more strongly associated with increased sensitivity to thermal stimuli.

In contrast, central sensitisation is characterised by a broader and more sustained enhancement of pain sensitivity beyond the injury site. It produces pain hypersensitivity in noninflamed tissue by changing the sensory response elicited by normal inputs. It increases pain sensitivity long after the initiating cause disappears and when no peripheral pathology is present. Central sensitisation arises from a change in the properties of neurons within the central nervous system. It reflects a significant functional alteration in the somatosensory system from high-threshold nociception to low-threshold pain hypersensitivity. Thus, it can manifest as allodynia, a reduction in threshold; hyperalgesia, an amplified and prolonged pain in a receptive field; and secondary hyperalgesia, which refers to the expansion of the receptive field in which stimuli applied to non-injured surrounding tissue elicit pain (Latremoliere & Woolf, 2009; Woolf, 2011).

Another crucial maladaptive mechanism is the loss of inhibitory control. Under normal conditions, inhibitory neurons in the spinal cord and brain modulate nociceptive signals. However, in chronic pain conditions, this inhibitory modulation may become compromised, leading to impaired regulation

of pain transmission. This reduction in inhibitory control plays a significant role in the persistence and heightened intensity of pain experienced in chronic pain syndromes (Sandkuhler, 2009).

Persistent pain also engages immune system cells, specifically microglial cells within the central nervous system. These cells release pro-inflammatory cytokines and chemokines, contributing to the maintenance and amplification of pain signalling, initiating a feedback loop that sustains the chronic pain (Grace et al., 2014).

All these phenomena fall within the domain of *maladaptive plasticity*. Unlike *adaptive plasticity*, which enhances pain sensitivity as a protective response to injury, maladaptive plasticity leads to pain perception in response to typically non-painful stimuli, thus contributing to the persistence and chronification of pain (Zhang et al., 2025).

### 1.4. Chronic head pain: clinical features and psychological correlates from the view of the biopsychosocial model

When Melzack and Wall (Melzack & Wall, 1965) summarised the gate control theory of pain, they explained a modulatory mechanism in the spinal cord's dorsal horn, specifically within the substantia gelatinosa. This theoretical "gate" comprises interneuronal circuits that regulate the transmission of nociceptive signals by balancing the activity between large-diameter afferent fibres (Aβ) and small-diameter fibres (Aδ and C). These peripheral fibres and the descending modulatory brain signals influence the gate-opening/closing process. This mechanism determines whether peripheral sensory information can ascend via the spinothalamic tract to higher cortical centres, where it is ultimately perceived as pain. Importantly, this theory elucidates how pain perception may occur independently of tissue damage and how psychological factors can influence it.

Additionally, descending pain-modulatory systems play a key role as neurobiological substrates in pain control. It primarily operates through the periaqueductal gray, which serves as a crucial relay between higher cortical and limbic structures and the brainstem nuclei involved in descending inhibition (Basbaum & Fields, 1984; Jermakowicz et al., 2017). The PAG integrates inputs from regions such as the prefrontal cortex and amygdala, which underlie coordinated descending control over spinal nociceptive processing, modulating both the sensory-discriminative and affective-motivational components of pain (Millan, 2002).

The descending pain-modulatory process involves noradrenergic projections from the locus coeruleus and serotonergic pathways from the nucleus raphe magnus, which terminate in the dorsal horn of the spinal cord, where they exert inhibitory control over nociceptive transmission (Heinricher et al., 2009). Norepinephrine released from locus coeruleus terminals primarily acts to reduce excitatory neurotransmission and attenuate pain signalling (Millan, 2002). In parallel, serotonergic neurons

originating from the nucleus raphe magnus modulate pain, producing either inhibitory or facilitatory effects depending on receptor distribution and physiological context (Hao et al., 2023; Liu et al., 2024). The interaction between the locus coeruleus, dorsal raphe nucleus, and supraspinal structures, such as the prefrontal cortex and amygdala, underlies the influence of psychological states, including attention, mood, and stress, on nociceptive modulation (Segal, 1979; España et al., 2024). Dysregulation of these descending pathways, particularly under conditions of anxiety, depression, or chronic stress, contributes to pain amplification and the persistence of pain beyond tissue healing (Ossipov et al., 2010). Thus, the integration of the gate control concept with the functional roles of the locus coeruleus and raphe nuclei provides a neurobiological bridge between the sensory and affective dimensions of pain, marking a paradigm shift in the understanding of pain to a more comprehensive framework, such as the biopsychosocial model (Nielson & Weir, 2001).

This model considers the biological and psychosocial factors that influence migraine and its individual impact (Asmundson & Wright, in Chapman, 2004).

Initially proposed for the conceptualisation of psychiatric disorders, the model was extended to encompass pain-related conditions due to its ability to capture the intricate interplay among medical conditions, individual psychosocial features, and surrounding social environmental contexts. Disease is an objective biological phenomenon, typically marked by disruptions in the structure or function of specific organs or physiological systems. These disruptions arise from identifiable anatomical, pathological, or physiological abnormalities. In contrast, illness denotes the subjective experience of the presence of a disease that encompasses an individual and their family's perception and interpretation of symptoms and their meaning. This conceptual distinction between disease and illness equivalents lies in the distinction between nociception and pain**.** Nociception is the neurophysiological process of detecting harmful or potentially damaging stimuli. Conversely, pain is the conscious and subjective experience from processing these nociceptive signals. Various factors influence pain perception, including genetic predispositions, past experiences, current psychological state, and sociocultural context (Gatchel et al., 2007). Psychological components embody cognitive processes, emotional states, and behavioural patterns, while social influences include cultural norms and interpersonal contexts that shape an individual's interpretation and response to somatic experiences.

In contrast to traditional biomedical or psychodynamic frameworks, the biopsychosocial perspective offers a more integrative and nuanced understanding of pain, applicable to both acute and chronic conditions. However, its utility has been evident in managing chronic pain syndromes. This framework facilitates a more comprehensive understanding of health outcomes, particularly in relation to functional impairment and disability. Unlike the biomedical paradigm, which is grounded

in pathophysiological mechanisms, the biopsychosocial approach emphasises the concept of illness as a behavioural construct. Illness behaviour refers to how individuals perceive, interpret, and respond to physical symptoms, shaped by psychological and sociocultural factors (Parsons, 1951; Mechanic, 1962). While biological mechanisms may initiate the disorder, psychological and social factors often assume a predominant role in its persistence and exacerbation. Moreover, the salience of each factor may differ across individuals and temporal phases of the illness. Thus, the biopsychosocial approach aims to be tailored and thorough in assessing and managing the contributors to pain that can change throughout life, while the diagnosis may remain the same. The biopsychosocial approach aims to be tailored and thorough in assessing and managing the contributors to pain that can change throughout life, while the diagnosis may remain the same. Furthermore, the biopsychosocial model, due to its holistic nature, may enhance therapeutic strategies, improve patient outcomes, and potentially mitigate the progression to chronic migraine (CM), medication overuse, and drug resistance (Rosignoli et al., 2022). Besides, the biopsychosocial model is widely recognised as a valuable framework for understanding and managing chronic pain syndromes; it can be adapted to headache pain disorders where pain is accompanied by distressing symptoms that can significantly disrupt multiple dimensions of an individual's daily functioning and overall quality of life.

The third edition of the International Classification of Headache Disorders (ICHD-3) (International Headache Society, 2018; Olesen & Lipton, 2004) consolidated the basis of diagnosis and management of headache disorders in clinical practice and research. It includes a classification of primary headaches (90% of all headache disorders), which are categorised as follows: Migraine, Tension-type headache, Trigeminal autonomic cephalalgias, Cluster Headache, and Other primary headache disorders. There are also eight categories of secondary headache, one for cranial neuralgias and a fourteenth for headache not classifiable elsewhere. The criteria for primary headaches are clinically descriptive; a few exceptions, such as familial hemiplegic migraine, are based on headache features rather than aetiology.

Tension-type headache is one of the most prevalent primary headache disorders. The 2004 version of the IHS distinguishes it: infrequent episodic (less than one attack/month), frequent episodic (1-14 attacks/month), and chronic (more than 15 attacks/month). Chronic tension-type headache is diagnosed when headache attacks occur for approximately three months. Tension-type headache usually presents bilateral localisation with mild-to-moderate intensity, is not exacerbated by physical activity, and is not accompanied by nausea. Photophobia, or phonophobia, may be present.

Migraine is divided into six major categories, the two most important of which are migraine with and without aura (a constellation of reversible neurological impairment that may be visual, sensory, speech-related, or motor) and chronic migraine. Migraine without aura is characterised by recurrent

headache episodes, at least five lifetime attacks, which last from 4 to 72 h. The pain is usually unilateral and pulsating, moderate to severe, and is aggravated by physical activity, causing avoidance of it. These episodes are frequently accompanied by nausea and/or vomiting, as well as photophobia and phonophobia. When the attack frequency is greater than or equal to 15 days/month, a diagnosis of chronic migraine can be made (Olesen & Lipton, 2004; Tinsley & Rothrock, 2018; Rosignoli et al, 2022; Olesen, 2024).

The pathophysiology of migraine is multifaceted, involving an interplay of several psychological and neurobiological factors. As migraine is the most common chronic pain affecting the clinical population engaged in this research project, it will be deeply investigated, also because its recurrent frequency can have a significant impact on everyday life in terms of lost productivity, family, and social life, and medication overuse is not an unusual strategy to try to manage them.

Genetic susceptibility, as evidenced by the familial clustering commonly observed in migraine, plays a significant role in the pathogenesis of this disorder. However, it is equally important to acknowledge that the clinical path of migraine is influenced by a complex interplay of multifactorial elements, following the biopsychosocial model (Gatchel et al., 2007; Rosignoli et al., 2022).

Migraine, particularly in its high-frequency and chronic forms (chronic migraine, CM), shares notable pathophysiological features with other pain conditions, especially those classified as nociplastic, a condition that exhibits enhanced central sensory processing and diminished efficacy of descending inhibitory mechanisms. Nociplastic pain and CM have in common the *central sensitization*, i.e., the pain perception beyond the peripheral tissue where the pain originates. Thus, it is usual to find comorbidity between migraine and syndromes characterised by central sensitization, such as fibromyalgia.

From a biological standpoint, migraine is increasingly understood as a disorder of sensory processing involving dynamic alterations across both the central and peripheral nervous systems. Functional neuroimaging studies have demonstrated enhanced connectivity among various sensory cortical areas in individuals with migraine, supporting the conceptualisation of migraine as a "connectopathy", a disorder arising from aberrant neural network interactions rather than localised structural abnormalities (Silvestro et al., 2021).

Moreover, migraine is associated with increased connectivity between sensory regions and limbic structures, which are implicated in affect regulation and pain modulation. This heightened integration may explain the pronounced sensitivity of migraineurs to external stimuli and their vulnerability to sensory overload. Clinically, individuals with migraine exhibit reduced thresholds for sensory input, including tactile, thermal, visual, auditory, and olfactory stimuli, as reported by patients who describe hypersensitivity to light and sound. These premises predispose migraineurs to allostatic overload, an

impaired ability to adapt to sustained or recurrent stressors such as headache attacks, fostering the transition from episodic to chronic migraine. Furthermore, the peripheral sensitisation of the trigeminovascular system contributes to the emergence of central sensitisation through the repeated activation of second-order trigeminal neurons, which can result in a lowered threshold for pain perception at the cortical level. A prominent clinical manifestation of central sensitization in migraine is cutaneous allodynia, a pain elicited by normally innocuous skin stimuli that can also be exacerbated by stressful events and associated with the transition from episodic migraine to CM (Rosignoli et al., 2022).

Affect states may also be dysregulated in chronic pain and specifically in migraine. The sensory pathways in pain perception are closely interconnected with brain regions responsible for mood regulation. Key structures implicated in this overlap include the insula, prefrontal cortex, anterior cingulate cortex, thalamus, hippocampus, and amygdala.

Emotional distress may act as a predisposing or precipitating factor, modulating an individual's vulnerability to pain. It can contribute to the emergence of chronic pain, or maintain or exacerbate pain over time. The emotional mood can significantly influence subjective pain reports and tolerance to acute pain, as the levels of anxiety can affect the perceived pain severity. This underscores the complex bidirectional relationship between affective states and the pain experience. Not surprisingly, psychiatric comorbidities are commonly observed across all chronic pain populations (Gatchel et al., 2007) as well as in CM and chronic tension-type headache, which express comorbidity with anxiety, depression, post-traumatic stress disorder, substance use disorder, bipolar disease, and even psychosis. This comorbidity between migraine and psychiatric disorders appears to involve overlapping neural circuits. The serotonergic system plays a central role in modulating affective states and nociceptive processing, while dopaminergic pathways are primarily associated with behavioural regulation and reward mechanisms.

Additionally, the hypothalamic-pituitary axis contributes to the shared pathophysiology of these conditions. Notably, the hypothalamus is recognised in maintaining homeostatic functions and has been proposed as a key generator in migraine pathogenesis. Anxiety and depression are highly prevalent among migraine sufferers and are linked to worse responses to pharmacological treatment (Rosignoli et al, 2022). The severity of depressive symptoms is strongly associated with the presence of chronic pain (Gatchel et al., 2007). It has been identified as a significant predictor of early withdrawal from interdisciplinary pain rehabilitation programs. Brain regions and the neurological function system in chronic pain and depression are closely correlated. Common neuroplasticity changes of the two disorders may be a crucial factor for chronic pain leading to depression (Sheng et al., 2017). Also, biochemical imbalances are associated with the experience of pain and depression

in chronic pain patients. However, there is no evidence of a direct relationship between pain and depression, but the presence of psychological mediators, such as cognitive appraisal and lowered self-control, has been observed. It's also speculated that there is a bidirectional influence between chronic pain and depression, implying that the conditions often coexist, respond to similar treatments, and exacerbate one another.

Anxiety usually coexists with negative mood in chronic pain. Patients with chronic pain conditions often experience heightened anxiety and concern regarding the meaning of their symptoms, the possible trajectory of their illness, and especially the future impact on their lives (Gatchel et al., 2007). Also, the uncertainty of their condition and the unforeseeability of a migraine attack in CM increase the idea that external or random factors control their migraine, thus worsening the frustration and the lack of sense of self-efficacy, improving fear-avoiding behaviours. (Rosignoli et al., 2022). In relation to persistent fear and avoidance behaviours, chronic pain and post-traumatic stress disorder (PTSD) may exhibit overlapping psychopathological patterns and comorbidity (Bosco & Clark, 2013).

The presence of prior psychological trauma is linked with increased risk in the development of chronic pain, as well as in the onset of migraine and in its chronification. Hyperactivation of the two stress-responsive systems, the sympathetic nervous system and the hypothalamic axis, could potentially affect migraine and promote pain attacks (Rosignoli et al, 2022). Although the underlying etiologies and clinical manifestations of these conditions are distinct, chronic avoidance is a central mechanism believed to contribute to the maintenance of both disorders. This avoidance reflects core fears associated with each condition and indicates a disruption in the natural processes of recovery and rehabilitation following physical and/or psychological trauma. Individuals experiencing chronic pain may avoid therapeutic activities due to a fear of re-injury, or cognitive patterns such as catastrophizing may consistently anticipate the pain, figuring the worst possible outcomes, which can exacerbate pain experiences and limit engagement in beneficial treatments. This anticipatory pain serves as a critical link between psychological and physiological processes. Alterations in pain anticipation mechanisms and fear avoidance have significantly affected reported pain tolerance. Such psychological distress is commonly associated with increased muscular tension and sympathetic physiological arousal factors that can maintain or even exacerbate the pain experience (Vlaeyen & Linton, 2000). Also, hypervigilance and persistent monitoring of both painful and non-painful bodily sensations may intensify anxiety and reinforce avoidance behaviours. These processes can significantly lower the individual's threshold for tolerating low-intensity unpleasant sensations. A comparable mechanism is observed in PTSD, where individuals may avoid trauma-related cues, even when these are objectively non-threatening, leading to withdrawal from previously meaningful activities and avoidance of stimuli that provoke anxiety. Over time, such avoidance fosters

maladaptive beliefs which obstruct engaging in effective behaviours for recovery. Ultimately, individuals with chronic pain and/or PTSD may become increasingly governed by their pain or psychological distress, leading to further functional impairment (Bosco & Clark, 2013).

Even in the absence of formal psychiatric diagnoses, chronic migraine is frequently associated with behavioural and psychological factors such as pain catastrophizing, sleep disturbances, anxiety, hopelessness, low psychological flexibility, perfectionism, meticulousness, conscientiousness, and ruminative thinking. These traits contribute to heightened vulnerability to stress and promote hypervigilance and excessive control over one's environment and bodily sensations (Pistoia et al., 2022).

Furthermore, according to the biopsychosocial model, relationships and social context must be considered in the emergence and maintenance of chronic pain. Emotional distress is frequently reported among individuals experiencing chronic pain who may feel stigmatised or dismissed by healthcare providers, family members or employers. Also, low socioeconomic status is bidirectionally associated with migraine: a low income may cause difficulty in accessing medical care and increased stress, which increases the likelihood of developing the disease or worsening its trajectory. Work life can also be affected by pain. Stressful jobs may trigger or worsen migraine, as well as sensory triggers in the workplace (lights, noises). The evidence of the impact of migraines on employment can be evaluated in terms of lost workdays (absenteeism) and days worked with reduced performance (presenteeism). These measures are relevant to the impact on individual lives and the connection to social costs.

Leisure and exercise are bidirectionally connected to migraine. A sedentary life with low levels of exercise is associated with a higher prevalence of migraine; otherwise, avoidance behaviours in migraineurs reduce the motivation to practice sport or even easy walks. In contrast, regular physical activity can be an effective prophylaxis for migraine (Moschiano et al., 2013).

All this evidence establishes that the single-factor pain models are no longer reliable (Rudy et al., 1988).

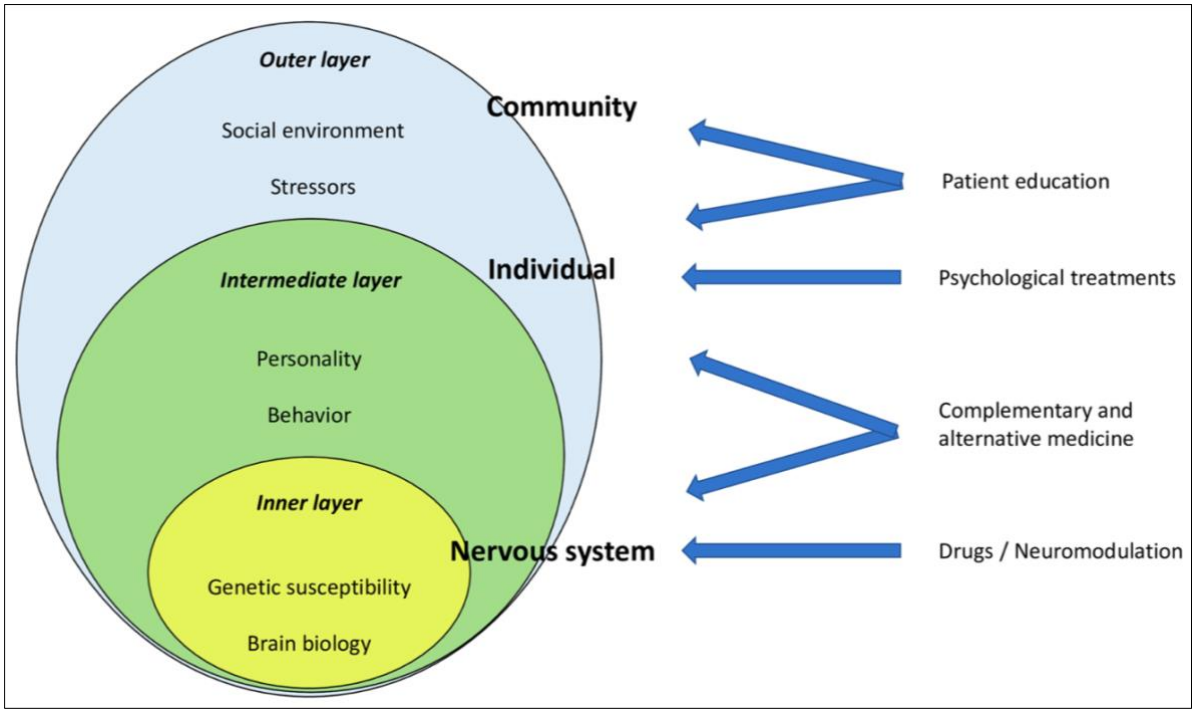


Figure 1.3: A hierarchical view of the biopsychosocial model applicable to migraine (From Rosignoli et al, 2022).

The biopsychosocial model suggests a multi-layered approach to the prevention and management of migraine (see Figure 1.3). An ideal effective approach to migraine treatment should be individualised, considering pharmacological interventions and managing other contributing factors relevant to the specific patient's condition. A comprehensive strategy must address the multifaceted nature of migraine and be tailored to the unique clinical profile of each individual. Nowadays, migraine management predominantly relies on pharmacological therapies. However, considering the multifactorial nature of the disorder, it is essential to implement a comprehensive, individualised approach that addresses the various factors influencing the disease's impact. Such an approach is critical for reducing symptom burden and preventing long-term adverse outcomes and progression of the condition. The biopsychosocial model can be applied through a multi-layered framework when addressing the individual. At the core lies the biological dimension (including comorbidities), surrounded by psychological and behavioural components that significantly shape how individuals perceive and manage everyday challenges. The outermost layer is the social dimension, capturing the dynamic and often complex interactions between individuals and their broader social environment.

Also, cultural frameworks to which an individual has been exposed within their familial and social environment significantly influence the modulation of pain perception (Bachiocco et al., 1993).
At the intermediate layer, education and non-pharmacological approaches are fundamental, as well as research that disseminates knowledge and scientific evidence of these approaches. In fact, there are still barriers to implementing the biopsychosocial model in the treatment of headaches. One is the uncertainty of optimal management of non-pharmacological therapies, coupled with the difficulty of implementing a tailored individual pain management plan through research, aiming to standardise results and procedures (Rosignoli et al., 2022).

### 1.5. Aim of the thesis

Pain is a complex psychological experience; psychology plays a significant role in pain research and management, where multidisciplinary teams are often required. (Schork, 2015; Ashina et al., 2021; Fitzcharles et al., 2021).
Physicians often lack training in how to treat patients from a psychological and social perspective. Hence, a straightforward integration between the physiological mechanisms underlying pain and psychological clinical practice has yet to be fully established. Psychology should be central in pain research, bridging fundamental scientific discoveries with clinical pain assessment and management approaches.
Despite the growing recognition of pain as a multidimensional phenomenon, many clinicians remain insufficiently trained in addressing its psychological and social dimensions. Consequently, a cohesive integration between the physiological underpinnings of pain and psychological clinical practice has yet to be fully realised. Advancing this integration is essential, as psychology should play a central role in pain research, bridging the gap between foundational neurobiological discoveries and the development of comprehensive pain assessment and therapeutic intervention strategies. Furthermore, although the biopsychosocial model is widely recognised as a valuable framework for understanding and managing chronic pain syndromes, its application within the domain of migraine remains comparatively limited and underexplored.
This doctoral project aims to contribute to the development of robust theoretical frameworks supported by a psychophysiological foundation for psychological constructs. For this reason, the experiments detailed in the following chapters were conducted in collaboration with the Headache Centre-Neuroalgology Department of the IRCCS Foundation "Carlo Besta" Neurological Institute in Milan, Italy, focusing on four main domains of pain perception: interoception, allodynia, psychophysiological responses, and behavioural therapies.

Chapter 2 explores the domain of psychological states in the anticipation phase of pain perception. This study investigated the influence of transiently induced anxiety on anticipatory responses to pain in a sample of healthy adults. Participants were exposed to an anxiety-inducing manipulation involving forced respiration through a narrow straw (straw respiration task, Teachman et al., 2007). Throughout the experimental procedure, skin conductance response (SCR) was monitored to assess psychophysiological arousal elicited by visual cues signalling the impending administration of either painful or neutral stimuli.

Chapter 3 examines the interplay between affectivity and pain using a novel experimental paradigm that combines direct and vicarious tactile experiences within the same participants. Pain and affective touch are interoceptive stimuli that share neural networks involving multiple features. Several studies have focused on these stimuli, independently, evaluating pain or affective touch perception in direct or vicarious (observed) stimulation modalities. Therefore, it is relevant to study whether and how they interact. Specifically, the study aimed to determine whether the perception of affective touch is modulated by individual differences in direct pain or empathic sensitivity toward others' pain (vicarious pain). Participants underwent quantitative sensory testing to evaluate their response to direct electrical painful stimuli. The Vicarious Pain Questionnaire (VPQ) (Ward & Li, 2022) was applied to assess vicarious pain. The results of these dimensions were used as variables to investigate their effect on the pleasantness and vividness of direct and vicarious affective touch stimulations. This study also included patients with Chronic Migraine (CM), the main target of this research project. To disentangle whether pain perception can influence the vicarious or direct experience of affective touch could reinforce knowledge in the treatment of pain with a biopsychosocial approach.

Chapter 4 explores cutaneous allodynia (CA), building on previous studies that have identified its presence even in the general healthy population. The investigation of CA has been limited to chronic pain conditions, assuming it is a marker of dysfunction of pain processes. This study aims to investigate the relationships within the network of features that contribute to CA. The findings can contribute to the detection of early signals of CA as part of diagnosing and preventing chronic pain disorders.

Chapter 5 addresses the behavioural therapies for chronic pain interventions. The scientific literature has widely demonstrated that patients suffering from chronic pain can benefit from traditional therapies combined with behavioural approaches, such as mindfulness, that could significantly improve clinical benefits and the efficacy of pharmacological treatments.

As an awareness-based intervention, mindfulness is a valuable tool for patients to learn how to manage pain, use medications effectively, and adopt beneficial lifestyle habits that can enhance well-being and overall health.

The first study investigates the usability of BBMIND, a mobile phone application for mindfulness practice developed by the BiCapP, part of the Psychology Department of the University of Milano Bicocca.

The second study proposes a BBMIND mindfulness intervention to evaluate the effect of meditation practice on pain processing and perception in sufferers of chronic pain. This investigation contributes to the ongoing search for evidence on the effectiveness and adherence to online mindfulness practice protocols in patients suffering from chronic pain conditions.

It is essential to emphasise that pain cannot be fully understood by focusing on a single domain in isolation. This rationale underlies this investigation project, which aims to build an interconnected network of neurobiological, psychological, and social domains as a basis for an integrated whole.

Pain perception, especially in its chronic form, exemplifies the need to expand the boundaries of the dualistic view of mind and body, embracing a more comprehensive understanding and approach in both clinical and everyday contexts.

# 2. PAIN ANTICIPATION AS A PSYCHOPHYSIOLOGICAL PREPARATORY RESPONSE TO PAIN PERCEPTION

## 2.1. Introduction

Pain anticipation refers to the complex psychophysiological responses associated with an individual's expectation of subsequent noxious stimuli. It may influence the immediate unpleasantness of pain and the perception of non-painful stimuli (Sawamoto et al., 2000; Palermo et al., 2014). Pain anticipation embraces emotional, cognitive and reactive behaviours, involving sympathetic nervous system activation in response to aversive stimuli. This complex relationship between anticipation and the perception of pain originates in the cortical network responsible for pain processing, which aims to protect the organism and prevent bodily harm. Pain anticipation involves a widespread neural activation across the pain matrix, showing an overlap in the anticipation and perception of acute pain, although less intense (Porro et al., 2002; Brown & Jones, 2008). The early phase of pain anticipation activates the midcingulate and posterior cingulate cortex, as well as bilateral inferior parietal regions, a pattern not observed during the mid or late stages of anticipation. Also, intense interconnections exist between the right inferior parietal and the midcingulate cortex. This evidence supports their involvement in attentional processes related to pain.

Notably, the type of attention involved in pain anticipation is basically involuntary. It involves automatic and arousal responses, as well as heightened vigilance toward pain-predictive cues. During the late anticipation phase, functional connectivity between the midcingulate cortex and inferior parietal regions increases, leading to a dynamic reorganisation of attention networks as pain arrives. These brain connection changes may also involve subcortical structures, such as the amygdala, generating consequent behavioural reactions modulated by the emotional appraisal of pain (Brown et al., 2008). Initial adaptive behaviours, such as avoidance (Gatchel et al., 2007; Jensen et al., 1994; Turner et al., 2000), try to prevent physical harm (Palermo et al., 2014). Additionally, physiological changes occur as a result of sympathetic nervous system activation in response to aversive stimuli. Consequently, pain anticipation reflects changes in key physiological parameters such as skin conductance (Romano & Maravita, 2014) and heart rate (Porro et al., 2002).

### 2.1.1. Pain anticipation in clinical and experimental contexts

The importance of evaluating pain anticipation, especially in individuals with chronic headache disorders, lies in the involvement of multiple interrelated neurophysiological mechanisms. Central sensitisation has been identified as a key contributor to the chronification of headaches, with dysregulated pain processing closely linked to headache frequency (Buchgreitz et al., 2006).

The anticipatory processes of pain perception can influence affective states and behavioural responses, potentially intensifying the overall burden of chronic pain (Ploghaus et al., 1999). Furthermore, anticipatory neural activity has been shown to predict subsequent pain intensity ratings; specifically, greater suppression of alpha oscillations during anticipation is associated with higher subjective pain reports (Babiloni et al., 2006). The anticipation of pain is also closely related to top-down attentional modulation, which may subsequently result in attenuated sensory processing upon actual stimulus delivery to the body. Possible explanations for this phenomenon can be attributed to the anticipatory modulation of pain, which may involve the engagement of endogenous descending analgesic pathways. In this context, nociceptive transmission is modulated by attenuating afferent pain signals, in line with noxious inhibitory controls. Alternatively, it may be explained by the cognitive anticipation of pain, which can pre-activate early somatosensory cortical areas, resulting in weakened neural responses when nociceptive inputs ultimately reach the cortex (Porro et al., 2002; Romano & Maravita, 2014).

Nevertheless, among individuals with migraine, variability in anticipatory responses has been correlated with differential activation in brain regions such as the midcingulate cortex and caudate nucleus, with increased migraine frequency linked to heightened anticipatory neural responses (Kökönyei et al., 2021). In addition, cognitive and emotional factors, including pain-related fear and avoidance beliefs, have been found to significantly contribute to functional impairments in chronic pain populations (Al-Obaidi et al., 2000). These consequences are particularly relevant in individuals suffering from chronic pain syndromes, in which emotional responses frequently include depressive symptoms, anxiety, and fear. Notably, increased pain sensitivity appears to emerge as a result of recurrent headache episodes rather than as a predisposing factor (Buchgreitz et al., 2006).

Experimental contexts can serve as a stage for experimenting with pain anticipation, eliciting a complex individual response that influences subjective pain perception and broader psychophysiological dynamics (Rhudy et al., 2008). Deepening acute pain anticipation mechanisms, mainly related to anxiety, in experimental contexts, can contribute to implementing interventions in patients with chronic pain conditions, in which the anticipatory fear is more predictive of disability than the actual intensity of the pain (Brown & Jones, 2008).

### 2.1.2. Skin conductance response as a measure of pain anticipation and perception

The autonomic nervous system (ANS) governs the complex vegetative functions of the organism and operates primarily independently of voluntary control. The ANS plays a central role in the physiological responses to internal and external stimuli, maintaining the body's homeostatic balance. It is divided into the sympathetic and parasympathetic divisions, which are anatomically

complementary and typically produce opposing physiological effects. When an emotionally relevant stimulus is perceived, whether cognitive or sensory, the organism automatically initiates a cascade of physiological changes primarily driven by the sympathetic branch of the autonomic nervous system. These changes typically include increased heart rate, arterial blood pressure, and perspiration levels, synonymous with heightened physiological arousal.

One of the key physiological markers of sympathetic arousal in response to alerting stimuli is the skin conductance response (SCR), a transient increase in electrodermal activity associated with the skin conductance activity of eccrine sweat glands (Damasio, 1994; Dawson et al., 2011).

Electrodermal activity is typically measured by applying a low-voltage direct current between two electrodes placed on the second and third fingers of the hand's palmar surface, where eccrine sweat gland density is highest. Recording equipment, operate by passing a tiny direct electrical current through the electrodes and then measures the skin's electrical conductance.

Skin conductance activity consists of two main components: the skin conductance level (SCL), also known as the tonic level, which reflects the basal activity level and continuous changes within the person, and can differ markedly between individuals. The skin conductance response (SCR) is a phasic change in skin conductance elicited by a stimulus. These changes, measured in microsiemens (μS), appear as increases in skin conductance and indicate heightened sympathetic arousal (Schwartz & Andrasik, 2003; Boucsein, 2012).

The delay between the onset of the eliciting stimulus and the onset of the SCR (latency) ranges from 1 to 3 seconds; the peak response typically occurs within another 1 to 3 seconds (rise time) (see Figure 2.1).

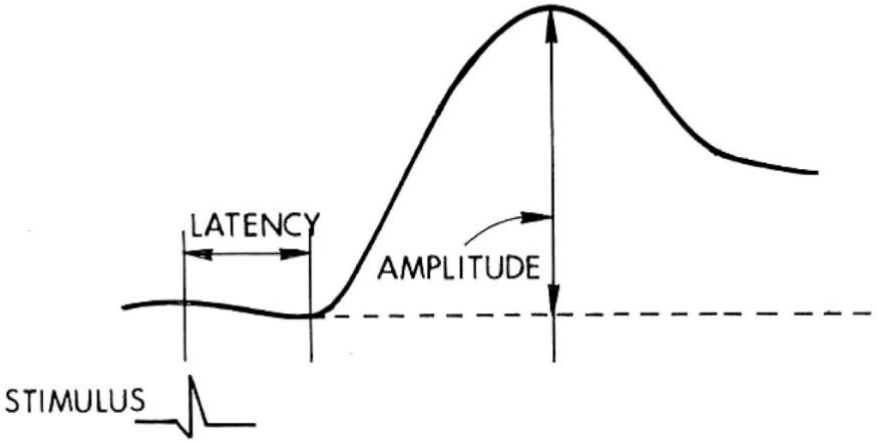


Figure 2.1: Example of a typical SCR: the 1 to 3 s latency time following stimulus onset, then the peak amplitude within 1 to 3 s after the onset of the response (from Dawson et al., 2011).

SCR is subordinated to processes of attention, evaluation and anticipation of significance and peculiar affective characteristics of stimuli. As many psychological factors and stimuli can affect the SCR, many cortical and subcortical brain areas are involved. For example, the hypothalamus and limbic structures, particularly the amygdala, play a key role in modulating the arousal response to emotional or sensory stimuli.

Pain experiences, as emotional noxious stimuli, put into operation the innate biological sense of pain, which is the response to noxious events and the recognition of their potential for tissue damage to protect the body's integrity. It can trigger perceptual, emotional, autonomic, and motor responses, leading to physiological arousal and rapid, automatic reactions to potentially harmful stimuli (Boucsein, W., 2012). The experience of pain is a sensory phenomenon closely tied to cognitive and emotional aspects, strongly related to an activation of the sympathetic nervous system (Breimhorst et al., 2011). The nociceptive and autonomic systems form two interconnected components within a central regulatory network that aims to maintain adaptive responses to internal and external environmental stressors. This dynamic interaction between pain processing and autonomic system mechanisms also engages the peripheral nervous system, the spinal dorsal horn, the brainstem, and the forebrain. In response to similar somatic or visceral stimuli, key regions responsible for nociceptive and autonomic regulation frequently exhibit integration and convergence of nociceptive and visceral sensory input, resulting from a cascade of actions by neuronal populations that coordinate autonomic, antinociceptive, and behavioural reactions to noxious and visceral signals. This complex

interaction plays a fundamental role in research on experimental models and interventions for chronic pain disorders. Typical clinical examples of sympathetic-nociception interactions include chronic regional pain syndromes and trigemino-autonomic cephalalgia, which involve interactions between trigeminal input and superior salivatory nucleus output (Benarroch, 2001; Benarroch, 2006).

The interface between pain processing and the autonomic system begins with pain anticipation. fMRI studies have revealed that pain anticipation activates brain networks analogous to those activated by pain experience, but with more anterior activity in the medial prefrontal cortex and the anterior insula. This evidence suggests that anxiety about pain can exacerbate pain sensation (Ploghaus et al., 2001). Both anticipation and the experience of pain are associated with autonomic responses, such as SCR. Also, the anticipation of pain leads to autonomic arousal, which, together with the anxiety or the pain-related fear, can predict pain intensity and increase it, especially in chronic pain conditions (Seifert et al., 2013). Pain anticipation is not a passive state but an active experience in which the organism prepares physiologically and psychologically to confront an impending aversive stimulus. Individual expectations and emotional states, such as anxiety, can further modulate physiological arousal, the body's groundwork activation in response to actual or anticipated threats (Barnes et al., 2021). Expectations held by the individual, along with potential anxiety states, also influence physiological aspects, such as the level of arousal, which refers to the body's activation in response to real or perceived threats (Barnes et al., 2021). This activation reflects the engagement of the sympathetic branch of the autonomic nervous system (ANS), which prepares the body to react quickly and automatically to potentially dangerous stimuli or situations (Boucsein, 2012). Moreover, individual variability in anticipatory SCRs may serve as a meaningful marker of vulnerability or resilience to chronic pain conditions or emotional processing dysfunctions (Li & Jackson, 2022). Indeed, the study by Li and Jackson (2022) reported significant differences in subjective perceptions and physiological responses among individuals with different levels of pain resilience. Specifically, participants with high pain resilience (HPR) exhibited significantly lower skin conductance levels compared to those with moderate (MPR) and low (LPR) resilience, both during anticipation and during the experience of painful stimuli. Given these characteristics, SCR can be considered a valid index of pain anticipation, as it is influenced by the organism's activation level in response to and anticipating potentially harmful stimuli (Colagiuri & Quinn, 2018).

### 2.1.3. The role of anxiety in pain anticipation

Staying focused when a painful stimulation is about to occur or is already happening may help reduce the perceived pain intensity compared to conditions in which we are distracted (Keogh et al., 2011). Furthermore, verbalising one’s bodily sensations during pain exposure reduces pain perception

(Nouwen et al., 2006). These findings seem to be inconsistent with the analgesic effectiveness of distraction, but to better understand this mechanism, the role of anxiety must be brought into the game. People with low levels of pain-related trait anxiety benefit from distraction, while individuals with high trait anxiety frequently exhibit hypervigilance, which contributes to an attentional bias that leads to preferential processing of pain-related over neutral stimuli that can impair the ability to disengage attention, thereby reducing the efficacy of distraction-based strategies in modulating pain perception. A sensory-focused strategy may be more effective for those with elevated levels of pain-related anxiety (Chayadi & McConnell, 2019).

As an emotional or sensory pathway can process the pain information, the first accentuates worry and distress, promoting pain catastrophizing and intensifying the pain experience. The sensory route, on the other hand, directs attention toward the more objective sensory characteristics of the pain, thereby reducing catastrophic thoughts and pain perception. Moreover, the predictability or rather unpredictability of the upcoming painful stimulus is a primary factor in anxiety and pain anticipation. The predictability of pain facilitates the preparation of an appropriate behavioural response that enhances the perception of cognitive control over the situation, reducing anxiety and lowering self-reported pain intensity. However, that predictability may, under certain conditions, contribute to pain amplification. In particular, the anticipation of intense discomfort has been identified as a significant predictor of elevated anxiety and increased subjective distress. Expecting severe pain heightens state anxiety and physiological arousal, which subsequently intensifies the neural and behavioural responses to pain. Besides, anxiety modulates the relationship between pain anticipation and pain perception. Although the predictability of threatening stimuli is generally associated with reduced anxiety and physiological arousal, thereby attenuating pain perception, this effect may not be generated in people with high levels of anxiety. In such individuals, additional pain-related information may exacerbate selective attentional bias and fixate on it due to difficulty in disengaging from threat-related cues. This impaired attentional flexibility may amplify pain perception (Chayadi & McConnell, 2019).

Expectation of significant discomfort is also associated with nocebo-induced hyperalgesia and elevated anxiety levels. The nocebo effect is the outcome of the underlying interaction between anxiety and pain perception. Negative expectations heighten stress responses, as adrenocorticotropic hormone and cortisol levels, and pain responses (Benedetti et al., 2006): anticipation of pain triggers anxiety that can lead to reduced pain tolerance (Woo, 2015). Anxiety and fear notably influence the arousal state of the entire organism, thereby affecting psychophysiological responses such as pain anticipation (Gatchel et al., 2007). This bidirectional influence between emotions and pain anticipation is supported by evidence indicating that cortical regions, such as the anterior insula,

cingulate cortex, and medial prefrontal cortex, are involved in cognitive and emotional processing, as well as autonomic control. These regions exhibit activation clusters that encode pain intensity and show modulations during pain anticipation (Porro et al., 2002).

Given the limited number of studies examining this moderating effect, further research is warranted to investigate how pain-related trait anxiety influences the effectiveness of attentional strategies during pain anticipation. Although anxiety is a normal emotional response to actual or anticipated threats, excessive or persistent anxiety may become maladaptive. Such heightened levels of worry can negatively impact an individual's capacity to effectively cope with pain, potentially exacerbating the overall pain experience and impairing treatment outcomes. It is essential to integrate the psychosocial dimensions of pain, including anxiety and individual expectations, into a comprehensive and holistic approach to pain management.

### 2.1.4. The straw breathing task: a manipulation of transitory anxiety in pain anticipation

The Straw Breathing Task (SBT) is widely used in research to induce mild to moderate levels of anxiety. It consists of 2 minutes breathing in and out through a narrow straw (approximately 2 mm), while keeping the nose plugged, which achieves shortness of breath, a condition of "air hunger" capable of eliciting mild to moderate anxiety (Teachman et al., 2007; Graydon et al., 2012; Spaccasassi & Maravita, 2020). Air hunger in anxiety is closely tied to activation of the body's sympathetic nervous system, which is the system that drives the fight-or-flight response. Hence, SBT represents a valid tool to safely trigger bodily and cognitive anxiety symptoms, such as transitory dizziness and light-headedness (Antony et al. 2006; Teachman et al. 2007; Zahler et al., 2020). Differently, someone may report a relaxing effect of the experimental breathing task (Spaccasassi & Maravita, 2020), which aligns with interoceptive exposure therapy, aimed at reducing anxiety sensitivity and discomfort associated with somatic sensations typically found in panic disorder (Boettcher et al., 2016).

SBT is as measured by the 11-point Likert Anxiety Scale, from 0 " calm enough to fall asleep" to 10 "feeling as if they may have a panic attack" (Graydon et al., 2012; Spaccasassi & Maravita, 2020).

It poses no serious harm or risk to participants, who can stop it at any point if it becomes too unpleasant. High state anxiety levels, after the anxious breathing, can modulate somatosensory stimuli perception and the extension of peripersonal space, perceived as more threatened than usual (Sambo & Iannetti, 2013; Spaccasassi & Maravita, 2020). In the present study, the SBT was selected to simulate conditions of pain anticipation that sufferers of chronic pain can face in their daily lives, which makes them feel nervous or anxious when they forecast pain attacks. Also, pain anxiety can reinforce cognitive pain expectations (placebo/nocebo effect), worries, and anxious mood, while

decreasing self-confidence in managing pain (Staats et al., 2001). So, the main aim was to evaluate whether state anxiety could affect pain anticipation and somatosensory perception.

### 2.1.5. Aim of the research

Many studies have examined the complex interplay between pain and anxiety, demonstrating that the intensity of the nociceptive input is modulated by psychological variables, including emotional and motivational states (Rhudy & Meagher, 2000). Anxiety, a negative affective state characterised by anticipatory apprehension regarding potential future threats, is frequently associated with heightened vigilance and arousal. This state of hypervigilance is characterised by heightened sensitivity to sensory input and a cognitive bias toward both external stimuli and internal bodily sensations. It may enhance attentional focus on pain-related information and augment the subjective experience of pain (Barlow et al., 1996). Based on the available evidence, especially of the influence of anticipatory fear of pain on its course, it can be hypothesised that an acute anxiety state enhances anticipatory mechanisms toward painful stimuli, resulting in increased emotional and physiological reactivity in the pain anticipation phase. Anticipatory anxiety can reduce pain thresholds and promote hyperalgesic responses, suggesting that anxiety contributes not only to the modulation but also to the amplification of pain through anticipatory, body-centred mechanisms (Rhudy & Meagher, 2000).
According to embodied cognition (Damasio, 2010), anticipatory processes are deeply rooted in the dynamic interaction between brain, body, and environment. Predictive mechanisms are enacted within conscious homeostatic sensations, such as comfort, discomfort, or pain, constituting core elements of embodied knowledge that guide adaptive behaviour in response to physiological demands (Damasio & Damasio, 2022). States of heightened anxiety may dysregulate this predictive system, resulting in exaggerated bodily awareness and misinterpretation of somatic cues. Such a state can lead to perceptual distortions and excessive internal signal monitoring, even in the absence of actual nociceptive input. While the influence of anxiety on pain perception is well documented (Barlow et al., 1996; Keogh & Cochrane, 2002; Rhudy & Meagher, 2000; Scaini et al., 2025), its role in modulating pain anticipation is less investigated.
The research project comprises two identical experimental studies: an initial exploratory study on the general population and a second on patients suffering from chronic pain.
The aim is to clarify how individual anxiety levels may modulate autonomic responses related to pain anticipation, particularly in individuals with chronic pain disorders, such as chronic tension headache. The project points to explore the influence of temporary states of anxiety, induced by the straw task, on modulating anticipatory responses to pain-related cues, as a probe of the effect of anxiety on pain perception.

We tested the central hypothesis that the induction of a transient state of anxiety may influence pain anticipation responses, as measured by skin conductance recordings, in both the general population and individuals with chronic pain conditions.

We expected to find :

- The forced respiration, by the straw task, can induce a temporary state of anxiety
- The state of anxiety can induce increased cognitive and autonomic pain reactions.
- Unlike unforced respiration, forced respiration can provoke a greater autonomic response to real and simulated pain stimuli.
- A greater autonomic response to painful stimuli than to non-painful stimuli.
- Sufferers of chronic headache are more sensitive to the effect of the state of anxiety on pain anticipation than the healthy population.

This chapter presents only information regarding the exploratory study on the general population. The procedure explained is equal for both proposed experiments. The testing on chronic migraine is still ongoing, and there are not enough data to be reported.

## 2.2. Materials and Methods

### 2.2.1. *Participants*

A priori power analyses were conducted using G*Power (Faul et al.,2007) to determine the minimum sample size of twenty-four participants, based on Repeated Measures Analysis of Variance (ANOVA – *within factors*), with an Effect Size F= 0.25; Alpha Error Level: p= 0.05; Statistical Power= 0.80, Actual Power= 0.80, Correlation Among Measures: 0.50, (Faul et al., 2007; Camerone et al.,2022)

Thirty-nine volunteers participated in this experiment. We decided to recruit a larger number of participants to mitigate potential technical issues that could have led to the removal of unusable data (Ahn & Jung, 2005), as it had happened in our previous experimental work. Also, a sample larger than the minimum indicated by power analysis can enhance the precision and reliability of effect estimates and maintain robustness, especially in ANOVA or repeated-measures designs, as well as in psychophysiological studies with high within-subject variability, where individual measurements can be very noisy, such as in sensory threshold and SCR measurements (Maxwell et al., 2008; Baker et al., 2021).

All participants had normal or corrected-to-normal vision. All of them self-declared they did not suffer from any of the following diagnosed conditions, as exclusion criteria:
Neuropathic pain, chronic migraine, severe and documented medical or psychiatric conditions, epilepsy, sensory abnormalities such as multiple sclerosis and peripheral neuropathy, abnormal cutaneous perception or dermatological disease (Ashkenazi et al., 2007). Nevertheless, two of them reported suffering from migraine in the self-report questionnaires, and they were excluded from the analysis.
The final sample comprises thirty-seven participants (mean age: 25 ± 5 years; range: 20-53; 21 female).
The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and received ethical approval from the local ethics committee. All participants provided informed consent before participating in the study.

2.2.2. *Procedure*

First, participants sat at a table, 50 cm away from a monitor, and were connected to a computer.
Using the Qualtrics software, participants filled in self-report questionnaires:

(i) The Beck Depression Inventory (BDI-II) (Beck et al., 1996) and State-Trait Anxiety Inventory (STAI-Y1,2) (Spielberger, 1983) were used to assess proneness to depressive and state-trait anxiety
(ii) The Allodynia Symptom Checklist-12 (ASC-12) was used to evaluate the presence of cutaneous allodynia. An adapted version was used to assess allodynia in daily life (Lipton et al., 2008)
(iii) The short version of the Pain Anxiety Symptoms Scale (PASS-20) to explore pain anxiety (McCracken & Dhingra, 2002)

Demographic information, including age, self-declared gender identity and the presence of pain conditions, was collected.

Tactile and Pain Threshold Assessment Procedure

Two Ag/AgCl electrodes were positioned on the ventral side of the left forearm and laid on the table at a distance from the wrist to the elbow equal to half the distance between the tip of the middle finger and the wrist line. Subsequently, the subjective thresholds of perception for tactile (t) and painful (T) stimuli were determined by administering 1-second-long electrical tactile stimuli of

increasing intensity using the Digitimer DS7A stimulator (Camerone et al., 2021a; Camerone et al., 2021b; Parhizgar & Ekhtiari, 2010; Ashkenazi et al., 2007).

An ascending method, starting from 0.5 mA and increasing in steps of 0.5 mA, was used to drive the stimulation intensity with a continuous current, accompanied by a square pulse of 500 μs duration delivered at a frequency of 1 Hz. Participants rated the perceived intensity of each stimulus using an 11-point Numerical Rating Scale (NRS) ranging from 0 to 10. Number 0 corresponded to a no-pain first tactile sensation perceived (tactile threshold = t), 1 represented the beginning of a painful feeling stimulus (pain threshold = T), and 10 represented an unbearable pain (Camerone et al., 2021). The participants were instructed to verbally indicate "zero" (0) when they perceived any sensation from the electrodes placed on the left forearm (t) and “one” (1) the minimum intensity at which the stimulus was subjectively perceived as painful (T). The procedure ended when the participants’ rating reached the pain threshold; it was run three times, yielding three tactile and three pain threshold values per participant.

The mean pain threshold was multiplied by 1.5 (T × 1.5) to obtain the final reference value for administering painful stimuli during the main experimental phase (Camerone et al., 2021a, 2021b).

To disentangle the individual perception of stimuli’ intensity and quality (i.e., neutral vs. painful), three tactile thresholds (neutral) and three T × 1.5 (painful) stimuli were randomly administered. Participants were then asked to rate each stimulus on an 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (the most intense pain imaginable) to distinguish three neutral stimuli, rated as zero, and three painful stimuli, rated as at least two or three, thereby validating the discrimination of the two stimulus categories.

Colour-Stimulus Familiarization

Participants underwent a brief association procedure as a final step before the actual experimental phase. The method was based on the same underlying principle, even if it cannot be considered an actual conditioning task. Participants underwent six randomised trials in which red or green colored squares (red/green cue) were presented on a monitor.

Green squares were consistently associated with neutral, non-painful stimulation (t), while red squares were associated with painful stimulation (T × 1.5) delivered by the Digitimer. At the end of the task, participants had to respond to two questions displayed on the screen to confirm their correct colour-stimulus association. The first question was: “Which stimulus do you associate with the green colour square?” with two possible answers: “neutral” or “painful”. The second question was: “Which stimulus do you associate with the red colour square ?” with the same answer options.

This phase aimed to induce a specific colour-stimulus association, such that green became linked to neutral stimulation and red to painful stimulation. This was intended to elicit an anticipatory response to pain during the central experimental phase (Kökönyei et al., 2021).

Throughout the procedure, participants wore headphones to listen to white noise, which masked environmental sounds, such as those produced by adjustments to the Digitimer dial (Forgiarini et al., 2011; Camerone et al., 2022).

Skin conductance signal acquisition

Two Ag/AgCl electrodes were positioned on the right hand's distal phalanges of the index and ring fingers to measure skin conductance response.

Skin conductance response (SCR) data were acquired using the BIOPAC system, consisting of a signal amplifier (MP150) and a dedicated module for optimising conductance recording (GSR100C). The signal was recorded using direct current mode, with a gain parameter set to 5 μS/V, and sampled at a rate of 100 Hz. Transducers (TSD203) equipped with the two Ag-AgCl electrodes were used for signal acquisition. An isotonic conductive paste (GEL101) was applied to the electrodes to enhance the signal-to-noise ratio.

Pain Anticipation Task

The participants were comfortably seated in front of a screen at a distance of 50 cm, while SCR was recorded. A 5-6 sec fixation cross screen spaced out the green or red squares (visual cues), similar to the familiarisation phase (Kökönyei et al., 2021). Green squares were associated with real, neutral tactile stimuli (t) or simulated (null), without electrical stimulation. Red squares were associated with either real painful stimuli (T x 1.5) or simulated (null) painful trials, in which no stimulation was administered.

The Digitimer delivered 5-millisecond real painful and non-painful tactile stimuli, and their onset delay following the visual cues was manipulated to minimise expectation adaptation in participants that would have influenced pain anticipation (Atlas & Wager, 2012; Levinson & Edelberg, 1985)- The Open Sesame Software script ensured the correct presentation of visual cues (coloured squares) and electrical stimuli with high temporal precision, as specified by the aforementioned timing parameters. The experimenter manually adjusted the stimulus intensity for each trial. To allow the experimenter sufficient time to change the Digitimer's intensity dial before each trial, on-screen instructions indicating the type of upcoming stimulus (e.g., “next: red square – painful stimulus”) were shown immediately after the previous stimulus delivery. The approximate 5-second pause between trials allowed the researcher to adjust the intensity appropriately. These instructions were

hidden from participants to ensure they remained unaware of the upcoming stimulus type, as was the case during the familiarisation phase (see Figure 2.2).

The onset of stimuli occurred within three predefined time windows:
Delay 0: simulated stimuli. No tactile stimulation after the cue presentation
Delay 1: real stimuli after 2–4 seconds of cue presentation
Delay 2: real stimuli after 5–7 seconds of cue presentation
A total of sixteen stimuli, divided into:

- Three Simulated painful stimuli – delay 0
- Six Real painful stimuli – delay 1
- Three Real painful stimuli – delay 2
- One Simulated neutral stimulus – delay 0
- Two Real neutral stimuli – delay 1
- One Real painful stimulus – delay 2

Non-painful stimuli (neutral) likely elicit a minimal arousal response and cannot be reliably detected using the SCR paradigm. Thus, they were designed to reduce SCR adaptation, which typically follows repetitive stimulation. (Levinson & Edelberg, 1985; Romano & Maravita, 2014).
Four experimental conditions were assigned: Red-Painful Real, Red-Painful Simulated, Green-Neutral Real, Green-Neutral Simulated.
Null trials (delay 0) indicate pure anticipatory responses, as no actual nociceptive stimulation occurred; thus, any SCR variation refers to an autonomic stimulus anticipation response.
Stimuli between 2 and 4 seconds after the cue (delay 1) were typically associated with producing a mixed SCR response comprising both anticipatory and sensory components.
Stimuli occurring within a 5-7-second delay (delay 2) allow separation between the anticipatory and sensory components. Since the anticipatory response occurs within the first 5 seconds, and the stimulus arrives only afterwards. Since the anticipatory response occurs within the first 5 seconds and the stimulus arrives only afterwards, SCR recorded within this initial window can be attributed exclusively to the anticipatory response (Forgiarini et al., 2011).
In summary, delay 0 and delay 2 stimuli have been accounted for in anticipatory SCR (in statistical analysis labelled as “Null”); delay 1 stimuli, as they include sensory features, will be labelled “Real”.

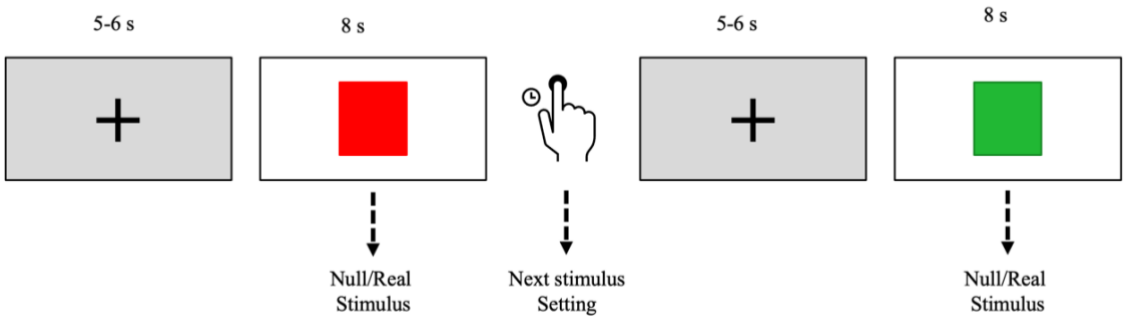


Figure 2.2: Schematic representation of the temporal sequence for visual stimulus presentation. The stimuli could be delivered in two contact conditions: real or simulated.

Pain Anticipation Task: experimental design

The stimuli were assigned into four blocks of sixteen stimuli each (one per condition) in a randomised order within each block. Ensuring that all stimulus types were delivered within each block allowed us to take control of the effect of habituation.

The four blocks were divided into two experimental sessions, each comprising two blocks, resulting in a total of four blocks per participant. The two sessions differ in the type of breathing manipulation used, either normal or forced. Since the STP anxiety effect duration is unknown, the rationale of the design was to repeat the same type of respiration in the same session, split into two blocks, to minimise the risk of excessive time elapsing between the breathing phase and the presentation of the final stimuli within each block. Thus, the same breathing condition (normal or forced) was maintained in both blocks within a session.

Each participant took part in two experimental sessions, comprising two blocks, resulting in a total of four blocks per participant. At the beginning of each block, participants underwent a breathing phase, either normal or forced, consistent with the corresponding session.

The order of the four trials of the breathing task was pseudo-randomly assigned within the four experimental blocks. The breathing exercise was coupled every two blocks. For example, if the first and the second respiration were forced, the following two were normal (unforced). In contrast, the participants who began with the first two normal respirations, consequently, underwent two straw forced respirations. This respiration order was established to better explore its effect during the blocks, avoiding alternating it before every block (see Figure 2.3).

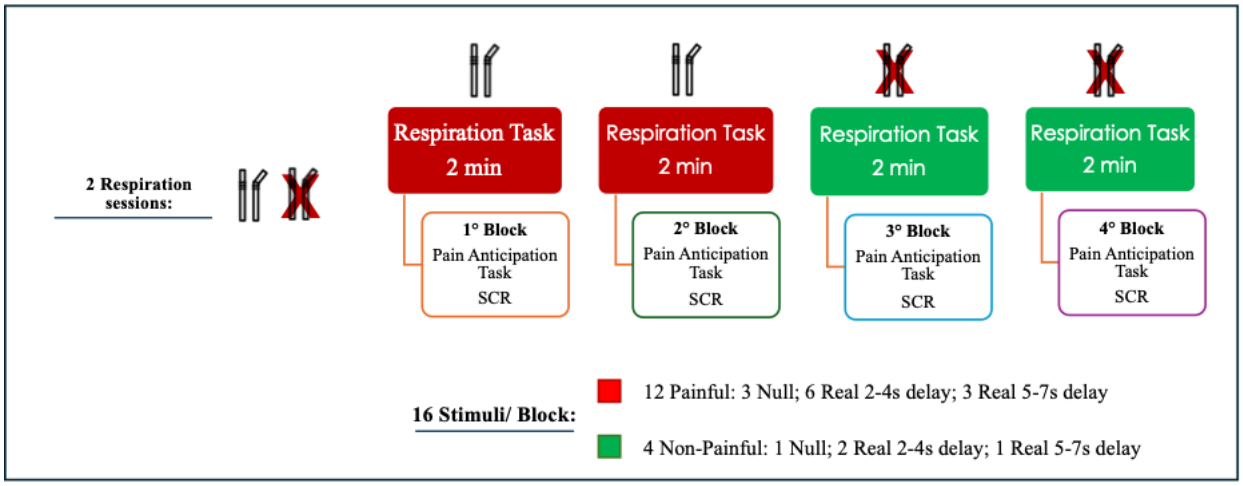


Figure 2.3: Graphical representation of the experimental design of the pain anticipation task.

Each session was administered to each participant before and after the breathing manipulation. The four experimental sessions differed only in the breathing manipulation. In this example, participants first underwent the straw breathing condition, i.e., a two-minute breathing exercise through a straw between their lips with their nose plugged. Then, they breathed normally for two minutes.

## 2.3. Results

Analyses were performed using Jamovi Software (version 2.3.28). Results are reported according to Mauchly's sphericity test; no corrections were needed.

Demographic and psychometric assessment

The final sample includes 37 healthy individuals aged between 20 and 53 years ($M = 25$, $SD = 5$). The sample consisted of 16 males and 21 females. Most participants were recruited through the participant management system used by the Sona System of the Department of Psychology at the University of Milano-Bicocca. Students received course credits for their participation in the program. Standardised self-report questionnaires were administered to participants: Beck Depression Inventory-II (BDI-II), State-Trait Anxiety Inventory (STAI-Y1, Y2), Allodynia Symptom Checklist-12 (ASC-12), and the Pain Anxiety Symptoms Scale (PASS-20).

Beck Depression Inventory-II (BDI-II): the sample average score, $M = 8.08$ ($SD = 6.58$), is compatible with proneness to mild depressive symptoms, as defined by a cut-off score of $\leq 9$ (Beck et al., 1961). State-Trait Anxiety Inventory (STAI-Y1, Y2): mean scores of state anxiety (STAI-Y1) and trait anxiety (STAI-Y2) were $M = 38.50$ ($SD = 9.31$) and $M = 42.70$ ($SD = 8.51$), respectively. According to normative values for the Italian adult population (Spielberger, 1983), these findings suggest a potential tendency to trait anxiety in the sample (cut-off $\leq 40$). No replicable inference can be made for trait anxiety levels.

Allodynia Symptom Checklist-12 (ASC-12): Mean score was $M = 1.41$ ($SD = 1.71$, range: 0-8). Asc-12 is usually implied in the chronic pain population; thus, we didn't expect to find any participant mean score above the clinical threshold (≥ 3). Nonetheless, the scores of seven participants suggested the possible presence of mild to moderate symptoms of allodynia.

Pain Anxiety Symptoms Scale (PASS-20): the average score was $M = 30.50$ ($SD = 12.70$). This Scale usually refers to the clinical population; the scores align with a healthy sample.

Anxiety and breathing task

A repeated-measures (RM ANOVA) was implemented to analyse the effect of the respiration task on perceived temporary anxiety, including factors: [2 *Respiration*: (Normal = N vs Forced = F); 2 *Time*: (Pre vs Post); 2 *Order session* (1 vs 2)]. As the experimental procedure, order 1 refers to the first, N or F, respirations executed; order 2 states the second normal or forced respirations (see Figure 2.3 for an example). The random order of the first respiration assigned (N or F) was controlled by putting *Resp-sequence* as a between-subject factor.

Results are reported according to Mauchly's sphericity test. As all factors included only two levels, the assumption of sphericity was inherently satisfied. Bonferroni correction for the pairwise comparisons was used as required.

A main effect of *Time* was found [$F(1, 35) = 9.08$, $p = .005$, $\eta^2_p = .206$]. Post hoc test comparisons indicated a significant difference ($M = - 0.399$; $SE = 0.132$) between the pre-respiration anxiety levels ($M = 1.80$, $SE = 0.17$) and post-respiration anxiety levels ($M = 2.20$, $SE = 0.20$).

A main effect of *Respiration* also emerged, [$F(1, 35) = 46.13$, $p < .001$, $\eta^2_p = 0.501$. Post hoc test comparisons indicated a significant difference ($M = - 1.14$; $SE = 0.193$): ($t(35) = -5.93$, $p < .001$) between N and F breathing. Forced respiration induced a significantly higher perceived anxiety ($M = 2.57$, $SE = 0.23$) compared to the normal respiration ($M = 1.43$, $SE = 0.16$).

An interaction effect of *Time* * *Respiration* was found [$F(1, 35) = 46.08$, $p < .001$, $\eta^2_p = 0.568$]. Post hoc test comparisons revealed a significant difference ($M = 0.57$; $SE = 0.11$): ($t(35) = 4.98$, $p < .001$) between PreN ($M = 1.72$, $SE = 0.18$) and PostN ($M = 1.14$, $SE = 0.16$); between PreF ($M = 1.89$, $SE = 0.20$) and PostF ($M = 3.26$, $SE = 0.31$) equal to $M = -1.37$; $SE = 0.25$: ($t(35) = -5.47$, $p < .001$; PreN and PostF ($M = -1.54$; $SE = .26$): ($t(35) = -5.92$, $p < .001$); PreF and PostN ($M = 0.74$; $SE = .20$): ($t(35) = 3.63$, $p = .005$); Post N and PostF ($M = -2.11$; $SE = 0.28$): ($t(35) = -7.44$, $p < .001$).

An interaction effect of *Time* * *Order* was found [$F(1, 35) = 9.96$, $p = .003$, $\eta^2_p = .221$]. Post hoc test comparisons showed a significant difference ($M = -.26$; $SE = 0.14$): ($t(35) = -4.42$, $p < .001$) between PreOrder1 (Pre 1st respiration: $M = 1.72$; $SE = 0.17$) and PostOrder1 (Post 1st respiration: $M = 2.34$; $SE = 0.21$). All other comparisons are not statistically significant (all $p > .05$).

An interaction effect of *Time* * *Order* * *Respiration* was not found [F(1, 35) = 2.046, p = .161, $\eta^2_p$ = 0.055] (see Table 2.1).

Anxiety comparison: Time ∗ Order ∗ Respiration

| | | | | | 95% Confidence Interval | |
|---|---|---|---|---|---|---|
| Order | Respiration | Time | Mean | SE | Lower | Upper |
| 1 | N | Pre | 1.790 | 0.225 | 1.333 | 2.25 |
| | | Post | 1.315 | 0.172 | 0.966 | 1.66 |
| | F | Pre | 1.646 | 0.215 | 1.209 | 2.08 |
| | | Post | 3.371 | 0.330 | 2.701 | 4.04 |
| 2 | N | Pre | 1.646 | 0.208 | 1.224 | 2.07 |
| | | Post | 0.972 | 0.172 | 0.623 | 1.32 |
| | F | Pre | 2.125 | 0.243 | 1.632 | 2.62 |
| | | Post | 3.146 | 0.320 | 2.497 | 3.79 |

Table 2.1: Estimated marginal means of perceived anxiety in the interaction between Time (pre-post), Respiration (Normal = F vs Forced = F), and Order of session (1 vs 2).

Also, the among *Time* * *Order* * *Respiration* * *Resp-sequence* revealed a significant effect [F(1, 35) = 9.57, p = .004, $\eta^2_p$ = .215].

Regarding the *Respiration sequence FN* (i.e. Order respiration within the four blocks: = F-F-N-N), post hoc test comparisons showed a significant difference (M =.95; SE = 0.20): (t(35) = 4.67, p = .005) between 1$^{st}$PreN and 1$^{st}$ PostN with a reduction of level anxiety after the normal breathing. In contrast, a significant difference between 1$^{st}$ PreF and 1$^{st}$ PostF: (M = -2.45, SE = 0.39, t(35) = -6.33, p < .001), highlighted that breath through the straw induced a higher perceived anxiety.
A significant difference (M = 0.70; SE = 0.18): (t(35) = 3.94, p = .04) was found between 2$^{nd}$ PreN and 2$^{nd}$ PostN, replicating the 1$^{st}$ normal respiration trend. However, the between 2$^{nd}$ PreF and 2$^{nd}$ PostF: (M = -1.15, SE = 0.39, t(35) = -2.82, p = .95) was not found significant. Similarly, other comparisons were not significantly different (all p > .05).

Regarding the *Respiration sequence NF* (i.e. Order respiration within the four blocks = N-N-F-F), post hoc test comparisons didn't show any significant difference (all p > .05). Even though the comparisons between: 1$^{st}$PreN and 1$^{st}$ PostN (M = -3.61e−16; SE = 0.22): (t(35) = -1.64e−15, p = 1.00); 1$^{st}$PreF and 1$^{st}$ PostF (M = -1. 00; SE = .42): (t(35) = -2.38, p = 1.00); 2$^{nd}$ PreN and 2$^{nd}$ PostN (M = 0.70; SE = .38): (t(35) = 1.87, p = 1.00); 2$^{nd}$ PreF and 2$^{nd}$ PostF (M = -0.94; SE = 0.42): (t(35)

= -2.22, p = 1.00), mime the opposite respiration sequence, they are not significant. All other comparisons are not significantly different (all p > .05) (see Figure 2.4).

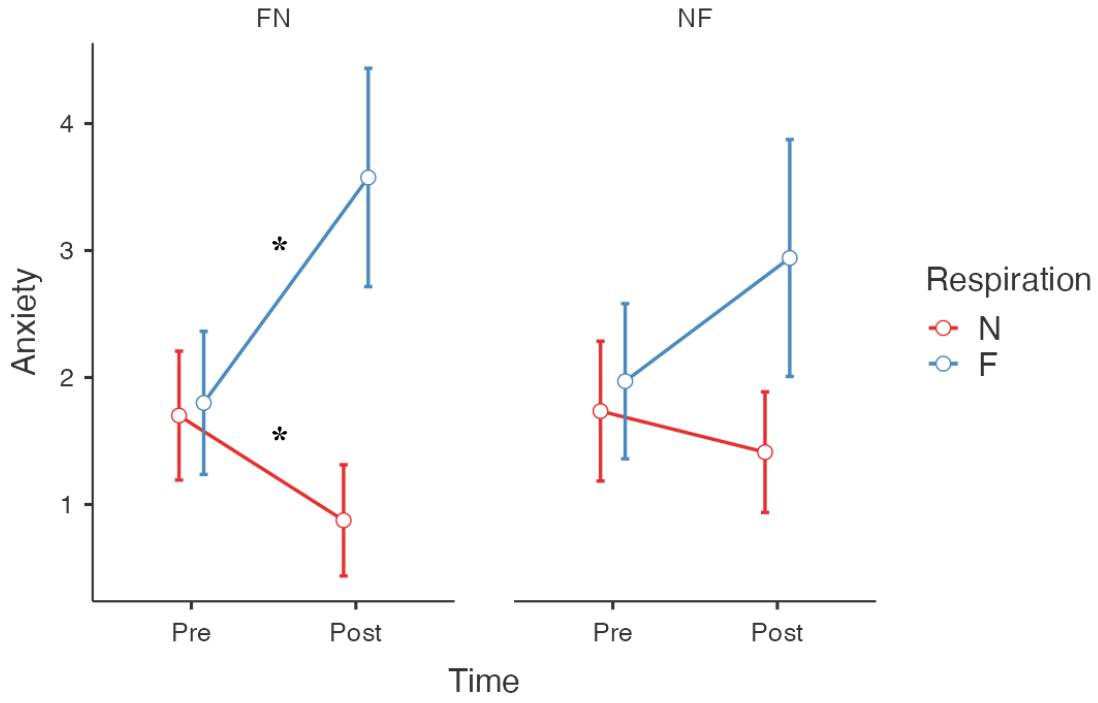


Figure 2.4: Graphic representation of perceived anxiety as a function of time (Pre-Post), respiration (Normal = F vs Forced = F) and order of respiration session sequence (NF vs FN). In the FN respiration session sequence, there is a significant difference (p = .005) between 1st PreN and 1st PostN, with a reduction in anxiety level after normal breathing. Additionally, the significant difference (p < .001) between 1st PreF and 1st PostF indicates that breath through the straw induced a higher perceived anxiety. In the NF respiration session sequence, no comparisons are significantly different (all p > .05).

This analysis suggested that the pre-post results were inconsistent, varying according to whether the first or second exposure was considered. This pattern may be attributable to a habituation effect that emerged during the second exposure to the breathing conditions. Separate RM ANOVAs were performed to provide a more accurate examination of the changes in perceived anxiety levels in the first and second exposures to the respiration task.

The first repeated-measures (RM ANOVA) assessed the effectiveness of the **first respiration exposure** (N o F) in reducing anxiety.

The resulting experimental design includes factors: [2 *Respiration* (Normal = N vs Forced = F) X 2 *Time* (Pre vs Post) X 2 *Resp-sequence* (NF vs. FN)].

A main effect of *Time* was found [F(1, 35) = 19.52, p < .001, $\eta^2_p$ = .358]. Bonferroni post hoc test comparisons revealed a significant difference (M = -0.62; SE = 0.141) between the pre-respiration anxiety levels (M = 1.72, SE = 0.17) and the post-respiration anxiety levels (M = 2.34, SE = 0.21). A main effect of *Respiration* also emerged, [F(1, 35) = 46.13, p < .001, $\eta^2_p$ = 0.501. Post hoc test comparisons indicated a significant difference (M = - 0.95; SE = 0.25): (t(35) = -3.83, p < .001) between N and F breathing. Forced respiration induced a significantly higher perceived anxiety (M = 2.51, SE = 0.24) compared to the normal respiration (M = 1.55, SE = 0.19).

An interaction effect of *Time* * *Respiration* was found [F(1, 35) = 37.78, p < .001, $\eta^2_p$ = 0.519]. Post hoc test comparisons revealed a significant difference between PreN and PostN [(M = 0.47; SE = 0.15), (t(35) = 3.17, p = .019)]; between PreF and PostF [(M = -1.72; SE = 0.29), (t(35) = -6.04, p < .001)]; between PreN and PostF [(M = -1.58; SE = 0.33), (t(35) = -4.76, p < .001)]; and between PostN and PostF [(M = -2.06; SE = 0.33), (t(35) = -6.32, p < .001)] (see Table 2.2).

Anxiety comparison: Time ⁎ Respiration

| | | | | 95% Confidence Interval | |
|---|---|---|---|---|---|
| Respiration | Time | Mean | SE | Lower | Upper |
| N | pre | 1.79 | 0.225 | 1.333 | 2.25 |
| | post | 1.31 | 0.172 | 0.966 | 1.66 |
| F | pre | 1.65 | 0.215 | 1.209 | 2.08 |
| | post | 3.37 | 0.330 | 2.701 | 4.04 |

Table 2.2: Estimated marginal means of perceived anxiety in the first exposure to the respiration task as a function of time (Pre-Post) and Respiration (Normal = F vs Forced = F).

An interaction effect of *Time* * *Respiration* * *Resp-sequence* was found [F(1, 35) = 11.24, p = .002, $\eta^2_p$ = .243]. Bonferroni post hoc revealed a significant difference between pre-post forced respiration in FN order: [(M = -2.45; SE = 0.39), (t(35) = -4.33, p < .001)]. While in NF order, no significant difference between pre-post forced respiration emerged: [(M = -1.00; SE = 0.42), (t(35) = -2.39, p = .0639)]. A significant difference between pre-post normal respiration in FN order was found: [(M = 0.95; SE = 0.20), (t(35) = 4.67, p = .001)]; but not in NF order: [(M = -3.61e-16; SE = 0.22), (t(35) = -1-64e-15, p = 1.00] (see Figure 2.5).

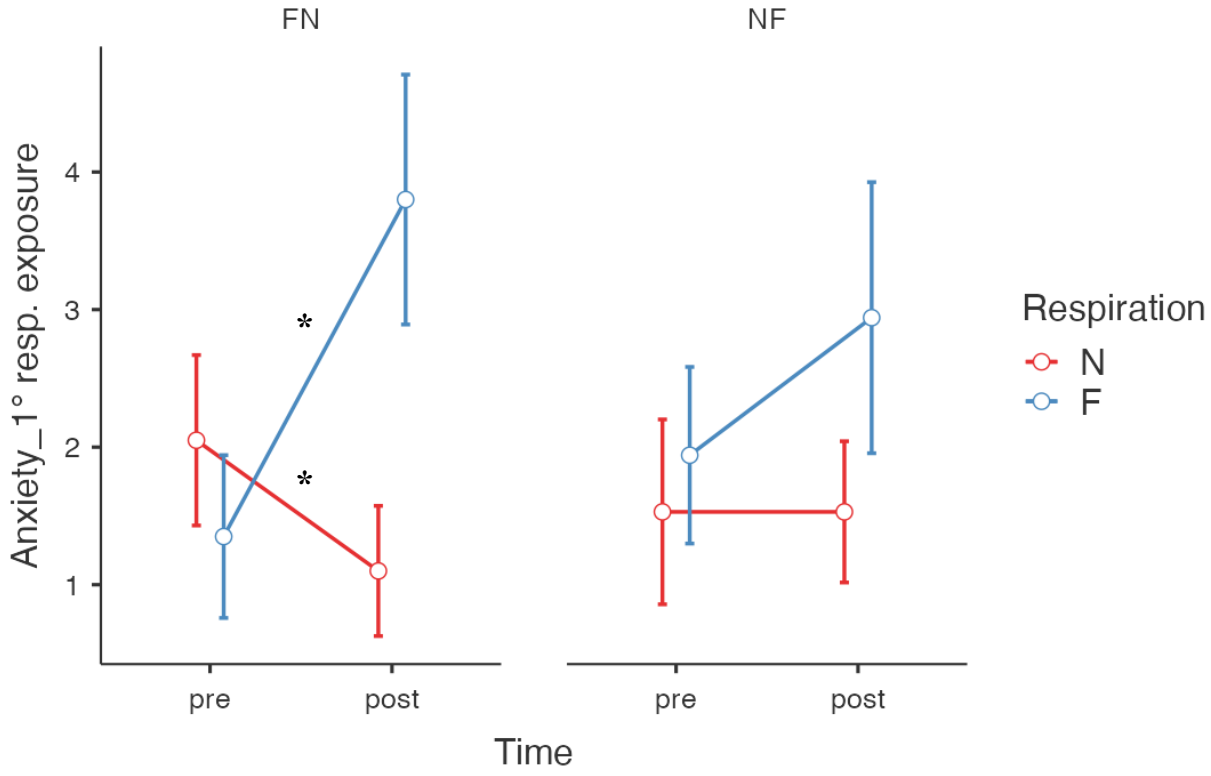


Figure 2.5: Graphic representation of perceived anxiety in the first exposure to the respiration task as a function of time (Pre-Post), respiration (Normal = F vs Forced = F) and order of respiration session sequence (NF vs FN). In the FN respiration session sequence, there is a significant increase in perceived anxiety ($p < .001$) between Pre and Post forced respiration and a reduction of anxiety level after normal breathing ($p = .001$).

A second repeated-measures (RM ANOVA) assessed the effectiveness of the **second respiration exposure** (N o F) on anxiety. The resulting experimental design includes factors: [2 *Respiration* (Normal = N vs Forced = F) X 2 *Time* (Pre vs Post) X 2 *Resp-sequence* (NF vs. FN)].

A main effect of *Respiration* emerged, [$F(1, 35) = 41.47$, $p < .001$, $\eta^2_p = 0.542$. Bonferroni post hoc test comparisons indicated a significant difference ($M = -1.33$; $SE = 0.21$): ($t(35) = -6.44$, $p < .001$) between N and F breathing. Forced respiration induced a significantly higher perceived anxiety ($M = 2.64$, $SE = 0.25$) compared to the normal respiration ($M = 1.31$, $SE = 0.18$).

A main effect of *Time* was not found [$F(1, 35) = 1.189$, $p = .283$, $\eta^2_p = 0.033$].

An interaction effect of *Time* * *Respiration* was found [$F(1, 35) = 29.00$, $p < .001$, $\eta^2_p = 0.453$]. Bonferroni post hoc test comparisons revealed a significant difference between PreN and PostN [($M = 0.67$; $SE = 0.13$), ($t(35) = 5.14$, $p < .001$)]; between PreF and PostF [($M = -1.02$; $SE = 2.89$), ($t(35) = -3.54$, $p = .007$)]; between PreN and PostF [($M = -1.50$; $SE = 0.26$), ($t(35) = -5.57$, $p < .001$)];

between PostN and PostF [(M = -2.17; SE = 0.29), (t(35) = -7.57, p < .001)]; and between PreF and PostN [(M = 1.15; SE = 0.26), (t(35) = 4.50, p < .001)].

Anxiety comparison: Time ∗ Respiration

| | | | | 95% Confidence Interval | |
|---|---|---|---|---|---|
| Respiration | Time | Mean | SE | Lower | Upper |
| N | pre | 1.646 | 0.208 | 1.224 | 2.07 |
| | post | 0.972 | 0.172 | 0.623 | 1.32 |
| F | pre | 2.125 | 0.243 | 1.632 | 2.62 |
| | post | 3.146 | 0.320 | 2.497 | 3.79 |

Table 2.3: Estimated marginal means of perceived anxiety in the first exposure to the respiration task as a function of time (Pre-Post) and Respiration (Normal = F vs Forced = F).

An interaction effect of *Respiration* * *Resp-sequence* was found [F(1, 35) = 5.285, p = .028, $\eta^2_p$ = 0.131]. Bonferroni post hoc revealed a significant difference between pre-post normal respiration in FN order was found: [(M = 0.70; SE = 0.19), (t(35) = 3.94, p = .010)]. In the NF order, the difference between pre-post normal respiration didn't emerge, even though it was close to significance: [(M = -0.65; SE = 0.19), (t(35) = 3.36, p = .053)]. No significant differences between pre-post forced respiration was found neither in the NF order: [(M = -0.94; SE = 0.42), (t(35) = -2.22, p = .919)], nor in the FN order: [(M = -1.10; SE = 0.39), (t(35) = -2.82, p = .222)] (see Table 2.3 and Figure 2.6).

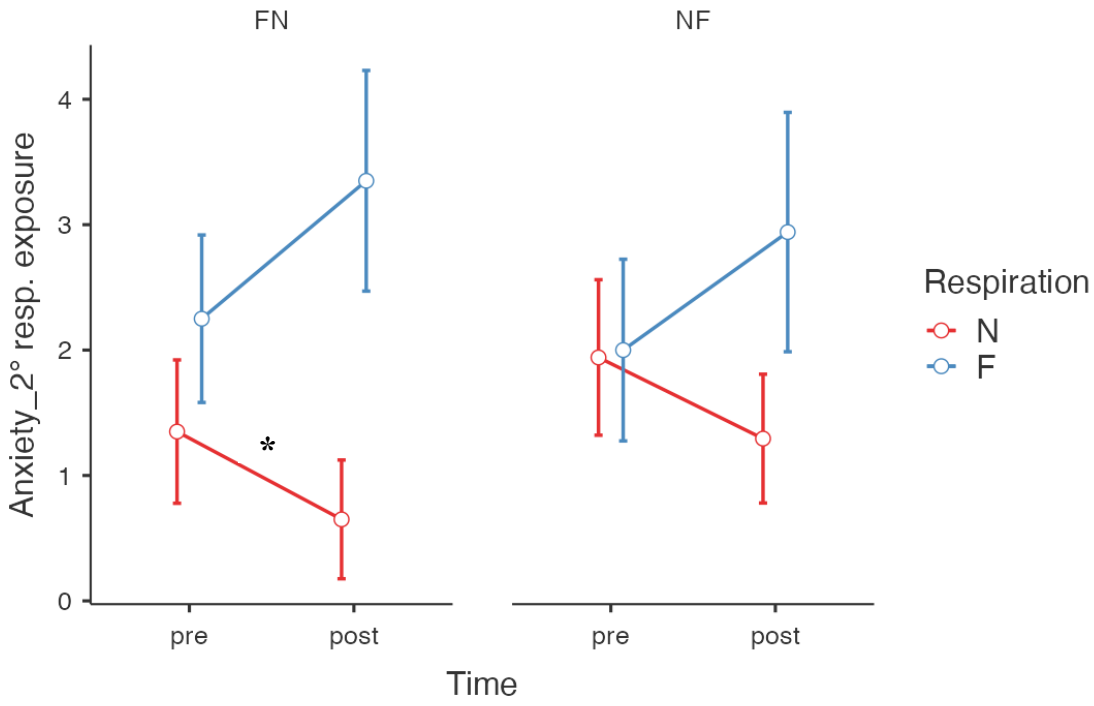


Figure 2.6: Graphic representation of perceived anxiety in the second exposure to the respiration task as a function of time (Pre-Post), respiration (Normal = F vs Forced = F) and order of respiration session sequence (NF vs FN). In the FN respiration session sequence, there is a significant reduction in perceived anxiety between Pre and Post normal respiration ($p = .010$).

The results indicate that timing and the type of breathing significantly influenced the perceived anxiety. Anxiety levels reveal distinct patterns depending on whether the breathing condition is normal or forced. Anxiety tends to decrease after normal breathing, whereas forced breathing leads to elevated anxiety levels.

However, the starting respiration affects the perception of anxiety level. Even if the increase in anxiety following forced breathing emerged during the first and second respiration exposures, it was influenced by the overall order of respirations (NNFF or FFNN) (see Figure 2.7). The forced respiration exploited its potential in inducing anxiety when it was tried as the absolute first respiration. Still, it reduced its effectiveness over time and when preceded by the normal one. Additionally, it appears that the anxiety associated with normal breathing has been influenced by the previous forced breathing, akin to a "reaction effect": after attempting forced respirations, participants may have found normal breathing to be relaxing.

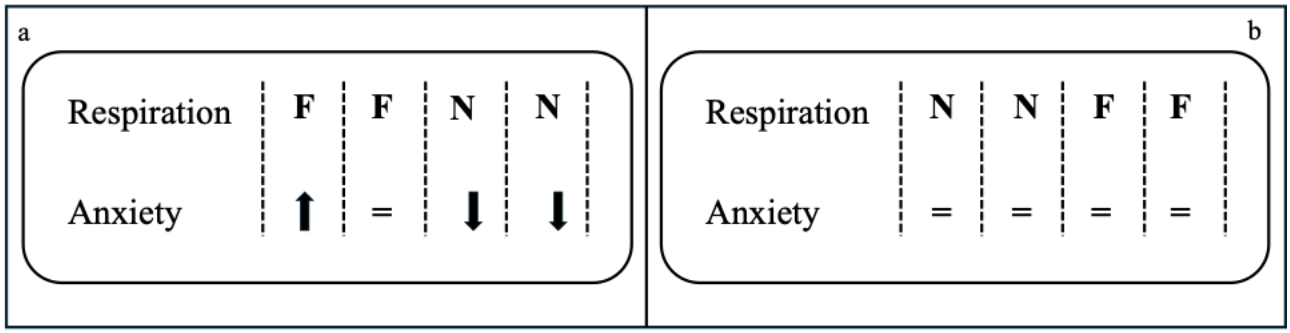


Figure 2.7: a schematic summary representation of the results of the whole task, respiration split by session order (N or F). (a) The sequence of order of respiration FFNN revealed a significant increase in perceived anxiety in the first F and an increase in perceived anxiety in both N respiration. (b) The sequence of order of respiration NNFF revealed no significant variation of perceived anxiety in any F or F respiration.

Pain Anticipation: Skin Conductance Response

SCR data were analysed using AcqKnowledge software version 4.2. An offline high-pass filter set at 0.05 Hz was applied to originate stimulus-dependent phasic skin conductance responses from the tonic level (Figner & Murphy, 2011).

The SCR peak-to-peak evoked response, as a marker for pain intensity (Breimhorst et al., 2011; Lykken & Venables, 1971; Rhudy et al., 2010; Camerone et al., 2022), was computed for each trial by a 4.95-s post-colored cue time window (Romano et al., 2014; Romano et al., 2016; Camerone et al., 2022). Manual event markers corresponding to each stimulus type were added to the skin conductance response (SCR) trace via keyboard input at the onset of the colored cue presented on the screen (Romano et al., 2014).

A first repeated-measures (RM ANOVA) assessed the effectiveness of the respiration task on autonomic responses, using skin conductance response (SCR) as the dependent variable, as the marker of anticipatory responses elicited by cues coupled to either a painful or neutral stimulus as follows: Red Cue – Painful Stimuli; Green Cue-Neutral stimuli.

The resulting mixed RM ANOVA includes two within factors: [2 *Cue*: (Green = G vs Red = R); 2 *Respiration*: (Normal = N vs Forced = F)] and one between factor [2 *Resp-sequence* (NF vs FN)] that represents the random order of the first respiration session assigned (N or F).

As all factors included only two levels, the assumption of sphericity did not need to be tested.

A main effect of *Cue* was found [$F(1, 35) = 8.15$, $p = .007$, $\eta^2_p = .189$]. Post hoc test comparisons indicated a significant difference [($M = 0.017$; $SE = 0.006$), ($t(35) = 3.36$, $p = .007$)] between the Red

(M = 0.10, SE = 0.01) and Green Cue (M = 0.83, SE = 0.01). There were no other main or interaction effects (all p>.05).

These results show that the possible painful stimuli warning (Red cue) elicited higher autonomic anticipation responses than the green cue, which signals neutral stimuli instead. The type of respiration and its execution order didn't affect this general trend (see Figure 2.8).

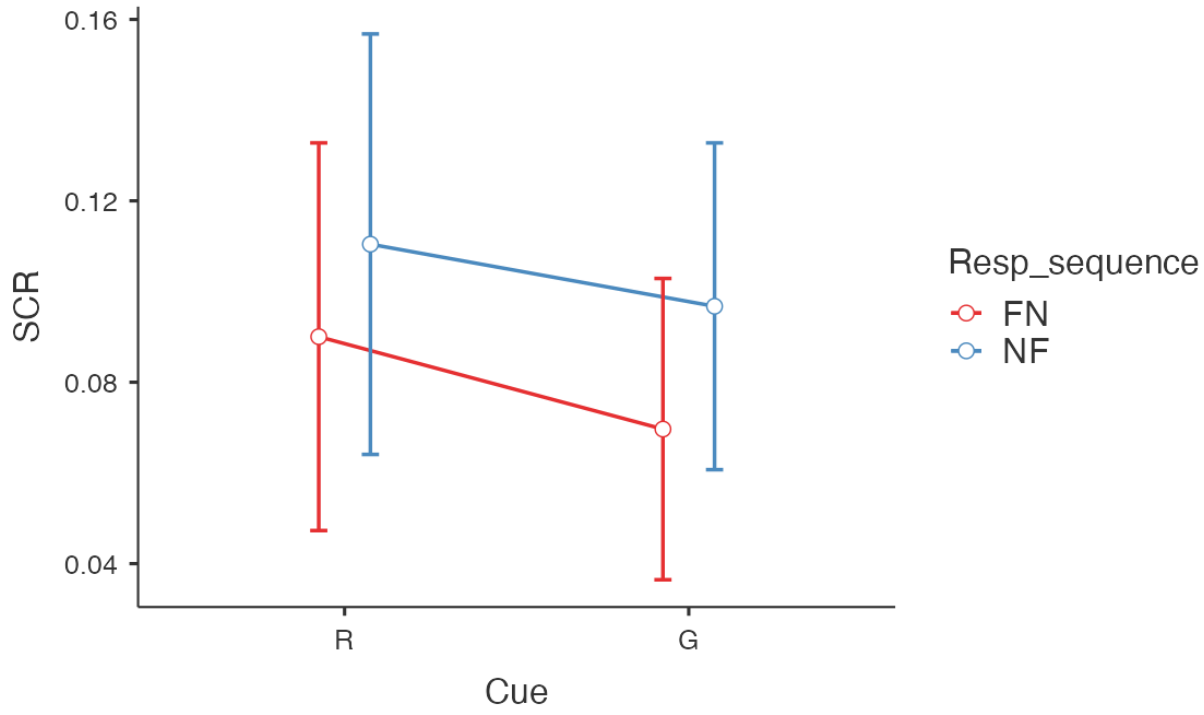


Figure 2.8: Graphic representation of SCR as a function of cue (Green = painful vs Red = neutral stimuli) and the order of respiration session sequence (NF vs FN). Red cues elicited higher autonomic anticipation responses than green ones (p = .007).

A second repeated-measures (RM) ANOVA measured the effect of the respiration task on skin conductance response (SCR), the dependent variable, elicited by real or simulated painful stimuli, the primary focus of this experiment. The resulting mixed RM ANOVA includes two within factors: [2 *Cue*: (Green = G vs Red = R); 2 *Stimulus*: (Null vs Real); 2 *Respiration*: (Normal = N vs Forced = F)] and one between factor [2 *Resp-sequence* (NF vs FN)] that represents the random order of the first respiration session assigned (N or F).

As specified above, Stimuli with delays equal to 0 and 2 are labelled "Null"; stimuli with delays equal to 1 are labelled "Real". In this analysis, the null mean refers to the mean of delays of 0 and 2 stimuli.

A main effect of *Cue* was found [F(1, 35) = 8.55, p = .006, $\eta^2_p$ = .196]. Post hoc test comparisons indicated a significant difference [(M = 0.018; SE = 0.006), (t(35) = 2.92, p = .006)] between the Red and Green Cue.

Neither a main effect of *Respiration* [F(1, 35) = 6.70e-4, p = .98, $\eta^2_p$ = 0.00] nor of *Stimulus* [F(1, 35) = 0.75, p = .39, $\eta^2_p$ = 0.02] was found. Furthermore, no other interaction effect reached statistical significance (all p >.05) (see Figure 2.9).

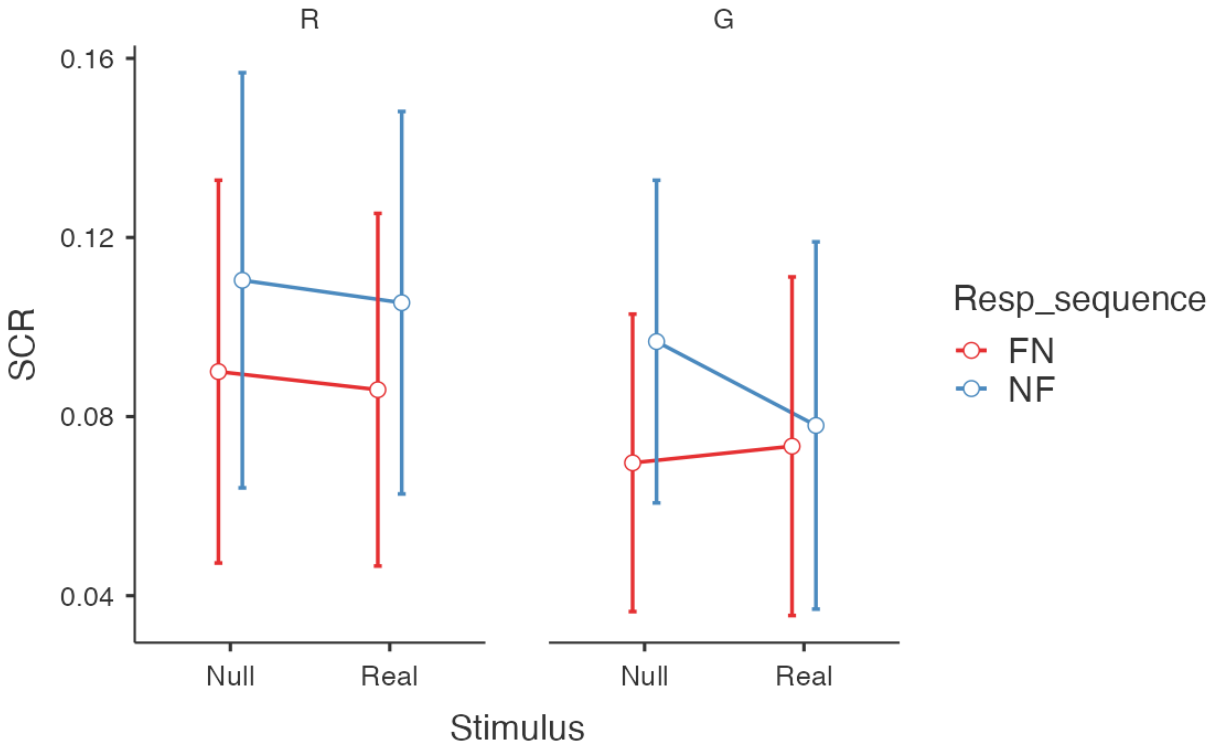


Figure 2.9: Graphic representation of SCR as a function of cue (Green = painful vs Red = neutral stimuli), type of stimulus (Null vs Real) and the order of respiration session sequence (NF vs FN). Red cues elicited significantly higher autonomic anticipation responses than green ones (p = .006).

Effects of the respiration task on the self-report conscious perception of pain

A paired-samples t-test was used to compare the effects of normal (N) and forced (F) respiration on reported pain sensitivity. The analysis revealed a significant difference (M = -0.92, Se = 0.18) between the two conditions: [$t$(37) = -5.13, $p$ < .001, Cohen's $d$ = -0.84]. Participants reported higher perceived pain sensitivity during forced breathing (M = 0.11, SE = 0.17) than during normal breathing

(M = -0.81, SE = 0.16). These findings support the hypothesis that forced breathing increases the conscious perception of pain compared to normal breathing (see Figure 2.10).

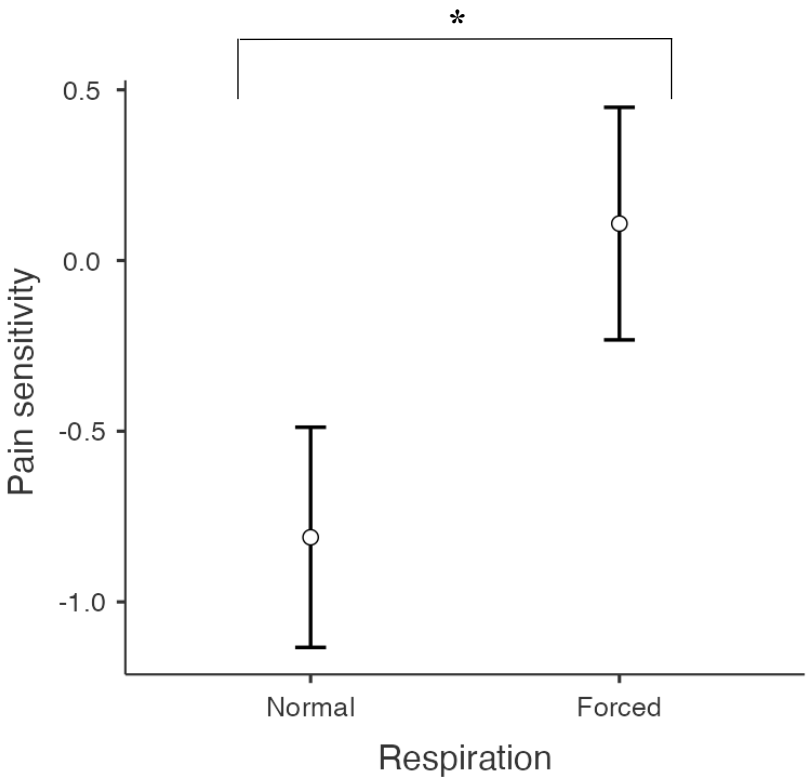


Figure 2.10: Graphic representation of the self-reported effect of respiration (Normal or Forced) on pain sensitivity. The perceived pain sensitivity during forced breathing was higher than during normal breathing ($p < .001$).

Correlational analyses

A Pearson correlation analysis was conducted (N = 37) to examine the relationship between perceived anxiety induced by the breathing task, pain threshold, and daily life psychological variables (see Table 2.4).

A significant correlation emerged between the perceived anxiety due to the forced (Anxiety_PostF) and normal respiration (Anxiety_PostN): ($r = 0.355$, $p = .031$). A significant correlation was found between the perceived anxiety due to the forced respiration (Anxiety_PostF) and the self-report perception of this breathing on pain sensitivity (RespF_effect): ($r = 0.357$, $p = .030$) and between self-report perception of forced (RespF_effect) and normal breathing on pain sensitivity (RespN_effect): ($r = 0.400$, $p = .014$).

A significant negative correlation was found between SCR to anticipation of pain stimuli in forced respiration (SCR_PostF) and pain anxiety (PASS) ($r = -0.326$, $p = .049$); no significant correlation was found between SCR to anticipation of pain stimuli in normal respiration (SCR_PostN) and pain

anxiety (PASS) (p = .349). A significant positive correlation was found between SCR_PostF and SCR_PostN (r = 0.622, p < .001), signifying a coherence of SCR.

The pain threshold (T) was positively correlated with SCR in anticipation of pain stimuli during normal respiration (r = 0.420, p = .010). No other correlation was found with pain threshold and different variables (all p > .053).

No other significant correlations were found between perceived anxiety due to the forced respiration with state anxiety; or trait anxiety; or anxiety for pain; or allodynia (ASC), or proneness to depression (all p >.05). Significant positive correlations were found between the perceived anxiety due to the normal respiration (Anxiety_PostN) and depression symptoms (BDI): (r = 0.443, p = .006); between (Anxiety_PostN) and (STAI-Y1) (r = 0.598, p < .001); and between (Anxiety_PostN) and (STAI-Y2) (r = 0.501, p = .002).

Significant correlations emerged between the two dimensions of anxiety: State (STAI-Y1) – Trait (STAI-Y2) (r = 0.712, p < .001) and these two scales and depression (BDI): STAI-Y1 – BDI (r = 0.744, p < .001), STAI-Y2 and BDI (r = 0.734, p < .001) (see Table 2.4).

Correlation Matrix

| | T | Anxiety_PostN | Anxiety_PostF | SCR_PostF | SCR_PostN | RespF_effect | ASC | RespN_effect | PASS | BDI | STAI-Y1 | STAI-Y2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T | — | | | | | | | | | | | |
| Anxiety_PostN | -0.320 | — | | | | | | | | | | |
| Anxiety_PostF | -0.220 | 0.355 * | — | | | | | | | | | |
| SCR_PostF | 0.128 | -0.103 | 0.022 | — | | | | | | | | |
| SCR_PostN | 0.420 ** | -0.214 | 0.106 | 0.622 *** | — | | | | | | | |
| RespF_effect | 0.050 | 0.069 | 0.357 * | 0.120 | 0.206 | — | | | | | | |
| ASC | -0.239 | 0.258 | -0.092 | -0.031 | -0.243 | 0.070 | — | | | | | |
| RespN_effect | 0.090 | 0.062 | 0.068 | 0.139 | 0.196 | 0.400 * | 0.053 | — | | | | |
| PASS | -0.032 | -0.191 | -0.031 | -0.326 * | -0.146 | 0.100 | 0.165 | 0.021 | — | | | |
| BDI | -0.083 | 0.443 ** | 0.200 | -0.149 | -0.098 | 0.205 | 0.118 | 0.067 | 0.064 | — | | |
| STAI-Y1 | 0.007 | 0.598 *** | 0.122 | -0.061 | -0.015 | 0.204 | 0.173 | 0.112 | -0.166 | 0.744 *** | — | |
| STAI-Y2 | -0.076 | 0.501 ** | 0.152 | -0.272 | -0.038 | 0.186 | 0.190 | 0.105 | 0.209 | 0.734 *** | 0.712 *** | — |

*Note.* * p < .05, ** p < .01, *** p < .001

Table 2.4: Correlation matrix of the study variables related to the respiration task. The variables include: T (pain threshold); perceived anxiety due to the forced (Anxiety_PostF) and normal respiration (Anxiety_PostN); SCR to anticipation of pain stimuli in forced respiration (SCR_PostF); SCR to anticipation of pain stimuli in normal respiration (SCR_PostN); self-report perception of forced (RespF_effect) and normal breathing on pain sensitivity (RespN_effect); Allodynia Symptom (ASC); pain anxiety (PASS); depression (BDI); state anxiety (STAI-Y1); trait anxiety (STAI-Y2). Statistically significant correlations are marked with asterisks (*p < .05, **p < .01, ***p < .001).

## 2.4. Discussion

This research project aimed to investigate the role of anxiety in the anticipation of pain.

The straw breathing task elicited a state of transitory anxiety, while pain stimuli were delivered via controlled electrical stimulation to ensure standardisation and reproducibility.
The main objective was to determine whether anxiety can affect the psychophysiological responses (SCR) to incoming pain stimuli.
The analysis focused on two main hypotheses:

(I) The effects of experimental manipulation on perceived anxiety in the normal vs. forced respiration condition

(II) The impact of anxiety on SCR in response to cues (Red or Green) signalling the painful or neutral upcoming stimuli.

The straw breathing task was applied to elicit a state of transitory anxiety, while pain stimuli were delivered via controlled electrical stimulation to ensure standardisation and reproducibility of experimental conditions.

Repeated-measure analyses of variance (RM ANOVA) were employed to analyse the data and verify the proposed hypotheses.
An RM ANOVA revealed that both types of breathing conditions significantly influenced anxiety levels. The straw task data suggest that the forced respiration had an effect, inducing a temporary state of anxiety. These findings are consistent with the original hypotheses and prior literature, confirming the anxiogenic role of forced breathing and the potential regulatory effect of normal breathing. The rise in anxiety during the forced breathing condition is plausibly linked to sensations of dyspnea, as previously documented in studies employing respiratory resistance paradigms. Such conditions heighten interoceptive awareness and, when perceived as threatening, can trigger transient elevations in subjective anxiety (Melzig et al., 2011; Paulus, 2013; Teachman et al., 2007). According to the participants' feedback, the first respiration, especially the forced one, had a greater impact on perceived anxiety than the second one. It's plausible that the novel effect of the first forced respiration and the usual bodily sensations generated a stronger state of anxiety. The second forced respiration made the uncertainty of the impact of the straw task more predictable, allowing participants to implement automatic coping strategies to mitigate the unpleasant breathing consequences, as reported by many participants.
As mentioned in Spaccasassi & Maravita (2020), the first normal respiration impacted the perceived anxiety. Even if the task order was "just breathe normally", people reported a significant decrease in their perceived anxiety; thus, it allows us to speculate that mindful breathing contributes to relaxation.

This phenomenon is especially evident when the participants tried the forced respiration first. The FN respiration order may have facilitated attention to the following normal breathing.

Further insight into autonomic responses, specifically the skin conductance response (SCR), was obtained through repeated-measures ANOVA analysis. The SCR data, analysed via ANOVA-RM, revealed that the autonomic response was significantly modulated by the type of cue (Red vs. Green). The main effect of the cue indicates that participants automatically react differently to the different colour cues. Red cues raised SCR more than the green ones, reinforcing the predictive role of the cue. It means that the procedure of familiarisation was correctly performed.

No significant difference was found between SCR to "null" and "real" pain stimuli, in contrast to previous literature, which reported that painful skin contacts, due to the somatosensory response, evoked a stronger SCR than stimuli that touched the arm (Romano & Maravita, 2014).

Additionally, respiratory conditions did not affect either the anticipatory responses or those related to real stimulation. We expected that anxiety could have affected the whole SCR, specifically by enhancing physiological reactivity to pain stimulus anticipation. The temporal state of anxiety should have stressed anticipatory uncertainty and pain responses (Staub et al., 1971; Grupe & Nitschke, 2013).

Overall, SCR appeared to be primarily driven by the informational content of the cues. Still, contextual variables such as anxiety due to a breathing condition didn't affect their predictive value regarding the upcoming event.

In contrast, self-report responses reflected a subjective consciousness of the effect of respiratory manipulation on pain sensitivity. Forced breathing led to heightened perception of pain sensations. Correlational analyses evaluated possible relationships among anxiety levels due to forced breathing, scores on anxiety-related questionnaires, the perceived effect of respiration on pain sensitivity and SCR to anticipation of pain.

Significant positive correlations between temporary anxiety induced by normal respiration (Anxiety_PostN), state anxiety (STAI-Y1), and trait anxiety (STAI-Y2) suggest that experimental experiences of perceived anxiety are consistent with standard psychometric assessments and reflect a degree of interindividual stability in anxiety levels.

The forced breathing condition (Anxiety_PostF), designed to be more stress-inducing, did not seem to be linearly correlated with the state or trait anxiety. While the straw breathing task effectively induced transient anxiety, this effect was not linked to individual differences in baseline anxiety trait or state. These findings reflect the outcomes of the breathing task and may indicate limitations in the experimental manipulation. However, the positive correlation between the perceived anxiety in forced respiration (Anxiety_PostF) and the perceived effect of respiration on pain sensitivity (RespF_effect)

may lead to the thought that participants consciously elaborated the experience of straw respiration as affecting pain perception, even if the bodily response of their autonomic nervous system (SCR) did not reflect this awareness. This can be related to the different stages, from unconscious nociception to mindful pain perception.

Contrary to initial hypotheses (Rhudy et al., 2010; Williams & Rhudy, 2009), no significant correlations were found between anxiety indexes: pain anxiety (PASS), state anxiety, trait anxiety, temporary anxiety induced by the forced respiration and the perceived effect of respiration on pain sensitivity. These standardised measures were chosen to explore associations between self-report more general anxiety indexes (STAI-Y1,2) and specific anxiety for pain (PASS) in an experimental context. PASS is usually used in sufferers of chronic pain; it may not mirror the healthy population trend completely. The negative correlation between anxiety for pain and the SCR due to pain stimuli after the forced respiration (SCR_PostF) is going in the opposite direction from the idea of an increasing interaction between pain arousal and anxiety.

The significant positive correlation between SCR and pain stimuli after forced or normal respiration adds significance to the overall coherence of SCR in this experimental design and a lack of significant effect of anxiety on it.

Fear or anxiety related to pain does not appear to be associated with subjective pain perception, nor with state or trait anxiety levels, contrary to what might reasonably have been expected.

We didn't find any correlation between general anxiety and depression indexes and allodynia (ASC). Considering that the data refer to a healthy sample, it is unsurprising. Yet, the presence of cutaneous allodynia is also reported in other studies (see chapter 3), suggesting that it's necessary to deepen the exploration of the interplay among them.

As expected, strong correlations were observed between anxiety and depression scores, reflecting the well-established and documented comorbidity between anxiety and depressive symptoms.

All these finding supports the RM ANOVA's results, suggesting on one side that there are no correlations between state and trait anxiety, as well as pain-related anxiety, with induced anxiety, and on the other side, that anxiety didn't influence autonomic responses to pain. This suggests that pain anticipation and perception are part of a complex phenomenon that involves processing the pain experience, albeit not uniformly influencing psychophysiological indices.

### 2.4.1. Limitations, conclusions, and future perspectives

This study confirmed the effectiveness of using colored squares as predictive cues to elicit anticipatory responses to pain (Kökönyei et al., 2021). This result highlights the impact of prior experiences and individual expectations (Benedetti et al., 2006; Damasio, 1994) on the contextual

environment. Even if the cue familiarisation resulted in different SCR, no other significant outcomes were observed when delivering the pain and neutral stimuli with or without skin contact ("real" or "null" stimuli). It's plausible to speculate that the nature of the current cues, red or green colored square, is quite different from a needle (intrinsically threatening cue) and a cotton swab (neutral cue), usually implied in pain anticipation experiments (Romano & Maravita, 2014; Romano et al., 2014). In daily life, red is often associated with the concept of "stop". At the same time, a needle may have a stronger emotional valence, inducing a stronger autonomic and affective response than a red sign. However, it is relevant to note that skin conductance, as a measure of autonomic responses, reflects arousal, which is inherently nonspecific for pain. It can be associated with other emotionally salient events, or surprise, pleasant and unpleasant imagery. Therefore, a portion of the skin conductance response possibly elicited by the cue may be attributable to non-specific factors, such as a surprise effect associated with the appearance or other features of the stimulus (Mischkowski et al., 2018).

Thus, the following studies should re-evaluate the intrinsic valence of the stimuli, considering that the ones used in this experiment may have had an effect during the experiment.

Also, the procedure may have affected the SCR results. Some participants reported that the task was boring and repetitive, and they didn't feel alert while watching green or red cues.

Potential habituation resulting from procedural repetition could have affected the SCR results, as it likely did with the respiration task. We noticed that the second forced respiration did not induce a significant increase in anxiety, in contrast to the first one. The impact of procedural learning and task familiarisation variables further emphasises the importance of adopting a multidimensional perspective in pain studies (Gatchel, 2007). Subtle contextual factors appear capable of shaping psychological responses to a degree that may challenge the reliability of well-established respiratory regulation techniques.

Regarding respiration, we can assume that the significant reduction in anxiety due to normal respiration may be related to interoceptive attention, which can have a relaxing effect. It can be taken into consideration in clinical and research pain contexts.

It is crucial to consider that all data refer to a non-clinical sample; all participants in this study were healthy volunteers, not clinically anxious individuals or patients with chronic pain. We hypothesise different and more consistent results in the migraineurs sample.

In conclusion, this exploratory study contributes to an expanding body of research on the psychophysiological mechanisms underlying anxiety and pain. The findings point out the necessity of future investigations to compare different research procedures to deepen the intricate relationship between anxiety, anticipation, and pain, with the ultimate goal of enhancing knowledge for more effective clinical interventions.

# 3. SEEING AND FEELING PAIN AND AFFECTIVE TOUCH: VICARIOUS AND FIRST-HAND SOMATOSENSORY EXPERIENCE

## 3.1. Introduction

### 3.1.1. An overview of affective touch

The skin, the human body's largest organ, serves as a crucial interface between the internal and external environments. It serves as a protective barrier against potentially harmful agents and a sensory medium for interaction with the external world through tactile perception. Traditionally, the processing of tactile stimuli was thought to occur via a single neural pathway: mechanoreceptors in the skin detect stimuli, which are transmitted by fast-conducting myelinated Aβ afferent fibres through the spinal cord to the thalamus and subsequently to the primary somatosensory cortex. This mechanism underlies fast, discriminative touch, which enables the detection of detailed sensory and perceptual qualities of stimuli.

Besides these low-threshold cutaneous mechanoreceptors involved in discriminative touch, there are also unmyelinated C-tactile (CT) afferent fibres, which respond preferentially to slow, gentle tactile stimulation such as caresses; thus, they carry the affective properties of touch, also known as affective touch. The technique of microneurography provided evidence of the presence of these afferents in humans, which were defined as a "second system of coding tactile stimuli", more closely related to limbic functions than to cognitive and motor ones (Vallbo et al., 1999). Subsequent works identified the characteristic of its affiliative and caress-like touch (Ackerley et al., 2014; Löken et al., 2009; Wessberg et al., 2003), which commonly occurs during naturalistic social contact, including spontaneous physical interactions between individuals (Croy et al., 2016; Morrison et al., 2010; McGlone et al., 2014) (see Figure 3.1). Consequently, two partially distinct tactile processing systems can be identified: a fast, discriminative pathway that supports sensory precision and survival-relevant behaviours, and a slower, affective pathway implicated in socio-emotional development and interpersonal bonding (Morrison, 2016a). Anatomically, these pathways diverge at the level of the spinal cord. While Aβ fibres bypass Lamina I of the dorsal horn, CT afferents project specifically to this region, which is known to relay information associated with interoception and affect (Björnsdotter et al., 2010)

The slow, affective tactile stimulation, such as gentle skin brushing, not only activates the primary and secondary somatosensory cortices (SI and SII) but also engages the contralateral posterior insula, a region involved in emotional and affective processing (Craig, 2008). In addition to the insula, the

posterior superior temporal sulcus, medial prefrontal cortex, and dorsal anterior cingulate cortex are also recruited during affective touch, reflecting the broader integration of social, cognitive, and emotional dimensions in tactile experience (Gordon et al., 2013).

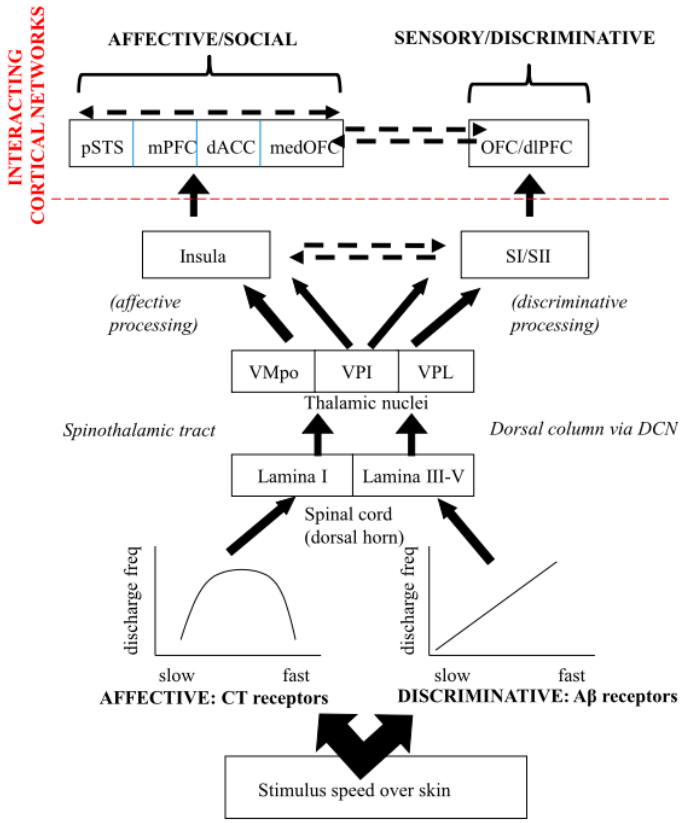


Figure 3.1: Diagram illustrating the pathways of discriminative and affective touch in response to tactile stimulation of hairy skin (from McGlone et al., 2014).

Initially, CT afferent fibres were believed to be exclusively located in hairy skin and absent in glabrous skin. However, more recent evidence supports the presence of CT afferents in the glabrous skin of the hand, exhibiting response characteristics comparable to those observed in the hairy skin of the forearm. As the CT afferents likely do not convey conscious tactile sensations, their presence in glabrous skin may subconsciously reinforce the perception of gentle touch, complementing the conscious, discriminative input transmitted by fast-conducting myelinated mechanoreceptors. The

perceived slow touch on the palm as pleasant reinforces the positive affective of the gentle tactile interactions during touch using the hands (Watkins et al., 2021). Also, the presence of CT afferents in the glabrous skin of the hand may contribute to the modulation of the painful condition of mechanical allodynia (Nagi & Mahns, 2013). CT afferents exhibit maximal responsiveness to stimuli delivered at velocities between 1 and 10 cm/s, which corresponds closely with subjective reports of pleasantness. Their peak responsiveness occurs at a stroking velocity of approximately 3 cm/s, a range referred to as CT-optimal touch, then their firing rate decreases, resulting in an inverted U-shaped relationship between stroking speed and neuronal discharge frequency (Essick et al., 2010; Löken et al., 2009).

The subjective experience of pleasant touch is assumed to be an interoceptive submodality of CT-mediated tactile processing (Löken et al., 2009; Morrison et al., 2010; Olausson et al., 2002; Walker & McGlone, 2013; Crucianelli et al., 2022a). The perception of pleasant touch arises from a complex interplay between bottom-up sensory input and higher-order central processing mechanisms.

Prior experience, contextual cues, cognitive expectations, and concurrent inputs from other sensory modalities influence this processing. Thus, the interindividual variability in the shape and peak of the pleasantness response curve can be modulated by external factors, including stimulus temperature and multisensory integration, such as olfactory-tactile interactions (Watkins et al., 2021; Crucianelli et al., 2022a). CT fibres' responsiveness prefers tactile stimuli at temperatures approximating skin temperature (around 37°C), further emphasising the role of CT afferents in encoding socially relevant, affective touch (Ackerley et al., 2013). These touch characteristics are particularly prominent in affiliative tactile exchanges between individuals (Gallace & Spence, 2010). All these empirical findings support that touch encompasses functions beyond physical sensation, which is critical in social and emotional communication. Drawing upon the similarities between socially relevant touch and the preferred stimuli for CT activation, the "CT affective (or social) touch hypothesis" (Liljencrantz & Olausson, 2014) proposes that affective touch has social relevance and is associated with subjective experiences. Socially meaningful tactile interactions are thought to engage neural mechanisms that rely on a specialised organisational framework. In particular, C-tactile (CT) afferents potentially serve as a dedicated peripheral channel for conveying affectively salient tactile stimuli, such as those associated with affiliative or interpersonal physical contact (Morrison & Olausson, 2010; Liljencrantz & Olausson, 2014).

### 3.1.2. Affective touch and pain perception

"*Where there is sensation, there is pleasure and pain"*

*(Aristotle)*

The comprehensive perception of the body and its interaction with the inside and outside world results from integrating both exteroceptive and interoceptive signals.

Over recent decades, neuroscience has made substantial advances in elucidating exteroception, the way we perceive and interact with the external environment, through primary sensory systems, including somatosensory modalities, such as proprioception, which relates to the musculoskeletal system. Less is known about the interoceptive system. Interoception was initially conceptualised as the sensory processing of signals originating from the viscera, serving primarily reflexive and homeostatic functions, involving signals within the body (e.g., cardiac, respiratory, and digestive functions) (Sherrington, 1906; Sherrington, 1948). However, the more contemporary perspective, most notably articulated by Craig (2002), defines interoception as "a distributed integrative system that represents the physiological condition of the organism as a whole". It represents a distributed integrative system that incorporates information arising from multiple tissues, including not only the viscera but also somatic sources such as the skin (e.g., temperature, itch, pleasure from gentle touch, pain).

Furthermore, this multimodal integration encompasses learned associations, memories, and emotions within the total subjective representation of the body-state experience (Ceunen et al., 2016). One pivotal question in the study and in conceptualising interoception concerns whether it represents a singular, unified construct or a constellation of functionally distinct subcomponents. Contemporary evidence increasingly favours a modular framework, wherein interoceptive processes operate through partially independent parallel streams, reflecting the complex and multidimensional nature of internal bodily signal processing (Crucianelli et al., 2022a; Garfinkel et al., 2016). Following this multidimensional outlook, which processes can be included in the domain of interoception remains a matter of ongoing debate. Beyond the more traditional definitions of interoception, a contemporary reformulation defines it as the bidirectional communication between the brain and peripheral organs that gives rise to an integrated representation of the organism's internal physiological condition, encompassing the sensing, interpretation, integration, and regulatory processing of signals originating from within the body. It includes the descending body regulation component, encompassing not only

the peripheral and central nervous systems but also components of the vascular, endocrine, and immune systems (Chen et al., 2021).

The perception of interoceptive signals is associated with the activation of several brain regions, including the insular cortex, the somatosensory cortex, and the cingulate cortex. More specifically, the capacity to accurately detect one's own heartbeat is predicted by activity in the right anterior insula, a region also implicated in the processing of negative emotional states, such as anxiety (Critchley et al., 2004).

The insular cortex plays a central role in integrating this heterogeneous array of sensory inputs, ultimately contributing to the construction of the bodily self. It exhibits a rostro-caudal hierarchical organisation, wherein primary sensory inputs project to the posterior insula, processing gustatory, somatosensory, vestibular, and visceral information. These inputs are progressively integrated as they are transmitted to the mid and anterior insular regions (Craig, 2008). The anterior insula, in particular, serves as the highest level of integration and maintains strong reciprocal connections with the anterior cingulate cortex (ACC). Together, these structures form a core component of the emotional limbic network. Within this network, the anterior insula is implicated in the sensory perception and conscious awareness of internal states. At the same time, the ACC is involved in the motivational and behavioural expression of these experiences (Critchley, 2005). The anterior insula thus plays a fundamental role in integrating subjective bodily sensations and emotional experiences (Craig, 2008). In the interoceptive domain, skin serves as a unique sensory and social interface, simultaneously attuned to the body's internal state and the external environment.

Skin-mediated sensations have traditionally been classified as exclusively exteroceptive. Nevertheless, due to its intrinsic properties, the skin serves as a sensory organ that is extensively and directly exposed to both the internal and external environments of the body. Skin-derived signals may simultaneously convey interoceptive and exteroceptive information; thus, they can be acknowledged for their interoceptive significance, as they convey information highly relevant to internal regulation and the preservation of bodily integrity, particularly in the context of homeostatic control and affective regulation (Crucianelli & Ehrsson, 2023).

Interoceptive sensory modalities are transmitted through distinct neural pathways compared to exteroceptive ones. Specifically, C-afferent fibres are primarily responsible for interoceptive signals, whereas Aβ fibres mediate exteroceptive input (McGlone & Olausson, 2014; Crucianelli et al., 2022b). C-fibres are responsive to both nociceptive and affective stimuli: affective touch and cutaneous pain likewise convey information about the physiological condition of the skin and the body as a whole, consistent with their reconceptualisation as interoceptive stimuli under the revised definition of interoception (Craig 2003a, 2008; Fotopoulou &Tsakiris, 2017; Crucianelli et al., 2018).

This dual characteristic suggests that such signals may serve as integrative mediators between the internal and external environments of the body, thereby playing a key role in developing a unified and coherent bodily self-awareness (Crucianelli et al., 2016). This distinctiveness can emerge from partially overlapping neural mechanisms of pain and CT-optimal touch (affective touch) in an interactive model between affective touch and nociceptive processing within the somatosensory system (Meijer et al., 2022). CT afferents and nociceptive fibres project to the spinal dorsal horn's laminae (I/II) and ascend via the spinothalamic tract. This anatomical convergence supports the hypothesis of an inhibitory system in which pleasant tactile input may attenuate the transmission of nociceptive signals to ascending pathways, thereby preventing their cortical processing and reducing the subjective experience of pain. Additionally, a second proposed mechanism involves top-down modulation of pain perception, engaging cortical structures such as the insular cortex and the anterior cingulate cortex (ACC), which play a central role in the subjective appraisal of pain. It is still not disentangled whether this observed downregulation is a consequence of a bottom-up inhibitory process, where the suppression of nociceptive input at the spinal level leads to reduced cortical activation, or whether the modulation occurs directly within the insula and ACC (Meijer et al., 2022) (see Figure 3.2).

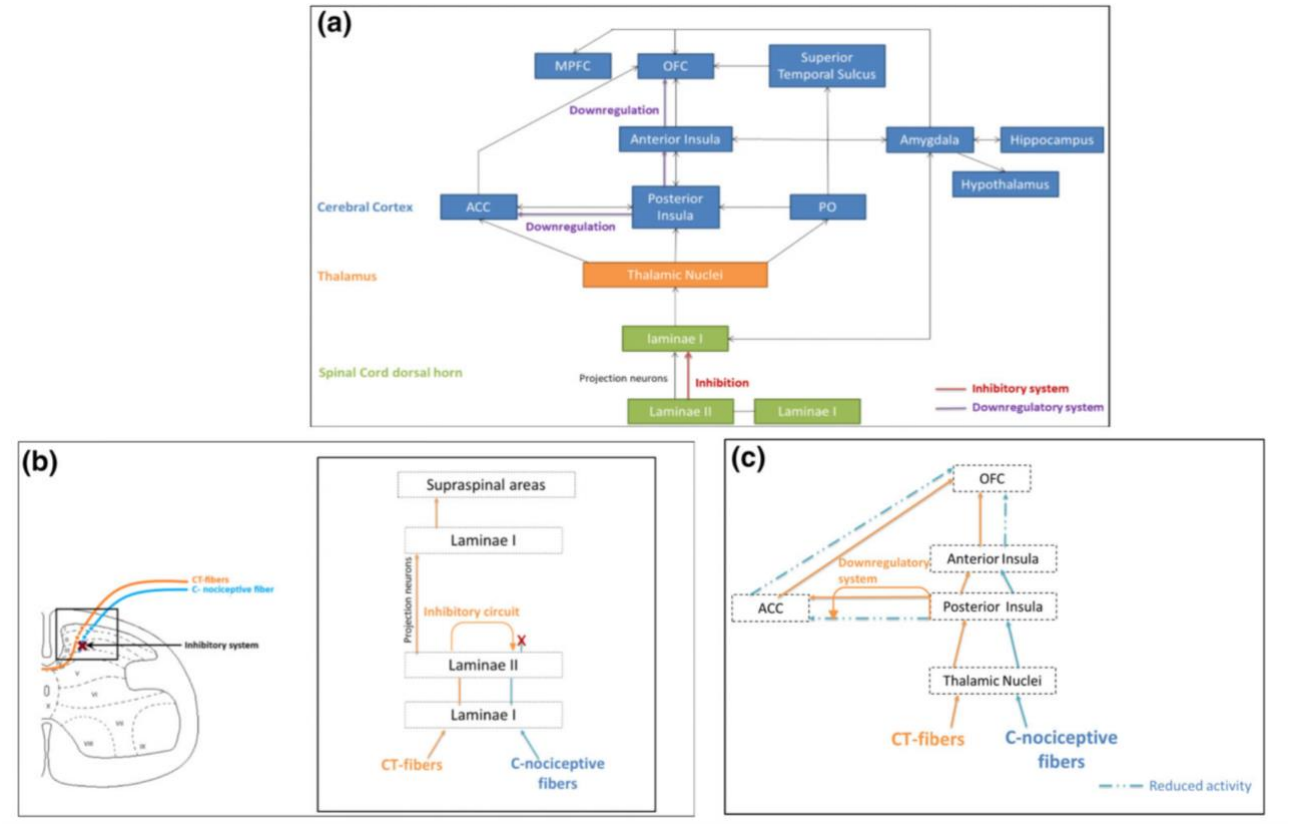


Figure 3.2: Schematic overview of the CT-afferent system, including the two ways of pain modulation (a); Dorsal horn inhibitory system (b); Cortical downregulatory system (c) (From Meijer et al., 2022).

Furthermore, the analgesic effect of affective touch is accompanied by increased oxytocin release during CT-optimal stimulation (Walker et al., 2017), indicating a neurochemical contribution to pain attenuation through social and affective touch. Also, given the established association between CT fibre activation and the perception of tactile pleasantness, it is plausible that the CT system contributes to pain attenuation via top-down mechanisms linked to pleasure-induced analgesia (Björnsdotter et al., 2010). Other research indicates that interpersonal touch, such as handholding, benefits well-being, including reductions in stress and acute pain (López-Solà et al., 2019). Moreover, the provision of social support via interpersonal touch correlates with decreased pain severity among individuals enduring chronic pain or cancer or those experiencing chronic pain in Parkinson's Disease (Goldstein et al., 2018; Meijer et al., 2024). Affective touch effectively reduces acute pain, while no unique trend exists in chronic pain conditions; many studies are growing the knowledge on this topic. It is assumed

that the structural and functional altered connectivity of brain regions, including the insula, ACC, and prefrontal cortex, is involved in pain processing.

Additionally, central sensitisation, a heightened state of excitability within the neurons of the spinal cord, and lowered thresholds for stimulus activation, are considered critical mechanisms in the development and maintenance of various chronic pain conditions, including fibromyalgia, musculoskeletal disorders, neuropathic pain, headache, and orofacial pain. Affective touch can interact with these disorders and has emerged as a potential non-pharmacological intervention for the management of chronic pain. A brief CT-optimal touch skin stroking resulted in a reduction in self-reported pain severity among individuals with various chronic pain conditions, including primary chronic pain, secondary musculoskeletal pain, and neuropathic pain (Di Lernia et al., 2020).

Furthermore, affective touch is a recognised factor in attenuating pain responses induced by a temporal summation of second pain protocols, which mimics spinal "wind-up"; the progressive increase in neuronal firing of dorsal horn neurons, usually deemed relevant for the functional evaluation of chronic syndromes. This effect reflects a neural mechanism by which the brain integrates repeated nociceptive input with affective regulatory processes associated with CT fibre activation. This modulation may reflect an interaction between pain processing and emotional regulation, mediated by the affective dimension of CT-optimal stimulation (Wakui et al., 2025). Notably, CT-optimal touch also appeared to alleviate symptoms in cases of central and peripheral neuropathic pain, possibly due to the association between CT fibre activation and tactile allodynia. Tactile allodynia is a common feature of neuropathic pain, characterised by painful sensations in response to normally innocuous stimuli such as light touch (Nagi et al., 2011). Given that CT-optimal touch consists of slow, gentle stroking, one might expect it to exacerbate allodynic responses. However, the study by Di Lernia et al. (2020) reported no such adverse effects. One possible explanation lies in the evidence that Aβ fibres, rather than CT fibres, are primarily responsible for mediating allodynia under central sensitisation conditions in the spinal cord's dorsal horn (Liljencrantz & Olausson, 2014). This fact may account for the absence of pain induction through CT-optimal stimulation and, importantly, supports the observed analgesic effects in chronic pain populations. Otherwise, CT-stimulation appears to be of no benefit in reducing pain intensity in individuals with complex regional pain syndrome (Habig et al., 2021).

Current research suggests that affective touch plays a modulatory role in influencing pain thresholds. In contrast, the influence of pain thresholds on the perception of affective touch has yet to be conclusively demonstrated. However, some results underline a bidirectional interaction between pain perception and affective touch in individuals with chronic pain, particularly those experiencing cutaneous allodynia. CT afferents predominantly terminate in the dorsal horn's inner layer of lamina

II, where their signals are processed by interneurons operating within local spinal circuits. Functional alterations in the interneurons within lamina II can amplify or alter CT fibre signals before transmission to ascending pathways, converting normally pleasant tactile sensations into painful experiences (Drew & MacDermott, 2009).
These findings tell the relationship between pain perception and affective touch, underscoring the potential utility of CT-optimal touch as a therapeutic modality for various chronic pain conditions, including those involving neuropathic mechanisms.

### 3.1.3. Embodied empathy for affective touch and pain

Affective touch and pain perception may reflect a complex interplay of personality traits, past and present experiences, and environmental factors.

Both fulfil their task of interoceptive stimuli within the bodily interactions that can be directly experienced or observed. In the second modality, empathy plays its role through an embodied simulation mechanism, wherein the brain replicates the observed state, enabling empathic resonance. This kind of empathy, observing the emotions, sensations, or actions of others, can elicit similar experiences in the observer. Mirror neurons were first discovered in the brains of macaque monkeys, where they were found to be active not only during the execution of goal-directed actions but also during the observation of those same actions performed by others (Di Pellegrino et al., 1992; Rizzolatti et al., 2001). This discovery has led to the hypothesis that a functionally analogous mirror neuron system may also be present in the human brain, especially for tactile events, which can lead to an embodied empathy (Schaefer et al., 2012). This visuotactile mirroring mechanism relies on the identified overlapping neural activation for tactile processing in the secondary somatosensory cortex (SII), along with a significant differentiation in the primary somatosensory cortex (SI), when someone observes intentional touch This somatosensory response may reflect a human predisposition to more strongly resonate with agents delivering intentional touch instead of passive or accidental contact with objects (Ebisch et al., 2008). Empathy for somatosensory experiences also concerns non-painful, affective touch and pain. Observing others in painful situations activates the anterior cingulate cortex, a key structure for the motivational–affective dimension of pain, suggesting a multisensory basis for vicarious pain and touch processing (Morrison et al., 2004; Downing, 2007). Two forms of empathy can be distinguished: an automatic, sensory-level resonance that involves mapping an observed sensory stimulus onto one's bodily representation. Another, a more complex form of empathy based on affective resonance, entails genuine emotional sharing (Avenanti et al., 2005). This second one may explain that the observer’s empathy modulated somatomotor responses to the pain of others.

Such findings support a strong link between empathic capacity and primary somatosensory cortex (SI) activation while observing nociceptive events (Avenanti et al., 2009).

In fact, the empathy for others' pain can activate a circularity of interactions between the sufferer and the witness of this pain. Given the influence of emotional factors on touch-induced analgesia, it is also plausible that the empathic disposition of the "toucher" may contribute to the modulation of pain. Understanding and attuning to another person's emotional state is a fundamental component of social touch. It may play a critical role in facilitating analgesic effects during interpersonal interactions. Additionally, during the pain with interpersonal touch experiment, brain-to-brain coupling in romantic partners, pain receivers, and pain observers is shown to be involved in interbrain synchrony, which facilitates pain mitigation. Furthermore, the magnitude of analgesia and the accuracy of the observer's empathy may be intertwined in touch-related analgesia (Morrison, 2016b; Goldstein et al., 2018). Social context, including the presence of others and the perceived level of empathy toward one's pain, significantly influences both subjective pain perception and autonomic responses to nociceptive stimuli. Individual differences in adult attachment further modulate these effects, shaping how social presence and perceived empathic engagement impact pain processing. Specifically, individuals with higher attachment anxiety report greater pain when they perceive empathy as low compared to high. In contrast, those with elevated attachment avoidance exhibit lower pain ratings when alone relative to conditions involving social observation (Sambo et al., 2010). Evidence from laser-evoked potential studies indicates that autonomic and cortical responses to pain are diminished in the presence of another person. Notably, affective support from a romantic partner appears to modulate pain at early cortical stages, as reflected in reductions in the N1 peak amplitude. Since the N1 component is considered a pre-perceptual sensory response, arising largely outside conscious awareness and involving the operculoinsular and primary somatosensory cortices (Garcia-Larrea et al., 2003; Valentini et al., 2012), these findings suggest that affective touch can decrease the sensory salience of impending noxious stimulation, potentially providing a mechanism for social modulation of pain at the earliest stages of cortical processing (Krahé et al., 2016; von Mohr et al., 2018). Visuotactile mirroring also involves affective touch; observing touch engages neural systems implicated in social and affective processing, with potential implications for pain and empathy. Viewing others being caressed at CT-optimal velocities elicits activity in the posterior insular cortex, a region associated with affective touch and interoceptive integration, similar to when touch is directly experienced (Björnsdotter & Olausson, 2011; Ciaunica et al., 2021).

Additionally, ratings of vicarious affective touch align with the velocity tuning of CT afferents (Walker et al., 2017). Observing affective touch reduces corticospinal excitability, suggesting a motor cortex selective sensitivity to affective, CT-optimal tactile stimuli, potentially prioritising

somatosensory simulation over motor simulation when processing observed touch. Additionally, the correlation between emotional awareness and motor resonance underscores the connection between interoceptive awareness and the processing of vicarious touch experiences (Butti et al., 2024). Also, social touch functions as a stress protector, modulating physiological responses and affiliative behaviour through distinct neural pathways tuned to affective contact (Morrison, 2016b). Within this framework, affective touch and its vicarious processing contribute to social modulation of pain and emotion, complementing findings that direct affective touch can attenuate pain and that attachment style influences the integration of social and somatosensory signals (Sambo et al., 2010; Krahé et al., 2016). Together, these lines of research support a model in which both direct and observed affective touch engage overlapping brain mechanisms that shape interpersonal experience and potentially modulate pain perception. In conclusion, we can state that direct and vicarious responses to affective touch and pain are not purely automatic or bottom-up; they are also modulated by top-down cognitive processes, such as prior expectations, emotional context, the social or moral evaluation of the target, and the perspective from which the experience is observed.

### 3.1.4. Aim of the research

A substantial body of research has investigated pain and affective touch separately, either in direct experience or in an observed (vicarious) modality. Additionally, previous works have focused on the potential therapeutic effect of affective and its regulatory role in pain perception. Nevertheless, only a few studies addressed their focus on the opposite direction and their interplay.

The primary objective of the present study is to assess pain and affective touch perception within the same individuals, compare their responses across direct and observed conditions, and explore the potential mutual influence between them.

Two main aims of the project are:

I. To compare the perception of affective touch in direct versus observed (vicarious) stimulation modalities.
II. To evaluate whether individual differences in pain perception and empathy for others' pain modulate the perception of affective touch when experienced firsthand and when observed.

Adopting a biopsychosocial framework, the study examines how variations in direct and vicarious pain perception may influence affective touch processing. These findings may hold significant implications for clinical practice, offering insights to optimise psychological and physical support strategies employed by healthcare professionals and others involved in pain management (Smit et al., 2024).

Hypothesised Outcomes

The following hypotheses are proposed:

- Affective touch is perceived as significantly more pleasant than neutral (non-affective) touch, in line with current literature (Crucianelli et al., 2013; Löken et al., 2009; Meijer et al., 2022).
- Affective touch is perceived as pleasant, even when observed in others, confirming previous research; however, it is experienced as more pleasant and vivid when experienced directly. This would support the hypothesis that direct affective experience is associated with greater perceptual intensity.
- Individual differences in pain threshold and empathy for others' pain will significantly modulate the perception of affective touch in sufferers of chronic pain, whether in direct or vicarious modalities.

The findings may contribute to a deeper understanding of complex somatosensory responses and their interrelations, with potential applications in research and clinical settings.

This research project consists of two identical experiments, the first (1) conducted on the general population, the second (2) on chronic migraine patients of the Headache Centre-Neuroalgology Department of IRCCS Foundation "Carlo Besta" Neurological Institute of Milan, Italy.

Experiments 1 and 2 received ethical approval from the Local Committee and were conducted in accordance with the Declaration of Helsinki. All participants provided informed consent before participating in the study. The procedures for both experiments are identical and will be detailed only in the first experiment.

## 3.2. Experiment 1: Healthy population

### 3.2.1. Materials and Methods

#### *3.2.1.1. Participants*

A priori power analyses were conducted using G*Power (Faul et al.,2007) to determine the minimum sample size of thirty-five participants, based on Repeated Measures Analysis of Variance (ANOVA – *within factors*), with an Effect Size F= 0.25; Alpha Error Level: p= 0.05; Statistical Power= 0.80, Actual Power= 0.80, Correlation Among Measures: 0.25, as suggested for exploratory studies.

Thirty-seven healthy volunteers participated in this experiment (mean age: 26 ± 6 years; age range: 20-51 years; 29 female). All of them self-declared they did not suffer from any of the following diagnosed conditions, as exclusion criteria:
Neuropathic pain, chronic migraine, severe and documented medical or psychiatric conditions, epilepsy, sensory abnormalities such as multiple sclerosis and peripheral neuropathy, abnormal cutaneous perception or dermatological disease (Ashkenazi et al., 2007).

*3.2.1.2. Procedure*

Upon arrival in the laboratory room, participants were asked to sit comfortably at a table, 50 cm away from a monitor, and connect to a computer.
They were to complete a ***psychometric assessment*** **(first phase)** (Figure 3.3a) consisting of the self-report questionnaires through the means of the Qualtrics software:

(iv) The Beck Depression Inventory (BDI-I) and State-Trait Anxiety Inventory (STAI Y1,2) to assess depressive and state-trait anxiety symptoms (Beck et al., 1996; Spielberger, 1983)
(v) The Allodynia Symptom Checklist-12 (ASC-12), adapted version, to evaluate the presence of Cutaneous allodynia in daily life (Lipton et al., 2008)
(vi) The Multidimensional Assessment of Interoceptive Awareness (MAIA), to measure interoception (Mehling et al., 2012)
(vii) The Social Touch Questionnaire (STQ) to consider the attitude toward the social touch, beyond the experimental setting (Wilhelm et al., 2001)

Additionally, demographic information, including age, self-declared gender identity, and the presence of pain conditions, was collected.

Then, participants underwent the ***pain perception assessment*** **(second phase)** to assess vicarious and direct pain perception.
The Vicarious Pain Questionnaire (VPQ) (Grice-Jackson et al., 2017; Ward & Li, 2022) (www.youtube.com/channel/UCT8goTgWGRsu14NjVaPCSGw/videos) evaluated the features of bodily pain perception while watching videos of mild-pain scenes. After viewing each video, participants were asked to report their subjective experience. They were required to indicate whether they had experienced any bodily pain sensation during the video (yes/no response). In case of affirmative response, three additional questions were presented to portray the vicarious pain experience: (1) the perceived intensity of pain, assessed using a 10-point Likert scale (1 = very mild pain, 10 = extremely intense pain); (2) the pain localization; (3) the selection of adjectives best

describing the vicarious pain experience, chosen from a list derived from the McGill Pain Questionnaire (Melzack, 1975).

Subsequently, the subjective thresholds of perception for tactile (t) and painful (T) stimuli were determined by administering electrical tactile stimuli of increasing intensity using the Digitimer DS7A stimulator (Parhizgar & Ekhtiari, 2010). Two Ag/AgCl electrodes were positioned on the ventral side of the left forearm and laid on the table at a distance from the wrist to the elbow equal to half the distance between the tip of the middle finger and the wrist line.

The stimulation intensity was calibrated using an ascending method, starting from 0.5 mA and increasing in steps of 0.5 mA of continuous current. Each stimulus was 1 second long, with a square pulse of 500 μs duration delivered at a frequency of 1 Hz.

Participants had to identify and rate the perceived intensity of each stimulus using an 11-point Numerical Rating Scale (NRS) ranging from 0 to 10. Number 0 corresponded to a no-pain first tactile sensation perceived (tactile threshold = t), 1 represented the beginning of a painful feeling stimulus (pain threshold = T), and 10 represented an unbearable pain (Camerone et al., 2021). The procedure ended when the participants' rating reached the pain threshold. The pain sensation the participant perceived was comparable to a low-intensity pain.

The complete procedure was run three times, and the participants' pain thresholds were calculated as the average of the three tactile and pain threshold intensities.

From this, tactile stimuli were defined as non-unpleasant and non-painful (equal to Tx0.5); unpleasant and painful (equal to T x 1,5, T x 1,6, T x 1,7, T x 1,8, T x 1,9, and T x 2).

For the assessment of tactile perception of neutral and painful stimuli, six stimuli perceived as clearly non-unpleasant (TX0.5) and six stimuli perceived as unpleasant (ranging from TX1.5 to TX2) were delivered by the Digitimer in random order. Firstly, the participants were asked to evaluate the feeling of the tactile sensation, responding with a dichotomic "yes or no". Then, similarly to the previous part of this experimental phase, participants reported the intensity of the tactile stimulus on an 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (the most intense pain imaginable). The entire procedure must be repeated if the participant rated tactile painful stimuli lower than 2. This further step guaranteed that the accurate distinction between painful and non-painful tactile perception was respected.

During this phase, participants listened to white noise through headphones to minimise the influence of the Digitimer's noise on the tactile stimulation (Figure 3.3b).

The **tactile affectivity assessment** presented the main experimental task **(third phase).** It consisted of two sessions, direct and vicarious (observed), respectively, each comprising twelve 10-

second tactile stimuli in a counterbalanced order, aimed at assessing the perception of pleasantness and vividness in the tactile experience.

The experimenter marked the 21 cm long stroking area, delimited by marks spaced 3 cm apart, on the hairy skin of the participants' left forearms with a washable marker to perform the direct touch session. The whole forearm width minimises habituation and CT fibres fatigue (Crucianelli et al., 2013; Vallbo et al., 1999). The experimenter was trained to deliver the touch at the exact speeds using a headphone connected to a metronome mobile app (Fidanza et al., 2021).

Within each session, the twelve stimuli were delivered, in random order, at different speeds: six CT-optimal (affective touch, AT): three stimuli at 3 cm/s; three stimuli at 6 cm/s, and six not CT-optimal (Non-affective touch, NAT):18 cm/s and 30 cm/s. (Ciaunica et al., 2021; Meijer et al., 2022a; Meijer et al., 2022b).

Before undergoing the tactile assessment, each participant, regardless of the assigned session order, underwent 5-second AT (6 cm/s) and NAT (30 cm/s) stimulation to familiarise themselves with the tactile sensations they would experience during the experiment.

In the direct session, the experimenter delivered the touch in the proximal-to-distal direction using her hand at four different speeds: CT-optimal (3 cm/s and 6 cm/s) and non-CT-optimal (18 cm/s and 30 cm/s).

In the vicarious trials, participants were asked to indicate their gender identity preference, which was used to select either a female or male arm video and watch 10-second videos that replicated the touches they had experienced directly.

Each participant received a total of twenty-four trials, divided into two sessions of twelve trials each. The order of the two sessions was randomised across participants. After each trial, participants used an 11-point Likert scale to judge the pleasantness (0 = extremely unpleasant, 10 = extremely pleasant) and vividness (0 = not vivid at all, 10 = extremely vivid) of their experience of direct and vicarious tactile sensations (Figure 3.3c).

The total duration of the experiment was approximately 60 minutes.


Figure 3.3: Schematic representation of the study procedure: (a) 1° phase: psychometric assessment; (b) 2° phase: direct and vicarious pain assessment; (c) 3° phase: direct and vicarious affective touch sessions in randomised order.

### *3.2.1.3. Design and data analysis*

Demographic and Mood Analysis

Demographic data were used to attest to the sample's psychometric features.

Also, we used the BDI-I and STAI Y1,2 questionnaires to assess participants' proneness to depressive and anxious mood.

The STQ and ASC-12 scores clarified experimental results, considering the daily attitude toward the social touch and the perception of neutral touch as painful, respectively.

MAIA evaluated the interoception, the field in which Affective touch and pain perception may play their role.

We used these data to deepen our understanding of the interaction pattern between pleasantness and pain perception.

Pain Perception Analysis

Pain perception assessment evaluated the direct pain using electrical stimuli administered by Digitimer. A Numerical Rating Scale (NRS) valued the pain responses to the six painful stimuli; the mean of these answers identified the variable Direct Pain: DP.

From the vicarious pain assessment, a quantitative measure of vicarious pain (VPQ_N), equal to the total number of pain responses across 16 videos and the average pain intensity reported (VPQ_INT) were estimated (Botan et al., 2018).

Main analyses: Tactile Affectivity

The tactile affectivity task of the third phase of the experiment had a 4 (Velocity: AT = CT-optimal 3 and 6 cm/s vs. NAT CT-non-optimal 18 and 30 cm/s) X 2 (Session: direct vs. vicarious) factorial design. The dependent variables evaluated were the pleasantness and vividness of the touch. Participants had to rate the pleasantness and vividness of tactile stimuli presented in both direct and vicarious sessions. The first two repeated-measures analyses of variance (ANOVAs) were conducted to assess the perceived pleasantness of AT and NAT velocities in direct and vicarious modality, exploring each possible condition and comparing the results to the current literature.

Then, the pleasantness and the vividness scores of the two AT (3 and 6 cm/s) and the two NAT (18 and 30 cm/s) velocities were averaged to obtain one value of pleasantness or vividness for AT/CT-optimal and one value for NAT/CT-non-optimal touch, which were then used to run RM ANCOVA, adding direct and observed pain perception variables as covariates. Direct pain perception resulted from the average mean of responses to noxious stimuli delivered via the Digitimer device (DPP). The VPQ_N and VPQ_INT variables were applied to measure vicarious pain. The Huynh-Feldt correction was applied in cases where sphericity was violated. Bonferroni correction for the pairwise comparisons was used as required.

Correlation Analysis: interplay between tactile affectivity and pain perception

A correlation matrix was used to deepen the relationships among the individual features, pain and AT perception.

### 3.2.2. Results

Demographic and Mood Assessment

Thirty-seven participants completed all the questionnaires, and the datasets had no missing values.

Allodynia Symptom Checklist-12 (ASC-12): (M = 1.41, SD = 2.37, range 0-10). Ten participants (27%) scored above the clinical threshold (≥3), reporting symptoms compatible with mild to moderate forms of allodynia, even in the absence of a diagnosis of a pain condition. These unexpected findings suggest that somatosensory sensitisation may exist even within non-clinical populations (Burstein et al., 2010).

Multidimensional Assessment of Interoceptive Awareness (MAIA): The MAIA subscales *Noticing* (M = 3.78, SD = 0.97), *Not-Distracting* (M = 3.48, SD = 0.77), *Not-Worrying* (M = 3.14, SD = 0.97) and were consistent with mean score values (Mehling et al., 2012).

However, *Self-Regulation* (M = 2,13, SD = 1.13), *Body Listening* (M = 2.15, SD = 1.15), *Attention Regulation* (M = 2.65, SD = 0.88), *Trusting* (M = 2.88, SD = 0.33), subscales scored a little lower-than-mean scores, reflecting some reduced capacity for attention-behavioural regulation and trust in one's own bodily sensations.

Beck Depression Inventory (BDI-I) scores (M= 11.2, SD = 8.49) showed a proneness to mild depressive symptomatology, according to the criteria proposed by Beck et al. (1961).

State-Trait Anxiety Inventory evaluated for state anxiety (STAI-Y1: M = 40.1, SD = 12.2) and state anxiety (STAI-Y2) and M = 48.1 (SD = 11.0), suggesting a moderate predisposition toward anxious activation as a situational response and a dispositional trait. (Spielberger et al., Italian adaptation, 1983).

Social Touch Questionnaire (STQ) scores (M = 45.2, SD = 11.6, range = 20-72) did not indicate that participants avoided social contact to an extreme degree.

Pain Perception

The Pain Threshold (T) score was equal to: M = 2.93, SD = 2.48, range 0.63-11.8

The Direct Pain value was equal to: M = 4.20, SD = 1.73, range 1.67-8.67

The number of Vicarious Pain responses (VPQ _N) was equal to: M = 7.11, SD = 4.36, range 0-14.

Among the participants, some reported vicarious pain watching the videos of VPQ: VPQ-Responder (N = 31; 83.8%), while the others were classified as VPQ NO-Responder (N = 6; 16.2%)

The Intensity of Vicarious Pain (VPQ_INT) perceived was equal to: M = 3.70, SD = 2.65, range 0-8.38.

Tactile Affectivity

Analyses were performed using Jamovi Software (version 2.3.28). First, the AT and NAT pleasantness and vividness mean intensity ratings were tested for normal distribution using the Shapiro-Wilk test. The test reported some significance for the variables (Vicarious NAT Vividness p=.022; AT vicarious pleasantness p=.041). According to Norman (2010), a parametric test (ANOVA) can be performed to analyse measurements based on the Likert scale, although it violates the normality of the data.

Pleasantness

A repeated-measures ANOVA (ANOVA RM) evaluated the effects of touch conditions: [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 4 (AT = 3 and 6 cm/s; NAT = 18 and 30 cm/s) on

perceived pleasantness. Huynh-Feldt corrections were applied because of the violated assumptions of Sphericity (Mauchly's test: velocity factor $p < .001$; session*velocity" $p= .021$).

A main effect of *Velocity* emerged [$F(1.39, 50.21) = 57.91$, $p < .001$, $\eta^2_p = 0.617$].

A main effect of *Session* was not found [$F(1, 36) = 2.67$, $p = .11$, $\eta^2_p = 0.069$].

The interaction between *Session*Velocity* was significant [$F(2.76, 99.21) = 9.04$, $p < .001$, $\eta^2_p = 0.201$].

Bonferroni post hoc test comparisons between *velocities* revealed that slow AT velocities (3-6 cm/s) were significantly more pleasant than the faster NAT velocities (18-30 cm/s).

Specifically, AT 3 cm/s ($M = 6.00$, $SE = 0.35$) was more pleasant than NAT 18 cm/s ($M = 3.51$, $SE = 0.25$): [Mean difference = 2.49, $SE = 0.33$, ($t(36) = 7.56$, $p < .001$)] and NAT 30 cm/s ($M = 2.96$, $SE = 0.24$): ($t(42) = 8.83$, $p < .001$), [Mean difference = 3.04, $SE = 0.38$, ($t(36) = 8.06$, $p < .001$)].

The difference between AT 6 cm/s and NAT 18 cm/s was also significant [Mean difference = 2.19, $SE = 0.28$, ($t(36) = 7.76$, $p < .001$)], as was the difference between AT 6 cm/s and NAT 30 cm/s [Mean difference = 2.74, $SE = 0.13$, ($t(36) = 8.11$, $p < .001$)]. Additionally, NAT 18 cm/s was significantly rated more pleasant than NAT 30 cm/s [Mean difference = 0.55, $SE = 0.13$, ($t(36) = 4.31$, $p < .001$)].

No significant difference between AT 3 cm/s and 6 cm/s was found [Mean difference = 0.30, $SE = 0.16$, ($t(36) = 1.90$, $p = .397$), suggesting that both velocities were perceived as highly pleasant and comparable.

Following the significant interaction between *Session*Velocity,* the Bonferroni post hoc test revealed that perceived pleasantness in direct and vicarious modalities decreased progressively with the increase in velocity. The AT 3 cm/s was rated as the most pleasant compared to direct and vicarious NAT 18 cm/s [Mean difference = 2.02, $SE = 0.34$, ($t(36) = 5.86$, $p < .001$); Mean difference = 2.66, $SE = 0.31$, ($t(36) = 8.65$, $p < .001$)] and to direct and vicarious NAT 30 cm/s [Mean difference = 2.45, $SE = 0.40$, ($t(36) = 6.13$, $p < .001$); Mean difference = 3.33, $SE = 0.35$, ($t(36) = 9.55$, $p < .001$)].

A similar pattern defines the other CT-optimal velocity AT 6 cm/s compared to direct and vicarious NAT 18 cm/s [Mean difference = 1.80, $SE = 0.31$, ($t(36) = 5.71$, $p < .001$); Mean difference = 2.45, $SE = 0.31$, ($t(36) = 7.96$, $p < .001$)] and to NAT 30 cm/s [Mean difference = 3.12, $SE = 0.34$, ($t(36) = 9.10$, $p < .001$)].

Notably, there was no significant difference between AT 3 cm/s and AT 6 cm/s in direct and vicarious sessions [Mean difference = 0.21, $SE = 0.21$, ($t(36) = 1.03$, $p =1.00$)]; [Mean difference = 0.39, $SE = 0.23$, ($t(36) = 1.65$, $p =1.00$)], highlighting an uniformity of pleasantness perception of 3 cm/s and 6 cm/s CT-Optimal velocities also comparable in the actual and observed mode.

The administration modality affects CT-non-optimal velocities, specifically NAT 18 cm/s and NAT 30 cm/s. NAT 18 cm/s was perceived as more pleasant in the direct condition than the vicarious one sessions [Mean difference = 0.65, SE = 0.15, (t(36) = 4.36, p =.003)], a similarly pattern for NAT 30 cm/s [Mean difference = 0.88, SE = 0.22, (t(36) = 3.94, p =.01)]. These findings suggest that watching NAT is assumed less pleasant than when it is experienced on one's skin.

Even if the pleasantness of direct NAT 18 cm/s and NAT 30 cm/s was similar [Mean difference = 0.43, SE = 0.16, (t(36) = 2.61, p =.37)], a significant difference was found between direct NAT 18 cm/s and vicarious NAT 30 cm/s [Mean difference = 1.31, SE = 0.18, (t(36) = 7.4, p < .001)] (see Table 3.1).

Pleasantness: comparison Velocity ∗ Session

| | | | | 95% Confidence Interval | |
|---|---|---|---|---|---|
| Session | Velocity | Mean | SE | Lower | Upper |
| Direct | 3 cm/s | 5.86 | 0.353 | 5.14 | 6.57 |
| | 6 cm/s | 5.64 | 0.341 | 4.95 | 6.33 |
| | 18 cm/s | 3.84 | 0.270 | 3.29 | 4.39 |
| | 30 cm/s | 3.41 | 0.311 | 2.78 | 4.04 |
| Vicarious | 3 cm/s | 6.15 | 0.391 | 5.36 | 6.95 |
| | 6 cm/s | 5.77 | 0.348 | 5.06 | 6.47 |
| | 18 cm/s | 3.19 | 0.252 | 2.68 | 3.70 |
| | 30 cm/s | 2.52 | 0.211 | 2.10 | 2.95 |

Table 3.1: Estimated marginal means of pleasantness in the interaction between Velocity (AT: 3 cm/s and 6 cm/s; NAT: 18 cm/s and 30 cm/s) and Session (Direct vs Vicarious).

These data indicate that stroking velocity and administration modality significantly modulate the perception of touch pleasantness. Slow AT velocities were consistently rated as more pleasant across both modalities. On the contrary, NAT velocities showed a different impact on pleasantness depending on the session: the direct touch maintained a relatively constant level of pleasantness (see Figure 3.4).

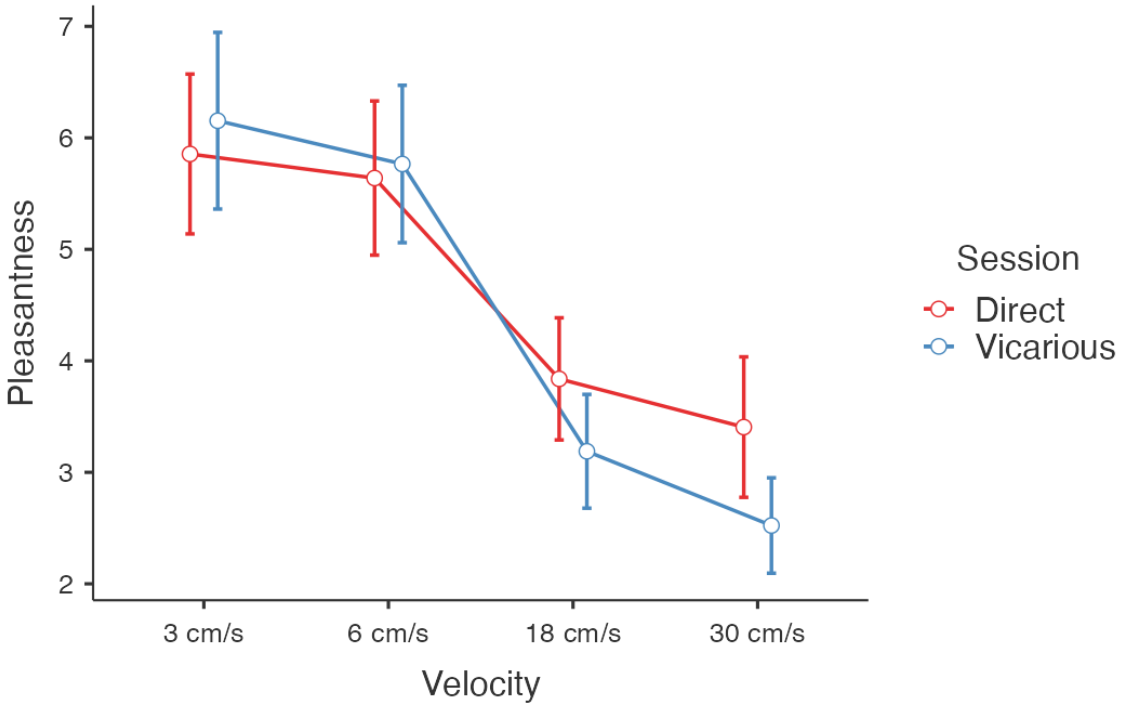


Figure 3.4: Graphic representation of perceived pleasantness of touch as a function of session type (Direct vs. Vicarious) and stroking velocity (AT: 3 cm/s and 6 cm/s; NAT: 18 cm/s and 30 cm/s). Slow AT velocities (3-6 cm/s) were significantly more pleasant than the faster NAT velocities (18-30 cm/s) (all $p < .001$). Direct and vicarious AT 3 cm/s were perceived as more pleasant compared to direct and vicarious NAT 18 cm/s ($p < .001$) and NAT 30 cm/s ($p < .001$). Direct and vicarious AT 6 cm/s was rated more pleasant than direct and vicarious NAT 18 cm/s ($p < .001$) and NAT 30 cm/s ($p < .001$). While perceived pleasantness between AT 3 cm/s and AT 6 cm/s in direct and vicarious sessions was similar, NAT 18 cm/s ($p = .003$) and NAT 30 cm/s velocities were perceived more pleasant in the direct session than in the vicarious one ($p = .01$).

Pleasantness and Pain Perception

Three repeated-measures ANCOVA (RM ANCOVA) evaluated the probability of the influence of direct or vicarious pain perception on the pleasantness. As the AT pleasantness perception is the main object of the analysis, and the two CT-Optimal cms/s and 6 cms/s velocities showed significant similarities, for the following analyses, we considered the overall AT (mean of 3 cms/s and 6 cms/s velocities ) and NAT (mean of 18 cms/s and 30 cm/s velocities) tactile experience.

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding VPQ Intensity representing a measure of empathy to others' pain perception, i.e. vicarious pain perception (VP_INT: M=3.70, SD=2.65) as the continuous covariate, to evaluate the effects on perceived pleasantness.

A main effect of *Velocity* was found [$F(1, 35) = 14.86$, $p < .001$, $\eta^2_p = 0.298$]. Bonferroni Post hoc test comparison revealed that AT (M=5.85, SE=0.32) was significantly perceived as more pleasant than the NAT (M=3.24, SE=0.24), [Mean difference = 2.61, SE = 0.31, ($t(35) = 8.28$, $p < .001$)].
A main effect of *Session* was not found [$F(1, 35) = 1.97$, $p = .169$, $\eta^2_p = 0.053$].
A significant interaction between *Session*Velocity* emerged [$F(1, 35) = 15.90$, $p < .001$, $\eta^2_p = 0.312$] (see Figure 3.5).

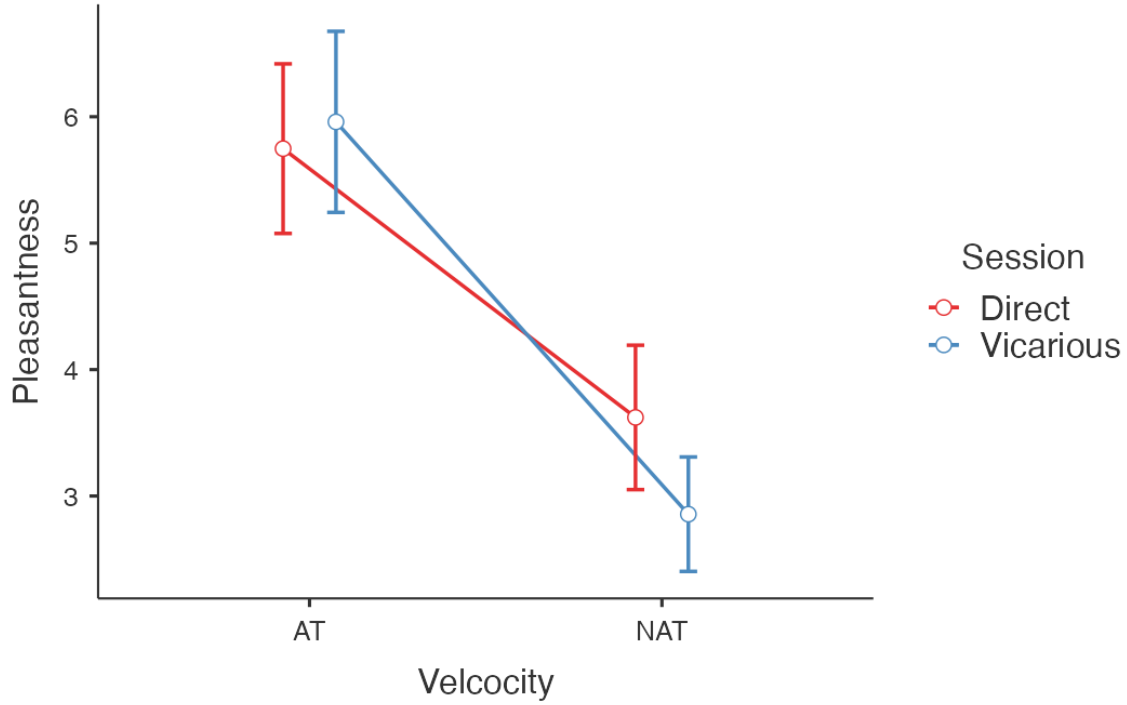


Figure 3.5: Graphic representation of perceived pleasantness of affective touch (AT) and no-affective touch (NAT) in function of session type (Direct vs. Vicarious). AT was significantly perceived as more pleasant than the NAT in both direct and vicarious modalities ($p < .001$).

The Bonferroni Post hoc test confirmed that pleasantness in both direct and vicarious modalities decreased progressively with an increase in velocity.
The direct AT (M=5.75, SE=0.33) was rated more pleasant than direct NAT (M=3.62, SE=0.28) and vicarious NAT (M=2.86, SE=0.22)
Likewise, vicarious AT (M = 5.96, SE = 0.35) was rated as more pleasant than both direct NAT and vicarious NAT. These data support the superiority of AT pleasantness, which also does not differ

between the direct and vicarious administration. On the contrary, NAT pleasantness was greater in the direct session than in the vicarious one (See Table 3.2).

Pleasantness: comparison Session ∗ Velcocity

| Comparison | | | | | Mean Difference | SE | df | t | $p_{bonferroni}$ |
|---|---|---|---|---|---|---|---|---|---|
| Session | Velcocity | | Session | Velcocity | | | | | |
| Direct | AT | - | Direct | NAT | 2.126 | 0.329 | 35.0 | 6.471 | < .001 |
| | | - | Vicarious | AT | -0.212 | 0.232 | 35.0 | -0.913 | 1.000 |
| | | - | Vicarious | NAT | 2.891 | 0.302 | 35.0 | 9.572 | < .001 |
| | NAT | - | Vicarious | AT | -2.338 | 0.408 | 35.0 | -5.728 | < .001 |
| | | - | Vicarious | NAT | 0.765 | 0.163 | 35.0 | 4.687 | < .001 |
| Vicarious | AT | - | Vicarious | NAT | 3.103 | 0.337 | 35.0 | 9.212 | < .001 |

Table 3.2: Estimated marginal means of pleasantness in the interaction between Velocity (AT vs NAT) and Session (Direct vs Vicarious)

No effect of the interaction between *VP_INT* and *Session* [F(1, 35) = 0.33, p = .569, $\eta^2_p$ = 0.009)] or *Velocity* [[F(1, 35) = 1.30, p = .262, $\eta^2_p$ = 0.036] or among *VP_INT* * *Session*Velocity* [F(1, 35) = 2.53, p = .121, $\eta^2_p$ = 0.067] was found.

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding VPQ_N representing a measure of empathy to others' pain perception, specifically the number of times participants perceived bodily pain while watching the VPQ videos (VP_N: M=7.11, SD=4.36) as the continuous covariate, to evaluate the effects on perceived pleasantness.

A main effect of *Velocity* was found [F(1, 35) = 11.44, p = .002, $\eta^2_p$ = 0.246]. Bonferroni Post hoc test comparison revealed that AT (M=5.85, SE=0.32) was significantly perceived as more pleasant than the NAT (M=3.24, SE=0.24), [Mean difference = 2.61, SE = 0.31, (t(35) = 8.28, p < .001)].
A main effect of *Session* was not found [F(1, 35) = 0.62, p = .435, $\eta^2_p$ = 0.018].
A significant interaction between *Session*Velocity* emerged [F(1, 35) = 12.67, p = .001, $\eta^2_p$ = 0.266]. The Bonferroni Post hoc test confirmed that pleasantness in both direct and vicarious modalities decreased progressively with an increase in velocity, consistent with the previous RM ANCOVA results.

These RM ANCOVA results suggest that individual sensitivity to vicarious pain perception did not influence the perception of tactile pleasantness.

A last RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding Direct Pain Perception (Direct Pain), which represents a measure of direct pain perception (DP: M=4.20, SD=1.7) as the continuous covariate, to evaluate the effects on perceived pleasantness.

No main effect of *Velocity* [$F(1, 35) = 3.75$, $p = .061$, $\eta^2_p = 0.097$] or *Session* [$F(1, 35) = 0.044$, $p = .834$, $\eta^2_p = 0.001$] was found. Neither the interaction effect between *Session*Velocity* emerged [$F(1, 35) = 2.65$, $p = .11$, $\eta^2_p = 0.071$], meaning that the effect of velocity on pleasantness was comparable across the two delivery modes. Also, no significant interaction effect between *DP* and *Session* [$F(1, 35) = 0.18$, $p = .671$, $\eta^2_p = .005$] or *Velocity* [$F(1, 35) = 1.65$, $p = .206$, $\eta^2_p = .045$] or among *DP * Session*Velocity* [$F(1, 35) = 0.004$, $p = .949$, $\eta^2_p = .000$] was found.

These results suggest that individual threshold sensitivity to direct painful stimuli does not affect the perception of tactile pleasantness.

Vividness

A repeated-measures ANOVA (ANOVA RM) evaluated the effects of touch condition [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 4 (AT = 3 and 6 cm/s; NAT = 18 and 30 cm/s)] on perceived vividness. Huynh-Feldt corrections were applied because of the violated assumptions of Sphericity (Mauchly's test: velocity factor $p < .001$; session*velocity" $p < .001$).

A main effect of *Session* emerged, [$F(1, 36) = 29.92$, $p < .001$, $\eta^2_p = 0.454$].

A main effect of *Velocity* was not found [$F(1.36, 48.95) = 0.948$, $p = 0.363$, $\eta^2_p = 0.026$].

The interaction between *Session*Velocity* was significant [$F(1.97, 70.79) = 3.31$, $p = .043$, $\eta^2_p = 0.084$] (See Figure 3.6).

Bonferroni post hoc test comparisons between *sessions* showed that the direct touch condition (M = 6.64, SE = 0.33) was significantly more vivid than the vicarious (M = 4.61, SE = 0.32) [Mean difference = 2.03, SE = 0.37, ($t(36) = 5.47$, $p < .001$)].

Following the significant interaction between *Session*Velocity, it was* suggested that the perceived vividness increases progressively with an increase in velocity. The direct NAT at 30 cm/s was rated as the most vivid touch. Else, the Bonferroni post hoc test revealed no significant difference in vividness among all the velocities within the observed or direct sessions (all $p > .05$).

Significant differences were found comparing direct and vicarious modalities: the direct NAT 30 cm/s was rated as the most vivid touch compared to the vicarious NAT 30 cm/s [Mean difference = 2.50,

SE = 0.43, (t(36) = 5.76, p < .001); NAT 18 cm/s [Mean difference = 2.62, SE = 0.42, (t(36) = 6.24, p < .001); AT 6 cm/s [Mean difference = 2.38, SE = 0.43, (t(36) = 5.48, p < .001)]; and AT 3 cm/s [Mean difference = 2.47, SE = 0.48, (t(36) = 5.12, p < .001)]. Similarly, the direct NAT 18 cm/s was rated more vivid compared to the vicarious NAT 18 cm/s [Mean difference = 2.20, SE = 0.43, (t(36) = 5.16, p < .001); NAT 30 cm/s [Mean difference = 2.08, SE = 0.44, (t(36) = 4.71, p = .001); AT 3cm/s [Mean difference = 2.04, SE = 0.48, (t(36) = 4.29, p = .004)]; and AT 6 cm/s [Mean difference = 1.95, SE = 0.44, (t(36) = 4.28, p < .002)].

An analogous tendency was observed for the AT direct touches compared to the vicarious ones. Direct AT 3 cm/s resulted more vivid than vicarious AT 3 cm/s [Mean difference = 1.63, SE = 0.41, (t(36) = 3.94, p = .010)]; AT 6 cm/s [Mean difference = 1.54, SE = 0.43, (t(36) = 3.57, p = .029)]; NAT 18 cm/s [Mean difference = 1.78, SE = 0.51, (t(36) = 3.52, p = .033)]; but not compared to vicarious NAT 30 cm/s [Mean difference = 1.66, SE = 0.53, (t(36) = 3.12, p = .098)].

Direct AT 6 cm/s was perceived more vivid than vicarious AT 6 cm/s [Mean difference = 1.78, SE = 0.39, (t(36) = 4.58, p = .001)]; AT 3 cm/s [Mean difference = 1.87, SE = 0.40, (t(36) = 4.71, p = .001)]; NAT 18 cm/s [Mean difference = 2.02, SE = 0.44, (t(36) = 4.65, p = .001)]; NAT 30 cm/s [Mean difference = 1.90, SE = 0.46, (t(36) = 4.17, p = .005)] (See Table 3.3).

In summary, a significant difference in perceived vividness is noted between direct and observed touch. Furthermore, any touch is experienced more vividly when it involves direct skin contact rather than being observed in a video, leading to speculation about the complex role of the skin in social touch.

Vividness: comparison Velocity ✻ Session

| | | | | 95% Confidence Interval | |
|---|---|---|---|---|---|
| Session | Velocity | Mean | SE | Lower | Upper |
| Direct | 3 cm/s | 6.27 | 0.370 | 5.52 | 7.02 |
| | 6 cm/s | 6.51 | 0.352 | 5.80 | 7.23 |
| | 18 cm/s | 6.68 | 0.355 | 5.96 | 7.40 |
| | 30 cm/s | 7.11 | 0.354 | 6.39 | 7.83 |
| Vicarious | 3 cm/s | 4.64 | 0.371 | 3.89 | 5.39 |
| | 6 cm/s | 4.73 | 0.348 | 4.02 | 5.44 |
| | 18 cm/s | 4.49 | 0.381 | 3.71 | 5.26 |
| | 30 cm/s | 4.60 | 0.418 | 3.76 | 5.45 |

Table 3.3: Estimated marginal means of vividness in the interaction between Velocity (AT: 3 cm/s and 6 cm/s; NAT: 18 cm/s and 30 cm/s) and Session (Direct vs Vicarious).

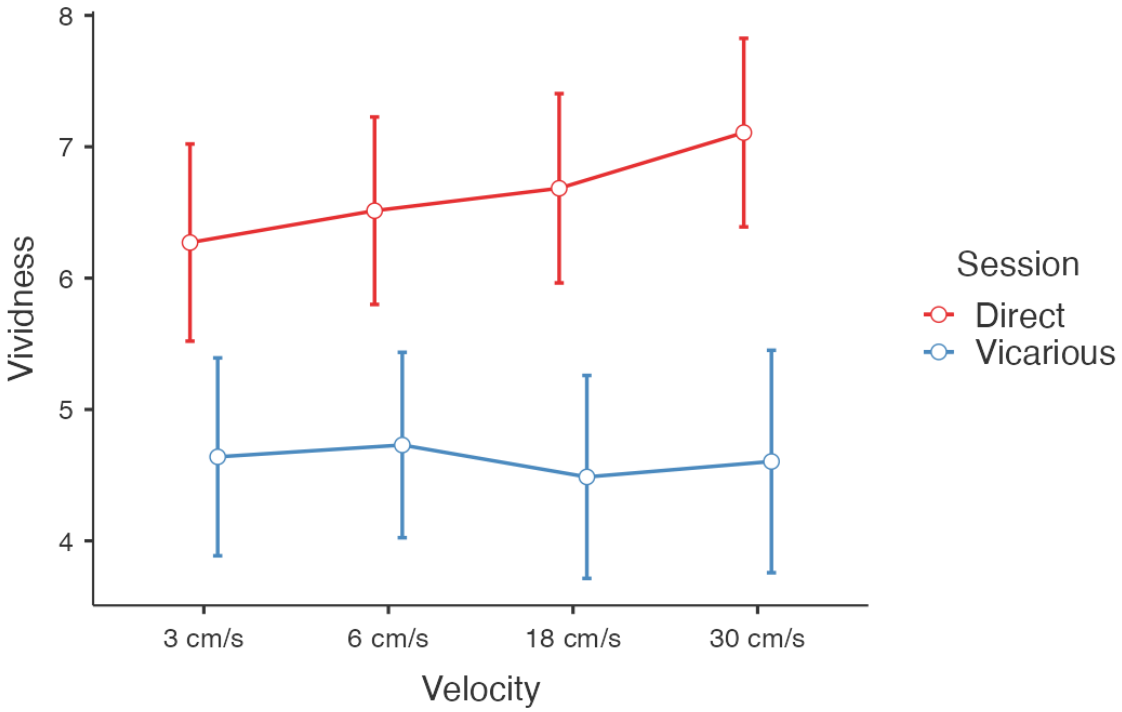


Figure 3.6: Graphic representation of perceived vividness of touch as a function of session type (Direct vs. Vicarious) and stroking velocity (AT: 3 cm/s and 6 cm/s; NAT: 18 cm/s and 30 cm/s). The direct touch condition was significantly more vivid than the vicarious one ($p < .001$). The direct NAT at 30 cm/s was rated as the most vivid touch, compared to the vicarious NAT 30 cm/s; NAT 18 cm/s; AT 6 cm/s; and AT 3 cm/s (all $p < .001$). The direct NAT 18 cm/s was rated more vivid compared to the vicarious NAT 18 cm/s ($p < .001$); NAT 30 cm/s ($p = .001$); AT 3cm/s ( $p = .004$)]; and AT 6 cm/s ($p < .002$). Direct AT 3 cm/s resulted more vivid than vicarious AT 3 cm/s ($p = .010$), AT 6 cm/s ($p = .029$) and NAT 18 cm/s ($p = .033$). Direct AT 6 cm/s was perceived more vivid than vicarious AT 6 cm/s $p = .001$)]; AT 3 cm/s ($p = .001$), NAT 18 cm/s ($p = .001$), and NAT 30 cm/s ($p = .005$).

Vividness and Pain Perception

Three repeated-measures ANCOVA (RM ANCOVA) assessed the effect of direct or vicarious pain perception on the vividness of AT (mean of 3 cms/s and 6 cms/s velocities ) and NAT (mean of 18 cms/s and 30 cm/s velocities) tactile experience.

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding VPQ Intensity (VP_INT), the measure of intensity of empathy to others' pain perception, i.e. vicarious pain perception, as the continuous covariate, to evaluate the effects on perceived vividness.

A main effect of *Velocity* was found [F(1, 35) = 4.51, p = .041, $\eta^2_p$ = 0.114], but Bonferroni Post hoc test comparison did not reveal a significant difference in vividness between AT (M=5.54, SE=0.28) and NAT (M=5.72, SE=0.31), [Mean difference = -0.18, SE = 0.25, (t(35) = -0.71, p = .480)].
A main effect of *Session* emerged [F(1, 35) = 15.43, p < .001, $\eta^2_p$ = 0.306]. Bonferroni Post hoc test comparison shows that direct touch (M=6.64, SE=0.33) is more vivid than the vicarious (M=4.61, SE=0.32), [Mean difference = 2.03, SE = 0.37, (t(35) = 5.46, p < .001)] (see Figure 3.7).
A significant interaction between *Velocity* VP_INT* emerged [F(1, 35) = 4.40, p = .043, $\eta^2_p$ = 0.112].
No significant interaction effect between *Session*Velocity* [F(1, 35) = 0.30, p = .590, $\eta^2_p$ = 0.008] or *VP_INT* [F(1, 35) = 0.89, p = .351, $\eta^2_p$ = 0.025] or among *VP_INT * Session*Velocity* [F(1, 35) = 0.61, p = .439, $\eta^2_p$ = 0.017] was found.

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding VP_N, which represents the number of times participants perceived bodily pain in vicarious pain experiences.
A main effect of *Session* emerged [F(1, 35) = 16.54, p < .001, $\eta^2_p$ = 0.321]. Bonferroni Post hoc test comparison confirmed that direct touch is more vivid than the vicarious: [Mean difference = 2.03, SE = 0.37, (t(35) = 5.54, p < .001)].
No main effect of *Velocity* was found [F(1, 35) = 2.19, p = .148, $\eta^2_p$ = 0.059], neither any interaction effects: *Velocity* Session* [F(1, 35) = 0.030, p = .864, $\eta^2_p$ = 0.001]; or *Velocity* VP_N* [F(1, 35) = 1.72, p = .198, $\eta^2_p$ = 0.047]; or *Session* VP_N* [F(1, 35) = 1.97, p = .170, $\eta^2_p$ = 0.053]; or *Velocity* Session*VP_N* [F(1, 35) = 1.09, p = .304, $\eta^2_p$ = 0.030].

Another RM ANCOVA within-subjects analysis [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding Direct Pain Perception (DP) as a continuous covariate, to evaluate the effects on perceived pleasantness.

A main effect of *Session* emerged [F(1, 35) = 14.83, p < .001, $\eta^2_p$ = 0.298]. Bonferroni Post hoc test comparison confirmed that direct touch is more vivid than the vicarious: [Mean difference = 2.03, SE = 0.37, (t(35) = 5.62, p < .001)].
No main effect of *Velocity* was found [F(1, 35) = 0.02, p = .890, $\eta^2_p$ = 0.001], neither any interaction effects: *Velocity* Session* [F(1, 35) = 0.05, p = .818, $\eta^2_p$ = 0.002]; or *Session*DP* [F(1, 35) = 2.93, p = .093, $\eta^2_p$ = 0.079] or *Velocity*DP* [F(1, 35) = 0.015, p = .903, $\eta^2_p$ = 0.000]; or *Velocity* Session*DP* [F(1, 35) = 0.33, p = .567, $\eta^2_p$ = 0.009].

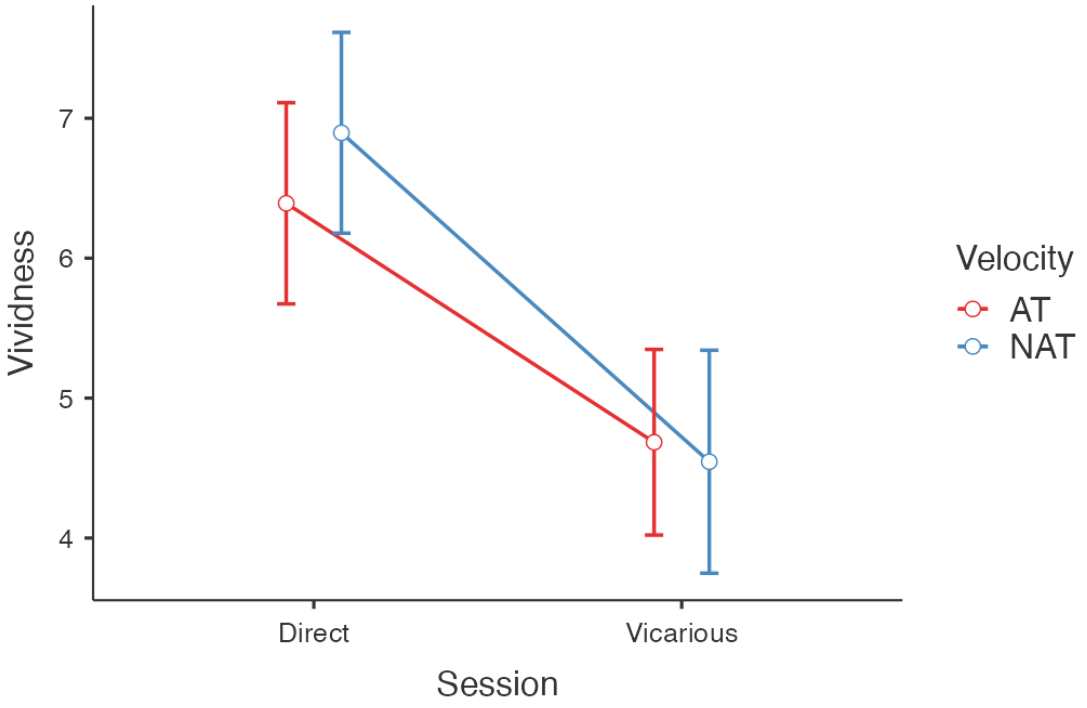


Figure 3.7: Graphic representation of perceived vividness of affective touch (AT) and no-affective touch (NAT) in function of session type (Direct vs. Vicarious). Direct touch was significantly perceived as more vivid than the vicarious one ($p < .001$).

Pleasantness, Vividness and Cutaneous Allodynia

The unexpected presence of eleven participants presenting mild to moderate cutaneous allodynia led us to investigate its role in the pleasantness and vividness experienced with touch.
A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding ASC-12 in daily life (ASC-Daily) as a measure of cutaneous allodynia as the continuous covariate, to evaluate the effects on perceived pleasantness. No interaction effect *Session** ASC-Daily, nor *Velocity** ASC-Daily, nor *Session***Velocity** ASC-Daily was found (all $p > .281$).

Similarly, the A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, ASC-12 in daily life (ASC-Daily) as a measure of cutaneous allodynia as the continuous covariate, to evaluate the effects on perceived vividness. No interaction effect *Session** ASC-Daily, nor *Velocity** ASC-Daily, nor *Session***Velocity** ASC-Daily was found (all $p > .398$).

Interplay between tactile pleasant affectivity and pain perception

A Pearson Correlation Matrix (N = 37) was used to evaluate the relationships among the perceived hedonic experience of direct and observed touch, pain perception (DP), vicarious pain (VP_INT; VP_N), and psychological variables (Table 3.4).

A significant positive correlation was found between the pleasantness of direct and observed AT touch ($r = .776$, $p < .001$), confirming consistency in hedonic touch perception across perceptual modalities. Moreover, a positive and significant correlation was found between pleasantness and vividness in the vicarious AT ($r = .363$, $p = .027$), but not in the direct AT ($r = .1966$, $p = .244$), highlighting how observed AT is perceived as more pleasant when experienced as more vivid. A positive correlation was found between the direct AT pleasantness and the vicarious AT vividness ($r = 0.349$, $p = .034$).

No significant correlations were found between pain measures and the pleasantness of affective touch: VP_INT - Direct AT ($r = .174$, $p = .304$); VP_INT -Vicarious AT ($r = .131$, $p = .440$); DP - Direct AT ($r = .173$, $p = .307$); DP - Vicarious AT ($r = .131$, $p = .438$). A similar pattern was found between VP_N and AT experiences (all $p > .191$). No significant correlation was found between DP and VP_INT or VP_N (all $p > .087$).

The significant negative correlations between the Social Touch Questionnaire (STQ) and the pleasantness of direct AT ($r = –.326$, $p = .049$) and observed AT ($r = –.336$, $p = .042$), suggested that a negative attitude toward social touch is related to a lower tactile pleasant affective experience. Furthermore, STQ and depressive mood were close to statistical significance ( $r = .321$, $p = .052$). No significant correlations were found between STQ and state anxiety (STAI-Y1) or trait anxiety (STAI-Y2) (all $p >.085$). Significant positive correlations were found between the BDI ($r = .302$, $p = .049$), STAI-Y2 ($r = .536$, $p < .001$) and STAI-Y1 ($r = .620$, $p < .001$) and STAI-Y2 with VP_N ($r = .336$, $p < .042$). Allodynia-like symptoms (ASC-Daily) didn't show any significant correlation with the other variables (all $p > .148$) (see Table 3.4).

Correlation Matrix

| | Direct Pain | VP_INT | AT_DPLS | AT _DVIV | ASC-Daily | STQ | AT_VPLS | AT_VVIV | BDI | STAY S | STAY T |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Direct Pain | — | | | | | | | | | | |
| VP_INT | 0.172 | — | | | | | | | | | |
| AT_DPLS | 0.173 | 0.174 | — | | | | | | | | |
| AT _DVIV | -0.078 | 0.144 | 0.196 | — | | | | | | | |
| ASC-Daily | -0.050 | 0.002 | 0.068 | -0.096 | — | | | | | | |
| STQ | 0.320 | 0.183 | -0.326 * | 0.099 | 0.061 | — | | | | | |
| AT_VPLS | 0.131 | 0.131 | 0.776 *** | 0.072 | 0.166 | -0.336 * | — | | | | |
| AT_VVIV | 0.264 | 0.374 * | 0.349 * | 0.379 * | -0.037 | -0.023 | 0.363 * | — | | | |
| BDI | -0.039 | 0.170 | -0.207 | 0.010 | 0.315 | 0.321 | -0.275 | -0.027 | — | | |
| STAY S | 0.105 | 0.059 | -0.150 | 0.034 | 0.022 | 0.287 | -0.244 | 0.007 | 0.620 *** | — | |
| STAY T | 0.295 | 0.281 | 0.057 | 0.236 | 0.243 | 0.206 | 0.075 | 0.239 | 0.536 *** | 0.387 * | — |

*Note.* * p < .05, ** p < .01, *** p < .001

Table 3.4: Correlation matrix of the main study variables. The variables include: Direct Pain; Vicarious pain intensity (VPQ_INT); times of perceived vicarious pain (VP_N); Direct AT pleasantness (AT_DPLS); Vicarious AT pleasantness (AT_VPLS); Direct AT vividness (AT_DVIV); Vicarious vividness (AT_VVIV); Allodynia Symptom in daily life (ASC-Daily); Social Touch avoidance (STQ); Depression (BDI); State anxiety (STAI-Y1); Trait anxiety (STAI-Y2). Statistically significant correlations are marked with asterisks (*p < .05, **p < .01, ***p < .001).

The data suggest no mutual influence between pain and affective touch perception in direct and vicarious experience.

The pleasant AT interlaces the experience of being touched and watching someone else being touched. Additionally, the relationship between vividness and pleasantness of AT is modality-dependent: they are correlated when the experience is vicarious, and there is an interaction between direct and vicarious conditions.

Furthermore, the hedonic experience of affective touch is related to variables of everyday social contact, attitude and emotional state.

However, no significant correlations emerged between experiencing pain on one's skin and empathy for the other's pain.

### 3.2.3. Discussion

First, the results confirmed our first predictions, showing that AT, at 3cm/s and 6 cm/s, is perceived as more pleasant than NAT, confirming the involvement of C-tactile fibres in mediating the hedonic dimension of slow affective touch, as in the current literature (Crucianelli et al., 2013, 2016; Ciaunica et al., 2021; Meijer et al., 2022a,2022b). The AT established its supremacy regarding

pleasantness over NAT in direct and observed administration. Also, for the first time, we found that the direct and observed AT can induce similar hedonic responses, proposing that the affective perception of observed touch may activate sensory representations similar to those elicited by first-person touch, converging with theoretical perspectives that highlight the central role of observation in sensory simulation and empathic tactile processes (Butti et al., 2024). This finding leads us to speculate about AT intervention in people who dislike being touched or suffer from allodynia, which was unexpectedly present in the general population. Specifically, the following studies could investigate the efficacy of vicarious affective touch interventions compared to direct touch in enhancing the bodily self and reducing pain and negative emotions.

Furthermore, vicarious AT was considered more pleasant than direct NAT, meaning that even observing someone else effectively touch is judged more pleasant than non-affective touch, suggesting that the intrinsic affective quality of the stimulus can sometimes outweigh the somatosensory immediacy of direct perception.

However, experiencing real touch is more agreeable and vivid than watching the same stimulation in a video, underscoring the multisensory nature of touch, in which skin contact sensations play a significant role. Indeed, these experimental results find their equivalent in daily life attitude, the avoidance of personal contact negatively correlates with the first-hand and observed AT pleasantness, asserting that AT involves personal beliefs and real or imagined bodily sensations affecting interpersonal relationships. Summarising, the data suggest that intrinsic physiological and affective relational features primarily drive tactile pleasantness.

The analysis of vividness highlighted the crucial role of perceptual modality in shaping the subjective experience. AT and NAT direct touches were reported as more vivid than observed, emphasising that first-person bodily engagement enhances perceptual richness and integration of somatosensory afferents and interoceptive signals (Cruccianelli et al., 2013; Craig, 2003a, 2023b). Additionally, touch velocity (affective vs. non-affective) did not significantly affect the perception of vividness, supporting the idea that it is more influenced by perceptual modality (direct vs. observed) than by the affective quality of the touch.

Regarding the interplay between pain and affective touch perception, data did not show any influence of pain on AT, nor a correlation among their measures. We can speculate that they cannot be mutually influenced; they seem to be distinct phenomena. Individual differences in pain perception and empathic responsiveness do not substantially influence affective evaluation; this is likely due to their different natures: while pain is more alerting, touch is more focused on interpersonal relationships.

Additionally, the data revealed no significant relationship between empathy for others' pain or first-hand pain perception, suggesting that pain elaboration may differ from AT, which showed a correlation and no significant differences between direct and observed perception modalities.

Also, the significant interaction between direct pain and the modality of touch administration on vividness of the tactile experience suggests that the intensity of tactile bodily sensations can be modulated by individual pain sensitivity. This result aligns with neurocognitive models of interoception (Craig, 2003a, 2023b; Critchley & Garfinkel, 2017), which propose that heightened somatic responsiveness can amplify the intensity of even non-noxious stimuli. On the contrary, empathic responses to others' pain did not influence vividness. We can propose that while pain sensitivity is more closely related to the individual's somatic experience, empathy may be more involved in the affective understanding of it, without affecting the intensity of the perceptual experience.

Psychological variables showed a substantial impact on pain and AT involvement. Specifically, a negative attitude toward social touch was accompanied by lower hedonic ratings of touch in both perceptual modes. This finding strengthens the role of relational features in the affective processing of tactile stimuli. This pattern is reinforced by positive correlations between state anxiety and vicarious pain (VPQ_N), signifying that bodily pain sensation while watching others' pain may share features, possibly related to interoception, that must be considered.

Additionally, the finding that 27% of participants reported mild to moderate cutaneous allodynia symptoms must be taken into consideration in the general population, even in the absence of a diagnosis of a pain condition, suggesting somatosensory sensitisation even within non-clinical populations (Burstein et al., 2010). Cutaneous allodynia should be considered a potential variable influencing pain and affective touch perception; however, this study found no evidence to support this.

In conclusion, the results highlight that the pleasantness of affective touch is more sensitive to psychological facets than pain-related factors. Affective touch reaffirms its multidimensional nature, which is also shaped by individual psychological factors and experiences.

## 3.3. Experiment 2: Chronic Migraine Population

### 3.3.1. Materials and Methods

The procedure of this second experiment is equal to that of the first experiment. See paragraph 3.2.1.2 for all details.

#### *3.3.1.1. Participants*

Thirty-seven participants (Mean age: 49 years, SD = 15; age range: 18-71 years; 34 female) with a diagnosis of Chronic migraine were enrolled at the Headache Centre, Neuroalgology Department of IRCCS Foundation "Carlo Besta" Neurological Institute of Milan, Italy.

None of them matched the following exclusion criteria: severe and documented medical or psychiatric conditions, epilepsy, sensory abnormalities such as multiple sclerosis and peripheral neuropathy, abnormal cutaneous perception or dermatological disease (Ashkenazi et al., 2007).

### 3.3.2. Results

Demographic and Mood Assessment

Thirty-seven participants completed all the questionnaires, and the datasets had no missing values.

Allodynia Symptom Checklist-12 (ASC-12):

ASC-12 assessed allodynia in daily life: (M = 2.35, SD = 3.58, range 0-12). Thirteen participants (35.1%) scored above the clinical threshold (≥3), reporting symptoms compatible with mild to moderate forms of allodynia. Additionally, ASC-12 was used to assess the presence of allodynia during the pain attack (M = 4.19, SD = 5.47, range 0-18). Fifteen participants (40.5%) scored above the clinical threshold (≥3).

Multidimensional Assessment of Interoceptive Awareness (MAIA): The MAIA subscales Noticing (M = 2.99, SD = 1.31), Attention Regulation (M = 2.50, SD = 1.01), Trusting (M = 2.84, SD = 1.37), and Emotional Awareness (M = 5.70, SD = 2.30), Not-Distracting (M = 3.25, SD = 0.64) and Not-Worrying (M = 3.43, SD = 1.13) were consistent with mean values scoring (Mehling et al., 2012).

The Self-Regulation (M = 2.16, SD = 1.14) and Body Listening (M = 2.10, SD = 1.16) subscales scored lower than the mean, reflecting difficulties with appropriately listening to and recognising bodily sensations, as well as difficulties with self-regulation.

Beck Depression Inventory (BDI-I) scores (M= 8.19, SD = 5.73) did not show a proneness to depressive symptomatology, according to the criteria proposed by Beck et al. (1961).

State-Trait Anxiety Inventory (STAI-Y1,2) evaluated for state anxiety (STAI-Y1: M = 38.4, SD = 9.41) and trait anxiety (STAI-Y2: M = 43.9, SD = 10.2), suggesting a moderate anxious dispositional trait. (Spielberger et al., Italian adaptation, 1983).

It must be taken into account that the majority of CM patients, as participants in this experiment, regularly assume antidepressant and/or anxiolytic medication.

Social Touch Questionnaire (STQ) scores (M = 42.6, SD = 12.1, range = 20-68) did not indicate that participants avoided social contact to an extreme degree.

Pain Perception

The Pain Threshold (T) score was equal to: M = 7.32, SD = 3.94, range 1.33-20.03.

The Direct Pain (DP) value was equal to: M = 4.42, SD = 1.81, range 1.17-9.00.

The number of Vicarious Pain responses (VPQ _N) was equal to: M = 3.89, SD = 3.80, range 0-14.

Some participants reported vicarious pain, as indicated by the VPQ-Responder (N = 23; 62.2%), while the others were classified as VPQ NO-Responder (N = 14; 37.8%).

The Intensity of Vicarious Pain (VPQ_INT) perceived was equal to: 2.59, SD = 2.99, range 0-8.75.

Tactile Affectivity

Analyses were performed using Jamovi Software (version 2.3.28).

First, the AT and NAT pleasantness and vividness mean intensity ratings were tested for normal distribution using the Shapiro-Wilk test. The test reported no significance for the variables.

Pleasantness

A repeated-measures ANOVA (ANOVA RM) evaluated the effects of touch condition [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 4 (AT = 3 and 6 cm/s; NAT = 18 and 30 cm/s) on perceived pleasantness. Huynh-Feldt corrections were applied because of the violated assumptions of Sphericity (Mauchly's test: velocity factor $p < .001$; session*velocity" $p < .001$).

A main effect of *Session* was found [$F(1, 36) = 6.75$, $p = .013$, $\eta^2_p = .158$]. Post hoc test comparisons indicated a significant difference [Mean difference = 0.34, SE = 0.13, ($t(36) = 2.60$, $p = .013$)] (between perceived pleasantness in the Direct touch condition (M = 4.93, SE = 0.31) compared to the vicarious one (M = 4.59, SE = 0.27).

A main effect of *Velocity* also emerged, [$F(1.19, 42.95) = 48.14$, $p < .001$, $\eta^2_p = .572$].

The interaction between *Session*Velocity* was significant [$F(2.02, 72.58) = 5.69$, $p = .005$, $\eta^2_p = .137$].

Bonferroni Post hoc test comparisons between *velocities* revealed that slow AT velocities (3-6 cm/s) were perceived as significantly more pleasant than the faster NAT velocities (18-30 cm/s). Precisely,

AT 3 cm/s (M = 5.87, SE = 0.33) was more pleasant than NAT 18 cm/s (M = 3.97, SE = 0.31) [Mean difference = 1.90, SE = 0.31, (t(36) = 6.43, p < .001)] and NAT 30 cm/s (M = 3.52, SE = 0.32) [Mean difference= 2.35, SE = 0.32, (t(36) = 7.42, p < .001)].

The difference between AT 6 cm/s (M = 5.66, SE = 0.32) and NAT 18 cm/s was also significant: [Mean difference = 1.69, SE = 0.26, (t(36) = 6.57, p < .001)], as the difference between AT 6 cm/s and NAT 30 cm/s: [Mean difference = 2.14, SE = 0.28, (t(36) = 7.58, p < .001)). NAT 18 cm/s was significantly rated more pleasant than NAT 30 cm/s: [Mean difference = 0.45, SE = 0.08, (t(42) = 5.47, p < .001)]. No significant difference between AT 3 cm/s and 6 cm/s [Mean difference = 0.212, SE = 0.096, (t(42) = 2.21, p = .203)], signifying that both CT Optimal velocities were perceived as the most pleasant and comparable.

Bonferroni Post hoc analysis of the *Session*Velocity* interaction revealed a systematic decline in perceived pleasantness with increasing stimulation velocity, observed consistently across direct and vicarious modalities. (see Table 3.5).

Direct AT 3 cm/s were rated as the most pleasant compared to direct and vicarious NAT 18 cm/s [(Mean difference = 1.55, SE = 0.34, (t(36) = 4.49, p = .002)]; [Mean difference = 2.18, SE = 0.35, (t(36) = 6.20, p < .001)] and to direct and vicarious NAT 30 cm/s [Mean difference = 1.92, SE = 0.39, (t(36) = 5.03, p < .001)]; [Mean difference = 2.71, SE = 0.36, (t(36) = 7.65, p < .001)];

Likewise direct AT 6 cm/s compared to direct and vicarious NAT 18 cm/s [Mean difference = 1.37, SE = 0.30, (t(36) = 5.60, p = .001); [Mean difference = 2.00, SE = 0.29, (t(36) = 6.92, p < .001)] and to NAT 30 cm/s [(Mean difference = 1.74, SE = 0.33, (t(36) = 5.19, p < .001)]; [Mean difference = 2.53, SE = 0.30, (t(36) = 8.42, p < .001)].

No significant mean difference was found between Direct and Vicarious AT 3 cm/s [(Mean difference = -0.07, SE = 0.25, t(36) = -0.29, p =1.00)]; between Direct and Vicarious AT 6 cm/s [Mean difference = -0.009, SE = 0.14, (t(36) = -0.06, p =1.00)]. Also, significant mean difference between Direct AT 3 cm/s and Vicarious AT 6 cm/s [Mean difference = 0.17, SE = 0.20, (t(36) = 0.83, p =1.00)]; between Direct AT 6 cm/s and Vicarious AT 3 cm/s [Mean difference = -0.25, SE = 0.193, (t(36) = -1.31, p =1.00)] were not found. These data underscore the consistency of pleasantness perception at CT-optimal velocities of 3 cm/s and 6 cm/s in both direct and vicarious modes.

NAT 18 cm/s and NAT 30 cm/s velocities were also affected by the different modalities of touch administration. NAT 18 cm/s was perceived as pleasant in the same way in the direct and in the vicarious session [Mean difference = 0.63, SE = 0.20, (t(36) = 3.10, p =.104)].

Differently, NAT 30 cm/s was perceived as more pleasant in the direct mode than the vicarious one. [Mean difference = 0.79, SE = 0.22, (t(36) = 3.65, p =.023)].

Also, the pleasantness of direct NAT 18 cm/s and direct NAT 30 cm/s was significantly different [Mean difference = 0.37, SE = 0.10, (t(36) = 3.64, p = .024)], between direct NAT 18 cm/s and vicarious NAT 30 cm/s was significantly different [Mean difference = 1.16, SE = 0.20, (t(36) = 5.70, p < .001)], also between vicarious NAT 18 cm/s and vicarious NAT 30 cm/s [Mean difference = 0.53, SE = 0.13, (t(36) = 3.99, p =.009)].

Pleasantness: Comparison Velocity ✻ Session

| | | | | 95% Confidence Interval | |
|---|---|---|---|---|---|
| Session | Velocity | Mean | SE | Lower | Upper |
| Direct | 3 cm/s | 5.84 | 0.360 | 5.11 | 6.57 |
| | 6 cm/s | 5.66 | 0.343 | 4.96 | 6.35 |
| | 18 cm/s | 4.29 | 0.356 | 3.57 | 5.01 |
| | 30 cm/s | 3.92 | 0.361 | 3.19 | 4.65 |
| Vicarious | 3 cm/s | 5.91 | 0.343 | 5.21 | 6.61 |
| | 6 cm/s | 5.67 | 0.312 | 5.03 | 6.30 |
| | 18 cm/s | 3.66 | 0.304 | 3.04 | 4.27 |
| | 30 cm/s | 3.13 | 0.309 | 2.50 | 3.75 |

Table 3.5: Estimated marginal means of pleasantness in the interaction between Velocity (AT: 3 cm/s and 6 cm/s; NAT: 18 cm/s and 30 cm/s) and Session (Direct vs Vicarious).

The results indicate that both stroking velocity and administration modality have a significant effect on the perception of touch pleasantness. Affective touch (AT) velocities were consistently associated with higher pleasantness ratings across direct and vicarious conditions. In contrast, non-affective touch (NAT) velocities exhibited session-dependent effects: while pleasantness ratings for direct touch remained relatively stable, variations were observed in the vicarious modality (see Figure 3.8).

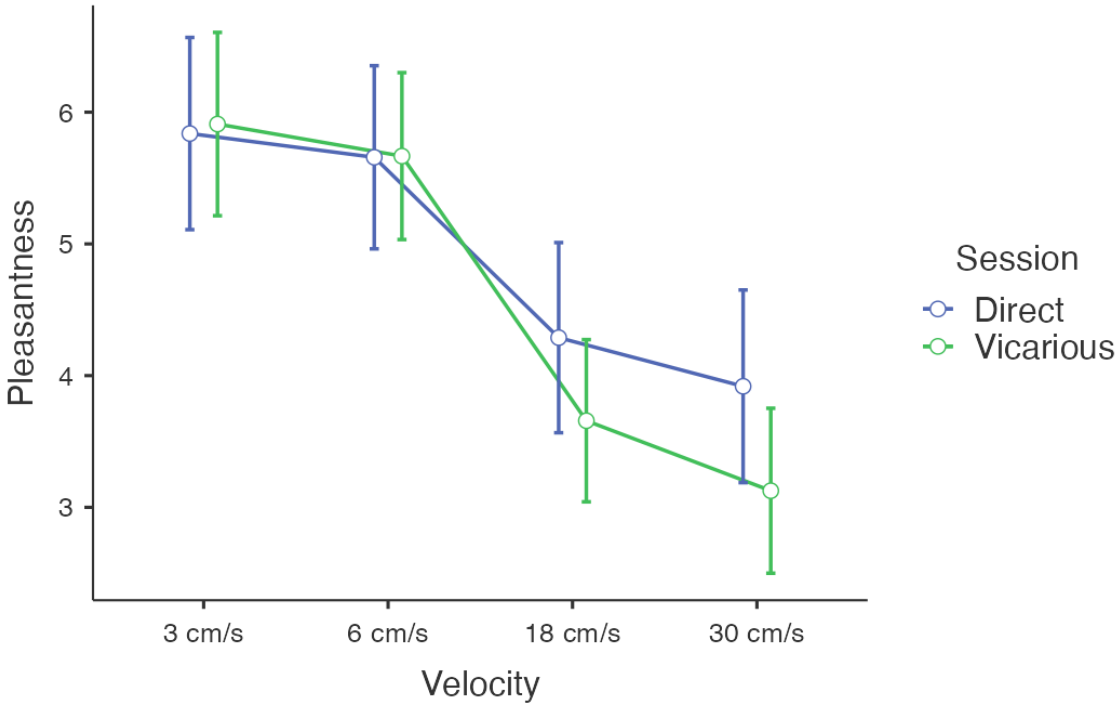


Figure 3.8: Graphic representation of perceived pleasantness of touch as a function of session type (Direct vs. Vicarious) and stroking velocity (AT: 3 cm/s and 6 cm/s; NAT: 18 cm/s and 30 cm/s). Perceived pleasantness was greater in the direct touch condition than in the vicarious one ( $p = .013$). Direct AT 3-6 cm/s were rated as the most pleasant compared to direct and vicarious NAT 18-30 cm/s (all $p < .001$). While perceived pleasantness between AT 3 cm/s and AT 6 cm/s in direct and vicarious sessions was similar, direct NAT 18 cm/s was perceived as more pleasant than direct ($p = .024$) and vicarious NAT 30 cm/s ($p < .001$). Also, vicarious NAT 18 cm/s was perceived as more pleasant than vicarious NAT 30 cm/s ($p = .009$).

Pleasantness and Pain Perception

Three repeated-measures ANCOVA (RM ANCOVA) evaluated the probability of the influence of direct or vicarious pain perception on the pleasantness of the overall AT (mean of 3 cms/s and 6 cms/s velocities ) and NAT (mean of 18 cms/s and 30 cm/s velocities) tactile experience.

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding VPQ Intensity representing a measure of empathy to others' pain perception, i.e. vicarious pain perception (VP_INT: M= 2.59, SD = 2.99) as the continuous covariate, to evaluate the effects on perceived pleasantness.

A main effect of *Velocity* was found [$F(1, 35) = 21.57$, $p < .001$, $\eta^2_p = 0.381$]. Bonferroni Post hoc test comparison revealed that AT (M=5.77, SE=0.32) was significantly perceived as more pleasant than the NAT (M=3.75, SE=0.32), [Mean difference = 2.02, SE = 0.28, ($t(35) = 7.21$, $p < .001$)].

A main effect of *Session* was found [F(1, 35) = 4.59, p = .039, $\eta^2_p$ = 0.116]. Bonferroni Post hoc test comparison revealed that direct modality (M=4.93, SE=0.31) was significantly perceived as more pleasant than the vicarious (M=4.59, SE=0.28), [Mean difference = 0.34, SE = 0.13, (t(35) = 2.57, p = .015)].

A significant interaction between *Session*Velocity* emerged [F(1, 35) = 4.97, p = .032, $\eta^2_p$ = 0.124]. The Bonferroni Post hoc test confirmed that pleasantness in both direct and vicarious modalities decreased progressively with an increase in velocity.

The direct AT (M=5.75, SE=0.34) was rated more pleasant than direct NAT (M=4.10, SE=0.36) and vicarious NAT (M=3.39, SE=0.31)

Likewise, vicarious AT (M = 5.79, SE = 0.33) was rated as more pleasant than both direct NAT and vicarious NAT.

No effect of the interaction between *VP_INT* and *Session* [F(1, 35) = 0.11, p = .747, $\eta^2_p$ = 0.003)] or *Velocity* [[F(1, 35) = 1.35, p = .252, $\eta^2_p$ = 0.037] or among *VP_INT * Session*Velocity* [F(1, 35) = 0.02, p = .895, $\eta^2_p$ = 0.001] was found.

These data support the superiority of AT pleasantness, which also does not differ between the direct and vicarious administration. Instead, NAT pleasantness was greater in the direct session than in the vicarious one (See Table 3.6 and Figure 3.9).

Pleasantness: Comparisons Session ✻ Velcocity

| Comparison | | | | | Mean Difference | SE | df | t | $p_{bonferroni}$ |
|---|---|---|---|---|---|---|---|---|---|
| Session | Velocity | | Session | Velcocity | | | | | |
| Direct | AT | - | Direct | NAT | 1.6441 | 0.327 | 35.0 | 5.027 | < .001 |
| | | - | Vicarious | AT | -0.0405 | 0.176 | 35.0 | -0.230 | 1.000 |
| | | - | Vicarious | NAT | 2.3559 | 0.308 | 35.0 | 7.643 | < .001 |
| | NAT | - | Vicarious | AT | -1.6847 | 0.310 | 35.0 | -5.427 | < .001 |
| | | - | Vicarious | NAT | 0.7117 | 0.195 | 35.0 | 3.650 | 0.005 |
| Vicarious | AT | - | Vicarious | NAT | 2.3964 | 0.292 | 35.0 | 8.218 | < .001 |

Table 3.6: Estimated marginal means of pleasantness in the interaction between Velocity (AT vs NAT) and Session (Direct vs Vicarious)

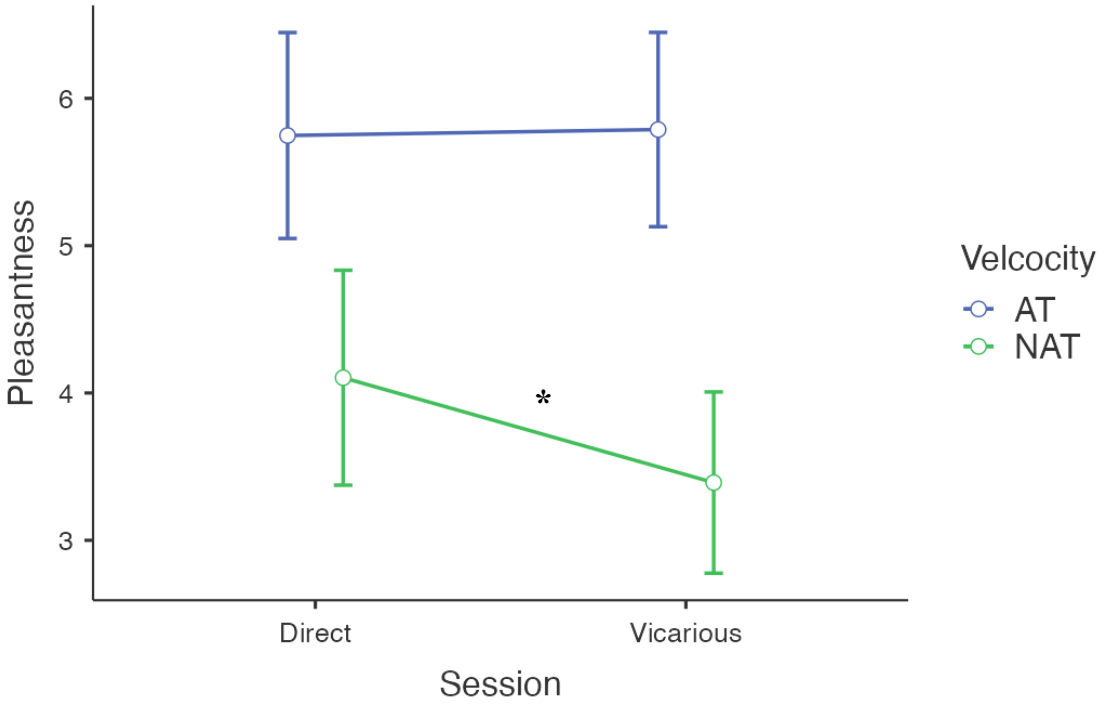


Figure 3.9: Graphic representation of perceived pleasantness of affective touch (AT) and no-affective touch (NAT) in function of session type (Direct vs. Vicarious). Direct AT was rated more pleasant than direct and vicarious NAT ($p < .001$). Vicarious AT was perceived as more pleasant than both direct and vicarious NAT ($p < .001$). Also, NAT pleasantness was greater in the direct session than in the vicarious one ($p = .005$).

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding VPQ_N representing a measure of empathy to others' pain perception, specifically the number of times participants perceived bodily pain while watching the VPQ videos (VP_N: M= 3.89, SD = 3.80) as the continuous covariate, to evaluate the effects on perceived pleasantness.

A main effect of *Velocity* was found [$F(1, 35) = 20.92$, $p < .001$, $\eta^2_p = 0.374$]. Bonferroni Post hoc test comparison revealed that AT (M=5.77, SE=0.32) was significantly perceived as more pleasant than the NAT (M=3.75, SE=0.32), [Mean difference = 2.02, SE = 0.28, ($t(35) = 7.09$, $p < .001$)].

A main effect of *Session* was also found [$F(1, 35) = 5.03$, $p = .031$, $\eta^2_p = 0.126$]. Bonferroni Post hoc test comparison revealed that direct modality (M=4.93, SE=0.31) was significantly perceived as more pleasant than the vicarious (M=4.59, SE=0.28), [Mean difference = 0.34, SE = 0.13, ($t(35) = 2.578$, $p = .014$)].

A significant interaction between *Session*Velocity* didn't emerged [$F(1, 35) = 1.43$, $p = .240$, $\eta^2_p = 0.039$].

No effect of the interaction between *VP_N* and *Session* [F(1, 35) = 0.40, p = .532, $\eta^2_p$ = 0.011)] or *Velocity* [F(1, 35) = 0.633, p = .252, $\eta^2_p$ = 0.007] or among *VP_N* * *Session*Velocity* [F(1, 35) = 1.29, p = .264, $\eta^2_p$ = 0.036] was found.
The results of these two RM ANCOVAs indicate that individual sensitivity to vicarious pain perception did not affect the perception of tactile pleasantness.

A last RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding Direct Pain Perception (Direct Pain), the measure of direct pain perception (DP: M= 4.42 SD = 1.81) as the continuous covariate, to evaluate the effects on perceived pleasantness.
A main effect of *Velocity* [F(1, 35) = 4.13, p = .005, $\eta^2_p$ = 0.105]. Bonferroni post hoc test revealed a significant Mean difference [M = 2.02, SE = 0.28, (t(35) = 7.12, p < .001)], between (M=5.77, SE=0.32) and NAT (NAT (M=3.75, SE=0.32).
No main effect of *Session* [F(1, 35) = 0.77, p = .384, $\eta^2_p$ = 0.001] was found.
Neither the interaction effect between *Session*Velocity* emerged [F(1, 35) = 3.65, p = .064, $\eta^2_p$ = 0.094]. Also, no significant interaction effect *DP*Session* [F(1, 35) = 0.007, p = .932, $\eta^2_p$ = .000] or **Velocity* [F(1, 35) = 0.47, p = .497, $\eta^2_p$ = .013] or among *DP* * *Session*Velocity* [F(1, 35) = 0.800, p = .377, $\eta^2_p$ = .022] was found.
These results suggest that individual direct painful perception does not affect the tactile pleasantness experiences.

Vividness

A repeated-measures ANOVA (ANOVA RM) evaluated the effects of touch condition [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 4 (AT = 3 and 6 cm/s; NAT = 18 and 30 cm/s) on perceived vividness. Huynh-Feldt corrections were applied because of the violated assumptions of Sphericity (Mauchly's test: velocity factor p < .001; session*velocity" p = .011).
A main effect of *Session* emerged, [F(1, 36) = 22.79, p < .001, $\eta^2_p$ = 0.388].
A main effect of *Velocity* was not found [F(1.16, 41.86) = 3.01, p = 0.085, $\eta^2_p$ = 0.077].
The interaction between *Session*Velocity* was significant [F(2.44, 88.02) = 4.54, p = .009, $\eta^2_p$ = 0.112].
Bonferroni post hoc test comparisons between *sessions* revealed that the direct touch (M = 6.08, SE = 0.38) was significantly more vivid than the vicarious (M = 4.35, SE = 0.34) [Mean difference = 2.03, SE = 0.37, (t(36) = 5.47, p < .001)].

Bonferroni post hoc test of the interaction *Session*Velocity* suggested that the perceived vividness is homogeneous within the admiration modality: no significant differences in vividness among all the velocities within the observed or direct sessions were found (all $p > 1.000$) (see Table 3.7).

Direct AT 3 cm/s resulted more vivid than vicarious AT 3 cm/s [Mean difference = 1.46, SE = 0.39, ($t(36) = 3.70$, $p = .020$)]; AT 6 cm/s [Mean difference = 1.52, SE = 0.38, ($t(36) = 4.05$, $p = .007$)]; NAT 18 cm/s [Mean difference = 2.42, SE = 0.48, ($t(36) = 5.07$, $p < .001$)]; but not compared to vicarious NAT 30 cm/s [Mean difference = 2.43, SE = 0.53, ($t(36) = 4.62$, $p = .001$)].

Direct AT 6 cm/s was perceived more vivid than vicarious AT 6 cm/s [Mean difference = 1.42, SE = 0.35, ($t(36) = 4.07$, $p = .007$)]; AT 3 cm/s [Mean difference = 1.36, SE = 0.38, ($t(36) = 3.55$, $p = .030$)]; NAT 18 cm/s [Mean difference = 2.32, SE = 0.42, ($t(36) = 5.52$, $p < .001$)]; NAT 30 cm/s [Mean difference = 2.33, SE = 0.46, ($t(36) = 5.03$, $p < .001$)].

Significant differences emerged across direct and vicarious modalities: the direct NAT 30 cm/s was rated as the most vivid touch compared to the vicarious NAT 30 cm/s [Mean difference = 2.14, SE = 0.43, ($t(36) = 4.99$, $p < .001$); NAT 18 cm/s [Mean difference = 2.13, SE = 0.40, ($t(36) = 5.3$, $p < .001$); but not compared to AT velocities: AT 6 cm/s [Mean difference = 1.23, SE = 0.55, ($t(36) = 2.23$, $p = .898$)]; and AT 3 cm/s [Mean difference = 1.17, SE = 0.60, ($t(36) = 1.96$, $p = 1.000$)].

Likewise, the direct NAT 18 cm/s was rated more vivid compared to the vicarious NAT 18 cm/s [Mean difference = 1.91, SE = 0.39, ($t(36) = 4.96$, $p < .001$); NAT 30 cm/s [Mean difference = 1.93, SE = 0.42, ($t(36) = 4.57$, $p = .002$), but not compared to AT 3cm/s [Mean difference = 0.95, SE = 0.57, ($t(36) = 1.67$, $p = 1.000$)]; and AT 6 cm/s [Mean difference = 1.02, SE = 0.53, ($t(36) = 1.92$, $p = 1.000$)].

In summary, a significant difference in perceived vividness is observed between direct and observed touch. Furthermore, any touch is experienced more vividly when it involves direct skin contact instead of being observed in a video (see Figure 3.10).

Vividness: Comparison Velocity ✻ Session

| Session | Velocity | Mean | SE | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Direcct | 3 cm/s | 6.31 | 0.392 | 5.51 | 7.10 |
| | 6 cm/s | 6.21 | 0.380 | 5.44 | 6.98 |
| | 18 cm/s | 5.80 | 0.458 | 4.87 | 6.73 |
| | 30 cm/s | 6.02 | 0.469 | 5.07 | 6.97 |
| Vicarious | 3 cm/s | 4.85 | 0.400 | 4.04 | 5.66 |
| | 6 cm/s | 4.78 | 0.357 | 4.06 | 5.51 |
| | 18 cm/s | 3.88 | 0.404 | 3.06 | 4.70 |
| | 30 cm/s | 3.87 | 0.432 | 3.00 | 4.75 |

Table 3.7: Estimated marginal means of vividness in the interaction between Velocity (AT: 3 cm/s and 6 cm/s; NAT: 18 cm/s and 30 cm/s) and Session (Direct vs Vicarious).

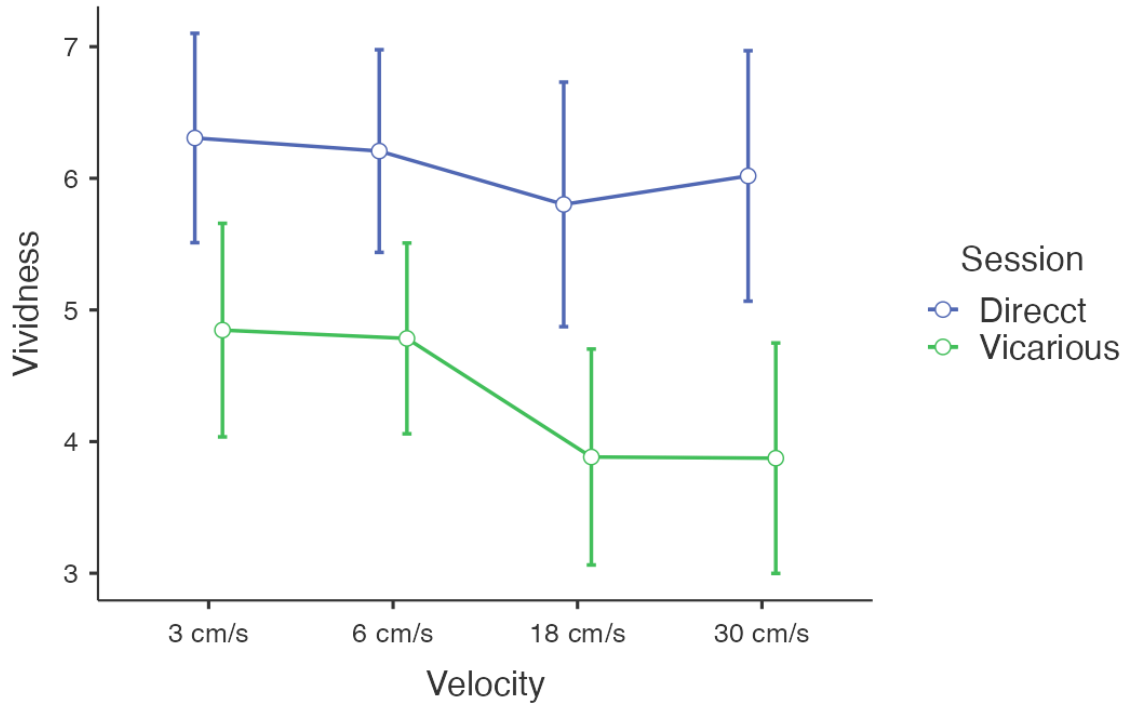


Figure 3.10: Graphic representation of perceived vividness of touch as a function of session type (direct vs. vicarious) and stroking velocity (AT: 3 cm/s and 6 cm/s; NAT: 18 cm/s and 30 cm/s). Perceived vividness was greater in the direct touch condition than in the vicarious one ( $p < .001$). Direct AT 3 cm/s resulted in more vivid responses than vicarious AT (3-6 cm/s) and NAT (18-30 cm/s ) (all $p < .020$). Direct AT 6 cm/s was perceived more vivid than vicarious AT (3-6 cm/s) and NAT (18-30 cm/s ) (all $p < .030$). The direct NAT 30 cm/s was rated as the most vivid touch compared to the vicarious NAT (18-30 cm/s) (all $p < .001$). Likewise, the direct NAT 18 cm/s was rated more vivid compared to the vicarious NAT (18-30 cm/s) ($p < .002$).

Vividness and Pain Perception

Three repeated-measures ANCOVA (RM ANCOVA) assessed the effect of direct or vicarious pain perception on the vividness of AT (mean of 3 cms/s and 6 cms/s velocities ) and NAT (mean of 18 cms/s and 30 cm/s velocities) tactile experience.

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding VPQ Intensity (VP_INT), the measure of intensity of empathy to others' perception, i.e. vicarious pain perception, as the continuous covariate, to evaluate the effects on perceived vividness.

A main effect of *Session* emerged [$F(1, 35) = 14.128$, $p < .001$, $\eta^2_p = 0.288$]. Bonferroni Post hoc test comparison shows that direct touch (M=6.08, SE=0.38) is more vivid than the vicarious (M=4.35, SE=0.35), [Mean difference = 1.74, SE = 0.37, ($t(35) = 4.71$, $p < .001$)].

A main effect of *Velocity* was not found [$F(1, 35) = 0.167$, $p = .0685$, $\eta^2_p = 0.005$].

No significant interaction between *Session*Velocity* [$F(1, 35) = 2.22$, $p = .145$, $\eta^2_p = 0.060$]; or *Session* VP_INT* [$F(1, 35) = 0.109$, $p = .743$, $\eta^2_p = 0.003$], or *Velocity * VP_INT* [$F(1, 35) = 2.105$, $p = .156$, $\eta^2_p = 0.057$], or among *VP_INT * Session*Velocity* [$F(1, 35) = 0.70$, $p = .408$, $\eta^2_p = 0.020$] emerged.

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding VP_N, which represents the number of times participants perceived bodily pain in vicarious pain experiences.

A main effect of *Session* emerged [$F(1, 35) = 13.97$, $p < .001$, $\eta^2_p = 0.285$]. Bonferroni Post hoc test comparison confirmed that direct touch is more vivid than the vicarious: [Mean difference 1.74, SE = 0.37, ($t(35) = 4.73$, $p < .001$)].

No main effect of *Velocity* was found [$F(1, 35) = 1.53$, $p = .225$, $\eta^2_p = 0.042$], neither any interaction effects: *Velocity* Session* [$F(1, 35) = 2.26$, $p = .142.$, $\eta^2_p = 0.061$]; or *Velocity* VP_N* [$F(1, 35) = 1.42e\text{-}4$, $p = .991$, $\eta^2_p = 0.000$]; or *Session* VP_N* [$F(1, 35) = 038$, $p = .533$, $\eta^2_p = 0.011$]; or *Velocity* Session*VP_N* [$F(1, 35) = 0.27$, $p = .607$, $\eta^2_p = 0.008$].

Another RM ANCOVA within-subjects analysis [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding Direct Pain Perception (DP) as a continuous covariate, to evaluate the effects on perceived vividness.

A main effect of *Session* was found [$F(1, 35) = 9.46$, $p = .004$, $\eta^2_p = 0.213$]. Bonferroni Post hoc test comparison confirmed that direct touch is more vivid than the vicarious: [Mean difference = 1.74, SE = 0.37, ($t(35) = 4.83$, $p < .001$)].

No main effect of *Velocity* was found [F(1, 35) = 0.88, p = .354, $\eta^2_p$ = 0.025].

An interaction effect between *Velocity* Session* emerged [F(1, 35) = 5.83, p = .021, $\eta^2_p$ = 0.059].

No interaction effect of *Session*DP* [F(1, 35) = 1.86, p = .181, $\eta^2_p$ = 0.050] or *Velocity*DP* [F(1, 35) = 0.09, p = .768, $\eta^2_p$ = 0.003]; or *Velocity* Session*DP* [F(1, 35) = 2.20, p = .147, $\eta^2_p$ = 0.059] was found.

Bonferroni Post hoc test comparison of the interaction *Velocity* Session* confirmed that direct AT (M=6.26, SE=0.38) is more vivid than vicarious AT (M=4.82, SE=0.36): [Mean difference = 1.44, SE = 0.36, (t(35) = 3.99, p = .002)]; direct NAT (M=5.91, SE=0.46) is more vivid than vicarious NAT (M=3.88, SE=0.39): [Mean difference = 2.03, SE = 0.38, (t(35) = 5.23, p < .001)]; direct AT is more vivid than vicarious NAT [Mean difference = 2.03, SE = 0.38, (t(35) = 5.23, p < .001)]. (See Figure 3.11).

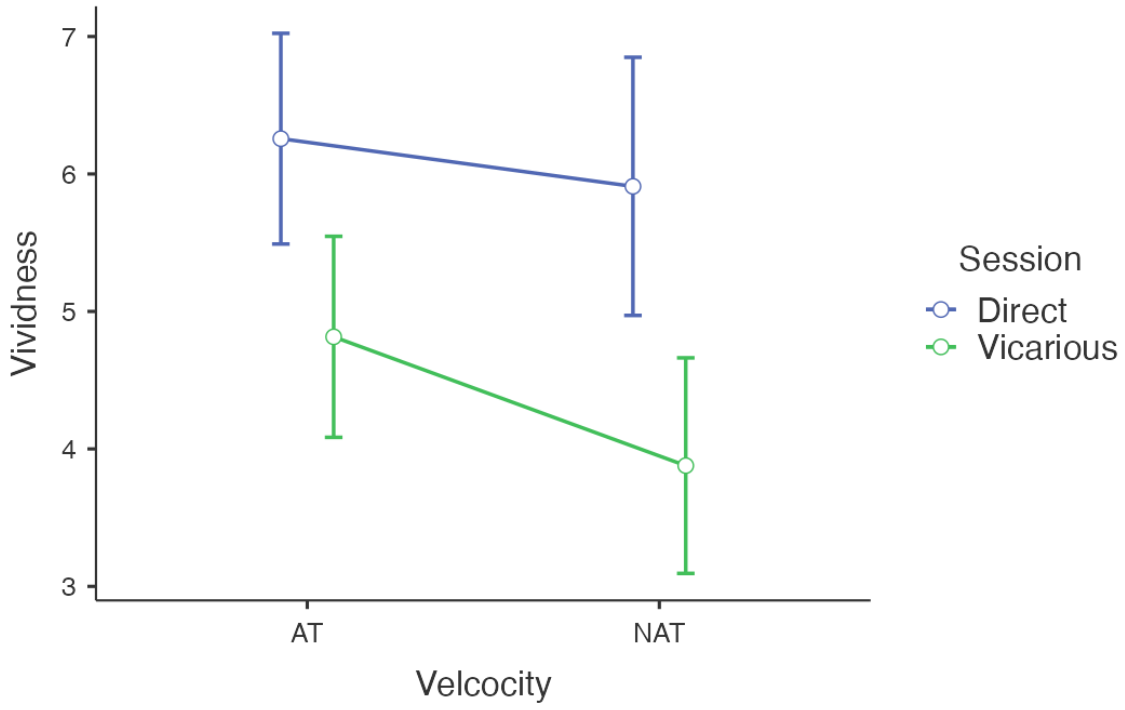


Figure 3.11: Graphic representation of perceived vividness of affective touch (AT) and no-affective touch (NAT) in function of session type (Direct vs. Vicarious). Direct touch was perceived more vivid than the vicarious one (p < .001). Direct AT was rated more vivid than vicarious AT (p = .002); direct NAT was more vivid than vicarious NAT (p < .001), and direct AT was considered more vivid than vicarious NAT (p < .001).

Pleasantness, Vividness and Cutaneous Allodynia

The descriptive analysis revealed the presence of cutaneous allodynia in the participants. We investigate its role in the pleasantness and vividness experienced with touch.

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding ASC-12 in daily life (ASC-Daily) as a measure of cutaneous allodynia as the continuous covariate, to evaluate the effects on perceived pleasantness. An interaction effect, *Session* *ASC-Daily in daily life [$F(1, 35) = 10.30$, $p = .003$, $\eta^2_p = 0.227$]. No other interaction effect of *Velocity** ASC-Daily, nor *Session***Velocity** ASC-Daily was found (all p >.539). (see Figure 3.12).

A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding ASC-12 during the Pain Attacks (ASC-PA) as a measure of cutaneous allodynia as the continuous covariate, to evaluate the effects on perceived pleasantness. The analysis results replicate the previous ANCOVA's one. An interaction effect, *Session**ASC-PA [$F(1, 35) = 5.9$, $p = .028$, $\eta^2_p = 0.131$]. No other interaction effect of *Velocity** ASC-PA, nor *Session***Velocity** ASC-PA was found (all p >.614) (see Figure 3.13).

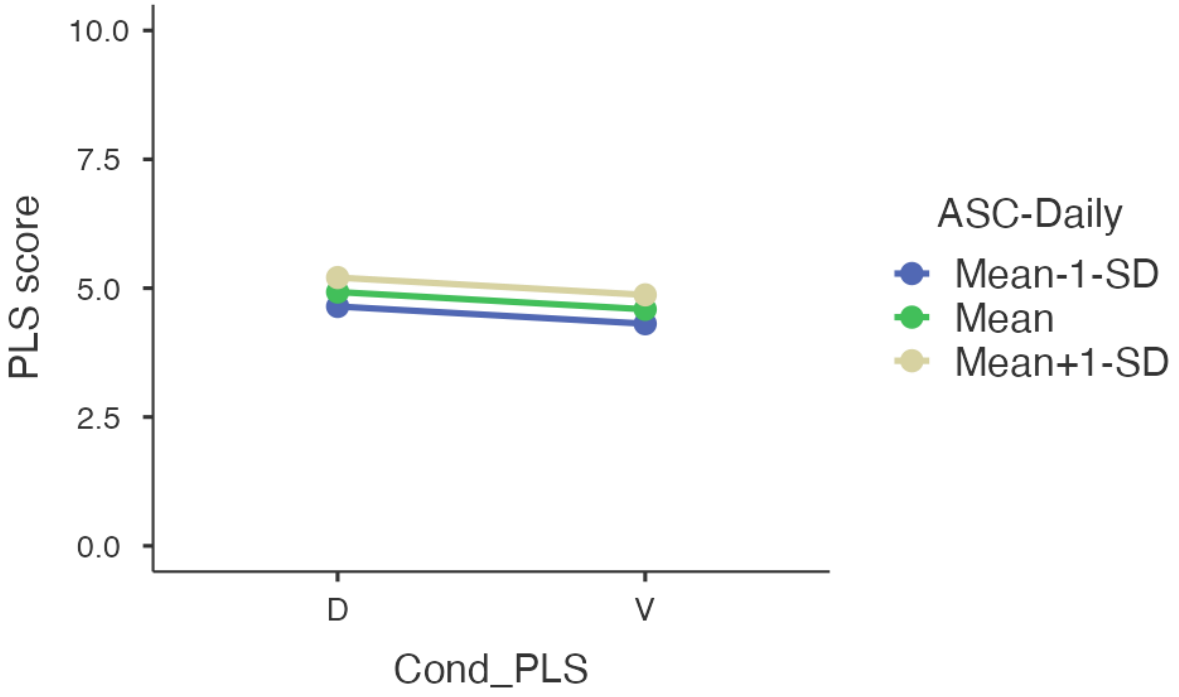


Figure 3.12: Graphic representation of perceived pleasantness as a function of session type (Direct vs. Vicarious) at varying ASC-Daily.

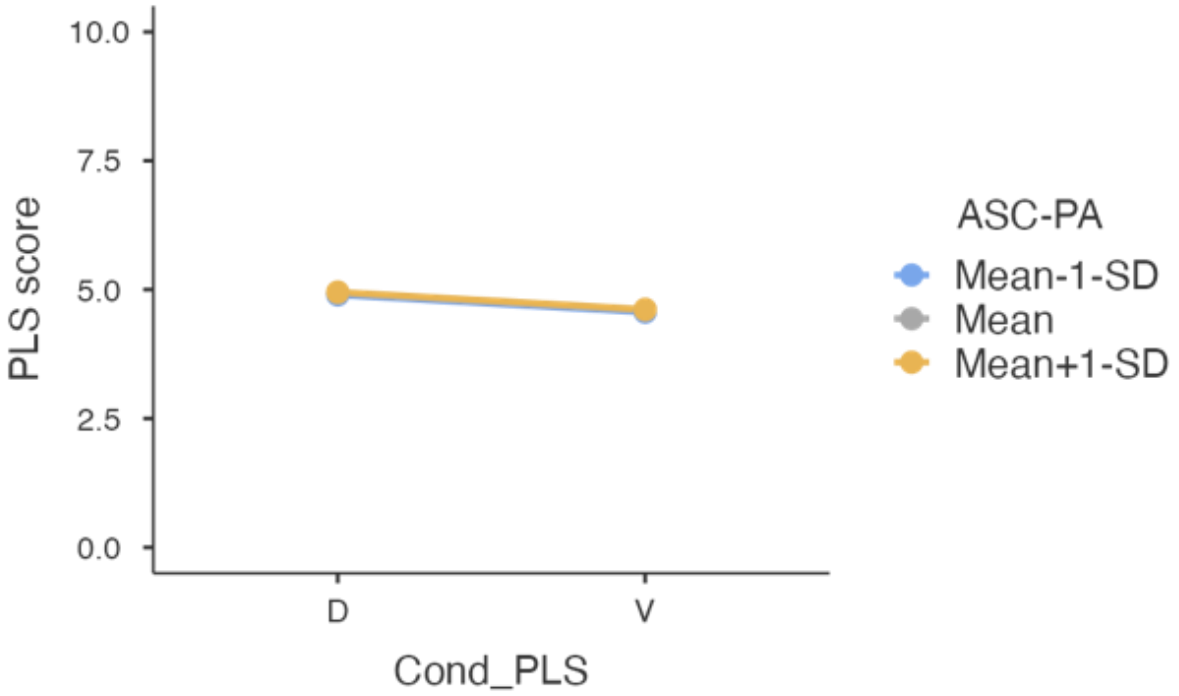


Figure 3.13: Graphic representation of perceived pleasantness as a function of session type (Direct vs. Vicarious) at varying ASC-PA.

Similarly, the A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding ASC-12 in daily life (ASC-Daily) as a measure of cutaneous allodynia as the continuous covariate, to evaluate the effects on perceived vividness. No interaction effect *Session** ASC-Daily, nor *Velocity**ASC-Daily, nor *Session***Velocity** ASC-Daily was found (all p >.2.77).

Another A RM ANCOVA within-subjects [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT)] was conducted, adding ASC-12 during the Pain Attacks (ASC-PA) as a measure of cutaneous allodynia as the continuous covariate, to evaluate the effects on perceived vividness. No interaction effect *Session**ASC-PA, nor *Velocity**ASC-PA, nor *Session***Velocity**ASC-PA was found (all p >.059).

Interplay between tactile pleasant affectivity and pain perception

A Pearson Correlation Matrix (N = 37) was used to explore the relationships among the perceived hedonic experience of direct and observed touch, direct pain perception, vicarious pain (VP_N and VP_INT), and psychological variables (see Table 3.8).

A significant positive correlation was found between the pleasantness of direct and vicarious AT ($r = .865$, $p < .001$) and between the vividness of direct and vicarious AT ($r = .538$, $p < .001$), confirming the consistency in hedonic touch perception across perceptual modalities. Positive significant correlations were found between the direct AT pleasantness and direct vividness ($r = .761$, $p < .001$); direct AT pleasantness and vicarious vividness ($r = .754$, $p < .001$).

No significant correlations were found between pain measures and the pleasantness of affective touch: VP_ INT - Direct AT ($r = .121$, $p = .477$); VP_ INT - Vicarious AT ($r = .140$, $p = .407$); DPP - Direct AT ($r = .294$, $p = .078$); DPP - Vicarious AT ($r = .244$, $p = .145$).

No significant correlations were found between Allodynia measures (ASC-Daily and ASC-PA) and any pain variables (DPP; VP_ N; VP_ INT): all $p > .394$; or between Allodynia measures (ASC-Daily, ASC-PA) and direct AT or vicarious pleasantness and vividness: all $p > .234$.

No significant correlations were found between DP and VP_ INT or VP_N (all $p > .352$), suggesting a lack of correlation between social and individual pain perception.

Direct pain perception was found to be negatively correlated with state (STAI-Y1): $r = -.346$, p .036), and trait anxiety

(STAI-Y2): $r = -.411$, p .011).

No significant negative correlations were found between the Social Touch Questionnaire (STQ) and direct or vicarious affective tactile experiences (all $p > .072$).

STQ score was positively correlated with the presence of allodynia during the pain attacks (ASC-PA): $r = .468$, $p = .003$, and BDI: $r = .426$, $p = .008$, with STAI-Y1 ($r = .497$, $p = .002$) and STAI-Y2 ($r = .721$, $p < .001$).

Significant positive correlations were found between the mood BDI and anxiety indexes STAI-Y2 ($r = .767$, $p < .001$) and STAI-Y1 ($r = .571$, $p < .001$) (see Table 3.8).

Correlation Matrix

| | VPQ_INT | Direct Pain | AT_DPLS | AT_VPLS | AT_DPVIV | AT_VVIV | ASC-Daily | ASC-PA | STQ | BDI | STAY-Y1 | STAY-Y2 | VPQ_NPain |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VPQ_INT | — | | | | | | | | | | | | |
| Direct Pain | -0.285 | — | | | | | | | | | | | |
| AT_DPLS | 0.121 | 0.005 | — | | | | | | | | | | |
| AT_VPLS | 0.140 | 0.050 | 0.865*** | — | | | | | | | | | |
| AT_DPVIV | 0.026 | -0.201 | 0.761*** | 0.600*** | — | | | | | | | | |
| AT_VVIV | 0.121 | 0.093 | 0.754*** | 0.848*** | 0.538*** | — | | | | | | | |
| ASC-Daily | -0.053 | 0.028 | 0.288 | 0.074 | 0.200 | -0.028 | — | | | | | | |
| ASC-PA | 0.066 | -0.009 | 0.132 | -0.035 | 0.190 | -0.163 | 0.844*** | — | | | | | |
| STQ | 0.267 | -0.206 | -0.300 | -0.299 | -0.184 | -0.267 | 0.322 | 0.468** | — | | | | |
| BDI | 0.232 | -0.277 | 0.135 | 0.091 | 0.273 | 0.113 | 0.273 | 0.270 | 0.426** | — | | | |
| STAY-Y1 | 0.034 | -0.346* | -0.123 | -0.206 | 0.011 | -0.048 | 0.232 | 0.168 | 0.497** | 0.571*** | — | | |
| STAY-Y2 | 0.265 | -0.411* | -0.162 | -0.217 | -0.063 | -0.187 | 0.274 | 0.305 | 0.721*** | 0.767*** | 0.779*** | — | |
| VPQ_NPain | 0.723*** | -0.156 | -0.127 | -0.016 | -0.185 | -0.058 | -0.144 | 0.087 | 0.321 | 0.153 | 0.087 | 0.268 | — |

*Note.* * p < .05, ** p < .01, *** p < .001

Table 3.8: Correlation matrix of the main study variables. The variables include: Direct Pain; Vicarious pain intensity (VPQ_INT); times of perceived vicarious pain (VP_N); Direct AT pleasantness (AT_DPLS); Vicarious AT pleasantness (AT_VPLS); Direct AT vividness (AT_DVIV); Vicarious vividness (AT_VVIV); Allodynia Symptom in daily life (ASC-Daily); Social Touch avoidance (STQ); Depression (BDI); State anxiety (STAI-Y1); Trait anxiety (STAI-Y2). Statistically significant correlations are marked with asterisks (*p < .05, **p < .01, ***p < .001).

The matrix of correlation evidences the relation between direct and vicarious AT pleasantness. Additionally, the vividness and pleasantness of AT are not modality-dependent. The pleasant AT experience of being touched and watching someone else being touched is positively related to the perception of vividness of the same experiences.

No significant correlations emerged between experiencing pain on one's own skin and empathy for others' pain, suggesting a potential role of the individual vs the social context.

The allodynia symptoms seem unrelated to either the AT experience or the pain in this experimental context. However, allodynia during pain attacks (ASC-PA) is positively linked to the avoidance of social touch in daily life (STQ) that, in turn, is positively related to depressive (BDI) and anxiety mood (STAI-Y1, STAI-Y2).

The positive correlations between mood variables (BDI, STAI-Y1, and STAI-Y2) confirm their interplay in chronic pain conditions.

### 3.3.3. Discussion

Tactile affectivity results further consolidate that the stroking velocity and administration modality modulate the perception of touch pleasantness. AT (3 cm/s and 6 cm/s) velocities were consistently associated with higher pleasantness ratings across direct and vicarious conditions than NAT (18 cm/s and 30 cm/s). These findings contribute new insights to the existing literature on AT perception in chronic pain, particularly in headache conditions. It is not surprising that the CM

population in this study showed a significant preference for AT in terms of pleasantness perception. Previous studies have reported that migraineurs typically exhibit a consistent pattern of pleasantness ratings (Lapp et al., 2020). Gossrau et al. (2021) highlighted that individuals with postherpetic neuralgia perceived pleasant touch as less enjoyable than healthy controls. Consistent with these results, Nees et al. (2019) investigated affective touch processing in individuals with chronic back pain and reported similar patterns.

In contrast, non-affective touch (NAT) velocities exhibited session-dependent effects on pleasantness, with a preference for slower velocities in the direct modality.

As in the healthy population, direct and observed AT induced similar hedonic responses in CM.

Also, some CM participants (35.1%) showed symptoms of cutaneous allodynia in their daily life (ASC-Daily), and 40.5% reported the presence of allodynia during the pain attack (ASC-PA)

A significant effect of ASC-Daily/ASC-PA on pleasantness perception in the direct/vicarious session of the affective tactile experience emerged. A further analysis tracked a similar general pattern of greater perceived pleasantness in the direct session, independently of the severity of allodynia.

Notably, avoiding personal contact in daily life (STQ) is positively correlated with the score for allodynia during pain attacks. The avoidance of touch and the presence of cutaneous allodynia may represent a mutual influence of social interpersonal relationship conduct and the risk of feeling pain. These findings remark the importance of considering the presence of cutaneous allodynia in pleasant touch perception, and, more generally, on everyday touch experiences in such patients. Vividness evaluation of the tactile experience suggested that the perceived vividness is homogeneous within the administration modality. Yet, a significant difference emerged when comparing direct to observed touch. Experiencing real touch is more vivid than watching the same velocity stimulation in a video, suggesting that skin contact sensations play a significant role (Crucianelli et al., 2013; Craig, 2003a, 2023b). Furthermore, AT/NAT velocity did not significantly affect the perceived vividness of the touch experience. The vividness of touch perception may be more influenced by the modality through which the stimulus is delivered (i.e., direct physical contact versus vicarious touch) than by the affective quality associated with the touch itself.

Investigating the main object of this study, i.e. the interaction between pain and affective touch perception, the data revealed no significant influence of pain on AT ratings, nor any correlation between the two sets of measures. These findings suggest again that pain and affective touch may operate as distinct and independent processes, with limited mutual influence. Furthermore, individual variability in pain sensitivity and empathic traits did not significantly modulate the evaluation of affective touch. This dissociation may be attributable to the differing functional roles of the two

modalities: pain primarily serves an alerting and protective function, whereas affective touch is more closely associated with social bonding and interpersonal connection.

Even if individual sensitivity to vicarious pain perception did not affect the perception of tactile pleasantness, the empathy for others' pain influenced the vividness of the touch.

The significant interaction between the modality of touch administration and its velocity with VP_INT and VP_N could suggest that empathy for others' pain influences the grade of vividness in CM. Non-significant correlations between vicarious pain and AT vividness did not support the idea of a positive or negative relation.

Moreover, no significant association was found between empathy for others' pain and the perception of first-hand pain. This suggests that the cognitive and affective processes underlying pain empathy may differ from those involved in experiencing pain directly. This contrasts with the findings related to affective touch (AT), which demonstrated a significant correlation between direct and observed modalities and no significant differences in perceived pleasantness across these conditions.

Also, the significant interaction between *DP* and the modality of touch administration on vividness of the tactile experience suggests that the intensity of tactile bodily sensations can be modulated by individual pain sensitivity.

This result aligns with neurocognitive models of interoception (Craig, 2003a, 2023b; Critchley & Garfinkel, 2017), which propose that heightened somatic responsiveness can amplify the intensity of even non-noxious stimuli. On the contrary, empathic responses to others' pain did not influence vividness. We can propose that while pain sensitivity is more closely related to the individual's somatic experience, empathy may be more involved in the affective understanding of it, without affecting the intensity of the perceptual experience.

Psychological variables did not evidence a significant relation to AT experiences. However, anxiety was negatively related to the direct pain perception, a possible opposite trend compared to the current hypothesis of a mutual reinforcement.

The positive correlations between social touch avoidance and propensity to emotional pain, such as depression and anxiety, suggest a mingling of emotional vulnerability with social interaction behaviours. The negative correlation between direct pain and anxiety suggests further evidence of their interplay, even apparently in the opposite way compared to the current literature.

In conclusion, findings underscore that the perception of affective touch pleasantness in chronic migraineurs seems to be influenced by psychological dimensions and pain-related factors.

These results further support the conceptualisation of affective touch as a multidimensional construct, shaped not only by sensory input but also by individual psychological characteristics and personal experiences.

### 3.4. Pain and pleasantness comparison between the two populations

The previous analysis in healthy populations and in chronic migraine sufferers suggested similar patterns in the tactile experience pleasantness, but some differences in pain perception.
Thus, further analysis was implied to explore a comparison between the two populations to add more details to the discussion.

A repeated-measures ANOVA (ANOVA RM) evaluated the effects of touch condition [*Session*: 2 (Direct vs. Vicarious)] and [*Velocity*: 2 (AT; NAT) on perceived pleasantness in 2 Groups: (Healthy population: H and Chronic migraine: CM).
A main effect of *Session* emerged, [$F(1, 72) = 8.26$, $p = .005$, $\eta^2_p = 0.103$].
A main effect of *Velocity* was not found [$F(1,72) = 119.43$, $p < .001$, $\eta^2_p = 0.624$].
The interaction between *Session*Velocity* was significant [$F(1,72) = 26.30$, $p < .001$, $\eta^2_p = 0.268$].
No interaction effect between *Session*Group* [$F(1,72) = 0.076$, $p = .783$, $\eta^2_p = 0.001$], or *Velocity*Group* [$F(1,72) = 1.96$, $p = .165$, $\eta^2_p = 0.027$] or *Session*Velocity*Group* [$F(1,72) = 0.44$, $p = .507$, $\eta^2_p = 0.006$] were found (see Figure 3.14).
These findings support the evidence that CM patients did not diverge from the healthy population, as their chronic pain does not seem to affect their perception of pleasant touch.

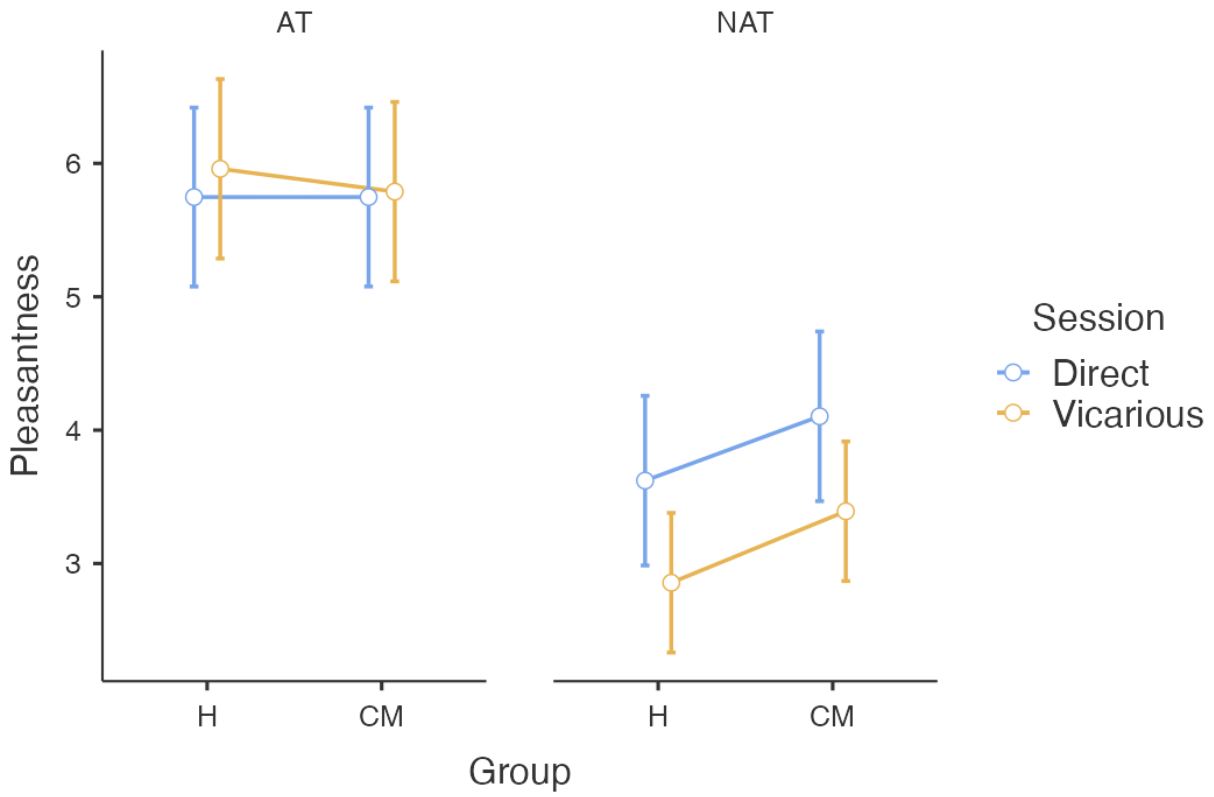


Figure 3.14: Graphic representation of perceived pleasantness of affective touch (AT) and no-affective touch (NAT) in function of session type (Direct vs. Vicarious) in the healthy (H) and chronic migraine (CM) group. In the group comparison, no significant differences were found in Session*Group, Velocity*Group, or Session*Velocity*Group (all $p > 0.165$).

Also, the pain perception scores were compared in detail between the two populations.

Normal distributions of each variable were tested via the Kolmogorov-Smirnov test. Therefore, between-groups differences in ASC-Daily and VP_INT were investigated using the non-parametric independent samples Mann-Whitney U test. In contrast, T, VP_N, and DP were examined via the independent samples T-test.

The analysis revealed a significant mean difference of pain threshold (T) between H ($M = 2.93$, $SD = 2.48$) and CM ($M = 7.92$, $SD = 3.94$): $t = p < .001$, $d = -1.336$ (see Figure 3.15).

Also a significant difference in VP_N between H ($M = 7.11$, $SD = 4.36$) and CM ($M = 3.89$, $SD = 3.80$): $t = p = .001$, $d = 0.787$ (see Figure 3.16).

VP_INT difference was at the limit of significance: $u = p = .055$, $r = 0.2564$: H ($M = 3.70$, $SD = 2.65$) and CM ($M = 2.59$, $SD = 2.99$) (see Figure 3.17).

No significant difference emerged in ASC-Daily and DP between the groups ($p > 0.337$).

These findings revealed that CM patients have a higher pain threshold and are less sensitive to others' pain than the healthy population.

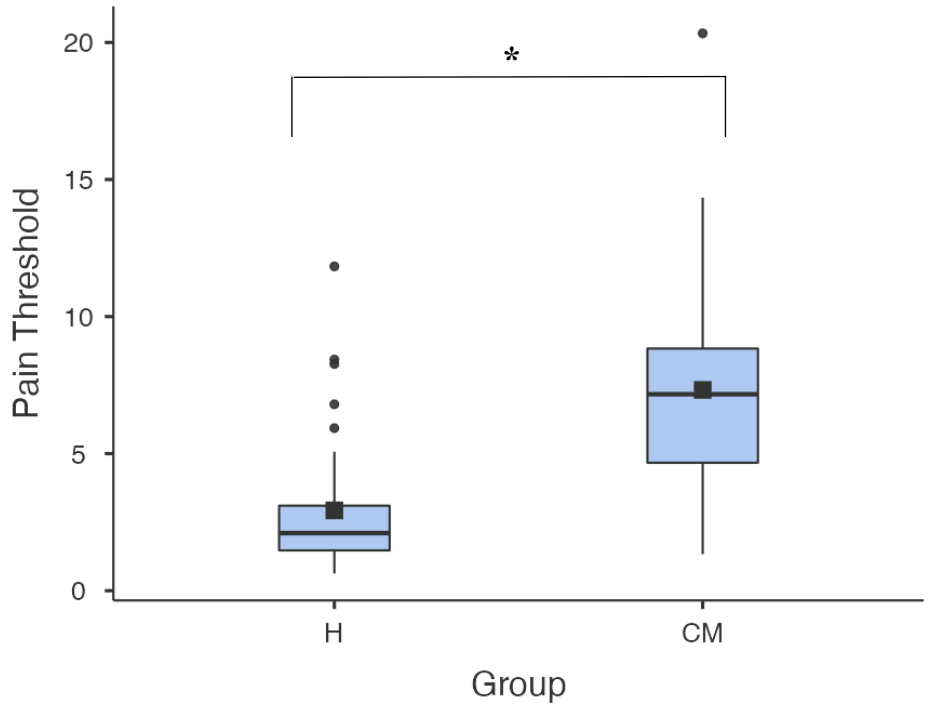


Figure 3.15: Graphic representation of comparison of pain threshold (T) in the healthy (H) and chronic migraine (CM) group. Pain threshold (T) was higher in the chronic migraine group compared to the healthy one ($p < .001$).

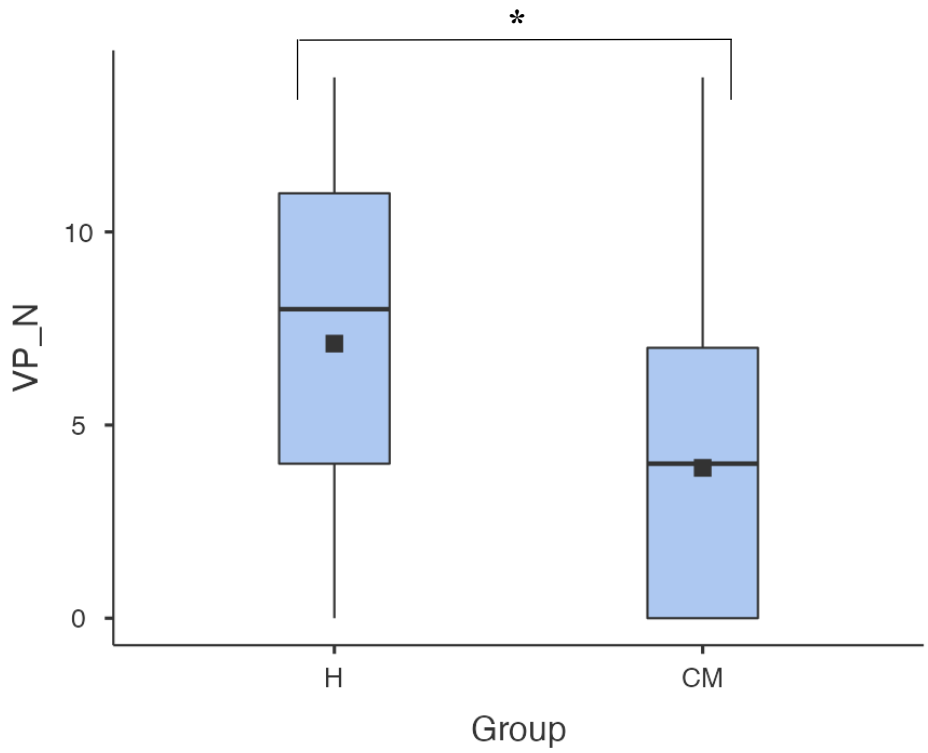


Figure 3.16: Graphic representation of comparison of the number of vicarious pain responses (VP_N) in the healthy (H) and chronic migraine (CM) groups. The number of pain responses was significantly greater in the healthy group compared to the chronic migraine group (p = .001).

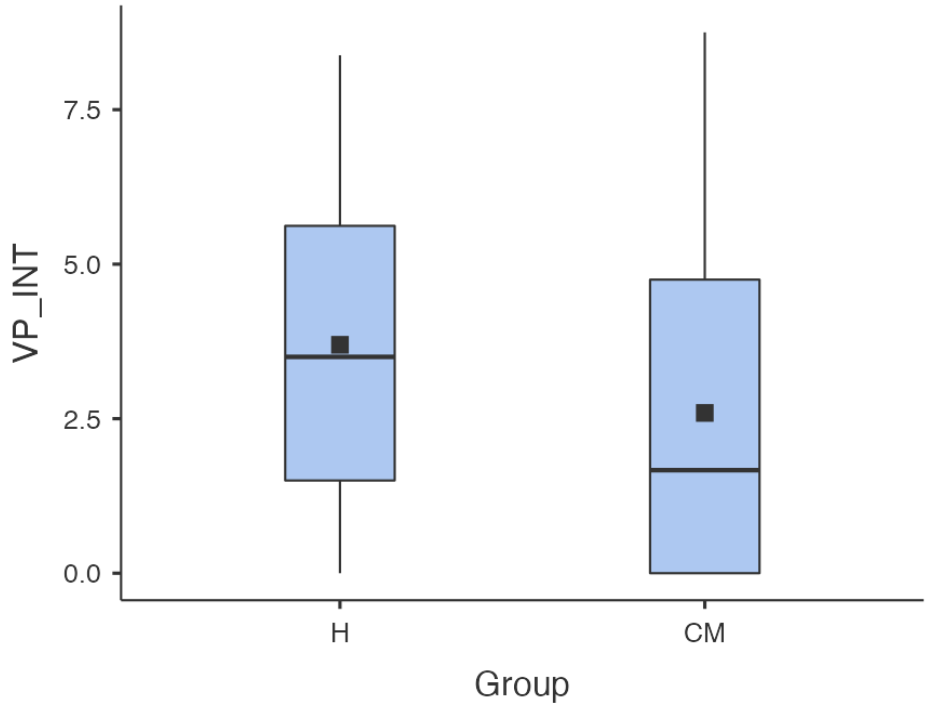


Figure 3.17: Graphic representation of comparison of vicarious pain intensity (VP_INT) in the healthy (H) and chronic migraine (CM) group. The VP_INT group difference was at the limit of significance: (p = .055).

### 3.5. General discussion

This research project guided the development of an experimental framework for assessing the direct and vicarious somatosensory experiences of affective touch and pain, and exploring their relationship in healthy and chronic migraine populations.

The investigation tried to disentangle three main queries:

- According to previous findings, AT, typified by slow tactile stimulation (3 and 6 cm/s), is perceived as inherently more pleasant and vivid than NAT (18 and 30 cm/s).
- Whether direct or vicarious experience of AT leads to different hedonic and perceptual experiences of touch.
- Whether individual pain perception and empathy for others' pain influence the perception of vicarious or direct experiences of affective touch.

The two distinct experiments, conducted in healthy individuals and those with chronic migraine (CM), reveal shared dynamics in affective touch (AT) perception, thereby enriching our understanding of the interplay between pain, social touch, and psychological variables.

Both groups demonstrated the evidence of the hedonic superiority of affective touch (i.e., slow, C-tactile optimal velocities of 3–6 cm/s), consistent with the activation of C-tactile afferents and the literature on affective tactile processing. Also, pleasantness perception related to stroking velocities followed the usual U-shape slopes (Crucianelli et al., 2013).

In healthy and CM populations, the similarity of hedonic ratings between direct and observed AT suggests that vicarious touch can evoke affective resonance akin to actual physical contact, likely engaging shared neurocognitive mechanisms such as sensory simulation and social-affective mirroring (Ciaunica et al., 2021)

In CM, despite a prevalence of cutaneous allodynia, the pleasantness of affective touch remained relatively preserved, particularly in the direct modality, even though allodynia modulated the subjective experience of touch. This preservation could indicate a compensatory or dissociative mechanism, where affective touch continues to function as a potential source of positive sensory input despite altered nociceptive processing.

The perception of vividness across groups was similarly more dependent on modality (direct vs. observed) than on velocity (AT vs. NAT), underscoring the role of direct somatosensory engagement in shaping the intensity of tactile experiences. Individual differences in pain sensitivity (DP) significantly modulated this vividness in the healthy population, consistent with interoceptive models of somatic amplification (Craig, 2002; Critchley & Garfinkel, 2017), which propose that heightened somatic responsiveness can amplify the intensity of even non-noxious stimuli.

In contrast, empathy for others' pain modulated the vividness of the touch in CM. Nevertheless, non-significant correlations between vicarious pain and AT vividness did not support the idea of a positive or negative relation.

Individuals in both clinical and non-clinical populations experienced allodynia. Although its prevalence is lower among healthy individuals than among those with migraines, the reported intensity is typically mild to moderate. These findings highlight the importance of considering allodynia within the general population. Cutaneous allodynia should be viewed as a potential variable influencing pain and affective touch perception; however, this study found no evidence to support this. Otherwise, the presence of allodynia during pain attacks in CM was positively related to social touch avoidance, suggesting an underlying defensive reaction against cutaneous hypersensitivity via avoidance of interpersonal touch. This finding enriches the data regarding the different influences of social touch avoidance in daily life between the two populations. While healthy individuals showed greater sensitivity to the pleasantness of AT in relation to social touch avoidance, these psychological parameters did not influence the hedonic responses of CM individuals to touch.

The assessment of psychological variables revealed a similarity to depression proneness in both populations, while healthy participants declared a stronger anxious disposition, compared to CM ones. It is possible that, as many CM patients assume mood-modulating medication, the data about their interaction with other variables may be affected. The interoceptive awareness assessment revealed some critical issues in both populations. Healthy participants exhibited a low capacity of attentional and behavioural regulation, as well as a lack of trust in one's own bodily sensations. The data are consistent with the variability observed in the general population that did not undergo specific interoceptive training. Migraineurs revealed difficulties with appropriately listening to and recognizing bodily sensations, as well as challenges with self-regulation. These results may reflect the struggle of pain sufferers in managing their sensations, which are often accompanied by pain (Mehling et al., 2013).

The social touch avoidance had a different impact on the two populations. In the healthy group, it was related to affective touch perception. At the same time, in the CM patients, it was more related to mood traits, suggesting a complex interplay between individual behaviour and the interpersonal context.

Direct comparison between healthy (H) and chronic migraine (CM) populations regarding pain and AT perception allowed for further speculation on whether they can be atypical in chronic pain conditions. AT experiences are similar in both populations; chronic pain does not seem to affect their perception. Since the findings about AT perception in chronic pain in the literature vary, our data can be explained in two ways. One, it is that CM does not affect AT perception; another explanation can refer to the fact that migraineurs usually have alterations in C-tactile afferent, which lead to an atypical habituation response to repeated affective touch, also related to the controversial role of tactile allodynia, which can mask classic rating patterns (Lapp et al, 2020).

Moreover, affective touch (AT) findings revealed a significant correlation between direct and vicarious experiences, with no notable differences in perceived pleasantness across these conditions. These findings align with previous studies and the evidence supporting the key role of the insula and its tuning in the mechanisms underlying the vicarious perception of pleasant touch. Insula allows the recognition of the affective valence of touch, even when the touch is only observed, inducing responses similar to first-hand touches (Fusaro et al., 2022).

In contrast to AT perception, no significant relation was identified between empathy for others' pain and the subjective experience of first-hand pain. This suggests that the cognitive and affective mechanisms underlying pain empathy may be distinct from those engaged during the direct experience of pain. Empathy can be distinguished into cognitive, the skill to attribute and understand others' mental states by taking another person's perspective, and affective empathy, which involves

the ability to separate others' affective states from one's own. Significantly, affective and cognitive empathy, which also encompasses others' pain, are intertwined with social relationships and behaviour. It can explain the lack of a clear relation between direct and vicarious pain in both populations (Pizzarro et al., 2025).

Nevertheless, the two groups' pain threshold (T) and vicarious pain significantly differed. CM showed a higher T, even if the response to direct painful stimuli did not diverge substantially from that of healthy people. Interestingly, CM patients appeared to be significantly less empathetic to others' pain. Data referring to pain empathy in chronic pain conditions are still not univocal. Our findings provide new insights into understanding vicarious pain in CM, who showed significantly lower perception of vicarious pain compared to the healthy group. One explanation can be traced to the interpersonal dimension. Older individuals and individuals with mental health conditions often experience diminished interpersonal relationships and lower levels of social engagement, which can lead to poor communication skills and reduced social competencies, such as empathy. In the context of chronic pain, individuals may become chronically sensitised to cues of social and physical pain, leading to catastrophizing, increased fear and anxiety, hyper-vigilance, attentional bias toward pain-related stimuli, and avoidance behaviours. Chronic pain sufferers may react by defending themselves against their hypersensitivity via avoidance, leading to a disabling and self-perpetuating cycle of chronic social and physical pain. This hypothesis suggests that deficits in social cognition, including empathy, may either precede the onset of chronic pain or develop as a consequence, ultimately playing a role in the persistence of pain and hindering recovery (Bouteloup et al., 2021; Romozzi et al., 2022; Pizzarro et al., 2025). This model may be supported by the evidence in this study of the positive correlation between avoidance of social touch in daily life and allodynia during pain attacks, and with depressive and anxiety mood in the CM population.

Since the gender in the two populations is not entirely balanced, as the prevalence of females in migraineurs was greater than in the healthy population, a mention of current literature is due. Still, no single pattern of gender effect modulation on pain empathy was found across studies. Females tend to exhibit heightened pain empathy, as evidenced by increased neural activation in somatomotor regions and higher scores on behavioural measures of empathy. In contrast, males demonstrate greater amygdala activation and a higher propensity for retaliatory behaviours in response to perceived unfairness (Yang et al., 2009; Singer et al., 2006).

### 3.5.1. Limitations, conclusions, and future perspectives

This study advances the understanding of affective touch by demonstrating that:

- Affective touch maintains its hedonic quality across both healthy and chronic migraine populations.
- Pain and affective touch are functionally dissociable
- The modulation of touch vividness is shared across groups and is not influenced by modality and pain sensitivity, with a limited influence of vicarious pain in the healthy population
- Psychological traits may be influential in both populations (see Table 3.9)

| ASPECT | HEALTHY POPULATION | CM POPULATION |
|---|---|---|
| **AT PLEASANTNESS (AT PLS)** | Higher pleasantness at AT velocities. Similarity between direct and observed AT. | Higher pleasantness at AT velocities. Similarity between direct and observed AT. |
| **AT VIVIDNESS** | Direct touch is more vivid than observed. | Direct touch is more vivid than observed. |
| **PAIN – AT PLS** | No influence of DP or VP on AT pleasantness | No influence of DP or VP on AT pleasantness |
| **DIRECT PAIN (DP)** | No Influence on pleasantness or vividness | Did not influence pleasantness. |
| **VICARIOUS PAIN (VP)** | No influence on pleasantness<br>Influence on vividness by velocitiy | No influence on touch pleasantness ot vividness |
| **ALLODYNIA (ASC-Daily; ASC-PA)** | 27% of participants present daily allodynia.<br>No influence on AT perception. | ASC-Daily in 35% of participants.<br>ASC-PA in 40 % of participants: light influence on pleasantness/vividenss perception depending on the touch modality |
| **PSYCHOLOGICAL VARIABLES** | Correlations:<br>(-) social touch avoidance –AT PLS<br>(+) anxiety-VP_N | Correlations:<br>(-) Anxiety-DP<br>(+) social touch avoidance-ASC-PA,<br>(+) social touch avoidance with BDI and Anxiety |

Table 3.9: Comparison of key findings of main variables in the healthy (H) and chronic migraine (CM) group.

These results suggest potential clinical implications for leveraging affective touch in therapeutic interventions, especially for individuals with chronic pain, by recognising its preserved pleasantness despite altered somatosensory conditions. They further highlight the need for personalised approaches, where sensory and psychological dimensions are considered when addressing touch-related experiences in health and disease.

In conclusion, this research study highlights that the body is not a passive receptor of stimuli, but rather a site of meaning-making in interactions with both the internal and external worlds, where vulnerability, relational predispositions, and perceptual processing capacities converge. This research revealed that pleasant or painful affective experiences do not always follow our expected theoretical trajectories. While empathy, pain, and affective touch are often assumed to be interdependent and mutually reinforcing, the current results suggest a more complex reality. Specifically, sensitivity to affective touch does not appear to correlate with either sensitivity to others' suffering or the intensity of one's pain perception, not even in CM, contrary to our expectations. Rather than being an anomaly, this discrepancy reflects the fundamentally multidimensional nature of affective bodily experience**.** Such experience does not arise from a single stimulation modality or a unified neurocognitive mechanism, but from the interaction of distinct, partially autonomous and sometimes divergent processes**.** From a theoretical standpoint, the most significant value of this work may lie precisely in its embrace of this complexity**,** treating it not as a methodological limitation but as an essential feature of the phenomenon under investigation.

The motivation behind this research project was grounded in the potential clinical applications of affective touch, particularly in pain treatment (Krahé et al., 2016). Affective touch has been shown to provide effective analgesia than either discriminative touch or the absence of touch, even in the temporal summation of second pain, a phenomenon associated with central sensitisation and considered a clinically relevant model for chronic pain mechanisms (Fidanza et al., 2021; Wakui et al., 2025). Also, numerous clinical studies have demonstrated the benefits of therapeutic touch in fibromyalgia (Denison, 2004), headaches and migraines (Keller & Bzdek, 1986), and neurodegenerative disorders (Meijer et al., 2024). As chronic pain conditions may impair the perception of pleasant touch in specific individuals, further research is required to establish standardised and effective treatment protocols (Fusaro et al., 2022).

Given the significance of the present findings in the H and CM population and the emerging clinical interest in touch-based interventions, the study aims to determine whether the capacity to perceive the pleasant, affective quality of touch is maintained or impaired in the presence of well-documented sensory alterations such as hyperalgesia and allodynia (Mathew et al., 2004). AT-based interventions, already recognised as carriers of analgesic effects (Björnsdotter et al., 2010), can offer a promising alternative or support to the pharmacological treatment. Such interventions represent a valuable complement to existing pain management strategies, supporting both symptom relief and emotional well-being in individuals living with chronic pain.

One promising avenue is the application of immersive virtual reality to simulate tactile sensations, including affective touch, in populations with chronic pain. This approach enables the induction of

emotionally meaningful sensory experiences without tactile stimulation (Seinfeld et al., 2022). Studies have shown that visual simulations of gentle touch**,** projected into a virtual body perceived as one's own**,** can elicit subjectively pleasant responses and activate interoceptive and affective processing pathways, even without real somatosensory input (Fusaro et al., 2022; Mello et al., 2022). Moreover, Harvie et al. (2022) demonstrated that, in a patient with complex regional pain syndrome, pain sensations could be elicited purely through the visual observation of virtual touch within an immersive virtual reality environment, without actual tactile stimulation. This finding highlights the powerful influence of visually mediated touch on both affective and somatosensory processing. It offers insights into the mechanisms underlying vicarious sensory experiences and their potential therapeutic relevance in clinical populations.

Despite the robustness of the findings, the study has some limitations. Firstly, no physiological measures (e.g., skin conductance response) were collected to complement subjective reports. The absence of such data limits the ability to link affective experience to underlying autonomic processes and impedes inferences. Another limitation refers to the difference between direct and vicarious pleasant stimuli. Vicarious AT stimuli were a video representation of a real hand stroking stimulation, which made the comparison between direct and vicarious sessions more explicit and more transparent. In contrast, direct pain experience could not replicate the scene of the vicarious pain questionnaire videos; this discrepancy may have had an effect.

Moreover, although the experimental design innovatively integrated direct and vicarious stimulation, it did not manipulate relational or contextual variables. All touch stimuli were delivered in emotionally neutral conditions, with no prior relationship between experimenter and participant. This constrains the ecological validity of the findings and limits conclusions about how factors such as familiarity, trust, or social context, known to influence affective responses to touch (Triscoli et al., 2017; Schirmer et al., 2021), might modulate tactile experience.

Additionally, even though the primary objective of the research study was a within-subjects assessment, the unbalanced distribution of males and females, as well as the age of participants in the two populations, may have influenced the results.

# 4. CUTANEOUS ALLODYNIA AND PSYCHOLOGICAL INFLUENCING FACTORS: A NETWORK ANALYSIS

## 4.1. Introduction

Pain is a common aspect of daily life, and its role is fundamentally protective. It is mediated by both bottom-up sensory processes and top-down modulatory mechanisms, the latter encompassing cognitive and affective factors such as expectations, attentional focus, and prior experiences (Rhudy et al, 2010). Among the phenomena associated with altered pain processing are hyperalgesia and allodynia. Initially, these terms were often used interchangeably to describe a heightened pain response resulting from either noxious stimuli or stimuli that are typically non-noxious applied to peripheral tissues. Evoked pain may elicit greater distress than spontaneous pain and is classified based on the nature of the stimulus and the response it provokes. When pain is induced by stimuli that are typically non-painful, such as light touch or mild temperature changes, it is referred to as allodynia, a form of pain that is clearly caused by excitation of low-threshold sensory nerve fibres (Sandkuhler, 2009). Conversely, when a usually painful stimulus produces an exaggerated pain response, the phenomenon is termed hyperalgesia (Moisset & Bouhassira, 2007) (see Figure 4.1).
Cutaneous allodynia is commonly observed in individuals with chronic pain, particularly during periods of acute symptom flare-ups. It is known to exacerbate both the sensory intensity of pain and the accompanying maladaptive cognitive and emotional responses (Ashkenazi et al., 2007).

### 4.1.1. Mechanisms underlying cutaneous allodynia

Cutaneous allodynia represents a paradigmatic shift in the understanding of pain, not merely as a sensory experience, but as an emergent property of complex neural, cognitive, and affective systems. Defined as the experience of pain from stimuli that are generally not painful, allodynia is often conceptualised as a prominent clinical manifestation of central sensitisation, an enhancement of neural signalling that shifts the sensitivity of the pain system: usually, innocuous inputs can activate it, and the perceptual responses to noxious inputs are exaggerated, prolonged, and spread widely (Woolf, 2011). Additionally, pain perception is not proportional to peripheral nociceptive input, but rather reflects altered processing and modulation at spinal and supraspinal levels. Allodynia is not exclusive to neuropathic pain syndromes. However, it is usually observed in concurrence with spontaneous pain, either continuous or paroxysmal, in individuals with peripheral or central nervous system lesions. Low-intensity mechanical or thermal stimuli may trigger allodynia. The two most

prevalent forms are dynamic mechanical allodynia, typically provoked by light tactile stimulation such as brushing, and cold-induced allodynia (Moisset & Bouhassira, 2007).

The exaggerated pain response to normally innocuous stimuli is primarily mediated by hypersensitivity of Aβ fibres, as well as low-threshold Aγ and C fibres. These afferent fibres may become sensitised through mechanisms that occur at both the peripheral and central levels of the nervous system, contributing to the development of peripheral and central sensitisation. Clinically, allodynia is categorised based on the nature of the triggering stimulus into mechanical and thermal subtypes. Mechanical allodynia can be further subdivided into static and dynamic forms. Large, myelinated Aβ fibres predominantly mediate static mechanical allodynia, whereas dynamic mechanical allodynia involves both central and peripheral sensitisation of Aγ fibres. In contrast, thermal allodynia, which is provoked by exposure to non-noxious cold or warm stimuli, is predominantly mediated by unmyelinated C fibres and thinly myelinated Aγ fibres (Melvin et al., 2025).

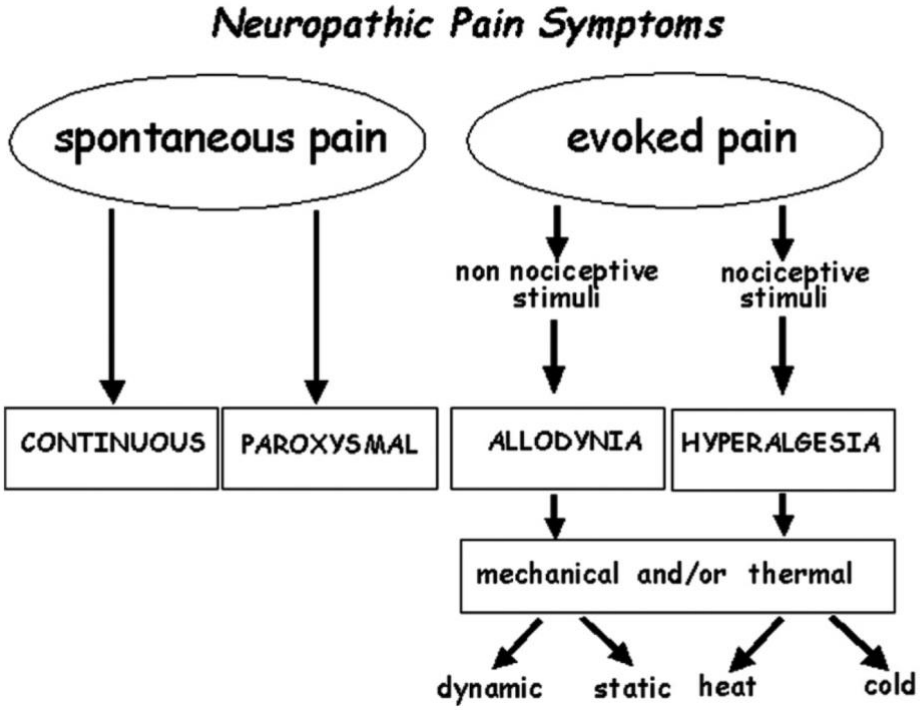


Figure 4.1: Multiple symptoms in patients with neuropathic pain. Evoked pain includes both allodynia and hyperalgesia induced by various types of mechanical and thermal stimuli. (from Moisset & Bouhassira, 2007).

Central sensitisation arises from a change in the properties of neurons within the central nervous system. This phenomenon represents a substantial alteration in somatosensory processing, characterised by a transition from normal, high-threshold nociceptive signalling to enhanced sensitivity to stimuli, such as in allodynia, characterised by a reduction in the threshold (Latremoliere & Woolf, 2009; Woolf, 2011). In chronic pain conditions, like chronic migraine, experiencing cutaneous allodynia can also be exacerbated by stressful events and associated with the transition from episodic migraine to CM (Rosignoli et al, 2022). This phenomenon not only complicates diagnosis and treatment but also reflects the underlying mechanisms of central sensitisation, a key process in the chronicification of pain.

In cutaneous allodynia, several central mechanisms contribute to pain processing, including hyperexcitability of wide-dynamic-range neurons in the dorsal horn, disinhibition of pain-modulatory pathways, and neuroplastic alterations within the thalamus and somatosensory cortex. Neuroimaging studies have investigated alterations in brain activity associated with allodynia and determined that it is linked to changes in activity in regions comprising the pain matrix. The pattern of brain activation observed during neuropathic hyperalgesia and allodynia largely, but not wholly, overlaps with the pain matrix. Although data findings are not definitive and sometimes inconsistent, they suggest that dynamic mechanical allodynia does not involve the whole pain matrix and that its mechanisms differ from those of spontaneous continuous pain. The most consistently reported alterations in neuropathic pain include tonic hypoactivity of the thalamus contralateral to the affected region, as well as reduced activation of the ventromedial and, frequently, the dorsolateral and anterolateral prefrontal cortices during neuropathic allodynia (Moisset & Bouhassira, 2007; Garcia-Larrea & Peyron, 2013). Pathological disinhibition of nociceptive signalling by the thalamic reticular nucleus, acting on the medial thalamic nuclei, has been observed during allodynia. Neural sensitisation reduces pain thresholds and enhances responsiveness to otherwise innocuous stimuli. Beyond spinal mechanisms, supraspinal modulation exerts a significant influence on pain perception, with top-down processes critically shaping the experience of allodynia. Cortical regions, including the prefrontal cortex, anterior cingulate cortex (ACC), insula (IC), and amygdala, interact with subcortical pain-processing centres to regulate attention, emotional responses, and cognitive appraisal of nociceptive input (Moisset & Bouhassira, 2007; Sandkuhler, 2009; Bushnell et al., 2013) (see Figure 4.2).

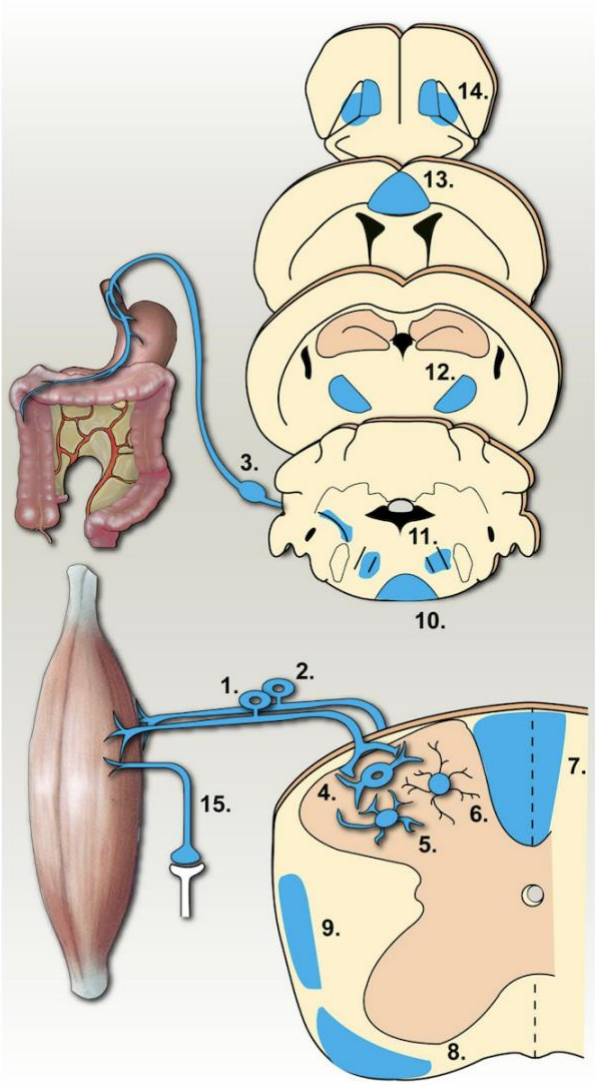


Figure 4.2: Neuronal components critically involved in some forms of hyperalgesia and/or allodynia. Among afferent fibre systems: (1) C-fibres expressing the transient receptor potential vanilloid 1 (TRPV1) ion channel, (2) C-fibres marked by isolectin B4 (IB4) binding, and (3) vagal afferent fibres. Within the spinal cord, essential elements include dorsal horn neurons, specifically: (4) lamina I neurons expressing the neurokinin 1 (NK1) receptor, (5) microglia and (6) astrocytes. Relevant spinal pathways comprise: (7) dorsal column fibres, (8) fibres within the anterolateral funiculus, and (9) those in the lateral funiculus, all of which contribute to the transmission of nociceptive information. Also, at the supraspinal level, several brain regions are implicated in pain modulation and perception, including: (10) the rostral ventromedial medulla, (11) the gigantocellular reticular nucleus, (12) thalamic relay nuclei, (13) the anterior cingulate cortex, and (14) both the lateral and ventral regions of the orbital cortex. Efferent systems, such as sympathetic postganglionic neurons (15), are involved and recognised for their role in modulating pain sensitivity (from Sandkuhler, 2009).

Additionally, brush-evoked allodynia has been associated with activity changes in regions comprising the pain matrix, including the primary (S1) and secondary (S2) somatosensory cortices, the anterior cingulate cortex (ACC), the thalamus, the insula (IC), and the prefrontal cortex (PFC). A lack of activation on the ACC has been reported during brush-induced allodynia (Witting et al., 2006). Additionally, comparing patterns of brain activity associated with allodynia and acute physiological pain revealed a specific correlation between changes in the activity of different sectors of the insular cortex and ratings of pain intensity and allodynia. The abnormal activation of the posterior insula by innocuous stimuli in patients with allodynia has been confirmed; this may reflect plastic changes in the somatosensory system. Instead, the pattern of activation in the anterior portion of the insula is more complex. Consistent with findings from experimental pain research, the magnitude of activation in the caudal region of the anterior insula was positively correlated with allodynia intensity, independent of the severity of ongoing pain. Under allodynic conditions, however, peak activation shifted toward a more rostral area of the anterior insula. This spatial dissociation between allodynia and pain intensity encoding within the anterior insula suggests a functional subdivision of this region and cortical reorganisation associated with clinical pain. In contrast, no significant correlation was observed between allodynia intensity and activation of the anterior cingulate cortex (ACC). These findings suggest that alterations within these regions primarily contribute to the evaluation of pain intensity, representing the sensory-discriminative component of pain processing, additionally reflecting interindividual variability in the perceived intensity of ongoing spontaneous pain, rather than to the differentiation between pain types, such as spontaneous continuous pain and allodynia (Moisset & Bouhassira, 2007).

A few studies also analysed changes in brain activity associated with cold allodynia. Marked differences have been observed in the brain activity changes associated with cold and brush-evoked allodynia in patients with syringomyelia. In contrast to dynamic allodynia, cold allodynia elicited activation within a network of brain structures similar to those engaged during normal cold-induced pain in healthy individuals. These findings suggest that distinct subtypes of allodynia correspond to specific patterns of neural activation, reflecting divergent pathophysiological mechanisms. Supporting this interpretation, neurological and quantitative sensory assessments revealed differing profiles of thermal and mechanical sensory deficits between regions affected by cold and brush-evoked allodynia in these patients (Ducreux et al., 2006).

In conclusion, neuroimaging evidence on neuropathic pain indicates that acute physiological pain and clinical pain engage distinct yet partially overlapping patterns of brain activation. The several components of neuropathic pain syndromes, such as spontaneous and stimulus-evoked pain, likely depend on different underlying mechanisms. This is exemplified by the marked differences in

thalamic activity observed between spontaneous continuous pain and allodynia. Similarly, the divergent activation patterns elicited by mechanical and cold allodynia support the notion that there is no singular "allodynia network" (Moisset & Bouhassira, 2007).

These findings support a model in which allodynia arises not only from bottom-up amplification of peripheral nociceptive input but also from maladaptive top-down mechanisms that influence pain appraisal and emotional processing. Beyond its physiological basis, allodynia constitutes a psychophysiological phenomenon. This indicates that allodynia is embedded within a broader emotional and sensory network, where perception of pain is modulated by attention, affect, and belief. Individuals experiencing allodynia tend to exhibit pain vigilance, anxiety sensitivity, and heightened interoceptive salience (Meulders & Vlaeyen, 2013). These factors amplify bodily awareness and bias sensory interpretation toward threat, creating a self-perpetuating cycle of attentional focus and emotional arousal.

The subjective experience of allodynia is particularly significant, as it encompasses not only nociceptive alterations but also higher-order cognitive and emotional processing that influence pain perception. Notably, the transition from acute to chronic pain often involves a sustained state of central sensitisation, during which cutaneous allodynia becomes a persistent and debilitating symptom. It has been identified in a wide range of pain disorders, including migraine, fibromyalgia, neuropathic pain, and complex regional pain syndrome.

### 4.1.2. Cutaneous allodynia in healthy and clinical populations

Cutaneous allodynia is typically associated with chronic pain conditions, but it can also occur in individuals without overt pathology, under certain conditions. Allodynia does not inherently represent a pathological condition or an inappropriate physiological response; instead, it may constitute an adaptive modulation of the pain threshold aimed at protecting against additional tissue injury. When the spatial distribution, temporal persistence, or intensity of pain becomes maladaptive rather than protective, allodynia ceases to serve as a meaningful homeostatic signal or a symptom of underlying pathology. Instead, it constitutes a pathological condition in its own right (Sandkuhler, 2009).

Distinct and similar neural circuits are found in both healthy individuals and patients with chronic pain. In healthy subjects, dynamic mechanical allodynia is associated with large myelinated (Aβ) fibre signalling, indicating that these afferents are crucial for pain transmission. Following capsaicin injection, neurologically intact subjects exhibited numbness surrounding the allodynic region and a decrease in tactile perception within the affected area. A presynaptic inhibition of Aβ-fiber transmission by C-fibre input in the dorsal horn has been proposed as a potential underlying

mechanism (Liljencrantz et al., 2013). Experimental models employing irritants and nerve blocks, achieved by compressing the superficial radial nerve, demonstrate that brush-evoked pain can arise from brief periods of nociceptive C-fibre activation, which can induce spinal sensitisation and elicit a focused central response. These mechanisms may underlie spontaneous and brush-evoked pain in chronic neuralgia, suggesting that persistent nociceptor activation is a key contributor to neuropathic pain. At the same time, the resulting central sensitisation represents a normal consequence of nociceptor activity (Koltzenburg et al., 1994).

Additionally, healthy individuals, as well as those with chronic pain, exposed to prolonged nociceptive input or stress induction, may temporarily develop reversible allodynia, reflecting transient central sensitisation, a temporary increase in the excitability of dorsal horn neurons following noxious input or inflammation. This typically enables non-painful stimuli to activate nociceptive pathways (Latremoliere & Woolf, 2009). In a healthy population, allodynia is usually acute, reversible, and context-dependent. It represents an adaptive protective response that vanishes when the stimulus or stressor is removed. The descending inhibitory systems remain intact, and the prefrontal and periaqueductal pathways rapidly restore normal sensory thresholds (Woolf, 2011). As in pain conditions, cutaneous allodynia, a manifestation of altered pain perception, engages similar pain processing mechanisms. The limbic and insular regions mediate affective–motivational pain perception, which also interacts with cognitive and emotional judgment, where expectation and attention modulate sensory thresholds. Thus, the possibility of experimentally inducing allodynia in healthy individuals demonstrates the close coupling between physiological input and psychological modulation, providing a model for understanding the early stages of pain chronification. For example, migraine sufferers, even if generally healthy, commonly experience cutaneous allodynia during or preceding migraine attacks, reflecting sensitisation of the trigemino-thalamic system and during aura headache (Burstein et al., 2000). Experimental models, primarily involving animals and a few healthy individuals, revealed that one key mechanism is the loss of inhibitory control in the spinal dorsal horn. For example, dysfunction or blockade of GABAergic interneurons allows Aβ inputs to access nociceptive-specific neurons in the superficial laminae (I–II), which are typically unresponsive to such inputs. Protein kinase C gamma (PKCγ), expressed by interneurons, is central to this process, forming excitatory circuits that, when disinhibition occurs, permit Aβ fibre input to activate pain pathways, particularly through NMDA receptor–dependent mechanisms (Andersen eta al., 1996; Miraucourt et al., 2007). In rare cases, reported allodynia in healthy individuals may reflect early or subclinical neuropathic changes, preceding a diagnosable condition such as fibromyalgia or small fibre neuropathy (Oaklander & Nolano, 2019). Therefore, while often benign and self-limiting,

cutaneous allodynia in healthy populations may involve complex interactions between peripheral input, central sensitisation, and cognitive-emotional modulation of pain.

In patients with chronic pain, evidence suggests additional mechanisms. Although patients with peripheral neuropathy frequently present with allodynia, its underlying mechanisms remain open to discussion. Individuals with chronic pain exhibit persistent and generalised allodynia, often extending beyond the original site of injury. In this chronic form, peripheral sensitisation appears to be prominent. For instance, a study involving a cohort of 200 patients with distal symmetric polyneuropathy (Truini et al., 2013) revealed preserved Aβ-fibre function even in the presence of allodynia. Conversely, patients with allodynia exhibited enhanced excitability of nociceptive pathways, relative to those with ongoing pain but no allodynia. These findings challenge the traditional central sensitisation model and instead support a peripheral mechanism in which sensitisation of intraepidermal nociceptive terminals lowers mechanical thresholds, producing allodynia. The results imply that the presence of partially preserved and hyperexcitable nociceptors is necessary for the development of allodynia, whereas extensive nociceptor loss may prevent it. Thus, while healthy individuals exhibit cutaneous allodynia primarily through Aβ-mediated signalling and focused central responses, chronic pain conditions involve enhanced peripheral nociceptor sensitivity and more diffuse central network recruitment, with bilateral activation of somatosensory cortices, thalamus, periaqueductal grey, and motor areas (Peyron et al., 2004; Schweinhardt et al., 2006). Furthermore, chronic pain patients often display psychological inflexibility and a maladaptive reward circuit that can lead to drug abuse.

In summary, cutaneous allodynia arises from a constellation of alterations in both the peripheral and central nervous systems. It is also recognisable in ostensibly healthy individuals and can result from transient alterations in nociceptive processing, typically involving temporary central sensitisation mechanisms. Factors such as acute inflammation, episodic neurological disorders (e.g., migraine), heightened interoceptive sensitivity, and psychological stress can modulate the function of pain circuits, leading to aberrant pain perception in the absence of overt pathology. In healthy individuals, allodynia is often benign and reversible; when it becomes persistent or unexplained, it can warrant further clinical evaluation to rule out subclinical neuropathic processes. In chronic pain conditions, such as neuropathic pain, fibromyalgia, or migraine**,** central sensitisation is maintained through long-term synaptic plasticity, including the potentiation of excitatory synapses, phenotypic changes in dorsal horn interneurons, and the recruitment of non-nociceptive Aβ fibres into nociceptive circuits (Kuner, 2010). Supraspinal mechanisms, such as decreased descending inhibitory modulation from the brainstem, further contribute to the persistence of allodynia (Latremoliere & Woolf, 2009). In summary, while experimentally induced allodynia in healthy systems is transient and reversible,

chronic pain states involve lasting neuroplastic changes that alter pain processing at multiple levels of the nervous system.

### 4.1.3. Psychological factors influencing cutaneous allodynia in a biopsychosocial perspective

In both healthy individuals and those with chronic pain, cutaneous allodynia engages limbic and insular regions, also mediating the affective and motivational aspects of pain processing. Thus, mechanisms of allodynia are also modulated by cognitive and emotional factors. Psychological stress and emotional states are also known to modulate pain processing via descending pathways, amplifying sensory input and possibly unmasking latent allodynia (Bushnell et al., 2013). Psychological variables such as pain catastrophizing, anxiety, depression, and attentional bias toward pain have all been shown to increase the intensity and prevalence of allodynic symptoms. A substantial body of research has demonstrated that negative emotional states are linked to heightened pain sensitivity and that psychological stress can similarly amplify the perception and severity of pain symptoms (Rhudy et al, 2010; Woda et al., 2016). Depression and migraine have a bidirectional relationship: migraine increases the risk of depression, and depression increases the risk of migraine. Also, cutaneous allodynia is a common symptom in migraine, and it correlates with higher depression. Anxiety and depressive symptoms are more common in migraineurs with allodynia than in those without allodynia (Mendonça et al., 2016). Experimentally induced psychosocial stress leads to heightened mechanical pain sensitivity (stress-induced allodynia) in both healthy individuals and patients with chronic pain. The effect was significantly more substantial and more persistent in the chronic pain group, indicating impaired descending pain inhibitory control. These findings suggest that acute stress can facilitate central sensitisation mechanisms, thereby contributing to the maintenance and amplification of chronic pain states (Crettaz et al., 2013). This experience of experimentally induced allodynia demonstrates the close coupling between physiological input and psychological modulation, providing a possible model for understanding the early stages of pain chronification.

Furthermore, individual variability in pain perception appears to be modulated by sex, hormonal influences, and genetic predispositions, with specific polymorphisms associated with increased pain sensitivity and diminished inhibitory control. Female individuals exhibit higher levels of pain intensity, pain interference, and overall pain sensitivity compared to males. The attenuated correlation between pain intensity and pain interference in women suggests a more multifactorial underlying mechanism, potentially involving more substantial contributions from psychosocial and additional biological factors (McDonnell, 2021). Emotions not only affect the perception of pain but also

subsequent behaviour, such as decision-making. The impact of negative emotions refers to fear, anxiety and avoidance behaviour.

In contrast, feelings of safety and the optimistic belief in pain evolution are equally powerful and related to reward processing in the context of placebo analgesia (Wiech & Tracey, 2009). It is also well known that the nocebo effect is caused by negative information. Negative verbal suggestions concerning an anticipated painful stimulus can develop nocebo allodynia and hyperalgesia, whose intensity is related to prior negative experiences, social influences, and other mechanisms that exacerbate signs and symptoms (Colloca, 2024). Thus, beliefs and cognitive appraisal are recognised as relevant facets in pain sensibility and may be relevant in allodynia. In fact, pain catastrophizing was not associated with activity in regions related to the sensory-discriminative aspects of pain, but rather with those associated with affective, attentional, and motor aspects of pain.

Additionally, in cases of intense pain, prefrontal cortical regions implicated in the top-down modulation of pain were found to be negatively correlated with catastrophizing. These observations can be interpreted within the framework of an attentional model of pain catastrophizing. Catastrophizing may contribute to the development and maintenance of chronic pain through impaired top-down modulation and sustained attentional focus on pain (Seminowicz & Davis, 2006). Collectively, all these evidences reinforce the vision of subjective experience of pain and its manifestation, such as allodynia, within a biopsychosocial framework, where pain is conceptualised as the product of dynamic interactions between biological mechanisms, psychological states, and social context (Gatchel et al., 2007). Thus, biological and psychological determinants substantially shape the subjective experience of pain and its manifestation, such as allodynia, in both positive and negative ways. Cultivation of reflexive awareness of positive emotional states, as in mindfulness protocols, can help to increase the ability to decenter from sensory experiences or to employ cognitive strategies for pain and daily life regulation (Garland et al., 2015). Consequently, allodynia may become a signal of a maladaptive homeostatic error, perpetuated by the coupling of emotional distress and sensory hypersensitivity.

Given the multidimensional nature of cutaneous allodynia, a comprehensive theoretical model must account for the interplay between peripheral nociceptive input, central sensitisation, and psychological modulation. Cognitive and emotional processes not only modulate the sensory aspects of pain but also contribute to neural plasticity that reinforces maladaptive pain circuits. Predictive coding and Bayesian brain theories suggest that chronic pain may also result from prior expectations of pain (Geuter et al., 2017). This indicates that, in addition to neurological assessment and pharmacological interventions, there is a need for integrated assessment strategies that combine sensory profiling with psychometric evaluation. Also, interventions targeting psychological domains,

such as cognitive-behavioural therapy (CBT), mindfulness-based stress reduction (MBSR), and acceptance and commitment therapy (ACT), may thus be effective in reducing the burden of allodynia by addressing the affective-cognitive components that sustain central sensitisation.

In conclusion, we support the hypothesis of a continuum model of tactile allodynia, rather than a dichotomy of presence/absence, which has been primarily considered in clinical populations. Cutaneous allodynia in healthy individuals may serve as an antecedent marker of chronic pain-related allodynia. A short-term, functional context-sensitive activation of the exact neurocognitive mechanisms that, when dysregulated, become chronic and maladaptive. This supports the view that pain chronification reflects not a categorical change but a gradual multi-component shift in network organisation, from a flexible, self-limiting system to a rigid, self-sustaining one. Indeed, chronic pain patients often display psychological inflexibility, a diminished capacity to decenter from sensory experiences or to employ cognitive strategies for regulation (Garland et al., 2015). Consequently, allodynia becomes a maladaptive homeostatic cycle, perpetuated by the coupling of emotional distress and sensory hypersensitivity. This is a reason to investigate allodynia in healthy and clinical populations.

### 4.1.4. Clinical relevance and research gaps

The proper functioning of the nociceptive system is crucial for initiating protective behavioural responses, such as withdrawal or avoidance, in response to acutely painful stimuli. Following tissue injury, the affected area becomes more vulnerable, prompting the nociceptive system to adapt by locally reducing nociceptive thresholds and enhancing defensive responses. The behavioural manifestations of such changes include hyperalgesia and allodynia. Consequently, neither hyperalgesia nor allodynia should be regarded as inherently pathological; instead, they may represent adaptive shifts in pain sensitivity aimed at minimising further tissue damage. Thus, it would not be so surprising to find cutaneous allodynia even in the non-clinical population (Sandkuhler, 2009). But, the presence of cutaneous allodynia may be an indicator of, even transient, distorted cognitive and emotional processes of pain perception. Also, pain is a common feature of numerous pathological conditions, and allodynia is one of the markers of disease progression or therapeutic efficacy. The manifestation of cutaneous allodynia has substantial implications for clinical outcomes. Thus, its presence may be underestimated and unacknowledged in the general population. Adding knowledge on cutaneous allodynia could also help prevent painful conditions, as it is associated with increased pain intensity, longer disease duration, and reduced response to standard pharmacological treatments. The diagnosis of allodynia remains clinically challenging due to its heterogeneous nature of presentation, as allodynia is not a disease, but rather a symptom. Accurate identification necessitates

a comprehensive clinical approach that integrates patient history, medical examination, and quantitative sensory testing. Important historical factors include the presence of comorbidities such as diabetes mellitus, infections, or recent surgical interventions; the use of neurotoxic medications; and a history of psychological conditions such as anxiety or depression. Also, basic metabolic panel and complete blood count analysis can provide valuable information regarding systemic diseases that may contribute to the development of allodynia. Given that several rheumatologic disorders may present with sensory disturbances such as allodynia, inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein, should be considered when underlying autoimmune pathology is suspected. Additionally, peripheral neuropathies, which commonly feature allodynia as a symptom, warrant assessment through metabolic and endocrine evaluations. These investigations help guide further diagnostic workups and inform the development of tailored management strategies (Melvin et al., 2025).

In the research context, tools such as the Allodynia Symptom Checklist (ASC-12) (Lipton et al., 2008) and quantitative sensory testing are increasingly used to quantify the perception of allodynia. These instruments primarily capture observable responses and may not fully reflect the subjective experience. Despite growing interest in allodynia, several comprehension gaps remain, particularly in the context of the biopsychosocial perspective. The interplay between peripheral nociceptive input, central sensitisation, and psychosocial modulation in shaping perceived cutaneous allodynia remains insufficiently portrayed. Furthermore, the majority of current research has been conducted within disease-specific cohorts, thereby limiting the broader applicability of these findings to chronic pain conditions in general. To advance understanding of the complex mechanisms underlying allodynia, a more comprehensive and integrative research approach is required, one that accounts for its multifactorial origins and its contribution to the pathophysiology of chronic pain.

### 4.1.5. Aim of the research

Cutaneous allodynia is typically assessed in clinical populations suffering from chronic pain conditions, particularly migraine. However, existing literature has also examined this phenomenon within the general population, suggesting that it may be present even in the absence of a chronic pain diagnosis. Additionally, exploratory evaluation of cutaneous allodynia in other studies related to this PhD research project revealed its presence in the general healthy population (see Chapters 2 and 3). The network approach to psychopathology (Borsboom, 2017; Robinaugh et al., 2020) offers an innovative hint for examining how the affective, cognitive, and sensory components of allodynia interact. Within this framework, and following the theoretical framework detailed above, we planned to conceptualise affective, sensory, interoceptive, and regulatory facets as nodes connected through

mutual influences, promoting or sustaining cutaneous allodynia. Changes in connectivity patterns may reflect the transition from transient, reversible allodynia to chronic, established pain. This approach locates allodynia not as an isolated symptom but as a central organising feature of the pain network, bridging emotional dysregulation and somatic awareness.

It is hypothesised that emotional and interoceptive factors may predispose individuals to the experience of cutaneous allodynia, independently of clinically diagnosed pain conditions.

The present study aims to combine self-assessment of cutaneous allodynia with the investigation of cognitive and emotional factors that may serve as predictive markers of its occurrence and to investigate their relevance for individualised pain management strategies.

We expected to find:

- In the general population, there may be a predisposition to perceive cutaneous allodynia.
- The perception of cutaneous allodynia may be mediated by physical and/or emotional pain conditions, as well as by stress-related states.
- An excessive attentional focus on bodily pain signals may be positively associated with cutaneous allodynia.
- Interoceptive ability, defined as the capacity to perceive internal bodily sensations, such as visceral signals (Craig, 2003a), along with mindfulness skills, conceptualised as the ability to remain present in the "here and now" (Kabat-Zinn, 2013), may instead be negatively associated with cutaneous allodynia.

The findings of this preliminary study could contribute to a deeper understanding of how cutaneous allodynia may occur even in the absence of chronic pain conditions, as well as which psychological factors might influence its manifestation. Whether the hypotheses will be confirmed, these results would lay the groundwork for future research and preventive interventions in populations suffering from chronic pain disorders, such as migraine, particularly during the early stages of clinical assessment. Early identification and intervention may be crucial for mitigating symptom exacerbation and improving patient outcomes. The overarching goal is to contribute to the development of a more nuanced and patient-centred framework for understanding and treating chronic pain syndromes that involve cutaneous allodynia.

## 4.2. Materials and Methods

### *4.2.1. Participants*

A sample of 214 volunteers participated in the study, meeting the inclusion criteria: individuals of all genders aged 18 years or older at the time of providing informed consent.
We considered only subjects who completed 99% of the questionnaires; thus, the final sample consisted of 171 participants (mean age: 35 ± 16 years; range: 18-81; 48 male, 122 female, 3 not disclosed). Each participant provided informed consent, and the study was approved by the University of Milan-Bicocca's Internal Review Board. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

### *4.2.2. Procedure*

Participants had access to the questionnaires via a Qualtrics link. The data collection was conducted through Qualtrics, an online survey software. The test battery, which lasted approximately 30 minutes, was disseminated through word of mouth, personal contacts, and mailing contacts associated with the Headache Centre-Neuroalgology Department of IRCCS Foundation "Carlo Besta" Neurological Institute of Milan, Italy, and Sona System of the University of Milan-Bicocca. ECTS (0.1) were awarded to students of Psychology at the University of Milan-Bicocca.

Participants filled in self-report questionnaires:

(i) The Allodynia Symptom Checklist-12 (ASC-12) was used to evaluate the presence of cutaneous allodynia. An adapted version was used to assess allodynia in daily life (Lipton et al., 2008)

(ii) Pain Vigilance and Awareness Questionnaire (PVAQ) assessed the attention to bodily pain (McCracken, 1997)

(iii) Self-awareness questionnaire (SAQ) (Lleras, 2005) evaluated the interoceptive and self-awareness

(iv) Five-Facet Mindfulness Questionnaire (FFMQ) (Baer et al., 2006) measured mindfulness abilities

(v) Mental Pain Questionnaire (MPQ) (Fava, 2016)

(vi) Perceived Stress Scale (PSS) (Cohen et al., 1983)

(vii) The Beck Depression Inventory (BDI-II) (Beck et al., 1996) and State-Trait Anxiety Inventory (STAI-Y1,2) (Spielberger, 1983) were used to assess proneness to depressive and state-trait anxiety.

Additionally, demographic information, including age, self-declared gender identity, and the presence of pain conditions, was collected.

*4.2.3. Statistical analysis*

Network analysis is a valuable tool for exploring complex patterns of relationships.

The principle behind the networks is to take a set of variables of interest (nodes) and identify their direct and indirect relationships (edges), estimated through the Gaussian Graphical Model, which estimates regularised partial correlations.

The regularisation was carried out using the graphical "least absolute shrinkage and selection operator" (LASSO) algorithm. The LASSO is tuned by selecting the best operator through the extended Bayesian Information Criterion (eBIC), which is regulated by a parameter γ that we set at 1, a value that optimises the sensitivity and specificity of edge estimation.

Betweenness centrality is the network metric used to quantify the centrality of a node by measuring the number of times it acts as a bridge along the shortest path between two other nodes (Costantini et al., 2015).

To assess the stability and reliability of the estimated network, centrality indices and network structure were re-estimated using 1000 bootstrap resamples from the dataset. This procedure enabled the calculation of average, minimum, and maximum edge weights, as well as the proportion of times each edge was non-zero across all 1000 resamples.

These proportions offer an index of edge stability. The networks were estimated with JASP 0.95.1.

Standard tests (Parametric or Non-parametric One-way ANOVAs) were used to assess whether socio-demographic, clinical, psychological/psychiatric, somatic pain, and social features affected the presence of allodynia.

All p-values were two-tailed, and statistical significance was set at the 0.05 level. In the event of a violation of the normality assumption (as determined by the Shapiro–Wilk test), non-parametric procedures were employed. Statistical analyses of the mean comparisons were performed using Jamovi 2.3.28.

## 4.3. Results

Demographic and psychometric assessment

The final sample comprises 171 participants (mean age: 35 ± 16 years; range: 18-81; 48 male, 122 female, 3 not disclosed).

Pain condition

Sixty-four individuals (37.4%) reported a neurological-based pain condition, of whom mentioned suffering from head pain (56.2%), for more than two years (80%). Most of them (68.8%) received a formal medical diagnosis for their pain condition.

Investigating other pathological conditions affecting any bodily system, apart from neurological conditions, sixty-seven individuals (39.2%) of the entire sample reported ill health, with the majority (83.3%) experiencing symptoms for more than two years before receiving a formal medical diagnosis (83.3%).

Overall, nearly half of these conditions (53.7%) are capable of evoking pain.

Following multiple organ affections, nervous system conditions represent the 7 % impaired health states, which include psychological and psychiatric conditions (see Figure 4.3).

| BODILY SYSTEM | COUNTS | % |
|---|---|---|
| MULTIPLE SYSTEMS | 19 | 11.1% |
| NERVOUS SYSTEM | 12 | 7.0% |
| ENDOCRINE SYSTEM | 7 | 4.1% |
| IMMUNITARY SYSTEM | 7 | 4.1% |
| OTHER | 6 | 3.5% |
| CARDIOVASCULAR SYSTEM | 5 | 2.9% |
| DIGESTIVE SYSTEM | 5 | 2.9% |
| RESPIRATORY SYSTEM | 3 | 1.8% |

Figure 4.3: Descriptive frequencies of ill health states, apart from neurological conditions.

Overall, Ninety-six (56%) of all participants declared to suffer from a form of pain, and sixty-one (36%) have a formal diagnosis for their ill health. Sixty individuals (35%) reported pain coupled with a health diagnosis.

Cutaneous allodynia assessment

To assess the incidence of cutaneous allodynia, the ASC-12 score in daily life (ASC_D) was assumed as the discriminative factor, because ASC-12 scores during pain attacks (ASC_PA) would have reduced the analysis to people suffering from painful conditions with pain attacks.

Overall, forty-six participants (27%) presented cutaneous allodynia in daily life (mean score ≥ 3), and twenty-four (14%) during pain attacks. In the presence of cutaneous allodynia in daily life, women were more affected (78.3%). Considering that suffering of pain is not synonymous with cutaneous allodynia, we found that in the presence of pain, 16% of sufferers also had allodynic symptoms. Notably, eighteen persons exhibited allodynia symptoms without a declared pain (see Figure 4.4 and Table 4.1).

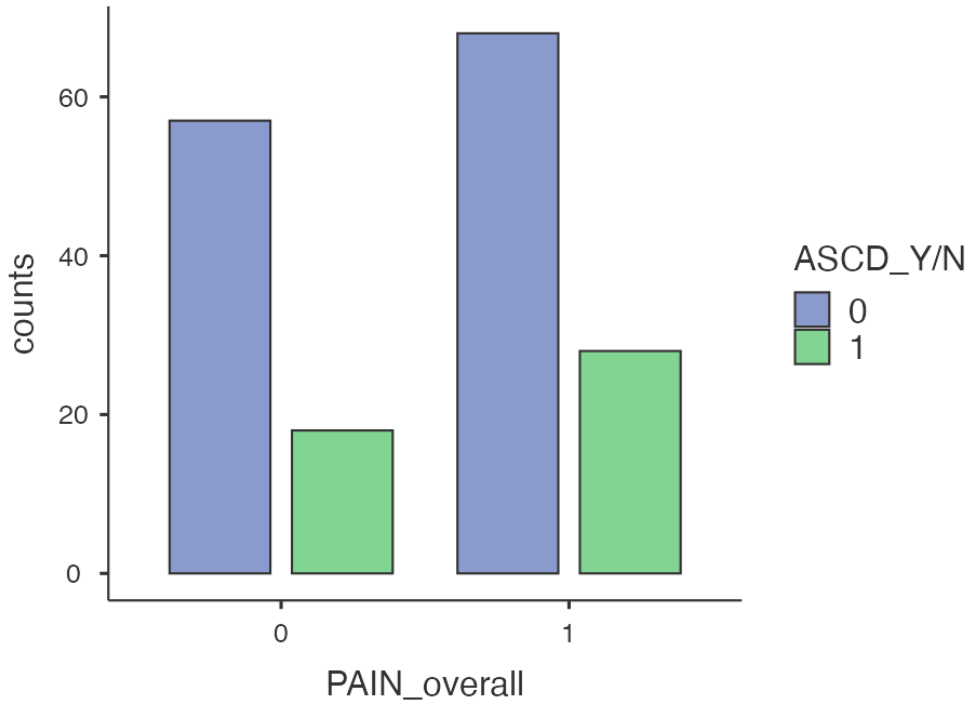


Figure 4.4: Graphic representation of the comparison of the number of cases of presence (ASD_Y) or absence (ASD_N) of cutaneous allodynia in the presence (1) or absence (0) of pain.

Frequencies of PAIN_overall

| PAIN_overall | ASCD_Y/N | Counts | % of Total | Cumulative % |
|---|---|---|---|---|
| 0 | 0 | 57 | 33 % | 33 % |
| | 1 | 18 | 11 % | 44 % |
| 1 | 0 | 68 | 40 % | 84 % |
| | 1 | 28 | 16 % | 100 % |

Table 4.1: Detailed count of cases of presence (ASD_Y) or absence (ASD_N) of cutaneous allodynia in the presence (1) or absence (0) of pain.

Moreover, having or not having a formal medical diagnosis, coupled with pain, affected the incidence of allodynia. In the overall presence of pain and a medical diagnosis, 11% of this subsample presented cutaneous allodynia in daily life (see Figure 4.5 and Table 4.2).

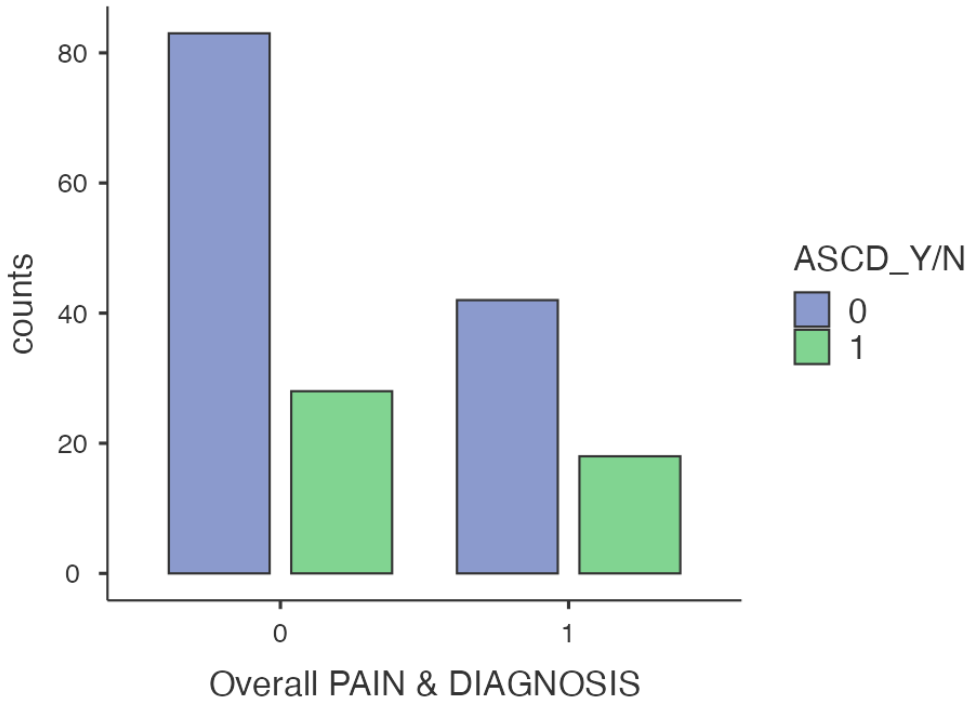


Figure 4.5: Graphic representation of the comparison of the number of cases of presence (ASD_Y) or absence (ASD_N) of cutaneous allodynia in the occurrence of pain, with (1) or without (0) any medical diagnosis.

Frequencies of Overall PAIN & DIAGNOSIS

| Overall PAIN & DIAGNOSIS | ASCD_Y/N | Counts | % of Total | Cumulative % |
|---|---|---|---|---|
| 0 | 0 | 83 | 49 % | 49 % |
| | 1 | 28 | 16 % | 65 % |
| 1 | 0 | 42 | 25 % | 89 % |
| | 1 | 18 | 11 % | 100 % |

Table 4.2: Detailed count of cases of presence (ASD_Y) or absence (ASD_N) of cutaneous allodynia in the overall presence of pain, with (1) or without (0) any medical diagnosis.

Before comparing the affect, interoceptive, and mindfulness facets in the presence (Group 1) or absence (Group 0) of cutaneous allodynia, the normal distribution of standardised self-report questionnaires was checked. The Shapiro–Wilk test revealed violations of normal distribution for all variables, except for FFMQ. Thus, non-parametric ANOVA comparison was employed in the case of normality violation.

The between-group comparison did not show evidence of a significant difference in age ($p = .089$) or gender ($p = 3.05$). Similarly, no significant differences were found in mindfulness abilities (FFMQ: $p = .965$), state anxiety (STAY-1: $p = 1.166$), and trait anxiety (STAY-2: $p = .062$). Depression symptoms (BDI): $\chi^2(1) = 8.23$, $p = .004$, $\varepsilon^2 = .048$, resulted in significantly higher scores in the allodynic group (Group 1: $M = 10.3$, $SD = 7.66$; Group 0: $M = 10.6$, $SD = 8.77$). Similar trend was found for mental pain (MPQ): $\chi^2(1) = 6.78$, $p = .009$, $\varepsilon^2 = .040$ (Group 1: $M = 3.02$, $SD = 2.44$; Group 0: $M = 1.98$, $SD = 2.08$), and perceive stress (PSS): $\chi^2(1) = 7.11$, $p = .008$, $\varepsilon^2 = .042$ (Group 1: $M = 22.5$, $SD = 3.56$; Group 0: $M = 20.9$, $SD = 4.63$). As well as somatic measures, such as pain vigilance and attention (PVAQ): $\chi^2(1) = 9.84$, $p = .002$, $\varepsilon^2 = .058$ (Group 1: $M = 0.55$, $SD = 0.17$; Group 0: $M = 0.46$, $SD = 0.16$); interoceptive and self-awareness (SAQ): $\chi^2(1) = 11.01$, $p < .001$, $\varepsilon^2 = .065$ (Group 1: $M = 36.8$, $SD = 19.6$; Group 0: $M = 25.7$, $SD = 12.7$). As predictable, cutaneous allodynia in daily life (ASC_D): $\chi^2(1) = 112.88$, $p < .001$, $\varepsilon^2 = .664$ (Group 1: $M = 5.50$, $SD = 3.28$; Group 0: $M = 0.528$, $SD = 0.779$) and cutaneous allodynia in pain attacks (ASC_PA): $\chi^2(1) = 14.69$, $p < .001$, $\varepsilon^2 = .086$ (Group 1: $M = 3.00$, $SD = 4.46$; Group 0: $M = 0.512$, $SD = 1.56$), both results were significantly stronger in Group 1 (see Table 4.3).

Descriptives

| | ASCD_Y/N | ASC_D | ASC_PA | BDI | MPQ | PSS | STAI-Y1 | STAI-Y2 | PVAQ | SAQ | FFMQ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 0 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 | 125 |
| | 1 | 46 | 46 | 46 | 46 | 46 | 46 | 46 | 46 | 46 | 44 |
| Mean | 0 | 0.528 | 0.512 | 10.3 | 1.98 | 20.9 | 42.3 | 42.9 | 0.463 | 25.7 | 3.30 |
| | 1 | 5.50 | 3.00 | 13.6 | 3.02 | 22.5 | 45.5 | 47.2 | 0.555 | 36.8 | 3.29 |
| Standard deviation | 0 | 0.779 | 1.56 | 8.77 | 2.08 | 4.63 | 11.7 | 11.1 | 0.160 | 12.7 | 0.542 |
| | 1 | 3.28 | 4.46 | 7.66 | 2.44 | 3.56 | 13.3 | 12.8 | 0.171 | 19.6 | 0.543 |

Table 4.3: Psychometric assessment in the absence (Group 0) or presence (Group 1) of cutaneous allodynia. Abbreviations: ASC_D = cutaneous allodynia in daily life (ASC_D), ASC_PA = cutaneous allodynia during pain attacks; BDI = Beck depression Inventory II; MPQ = mental pain questionnaire; PSS = perceived stress scale; STAI-Y1,2 = State-Trait Anxiety Inventory; PVAQ = pain vigilance and attention questionnaire; SAQ = Self-awareness questionnaire; FFMQ = Five Facets Mindfulness Questionnaire total score.

Network analysis of overall cutaneous allodynia

This first network analysis aimed to explore the connections across features that we supposed to be linked to cutaneous allodynia, and served as the reference network for all subsequent analyses. It includes ten variables: Allodynia in daily life (ASC-12 daily); Allodynia in pain attack (ASC-12 Pain attack); Depressive Symptoms (BDI); State and Trait Anxiety (STAI-Y1, STAI-Y2); Mental Pain (MPQ); Perceived Stress (PSS); Pain Vigilance and Awareness (PVAQ); Interoceptive/Self-awareness (SAQ); Mindfulness abilities (FFMQ). The network contained 27 non-zero edges out of 45 possible connections (sparsity = 0.40), estimated using the EBICglasso method ($\gamma = 0.5$), with 1,000 non-parametric bootstraps to evaluate edge stability and centrality accuracy.

The visual structure of the network revealed numerous interconnections; thus, the nodes are spatially homogeneous, with no isolated elements, reflecting an interdependence among all the variables. Specifically, the blue thick edges revealed a positive, strong interconnected configuration across affective nodes (depression, anxiety, mental pain) and within allodynia domains. Red medium to thick edges between mindfulness and anxiety express antagonistic regulatory relationships. The strongest positive partial correlations were observed among psychological measures, forming a stable affective core cluster (BDI – STAI-Y2 = 0.35; BDI – MPQ = 0.31; STAI-Y1 – STAI-Y2 = 0.29). Weaker positive edges linked Allodynia in Daily Life to attention to Interoceptive and bodily pain (Allodynia Daily Life – SAQ = 0.17; Allodynia Daily Life – PVAQ = 0.15), supporting the role of attentional

hypervigilance toward pain as a factor amplifying allodynic experiences. In contrast, a negative correlation appeared between FFMQ and STAI-Y2 (–0.38), highlighting mindfulness as a protective factor against anxiety, consistent with theoretical models that posit mindfulness as a resilience or regulatory factor in affective disorders.

The centrality profile delineates a system organised around affective nodes, especially of depression and anxiety, that extends outward to somatic–interoceptive domains. Emotional dysregulation (depression, anxiety) emerged as the most central, strong and robust actor. Allodynia, particularly the daily-life form, lacks structural independence; thus, it appears to be a downstream expression of emotional dysregulation, and its centrality values confirm its receiving rather than driving role. Mindfulness emerges as a negative node**,** weakening network propagation and highlighting the potential for top-down regulation of negative emotions, which indirectly mitigates allodynic sensitivity (see Figures 4.6 and 4.7; Tables 4.4 and 4.5).

**Overall Cutaneous Allodynia Network**

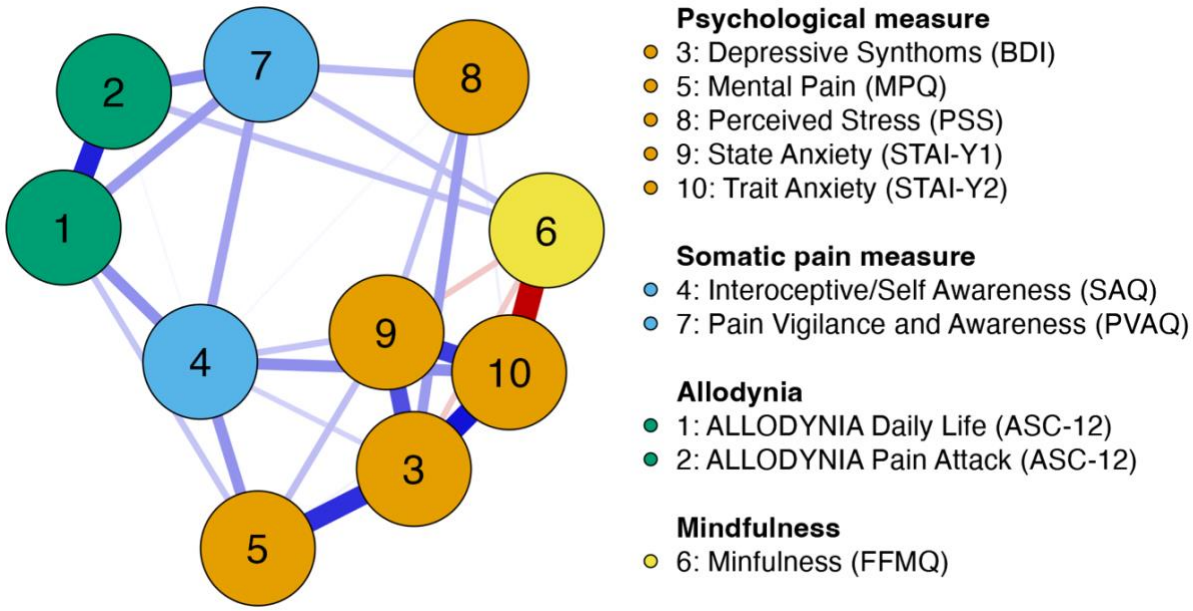


Figure 4.6: Network analysis plot of Cutaneous Allodynia of the sample across Affective (Psychological) measure: depressive symptoms (BDI), Mental Pain (MPQ), Perceived stress (PSS), anxiety (STAI-Y1,2); Somatic pain measure: Interoceptive/Self-awareness (SAQ), Pain Vigilance and Awareness (PVAQ). Mindfulness abilities: FFMQ. Allodynia (ASC-12): allodynia symptoms in daily life and during pain attacks. Legend: Red lines indicate a negative relation; Blue lines indicate a positive relation. The thickness of the lines is proportional to the strength of the relationships (edges) and the partial correlations across the variables of interest (nodes).

| Overall Allodynia Weights matrix | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **BDI** | **MPQ** | **STAI-Y1** | **STAI-Y2** | **SAQ** | **PVAQ** | **PSS** | **FFMQ** | **ASC-D** | **ASC-PA** |
| **BDI** | 0.00 | 0.31 | 0.26 | 0.35 | 0.07 | 0.00 | 0.15 | -0.08 | 0.00 | 0.00 |
| **MPQ** | 0.31 | 0.00 | 0.10 | 0.02 | 0.16 | 0.00 | 0.00 | 0.00 | 0.09 | 0.00 |
| **STAI-Y1** | 0.26 | 0.10 | 0.00 | 0.29 | 0.09 | 0.00 | 0.09 | -0.08 | 0.00 | 0.00 |
| **STAI-Y2** | 0.35 | 0.02 | 0.29 | 0.00 | 0.17 | 0.00 | 0.02 | -0.38 | 0.00 | 0.00 |
| **SAQ** | 0.07 | 0.16 | 0.09 | 0.17 | 0.00 | 0.14 | 0.01 | 0.00 | 0.17 | 0.01 |
| **PVAQ** | 0.00 | 0.00 | 0.00 | 0.00 | 0.14 | 0.00 | 0.11 | 0.10 | 0.15 | 0.17 |
| **PSS** | 0.15 | 0.00 | 0.09 | 0.02 | 0.01 | 0.11 | 0.00 | 0.00 | 0.00 | 0.00 |
| **FFMQ** | -0.08 | 0.00 | -0.08 | -0.38 | 0.00 | 0.10 | 0.00 | 0.00 | 0.00 | 0.10 |
| **ASC-D** | 0.00 | 0.09 | 0.00 | 0.00 | 0.17 | 0.15 | 0.00 | 0.00 | 0.00 | 0.33 |
| **ASC-PA** | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.17 | 0.00 | 0.10 | 0.33 | 0.00 |

Table 4.4: Weight matrix of Overall Cutaneous Allodynia Network variables. Strongest positive partial correlations were observed among affective constructs (BDI, STAY 1,2, MPQ). Weak positive edges linked allodynia and somatic domains (SAQ, PVAQ). A negative correlation was observed between FFMQ and Anxiety, suggesting that mindfulness may serve as a protective factor.

| Centrality measures | | | | |
|---|---|---|---|---|
| **Variable** | **Betweenness** | **Closeness** | **Strength** | **Expected influence** |
| **ASC-D** | -0.38 | -0.88 | -0.23 | 0.41 |
| **ASC-PA** | -0.62 | -1.12 | -0.71 | 0.08 |
| **BDI** | 1.05 | 0.74 | 1.60 | 1.28 |
| **SAQ** | -0.14 | 0.78 | 0.06 | 0.62 |
| **MPQ** | -0.62 | 0.43 | -0.47 | 0.25 |
| **FFMQ** | 0.57 | 0.70 | -0.22 | -2.47 |
| **PVAQ** | -0.38 | -0.85 | -0.52 | 0.21 |
| **PSS** | -0.86 | -1.25 | -1.57 | -0.53 |
| **STAI-Y1** | -0.86 | -0.21 | 0.43 | 0.44 |
| **STAI-Y2** | 2.24 | 1.68 | 1.63 | -0.29 |

Table 4.5: Centrality Analysis Matrix across the nodes of the Overall Cutaneous Allodynia Network.

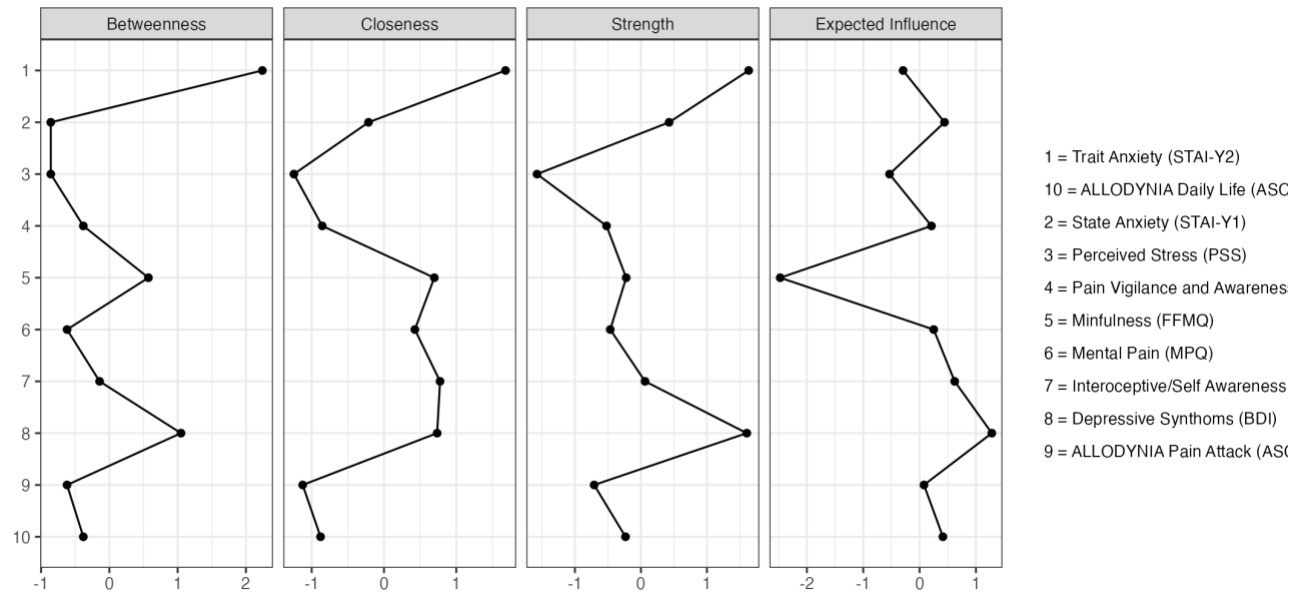


Figure 4.7: Graphic representation of Centrality Analysis of the nodes of the Overall Cutaneous Allodynia Network

Edge stability was estimated by adopting 1000 bootstraps. The plot reports, for each edge, the sample-estimated edge value (red dots), the average of the bootstrapped estimated networks (black dots), and the 95% confidence intervals of the bootstrapped networks (grey shadows). The edge stability analysis indicates that the most stable and replicable edges were those linking Depression to Anxiety measures, and the two forms of Allodynia, showing minimal bootstrap fluctuation. This stability validates the centrality of affective distress within the model.

In contrast, the red sample line declined, indicating that some edges (especially peripheral ones involving allodynia) fluctuated under case-dropping and were less stable, due to smaller partial correlations and higher sampling variability. The links Allodynia Daily–SAQ and Allodynia Daily–MPQ persist in a directionally positive manner across bootstraps, but their magnitude varies, indicating fragile yet consistent associations. The pattern suggests that the sensory-affective interface is weakly stable, i.e., allodynia is associated with affective distress; however, these connections are small and fluctuate with sample composition. This is typical for peripheral nodes with low strength. Given the bootstrapped edge stability pattern, the affective variables (BDI–MPQ–STAI-Y2) can be considered a robust structural core.

In contrast, the allodynia-related edges should be interpreted cautiously rather than as reliable pathways and should be viewed exploratorily. This pattern implies moderate overall stability: the central affective edges (BDI–MPQ–STAI-Y2) are highly stable (CS $\approx$ 0.5–0.6), and the peripheral sensory edges (Allodynia Daily–SAQ, Allodynia Daily–PVAQ) are less stable (CS $\leq$ 0.25). Mindfulness and perceived stress appeared to be peripheral nodes, displaying lower edge stability, suggesting that their roles may vary across contexts or depend on other moderators (see Figure 4.8).

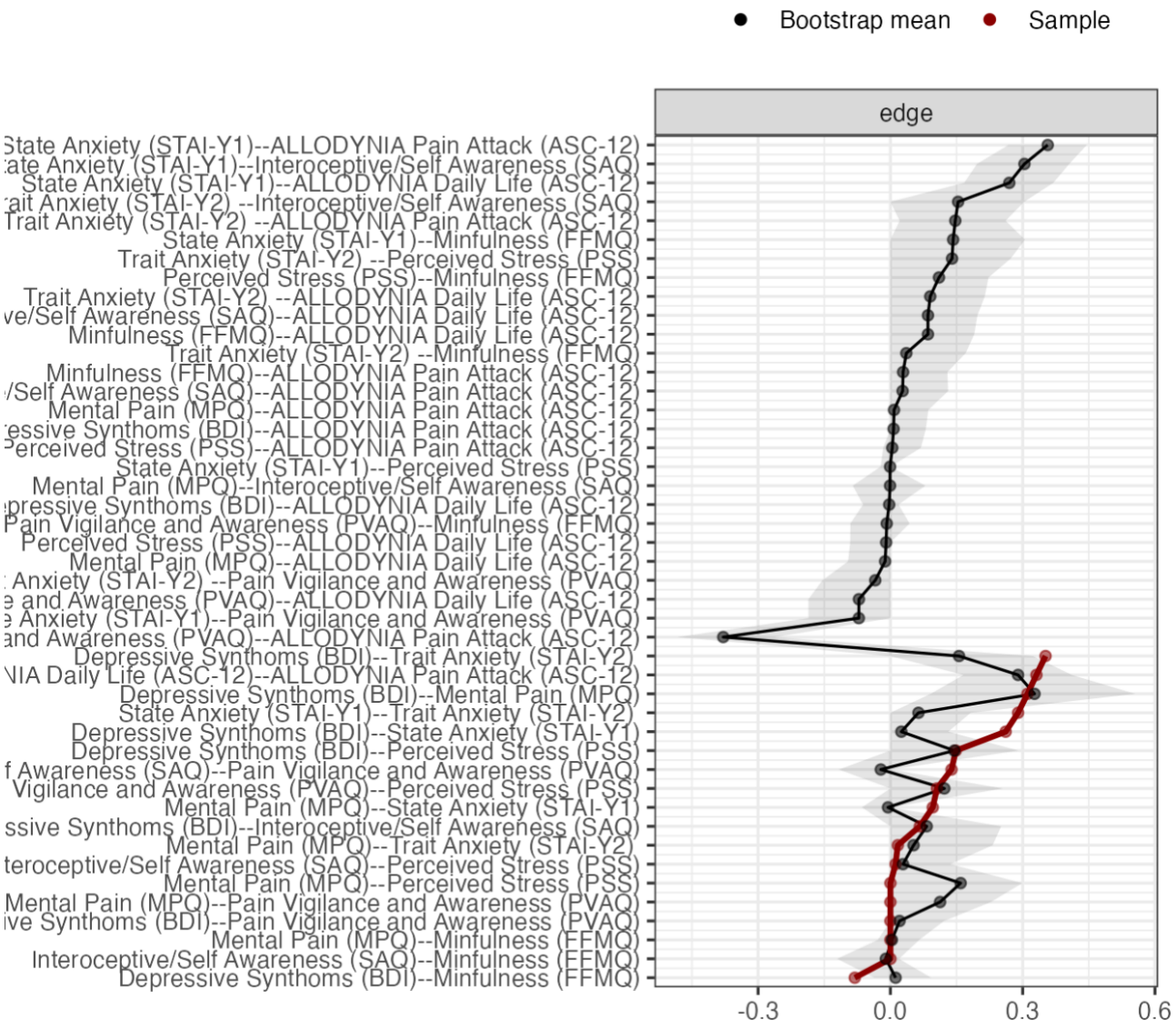


Figure 4.8: Edge stability of the Overall Cutaneous Allodynia Network. The black line represents the average edge-weight correlation across 1000 bootstrap replications. The red line represents the result of correlations between the edge weights in the full-sample network, indicating the network's robustness to variations in data size. Affective variables (BDI–MPQ–STAI-Y2) can be considered a robust structural core, while allodynia-related edges present fragile associations.

## Correlation Matrix

A correlation analysis was performed to investigate the relationship between allodynia and selected variables. Allodynia in daily life (ASC_D) exhibited positive correlation with mood features: depression (BDI, r = 0.232), mental pain (MPQ, r = 0.281), and anxiety (STAY-1, r = 0.152; STAY-2, r = 0.185), suggesting an interplay between emotional distress and altered pain perception. Additionally, Allodynia in daily life (ASC_D) showed a positive relationship with interoception and

attention to bodily pain sensations (SAQ, r = 0.363; PVAQ, r = 0.349). Allodynia in pain attack (ASC_PA) is connected only to somatic indices (SAQ, r = 0.184; PVAQ, r = 0.341), supporting the hypothesis of a vicious cycle among these facets (see Table 4.6).

**Correlation Matrix**

| | ASC_D | ASC_PA | PVAQ | PSS | BDI | STAI-Y1 | STAI-Y2 | MPQ | SAQ | FFMQ |
|---|---|---|---|---|---|---|---|---|---|---|
| **ASC_D** | — | | | | | | | | | |
| **ASC_PA** | 0.459*** | — | | | | | | | | |
| **PVAQ** | 0.349*** | 0.341*** | — | | | | | | | |
| **PSS** | 0.148 | 0.055 | 0.212** | — | | | | | | |
| **BDI** | 0.232** | -0.003 | 0.085 | 0.434*** | — | | | | | |
| **STAI-Y1** | 0.152* | -0.026 | 0.043 | 0.398*** | 0.758*** | — | | | | |
| **STAI-Y2** | 0.185* | 0.022 | 0.069 | 0.380*** | 0.807*** | 0.767*** | — | | | |
| **MPQ** | 0.281*** | 0.054 | 0.161* | 0.230** | 0.667*** | 0.566*** | 0.565*** | — | | |
| **SAQ** | 0.363*** | 0.184* | 0.285*** | 0.295*** | 0.549*** | 0.524*** | 0.565*** | 0.510*** | — | |
| **FFMQ** | -0.008 | 0.180* | 0.133 | -0.246** | -0.600*** | -0.578*** | -0.711*** | -0.412*** | -0.385*** | — |

**Note. * p < .05, ** p < .01, *** p < .001**

Table 4.6: Correlation matrix of the main study variables. The variables include: ASC_D = cutaneous allodynia in daily life (ASC_D), ASC_PA = cutaneous allodynia during pain attacks; BDI = Beck depression Inventory II; MPQ = mental pain questionnaire; PSS = perceived stress scale; STAI-Y1,2 = State-Trait Anxiety Inventory; PVAQ = pain vigilance and attention questionnaire; SAQ = Self-awareness questionnaire; FFMQ = Five Facets Mindfulness Questionnaire total score. Statistically significant correlations are marked with asterisks (*p < .05, **p < .01, ***p < .001).

Network analysis of the presence vs absence of diagnosis of a pain condition

This network analysis compared the connections across features that we supposed to be linked to cutaneous allodynia in people with (Group 1) and without (Group 0) a diagnosis of a pain condition. Each network consisted of ten nodes, reflecting affective, sensory, and regulatory variables. The network comprised ten variables: Allodynia Daily Life (ASC-12), Allodynia Pain Attack (ASC-12), Depression (BDI), State and Trait Anxiety (STAI-Y1/Y2), Mental Pain (MPQ), Pain Vigilance (PVAQ), Interoceptive-Self-Awareness (SAQ), Perceived Stress (PSS), and Mindfulness (FFMQ). Networks were estimated using EBICglasso ($\gamma = 0.5$), with 1,000 bootstraps to evaluate edge stability and centrality accuracy. The network of participants without a pain condition diagnosis (Group 0)

comprised 31 non-zero edges (sparsity = 0.311), whereas that of participants with a pain diagnosis (Group 1) contained 10 non-zero edges (sparsity = 0.778). This difference indicates a markedly denser and more integrated structure among participants without a diagnosis of a pain condition (see Figures 4.9 and 4.10).

Group 0 = Absence of Pain Condition Diagnosis

The network structure exhibited a moderately dense configuration (sparsity = 0.311; 31/45 edges retained). The visual structure of the network showed some medium-to-thick edges, creating a tightly interconnected configuration across nodes from both the affective (depression, anxiety, mental pain) and regulatory (mindfulness, interoception) domains. The overall colour distribution is predominantly blue (positive associations), with few red or negative connections, indicating coordinated coupling rather than antagonistic relationships. The nodes are spatially closer**,** with fewer isolated elements, reflecting stronger interdependence between emotional and somatic variables. Although all ten nodes were connected, the affective variables, mainly depression (BDI), trait and state anxiety (STAI-Y1,2), constituted the core of the network, displaying the strongest and most stable connections. In contrast, allodynia-related nodes (in daily life and pain attacks) were located at the periphery, characterised by weaker and more inconsistent edges (see Figure 4.9).

**Group 0 = Absence of Pain Condition Diagnosis Network**

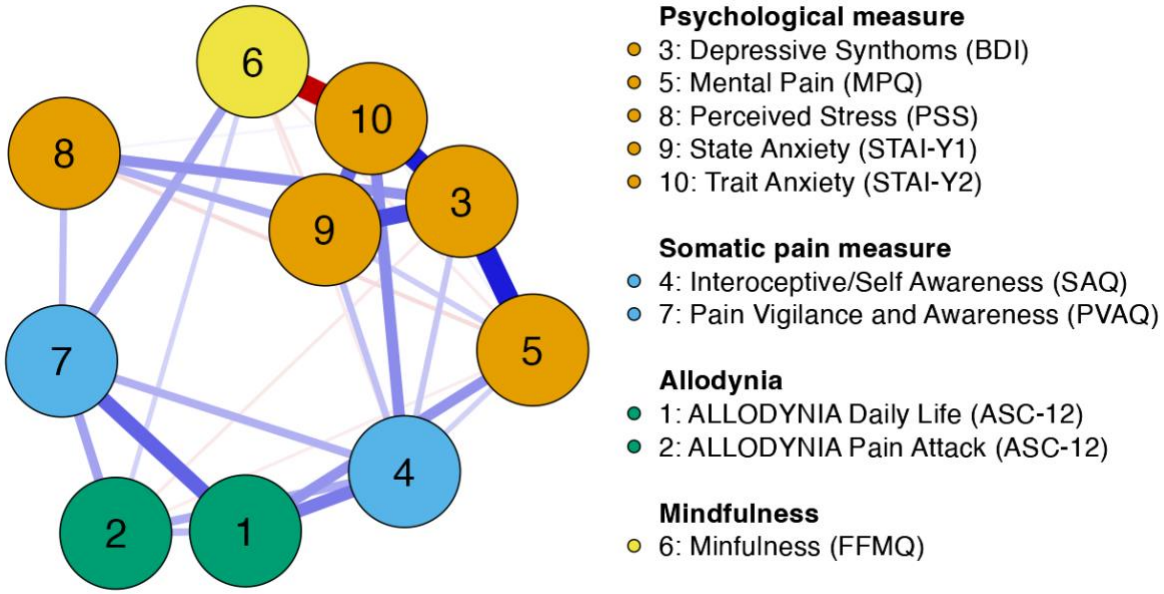


Figure 4.9: Group 0 = Absence of Pain Condition Diagnosis Network analysis plot across Affective (Psychological) measure: depressive symptoms (BDI), Mental Pain (MPQ), Perceived stress (PSS), anxiety (STAI-Y1,2); Somatic pain measure: Interoceptive/Self-awareness (SAQ), Pain Vigilance and Awareness (PVAQ). Mindfulness abilities: FFMQ. Allodynia (ASC-12): allodynia symptoms in daily life and during pain attacks.

The strongest edges in the network linked the affective variables: BDI – STAI-Y2 = 0.36, BDI – STAI-Y1 = 0.29, STAI-Y1 – STAI-Y2 = 0.24, and BDI – MPQ = 0.37.

This pattern delineated a robust emotional connection, reflecting a stable dimension of affective distress. Allodynia nodes were partly independent: Allodynia Daily life seems to be more related to attentional and interoceptive awareness (Allodynia Daily Life – SAQ = 0.21), while Allodynia Pain Attack is more related to pain perception, anxiety, and lightly to mindfulness ALLODYNIA Pain Attack (ASC-12) – SAQ = 0.22, ALLODYNIA Pain Attack (ASC-12) – STAI-Y2 = 0.33, ALLODYNIA Pain Attack (ASC-12) – FFMQ = 0.34). Additionally, FFMQ - STAI-Y2 = -0.473 indicates that higher mindfulness is linked to lower trait anxiety.

In the absence of a diagnosis of chronic pain, the network remains emotionally balanced and modular, where allodynia-related dimensions (ASC-D, ASC-PA) interact moderately with somatic and anxiety-related processes. The association of body awareness (SAQ) and pain vigilance (PVAQ) with daily-life allodynia suggests that attentional focus on bodily sensations may modulate perceived pain intensity even in the absence of pathology (see Table 4.7)

| GROUP 0 Weights Matrix | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **ASC-D** | **ASC-PA** | **BDI** | **MPQ** | **STAI-Y1** | **STAI-Y2** | **SAQ** | **PVAQ** | **PSS** | **FFMQ** |
| **ASC-D** | 0.000 | -0.06 | 0.055 | 0.000 | 0.066 | 0.007 | 0.226 | 0.081 | -0.128 | 0.000 |
| **ASC-PA** | 0.055 | 0.00 | 0.000 | 0.377 | 0.309 | 0.310 | 0.000 | 0.000 | 0.171 | -0.048 |
| **BDI** | 0.055 | -0.06 | 0.000 | 0.377 | 0.309 | 0.310 | 0.000 | 0.000 | 0.171 | -0.048 |
| **MPQ** | 0.000 | 0.17 | 0.377 | 0.000 | 0.065 | 0.000 | 0.240 | 0.000 | $-7.123\times10^{-4}$ | 0.000 |
| **STAI-Y1** | 0.066 | -0.14 | 0.309 | 0.065 | 0.000 | 0.299 | 0.134 | -0.052 | 0.038 | -0.019 |
| **STAI-Y2** | 0.007 | 0.33 | 0.310 | 0.000 | 0.299 | 0.000 | 0.082 | 0.000 | 0.104 | -0.473 |
| **SAQ** | 0.226 | 0.22 | 0.000 | 0.240 | 0.134 | 0.082 | 0.000 | 0.166 | 0.000 | -0.107 |
| **PVAQ** | 0.081 | 0.12 | 0.000 | 0.000 | -0.052 | 0.000 | 0.166 | 0.000 | 0.125 | 0.122 |
| **PSS** | -0.128 | -0.14 | 0.171 | $-7.123\times10^{-4}$ | 0.038 | 0.104 | 0.000 | 0.125 | 0.000 | 0.000 |
| **FFMQ** | 0.000 | 0.34 | -0.048 | 0.000 | -0.019 | -0.473 | -0.107 | 0.122 | 0.000 | 0.000 |

Table 4.7: Weight matrix of Group 0 = Absence of Pain Condition Diagnosis. Strongest positive partial correlations were observed among affective constructs (BDI, STAY 1,2, MPQ). Weak positive edges link allodynia and somatic domains (SAQ, PVAQ) and mental pain (MPQ). A negative correlation was observed between FFMQ and Anxiety (STAI-Y1,2), suggesting that mindfulness may serve as a protective factor.

Centrality analyses confirmed this organisation. BDI and STAI-Y2 had the highest Strength and Betweenness (BDI = 1.79, STAI-Y2 = 1.39), indicating that they are primary integrative cores. They also exhibited high closeness, suggesting that they can work as integrative hubs connecting distant components of the network. Interoceptive measures, SAQ and PVAQ, displayed moderate Betweenness, serving as a bridge between affective and sensory features.

In contrast, Allodynia Daily Life had a small positive Expected Influence (0.38) but low strength (−0.41), indicating that it received modest input from the affective system without transmitting activation onward. Allodynia Pain Attack displayed both negative strength and influence (EI = −0.46), reinforcing its marginal status. ASC-D (Allodynia Daily Life) and ASC-PA (Allodynia Pain

Attack) displayed low centrality and negative or near-zero influence, consistent with the absence of a pain diagnosis. Allodynia-related awareness remains a latent or peripheral construct, reflecting normal interoceptive variability rather than pathological hypervigilance. PSS (Perceived Stress) exhibited low centrality and a weak positive influence, indicating a peripheral role.

Lastly, Mindfulness (FFMQ) showed a markedly negative expected influence (−2.22) and a low strength (−0.32). The relative isolation of FFMQ in this group indicates that mindfulness operates independently as a self-regulatory system, consistent with adaptive emotional modulation.

Overall, depressive symptoms and trait anxiety function as key network hubs, bridging emotional, cognitive, and perceptual dimensions. The whole architecture reflects a network predominantly organised around internal psychological factors rather than sensory components (see Figure 4.11, Table 4.9).

Group 1 = Presence of Pain Condition Diagnosis

In Group 1, the network pattern was less dense and less integrated, suggesting that chronic pain diagnosis reduces network balance by increasing the dominance of affective distress and weakening integrative regulatory nodes. The visual structure of the network revealed fewer edges compared to Group 0, with medium-to-thick positive edges (blue) primarily connecting nodes from both the affective (depression, anxiety, mental pain) and allodynia nodes, which appear strongly associated and isolated. Mindfulness elicits negative connections with anxiety nodes, indicating antagonistic relationships. The affective nodes are spatially closer**,** while the somatic and allodynia measures seem isolated and poorly connected elements. This configuration reflects a rigid compartmentation, a strong interdependence between emotional variables, and a division of allodynia, somatic and stress nodes (see Figure 4.10).

**Group 1 = Presence of Pain Condition Diagnosis Network**

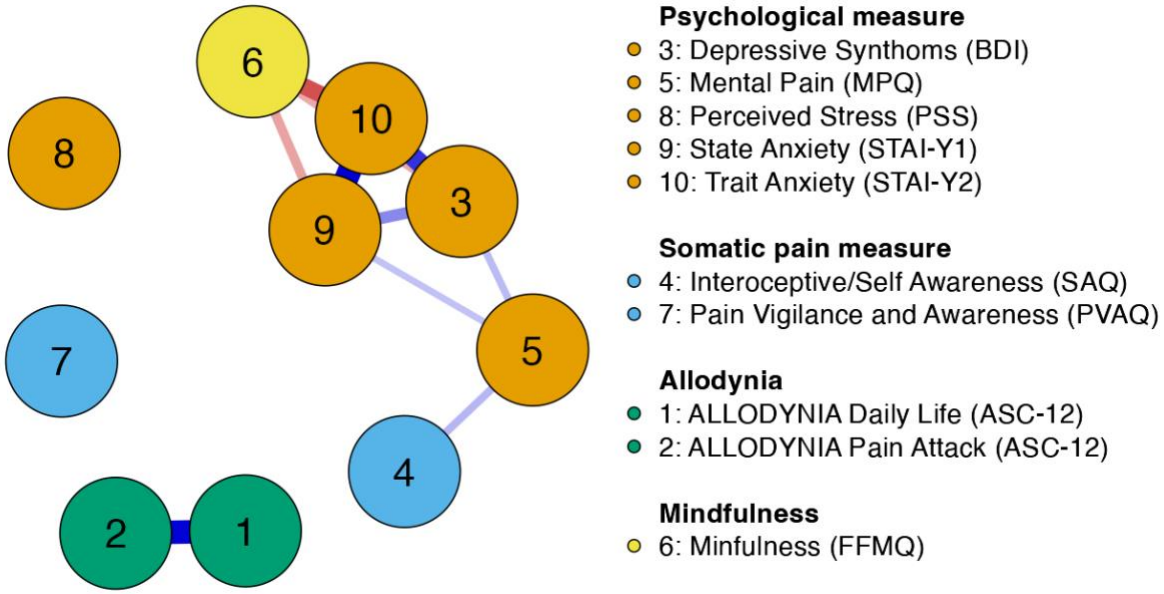


Figure 4.10: Group 1 = Presence of Pain Condition Diagnosis Network analysis plot across Affective (Psychological) measure: depressive symptoms (BDI), Mental Pain (MPQ), Perceived stress (PSS), anxiety (STAI-Y1,2); Somatic pain measure: Interoceptive/Self-awareness (SAQ), Pain Vigilance and Awareness (PVAQ). Mindfulness abilities: FFMQ. Allodynia (ASC-12): allodynia symptoms in daily life and during pain attacks.

The weight matrix revealed that the strongest edges in the network linked the affective variables: BDI – STAI-Y2 = 0.38, BDI – STAI-Y1 = 0.21, suggesting an emotional hyperconnectivity between depression and both forms of anxiety. Also, depressive symptoms are directly associated with mental pain perception: BDI – MPQ = 0.27, and heightened pain vigilance connected to perceived stress: PVAQ - PSS = 0.20. Mindfulness continued to exert an inverse regulatory effect on anxiety: FFMQ - STAI-Y2 = - 0.38. ALLODYNIA Pain Attack (ASC-12) - STAI-Y2 = 0.33. The weight matrix revealed a positive relation between ALLODYNIA Pain Attack (ASC-12) – PVAQ = 0.21, suggesting that pain vigilance is related to the presence of allodynia during the pain attacks, and a further positive relation between ALLODYNIA Daily (ASC-12) – SAQ = 0.11 confirm the role of interoceptive/self-awareness in allodynic symptoms. This pattern delineated a robust emotional connection, reflecting a stable dimension of affective distress.

Centrality analyses confirmed that, in sufferers of pain conditions, the network becomes emotionally saturated and structurally compact, with stronger interconnections among anxiety, depression, and within allodynia-related dimensions. The topology reflects functional integration at the cost of flexibility, a potential hallmark of chronic pain psychopathology.

The central dominance of emotional variables (anxiety and depression) was confirmed. BDI increased its centrality (Strength 0.90, EI 0.80) and remains highly interconnected with both trait and state anxiety. Anxiety STA Y1 strength rises markedly (1.13) with high positive EI (0.97), as well as STA Y2 (strength = 1.62, EI = 0.71), which means that anxiety gains structural weight in the pain network, reflecting heightened emotional reactivity. ASC-D (Allodynia Daily Life) and ASC-PA (Allodynia Pain Attack) exhibit increased strength and a positive expected influence (0.55), forming a closely linked subsystem. Their strengthened connection (edge weight 0.55) indicates synergistic activation between daily and episodic allodynia. Higher scores of allodynia in terms of betweenness and strength suggest an integration within the affective core; allodynia pain processing could have become affectively charged, no longer restricted to somatic dimensions.

Despite the negative expected influence of FFMQ (EI = -2.30), its centrality decreases compared to the non-pain group. This reduction in structural importance implies weakened self-regulatory capacity, consistent with findings that chronic pain disrupts the attentional–mindfulness system. The inverse relation with trait anxiety remains significant, confirming its persistent but marginalised regulatory role. PSS and PVAQ show negative strength (-1.26) and negative EI (-0.64).

Although structurally less central, they could have a possible maladaptive stress–vigilance coupling in which excessive vigilance no longer enhances awareness but promotes emotional weakening. SAQ exhibits a negative expected influence (-0.30), indicating that hyperattention to somatic sensations may contribute, albeit minimally, when emotional nodes dominate (see Tables 4.8 and 4.9, Figure 4.11).

| GROUP 1 Weights Matrix | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **ASC-D** | **ASC-PA** | **BDI** | **MPQ** | **STAI-Y1** | **STAI-Y2** | **SAQ** | **PVAQ** | **PSS** | **FFMQ** |
| **ASC-D** | 0.00 | 0.55 | 0.00 | 0.00 | 0.00 | 0.00 | 0.11 | 0.00 | $4.03\times10^{-3}$ | 0.08 |
| **ASC-PA** | 0.55 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | $6.12\times10^{-3}$ | 0.21 | 0.00 | 0.07 |
| **BDI** | 0.00 | 0.00 | 0.00 | 0.27 | 0.21 | 0.32 | 0.00 | 0.00 | 0.16 | -0.07 |
| **MPQ** | 0.00 | 0.00 | 0.27 | 0.00 | 0.16 | 0.00 | 0.21 | 0.00 | 0.00 | 0.00 |
| **STAI-Y1** | 0.00 | 0.00 | 0.21 | 0.16 | 0.00 | 0.45 | 0.13 | 0.00 | 0.00 | -0.04 |
| **STAI-Y2** | 0.00 | 0.00 | 0.32 | 0.00 | 0.45 | 0.00 | 0.07 | 0.00 | 0.11 | -0.38 |
| **SAQ** | 0.11 | $6.12\times10^{-3}$ | 0.00 | 0.21 | 0.13 | 0.07 | 0.00 | 0.12 | $5.55\times10^{-3}$ | 0.00 |
| **PVAQ** | 0.00 | 0.21 | 0.00 | 0.00 | 0.00 | 0.00 | 0.12 | 0.00 | 0.20 | 0.14 |
| **PSS** | $4.03\times10^{-3}$ | 0.00 | 0.16 | 0.00 | 0.00 | 0.11 | $5.55\times10^{-3}$ | 0.20 | 0.00 | 0.00 |
| **FFMQ** | 0.08 | 0.07 | -0.07 | 0.00 | -0.04 | -0.38 | 0.00 | 0.14 | 0.00 | 0.00 |

Table 4.8: Weight matrix of Group 1 = Presence of Pain Condition Diagnosis. The strongest edges in the network linked the affective variables, suggesting an emotional hyperconnectivity between depression and both forms of anxiety. Mindfulness continued to exert an inverse regulatory effect on anxiety. The positive relationship between allodynia and somatic measures (PVAQ, SAQ) confirms the role of interoception and self-awareness in the development of allodynic symptoms.

| Centrality measures in Absence /Presence of Pain diagnosis | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 0 | | | | Group 1 | | | |
| Variable | Betweenness | Closeness | Strength | Expected influence | Betweenness | Closeness | Strength | Expected influence |
| ASC-D | -0.16 | -0.14 | -0.41 | 0.38 | -0.62 | 0.00 | -0.11 | 0.55 |
| ASC-PA | -0.94 | -1.91 | -1.21 | -0.46 | -0.62 | 0.00 | -0.11 | 0.55 |
| BDI | 1.15 | 1.15 | 1.79 | 1.51 | 1.45 | 0.00 | 0.90 | 0.80 |
| SAQ | 0.10 | 0.11 | 0.38 | 0.73 | -0.62 | 0.00 | -0.93 | -0.30 |
| MPQ | -0.42 | 0.40 | -0.09 | 0.01 | 1.45 | 0.00 | -0.34 | 0.31 |
| FFMQ | -0.16 | 0.39 | -0.32 | -2.22 | -0.62 | 0.00 | 0.34 | -2.30 |
| PVAQ | 0.10 | -0.19 | -0.28 | 0.46 | -0.62 | 0.00 | -1.26 | -0.64 |
| PSS | -0.94 | -1.11 | -1.37 | -0.52 | -0.62 | 0.00 | -1.26 | -0.64 |
| STAI-Y1 | -0.94 | -0.23 | 0.11 | 0.51 | -0.62 | 0.00 | 1.13 | 0.97 |
| STAI-Y2 | 2.19 | 1.53 | 1.39 | -0.41 | 1.45 | 0.00 | 1.62 | 0.71 |

Table 4.9: Centrality Analysis Matrix in Group 0 = Absence of Pain Condition Diagnosis and Group 1 = Presence of Pain Condition Diagnosis across the nodes of the network.

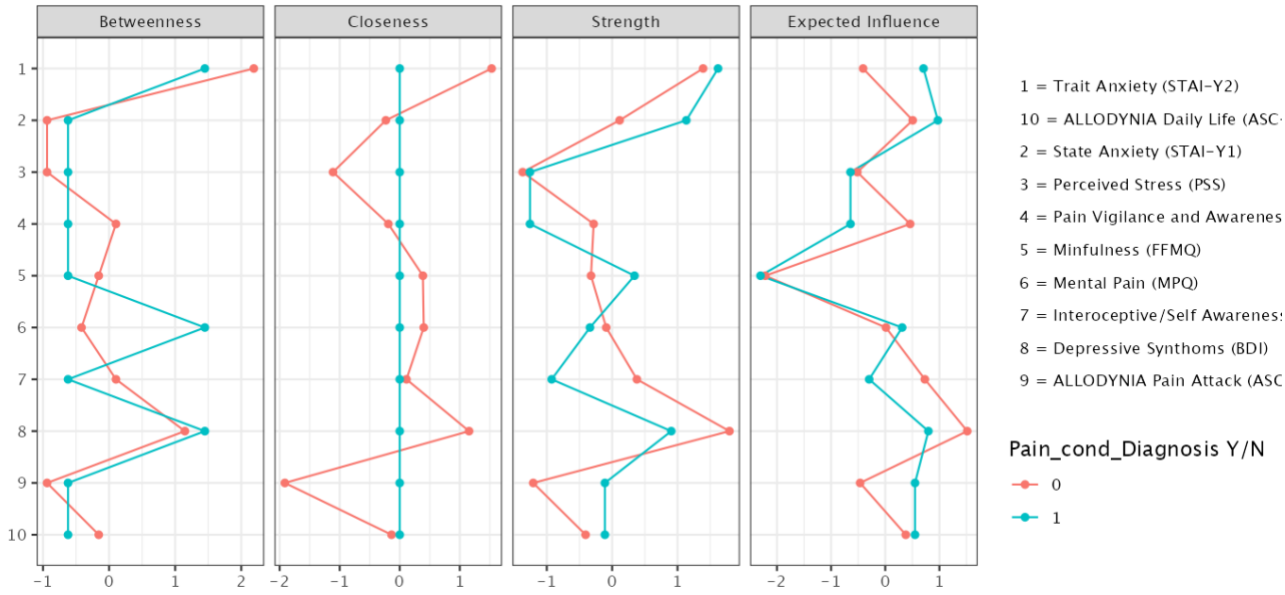


Figure 4.11: Graphic representation of Centrality Analysis of the nodes split by group (0 = absence of pain condition diagnosis; 1 = presence of pain condition diagnosis).

Network analysis of the absence or presence of pain in other medical conditions

This network analysis compared the connections across features that we supposed to be linked to cutaneous allodynia in people experiencing pain with (Group 1) and without (Group 0) a diagnosis of a medical condition.

Each network consisted of ten nodes, reflecting affective, sensory, and regulatory variables. The network comprised ten variables: Allodynia Daily Life (ASC-12), Allodynia Pain Attack (ASC-12), Depression (BDI), State and Trait Anxiety (STAI-Y1/Y2), Mental Pain (MPQ), Pain Vigilance (PVAQ), Interoceptive-Self-Awareness (SAQ), Perceived Stress (PSS), and Mindfulness (FFMQ). Networks were estimated using EBICglasso ($\gamma = 0.5$), with 1,000 bootstraps to evaluate edge stability and centrality accuracy. The network of participants without pain (Group 0) comprised 29 non-zero edges (sparsity = 0.36), whereas that of participants with pain (Group 1) contained 22 non-zero edges (sparsity = 0.51) (see Figures 4.12 and 4.13).

Group 0: Absence of Pain in the Medical Conditions Network

The visual structure of the network revealed numerous interconnections; the nodes are spatially homogeneous, with no isolated elements, indicating an interdependence among all the variables.

Specifically, the blue thick edges revealed a positive, strong interconnected configuration across affective nodes (depression, anxiety, mental pain) and within allodynia domains. Similarly, allodynia in daily life is strongly positively interrelated to pain and vigilance to pain, suggesting a coordinated interaction. Red medium to thick edges between mindfulness and anxiety, as well as between mindfulness and somatic interoceptive nodes, reveal antagonistic regulatory relationships.

**Group 0: Absence of Pain in the Medical Conditions Network**

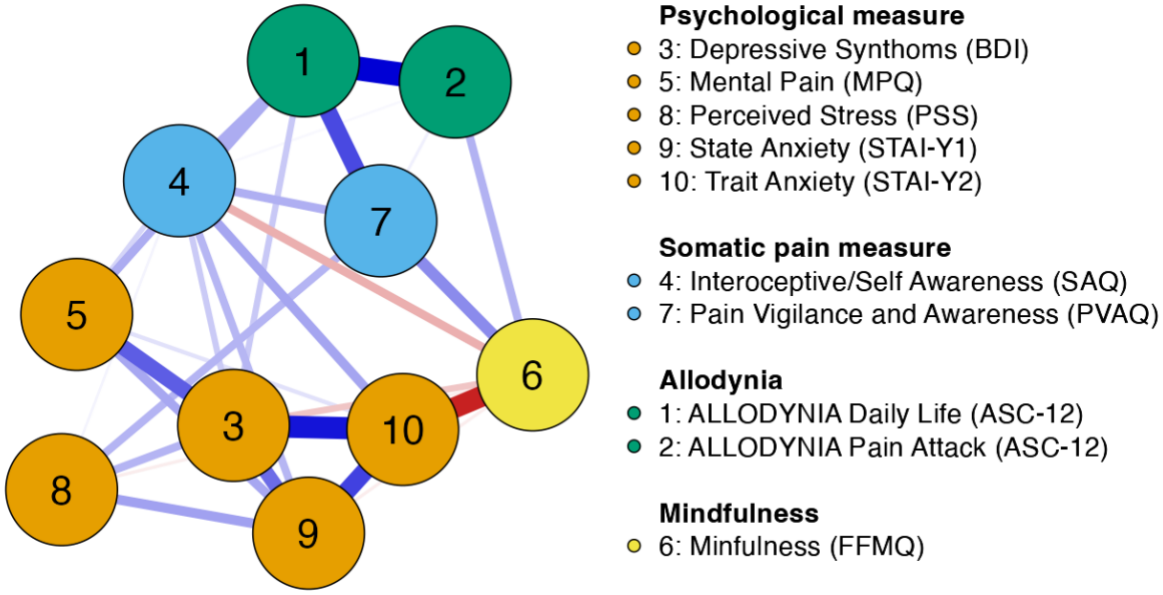


Figure 4.12: Group 0 = Absence of Pain in the Medical Conditions Network analysis plot across Affective (Psychological) measure: depressive symptoms (BDI), Mental Pain (MPQ), Perceived stress (PSS), anxiety (STAI-Y1,2); Somatic pain measure: Interoceptive/Self-awareness (SAQ), Pain Vigilance and Awareness (PVAQ). Mindfulness abilities: FFMQ. Allodynia (ASC-12): allodynia symptoms in daily life and during pain attacks.

Although all ten nodes were connected, the affective variables, mainly depression (BDI), trait and state anxiety (STAI-Y1,2), constituted the core of the network, displaying the strongest and most stable connections. In contrast, allodynia-related nodes (in daily life and pain attacks) were located at the periphery, characterised by weaker and more inconsistent edges.

In the absence of pain, the network configuration displayed moderate connectivity and a relatively balanced structure among psychological, cognitive, and emotional variables (see Figure 4.12). The strongest edges in the network linked the affective variables: BDI – STAI-Y2 = 0.37, BDI – STAI-Y1 = 0.23, and BDI – MPQ = 0.26, confirming the connection among anxiety, depression, and mental

pain symptoms. ALLODYNIA Daily (ASC-12) – PVAQ = 0.29; node relation suggests that pain vigilance is related to the presence of allodynia. Negative weights appeared mainly between mindfulness and anxiety (FFMQ - STAI-Y2 = -0.35), proposing that higher mindfulness may protect against anxiety (see Table 4.10).

The centrality analysis revealed a pattern of distributed importance across several psychological domains. The structure suggested no single dominant node, but rather a balanced interaction among variables, indicative of a psychologically stable and adaptive network. BDI ( strength = 1.43) had the highest strength, meaning it was strongly connected to multiple nodes (especially anxiety and stress). Its expected influence (EI = 1.13) suggests that although depressive symptoms are present, their net effect within the network is balanced by protective factors. For example, FFMQ, despite having moderate strength (strength = 0.27), had a negative expected influence (EI = -2.33), consistent with its inverse relationship with distress variables. STAI-Y2 (strength = 1.31), together with FFMQ, showed the highest betweenness was observed (STAI-Y2 betweenness = 1.98) and FFMQ (betweenness = 1.08). These findings indicate that anxiety regulation and mindfulness are pivotal in maintaining emotional balance when pain is absent. ASC-Daily also demonstrated positive betweenness (0.48), suggesting some contribution to network integration.

Negative betweenness values for variables such as ASC-PA (-1.02), PSS (-1.02), STA Y1 (-1.02), SAQ (-1.02), and MPQ (-0.72) indicate low connectivity and limited influence on other nodes, consistent with a non-pathological state. Consistent results came from closeness values; low or negative closeness for ASC-PA (-0.99) and PSS (-1.62) suggests peripheral placement and lower communication efficiency. FFMQ (1.12) and STAI-Y2 (1.60) displayed the highest closeness values, reflecting their proximity to all other nodes and their rapid access to information exchange across the network. High closeness of mindfulness implies rapid connectivity across domains, supporting top-down modulation of negative affect and attentional control. BDI (0.73) also presented moderate closeness, indicating that depressive symptoms are integrated within the network but not dominant.

Overall, the network configuration suggests a stable and efficient emotional regulation system, where mindfulness and trait anxiety facilitate functional coordination (see Table 4.12 and Figure 4.14).

| GROUP 0 Weights Matrix | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **ASC-D** | **ASC-PA** | **BDI** | **MPQ** | **STAI-Y1** | **STAI-Y2** | **SAQ** | **PVAQ** | **PSS** | **FFMQ** |
| **ASC-D** | 0.00 | 0.41 | 0.09 | 0.13 | 0.00 | 0.00 | 0.13 | 0.29 | 0.00 | 0.00 |
| **ASC-PA** | 0.41 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.02 | 0.00 | 0.12 |
| **BDI** | 0.09 | 0.00 | 0.00 | 0.26 | 0.23 | 0.37 | 0.08 | 0.00 | 0.12 | -0.09 |
| **MPQ** | 0.13 | 0.00 | 0.26 | 0.00 | 0.14 | 0.05 | 0.07 | 0.00 | 0.00 | 0.00 |
| **STAI-Y1** | 0.00 | 0.00 | 0.23 | 0.14 | 0.00 | 0.30 | 0.12 | 0.00 | 0.15 | -0.03 |
| **STAI-Y2** | 0.00 | 0.00 | 0.37 | 0.05 | 0.30 | 0.00 | 0.14 | 0.00 | 0.00 | -0.35 |
| **SAQ** | 0.13 | 0.01 | 0.08 | 0.07 | 0.12 | 0.14 | 0.00 | 0.13 | 0.02 | -0.13 |
| **PVAQ** | 0.29 | 0.02 | 0.00 | 0.00 | 0.00 | 0.00 | 0.13 | 0.00 | 0.12 | 0.18 |
| **PSS** | 0.00 | 0.00 | 0.12 | 0.00 | 0.15 | 0.00 | 0.02 | 0.12 | 0.00 | -0.03 |
| **FFMQ** | 0.00 | 0.12 | -0.09 | 0.00 | -0.03 | -0.35 | -0.13 | 0.18 | -0.03 | 0.00 |

Table 4.10: Weight matrix of Group 0 = Absence of Pain in the Medical Conditions. The strongest edges in the network linked the affective variables. Mindfulness shows a regulatory effect on anxiety. The positive relationship between allodynia and somatic measures (PVAQ) confirms the role of interoception and self-awareness in the development of allodynic symptoms.

Group 1: Presence of Pain in the Medical Conditions

The visual structure of the network showed many interconnections; the nodes are spatially homogeneous, with no isolated elements, reflecting an interdependence between all the variables, as well as the Group 0. However, the blue thick edges revealed a positive appearance, looking stronger and larger than in Group 0. In the presence of pain, the affective nodes (depression, anxiety, mental pain) are more widely interconnected to somatic nodes (interoception, bodily pain attention), which seemed to be potential mediators between allodynia and affective features. Allodynia measures are

strongly interconnected and spread their connections to other nodes, appearing as integrated and not isolated elements of the network. Red medium to thick edges between mindfulness and anxiety reveal antagonistic regulatory relationships. Also, light negative edges between state anxiety and daily allodynia and pain vigilance, the last one is also negatively connected to depression, suggest an interesting interplay among mood, sensory perception (allodynia), and attention to bodily pain. This change indicates that psychological interdependencies become tighter and more mutually reinforcing in the presence of pain, indicating reduced flexibility and increased emotional entanglement (see Figure 4.13).

**Group 1: Presence of Pain in the Medical Conditions Network**

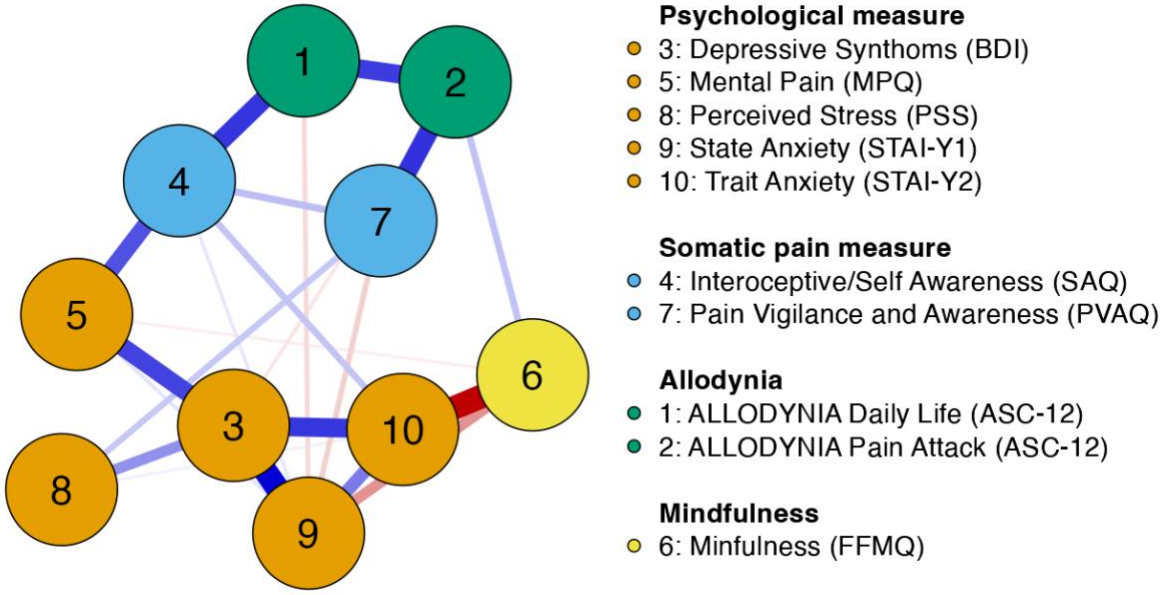


Figure 4.13: Group 1 = Presence of Pain in the Medical Conditions Network analysis plot across Affective (Psychological) measure: depressive symptoms (BDI), Mental Pain (MPQ), Perceived stress (PSS), anxiety (STAI-Y1,2); Somatic pain measure: Interoceptive/Self-awareness (SAQ), Pain Vigilance and Awareness (PVAQ). Mindfulness abilities: FFMQ. Allodynia (ASC-12): allodynia symptoms in daily life and during pain attacks.

The weight matrix indicated key high-weight edges (≥ 0.30). Depression and anxiety links are the strongest and most stable in the network: BDI – STAI-Y1 = 0.42, BDI – STAI-Y2 = 0.33. They form core nodes of the pain network. This connection supports the idea that pain experience amplifies emotional distress, producing an enduring depression–anxiety dyad. Also, depression resulted in being linked to mental pain (BDI – MPQ = 0.31), which is also related to (MPQ – SAQ = 0.29),

suggesting an interplay between managing painful emotions and bodily sensations. Allodynia reveals a cohesive subnetwork of self-awareness and attentional bias. The strong coupling between Allodynia Daily (ASC-12) – SAQ = 0.34 and Allodynia pain attacks (ASC-12) – PVAQ = 0.34 suggests that alterations in pain perception (allodynia) are associated with heightened pain vigilance and monitoring, an attentional mechanism often observed in chronic pain.

Several negative weights were observed, mostly involving mindfulness: FFMQ – STAI-Y2 = -0.42 and FFMQ – STAI-Y1 = -0.18, indicating that mindfulness still exerts a weak inhibitory role on anxiety, but with a diminished influence compared to Group 0 (see Table 4.11).

| GROUP 1 Weights Matrix | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **ASC-D** | **ASC-PA** | **BDI** | **MPQ** | **STAI-Y1** | **STAI-Y2** | **SAQ** | **PVAQ** | **PSS** | **FFMQ** |
| **ASC-D** | 0.00 | 0.32 | 0.00 | 0.00 | -0.06 | 0.00 | 0.34 | 0.00 | 0.00 | 0.00 |
| **ASC-PA** | 0.32 | 0.00 | -0.04 | 0.00 | 0.00 | 0.00 | 0.00 | 0.34 | 0.00 | 0.10 |
| **BDI** | 0.00 | -0.04 | 0.00 | 0.31 | 0.42 | 0.33 | 0.00 | 0.00 | 0.18 | 0.00 |
| **MPQ** | 0.00 | 0.00 | 0.31 | 0.00 | 0.04 | 0.00 | 0.29 | 0.00 | 0.00 | -0.03 |
| **STAI-Y1** | -0.06 | 0.00 | 0.42 | 0.04 | 0.00 | 0.22 | 0.04 | -0.08 | 0.00 | -0.18 |
| **STAI-Y2** | 0.00 | 0.00 | 0.33 | 0.00 | 0.22 | 0.00 | 0.10 | 0.00 | 0.02 | -0.42 |
| **SAQ** | 0.34 | 0.00 | 0.00 | 0.29 | 0.04 | 0.10 | 0.00 | 0.11 | 0.00 | 0.00 |
| **PVAQ** | 0.00 | 0.34 | 0.00 | 0.00 | -0.08 | 0.00 | 0.11 | 0.00 | 0.09 | 0.00 |
| **PSS** | 0.00 | 0.00 | 0.18 | 0.00 | 0.00 | 0.02 | 0.00 | 0.09 | 0.00 | 0.00 |
| **FFMQ** | 0.00 | 0.10 | 0.00 | -0.03 | -0.18 | -0.42 | 0.00 | 0.00 | 0.00 | 0.00 |

Table 4.11: Weight matrix of Group 1 = Presence of Pain in the Medical Conditions cross variables. The strongest edges in the network linked the affective variables. Mindfulness shows a regulatory effect on anxiety. The positive relationship between allodynia and somatic measures (PVAQ, SAQ) links the allodynia to heightened pain vigilance and interoceptive monitoring. Mindfulness exhibits a mild inhibitory role on anxiety,

The centrality analysis revealed a pattern of marked reorganisation of centrality structure, characterised by the dominance of depressive and anxiety symptoms. The centrality indices indicate a shift from balanced regulation to symptom clustering, where the BDI becomes the principal hub driving network dynamics, a centralisation of affective distress often seen in chronic pain conditions. BDI exhibited the highest strength (strength = 1.70) and expected influence (EI = 1.56) across the entire model, confirming its dominant and activating role. Its widespread positive connections with

STAI-Y1, STAI-Y2, MPQ, and PSS emphasise depression as the key driver of psychological dysregulation in pain. STAI-Y2 (strength = 1.01) and STAI-Y1 (strength = 0.80) remained active, forming a depression–anxiety dyad that sustains affective reactivity. MPQ (strength = -0.51) presented moderate strength, reinforcing the emotional distress. FFMQ (strength = -0.29, EI = -2.23) and PVAQ (strength = -0.70, EI = -0.05) exhibited negative strength and expected influence, indicating attenuated or inhibitory contributions with limited network control.

BDI (1.93) showed the highest betweenness, signifying its critical bridging function connecting pain-related, emotional, and cognitive variables. MPQ (1.12) and SAQ (0.71) also displayed elevated betweenness, suggesting tight coupling between affective and sensory domains. The decline of FFMQ (-0.71) in betweenness illustrates a loss of mindfulness's integrative capacity, indicating that mindful attitude is no longer mediating emotional reactivity. This supports a vicious-cycle model, where depression both amplifies and is maintained by pain-related and stress-related processes.

The closeness analysis revealed that BDI (1.48) and MPQ (1.43) displayed the highest closeness, indicating that these variables are highly accessible to the entire network and can rapidly influence other nodes. SAQ (0.61) maintained moderate closeness, reflecting its pervasive but secondary role in emotional processing deficits associated with pain. STAI-Y1 (0.20) and STAI-Y2 (0.26) retained modest centrality, suggesting that anxiety remains relevant but now subordinated to depression. FFMQ (-0.29) and PVAQ (-1.47) exhibited low closeness, confirming their marginalisation in the emotional–pain circuit (see Table 4.12 and Figure 4.14).

| Centrality measures Pain in OP | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 0 | | | | Group 1 | | | |
| Variable | Betweenness | Closeness | Strength | Expected influence | Betweenness | Closeness | Strength | Expected influence |
| ASC-D | 0.48 | -0.20 | 0.68 | 1.09 | 0.10 | -0.32 | -0.33 | 0.24 |
| ASC-PA | -1.02 | -0.99 | -1.11 | -0.12 | 0.10 | -0.67 | -0.02 | 0.51 |
| BDI | 0.18 | 0.73 | 1.43 | 1.13 | 1.93 | 1.48 | 1.70 | 1.56 |
| SAQ | -1.02 | -0.82 | -0.14 | -0.10 | 0.71 | 0.61 | 0.20 | 0.83 |
| MPQ | -0.72 | -0.35 | -0.81 | 0.08 | 1.12 | 1.43 | -0.51 | 0.28 |
| FFMQ | 1.08 | 1.12 | 0.27 | -2.33 | -0.71 | -0.29 | -0.29 | -2.23 |
| PVAQ | 0.18 | 0.46 | -0.44 | 0.33 | -0.91 | -1.47 | -0.70 | -0.05 |
| PSS | -1.02 | -1.62 | -1.57 | -0.58 | -1.12 | -1.22 | -1.86 | -0.42 |
| STAI-Y1 | -0.12 | 0.05 | 0.38 | 0.75 | -0.91 | 0.20 | 0.80 | -0.20 |
| STAI-Y2 | 1.98 | 1.60 | 1.31 | -0.24 | -0.30 | 0.26 | 1.01 | -0.53 |

Table 4.12: Centrality Analysis Matrix in Group 0 = Absence of Pain in the Medical Conditions and Group 1 =Presence of Pain in the Medical Conditions across the nodes of the network.

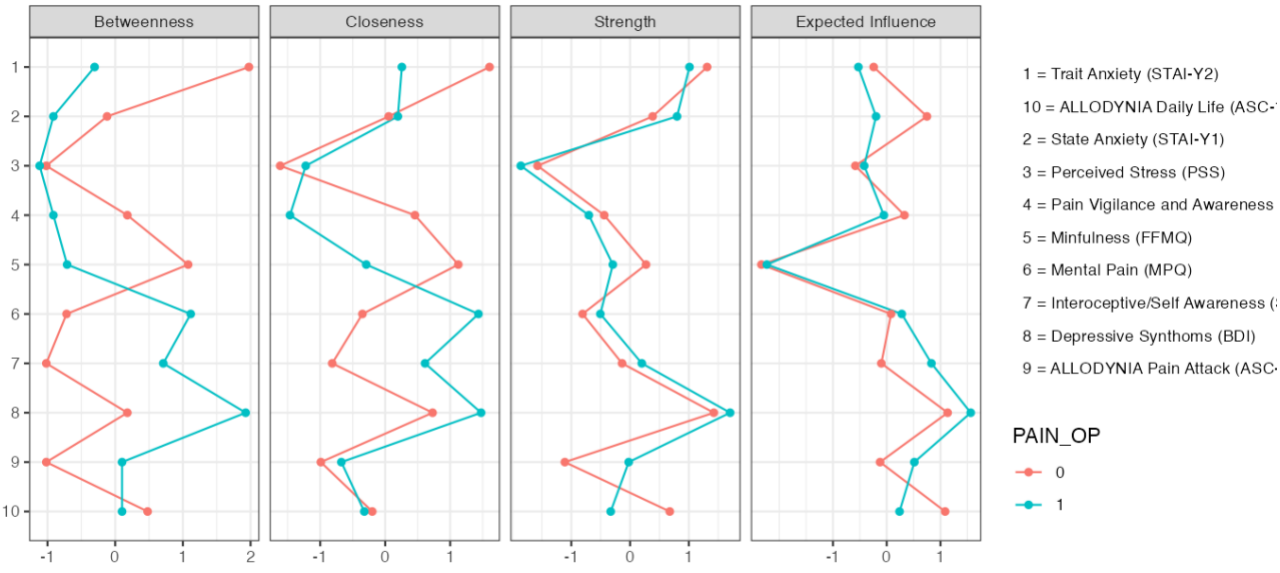


Figure 4.14: Centrality Analysis plot of the nodes of the network split by group (0 = absence of pain in other medical conditions; 1 = presence of pain in other medical conditions).

Network analysis of the presence of allodynia in the absence of pain or medical diagnosis

This network analysis compared the connections across features that we supposed to be linked to cutaneous allodynia in people who exhibited the presence of allodynia in daily life (ASC-12 score ≥ 3) without any reported pain or medical condition.

The network consisted of nine nodes, reflecting affective, sensory, and regulatory variables. The network comprised nine variables: Allodynia Daily Life (ASC-12), Depression (BDI), State and Trait Anxiety (STAI-Y1/Y2), Mental Pain (MPQ), Pain Vigilance (PVAQ), Interoceptive-Self-Awareness (SAQ), Perceived Stress (PSS), and Mindfulness (FFMQ). Networks were estimated using EBICglasso ($\gamma = 0.25$); the tuning parameter was reduced to $\gamma = 0.25$ to run an EBICglasso analysis with a reduced number of data and participants (N = 16).

The network comprised 18 non-zero edges (sparsity = 0.50), indicating that half of the potential connections between variables were present in the estimated network. This suggests a moderately connected structure, where several psychological constructs interact, but not all are directly linked to one another.

The visual structure of the network is a core–periphery configuration, where emotional and anxiety-related constructs dominate the network's centre, and mindfulness and self-awareness variables occupy a buffering periphery, indicating their possible modulatory or protective function within the network. Central nodes (STAY1,2 and BDI) are positioned toward the core of the network, surrounded by several direct connections, forming a cluster of emotional distress variables (trait and state anxiety, depression). These nodes exhibit thicker connecting lines, indicating stronger correlations or higher edge weights. Peripheral nodes, such as FFMQ (mindfulness), PSS (perceived stress), and SAQ (somatic awareness), are positioned toward the outer ring, connected by fewer and thinner edges, suggesting weaker associations. Allodynia in daily life (ASC_D) was strongly and positively correlated with mental pain (MPQ) and Pain vigilance (PVAQ), forming a well-established triad (see Figure 4.15).

**Allodynia in the Absence of Pain or Medical Diagnosis Network**

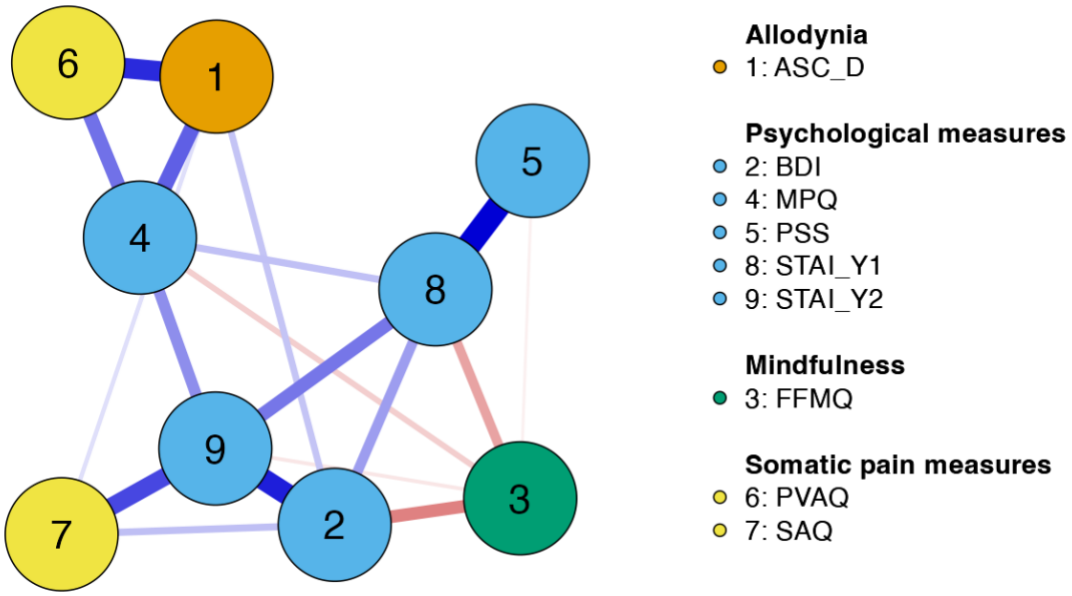


Figure 4.15: Network analysis plot across Affective (Psychological) measure: depressive symptoms (BDI), Mental Pain (MPQ), Perceived stress (PSS), anxiety (STAI-Y1,2); Somatic pain measure: Interoceptive/Self-awareness (SAQ), Pain Vigilance and Awareness (PVAQ). Mindfulness abilities: FFMQ. Allodynia (ASC-12): allodynia symptoms in daily life and during pain attacks.

The weight matrix supported the visual impression. Firm positive edges were found between: BDI – STAI-Y2 (0.399), PSS – STAI-Y1 (0.453), STAI Y2– SAQ (0.327) and STAI Y2– MPQ (0.201). Allodynia in daily life (ASC_D) revealed positive connections: ASC_D – PVAQ (0.378), ASC_D – FFMQ (0.378), ASC_D – MPQ (0.285). These results indicate a strong cluster among anxiety and depressive symptoms, as well as notable connections between allodynia and self-awareness, interoception and mental pain. A negative relation between: BDI – ASC_D (- 0.224) emerges for the first time in the analysis. Negative or near-zero weights of FFMQ with other nodes suggest inverse or negligible associations, still possibly reflecting the protective or regulatory role of mindfulness against distress-related constructs (see Table 4.13).

| Weights Matrix | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **PVAQ** | **PSS** | **BDI** | **STAI-Y1** | **STAI-Y2** | **SAQ** | **MPQ** | **ASC_D** | **FFMQ** |
| **PVAQ** | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.252 | 0.378 | 0.000 |
| **PSS** | 0.000 | 0.000 | 0.000 | 0.453 | 0.000 | 0.000 | 0.000 | 0.000 | -0.027 |
| **BDI** | 0.000 | 0.000 | 0.000 | 0.175 | 0.399 | 0.113 | 0.000 | 0.105 | -0.224 |
| **STAI-Y1** | 0.000 | 0.453 | 0.175 | 0.000 | 0.243 | 0.000 | 0.112 | 0.000 | -0.163 |
| **STAI-Y2** | 0.000 | 0.000 | 0.399 | 0.243 | 0.000 | 0.327 | 0.201 | 0.000 | -0.044 |
| **SAQ** | 0.000 | 0.000 | 0.113 | 0.000 | 0.327 | 0.000 | 0.000 | 0.057 | 0.000 |
| **MPQ** | 0.252 | 0.000 | 0.000 | 0.112 | 0.201 | 0.000 | 0.000 | 0.285 | -0.088 |
| **PVAQ** | 0.378 | 0.000 | 0.105 | 0.000 | 0.000 | 0.057 | 0.285 | 0.000 | 0.000 |
| **ASC_D** | 0.000 | -0.027 | -0.224 | -0.163 | -0.044 | 0.000 | -0.088 | 0.000 | 0.000 |
| **FFMQ** | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.252 | 0.378 | 0.000 |

Table 4.13: Allodynia in the Absence of Pain or Medical Diagnosis Network Weight matrix across variables. Strong positive partial correlations were observed among affective constructs and between allodynia, self-awareness, interoception and mental pain.

The centrality measures supported the high strength and expected influence of STAI-Y1 (strength = 1.182, EI = 0.540) and STAI-Y2 (strength = 1.423, EI = 1.195), followed by BDI (strength = 0.726, EI = 2.814 × 10^ -4). Additionally, STAI-Y2 showed the highest closeness (2.007) and the second-highest score for betweenness (1.355). This indicates that anxiety is the most influential and interconnected node in the network, possibly mediating interactions among other affective and cognitive variables. STAI Y1 (State Anxiety) is a candidate for a secondary but substantial role in

network connectivity. MPQ showed high betweenness (1.589), suggesting it may act as a bridge variable, mediating relationships between other constructs. FFMQ (Mindfulness), PSS (Perceived Stress), and SAQ (Somatic Awareness) presented negative centrality scores, indicating that they are more peripheral nodes, contributing less to overall connectivity (see Table 4.14 and Figure 4.16). Overall, the core structure of the network appears dominated by anxiety–depression interactions, forming a tightly connected emotional core. Trait anxiety serves as the primary hub, bridging to depressive symptoms and perceived stress. Peripheral but functionally significant nodes, such as allodynia and pain vigilance, connect self-awareness and attention to pain processes with emotional distress. In contrast, mental pain operates as an intermediary to affective states. Mindfulness may dampen connectivity across anxiety pathways, consistent with the literature on mindfulness as a resilience factor.

| Centrality measures | | | | |
|---|---|---|---|---|
| **Variable** | **Betweenness** | **Closeness** | **Strength** | **Expected influence** |
| **ASC-D** | -0.755 | -0.802 | 0.053 | 0.551 |
| **BDI** | -0.052 | 0.842 | 0.726 | 2.814×10-4 |
| **FFMQ** | -0.755 | -0.797 | -0.932 | -2.382 |
| **MPQ** | 1.589 | 0.380 | 0.451 | 0.417 |
| **PSS** | -0.755 | -0.714 | -1.164 | -0.303 |
| **PVAQ** | -0.755 | -1.079 | -0.636 | 0.133 |
| **SAQ** | -0.755 | -0.196 | -1.103 | -0.151 |
| **STAI-Y1** | 0.886 | 0.359 | 1.182 | 0.540 |
| **STAI-Y2** | 1.355 | 2.007 | 1.423 | 1.195 |

Table 4.14: Centrality Analysis Matrix across the nodes of the Allodynia in the Absence of Pain or Medical Diagnosis Network

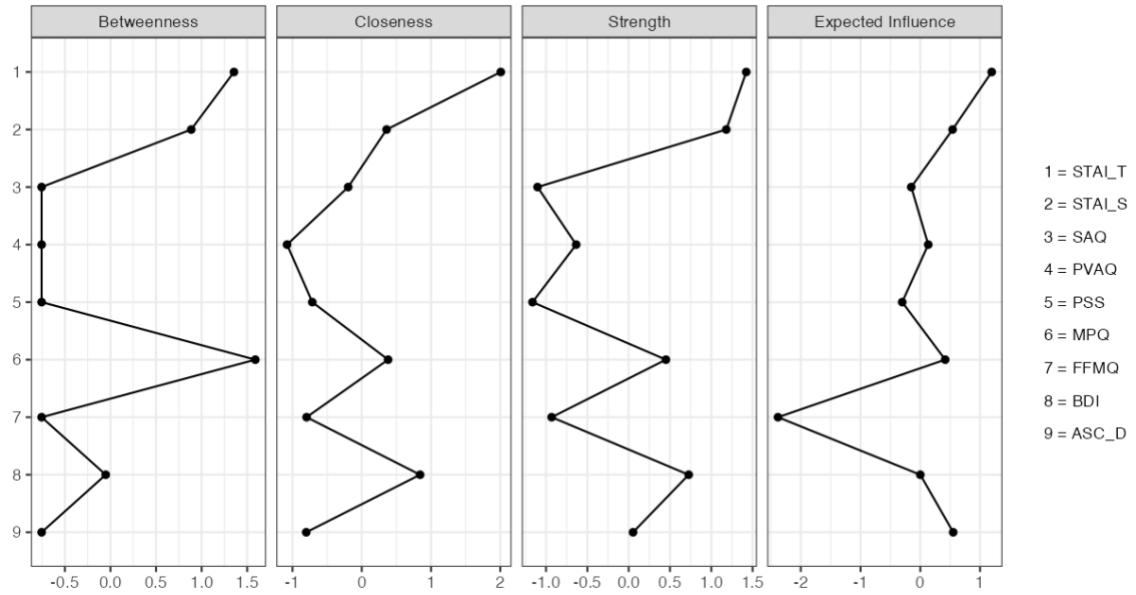


Figure 4.16: Centrality Analysis plot of the nodes of the Allodynia in the Absence of Pain or Medical Diagnosis Network

## 4.4. Discussion

The present study aimed to explore cutaneous allodynia in the general population, encompassing both clinical and non-clinical individuals. The focus was to capture the interplay between affective, interoceptive, and cognitive factors associated with cutaneous allodynia through network analysis.

The preliminary psychometric assessment of cutaneous allodynia revealed that it was present in 27% of participants. Women were predominantly affected (78.3%), consistent with previous evidence indicating a higher susceptibility to central sensitisation and sensory hyper-responsivity in females, likely related to specific hormonal assets. The relationship between pain and allodynia was only partial. This dissociation supports the notion that cutaneous allodynia may arise from distinct central mechanisms rather than as a direct consequence of nociceptive input. Among participants presenting both pain and a medical diagnosis, 11% experienced daily-life allodynia, suggesting that diagnostic and clinical factors may modulate its occurrence. Living with cutaneous allodynia is linked to higher levels of depression, mental pain, and perceived stress, together with increased pain vigilance and interoceptive self-awareness. These findings suggest that cutaneous allodynia is not merely a sensory symptom, but rather reflects a complex interaction between affective distress, attentional processes, and central sensitisation. Overall, the presence of daily-life cutaneous allodynia appears to represent a multidimensional phenomenon encompassing both emotional and somatic domains. Its partial overlap with chronic pain highlights the importance of assessing allodynia as a distinct yet related

dimension within chronic pain syndromes, contributing to a more comprehensive understanding of central sensitisation processes.

The first network analysis integrated all participants to investigate whether the chosen variables were related to cutaneous allodynia and, if so, in what way. The findings confirm that emotional dysregulation, especially anxiety, depression, and perceived mental pain, constitutes the most central and robust component of the network structure. In contrast, sensory and regulatory variables such as interoceptive awareness, pain vigilance, and mindfulness occupy peripheral yet functionally relevant positions. This pattern suggests that allodynia is not an isolated somatosensory event, but rather a multifaceted psychophysiological manifestation embedded within a broader affective-cognitive matrix. Additionally, allodynic perception in daily life is linked to attentional hypervigilance and heightened bodily awareness, which amplify sensory salience and emotional reactivity. Such mechanisms are consistent with prior findings that attention toward somatic sensations can increase pain perception and facilitate central sensitisation (Meulders & Vlaeyen, 2013; Geuter et al., 2017). In this network, mindfulness played a damping role, acting as a potential reducer of distress variables, implying its role in maintaining emotional homeostasis and protecting against dysfunctional affective activation (Garland et al., 2015).

The correlation matrix supported the data above, suggesting a vicious cycle among allodynia, increased attention to bodily pain, and interoception signals. Also, the repeated correlation of allodynia with anxiety and depressive symptoms seals the critical role of psychological affective state in pain perception and other bodily sensations.

The Network Comparison: Absence vs. Presence of Pain Condition Diagnosis aimed to delineate how the presence or absence of a diagnosed pain condition modulates the complex interplay between affective, sensory, and regulatory dimensions underlying cutaneous allodynia. The comparison of the two networks provides insight into whether pain diagnosis may modify the structure and connectivity of psychological and somatic processes, potentially reflecting a shift from adaptive to maladaptive configurations within the pain–emotion network. Specifically, in the absence of pain condition diagnosis (Group 0), the nodes were spatially homogeneous, with minimal isolation, reflecting robust interconnections between emotional, somatic, and regulatory variables. In contrast, in the presence of a pain condition diagnosis (Group 1), we observe a marked reduction in overall interconnectivity and modular balance compared to Group 0, indicating a decline in network flexibility. The substantial decrease in edges reflected fragmentation and loss of regulatory integration. Affective nodes are dominant in both networks; notably, the affective interconnectivity increases in Group 1, which, besides the loss of inhibitory node roles, results in a potentially emotionally imbalanced state. This progression from flexible integration to rigid centralisation may reflect the neural and psychological

transition to chronic pain conditions (Kucyi & Davis, 2017). In sufferers of pain conditions, the progression of the network from flexible integration to rigid centralisation may reflect the neural and psychological transition to chronic pain conditions. The chronic pain network's high emotional stability but low flexibility indicates rigid coupling of negative affective states. Such rigidity may explain the resistance to therapeutic change often seen in chronic pain patients and highlights the importance of interventions that restore network flexibility (e.g., mindfulness, cognitive reappraisal, acceptance-based therapy).

The Network Comparison: Presence vs. Absence of Pain in Other Medical Conditions examined how the presence of pain symptoms within medical conditions, excluding pain-based conditions, alters the structure and interconnections among affective, interoceptive, attentional, and regulatory domains involved in cutaneous allodynia. In this analysis, individuals were included even in the absence of a formal diagnosis, because, based on demographic inspection, some participants, mainly those suffering from a psychological/psychiatric condition, did not confirm having a formal diagnosis, which is plausible if they had not undergone a specific assessment. Thus, we decided to avoid splitting the participants into groups based on the presence or absence of a formal diagnosis to avoid excluding persons with a psychological/psychiatric disease. The goal was to determine how the subjective experience of pain in a medical condition affecting multiple body systems reshapes the architecture of psychological and sensory networks and how this reorganisation relates to the manifestation of allodynia. In the absence of pain (Group 0), as in the previous analysis, the overall configuration of the network revealed a functionally adaptive system**,** characterised by balanced affective activation, intact regulatory control, and low network rigidity. Affective facets play a primary role, as in the other networks. Anxiety regulation and mindfulness are essential in maintaining emotional balance when pain is absent. The negative betweenness values for allodynia variables indicate low connectivity and limited influence on other nodes, consistent with a non-pathological state. In the presence of pain, the strength of edges and internal clustering of affective nodes increased substantially**,** indicating that the experience of pain amplifies the interdependence between emotional, cognitive, and sensory domains. The affective subsystem displayed stronger and more stable internal connections between depressive and anxiety symptoms, reflecting an augmented emotional connectivity**,** suggesting that the subjective experience of pain activates shared neural and psychological resources for processing negative affect and nociceptive input (Garcia-Larrea & Peyron, 2013; Kucyi & Davis, 2017). Allodynia components became significantly more connected to interoceptive and attentional nodes, indicating that in the presence of pain, bodily self-awareness and vigilance become tightly coupled with sensory hypersensitivity. Attentional bias and sustained interoceptive monitoring are likely typical of sensitisation phenomena (Meulders & Vlaeyen, 2013).

The regulatory function of mindfulness maintained negative associations with anxiety, but its centrality and protective effect were substantially reduced in the pain group. This attenuation suggests that pain experience can compromise top-down control and reduce the individual's capacity to decouple emotional distress from sensory perception. Consequently, interventions aimed at enhancing mindfulness or cognitive flexibility could restore adaptive network balance (Garland et al., 2015).

Comparing this group of people who declared to suffer from pain in the context of several body system pathologies to the one who mainly present neurological pain conditions, it emerges that in the first group, the network connections are more preserved. Suffering from a painful condition can upset the emotional-sensory-interoceptive balance.

Finally, we assessed a small group of individuals who reported experiencing allodynia without any accompanying pain or medical condition. The network analysis provides valuable insights into the psychological and sensory architecture underlying non-pathological pain sensitivity. Although the configuration is less dense than that observed in clinical pain groups, the results reveal a complex and meaningful interaction between emotional distress, sensory vigilance, and mindfulness-based regulatory processes. The general pattern revealed three main functional domains, confirming other findings. An affective domain centred on depressive and anxious symptomatology, linking allodynia to the vigilance and interoception attention domain, a regulatory inhibitory domain associated with mindfulness. This interaction network may outline a psychophysiological configuration of a subclinical pain sensitivity. Here, the affective factors are engaged as the primary driving force of the network, transmitting activation toward sensory vigilance and allodynic perception.

This configuration supports a continuum model of pain perception vulnerability, in which emotional instability and attentional bias toward bodily sensations represent early markers of susceptibility to maladaptive pain processing. In this sense, allodynia in healthy individuals can be viewed not as a symptom of pathology but as an intermediate psychophysiological expression of affective sensitisation.

### 4.4.1. Limitations, conclusions, and future perspectives

Taken together, the network analyses illustrate a progressive reconfiguration of the psychological–sensory systems underlying cutaneous allodynia. Across all the models, the affective domain (depression, anxiety, and mental pain) repeated the same consistent pattern, establishing the structural and functional core of each network. Regulatory dimensions such as mindfulness progressively lost centrality as pain became clinically relevant. The emergence of pain, whether diagnosed or associated with another medical condition, produced emotional condensation and

network rigidity, marked by hyperconnectivity among affective nodes and weakened inhibitory influence of mindfulness. Allodynia, although assumed to play a marginal role in the networks and could not be considered an outcome of the other variable interactions, showed its link to interoception, bodily pain, and attention, as well as a changing interplay with affective factors, depending on the context, presence or absence of pain, or diagnosed pain conditions. The presence of allodynia in the absence of pain illustrated a transitional configuration, where affective–sensory coupling was present but not yet consolidated. This intermediate topology supports the notion of a continuum of pain vulnerability, spanning from non-clinical emotional sensitisation to chronic pain states. Such findings underscore that cutaneous allodynia is not merely a peripheral phenomenon but a psychological marker of central sensitisation, modulated by affective and cognitive dynamics.

One limitation was the temporal directionality of the relationships. These findings provide a snapshot view of allodynia. Longitudinal designs may be necessary to identify the evolution of network patterns, particularly during the transition from subclinical to overt pathological conditions.

Second, the use of self-report questionnaires introduces potential response biases and limits ecological validity. Future research should integrate behavioural measures (e.g., quantitative sensory testing, attentional bias tasks) to strengthen construct validity. Third, subgroup size, especially in the "allodynia without pain" condition, was relatively small, which may have reduced the stability of the estimated networks. Replication in larger and more diverse samples is therefore essential. Finally, while network analysis offers valuable insight into relational structures, psychological networks remain correlational representations and cannot directly infer mechanistic causality or underlying neural circuitry.

Future studies should pursue multimodal, longitudinal, and dynamic network approaches to elucidate further how emotional, interoceptive, and attentional processes interact over time to sustain or prevent pain chronification. Combining functional neuroimaging and computational modelling could help identify the neural correlates of network transitions. From a clinical standpoint, interventions such as mindfulness-based stress reduction (MBSR) and acceptance and commitment therapy (ACT) should be tested not only for symptom relief but also for their potential to reorganise network architecture, restoring regulatory balance and reducing emotional centralisation. By conceptualising pain and allodynia as dynamic systems rather than static conditions, future research can promote a shift toward a more integrated biopsychosocial approach, where prevention and treatment are tailored to individual psychological network profiles.

# 5. USABILITY AND EFFECTIVENESS OF A MOBILE APPLICATION, BBMIND, A TOOL FOR MINDFULNESS PRACTICE IN TREATING CHRONIC PAIN CONDITIONS

## 5.1. Introduction

### 5.1.1. Principles of mindfulness

Mindfulness may be defined as "*the intentional self-regulation of attention from moment to moment*" (Kabat-Zinn, 1982)

It is a detached and accepting observation of the present-moment experience, encompassing a compassionate attitude toward oneself and others. Mindfulness has its roots in Buddhism, where it is known as *sattipatana-vipassana* (Insight Meditation), and is also found in Soto Zen practices, presupposing concentration to maintain stable attention. Thanks to the pioneering work of Kabat-Zinn, mindfulness has left its spiritual and religious origins and gained considerable recognition within clinical, therapeutic, and well-being contexts. The basic principle of mindfulness is based on the evidence that the mind tends to wander and worry about thoughts and emotions that pull its attention to the past, such as memories and ruminative thinking, or to the future, leading to anticipations, concerns, and anxiety. As an awareness meditation, it embodies the ability to remain anchored in the present, in a constantly changing attention to objects. In mindfulness practice, every event, even the mind wandering, is a simple object of observation and is not judged as a distraction. Practising mindfulness means recognising the lapses in awareness, redirecting attention toward a specific element of present-moment experience, most commonly the breath or a bodily sensation, to re-establish attentional focus in the here and now. Standardised mindfulness protocols, such as MBSR (Mindfulness-Based Stress Reduction), train learners to cultivate attentional flexibility by focusing on a single primary object, usually one's own breathing. Then, once the attentional steadiness is achieved, the scope of awareness is progressively broadened to encompass a wide range of physical and mental phenomena. These may include bodily sensations, thoughts, memories, emotions, perceptions, intuitions, and imagery, all observed precisely as they arise in the present moment. This gradual expansion of the attentional field is systematically introduced over multiple training sessions. Bringing attention to a detailed event of the transient present, such as inbreath and outbreath, (re) anchors the attention in the here and now. Detached observation is not a lack of empathy, interest, or compassion, nor is it pathological distancing; instead, it's the ability to live in the moment without

being overwhelmed by life's flow, assuming the awareness and responsibility of one's responses to it with openness and equanimity (Kabat-Zinn, 1982).

Mindfulness is a specific mental state that individuals deliberately cultivate and develop. This state is characterised by an intentional and accepting relationship with internal and external experiences. A mindful attitude means a present-centred, non-elaborative, and non-judgmental awareness, in which every thought, feeling, or sensation that arises in the attentional field is recognised and accepted as it is (Segal, 2012). Achieving such a condition requires an open-minded approach and engagement in a structured meditative practice.

First, it is necessary to outline the seven attitudinal foundational pillars that constitute the optimal mindset for mindfulness meditation: non-judgment, patience, beginner's mind, trust, non-striving, acceptance, and letting go. They are interdependent, each influencing and reinforcing the development of the others. They collectively form the basis for establishing a robust and sustainable meditation practice. For this reason, these attitudinal qualities are introduced before the formal instruction in specific meditation techniques, through psychoeducational introduction, allowing practitioners to internalise them from the outset (Kabat-Zinn, 2013).

Mindfulness has become one of the most studied fields in neuroscience and a topic of scientific research aimed at standardising evidence-based practice protocols. Several studies have investigated effects on grey and white matter, capturing changes in cortical thickness, volume and/or density. A range of distinct yet interrelated mechanisms contribute to the observed benefits of mindfulness meditation (Hölzel et al., 2011) (see Figure 5.1):

1. Attention regulation
2. Body awareness
3. Emotion regulation (Reappraisal; Exposure, Extinction, Reconsolidation).
4. Change in perspective on the self

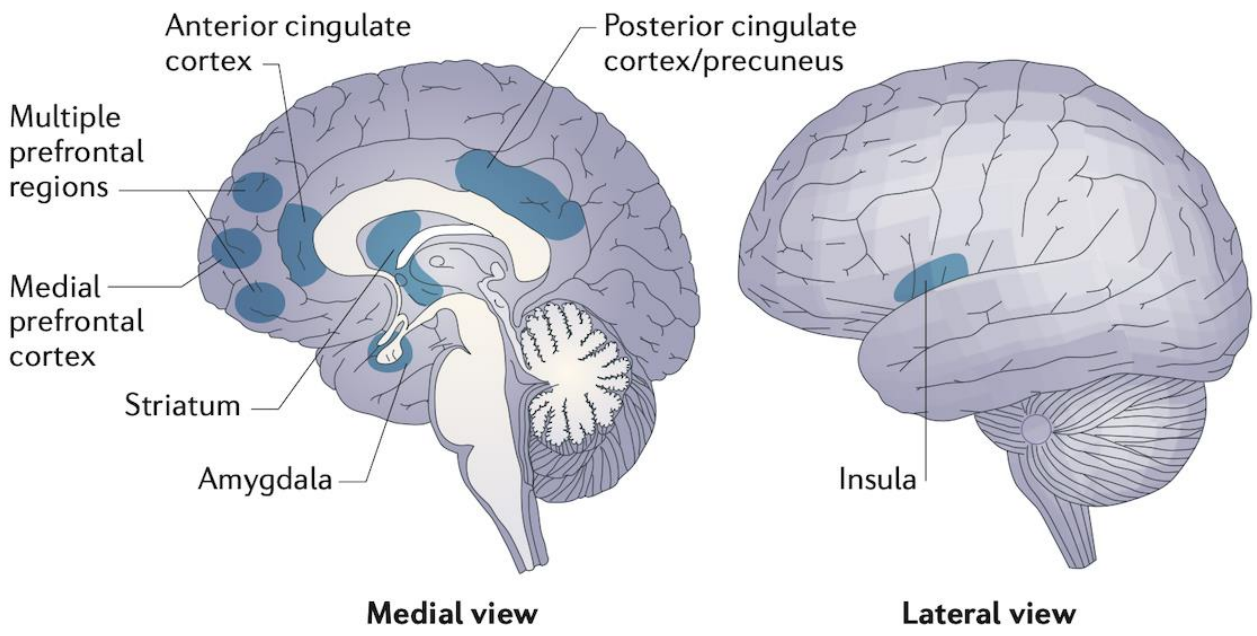


Figure 5.1: Schematic view of some brain regions involved in mindfulness meditation. Attention control (the anterior cingulate cortex and the striatum), emotion regulation (multiple prefrontal regions, limbic regions and the striatum) and self-awareness (the insula, medial prefrontal cortex, posterior cingulate cortex and precuneus) (from Tang et al, 2015).

Attention regulation is the cornerstone of mindfulness practice. Starting from focusing on a specific aspect of present-moment experience, most commonly the breath, the mind inevitably begins to wander. Practitioners are encouraged to gently redirect their attention to the breath, repeating this process as often as needed. In the initial stages of meditation, activation of the anterior cingulate cortex (ACC) has been consistently observed, alongside engagement of multiple attentional systems. These include the alerting network, involving the frontal cortex, right parietal cortex, and thalamus; the orienting network, which comprises the superior parietal cortex, temporoparietal junction, frontal eye fields, and superior colliculus; and the executive control network responsible for focused attention. The latter is further subdivided into two functional subsystems: the salience network, which includes the anterior insula, ventrolateral prefrontal cortex (PFC), and dorsal anterior cingulate cortex; and the executive network, encompassing the prefrontal cortex and basal ganglia (MacLean et al, 2010; Hölzel et al., 201; Tang et al, 2015). Structural changes have also been documented, with cortical thickness in several regions corresponding to cingulo-fronto-parietal attention networks (Grant et al., 2013).

Body sensations play a crucial role in the conscious experience of emotions (feelings), as noted not only by James (1884) but also by Damasio (1998, 2003). Enhanced awareness of bodily responses to emotional stimuli may facilitate a deeper understanding of one's emotional states, a prerequisite for effective emotion regulation. The development of bodily awareness is closely linked to attentional processes, which emerge through sustained focus on physical sensory experiences. Specific techniques, such as the body scan, educate the attentional orientation toward internal bodily processes, improving interoceptive ability. Training the bodily awareness induces an increase in cortical thickness and a higher concentration of grey matter in the insular cortex, associated with interoceptive awareness, as well as in the temporoparietal junction, implicated in embodiment and self-related processing (Lazar et al., 2005; Hölzel et al., 2011).

Furthermore, interoceptive awareness of one's bodily and emotional states is a fundamental prerequisite for developing empathic capacity. Accurate self-perception is considered essential for understanding the mental and emotional states of others (Decety & Jackson, 2004). Key regions such as the insular cortex and the temporoparietal junction are implicated in interoceptive awareness and social-cognitive processes, including empathy (Singer et al., 2004). Following mindfulness training, functional enhancement in these areas may underlie the increased empathic capacity and compassion often attributed to sustained meditative practice (Shapiro et al., 1998; Hölzel et al., 2011).

Concerning emotion regulation, a lowered intensity and frequency of negative affect, as well as improved positive mood states, have been reported to be associated with mindfulness practice. Mindfulness meditation supports the reduction of emotional interference from unpleasant stimuli, decreases physiological reactivity, and facilitates a return to the emotional baseline after responding to a stressor (Robins et al., 2012; Tang et al., 2015). A central hypothesis underlying much of the current research is that mindfulness-based emotion regulation enhances cognitive control processes mediated by the prefrontal cortex, thereby attenuating activity in brain regions associated with affective processing, such as the amygdala (Chiesa et al., 2013).

The concept of "self-related processing" in mindfulness refers to the flexible observation of the self as a dynamic and continuously evolving construct. Neurobiological evidence implicates several key regions in these processes, including the medial prefrontal cortex, posterior cingulate cortex, insula, and temporoparietal junction. Studies have reported structural changes in these areas following mindfulness interventions (Hölzel et al., 2011). Mindfulness may also have indirect physiological benefits given the known relationship between stress, immune function, and chronic pain. Improved psychosocial functioning, potentially facilitated by mindfulness training, could influence both the progression and maintenance of chronic pain conditions (Cherkin et al., 2016; Davidson et al., 2003) (see Figure 5.2 for a summary).

| Mechanism | Exemplary instructions | Self-reported and experimental behavioral findings | Associated brain areas |
|---|---|---|---|
| 1. Attention regulation | Sustaining attention on the chosen object; whenever distracted, returning attention to the object | Enhanced performance: executive attention (Attention Network Test and Stroop interference), orienting, alerting, diminished attentional blink effect | Anterior cingulate cortex |
| 2. Body awareness | Focus is usually an object of internal experience: sensory experiences of breathing, emotions, or other body sensations | Increased scores on the Observe subscale of the Five Facet Mindfulness Questionnaire; narrative self-reports of enhanced body awareness | Insula, temporo-parietal junction |
| 3.1 Emotion regulation: reappraisal | Approaching ongoing emotional reactions in a different way (nonjudgmentally, with acceptance) | Increases in positive reappraisal (Cognitive Emotion Regulation Questionnaire) | (Dorsal) prefrontal cortex (PFC) |
| 3.2 Emotion regulation: exposure, extinction, and reconsolidation | Exposing oneself to whatever is present in the field of awareness; letting oneself be affected by it; refraining from internal reactivity | Increases in nonreactivity to inner experiences (Five Facet Mindfulness Questionnaire) | Ventro-medial PFC, hippocampus, amygdala |
| 4. Change in perspective on the self | Detachment from identification with a static sense of self | Self-reported changes in self-concept (Tennessee Self-Concept Scale, Temperament and Character Inventory) | Medial PFC, posterior cingulate cortex, insula, temporo-parietal junction |

Figure 5.2: Components and mechanisms of mindfulness meditation (from Hölzel et al., 2011)

Research explored whether the duration of mindfulness protocols could modulate the changes mentioned above. Standardised mindfulness protocols, such as Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT), typically last eight weeks and require substantial time commitment. In addition to weekly in-person sessions and a full-day retreat, participants are encouraged to engage in individual practice for approximately 45 minutes daily, six days per week (Kabat-Zinn, 2013). Eight-week mindfulness-based interventions (MBIs) have consistently demonstrated significant efficacy in reducing psychological stress and enhancing overall well-being. Evidence from randomised controlled trials involving individuals with chronic pain, cancer, multiple sclerosis, and other health conditions has shown that participants undergoing 8-week mindfulness programs report significant improvements on measures such as the Perceived Stress Scale, the Profile of Mood States, and various affective and mindfulness-related scales. Comparing studies with different program durations, for example, 4-week and 8-week programs, both produced beneficial results; however, the 8-week intervention led to greater improvements. These findings suggest that an 8-week intervention can deliver meaningful benefits across a wide range of populations, whereas shorter ones may offer limited but measurable improvements (Demarzo et al., 2017). In conclusion, the benefits associated with mindfulness meditation extend beyond the

enhancement of self-awareness, acceptance, and cognitive detachment from mental events; they are also reflected in measurable changes in brain structure and specific cognitive domains, leading to functional improvements even over relatively short intervention periods.

### 5.1.2. Mindfulness meditation as a behavioural intervention in chronic pain

The growing interest in mindfulness meditation in clinical contexts began with the beneficial effects observed in the treatment of patients with chronic pain. The first application of mindfulness is attributed to the work of Jon Kabat-Zinn, who adapted Eastern-derived meditation for patients with chronic pain (Kabat-Zinn, 1982). Due to the growing evidence supporting its efficacy in improving mental health and overall psychophysical well-being, mindfulness has been increasingly recognised as an integrative support also for group, outpatient, and hospital settings.

Chronic pain conditions, such as chronic migraine, disrupt patients' daily lives, affecting them and their social networks. Also, they are frequently unresponsive to traditional treatments, leading to weak therapeutic compliance, psychiatric comorbidities, and drug abuse (Cohen et al., 2021). This condition results from a dynamic interaction between biological, psychological, and sociocultural factors, necessitating a multidimensional approach to patient care that encompasses both pharmacological and non-pharmacological therapeutic strategies. (Cohen et al., 2021; Gatchel et al., 2014; Andrasik et al., 2009). Indeed, patients suffering from chronic pain can benefit from conventional therapies combined with behavioural techniques, such as mindfulness. Mindfulness-based interventions (MBIs) are particularly effective in helping patients manage their symptoms more acceptingly and less judgmentally, modulating the subjective perceptual-psychological dimension of the nociceptive experience. The specific mental state developed by meditators promotes symptom acceptance, more functional emotional processing, and consequently, better management of the clinical condition.

Furthermore, the ability to pause and let go of sensations, thoughts, and emotions gradually enhances the capacity to control dysfunctional responses, reducing mental automatisms that underlie pain-related suffering. The acquisition of these mindful facets encourages breaking the vicious cycle of influence of the consequence of the pain condition, psychological variables included, in worsening the pathological conditions. Mindfulness can contribute to helping patients change the way they perceive themselves as fragile individuals with low autonomy and self-efficacy.

MBIs can express their benefit in different ways. The MBSR program can be an alternative treatment to improve migraine outcomes and related psychological processes. Although MBSR may not lead to greater reductions in migraine frequency compared to headache education, it was associated with significant improvements in migraine-related disability, quality of life, self-efficacy, pain catastrophizing, and depressive symptoms (Wells et al., 2021). These findings indicate that MBSR

may offer meaningful benefits in addressing the overall burden of migraine beyond attack frequency alone. In chronic head pain, the MBIs are also usually proposed to be added to the "treatment as usual" (TaU). A systematic review - meta-analysis (Rehman et al., 2022) argued that mindfulness-based stress reduction/cognitive therapy did not significantly reduce headache frequency, duration, or pain intensity compared to usual care. Nevertheless, some limitations, as low participant numbers and high risk of bias, may have partially invalidated the results. This is why the need for larger, more rigorous trials to demonstrate significant changes persists.

Another meta-analysis found limited evidence for the effectiveness of mindfulness-based interventions in treating primary headache; however, it demonstrated that mindfulness-based interventions might have a positive impact on headache intensity without any side effects (Gu et al., 2018). In this uncertain scenario, there is some encouraging evidence. Bakhshani et al. (2015) and Hilton et al. (2017) demonstrated that MBSR was significantly effective in reducing pain intensity and improving quality of life dimensions, including bodily pain, general health, and emotional health. It contributed to developing strategies to cope with pain in patients with chronic headaches. Other studies by Grazzi and colleagues (2017a, 2023) demonstrated that a combination of MBI and TaU significantly improved headache frequency, quality of life, and medication overuse in patients with chronic migraine and medication overuse headache compared to treatment as usual alone. Additionally, emerging findings suggest that mindfulness may influence biological markers, such as interleukin-6, a cytokine involved in regulating pain thresholds, trigeminal sensitisation, and the facilitation of nociceptive signalling during migraine attacks (Grazzi et al., 2017b).

Although further research is needed to clarify which patients may benefit most from mindfulness and to understand the essential mechanisms through which meditation leads to analgesia, it shows promise as an effective complement to existing treatment methods in reducing symptoms associated with chronic pain conditions.

### 5.1.3. Practising mindfulness by mobile applications: feasibility and potential benefits

Telemedicine has progressively increased access to remote clinical practice and the implementation of new tools to deliver online interventions, including pain management. Mobile applications may be particularly useful in addressing existing gaps in the treatment and management of chronic pain. These new tools can help healthcare professionals and patients take preventive action, such as participating in psychoeducation programs, or perform symptom tracking and pain management interventions (Alexander & Joshi, 2016; Adamse et al., 2018). A crucial aspect of online practice is evaluating the effectiveness of novel treatments, such as mindfulness-based online interventions.

The development of digital tools has increasingly facilitated mindfulness meditation at home, offering users greater flexibility and accessibility. Online mindfulness interventions provide a readily accessible therapeutic option for patients. When delivered by trained instructors, these interventions enable individuals to participate in guided audio or video call sessions that closely resemble in-person experiences. This format offers significant advantages, particularly for individuals with mobility constraints, while reducing travel-related logistical and financial burdens. Mobile applications and web-based mindfulness programs are gaining popularity due to the widespread availability of smartphones and the increasing integration of digital technology into healthcare. They present cost-effective, low-risk opportunities for promoting widespread mental health and implementing mindfulness interventions. A critical component of mindfulness practice is the time devoted to it and the consistency of practice to take advantage of its benefits. The in-person mindfulness program provides a rhythm to the weekly meetings and daily practices that can also facilitate motivation to practice at home. Additionally, sharing individual experiences in face-to-face groups can help prevent students from dropping out. Thus, adherence to the recommended duration and frequency of mindfulness exercises during treatment is a key factor influencing the feasibility of online protocols, which may be lacking in the collective dimension. Home-based practice is often considered a moderator of treatment efficacy in mindfulness-based interventions.

Empirical research has explored the effectiveness of online mindfulness-based interventions, comparing them to traditional in-person programs. Mindfulness meditation applications represent one of the most prevalent categories within the domain of mental health and well-being digital tools. Contrary to concerns about losing the interpersonal richness of face-to-face mindfulness courses, digital delivery methods preserved core therapeutic components, proving that these approaches enhance psychological well-being and may be as effective as traditional, in-person programs (Querstret et al., 2018). Furthermore, mindfulness interventions delivered via a mobile application resulted in effectively reducing self-reported anxiety and depression symptoms after four weeks of practice (Lahtinen et al., 2021). For example, mobile apps can be as effective as an in-person mindfulness-based training program in reducing anxiety and increasing self-compassion and mindfulness among healthcare students (Orosa-Duarte et al., 2021). A comprehensive meta-analysis of 34 trials demonstrated that mindfulness apps produced significant improvements in perceived stress, anxiety, depression, and well-being compared to control conditions (Gál et al., 2021). Additionally, adjunctive use of mindfulness apps alongside standard treatment showed significantly greater reductions in depression severity compared to treatment-as-usual alone (Sarlon et al., 2025). Brief smartphone-based mindfulness interventions have also been shown to effectively reduce stress, improve mood, and alleviate irritability in healthy adults (Economides et al., 2018).

In research settings, mobile applications can meet the dual needs of participant active self-management and researcher data collection. Applications or wearable devices (Gross et al., 2011) capable of tracking user interaction data offer innovative and practical solutions. This dual functionality enhances adherence monitoring and the collection of meaningful outcome data for clinical trials or longitudinal studies. Integrating mobile applications into mindfulness-based interventions presents a feasible and potentially practical approach to supporting home practice and clinical research. Digital tools may not only enhance accessibility and user engagement but also offer valuable functionalities for monitoring and optimising treatment outcomes. Digital platforms can provide real-time feedback on practice duration, frequency, and progression. Given the critical role of time commitment in mindfulness interventions, such features may serve as powerful motivators for individuals.

From a feasibility standpoint, delivering mindfulness interventions online through a mobile application necessitates careful attention to the platform's usability, which is crucial for engaging users and ensuring continuous device use. Usability is a fundamental attribute of any digital product. In the context of human-computer interaction, the concept of "usability" has evolved into the broader term "user experience", which emphasises the quality of the interaction itself rather than merely the accomplishment of a specific task (Forlizzi & Battarbee, 2004). User experience encompasses both pragmatic aspects, related to the application's functional objectives, and hedonic facets, which pertain to the interaction's pleasure, interest, and user-friendly nature. Key elements contributing to a positive user experience include engaging audio or video content, intuitive navigation, and ease of use for individuals with limited digital knowledge. This way, they can effectively support users' engagement with mindfulness practices. One can argue a contradiction between practising mindfulness meditation and the risk of being distracted by smartphones. Empirical evidence suggests that the mere presence of a smartphone can serve as a cognitive distractor, adversely affecting task performance. This raises significant concerns regarding the use of smartphones as delivery platforms for mobile mindfulness meditation interventions, as their inherent potential for distraction may undermine the intended outcomes of such programs. The challenge is particularly pronounced in mindfulness-based interventions that cultivate attentional control, enhance bodily awareness, and regulate emotions. These programs typically emphasise minimising both internal and external sources of distraction to optimise efficacy.

Consequently, smartphone-related distractions may represent a critical, yet little-underexplored, factor contributing to the relatively high attrition rates observed in mobile-based interventions. The frequency with which smartphones create diversions and their omnipresence may create a potent draw on attention orientation (Donker et al., 2013; Ward et al., 2017). Thus, developing a mobile

application for mindfulness interventions should strike a balance between the wealth of content and the frequency of notifications, with the essential aim of the device being to promote attention and emotional regulation.

### 5.1.4. BBMIND: a mobile application for mindfulness practice in treating chronic pain conditions

Public interest in mindfulness practices remains substantial, with people reporting that they practice mindfulness to improve their health and well-being. Nevertheless, concerns have been raised about disseminating inaccurate information and employing misleading promotional strategies, which are common in the digital mental health marketplace (Gál et al., 2021). Digital tools used in meditation protocols also appear promising in treating patients with chronic pain syndromes. These tools can meet individual needs, thus improving treatment adherence and increasing the likelihood of clinical improvement. In addition to benefits related to symptoms and psychological distress, using smartphone applications to manage painful conditions offers functional flexibility that standard prophylactic treatments often do not provide (Alexander & Joshi, 2016). Mobile apps can enable patients to take a more active role in managing their condition, improving medication compliance and deepening their understanding of their illness. Moreover, they facilitate communication between patients and healthcare teams, improving healthcare outcomes.

Specifically in the context of chronic migraine, the Carlo Besta Neurological Institute in Milan has already investigated the potential effects of online mindfulness delivery. The institute found that patients trained to meditate via smartphone, using a 12-minute daily audio track, reported an average 50% reduction in monthly migraine attack days and medication use (Grazzi et al., 2020). These results suggest the potential for a redefinition of therapies for patients with chronic pain conditions by integrating online meditation protocols with standard treatments.

In recent years, traditional programs have evolved into increasingly digital applications, offering increased spatial and temporal flexibility and individualised use. Nevertheless, evidence of effectiveness and adherence to online meditation protocols in chronic pain patients remains limited and is still being explored. The efficacy of long-term follow-up needs more evidence-based data (Donker et al., 2013).

In this context, the current research project was initiated through a collaboration between the Bicocca Centre for Applied Psychology of the Department of Psychology of the University of Milan (BiCApP) and the Carlo Besta Neurological Institute in Milan. The study aims to design a mobile app for the online delivery of mindfulness sessions to patients diagnosed with neuropathic pain or chronic headache. The project's goal is to provide patients with a supportive tool to help them cope with their

pain, to be used in conjunction with conventional prophylactic treatments prescribed by their primary physicians. Unlike other mindfulness mobile apps, this one offers a fundamental added value: it is part of the global patient care system. Patients who use a mobile app can contact their medical doctor for any issues related to their pain condition as part of their treatment.

The present study is part of a broader research initiative to develop and deliver mindfulness sessions to patients suffering from chronic migraines, currently being conducted at the Carlo Besta Neurological Institute in Milan. This project emerged from a collaborative effort between the Institute and a research team from the University of Milano-Bicocca, resulting in a structured development pathway, from initial design to preliminary testing, conducted within BiCApP, the Centre of Excellence of the University of Milano-Bicocca for mobile technologies applied to psychological research. The resulting product, the BBMIND App**,** represents the first application conceived and developed within the BiCApP. It is also the first to undergo empirical evaluation. The application is more broadly grounded in the biopsychosocial model of chronic migraine and pain (Andrasik et al., 2005). It is informed by empirical findings indicating that mindfulness-based interventions can reduce the frequency of migraine attacks and the use of medication among patients (Grazzi et al., 2017). The development of this digital tool contributes to ongoing research efforts focused on innovative treatment strategies for chronic pain-related conditions.

The name BBMIND is derived from the acronyms of *Besta* and *Bicocca*, reflecting the underpinning collaborative partnership. BBMIND‘s logo represents a butterfly, a symbol of lightness and transformation of pain, whose wings are shaped as two mirrored "B" letters, referencing the initials of the two Institutions and reinforcing the identity of the application.

The application was entirely developed using BiCApP's technological resources, following specific guidelines provided by the research team, particularly about its visual design and core functionalities. A certified mindfulness instructor, one of our researchers, created the mindfulness content.

It is essential to emphasise that the primary aim of the application is to support patients in their daily mindfulness practice and in managing their pain experience. The evaluation of this potential role as a supportive tool in chronic pain treatment is a consequence of the first usability evaluation.

A long-term research plan was formulated, comprising an initial study to assess the functionality and usability of the application, followed by a mindfulness intervention for individuals with chronic migraine. Online mindfulness has already demonstrated its functionality and flexibility in treatment. However, its adherence to the practice in chronic pain conditions needs more evidence.

### 5.1.5. Aim of the research

Thus, this research aims to assess the usability and efficacy of a mobile application (BBMIND) for online mindfulness practice in a healthy population (Study 1) and a clinical population suffering from neuropathic pain or chronic headache (Study 2). To this end, adherence to an eight-week mindfulness protocol and the usability and effectiveness of the app in terms of improvements in participants' mindfulness skills were assessed. These two studies were thought to be the ground to build a mindfulness intervention for sufferers of neuropathic pain or chronic headache (Study 3).
This project is the result of a collaboration between the University of Milan-Bicocca and the "C. Besta" Neurological Institute of Milan. The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and was approved by the local ethics committee.

## 5.2. Experiment 1: Healthy population

### 5.2.1. Materials and Methods

#### *5.2.1.1. Participants*

A priori power analyses were conducted using G*Power (Faul et al.,2007) to determine the minimum sample size of twenty-eight participants, based on Repeated Measures Analysis of Variance (ANOVA – *within factors*), with an Effect Size F= 0.25; Alpha Error Level: p= 0.05; Statistical Power= 0.80, Actual Power= 0.80, Correlation Among Measures: 0.5.
Taking into account possible dropouts, forty-one healthy participants were enrolled in the experiment: Sixteen participants (39.02%) completed the study (mean age = 25 years, SD = 6.56; 14 females), and these subjects were the subjects of the following analysis. None of the participants had a diagnosis of a chronic pain condition. Most participants (70,5%) were naïve, experiencing mindfulness for the first time.

#### *5.2.1.2. Measures*

Self-report

(i) The system Usability Scale (SUS) (Brooke, 1996) assesses the app's usability, ease of use, efficiency, and consistency. A 5-point Likert scale evaluates the level of agreement or disagreement with ten statements (1 = not at all, 2 = slightly, 3 = moderately, 4 = quite a bit, 5 = extremely).

(ii) The User Experience Questionnaire Plus (UEQ+) (Laugwitz et al., 2008) includes a broader set of pairs of antonyms arranged on 7-point scales, providing detailed information about users' experiences with the app. For this study, ten dimensions were selected as the most relevant: Attractiveness, Efficiency, Dependability, Stimulation, Novelty, Usefulness, Visual Aesthetics, Intuitive of Use, Trustworthiness of Content, and Quality of Content. Also, the Importance Rating evaluated the relevance of each dimension for each participant.

(iii) The Five Facets Mindfulness Questionnaire (FFMQ) (Baer et al., 2006; Italian version: Giovannini et al., 2014) is a self-report tool that assesses mindfulness through a five-dimensional model: Observe, Describe, Act with awareness; Non-judge; Non-react; and Mindfulness total mean.

It consists of 39 items, with responses organised on a 5-point Likert scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always).

Behavioural measure

N_Play*:* The number of guided mindfulness sessions played using the mobile app BBMIND.

*5.2.1.3. Materials*

BBMIND is a mobile application designed and developed by the BiCApP Centre of the University of Milan Bicocca to ease mindfulness practice at home. The first version consisted of four screens: a home screen, a guided meditation, meditation feedback, and a summary of the progress in mindfulness practice (see Figure 5.3).


Figure 5.3: A view of the screens of BBMIND: (a) home; (b) guided meditation, (c) meditation feedback, and (d) a summary of the progress in mindfulness practice

*5.2.1.4. Procedure*

Each participant accessed the Google Drive folder containing the app's link. The APP consists of an initial home screen or main menu, from which users can access the meditation practice, a single mindfulness audio track lasting approximately 12 minutes. Then, the participants were asked to evaluate the usefulness of the practice just completed. The APP automatically records the number of logins and the minutes of meditation playback for each user (N_Play), available in the "my progress" screen graph. (see Figure 5.3).

The study was structured in three phases:

- Phase 1 (T0): Upon their first access to the app, users completed the self-report questionnaires, including previous mindfulness experience, motivation for the study, and the FFMQ questionnaire.

- Phase 2 (T1): Participants were given full access to the app and instructed to practice mindfulness three times weekly. After the first four weeks, participants were asked to complete the self-report questionnaires (FFMQ) and provide feedback on the app's functionality (SUS, UEQ+). The failure to complete the questionnaires prevented continued access to the full content of the application.
- Phase 3 (T2): Participants were asked to complete the self-report questionnaires (FFMQ, SUS, UEQ+) at the end of the eighth week of use. After completing the questionnaires at the end of Phase 3, access to the application was blocked.

All questionnaires were administered through the app using the Qualtrics platform to facilitate data acquisition, matched with the number of app accesses and mindful practice recordings.

### 5.2.2. Results

Statistical analyses were performed using the software Jamovi. T-test, Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) with repeated measures (RM) were performed. The Huynh-Feldt correction was applied in cases where sphericity was violated. Bonferroni correction for the pairwise comparisons was used as required.

Self-report

SUS: Two one-sample t-tests were conducted to evaluate the app's usability and verify whether the mean SUS score in the two experimental phases was equal to or greater than the standard benchmark value ($M \geq 68$, range 0-100). Both analyses were statistically significant: Phase 2: $M=83.3$, $SD=8.20$, $p < .001$, Phase 3: $M=85.2$, $SD=8.14$, $p < .001$. These data ensured good usability of BBMIND.

UEQ+ User Experience: The users evaluated their experience with the APP positively, but disliked its Novelty, with no significant difference among the experimental phases. A RM ANOVA within-subjects [*Time* (T1= phase 2 = 1° month; T2 = phase 3 = 2° month)] showed no main effect of Time for any of the evaluated dimensions: Attractiveness [$F(1,15) = 0.80$, $p = .384$, $p\eta^2 = 0.05$]; Efficiency [$F(1,15) = 1.87$, $p = .192$, $p\eta2 = 0.111$], Dependability [$F(1,15) = 0.0945$ $p = .346$, $p\eta2 = 0.06$]; Stimulation [$F(1,15)=.19$, $p = .668$, $p\eta2 = 0.01$]; Novelty [$F(1,15) = 0.81$, $p = .382$, $p\eta2 = 0.05$]; Usefulness [$F(1,15) = 0.03$, $p = .874$, $p\eta2 = 0.02$]; Visual Aesthetics [$F(1,15) = 0.51$, $p = .488$, $p\eta2 = 0.03$]; Intuitive Use [$F(1,15) = 0.41$, $p = .650$, $p\eta2 = 0.01$]; Trustworthiness of Content [$F(1,15) = 0.20$, $p = .724$, $p\eta2 = 0.01$]; Quality of Content [$F(1,15) = 1.402$, $p = .255$, $p\eta2 = 0.09$]. (see Figure 5.4).

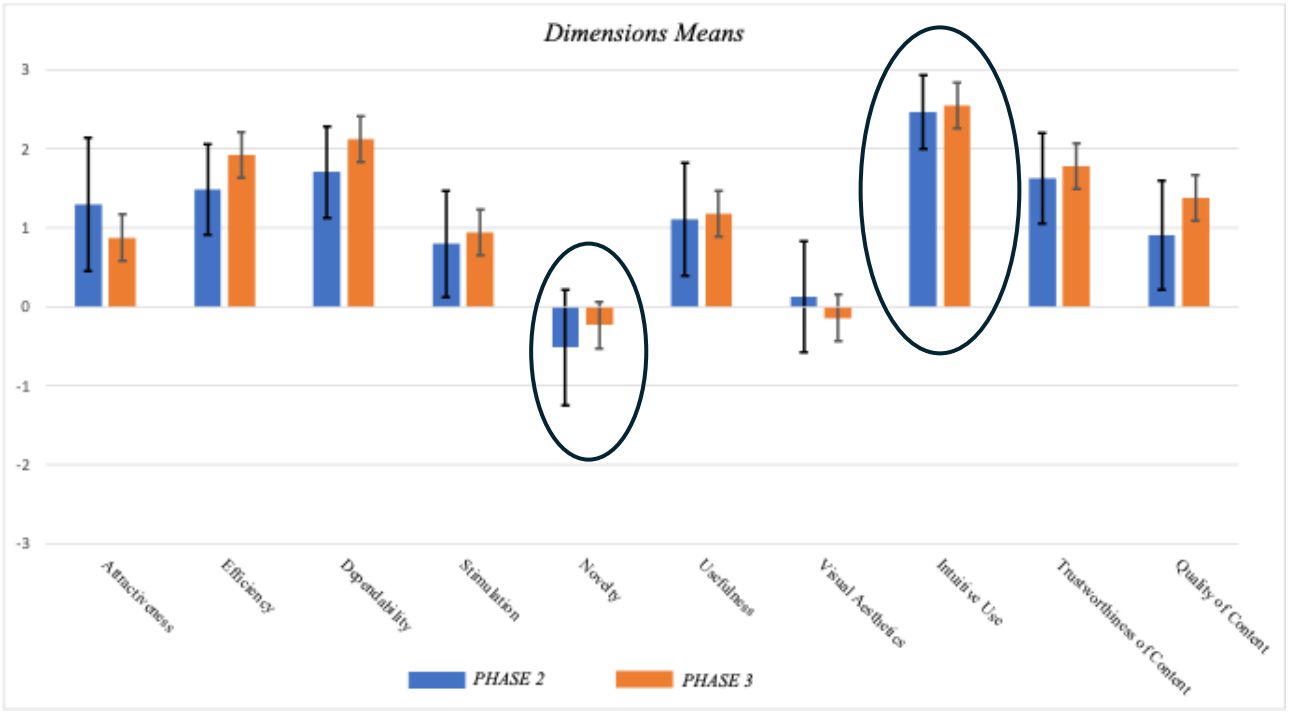


Figure 5.4: Mean of UEQ+ Dimensions in the experimental phases: phase 2 = 1° month; phase 3 = 2° month of usage of BBMIND. The intuitive use was the most appreciated feature, while novelty was not fully esteemed.

UEQ+ Importance rating. A RM ANOVA was conducted to analyse potential changes in the Importance Rating (IR) for each scale of the UEQ+ across the experimental phases The two phases of UEQ+ administration were selected as the within-subjects factor [*Time* (T1= phase 2 = 1° month; T2 = phase 3 = 2° month)], and the IR scores assigned to each scale were used as the dependent variable.

No main effect of Time was found for Attractiveness [$F(1,15) = 1.74$, $p = .638$, $p\eta2 = 0.01$]; Efficiency [$F(1,15) = 0.22$ $p=.644$, $p\eta2 = 0.02$], Dependability [$F(1,15) = 0.04$ $p = .850$, $p\eta2 = 0.02$]; Novelty [$F(1,15) = 0.04$, $p = 9.847$, $p\eta2 = 0.003$]; Usefulness [$F(1,15) = 0.37$, $p = .554$, $p\eta2 = 0.02$]; Visual Aesthetics [$F(1,15) = 0.82$, $p = .380$, $p\eta2 = 0.05$]; Intuitive Use [$F(1,15) = 1.21$, $p = .288$, $p\eta2 = 0.08$]; Trustworthiness of Content [$F(1,15) = 2.19$, $p = .151$, $p\eta2 = 0.13$]; Quality of Content [$F(1,15) = 0.48$, $p = .830$, $p\eta2 = 0.00$].

A main effect of Time was found for Stimulation dimension: [$F(1,15) = 6.61$, $p = .021$, $p\eta^2 = 0.306$], with higher levels of interest observed in the second month of the experiment ($M = .10$, $SD = .01$) compared to the first one ($M = .09$, $SD = .02$) (see Figure 5.5).

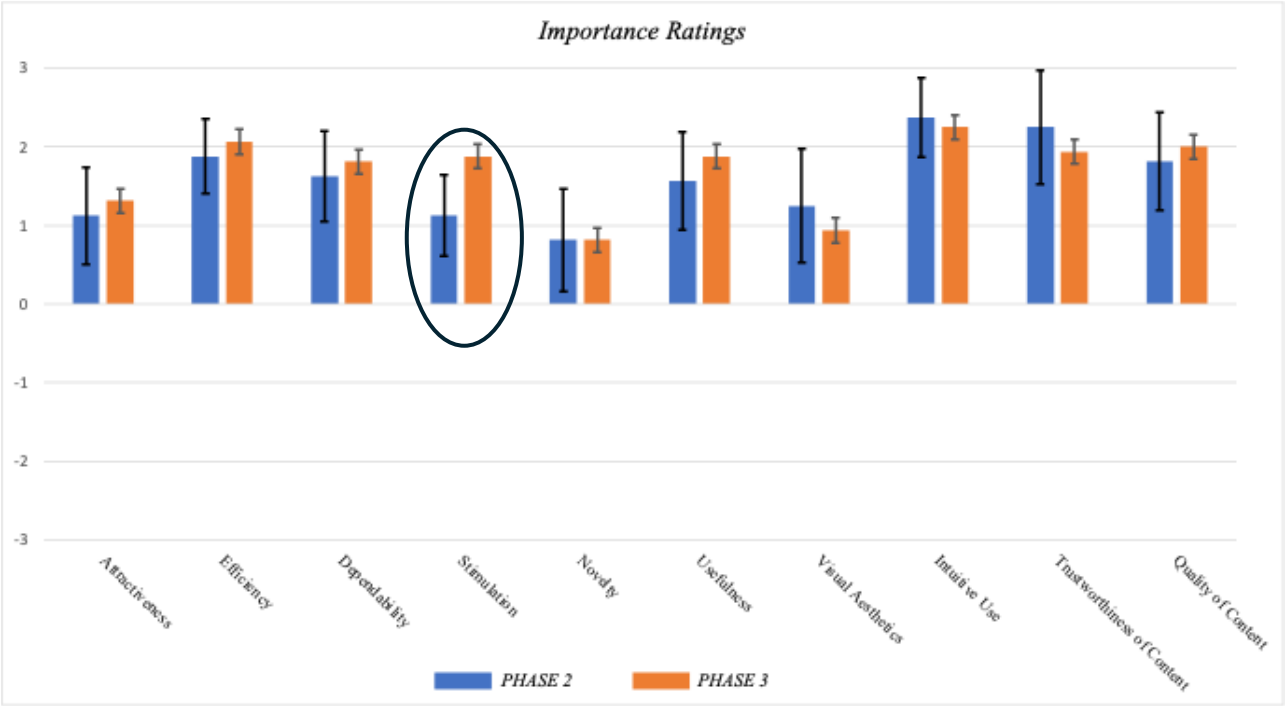


Figure 5.5: Importance Ratings of UEQ+ Dimensions in the experimental phases: phase 2 = 1° month; phase 3 = 2° month of usage of BBMIND. The stimulation rating yielded significantly higher values in the final phase of the study.

FFMQ: RM ANCOVAs within-subjects were conducted to assess the impact of meditation on mindfulness skills. [*Time* (T0 = phase 1 = baseline; T1= phase 2 = 1° month; T2 = phase 3 = 2° month)].

The number of meditation sessions completed by each participant (N_Play) was added as the continuous covariate (N_Play: M = 20.8, SD = 7.08).

Observe. A main effect of Time was found [$F(1.44, 18.68) = 7.70$, $p = .006$, $p\eta^2 = .372$] and significant higher scores in T2 (M = 3.59, SE = .69) than T0 (M = 3.08, SE = .15): Mean difference [M = 0.508, SE = 0.184, $t(13) = 2.77$, $p = .0048$]. Similarly, higher scores were found in T2 (M = 3.59, SE = .69) than T1 (M = 3.33, SE = .20): Mean difference [M = 0.267, SE = 0.092, $t(13) = 2.87$, $p = .0039$]. The interaction between phase and N_Play was significant [$F(1.44, 18.68) = 5.25$, $p = .023$, $p\eta^2 = .288$] (see Figure 5.6).

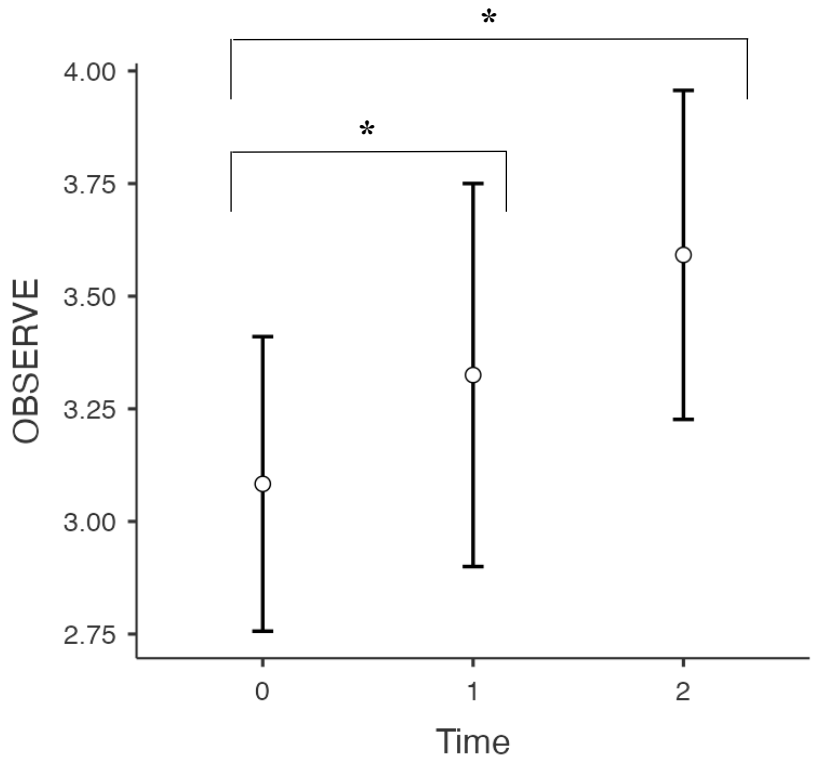


Figure 5.6: Estimated Marginal Means of Observe facet of FFMQ, increasing across the experimental phases. Higher scores were found in T2 compared to T0 (p = .0048) and T1 (p = .0039).

Non-react. A main effect of Time was found [F(1.32,18.42) =13.40, p<.001, pη2=0.489]. Otherwise, post hoc test comparisons did not show any significant mean differences between T0 (M = 2.58, ES = .15), T1 (M = 3.02, ES = .15), and T2 (M = 3.12, ES = .14) (all p > .095).ES Also, the interaction between Time * N_Play was significant [F(2,28)=10.00, p<.001, pη2=.416] (see Figure 5.7).

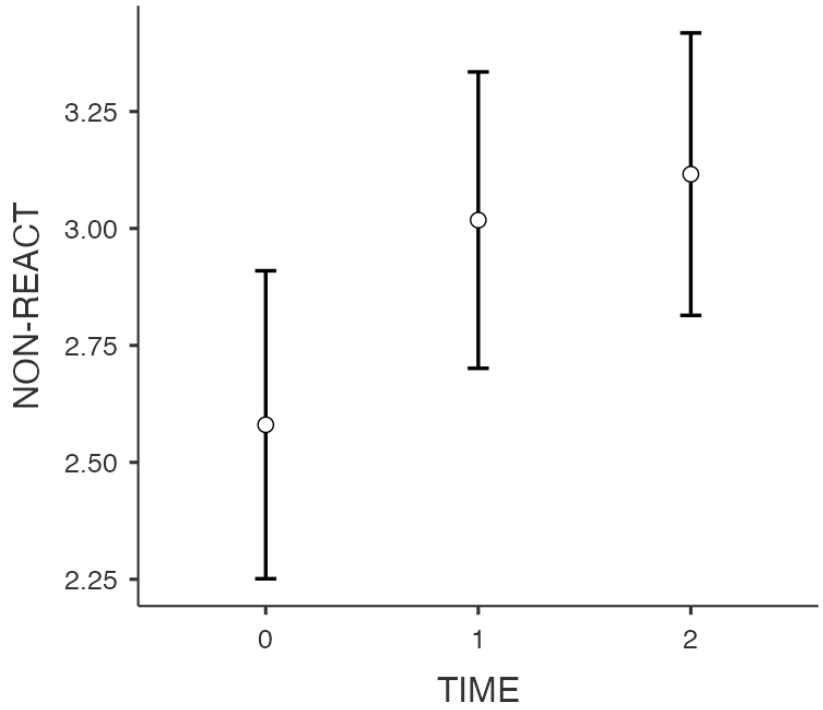


Figure 5.7: Estimated Marginal Means of Non-react facet of FFMQ, increasing, but not significantly different, across the experimental phases.

Describe. No main effect of the Time (p = .286) and of the interaction Time * N_Play (p = 0.513) was found.

Act with awareness. No main effect of the Time (p = .316) and of the interaction Time * N_play (p = .608) emerged.

Non-judge. No main effect of the Time (p = .324) and of the interaction Time * N_Play (p = .448) emerged.

Mindfulness total mean. No main effect of the Time, Main p = .499; or interaction effect Time * N_Play ( p = .841) was found.

Dropout Rate.

During the study, a dropout rate of 60.98% was observed, with 39.02% of the participants completing all experimental phases. The most critical time was between phases 2 and 3.

A logistic regression assessed the probability of abandonment of the study, selected as a dependent variable (abandonment: yes, no), with the independent variable, the number of meditations (N_Play: M=10.94, DS=10.22)

The model is statistically significant. $\chi 2(1) = 41.993$, p<. 001.

The constant is statistically significant: Exp(a)= 74.24, χ 2 of Waldt (1) =9.39, p =. 002. Also, the unique contribution of N_Play is statistically significant: Exp(b)= 0.63, χ 2 of Waldt (1) =5.22, p=. 022.

### 5.2.3. Discussion

Usability and user experience

The System Usability Scale (SUS) and the User Experience Questionnaire Plus (UEQ+) *yield*ed an upbeat assessment of the app. The mean SUS score during the two experimental phases, as established by standard guidelines, yielded statistically significant results in both cases. We can infer that the application demonstrated a consistently high level of usability, exceeding average expectations from the outset and throughout the study period, with mean scores surpassing those recommended by the relevant standards. The UEQ+ questionnaire provided a more comprehensive insight into the user experience of BBMIND. It resulted in a highly favourable perception across multiple dimensions, including attractiveness, efficiency, dependability, interest, usefulness, content reliability, content quality, and, notably, ease of use. However, participants reported low evaluation of the application's novelty and aesthetic appeal. As the analysis did not reveal any statistically significant main effects for any of the assessed dimensions across the two experimental phases, all these findings suggest that user perceptions of the application's usability remained stable over time. Additionally, importance ratings were evaluated, indicating the dimensions that participants perceived as necessary. "Stimulation" dimension resulted in a significant growing trend over time. This result suggests that users found the interaction with the application increasingly engaging as their experience with the system progressed.

Mindfulness skills

The mindfulness abilities were evaluated using the FFMQ dimensions and analysed across the experimental phases. Additionally, we assessed the impact of meditation engagement on changes in mindfulness abilities. We observed an improvement in the Observe facet, particularly when comparing the last phase to the first one. Also, the significant interaction effect between the number of meditation sessions and the Observe **s**cores suggests that the ability to notice internal states and emotions, which increased from the earlier phases to the final one, was also related to the frequency of mindfulness practice. These results suggest that participants who engaged more consistently in meditation may have derived greater benefits. Similarly, the Non-react dimension, indicating the

ability to experience thoughts and emotions without automatically reacting to them, increased between the first and last phases of the study.

Furthermore, a significant interaction between phase and number of meditation sessions suggests that this improvement was modulated by practice frequency, with more consistent meditators showing greater gains. No notable changes emerged for the Describe**,** Act with Awareness**,** or Non-judge dimensions. This indicates that the ability to verbally describe internal experiences (Describe), to maintain attention on present-moment experiences (Act with Awareness), and to adopt a non-judgmental stance toward thoughts and feelings (Non-judge) remained stable over time and were not influenced by the frequency of meditation practice. An analogous pattern emerged in the Mindfulness composite score. Overall, we can deduce that specific dimensions, such as observing and not automatically reacting to thoughts and emotions, benefited the most from the mindfulness practice. Observing without responding to the internal and external world is one of the first pillars of a mindful attitude. Considering that most participants (70,5%) were naïve, it can be recognised as a good achievement for those who completed the entire study. The dropout rate is a significant challenge, and it may be related to difficulties in maintaining engagement in regular meditation, particularly for individuals new to mindfulness. Prior mindfulness education can help maintain consistent motivation and prevent dropout, allowing practitioners to internalise mindfulness pillars from the beginning (Kabat-Zinn, 2013).

All these considerations about findings must be taken carefully, because the final sample size did not allow for robust statistical analysis.

## 5.3. Experiment 2: Patients with chronic pain conditions

### 5.3.1. Materials and Methods

#### *5.3.1.1. Participants*

Forty-one participants with chronic pain participated in the experiment, and twenty-one completed the study (mean age, 51 years; SD, 11; 18 females).

A priori power analyses were conducted using G*Power (Faul et al.,2007) to determine the minimum sample size of twenty-eight participants, based on Repeated Measures Analysis of Variance (ANOVA – *within factors*), with an Effect Size F= 0.25; Alpha Error Level: p= 0.05; Statistical Power= 0.80, Actual Power= 0.80, Correlation Among Measures: 0.5.

Thirty-three volunteers participated in the experiment; most of them (72.7%) had prior experience with mindfulness. Twenty-one participants (63.64%) completed the study (mean age = 53 years, SD = 11; 18 females), the subjects of the following analysis. All participants had a clinical diagnosis of neuropathic pain or chronic headache, and are currently patients of the Neuroalgology Department of the Headache Centre of the Neurological Institute "C. Besta" of Milan; Exclusion criteria included the presence of severe psychiatric or medical disorders, a diagnosis of epilepsy, and the use of opioids.

*5.3.1.2. Measures*

Self-report

In the second study, participants had to fill in the same questionnaires as in the first one:

(i) System Usability Scale (SUS) (Brooke, 1996);

(ii) Five Facets Mindfulness Questionnaire (FFMQ) (Baer et al., 2006; Italian version: Giovannini et al., 2014). Additionally,

(iii) General Self-Efficacy Scale (GSE) was used to assess perceptions of self-efficacy (Schwarzer & Jerusalem, 1995; Sibilia et al., 1995).

(iv) Medication Adherence Rating Scale (MARS-5) (adapted version to mindfulness practice) also indicated adherence to the mindfulness meditation (Chan et al., 2020; Italian version: Scribano et al., 2019).

Behavioural measure

N_ Play: The number of guided mindfulness sessions played using the APP.

Daily diary: the daily record of pain intensity and its impact on daily activities (working activity, leisure time and relationships) on a 0-10 Likert scale; the usage of painkillers.

5.3.1.3. *Materials*

Data on usability from the first study allowed us to introduce changes to the mobile app features. The number of mindfulness audio tracks changed from one to three (3, 12, and 15 minutes), focusing on breathing or body sensations. Mindful tips, such as push notifications, were also added to the app to enhance its dynamic nature. Additionally, a daily diary was used to record pain intensity and its impact on daily activities (see Figure 5.8).

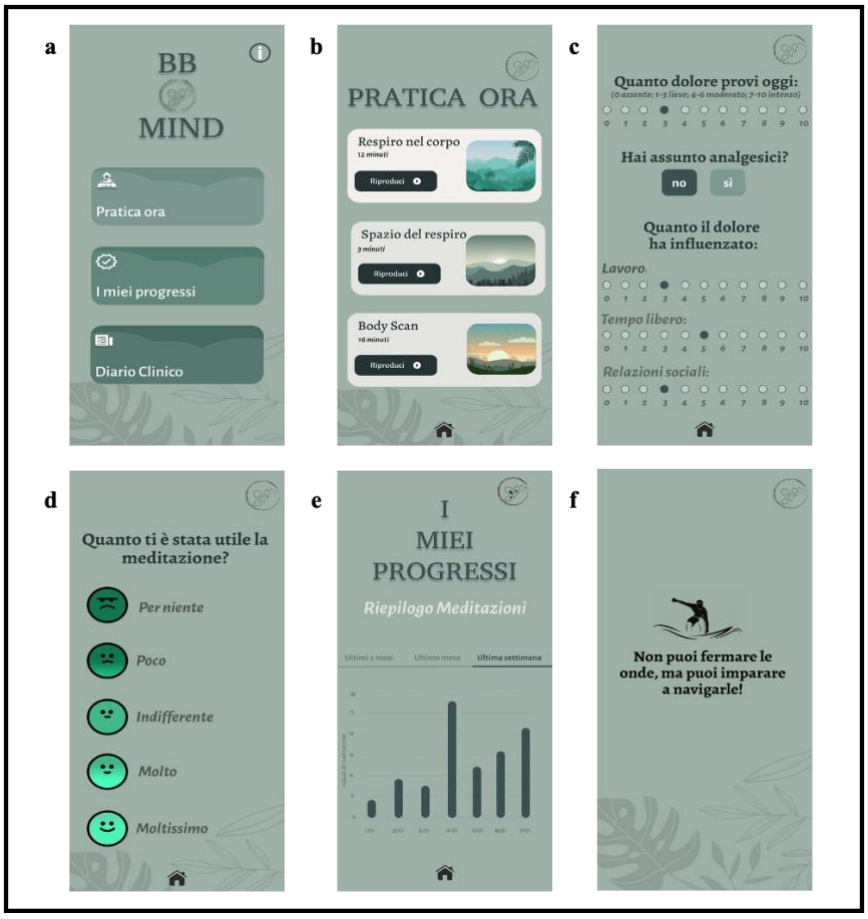


Figure 5.8: A view of the renewed screens of BBMIND: (a) home; (b) three guided meditations, (c) daily diary; (d) meditation feedback; (e) a summary of the progress in mindfulness practice; (f) a mindful tip.

### *5.3.1.4. Procedure*

The procedure is the same as that of the previous study and consists of three phases:

- Phase 1 (T0): Participants completed the self-report questionnaires when accessing the app, with instructions to practice meditation three times a week.
- Phase 2 (T1): Participants began using the app. After the first four weeks, participants were asked to complete the self-report questionnaires, and feedback on the app's usability was included.
- Phase 3 (T2): Participants completed the self-report questionnaires at the end of the eighth week of app use.

### 5.3.2. Results

Statistical analyses were performed using the software Jamovi. T-test, Analysis of variance (ANOVA), and analysis of covariance (ANCOVA) with repeated measures (RM) were performed. The Huynh-Feldt correction was applied in cases where sphericity was violated. Bonferroni correction for the pairwise comparisons was used as required.

Self-report

SUS. Two one-sample t-tests were performed to compare the average SUS score in the two experimental phases and the standard benchmark value ($M \geq 68$, range 0-100). Both tests yielded statistically significant results (Phase 2: $M=87.4$, $SD=9.40$, $p < .001$, Phase 3: $M=89.8$, $SD=8.91$, $p < .001$), confirming the good usability of the app.

MARS. A RM ANOVA within-subjects [*Time* (T1= phase 2 = 1° month; T2 = phase 3 = 2° month)], showed no main effect of phase ($p = .067$), indicating that the patient's adherence to the program was consistent over time.

FFMQ: RM ANCOVAs within-subjects were conducted to assess the impact of meditation on mindfulness skills. [*Time* (T0 = phase 1 = baseline; T1= phase 2 = 1° month; T2 = phase 3 = 2° month)].

The number of meditation sessions completed by each participant (N_Play) was added as the continuous covariate ($M = 45.80$, $SD = 40.70$).

Non-judge. A main effect of Time was found [$F(2,38) = 5.88$, $p = .006$, $p\eta2 = 0.236$]. Post-hoc analysis revealed a significant mean difference between T0 ($M = 3.24$, $SE = 0.135$) and T2 ($M = 3.63$, $SE = 0.150$): Mean difference ($M = -0.387$, $SE = 0.095$, $t(-4.04)$, $p = .002$). No effect of the interaction between phase and N. Play was found ($p = .265$) (see Figure 5.9).

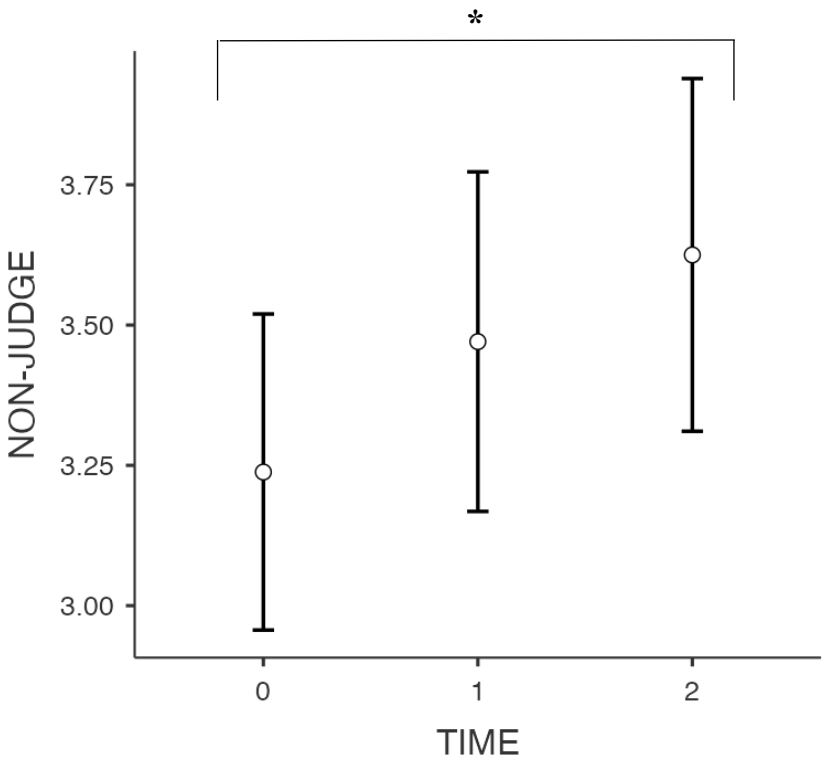


Figure 5.9: Estimated Marginal Means of Non-judge facet of FFMQ, increasing across the experimental phases. Higher scores were found in T2 compared to T0 (p = .002).

Non-react. A main effect of Time was found [F(2,38) = 3.45, p = .042, pη2 = .154]; T0 (M = 2.63, SE = 0.13) T1 (M = 2.91, SE = 0.11); T2 (M = 2.90, SE = 0.09). Post hoc test comparison did not show any significant mean difference of the non-react facet across time. No effect of the interaction between Phase and N_Play was found [F(2,38) = 1.52, p = .232, pη2=.0.074]. (see Figure 5.10).

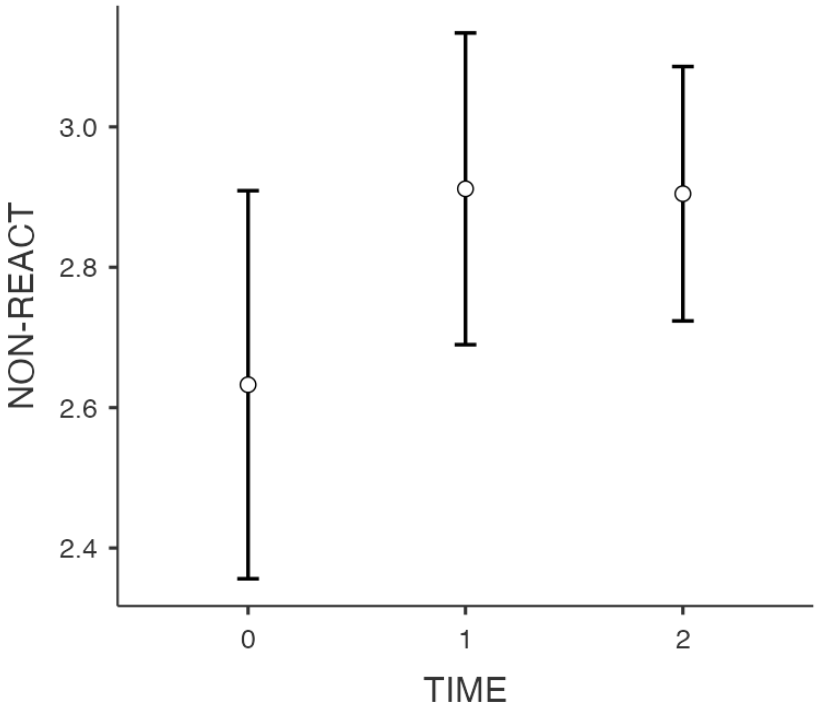


Figure 5.10: Estimated Marginal Means of Non-react facet of FFMQ, increasing tendency, but not statistically significant, across the experimental phases.

Observe. No main effect of the Time (p = .706) and of the interaction Time * N_Play (p = .918) was found.

Describe. No main effect of the Time (p = .300) and of the interaction Time * N_Play (p = .381) was found.

Act with awareness. No main effect of the Time (p = .918) or of the interaction Time * N_Play (p = .465) emerged.

Mindfulness total mean. A main effect of Time was close to significance [F(1.62, 3.84) = 3.34, p = .058, pη2 = 0.149]. T0 (M = 3.23, SE = 0.08) T1 (M = 3.33, SE = 0.07); T2 (M = 3.41, SE = 0.07). No effect of the interaction between phase and N_play was found (p = .521).

Behavioural measure

N_play. A one-sample t-test was conducted, using the benchmark of the N.Play that occurred in study 1. A significant difference was found (p = .009): the mean number of sessions completed by patients (M = 45.80, SD = 40.70) was higher than that of healthy participants (M = 20.81, SD = 7.08).

Daily diary. A one-sample t-test compared the mean number of completions with the expected number of times recommended to the participants, i.e., once daily for 60 days. A significant difference was found ($p < .001$): the diary was completed less frequently than expected ($M = 16.80$, $SD = 16.50$).

Dropout Rate

During the study, a dropout rate of 36.36% was observed. A binomial logistic regression was used to assess the probability of study abandonment, with the dependent variable (abandonment: yes, no) and the independent variable, the number of meditations (N_Play). The dropout status was set as the dependent variable (Y = Dropout, N = No Dropout).

The model is statistically significant, as indicated by the likelihood ratio test: $\chi^2$ (1) = 45.7, $p < .001$. The unique contribution of the coefficient NPLAY_TOT (M = 43, SD = 37.3) was negative and statistically significant: (B = −10.30, SE = 30.70, z = −0.0033, p = .043), with an odds ratio (OR) = 0.957. This indicates that, holding all else constant, each additional unit increase in NPLAY_TOT is associated with a 4.3% decrease in the odds of dropout. These results suggest that greater user engagement, as measured by total interactions (NPLAY_TOT), is significantly associated with a lower likelihood of dropping out.

A binary logistic regression was conducted to examine whether the total number of plays (NPLAY_TOT) significantly predicted the likelihood of dropout (coded as Y = Dropout, N = No Dropout). The overall model was statistically significant, $\chi^2(1) = 7.65$, $p = .006$, indicating that the predictor made a meaningful contribution to distinguishing between individuals who dropped out and those who did not. Analysis of the model coefficients revealed that NPLAY_TOT was a statistically significant negative predictor of dropout (B = −0.0368, SE = 0.0166, z = −2.21, p = .027), with an odds ratio (OR) = 0.964. This indicates that each additional unit increase in NPLAY_TOT was associated with a 3.6% decrease in the odds of dropout. The intercept term was not statistically significant (B = 1.03, p = .075). These findings suggest that greater engagement, as measured by the number of total plays (NPLAY_TOT), is associated with a reduced probability of dropout.

### 5.3.3. Discussion

Usability and adherence to mindfulness practice

Chronic pain patients and the participants in Study 1 appreciated the app. The SUS scores during the two experimental phases were above the standard benchmark value, confirming the good

usability of the app. Additionally, the adherence to the suggested meditation frequency, as evaluated by MARS, implies that the patient's participation in the program was consistent over time. Both findings revealed an appreciation for BBMIND and the improvements made to make it more appealing and variable. Most of the participants had previous experience with mindfulness, such as attending a mindfulness group course offered by the Headache Centre of the Neurological Institute "C. Besta" in Milan. They reported an initial enthusiasm for using the app, as it provided a chance to continue practising mindfulness at home at their own pace. Nevertheless, the dropouts continued to be a challenging issue, with a 36.36% dropout rate.

Mindfulness skills

The mindfulness abilities were evaluated using the FFMQ dimensions and analysed across the experimental phases. Additionally, we assessed the impact of meditation engagement (N_play) on changes in mindfulness abilities. We observed an improvement in the Non-judge facet, specifically the ability to adopt a non-judgmental stance toward thoughts and feelings, particularly when comparing the last phase to the first. The Non-react dimension, indicating the ability to experience thoughts and emotions without automatically reacting to them, showed a tendency to increase between phases of the study. The lack of significant changes in the other mindfulness facets, as well as the interaction effect between them and the number of meditation sessions, allows us to speculate on possible reasons. One reason could be that the sample size was insufficient to support a robust analysis. On the other hand, most participants (72.7%) had previous experience with mindfulness, typically through an 8-week practice course; thus, it is plausible not to expect drastic improvement in all mindfulness dimensions, but rather preservation of mindfulness skills or a slight upgrade.

## 5.4 Experiment 3: Mindfulness intervention in the chronic pain population

### 5.4.1. Aim of the study

Several studies have investigated the use of mindfulness-based practices for treating chronic pain, yielding promising results (Andrasik et al., 2016; Grazzi et al., 2022; Grazzi et al., 2023). However, sustaining mindfulness practice as a lifestyle beyond the duration of structured programs remains a significant challenge, limiting the long-term benefits of its therapeutic effects.

The present study has two primary objectives:

1. To evaluate the feasibility and long-term effectiveness of the BBMIND mobile application as a tool to support regular mindfulness practice.

2. To assess the efficacy of the intervention in enhancing mindfulness skills, improving pain management, and potentially reducing both pain intensity and the use of pharmacological treatments.

The findings of this study may provide a foundation for proposing mobile application-based mindfulness interventions as effective supportive therapies for individuals with chronic pain conditions.

### 5.4.2. Materials and Methods

#### *5.4.2.1. Participants*

A priori power analyses were conducted using G*Power (Faul et al.,2007) to determine the minimum sample size of fifty-four participants, based on Repeated Measures Analysis of Variance (ANOVA–*within-between factors*), with an Effect Size F= 0.5; Alpha Error Level: p= 0.05; Statistical Power= 0.80, Actual Power= 0.80, Correlation Among Measures: 0.50 (Faul et al., 2007).

To account for potential drop-outs during the two-month intervention period, each group will be oversampled to include 30 participants.

The participants were allocated as follows:

1) **Mindfulness group**: Individuals who have already experienced a guided mindfulness (MBSR) program, promoted by the "C. Besta, Neurological Institute, Headache Centre" of Milan.
2) **Control group**: Individuals who have never participated in a guided mindfulness (MBSR) program. They were currently on the waiting list for the BBMIND app intervention. They were informed that they would have the chance to use the app at the end of this experiment.

All participants had a clinical diagnosis of neuropathic pain or chronic headache, and are currently patients of the Neuroalgology Department of the Headache Centre of the Neurological Institute "C. Besta" of Milan. Exclusion criteria included the presence of severe psychiatric or medical disorders, a diagnosis of epilepsy, and the use of opioids.

The study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki and received ethical approval from the local ethics committee. All participants provided informed consent before participating in the study. All of them still received their usual medical support and pharmacological treatment.

Currently, fifty-three participants with chronic pain are participating in the experiment: twenty-three in the Mindfulness group (MG) (mean age = 48 years old; SD, 11; 22 females) and thirty in the Control group (CG) (mean age, 50 years; SD, 13; 26 females). This research project is still ongoing; the following data will refer to the current sample. We are aware that the sample groups are now

undersized and not perfectly balanced in terms of number, gender, and age. Present efforts are focused on obtaining accurate samples.

5.4.2.2. *Measures*

Self-report measures

(i) The Beck Depression Inventory (BDI-II) (Beck et al., 1996) and State-Trait Anxiety Inventory (STAI-Y1,2) to assess depressive and state-trait anxiety (Spielberger, 1983).

(ii) The Five Facets Mindfulness Questionnaire (FFMQ) (Baer et al., 2006, Italian version Giovannini et al., 2014) to assess mindfulness through a five-dimensional model: Observe, Describe, Act with awareness; Non-judge; Non-react; Mindfulness total mean.

(iii) Pain Catastrophizing Scale (PCS) evaluated the perceived catastrophism of pain (Sullivan et al., 1995)

(v) The Medication Adherence Rating Scale (MARS-5) (adapted version to mindfulness practice) also indicated adherence to the mindfulness meditation (Chan et al., 2020; Italian version: Scribano et al., 2019).

(iv) The Headache Impact Test (HIT6) measured the perceived consequences of headache (Kosinski et al., 2003).

(v) The General Self-Efficacy (Schwarzer & Jerusalem, 1995); Italian version: Sibilia et al., 1995).

Demographic information, including age, self-declared gender identity, assumption of analgesic or anti-inflammatory medications in the previous twelve hours, and the presence of pain conditions, was collected.

Behavioural measures

(i) N_Play: The type and number of guided mindfulness sessions played using the APP.

(ii) Daily diary: the daily record of pain intensity and its impact on daily activities (working activity, leisure time and relationships) on a 0-10 Likert scale; the usage of painkillers.

5.4.2.3. *Materials*

Data and feedback from the first usability studies allowed us to introduce changes to the mobile app features. The number of mindfulness audio tracks increased from one to five to add more variability in terms of time and topic. Two meditations focused on breathing: one on body sensations (body scan) and one on steadiness (mountain meditation), as well as one on pain management. A

rewarding system was implemented to encourage mindfulness practice: every ten meditations completed, the users earn a medal, a symbol of their dedication. It is important to note that the app does not interact with any other phone functionalities and does not collect or store any personal user data beyond the parameters specified above (see Figure 5.11).


Figure 5.11: A view of some screens of BBMIND: (a) home; (b) previous three guided meditations, (c) two new guided meditations; (d) daily diary; (e) a summary of the progress in mindfulness practice; (f) a reward pop-up screen.

### 5.4.2.4. *Procedure*

Experimental design:

Participants have been assigned to either the experimental group, the **Mindfulness group,** or the **Control group** based on their participation or non-participation in an eight-week MBSR protocol promoted by the “Carlo Besta" Neurological Institute. The control group has been placed

on a two-month waiting list for access to the BBMIND application and refrained from engaging in any mindfulness-related activities during this period.

The study adopted a 2×3 mixed factorial design**,** with between-subjects and within-subject factors: [Between-subjects factor**:** *Group* (Mindfulness vs. Control)]; [Within-subjects factor: *Time* (T0 = baseline phase; T1 = phase 1 = 1° month; T2 = phase 2 = 2° month)].

Experimental procedure:

The procedure consists of three phases, with a slight difference between the two groups.

Phase 1 (T0):

Mindfulness group: participants downloaded the BBMIND app on their mobile device from the App Store or Google Play**.** Every user received a personal, unique code to access BBMIND fully, which includes five audio tracks of mindfulness meditations ranging from approximately 5 to 30 minutes in length, as well as a guide on how to use the mobile app. They were instructed to practice meditation three times a week for eight weeks.

At the first login to the app, users were asked to complete the self-report questionnaires through a Qualtrics link within the app. Then, they could start to meditate, report in the app clinical diary data about their perceived pain, its impact on their life and the painkiller assumption.

Control group: participants received an automated email delivered by the Qualtrics software with a link to complete the self-report questionnaires. Every participant was assigned a unique user code, which was embedded in Qualtrics to facilitate automatic email delivery at one month (T1) and two months (T2) post-intervention. Participants were not asked to do any other activity until the next phase.

Phase 2 (T1):

After the first four weeks, both groups received the invitation to complete the self-report questionnaires.

The control group received it via email, while the mindfulness group received a notification in the app.

The mindfulness group had to continue practising mindfulness and completing the app diary, while the control group only had to wait for the next phase.

Phase 3 (T2):

The mindfulness group completed the second month of using BBMIND, meditating and recording in the app diary data about their perceived pain, its effect on their life and the painkiller assumption.

Both groups were asked to complete the self-report questionnaires at the end of the eighth week. BBMIND has been programmed to restrict access to users upon completion of this step, thereby concluding the experimental protocol.

Questionnaire and clinical diary data were supplemented with app usage data**,** specifically the number and time of day of usage, as well as the selection of guided meditations. The app automatically recorded these metrics**.**

### 5.4.3. Results

Data analysis and expected Outcomes

Based on the evidence and discussion from Study 2, we assumed that it could be very challenging for naïve participants to practice mindfulness regularly using a mobile app alone. This is why we decided to target mindfulness-trained patients in the mindfulness group intentionally for his third study. Consequently, we hypothesise that the BBMIND application may serve as an effective tool for supporting mindfulness practice, particularly by facilitating the transition from structured, group-based interventions, such as those delivered through mindfulness courses offered by the “Carlo Besta" Neurological Institute, to consistent, autonomous practice.

Specifically, we expected the following outcomes in the Mindfulness group:

- Higher frequency and consistency in mindfulness practice over time
- Improvement in mindfulness-related skills over time, compared to the control group
- Better management of chronic pain**,** accompanied by enhancements in overall well-being, compared to the control group

We assessed between-groups differences in socio-demographic features using standard tests (Chi-square tests ($\chi^2$) or Mann-Whitney U test). T-tests, linear mixed models (LMMs), and analysis of variance with repeated measures (RM ANOVAs) have been employed to evaluate both within- and between-group differences over time in mindfulness practice frequency and duration, as well as in pain-related symptoms. The Huynh-Feldt correction was applied in cases where sphericity was violated. Bonferroni correction for the pairwise comparisons was used as required.

The primary dependent variables will include:

- Acquisition of mindfulness skills
- Perceived self-efficacy

- Perceived quality of life
- Pain-related symptomatology following one and two months of mindfulness practice

Statistical significance was considered at the threshold of $p < .05$. In the event of a violation of the normality assumption (as determined by the Shapiro–Wilk test), non-parametric procedures were employed.

The software g*Power was used to calculate a sensitivity Power Analysis setting, alpha, and Power at the standard values of 0.05 and 0.8. The fixed sample size of 54 participants was nearly reached; however, we encountered some technical problems that prevented us from collecting the BBMID data properly. Also, the initial evidence of dropout in both groups complicated the between-group comparison. Then, we decided to use linear mixed models (LMMs) for our analyses, which seemed to be a more appropriate approach for comparing data with some missing values and unbalanced groups, while also accounting for individual variability, especially in mindfulness abilities, across the two groups. LMMs have greater statistical power than traditional statistical methods, such as ANOVAs, so our sample is sufficient to capture the expected effects (Green & MacLeod, 2016; Camerone et al., 2022). Statistical analyses were performed using Jamovi Software (version 2.3.28).

Demographic and psychometric assessment

The initial sample comprises fifty-four individuals: twenty-three in the Mindfulness group (MG) (mean age = 48 years; SD = 11; 22 females) and thirty in the Control group (CG) (mean age = 50 years; SD = 13; 26 females). All are chronic pain patients of the Headache Centre, Neuroalgology Department, at the IRCCS Foundation "Carlo Besta" Neurological Institute in Milan, Italy.

MG and CG are matched for age [$\chi^2(1) = 1.201$, $p = .273$] and gender [$\chi^2(1) = 1.207$, $p = .272$].

MG and CG patients had similar levels of frequency [$\chi^2(1) = 1.523$, $p = .217$] and duration [$\chi^2(1) = 1.651$, $p = .420$] of pain condition.

Pain condition

69.6% of MG patients experience migraine or headache (60.9% of whom are chronic migraineurs). Other reported conditions were facial pain (related to trigeminal nerve pain), neuropathic pain, and one case of multiple sclerosis.

96.7% of CG patients experience migraine or headache (70% of whom are chronic migraineurs). Also, a single case of fibromyalgia was reported (see Figure 5.12).

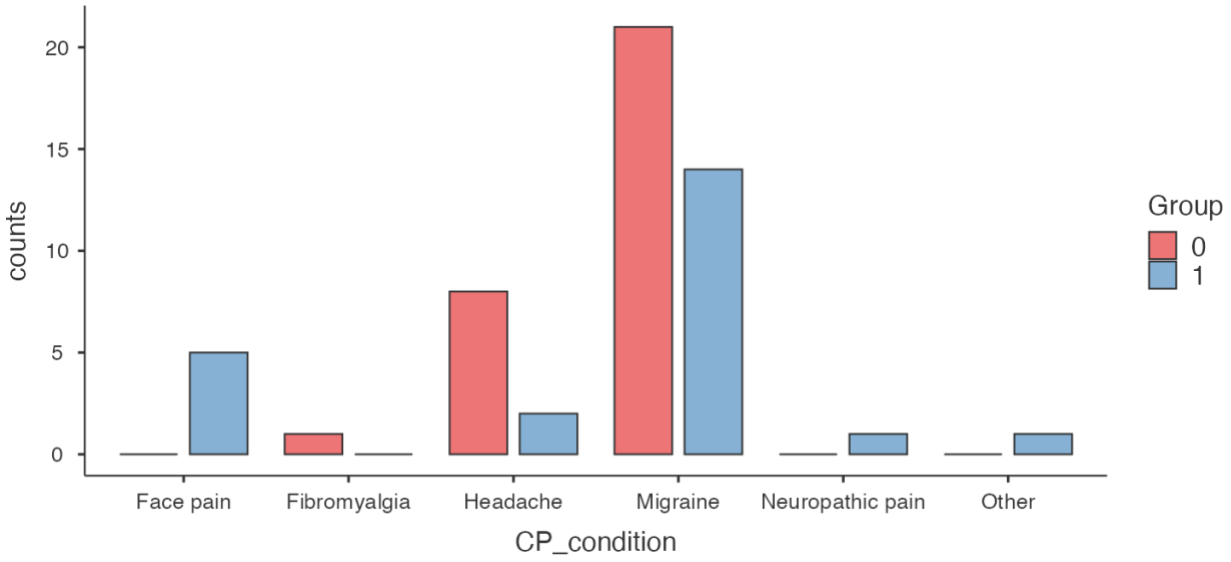


Figure 5.12: Descriptive comparison of chronic pain condition between Group 0 = control group and Group 1 = mindfulness group. In both groups, headache pain, especially chronic migraine, is the most common condition.

Pain frequency

An ordinal range of frequency (Rarely – sometimes – often – very often – always) was used to assess the pain condition state. The initial frequency of pain in MG was more variable than in CG, with the most common ranges being always (26.1%) and sometimes (30.4%). In comparison, CG reported a more evident tendency to often (17%) and very often frequency (22.6%) (see Figure 5.13).

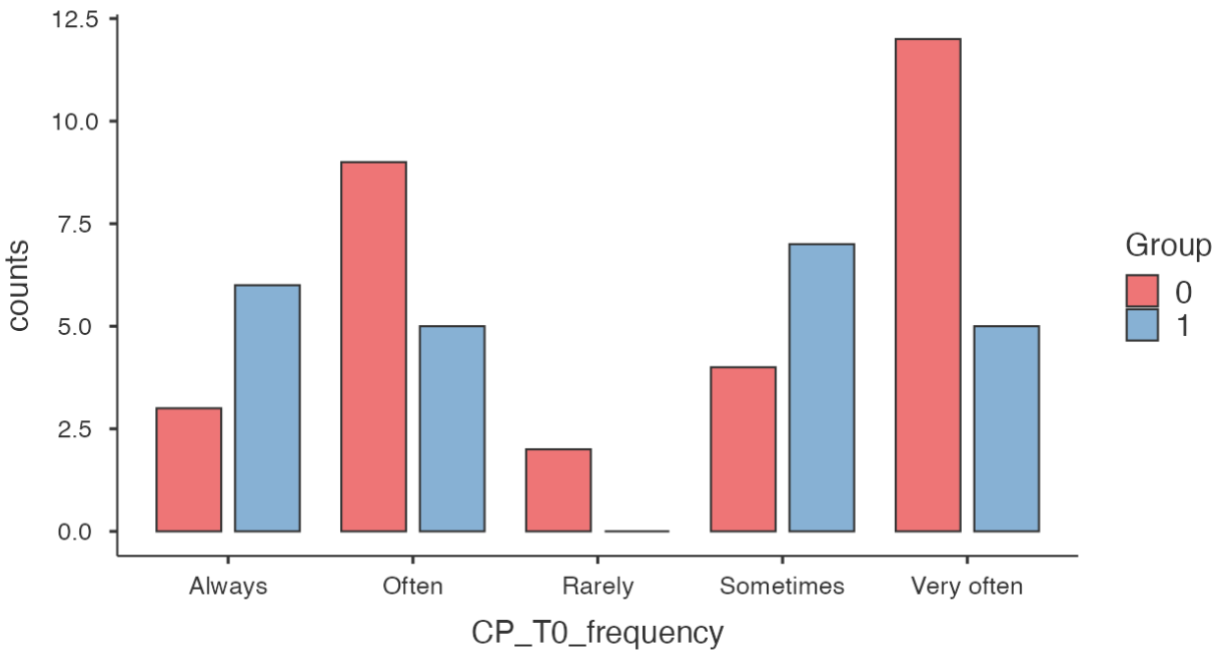

Figure 5.13: Descriptive comparison of chronic pain frequency between Group 0 = control group and Group 1 = mindfulness group.

Pain duration

An ordinal range of time (0-6 months, 6-12 months, 12-24 months, and more than 24 months) was used to assess the duration of the pain condition. In both groups (MG = 91.3%; CG = 96.7%), the most common duration was more than 24 months, consistent with the key feature of chronic pain. (see Figure 5.14).

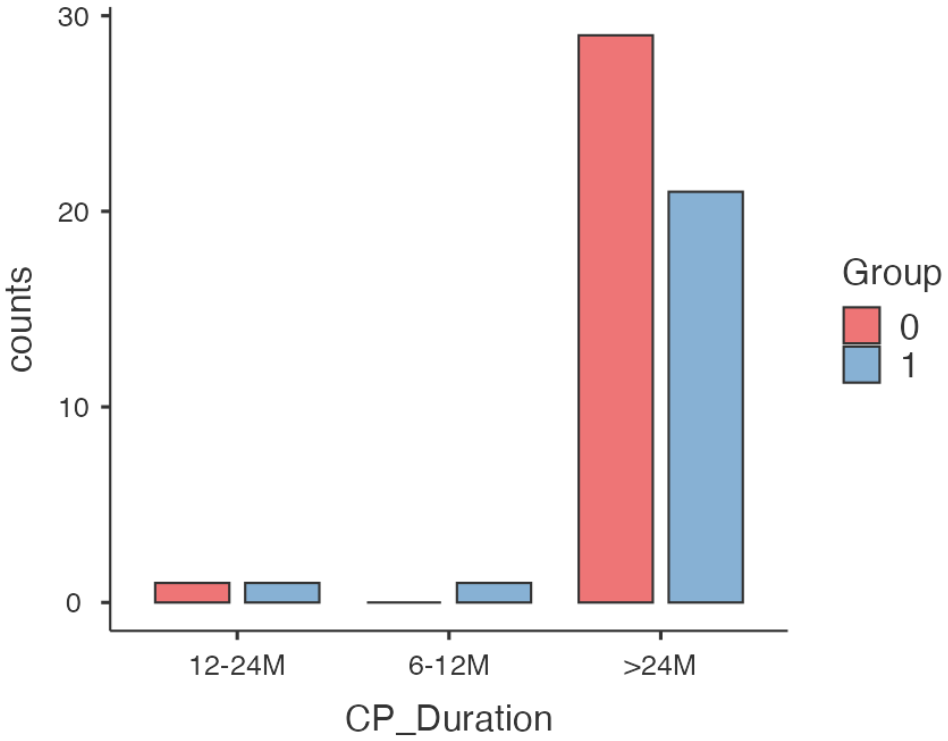


Figure 5.14: Descriptive comparison of chronic pain duration between Group 0 = control group and Group 1 = mindfulness group. In both groups, the most common duration was more than 24 months.

The normal distribution of standardised self-report questionnaires was checked. The Shapiro–Wilk test revealed violations of normal distribution for BDI ($p = .003$), HIT ($p < .001$), and GSE ($p = .041$). Thus, non-parametric comparison (Mann-Whitney U test) was employed instead of the Student T-test.

The between-group comparison did not show evidence of a significant difference at the study's launch (T0) in depression (BDI), state and trait anxiety symptoms (STAI-Y1, Trait STAI Y2), impact of pain

(HIT), Pain Catastrophizing (PCS), self-efficacy (GSE) or mindfulness abilities (FFMQ) (all $p > .110$).

Beck Depression Inventory-II (BDI-II): the CG average score, M = 9.73 (SD = 8.84), is compatible with proneness to mild depressive symptoms, as defined by a cut-off score of ≤ 9 (Beck et al., 1961).

State-Trait Anxiety Inventory (STAI-Y1, Y2): the CG and MG mean scores of state anxiety (STAI-Y1), equal to M = 43,37 (SD = 8.84) and M = 42,65 (SD = 42), respectively, suggest a potential tendency to trait anxiety in the sample (cut-off ≤ 40). A replicable inference can be made regarding trait anxiety levels: the CG average score is *M* = 48 (SD = 9.33), and the MG average score is *M* = 45.13 (*SD* = 8.11), according to normative values for the Italian adult population (cut-off ≤ 40).

The Pain Catastrophizing thoughts (PCS) scores were found to be below the cut-off of ≤ 30 in both groups. The impact of headache was evaluated as substantial in MG (M = 48 (SD = 9.33) and severe in CG M = 48 (SD = 9.33), according to the HIT-6 range of impact (cut-off ≤ 49: no effect; 50-55: some impact; 56–59 = substantial impact; 60–78 = severe impact). The sense of self-efficacy (GSE) resulted in a score higher than the cut-off ≤ 20, signifying no relevant deficit in this belief.

Since FFMQ does not have normative values, the FFMQ in T0 was recorded as a point of reference for the following phase of the study (see Table 5.1).

Group Descriptives

| | Group | N | Mean | Median | SD | SE |
|---|---|---|---|---|---|---|
| BDI_T0 | 0 | 30 | 9.73 | 8.50 | 8.843 | 1.6145 |
| | 1 | 23 | 7.87 | 7.00 | 6.070 | 1.266 |
| STAI-Y1_T0 | 0 | 30 | 43.37 | 42.00 | 11.544 | 2.1077 |
| | 1 | 23 | 42.65 | 42.00 | 7.327 | 1.528 |
| STAI-Y2_T0 | 0 | 30 | 48.00 | 47.50 | 9.329 | 1.7033 |
| | 1 | 23 | 45.13 | 43.00 | 8.109 | 1.691 |
| HIT_T0 | 0 | 30 | 60.50 | 63.00 | 7.196 | 1.3137 |
| | 1 | 23 | 57.22 | 61.00 | 13.987 | 2.916 |
| PCS_T0 | 0 | 30 | 21.37 | 21.50 | 10.053 | 1.8355 |
| | 1 | 23 | 20.70 | 20.00 | 8.065 | 1.682 |
| GSE_T0 | 0 | 30 | 34.50 | 37.50 | 8.407 | 1.5348 |
| | 1 | 23 | 37.22 | 37.00 | 5.213 | 1.087 |
| FFMQ_TOT_T0 | 0 | 30 | 3.06 | 3.06 | 0.405 | 0.0739 |
| | 1 | 23 | 3.26 | 3.42 | 0.535 | 0.111 |

Table 5.1: Demographic and psychometric assessment. Abbreviations: Group 0 = control group and Group 1 = mindfulness group; T0 = baseline score evaluated at the beginning of the 8-week study. BDI = Beck Anxiety Inventory II; STAI-Y1,2 = State-Trait Anxiety Inventory; HIT = Headache Impact Test (HIT6); PCS = Pain Catastrophizing Scale; GSE = General Self-Efficacy Scale; FFMQ_TOT = Five Facets Mindfulness Questionnaire total score.

Dropout rate

During the study, a dropout rate of 43.5% was observed in the MG group; 56.5% of the participants completed all experimental phases. The most critical period was between phases 1 and 2 (T1-T2), during which the dropout rate was 26.1%. In the CG, 33.3% of the participants left the study early, while 66.7% completed all experimental phases. Additionally, in CG, the most critical period was between phases 1 and 2 (T1-T2), during which 26.7% of the total dropout rate was recorded.

Between-groups comparisons

The premature abandonment of some participants affected the primary analysis that followed. A linear mixed model (LMM) was used to evaluate self-report scores as dependent variables during the 2 months: [Between-subjects factor**:** *Group* (Mindfulness vs. Control)]; [Within-subjects factor: *Time* (T0 = phase 1 baseline; T1 = phase 2 = 1° month; T2 = phase 3 = 2° month)]. Random effects have been fit with intercepts for Participants. Degrees of freedom were calculated using the Satterthwaite method.

GSE: perceived self-efficacy: The Fixed Effect Omnibus tests revealed no significant main or interaction effects. Specifically, the main effect of Group was not significant, [F(1, 53.0) = 1.524, p = .222], nor was the main effect of Time, [F(2, 78.0) = 0.425, p = .655]. Additionally, the interaction Group * Time was non-significant: [F(2, 78.0) = 0.114, p = .893].

HIT-6: The Headache Impact Test: The Fixed Effect Omnibus tests did not show significant main or interaction effects. Neither the main effect of Group, [F(1, 53.9) = 0.186, p = .668], nor the main effect of Time, [F(2, 81.1) = 0.306, p = .737] nor the interaction Group * Time was significant: [F(2, 81.1) = 1.547, p = .219].

PCS: Pain Catastrophizing Scale: The Fixed Effect Omnibus tests revealed no significant main or interaction effects. The main effect of Group was not significant, [F(1, 53.1) =0.411, p = .524], nor was the main effect of Time, [F(2, 78.3) = 1.621, p = .204], nor the interaction Group * Time was significant: [F(2, 78.3) = 0.537, p = .587].

FFMQ Total score: The Fixed Effect Omnibus tests revealed a significant main effect of Group: [F(1, 53.0) = 4.54, p = .038]. No main effect of Time, [F(2, 77.3) = 2.37, p = .100], nor the interaction Group * Time was significant: [F(2, 77.3) = 2.23, p = .114]. Parameter estimates revealed a significant difference between groups, with Group 1 scoring higher than Group 0 (Estimate = 0.265, SE = 0.124, 95% CI [0.021, 0.508], t(52.8) = 2.13, p = .038, Bonferroni correction). Although the omnibus test for the Time (p = .100) and Group * Time interaction was not significant (p = .114), parameter

estimates analysis revealed a significant effect of Time2 compared to baseline (T2-T0: Estimate = 0.1032, SE = 0.049, 95% CI [0.007, 0.199], t(77.9) = 2.10, p = .039), and a marginally significant parameter estimate for the Group1 * Time2 contrast (Estimate = 0.194, SE = 0.098, 95% CI [0.002, 0.386], t(77.9) = 1.98, p = .051), suggesting a possible differential effect of Time2 between groups. However, this result should be interpreted cautiously, given the non-significant overall interaction and non-significant post hoc test comparison (see Table 5.2 and Figure 5.15).

Group:Time

| | | | | | 95% Confidence Interval | |
|---|---|---|---|---|---|---|
| Group | Time | Mean | SE | df | Lower | Upper |
| 0 | 0 | 3.06 | 0.0855 | 65.0 | 2.89 | 3.23 |
| 1 | 0 | 3.26 | 0.0987 | 63.8 | 3.06 | 3.45 |
| 0 | 1 | 3.12 | 0.0865 | 67.5 | 2.94 | 3.29 |
| 1 | 1 | 3.33 | 0.1021 | 71.1 | 3.12 | 3.53 |
| 0 | 2 | 3.07 | 0.0914 | 80.4 | 2.89 | 3.25 |
| 1 | 2 | 3.46 | 0.1090 | 86.5 | 3.24 | 3.67 |

Table 5.2: Estimated Marginal Means of Five Facets Mindfulness Questionnaire in Group 0 (control group) and Group 1 (mindfulness group) at the beginning (Time 0), after 1 month (Time 1), and at the end of the study (Time 2).

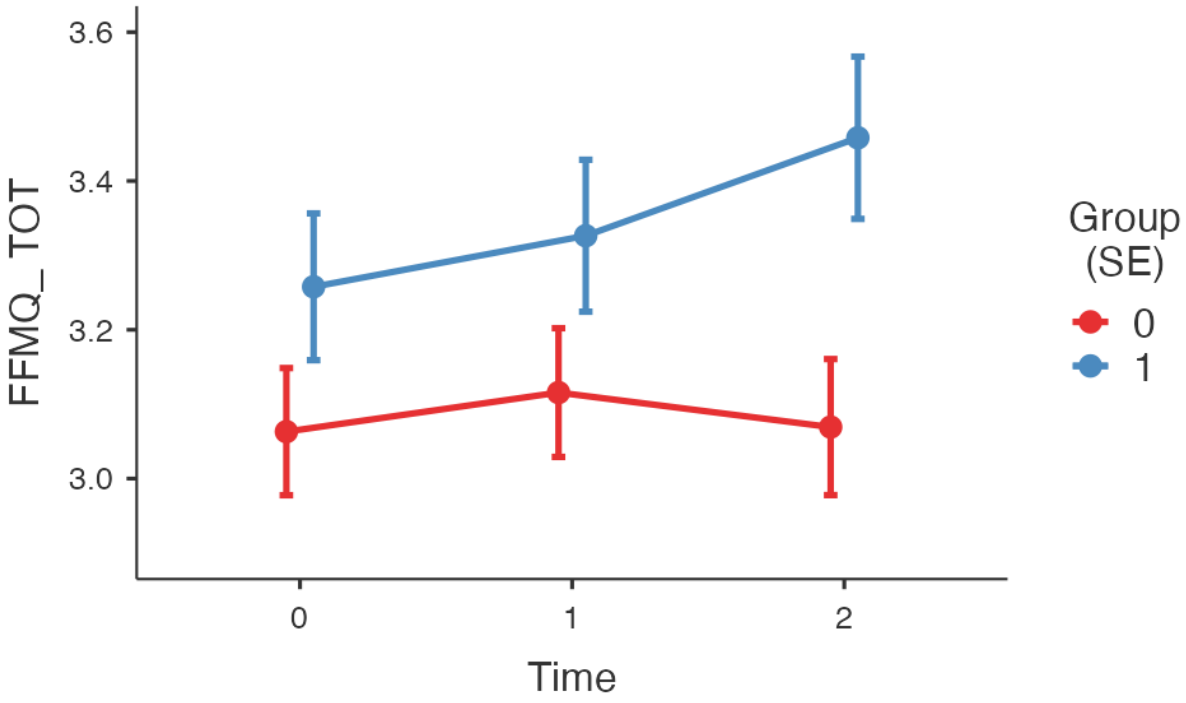


Figure 5.15: Estimated Marginal Means of FFMQ total score comparison between Group 0 (control group) and Group 1 (mindfulness group) show a difference between groups (FFMQ score in Group 1 was higher than in Group 0, p = .038); and a tendency for improved mindfulness abilities in the mindfulness group at the end of the study compared to the beginning.

Observe: The Fixed Effect Omnibus tests revealed a significant main effect of Group: [F(1, 51.6) = 12.510, p < .001]. No main effect of Time, [F(2, 76.7) = 2.507, p = .088], nor the interaction Group * Time was significant: [F(2, 76.7) = 0.411, p = .664]. Parameter estimates revealed a significant difference between groups, with Group 1 scoring higher than Group 0 (Estimate = 0.559, SE = 0.158, 95% CI [0.249, 0.869], t(53) = 3.54, p < .001, Bonferroni correction). Although the omnibus test for the Time (p = .088), parameter estimates analysis revealed a significant effect of Time1 compared to baseline (T1-T0: Estimate = 0.133, SE = 0.066, 95% CI [0.003, 0.264], t(77.9) = 2.007, p = .048), suggesting a possible differential effect of Time. However, the post hoc test comparisons of Time were not significant (all p > .145).

Describe: The Fixed Effect Omnibus tests did not show a significant main effect of Group: [F(1, 53.9) = 1.734, p = .193], nor main effect of Time, [F(2, 78.3) = 0.007, p = .993], nor the interaction Group * Time: [F(2, 78.3) = 0.621, p = .540].

Act with awareness: The Fixed Effect Omnibus tests did not show a significant main effect of Group: [F(1, 53.3) = 2.85e-4, p = .987], nor main effect of Time, [F(2, 77) = 0.017, p = .983], nor the interaction Group * Time: [F(2, 77) = 0.780, p = .462].

Non-judge: The Fixed Effect Omnibus tests revealed a significant main effect of Time: [F(2, 77.3) = 3.328, p = .041]. No main effect of Group, [F(1, 52.8) = 0.155, p = .695], nor the interaction Group * Time was significant: [F(2, 77.3) = 1.465, p = .237]. Parameter estimates revealed a significant difference in time, with Time2 scoring higher compared to baseline (T2-T0: Estimate = 0.263, SE = 0.102, 95% CI [0.622, 0.464], t(78) = 2.57, p = .012, Bonferroni correction). The post hoc test comparisons of Time confirmed a significant difference in non-judge ability at the end of the study compared to the beginning [T2-T0 = 0.263, SE = 0.102, t(78.1) = 2.57, p = .037]. Other time comparisons were not significant (all p > .231) (see Figure 5.16).

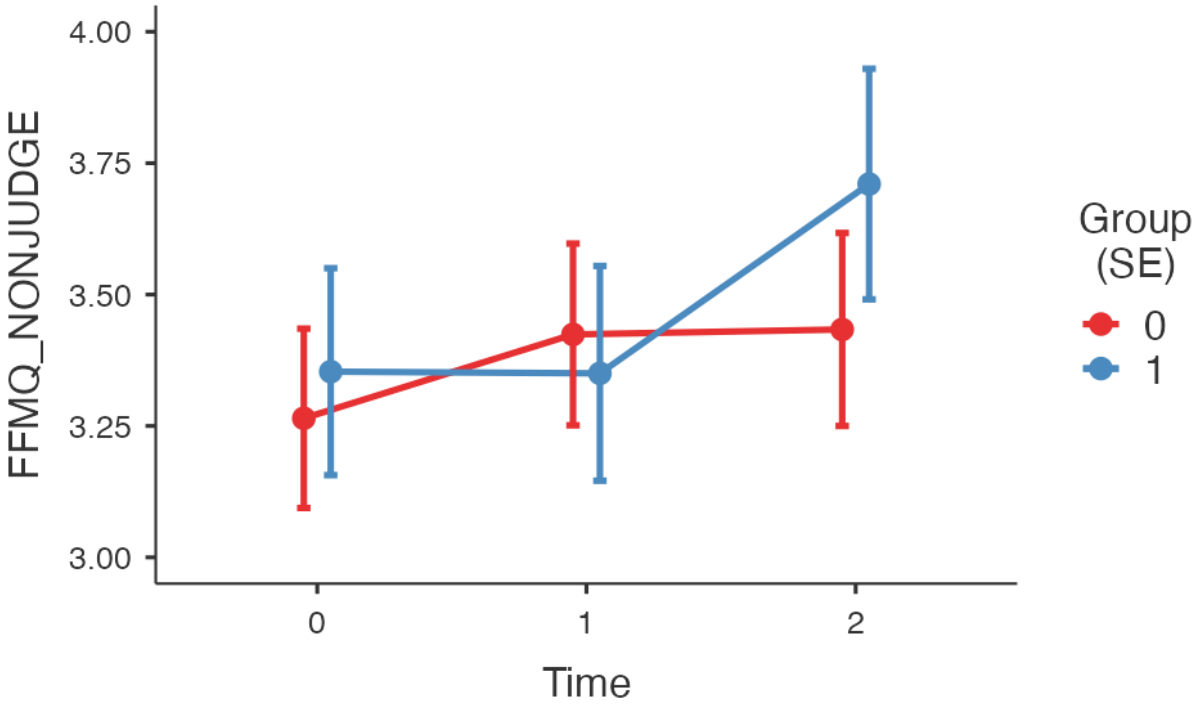


Figure 5.16: Estimated Marginal Means of Non-Judge dimension comparison between Group 0 (control group) and Group 1 (mindfulness group) shows a significant difference at the end of the study compared to the beginning of the study (p = .037), without any considerable specificity for group.

Non-react: The Fixed Effect Omnibus tests revealed a significant main effect of Group: [F(1, 53.5) = 8.19, p = .006]. No main effect of Time, [F(2, 80.2) = 1.92, p = .153], nor the interaction Group * Time was significant: [F(2, 80.2) = 2.73, p = .071].

Parameter estimates showed a significant difference between groups, with Group 1 scoring higher than Group 0 (Estimate = 0.407, SE = 0.142, 95% CI [0.128, 0.686], t(53.1) = 2.86, p = .006, Bonferroni correction). Although the omnibus test for the interaction Group * Time was not significant (p = .071), the parameter estimates analysis revealed a significant effect of Group1 * Time2 (Estimate = 0.407, SE = 0.175, 95% CI [0.065, 0.750], t(81.8) = 2.33, p = .022), suggesting a possible difference in non-react ability in the groups in the different phases of the study. The post hoc test comparisons confirmed a higher score in Group 1 compared to Group 0 in Time2 [Group1-Group0: Estimate = 0.622, SE = 0.188, t(11.5) = 3.307, p = .019] (see Figure 5.17).

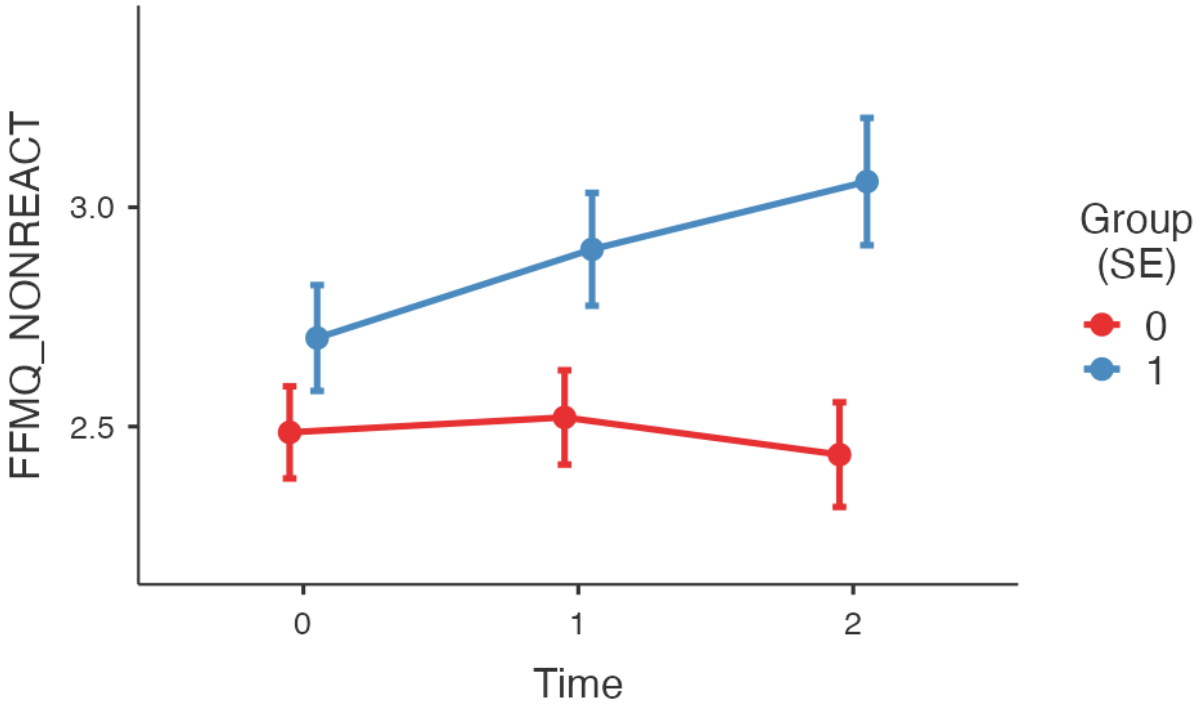


Figure 5.17: Estimated Marginal Means of Non-React dimension comparison between Group 0 (control group) and Group 1 (mindfulness group). The mindfulness group demonstrates a higher Non-React ability than the control group (p = .006), especially at the end of the study (Time2, p = .019).

The Beck Depression Inventory (BDI-II): The Fixed Effect Omnibus tests did not show a significant main effect of Group: [F(1, 53.8) = 1.651, p = .204], nor main effect of Time, [F(2, 78.4) = 0.311, p = .734], nor the interaction Group * Time: [F(2, 78.4) = 0.908, p = .408].

The State Anxiety Inventory (STAI-Y1): The Fixed Effect Omnibus tests did not show a significant main effect of Group: [F(1, 53.2) = 1.242, p = .270], nor main effect of Time, [F(2, 78.5) = 0.522, p = .595], nor the interaction Group * Time: [F(2, 78.5) = 1.609, p = .207].

The Trait Anxiety Inventory (STAI-Y2): The Fixed Effect Omnibus tests revealed a significant main effect of Time: [F(2, 76.5) = 3.11, p = .050]. No main effect of Group, [F(1, 56.2) = 1.55, p = .219], nor the interaction Group * Time: [F(2, 76.5) = 1.11, p = .334] was found. Parameter estimates showed a significant difference in Time, with a reduction in trait anxiety in T2 compared to the baseline. (Estimate = 2.12, SE = 0.87, 95% CI [-3.84, -0.408], t(77) = 2.86, p = .0053, Bonferroni correction).

Chronic Pain Frequency: The Fixed Effect Omnibus tests revealed a significant main effect of Time: [F(2, 75.5) = 6.31, p = .003]. No main effect of Group, [F(1, 52.3) = 1.75e-4, p = .989], was found. The interaction Group * Time was significant: [F(2, 75.5) = 3.15, p = .048].

Parameter estimates revealed a significant difference in Time, with Time 2 frequency of pain lower than the baseline (Estimate = -0.171, SE = 0.054, 95% CI [-0.278, -0.650], t(75.7) = -3.15, p = .002). Also, a significant effect of Group1 * Time2 was found (Estimate = -0.241, SE = 0.109, 95% CI [-0.454, -0.027], t(75.7) = -2-.20, p = .030). The post hoc test comparisons confirmed a decrease in pain frequency from T0 to T2 (p = .007, Bonferroni correction), but a little rise from T0 to T1 (p = .005, Bonferroni correction). Additionally, applying the post hoc test comparisons of the interaction Group * Time, a significant difference emerged in group 1 between T1 and T2 (difference: 0.302, SE = 0.084 t(75.3)= 3.56, p = .009, Bonferroni correction) and between T2 and T0 (difference: 0.292, SE = 0.084 t(75.7)= 3.45, p = .014, Bonferroni correction). No significant variance in pain frequency was found in Group 0 over time (all p = 1.00). The interaction comparison confirmed the fluctuation of pain frequency over time, with a significant decrease in Group 1 at the end of the study, compared to the baseline (see Figure 5.18).

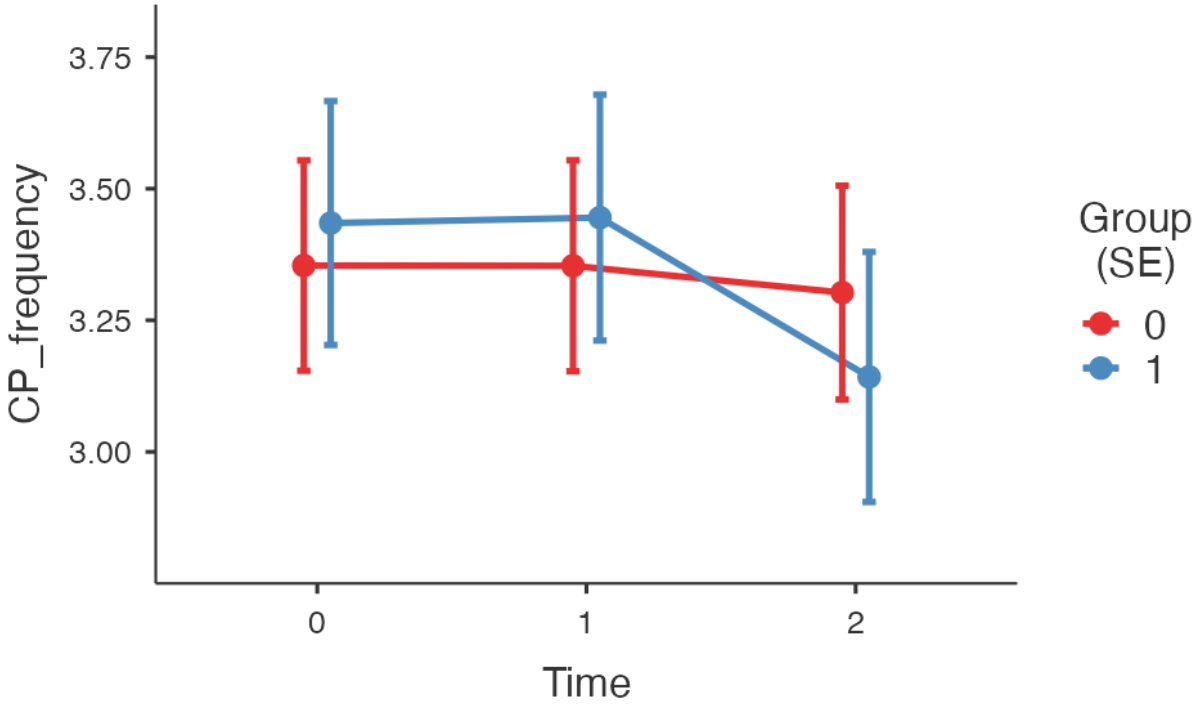


Figure 5.18: Estimated Marginal Means comparison of chronic pain frequency between Group 0 (control group) and Group 1 (mindfulness group) shows an effect of Time (T2 frequency of pain was lower than the baseline, p = .002). Additionally, in the mindfulness group there was a decrease in the frequency of pain over time, as indicated by the significant differences between T1 and T2 (p = .009) and between T2 and T0 (p = .014).

Behavioural measure within mindfulness group analysis

The motivation for participating in this experiment was explored. Most of the twenty-three patients (65.2%) reported that they did it to improve their well-being. A motivation option preferred to help the scientific research (30.4%) and to understand mindfulness (4.3%) better. No one participated to make a favour for someone or for simple curiosity (see Figure 5.19).

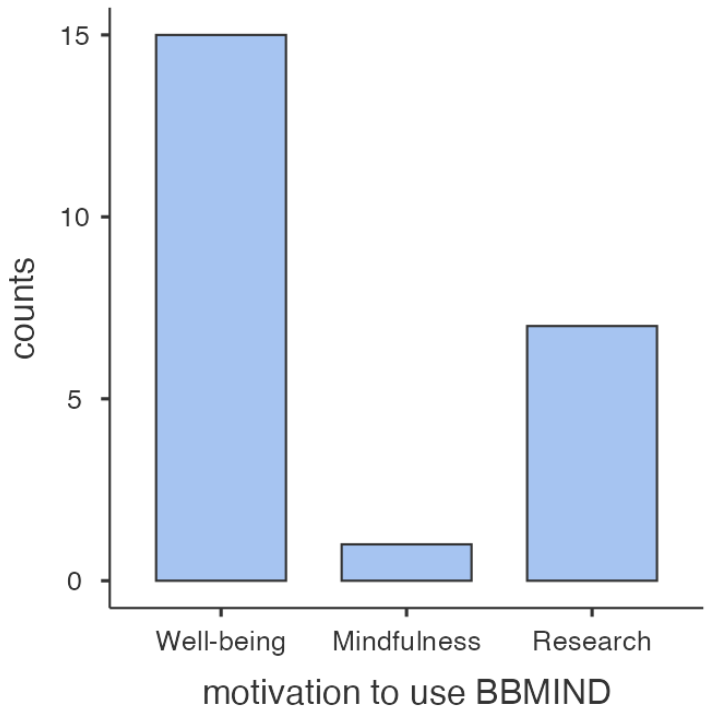


Figure 5.19: A comparison of motivation to use the app in the mindfulness group. Well-being is the first option chosen, followed by helping with scientific research and then understanding mindfulness better.

During the two months of using BBMIND, the mindfulness clinical diary data and the guided meditation play were recorded to monitor adherence to the recommended meditation frequency (three times a week) and the daily impact of pain.

Unfortunately, due to a technical issue, some diary data was lost. Additionally, the two phases (T0-T1 and T1-T2) experienced some dropouts among participants. Therefore, the following analysis results should be interpreted with caution.

LMMs were tested for potential differences in the impact of pain recorded in the clinical diary between Phase 1 (the first month) and Phase 2 (the second month). N_Play (the number of mindfulness meditation sessions) was considered as a covariate in the analyses.

Pain perception: The Fixed Effect Omnibus tests did not reveal either a significant effect of Phase [$F(1, 10.2) = 0.016$, $p = .900$], nor an effect of N_Play [$F(1, 15.1) = 2.945$, $p = .107$].

Painkillers assumption: The Fixed Effect Omnibus tests did not reveal either a significant effect of Phase [$F(1, 13.1) = 2.308$, $p = .152$], nor an effect of N_Play [$F(1, 16.7) = 0.628$, $p = .439$].

Impact of pain on work: The Fixed Effect Omnibus tests did not show either a significant effect of Phase [$F(1, 10.9) = 1.119$, $p = .313$], nor an effect of N_Play [$F(1, 15.8) = 0.925$, $p = .351$].

Impact of pain on leisure time: The Fixed Effect Omnibus tests did not show either a significant effect of Phase [F(1, 11.5) = 0.529, p = .482], nor an effect of N_Play [F(1, 15.8) = 1.715, p = .209].

Impact of pain on relationships: The Fixed Effect Omnibus tests did not show either a significant effect of Phase [F(1, 12.3) = 0.845, p = .376], nor an effect of N_Play [F(1, 16.5) = 1.510, p = .236].

Daily diary: A one-sample t-test compared the mean number of completions with the expected number of times recommended to the participants, i.e., once daily for 60 days. A significant difference was found ($p < .001$): the diary was completed less frequently than expected (M = 16, SD = 19.7).

N_Play: A one-sample t-test was conducted, using N = 24 as the benchmark, which corresponds to the recommended practice of three days a week in two months. A significant difference was not found (p = .305). Even the mean number of sessions completed by patients (M = 31.60, SD = 34.8) was higher than 24; however, the result is not statistically significant.

A further analysis explored the preference for different types of mindfulness practices. An RM ANOVA with factor Play (5: Play_1; Play_2; Play_3; Play_4; Play_5) showed a significant difference in the level of practice of the different practices [$F(2.39, 88.29)=8.74$, $p < .001$, $p\eta 2=.191$].

The short breathing meditation was the most popular, although its frequency did not yield significantly different results from the extended version (p = 1.00). The short (p = .007; p = .023) and long (p = .004; p = .011) breathing meditations were practised significantly more than the mountain and pain ones (see Figure 5.20).

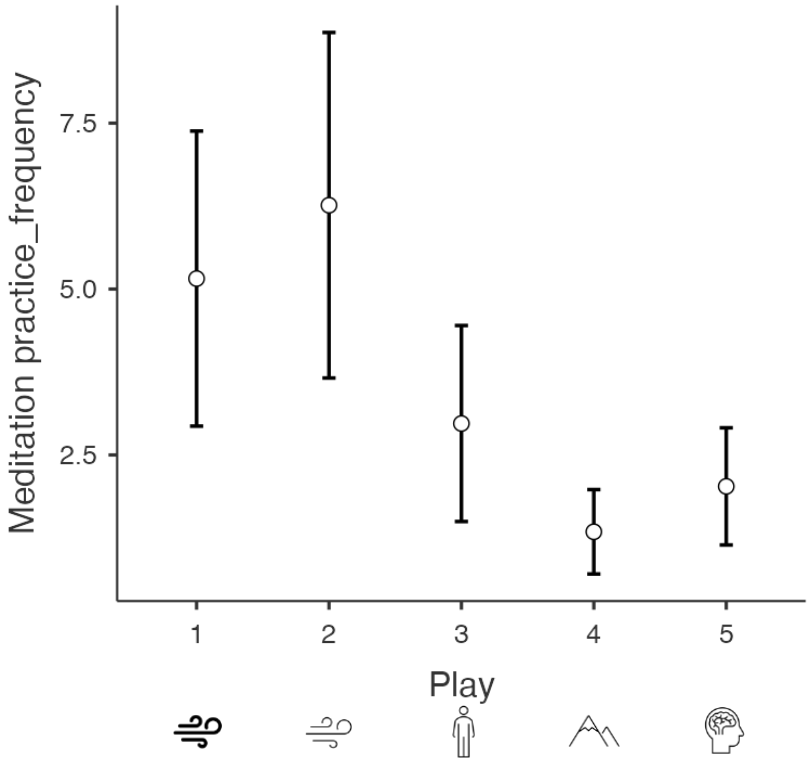


Figure 5.20: Estimated Marginal Means comparison of practising the different guided meditations: Play_1: Long Breathing meditation (12 minutes); Play_2: Short Breathing meditation (3 minutes); Play_3: Body Scan meditation (16 minutes); Play_4: Mountain meditation (20 minutes); Play_5: Pain meditation (12 minutes). The short breathing meditation was the most popular.

The Medication Adherence Rating Scale (MARS): An LMM was used to test the consistency of mindfulness practice in BBMIND users over time. The Fixed Effect Omnibus tests revealed no significant main effect of Time [F(1, 12.2) = 0.198, p = .664]. Indicating that the patient's adherence to the program was consistent.

Dropout rate:

During the study, a dropout rate of 43.5% was observed in the MG group. A binomial logistic regression was used to assess the relationship between the total number of meditations (NPLAY_TOT) and the likelihood of dropout. The dropout status was set as the dependent variable (1 = Dropout, 0 = No Dropout).

The model is statistically significant, as indicated by the likelihood ratio test: $\chi^2$ (1) = 6.83, p = . 009. The unique contribution of the coefficient NPLAY_TOT was negative and statistically significant: (B = −0.044, SE = 0.0218, z = −2.03, p = .043, with an odds ratio (OR) = 0.957). This indicates that,

holding all else constant, each additional unit increase in NPLAY_TOT is associated with a 4.3% decrease in the odds of dropout. These results suggest that greater user engagement, as measured by total interactions (NPLAY_TOT), is significantly associated with a lower likelihood of dropping out (see Figure 5.21).

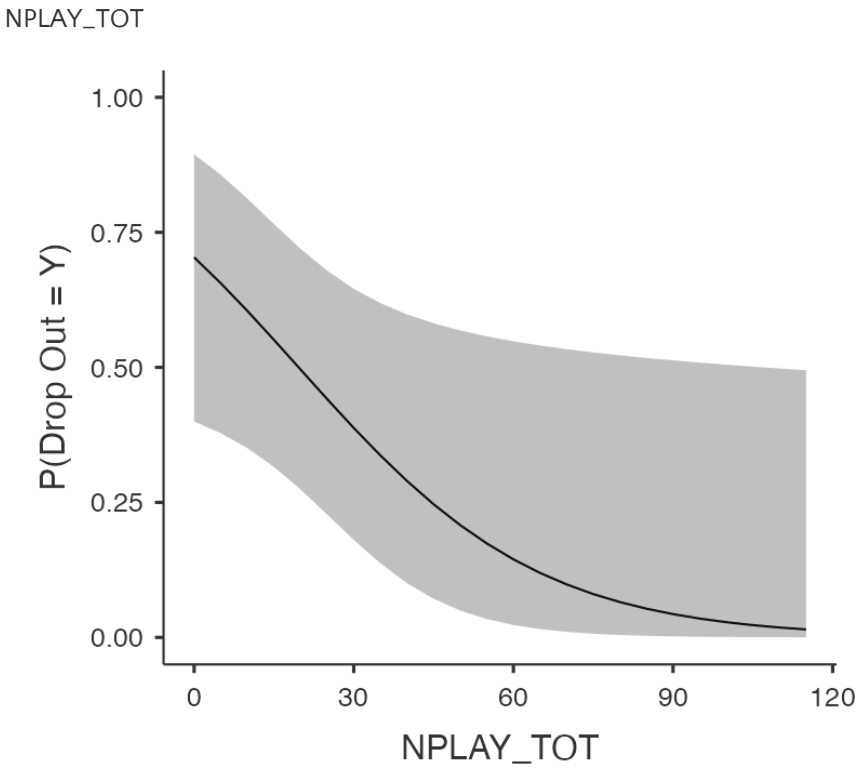


Figure 5.21: Estimated marginal probabilities of dropping out. The downward trend supports the interpretation that increased interaction is a protective factor against dropout.

### 5.4.4. Discussion

Comparisons between groups

A demographic assessment ensured that both groups were balanced in terms of frequency and duration of the pain condition. As all of the participants suffer from chronic pain, the duration beyond twenty-four months is one of the main features of their condition. Additionally, the lack of evidence of significant differences between groups in depression, state and trait anxiety symptoms, impact of pain, Pain Catastrophizing, self-efficacy or mindfulness abilities at the study's launch, allow us to consider the change over time related to the mindfulness intervention, which is the main aim of this study. In the 2 months, we did not find any significant difference in depression, state anxiety symptoms, impact of pain, pain catastrophizing and self-efficacy. Nevertheless, trait anxiety resulted

in a reduction at the final step of the study compared to the baseline, without differences between groups.

Mindfulness skills

The mindfulness abilities were evaluated using the FFMQ dimensions and analysed across the experimental phases and compared between the groups. We observed a difference in the total score of mindfulness abilities between the groups, with a higher score in the MG group and a tendency towards higher values in the MG at the end of the study compared to the CG. Similarly, the Non-React dimension, which is the ability to experience thoughts and emotions without automatically reacting to them, appeared superior in the MG, especially in the last phase of the study. Additionally, Observe dimension, i.e. the ability to notice internal states and emotions, resulted in stronger scores in MG compared to CG. We observed an improvement in the Non-judge facet, specifically the ability to adopt a non-judgmental stance toward thoughts and feelings, at the end of the study, compared to the beginning, without any notable differences between groups. The results also evidence a lack of significant changes in the other mindfulness facets in both groups. To summarise, some indices show promise in terms of improving mindfulness skills, as a result of the experimental study. We must consider that all MG participants had previously completed an 8-week mindfulness course; thus, it is plausible to expect preservation of mindfulness skills or a slight enhancement. However, there were no significant differences in the overall mindfulness abilities between groups before the kick-off. This data could suggest including the evaluation of mindfulness abilities in future studies, particularly before the 8-week mindfulness training that precedes app use. It could lead to the challenging issue of longitudinal studies and the risk of dropout. During this study, a dropout rate of 43.5% was observed in the MG group; 56.5% of the participants completed all experimental phases. The prior experience of mindfulness did not prevent such a rate of abandonment. A specific analysis in MG suggested that a greater meditation practice leads to a lower likelihood of dropping out. This aligns with one of Kabat-Zinn's teachings about practice: the more you practice, the greater the benefits you will reap (Kabat-Zinn, 2003).

Chronic Pain frequency

A reduction in pain frequency over time was observed, along with fluctuations in its occurrence. Although there was no peculiar variance in pain frequency in CG, MG underwent a significant reduction in pain frequency between the transition from the first to the second month and at the end of the study, compared to the baseline.

In-depth analysis of the mindfulness group

Although the within-group was not the primary focus of this study, further analyses were conducted to explore the specific mechanisms of BBMIND usage and its effects.

Considering the challenge of regular practice over two months, we sounded out the motivation to participate in the study. The preference for improving well-being may indicate an impulse in patients to take responsibility for their own care, such as practising mindfulness meditation. The adherence to the suggested meditation frequency was consistent. Even though the mean number of sessions completed by patients was higher than the recommended three times a week, the result was not statistically significant. These results consider the users who dropped out before completing the study; thus, it affects the findings, but it makes a trustworthy picture of the users' behaviour.

Additionally, the daily diary filling rate was less frequent than expected; however, we must consider that some data were lost due to technical issues with the app. Nevertheless, filling out the daily diary remains an issue that needs to be addressed. The data collected through the daily diary regarding the impact of the mindfulness intervention showed no evidence of changes in pain perception, the use of painkillers, the effect of pain on work, leisure time, or relationships related to the mindfulness practice.

All these considerations regarding the findings must be taken cautiously, due to the missing values resulting from dropout rates and data loss caused by technical issues with the app.

## 5.5. General discussion

Across three empirical studies, we examined complementary dimensions of the development, usability, feasibility and efficacy of BBMIND, a mindfulness-based mobile application designed to support individuals with chronic pain. Together, these studies contribute to the growing literature on digital mindfulness interventions and their applicability in pain management contexts, offering insights into both their promise and limitations.

The first two studies focused primarily on evaluating usability and user experience. The results collectively indicate that BBMIND demonstrates strong usability and user acceptability. System Usability Scale (SUS) and User Experience Questionnaire Plus (UEQ+) scores consistently exceeded established benchmarks, reflecting positive evaluations in efficiency, dependability, and content quality. Additionally, adherence to the mindfulness practice was consistent, a promising feature that can allow us to hope that BBMIND can be used to engage with mindfulness practices autonomously and at one's own pace, confirming previous evidence that accessibility and flexibility are crucial to the success of digital health interventions (Linardon & Fuller-Tyszkiewicz, 2020).

To summarise, BBMIND was an appreciated tool for promoting the consistent practice of mindfulness, primarily for patients, and consequently increasing mindfulness skills in both healthy and clinical populations.

Also, the majority of participants who dropped out in Studies 1 and 2 were naïve. This finding suggests that preliminary mindfulness practice and some psychoeducation are necessary to exploit the potential of BBMIND.

In conclusion, BBMIND has been proven to be an effective complement to behavioural strategies for psychophysical well-being in treating chronic pain conditions. BBMIND can help you with the initial practice of mindfulness at home, especially when transitioning from mindfulness experiences to autonomous practice. Indeed, naive mindfulness participants did not benefit from the APP in the same way as the experts.

Studies 1 and 2 evaluated only the completed course data because we did not have the opportunity to interact with participants through the app to remind them to complete the questionnaire, even in cases of dropouts. This is why, in Study 3, we implemented a push notification system to reach users who had stopped using the app and remind them to practice and complete the periodic questionnaires. Although this software implementation did not function properly, we were still able to collect some data from users who abandoned the research and incorporate it into the analysis.

In terms of psychological mechanisms, studies 1 and 2 have consistently identified improvements in specific facets of mindfulness, as measured by the Five Facet Mindfulness Questionnaire (FFMQ; Baer et al., 2006), such as Observe, Non-react, and Non-judge. These results align with theoretical models proposing that mindfulness training cultivates awareness and non-reactivity toward internal experiences (Kabat-Zinn, 2013). Additionally, the more consistent frequency of meditation practice emerged as a moderator, showing greater improvements in these dimensions. This pattern supports the “dose–response” hypothesis, which posits that greater exposure to mindfulness practice yields stronger psychological outcomes (Carmody & Baer, 2008).

Study 3 extended these findings by comparing the mindfulness group (MG) with a control group (CG), both of which included sufferers of chronic pain, especially migraine. At baseline, both groups were comparable in terms of psychological and clinical variables, allowing for a reliable attribution of post-intervention changes to the mindfulness program. The MG displayed significant reductions in pain frequency over time, along with higher overall mindfulness scores, particularly in the Non-react and Observe dimensions. These findings provide preliminary evidence that mobile mindfulness training can reduce the salience or intrusiveness of pain experiences even without shifts in mood or self-efficacy. It is reasonable to suggest that more significant changes in the behavioural

consequences of pain on daily life or mood fluctuations may require more time and/or more focused cognitive–attentional regulation intervention (Gu et al., 2015).

This experimental project contributed to ongoing research on how mindfulness operates in online formats, particularly through mobile applications. Findings suggest that even brief, app-based interventions can enhance attentional monitoring and emotional non-reactivity, two core mechanisms underlying mindfulness (Bishop et al., 2004). This lends support to the conceptualisation of mindfulness as a trainable metacognitive capacity rather than a purely context-dependent skill. Moreover, the observed association between practice frequency and outcomes reinforces the behavioural principle emphasised (Kabat-Zinn, 2003). BBMIND embodies the efforts to translate traditional contemplative training into evidence-based psychological interventions.

### 5.5.1. Limitations, conclusions, and future perspectives

Despite encouraging outcomes, the studies highlight significant methodological and implementation challenges. A substantial limitation of the three studies concerns the technical impairments of the BBMIND. The data loss limits fine-grained analyses of daily mindfulness and pain fluctuations. We attempted to resolve all the issues arising from the tests and practice of the app. Still, unfortunately, we have not yet found a formula to functionally incorporate automated data backups, adaptive reminders, and progressive engagement strategies to mitigate these impediments, record all the data and implement a more efficient app. We are still working on developing a more proper tool to implement other research studies and interventions.

Another limitation was the number of participants in the three studies. First of all, it is challenging to enrol patients. Thanks to the usability findings in Studies 1 and 2, we established that BBMIND would have been more helpful for expert users, or at least, with a previous minimum experience of mindfulness. Thus, we included in Study 3 only patients who attended the 8-week mindfulness course at the Neurological Institute “C. Besta” in Milan, so the enrolment process takes time and effort. Despite the continuous patients ‘ requests to have access to the app, the dropout rate is still an issue. Dropout rates may also mirror common attrition patterns in digital health trials (Melville et al., 2020). Qualitative feedback suggested that sustaining regular meditation practice was particularly challenging for participants new to mindfulness, echoing prior observations that guided support and social reinforcement are crucial for engagement (Cavanagh et al., 2014). Nevertheless, the dropout rate was also crucial in study 3, where all BBMIND users had mindfulness experience. One reason could be that mindfulness practice, especially the challenge of an 8-week course, can be influenced by many variables. Firstly, transitioning to an autonomous practice requires a significant amount of willpower and self-care, which can fluctuate from day to day and month to month. In any case, non-

adherence is a common issue in online psychological interventions (Linardon & Fuller-Tyszkiewicz, 2020). Future research should employ larger samples and extend follow-up periods to assess maintenance of benefits. The self-report measures may be more integrated with behavioural tasks. As mindfulness places a great emphasis on attention regulation and a non-judgmental attitude towards distraction, attentional tasks can be performed. A Stroop Task could examine attentional biases with emotional or pain-related stimuli and test reactivity to pain cues. A Sustained Attention to Response Task (SART) might evaluate mind-wandering and attentional gaps.

In conclusion, the BBMIND project demonstrates that a mobile mindfulness application can be both usable and beneficial for individuals with chronic pain, promoting improvements in key mindfulness facets and reductions in pain frequency. Nonetheless, technical reliability, engagement sustainability, and sample representativeness remain pressing challenges. Collectively, the three studies advance the understanding of digital mindfulness interventions in chronic pain contexts and make further steps toward future research that integrates behavioural data, ecological assessments, and personalised feedback mechanisms. BBMIND provides a valuable basis for developing accessible, evidence-informed, and patient-centred tools that empower individuals to cultivate mindfulness and resilience in managing chronic pain. Finally, the strength of the BBMIND project lies in combining a digital tool, in the form of a mobile application, with human and medical support, i.e., patient-centred care. This research project may represent a promising avenue for improving engagement and maximising the therapeutic potential of mobile mindfulness interventions, aligning with the biopsychosocial approach. Mindfulness teaching and practising is more than measurable scores; thus, even if the results seem not so significant at the moment, considering all the limitations of the studies, this research project succeeded in planting seeds that will blossom at the right time.

# 6. GENERAL DISCUSSION AND CONCLUSIONS

Pain is a universal and personally unique phenomenon that accompanies the human condition throughout one's entire life span. It assumes a dual role, performing a protective function by activating subsequent bodily defensive processes, which are, in turn, essential for mitigating the effects of pain. This intrinsic duality encompasses both adaptive and maladaptive dimensions, which are the most critical challenges for clinical practice and neuroscientific research. This chapter will integrate and critically examine the empirical findings of the four studies conducted within this doctoral thesis, aiming to provide a comprehensive synthesis that bridges theory, methodology, and clinical domains. Each study of this research project addressed a distinct feature of the multifaceted experience of pain, from anticipatory anxiety to affective touch, cutaneous allodynia, and mindfulness-based digital interventions. They jointly converge toward a unified proposal of the vision of pain as an embodied, predictive, and biopsychosocial phenomenon (Marturana & Varela, 1980; Craig, 2009; Friston, 2010; Gallagher, 2023).

Pain perception in both healthy and chronic pain populations was approached as a meaning-making process. This dynamic event arises through the interaction between the body, brain, and external context. The intent was to explore their interplay and contribute to contemporary research and clinical models in the approach to pain.

The discussion is organised into main sections. Starting from the synthesis and interpretation of empirical studies, a critical debate will follow on integrating results into theoretical, methodological, and clinical domains. The final part will be dedicated to limitations, future perspectives, and conclusive remarks.

## 6.1. Summary and interpretation of the studies

STUDY 1: Pain anticipation: as a psychophysiological preparatory response to pain perception

The first study examined the psychophysiological underpinnings of anxiety during pain anticipation, employing the Straw Breathing Task (SBT) to induce a transient state of anxious arousal. This study was grounded in the role of embodied cognition (Damasio, 2010) and predictive coding, which emphasise the anticipatory nature of emotional and sensory experiences (Friston, 2024; Seth & Friston, 2016). However, under conditions of heightened or prolonged uncertainty, pain-related predictive processes may become dysregulated, leading to expectations that exceed the actual probability of threat. This can result in anticipatory anxiety, perceptual distortions of expectations, and excessive top-down control, ultimately enhancing the salience and intensity of pain perception.

Thus, the central aim of this study was to examine the relationship between anxiety states and pain anticipation, as one of the first phases of pain perception. The study tested whether manipulating respiration (Straw breathing task) would alter both physiological reactivity, measured by Skin Conductance Response (SCR), and subjective reports of anxiety and pain sensitivity to pain stimuli. While forced breathing effectively induced transient anxiety, this heightened state did not produce a corresponding increase in autonomic activity during pain anticipation.

In contrast, subjective anxiety was positively associated with perceived pain sensitivity, mirroring the cognitive–evaluative predictive processes. Although SCR did not differentiate conditions, the paradigm successfully isolated transient anxiety and its cognitive correlates. They reflect top-down modulation of perception; anticipatory anxiety sharpens expectations of pain (Friston, 2024). It is plausible that, in this experimental context, the experimental design was unable to enhance autonomic responses. Yet, this decoupling between physiological and subjective markers may signal a failure of embodied coherence: the body cognitively anticipates danger but does not fully enact it physiologically. This pattern suggests advancing in the theoretical understanding of anxiety–pain interplay. This study highlights the importance of distinguishing between subjective anticipation and physiological arousal, particularly in interventions targeting anticipatory anxiety in pain (e.g., exposure therapy, breathing-based, or mindfulness programs). These protocols could help people to recalibrate their predictive models of threat, reducing maladaptive cognitive and autonomic pre-pain hypervigilance.

STUDY 2: Seeing and feeling pain and affective touch: vicarious and first-hand somatosensory experience

The second study examined the interaction between affective touch, pain perception, and empathy in both direct and vicarious modalities, comparing healthy participants and patients with chronic migraine (CM). It tested whether chronic pain affects the hedonic and perceptual qualities of touch. Grounded in embodied and social neuroscience, the study drew on theories proposing that affective touch serves as a regulatory and social-affiliative signal, contributing to homeostatic and emotional stability (Fotopoulou & Tsakiris, 2017; Gallese, 2018). The overlap between CT afferents and the insular cortex, a hub of interoception and affective representation, suggests that pleasant touch and pain share partially overlapping neural substrates while differing in affective valence (Morrison & Olausson, 2010). Direct (receiving touch) and vicarious (observing touch) trials involved affective touch and non-affective touch on the forearm. Pleasantness and vividness ratings were collected, along with measures of empathic pain sensitivity and psychological affect.

The main results showed that, in both populations, affective touch was consistently perceived as more pleasant than non-affective touch across both modalities, confirming the specificity of CT fibres. Pleasantness ratings did not differ significantly across direct and vicarious conditions, suggesting shared affective representation across first- and third-person experiences. Comparable pleasantness between direct and observed touch supports the hypothesis of embodied simulation, which posits that perceiving another's tactile experience activates one's own somatosensory-affective network (Gallese, 2018). CM patients exhibited preserved affective touch perception, indicating that chronic pain does not necessarily blunt hedonic responsiveness. Interestingly, CM patients appeared to be significantly less empathetic to others' pain. They may become chronically triggered to cues of social and physical pain, and react against their hypersensitivity via avoidance, leading to a vicious cycle of social and physical pain.

Additionally, individual differences in pain sensitivity and empathic traits did not significantly affect the perception of affective touch. Touch functions as a bodily language of care, capable of eliciting interoceptive comfort and reducing affective distress. Its preservation in chronic migraine suggests resilience of affective somatosensory circuits, even under chronic sensitisation. Moreover, affective touch and pain, although neuropsychologically close, operate through dissociable affective pathways, reinforcing the view that pleasure and pain are largely independent processes; both are structured by approach and withdrawal dynamics that sustain affective balance (Fuchs, 2018). These findings indicate that pain and affective touch function as distinct, largely independent processes. Clinically, these results support the integration of affective and social touch into pain rehabilitation through therapeutic touch, aiming to enhance interoceptive stability and emotional resilience. Methodologically, the dual-modality design provides a robust framework for studying interpersonal embodiment and empathic somatosensory processing across healthy and clinical populations, thereby bridging experimental neuroscience with relational therapeutic practice.

STUDY 3: Cutaneous allodynia and psychological influencing factors: a network analysis

The third study investigated cutaneous allodynia (CA), under the rationale that it is an underestimated continuum phenomenon spanning healthy and clinical populations. Traditionally conceptualised as a categorical symptom of neuropathic or migraine-related pain, this study proposed a biopsychosocial continuum model, where allodynia reflects a dynamic interaction between sensory hypersensitivity, affective dysregulation, and cognitive–interoceptive factors (Barrett & Simmons, 2015; Friston, 2024). Within this framework, cutaneous allodynia encompasses maladaptive top-down mechanisms that influence pain appraisal and emotional processing, including pain vigilance, anxiety sensitivity, and heightened interoceptive salience (Meulders & Vlaeyen, 2013). Additionally, it involves prior

negative experiences, social influences, and other mechanisms that exacerbate signs and symptoms (Colloca, 2024). Allodynia symptoms, as well as affective, cognitive, and interoceptive aspects, are assessed through a self-report online attitude and mindful attitude assessment, providing the basis for network analysis to explore the interplay among these features. Both healthy participants and patients with chronic pain were included to test dimensional continuity. The results confirmed the continuum hypothesis of allodynia, without bimodal separation between groups. Significantly, this study bridges a conceptual gap between pathological allodynia and subclinical hypersensitivity, supporting the view of pain vulnerability, spanning from non-clinical emotional sensitisation to chronic pain states. The presence of allodynia in healthy individuals, besides a maladaptive affective–sensory coupling, could be a marker of a transitional configuration of psychological and pain perception. The findings exemplified a progressive reconfiguration of the psychological–sensory systems underlying cutaneous allodynia. Depressive affect and stress resulted in a pivotal connection between sensory hypersensitivity and emotional dysregulation; allodynia seemed to be more related to attention to bodily sensations, pain included.

Additionally, the occurrence of pain, whether diagnosed or associated with another medical condition, produced emotional and network rigidity, marked by hyperconnectivity among affective nodes and weakened inhibitory influence of mindfulness. Clinically, recognising allodynia as a continuum rather than a binary symptom expands opportunities for preventive intervention. Screening for mild sensory hypersensitivity and affective stress could identify individuals at risk of pain chronification before the establishment of central sensitisation (Apkarian et al., 2023). From a therapeutic standpoint, this study supports the value of integrative interventions, such as mindfulness, cognitive reappraisal, or body-awareness training, which have emerged as protective factors in restoring adaptive interoception, reducing predictive hypervigilance, and enhancing the flexibility and functionality of the complex dynamic between affective, sensory, and cognitive domains of pain perception. Cultivation of reflexive awareness of positive emotional states, as in mindfulness protocols, can help to increase the ability to decenter from sensory experiences or to employ cognitive strategies for pain and daily life regulation (Garland et al., 2015).

Methodologically, the study's network analytic approach represents an innovative step in pain research, capturing non-linear relationships among variables. Visualising the dynamic interdependence between psychological and sensory domains provides an empirically grounded representation of the biopsychosocial model.

STUDY 4: Usability and effectiveness of a mobile application, BBMIND, a tool for mindfulness practice in treating chronic pain conditions

Building upon the previous findings, the fourth study operationalised the insights on interoceptive awareness and emotional regulation into a digital clinical intervention, the BBMIND, a mobile application developed for mindfulness practice. This project evaluated whether a self-guided mindfulness-based intervention could improve pain outcomes, psychological well-being, and engagement among individuals with chronic pain. The study aligns with the increasing interest in digital therapeutics and mobile health approaches for pain management. It reflects a translational progression from experimental paradigms (Studies 1–3) to real-world application, embodying the thesis's overarching objective of bridging psychophysiological theory and clinical practice.

In the first phase of the project, the usability of BBMIND was evaluated among healthy individuals and those suffering from chronic pain. The results indicated high usability and a positive user experience, with some benefits in terms of mindful attitude.

The following phase included an 8-week structured mindfulness program integrating guided meditation, addressed to migraine patients. Adherence to the protocol was moderate but stable, although the dropout rate reflected typical patterns in digital health interventions.

Clinically, participants exhibited increased mindfulness scores, particularly in the "acting with awareness" and "non-reactivity" subscales, as well as a reduction in headache frequency. However, pain intensity and medication use remained essentially unchanged. Higher engagement was predicted to result in both lower dropout rates and greater improvement, confirming the importance of active participation in digital self-regulation. These findings support the hypothesis that mindfulness training recalibrates interoceptive and affective processes. Regular mindfulness practice helps enhance metacognitive awareness of bodily sensations, thereby reducing the affective amplification that sustains chronic pain (Vago & Zeidan, 2023). From a clinical standpoint, the BBMIND results support the feasibility and efficacy of mobile mindfulness interventions in conjunction with traditional pain management. The programme's positive impact on mindfulness facets and headache frequency demonstrates that digital delivery can support embodied self-regulation beyond clinical settings.

This study contributed to the progression from experimental settings to ecological relevance in chronic pain research, complementing controlled laboratory studies with data from real-world, self-managed contexts.

## 6.2. Overall discussion

The converging findings across the four studies of this doctoral project advance a multidimensional, embodied, and context-dependent understanding of pain, consistent with the biopsychosocial model of chronic pain (Gatchel et al., 2007; Vlaeyen et al., 2016). Pain cannot be reduced to nociceptive transmission or cortical activation alone; it emerges from the dynamic interplay of biological, psychological, and social processes. Within this framework, pain is not treated as a static sensory datum, but as a dynamic phenomenon through which the organism constructs meaning, regulates uncertainty, and maintains adaptive engagement with its internal and external environment. Across experimental and clinical contexts, studies consistently demonstrate that pain is a disorder of multisystem dysregulation, encompassing neurophysiological sensitisation, affective distress, and attentional orientation, which profoundly modulate pain perception, consistent with central sensitisation and emotional hypervigilance (Latremoliere & Woolf, 2009).

Empirically, the studies undertaken in this project explored this integrative perspective from complementary viewpoints, trying to cover the majority of pain facets, as suggested by Garcia-Larrea & Peyron (2013) (see Figure 6.1).

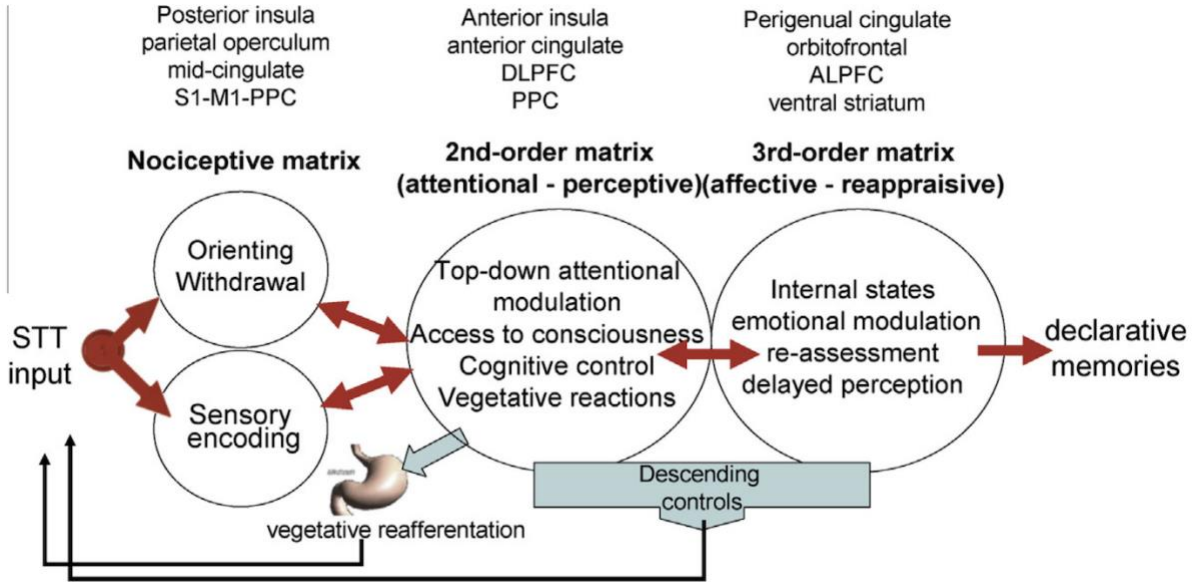


Figure 6.1: Schematic but not exhaustive representation of the regions that can participate in the processing of noxious signals. Continuous information transfer among matrices creates a dynamic and continuously reconstructing pattern of interactions. Additionally, embodied pain memories can also alter pain perception by influencing both internal affective states and attentional modulation. Attentional, perception, and vegetative reaction are mainly related to: Anterior Insula, Anterior Cingulate, DLPCF (Dorso-lateral prefrontal cortex and PCC (Posterior parietal cortex). Affective and reappraisal processes engage the Pregenual cingulate cortex, Orbitofrontal cortex, antero-lateral prefrontal cortex (ALPCF), and Ventral striatum (From Garcia-Larrea & Peyron, 2013).

The investigation of anticipatory anxiety revealed that cognitive expectations of pain can amplify distress even in the absence of proportional autonomic activation. It highlighted the role of psychological appraisal and affective meaning in pain perception, which mirrors the preparatory activation of brain areas involved in emotional appraisal and threat monitoring.

The exploration of affective touch findings provided behavioural evidence contrasting the hypothetical similarities and mutual interference between pleasant touch and pain that share partially overlapping neural substrates, including the insula and anterior cingulate cortex.

We suggest that pain and affective touch, although they share similar pathways, are functionally dissociable due to their distinct roles: pain primarily serves an alerting and protective function, whereas affective touch is more closely associated with social bonding and interpersonal connection. Additionally, affective touch and pain, as well as previous and current embodied experiences, are fundamental to creating unique and declarative memories.

This study exhibited that despite a prevalence of cutaneous allodynia, the pleasantness of affective touch remained relatively preserved in chronic migraine patients. It sparked my curiosity to enlarge the network analysis of cutaneous allodynia to affective touch in the future. Currently, our understanding of allodynia suggests that when affective regulation is compromised, as in chronic pain, this embodied network may shift from an adaptive state to a more rigid, hypervigilant one, leading to heightened pain attention sensitivity, allodynia-like responses, and emotional distress, in line with current literature (Latremoliere & Woolf, 2009). This constellation of findings aligns with clinical and theoretical perspectives that conceptualise chronic pain as a form of embodied dysregulation, a breakdown of adaptive integration among physiological, affective, and cognitive domains. Within this context, the mindfulness-based digital intervention ultimately demonstrated that it can serve as a helpful pathway to restore equilibrium in this dysregulated system. Mindfulness does not merely represent a cognitive coping strategy but an embodied retraining of awareness, enabling a non-judgmental and compassionate engagement with bodily sensations. Through this lens, mindfulness facilitates top-down modulation of limbic arousal and enhances interoceptive awareness, allowing patients to reinterpret pain as a fluctuating bodily event rather than a fixed threat (Farb et al., 2015; Kabat-Zinn, 2013). Mindfulness practice engages prefrontal–insula networks that enhance regulatory control and reduce affective reactivity, thereby weakening the feedback loop between anxiety, attention, and pain perception.

Taken together, the four studies articulate a coherent, integrative model of pain as a process of embodied meaning-making that is continuously negotiated between neurophysiological signals, emotional tone, and personal context. Pain is not merely a symptom but a dialogue between the body and its world, where attention, emotion, and expectation converge. The insula's role as the interface

between interoception and awareness exemplifies this integration, transforming bodily information into self-related experience. When this dialogue becomes dominated by fear, vigilance, and emotional dysregulation, chronic pain also emerges as a state of embodied hyper-awareness, where the body itself becomes the focus of distress and alienation. Theoretically, these findings support the view that pain should be understood as a multilayered construct, encompassing both neural, emotional, and relational aspects. Methodologically, the research contributes to cognitive science by integrating multimodal evidence, including psychophysiological indices, subjective reports, and digital data, within a coherent biopsychosocial framework. This pluralistic approach reflects an epistemological shift from reductionist models toward a combination of experimental paradigms, in which even psychophysiology must be adjusted to account for the bidirectional influence between the individual and the context. Pain can be investigated across both controlled and lived contexts, thereby bridging the gap between laboratory and real-life settings (Cacioppo, 1982).

### 6.3. Clinical and therapeutic implications for chronic pain

The integrative findings of this doctoral project have several implications for the understanding and treatment of chronic head pain, including chronic migraine and tension-type headache. From the biopsychosocial and embodied perspectives mentioned above, head pain emerges not merely as a neurovascular or nociceptive phenomenon, but as the outcome of complex interactions between neural sensitisation, emotional regulation, interoceptive awareness, and cognitive-affective patterns. Clinically, this framework highlights that chronic head pain is sustained by a persistent state of central sensitisation and interoceptive hypervigilance, engaging the insula, anterior cingulate cortex, and limbic networks. These structures integrate nociceptive, affective, and autonomic information; when dysregulated by anxiety or emotional stress, they amplify the salience of head-related sensations, leading to heightened pain perception and reduced tolerance to sensory stimuli. Parallel findings from affective touch and pain anticipation paradigms suggest that attentional bias toward bodily threat and affective dysregulation are key maintaining factors. Therapeutically, this understanding supports multimodal treatment strategies that combine pharmacological, behavioural, and psychophysiological interventions. Beyond symptom reduction, the goal is to restore adaptive embodiment, interoceptive, and emotional balance, helping patients reinterpret sensory signals not as alarms but as dynamic aspects of bodily communication between the inner and outer worlds. Evidence-based interventions, such as mindfulness-based stress reduction (MBSR) and cognitive behavioural therapy (CBT), have demonstrated efficacy in reducing attack frequency and pain-related disability by modulating autonomic reactivity and enhancing emotional regulation (Kabat-Zinn, 2013; Garland et al., 2017). Training patients to cultivate non-judgmental attention to sensory experiences can reduce anxiety-

driven avoidance and improve top-down modulation of limbic circuits. This shift from control to acceptance enables the reestablishment of homeostatic flexibility, improving coping strategies to manage pain. From a broader psychosocial standpoint, interventions should also consider the social and contextual dimensions of chronic head pain. Factors such as social stress, emotional suppression, and maladaptive coping styles often exacerbate pain persistence. Integrating psychoeducation, emotion-focused therapy, and interpersonal support within treatment programs can help patients rebuild agency and relational trust, counteracting the isolation and self-monitoring tendencies common in chronic headache populations.

In summary, the clinical implications of these findings suggest that treating chronic head pain requires a holistic, embodied, and psychologically informed approach. Recognising the role of interoceptive and affective mechanisms encourages clinicians to move beyond reductionist symptom management toward interventions that restore the individual's sense of embodied coherence, transforming head pain from a signal of threat into a potential site of self-awareness and therapeutic change. Additionally, clinicians should be encouraged to consider the continuum of pain perception in all its manifestations, such as cutaneous allodynia, which may serve as a marker of a transition from subclinical to overt pain conditions.

### 6.4. Limitations, strengths, and future perspectives

One methodological limitation included sample size. Limited sample size in each study may restrict the generalizability of the findings. This key point was particularly evident in the BBMIND Study, where the initial sample size was adequate, but the dropout rate drastically reduced the available data. This occurrence is also consistent with the current literature in digital health trials (Melville et al., 2020). It must be taken into account in ecological and long-term studies.

Similarly, the technical issue of developing and managing mobile applications is another specific limitation of this study. More efforts must be made to ensure the reliable functioning of mobile apps, especially in data recording. Another limitation related to the sample was the imperfect balancing of the head pain group with the control group, specifically in the affective touch and pain perception study.

Even though the thesis project primarily aimed to gather initial exploratory findings to interconnect with each other under a more comprehensive approach to pain, the use of many self-report measures as main findings or covariates is liable to participants' accuracy and social desirability bias. In general, addressing the breadth of measurements, sample issues, and challenges related to digital adherence will enhance the robustness of the research project. From theoretical and conceptual standpoints, the abundance of measures employed and the lack of examination of socio-cultural

moderators may run the risk of over-theorisation when integrating phenomenology into concrete clinical practice.

The strengths of this thesis lie in its comprehensive examination of pain perception. It included several layers of investigation. It included the first temporal phase of pain, i.e. pain anticipation, and the influence of belief and previous embodied experience. It expanded the conceptualisation of pain, testing the neural evidence of its partial overlap with affective touch, which seemed not to be replicated behaviorally. It confirmed the hypothesis of a continuum of cutaneous allodynia, rather than the usual dichotomy of absence and presence. Ultimately, I integrated all these acknowledgements to develop a mindfulness mobile app that targets psychologically modifiable factors of pain perception. Each study introduced some innovations relevant to pain science that can be replicated and improved in future studies.

The future directions of this thesis involve several key areas. First, increasing and balancing the sample size will allow for more robust conclusions. Future research could employ multilevel Bayesian models, multimodal imaging, and more efficient digital platforms to enhance mechanistic insight and user engagement. Specifically, behavioural measures related to pain and affective touch perception and anticipation could be enriched by EEG frequency analysis. Additionally, considering the features of C-tactile fibres, different pain stimuli, such as thermal stimuli, can be used to examine differences or similarities with electrical painful stimulation. Investigating interpersonal co-regulation using hyperscanning and dyadic designs could enhance the relational and affective valence of this research within the biopsychosocial model. From an enactive standpoint (Marturana & Varela, 1980; Stilwell & Harman, 2019; Di Paolo & Thompson, 2024), pain is not located within a disembodied, immaterial mind, nor can it be fully explained by processes occurring solely within the brain or other bodily parts. Rather, pain is a relational and emergent process of sense-making**,** arising through the lived body in constant interaction with its environment that both shapes and is shaped by the individual. Within this framework, the experience of pain is not entirely directly observable or quantifiable**;** qualitative pain narratives could be a reliable means for inferring the presence and nature of pain in others. Thus, an outstanding improvement in pain knowledge completeness would come from integrating these measures into a more daily life context. Experimental rooms, replicating homes or more ecologically oriented locations, are currently under construction at our university. They could be partners in virtual and augmented reality environments for pain research.

### 6.5. Concluding remarks

This doctoral research advances an integrative understanding of pain as an embodied, predictive, and relational phenomenon. It demonstrates that anxiety, affective touch, allodynia, and mindfulness are interconnected nodes within a regulatory system that shapes the experience of suffering and recovery. By bridging experimental psychophysiology, phenomenology, and digital therapeutics, the thesis offers a blueprint for a humane and scientifically rigorous approach to chronic pain. A recurring aspect of this thesis project is that the body is not a passive receptor, but an active agent that interacts with both the inner and outer worlds. Humans are often misled by the idea that they can control or predict all that is going to happen, embracing an egocentric view, rather than expanding their standpoint to include what is usually hidden from the senses. This is what partially happened to me when I began this research project. Time after time, I forced myself not to judge pain perception only as a negative occurrence to be defeated. Observing, studying, and practising experimental research. I have gradually reshaped my narrative on pain. In my research approach, I sought not only to attend to what painful conditions deprive us of, but also to what they grant in terms of adaptability and resilience. Pain exposes our vulnerabilities and fears, revealing the fractures in our relationship with the body that betrays us, as well as with other human beings.

Such experiences cannot be reduced to a single modality of stimulation or a single neurocognitive function, but emerge through the interplay of distinct, partially autonomous, and at times divergent processes, resulting in a unique and individual intensity of pain perception. The deep significance of this work lies precisely here, in embracing this complexity as an intrinsic part of the phenomenon, rather than viewing it as a limitation to be fixed. These reflections have led me to conceive this research project as a tool that can pair the classical guidelines for pain management from a biopsychosocial perspective. Collaboration with the Headache Centre of the Neurological Institute “C. Besta” in Milan aligns with and supports this direction in both research and care of pain.

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