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Vicarious fear conditioning: An investigation into the role of the motor system

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"*Dünyada her şey için, medeniyet için, hayat için, muvaffakiyet için en hakiki mürşit ilimdir, fendir. İlim ve fennin haricinde mürşit aramak gaflettir, cehalettir, dalalettir. İlim ve fennin yaşadığımız her dakikadaki safhalarının gelişmesini kavramak ve izlemek şarttır.*"

"Science is the most real guide for civilisation, for life, for success in the world. To search for a guide other than science is absurdity, ignorance and heresy. It is essential to understand and follow the developments of science and knowledge at every stage of every moment we live."

-Mustafa Kemal Atatürk

CONTENTS

ABSTRACT

Learning which stimuli or events may signal harm is crucial for survival. Through classical conditioning, neutral stimuli can gain emotional significance, becoming cues for potential threats in a process known as fear conditioning. Importantly, fear conditioning can occur not only through direct experience but also vicariously, by observing others' expressions of pain. This study investigates the role of motor and autonomic systems in vicarious fear conditioning. While autonomic expression is often measured through skin conductance responses in social fear learning, the role of the motor system remains largely unexplored. Here, participants watched video clips where a colored dot (the conditioned stimulus, CS+) was paired with an electric shock, causing the observed individual to display pain via facial expression. Another dot (CS-) was not followed by a shock, and no pain was expressed. In a subsequent experimental phase, only the colored dots were presented to test participants' learned fear responses. Participants rated the CS+ as more unpleasant and expected a shock significantly more often than for the CS-. Motor system involvement was assessed by measuring corticospinal excitability via motor-evoked potentials (MEP) elicited through transcranial magnetic stimulation (TMS) over the left primary motor cortex. Unlike the motor system, which did not differentiate between stimuli, electrodermal activity showed heightened arousal for the CS+ than the CS-. These findings suggest that while skin conductance response reliably indicates anticipation of pain in vicarious fear conditioning, the role of the motor system in socially transmitted fear requires further exploration.

Keywords

Vicarious pain, Threat conditioning, TMS, MEP, SCR

CHAPTER 1

Learning Fear

Learning is an essential component of human development that enhances our cognitive ability, emotional intelligence, and social interactions throughout life. Learning is a sort of ontogenetic adaptation that describes changes in an organism's behavior caused by persistent patterns or regularities in its environment (Houwer et al., 2013). The process of learning is shaped by various factors including individual experiences, cognitive awareness, personal biases, opinions, cultural standpoints and environment (Shemshack & Spector, 2020). Learning is also defined by Lachman (1997) as the process of steady adjustment in stimulus-response interactions that occurs through sensory engagement. Learning can take place through both conscious and unconscious mechanisms. Conscious learning is a process in which people deliberately focus on instructional information while attentively analyzing similarities and differences in word meanings. Prior knowledge improves this process by assisting in the creation of brain connections and the structuring of information into new comprehension structures (Boshuizen & Schmidt, 1992). On the other hand, unconscious learning is a learning process in which people are unconscious that their actions or involvement in particular activities contribute to modifications of their knowledge, skills, attitudes or learning capacities. It can also refer to a situation in which people do not know they have learned something (Simons, 2012).

Classical or Pavlovian conditioning, a type of unconscious learning, involves the pairing of an automatic, conditioned response with specific stimuli (Rehman et al., 2023). Through this process, a previously neutral stimulus becomes capable of eliciting a conditioned response by being repeatedly associated with an unconditioned stimulus that naturally triggers that response. Conditioning is evolutionarily essential as it enables organisms to form expectations that facilitate preparation for both good and bad events (Stangor & Walinga, 2014). In a basic

classical conditioning experiment, the aim is to enhance behavioral or physiological responses to events that are initially neutral in their effects. These initially neutral events are referred to as conditioned stimuli (CSs), and the responses that develop after a strengthening procedure are known as conditioned responses (CRs). The strengthening procedure involves establishing a contingent relationship between a CS and an event called the unconditioned stimulus (US), which is known to elicit a significant behavioral or physiological response prior to the experiment (the unconditioned response; UR). Also, the interstimulus interval has an important role in consolidating the CS-US relationship (Rescorla, 1988). In Pavlovian conditioning, the interstimulus interval refers to the duration between the start of a conditioned stimulus (CS) and the start of an unconditioned stimulus (US). Research generally shows that a shorter interstimulus interval increases the probability of a conditioned response and/or strengthens the intensity of that response (Akins, 2019).

1.1 Pavlovian Fear Learning

Fear can be defined as the neurophysiological processes which enable an organism to execute innate or acquired responses in presence of an immediate or imminent threat (Keifer et al., 2015). Our understanding of the physiology of fear relies primarily on fear learning models which focuses on fear conditioning and extinction. Pavlovian fear conditioning is a behavioral paradigm that provides organisms to anticipate aversive events (Maren, 2001). Fear conditioning is a type of associative learning characterized by the repeated pairing of a neutral conditioned stimulus, such as an acoustic tone or a visual stimulus (CS), with a noxious unconditioned stimulus, such as an electrical shock (US), so that the subsequent presentation of the CS alone elicits fear behaviors (conditioned response), such as freezing or aversion. Fear extinction implies repeatedly showing the CS alone until it no longer elicits fear responses (LeDoux & Pine, 2016; Torrents-Rodas et al., 2012). A state of fear is

characterized by freezing, autonomic responses (e.g. changes in heart rate, blood pressure, skin conductance, or pupillary dilation), endocrine responses (e.g. the release of stress hormones such as the adrenocorticotropic hormone, adrenal steroids, and adrenal catecholamines), and the activation of somatic reflexes (e.g. eyeblink and startle) (Byrne et al., 2014).

According to Joseph LeDoux's higher-order theory of consciousness, conscious experiences are the result of a cortical system that processes information received from subcortical areas (first-order networks) (LeDoux, 2012, 2017). In this case, visual information leads to consciousness of seeing something, while lower-order systems such as the amygdala provide awareness of emotions or feelings. Unconscious behaviors and physiological responses to emotional stimuli are driven by subcortical circuits and conscious emotional experiences involve cortical higher-order activities particularly in the ventromedial prefrontal cortex, rostral medial prefrontal cortex, dorsomedial prefrontal cortex, orbitofrontal cortex and dorsolateral prefrontal cortex. LeDoux defines fear as a conscious feeling triggered by subjective cortical experiences in the presence of real or perceived danger. The human brain can anticipate threats, even uncertain ones. Thus, it leads to an internal experience of fear and observable external reactions like freezing, fleeing or showing frightened expressions (LeDoux, 1998, 2003).

The amygdala is frequently referred to as a single entity in discussions about fear processing (LeDoux, 1998) but it is a complex structure composed of distinct nuclei with specialized roles. The lateral/basolateral nucleus is considered crucial for forming the association between conditioned stimuli and unconditioned stimuli, while the medial nucleus plays a role in predator odor-induced fear learning (Fanselow & LeDoux,1999; Maren, 2001; Takahashi et al., 2005). Also, the central nucleus of the amygdala is considered to be a primary output station in the fear circuit and presents a complex anatomical structure and

function (Samson et al., 2005). The central nucleus of the amygdala relays fear signals to other brain regions such as the lateral/paraventricular hypothalamus and the periaqueductal gray, which are responsible for producing fear responses. The medial and lateral subdivisions of the central nucleus of the amygdala have been shown to have distinct roles in fear processing, such as acquisition, expression and extinction of conditioned fear, suggesting that they are functionally separable components within the fear circuit (Duvarci & Pare, 2014; Lee et al., 2013). Fear conditioning and the unconditioned response to fear stimuli are regulated by two distinctive amygdala-mediated pathways in rats (Romanski & LeDoux, 1992; Campeau & Davis, 1995). The first is the direct thalamo-amygdala pathway leading to a quick and effective response to threats. The second, the thalamo-cortico-amygdala pathway instead evaluates inputs in a slower and more sophisticated way. These dual pathways enable the amygdala to manage both immediate and complex reactions to fear-inducing situations. Moreover, the amygdala has been demonstrated to be necessary for both tone (cued) fear conditioning and the expression of contextual fear conditioning which is a type of associative learning that causes intense emotional arousal after a sudden painful stimulus in a specific spatial context (Davis, 2000; Fanselow, 1994; Miserendino et al., 1990; Pause et al., 2013; Vazdarjanova & McGaugh, 1998). In addition, the anterior cingulate cortex controls threat reactions and modulates fear learning in fear conditioning (Bissière et al., 2008). On the other hand, alteration to the dorsal hippocampus, lateral entorhinal cortex, nucleus accumbens, or fimbria-fornix significantly impairs contextual fear conditioning, whereas tone (cued) fear conditioning is intact (Anagnostaras et al., 1999; Fanselow, 2000; Maren & Fanselow; 1997; Maren et al., 1997; Phillips & LeDoux, 1992, 1994). Furthermore, Phelps and her colleagues (2004) found that fear conditioning led to increased amygdala activity, while extinction produced decreased activity. In contrast, although the ventromedial prefrontal cortex activity declined during fear acquisition, it increased during extinction. Therefore, this pattern

indicates the role of ventromedial prefrontal cortex in top-down inhibitory regulation of fear reactions, preventing emotional perseveration and ensuring that threatening stimuli are evaluated as safe.

In sum, these structural differences highlight how the brain integrates and regulates fear responses, maintaining an adaptive balance between the acquisition, expression, and extinction of conditioned fear in response to environmental demands. This neural architecture of fear explains how the brain maintains the vital balance for immediate survival and long-term behavioral adaptation. The neural structures involved in fear learning are crucial for understanding vicarious fear learning, as the brain regions responsible for direct fear processing may also include a similar neural architecture that enables us to interpret and learn from the fearful experiences of others.

1.2 Vicarious Fear Learning

Learned fear stimuli can be acquired either directly or indirectly through social transmission. Rachman (1968) and Bandura (1969) introduced that individuals can develop fears vicariously by observing another person's frightened reaction to an animal, object, or condition. Based on this phenomenon, Rachman (1977) described vicarious learning as one of three primary paths for fear acquisition, in addition to direct conditioning and the transmission of information and instruction. Historically, direct conditioning, in which a neutral stimulus is associated with an unpleasant situation directly experienced by the individual resulting in a conditioned fear response, was considered the main route to fear. On the other hand, vicarious learning is an important aspect of fear acquisition and suggests that humans rely on social information to avoid direct threats (Skversky-Blocq et al., 2021). Unlike the direct conditioning, vicarious conditioning is an essential social adaptive transmission mechanism that enables individuals to gain knowledge about threat-predictive cues without the need for

direct exposure to the pairing of the cue and punishment (Allsop et al., 2018). Vicarious fear learning is an effective paradigm to examine how threat information is transmitted among individuals. There are notable similarities and differences between classical fear learning and vicarious fear learning. One of the core similarities is that both mechanisms essentially benefit from the generalization of fear to equivalent circumstances or cues, resulting in longer-term behavioral modifications that impact future responses to perceived threats. Another common point is that both classical and vicarious fear learning involve a particular neuronal network, which includes the amygdala, the anterior insula, and the anterior cingulate cortex (Gallo et al., 2018; Jauniaux et al., 2019; Murtha et al., 1996; Olsson et al., 2007; Soyman et al., 2022). On the other hand, the key distinction lies in their mechanisms of reinforcement. While classical fear learning can be reinforced through direct physical harm, vicarious fear learning depends entirely on the transmission of social information, making it reliant on the perception and processing of this type of information (Debiec & Olsson, 2017). Also, the information processing network differs between the two learning modalities. Classical fear learning relies significantly on the amygdala, whereas social fear learning it is thought to rely substantially on anterior insula (Lindström et al., 2018).

The vicarious fear learning paradigm contributes to provide a different perspective on understanding the mechanisms of fear learning. First, this paradigm allows us to study pre-linguistic and non-linguistic organisms with ecological validity (Debiec & Olsson, 2017). In respect of human studies, Chang and Debiec (2016) found that infant vicarious fear learning might develop without increased activation of the anterior cingulate cortex or the insular cortex. These regions are commonly associated with processing and responding to fear and empathy, suggesting that infants may use different neural pathways in the early stages of vicarious fear learning. This finding underscores developmental differences in the neurological processing of fear responses. Besides, infants and young children who are

exposed to novel stimuli associated with faces expressing fear, develop a fear of these stimuli (Askew & Field, 2007; Hoehl & Pauen, 2017). In respect of animal studies, monkeys were observed watching videos of model monkeys showing fear responses to fear-related stimuli (toy snakes or toy crocodiles) or non-fear-related stimuli (flowers or toy rabbits). After 12 sessions, the monkeys showed fear responses to fear-related stimuli (snakes and crocodiles) but not to non-fear-related stimuli (Cook & Mineka, 1989). Furthermore, the vicarious fear learning paradigm provides an evolutionary view to compare different species in various contexts. For instance, several studies revealed that the anterior cingulate cortex is greater in activity during vicarious fear learning in both humans and animals (Barros et al., 2002; Kim et al., 2012; Olsson et al., 2007). Additionally, according to humans and animal studies, there is a connection between the acquisition and expression of vicarious fear learning and increased activity of amygdala (Debiec & Sullivan, 2014; Jeon et al., 2010; Meffert et al., 2015). For example, fine-grained neuroscientific experiments in mice have demonstrated the involvement of the amygdala and the anterior cingulate cortex in observational fear conditioning, which has previously been identified in humans (Jeon et al., 2010). Also, maternal expression of fear increases the pups' levels of the stress hormone corticosterone and activates the amygdala, facilitating cue-specific fear learning (Debiec & Sullivan, 2014).

In summary, the vicarious fear learning paradigm enriches our understanding of fear mechanisms by revealing how social and neurological factors contribute to the spread of fear responses across different developmental stages and species.

1.3 Observing Others' Pain and Empathy for Pain

Pain is a phenomenon that involves complex interactions between neuroanatomical, neurochemical, cognitive and affective systems. According to the International Association for the Study of Pain (IASP) pain is defined as "An unpleasant sensory and emotional

experience associated with actual or potential tissue damage, or described in terms of such damage" (Raja et al., 2020). This concept emphasizes pain's multidimensional, biopsychosocial nature, as well as its dual sensory and emotional dimensions (Garland, 2012; Merskey et al., 1994). Interestingly, similar neural pathways observed in firsthand pain can also be activated when we observe someone else's pain; this phenomenon is called vicarious pain (Riečanský & Lamm., 2019). Vicarious pain, or "mirror-pain synesthesia", is the phenomenon by which observing the physical pain of others causes distress or discomfort, sometimes manifesting as shared physical sensations (Adiva et al., 2024; Blakemore et al., 2005; Osborn & Derbyshire, 2010). This means that when they see or become aware of someone else's pain, they automatically and involuntarily experience similar feelings of discomfort or pain, even though they are not physically affected (Fitzgibbon et al., 2010). This response stems from the brain's capacity to mirror the experiences of others, leading to a shared pain response without directly harming the observer. It highlights the deep connection between empathy and the neural processes that mimic the pain of others (Lamm et al., 2011). To deeply examine the concept of vicarious pain, it is critical to comprehend what is meant by 'empathy'. Empathy can be defined as the ability to understand and react to another person's emotional state, while keeping a clear distinction between their thoughts and emotions and our own. Empathy involves cognitive, affective and behavioral components (Decety & Jackson, 2006; Goubert et al., 2005. In particular, cognitive empathy is defined as perceiving another person's emotional state, and affective empathy consists of sharing or mirroring that state. Behavioral empathy could take the form of providing comfort or withdrawing from the distressed individual (Decety & Jackson, 2006; Goubert et al., 2006).

1.3.1 Theories of Empathy for Pain

There are numerous theories that examine the relationship between perception and action regarding the concept of empathy. Earlier, Lipps (1903) stated that observing expressions of others' emotions directly activate corresponding emotions in the observer. Similarly, McDougall (1908) suggested that instinctive responses are triggered by perceiving emotional expressions of others, highlighting an automatic mapping between perception and action. Later, the Perception-Action Hypothesis proposed that perception and action share a common code in the brain (Allport, 1987; Prinz, 1987; 1992; 1997; Rizzolatti & Arbib, 1998). According to Perception-Action Hypothesis, perceiving a behavior in others automatically activates internal representations of that behavior which then trigger motor responses in the observer. This automatic activation contributes to our ability to understand and connect with the actions and emotions of others. Expanding on this concept, the Active Intermodal Mapping Hypothesis (Meltzoff & Moore, 1997) has been proposed, which also explains the process underlying early facial imitation in infants. According to Active Intermodal Mapping Hypothesis, infants compare their own expressions to those they perceive in others through a shared representational space, refining their imitation to match what they observe (Meltzoff & Moore, 1977, 1983, 1994). These theories emphasize the importance of perception-action linkages as a neural and developmental basis for empathy. These mechanisms contribute to our understanding of the social transmission of fear by enabling individuals to reflect and respond to the emotional and fearful responses of others.

Subsequently, Preston and de Waal (2002) established the Perception-Action Model which has been influential in understanding empathy. According to this model, perceiving an action in others automatically triggers the observer's relevant motor representations, providing an intuitive understanding of the observed action. According to Perception-Action Model, empathy is an evolved function that enables vicarious learning and prosocial behavior. Based

on this model, observing someone in pain triggers representations in the observer's brain that correspond to the observer's own pain experiences. For instance, when someone observes another person who has a hot probe placed on their hand, the anterior cingulate cortex and the anterior insula, brain areas also responsible for first-hand pain, are activated (Lamm et al., 2011). According to Preston and de Waal (2002), this neural representation may be a reflexive consequence of perception that leads to automatic autonomic and somatic responses in the observer. It is thought that this neural mirroring can be facilitated by the activation of the mirror neuron system, which is involved in both the execution and observation of actions, sensations and emotions (Keysers & Gazzola, 2009). Mirror neurons are a type of neurons that show activity both during the execution of a specific motor action and when observing the same or similar action of another individual (Kilner & Lemon, 2013). Mirror neurons, first identified in the premotor area (F5) of monkeys, activate not only when performing goal-directed actions, such as grasping, but also when observing others perform the same actions (di Pellegrino et al., 1992). This visuo-motor activation suggests that these neurons form a neural basis for understanding and imitating others' actions by creating shared representations in the brain. Mirror neurons are central to the perception-action model. Essentially, the brain mirrors the observed activity, enabling it to represent and comprehend the action in a unified way (Rizzolatti & Craighero, 2004). The discovery of mirror neurons was a cornerstone for our understanding of how the brain links perception and action, providing critical insights into mechanisms like imitation, empathy, and social learning.

Over the past decades, brain imaging studies emphasized how the brain integrates observed actions into the motor system, offering insights into mechanisms like imitation and social learning. In a positron emission tomography (PET) study, Decety and colleagues (1997) demonstrated that observing actions activates critical brain regions involved in planning and executing movements such as the bilateral dorsolateral prefrontal cortex and the pre-

supplementary motor area. These regions play a key role in preparing and coordinating actions, indicating that simply watching someone else perform an action can trigger the observer's motor circuits. Furthermore, according to the functional magnetic resonance imaging (fMRI) findings of Iacoboni et al. (1999), both the left inferior frontal cortex and the right superior parietal lobule were activated when participants either observed or performed a finger movement. Remarkably, these brain areas showed the highest activation when the action was performed in response to observing another person's movement. According to Decety and colleagues, these results supported the direct matching hypothesis that suggests that perception and action share a common neural code. The direct matching hypothesis, similarly to the mirror mechanism, proposes that brain regions involved in action execution and observation should have neurons that are active during the execution of an action, independent of how it is triggered (Agnew et al., 2012). A subset of these neurons should additionally receive input unique to the action they represent. As a result, cortical areas with a matching mechanism should have motor features and increase in activity when an action is triggered by witnessing the same movement (Iacoboni et al., 1999). Consequently, these findings underline how observed actions are seamlessly integrated into the observer's motor system, enabling imitation and understanding. In summary, observing actions activates motor-related brain regions, supporting the direct mapping hypothesis that proposes a shared neural code for perception and action. The ability to mirror observed actions increases empathy and facilitates learning through observation, emphasizing its importance in social interactions.

1.3.2 Neural Basis of Vicarious Pain and Empathy

The vicarious experience of pain is believed to contribute to multifaceted social process such as empathy, and it changes significantly between individuals (Williams, 2002). Goubert and colleagues (2005) developed the a model for empathy in the context of pain, suggesting

that an observer's ability to empathize is critical for effectively evaluating the other person's pain. According to this model, top-down and bottom-up processes determine how people respond to the pain of others. Top-down processes include the observer's previous experiences, everyday knowledge and personal characteristics such as pain catastrophizing. Furthermore, observing the pain of others may activate top-down processes such as nociceptive representations, which are likely to be regulated by the observer's cognitive state and the contextual circumstances (Lehner et al., 2017). Hence, these processes require more advanced cognitive skills. These include the observer's prior experiences, knowledge and ideas regarding pain. In this respect, a person who has experienced the same sort of pain may have a greater empathic response than someone who has not. These quick clues may elicit automatic, emotional responses in the observer. On the other hand, bottom-up processes rely on direct sensory inputs such as watching another person's facial expression or hearing their statements of distress. Bottom-up processes also include immediate sensory and contextual clues such as the distressed person's pain expressions and the situational context. To conclude, the perception of pain not only results from processing nociceptive stimuli in a bottom-up manner, but is also regulated by top-down cognitive processes (Lehner et al., 2017).

Moreover, when someone observes another person in pain, various emotions might arise, such as sadness and discomfort to compassion and a wish to help. Several studies indicate that the affective dimension of pain, which is necessary for interpreting its level of severity and initiating appropriate actions, is similarly activated whether the pain is experienced directly by person or observed in others (Hutchison et al., 1999; Jackson et al., 2005; Morrison et al., 2004; Singer et al., 2004). Additionally, elements such as the observer's relationship with the person in pain as well as the context in which the pain is observed, have a substantial impact on empathic responses. To illustrate, observing someone in pain caused distress when the observer was in a cooperative relationship but not in a competitive one (Englis et al., 1982).

Another finding showed that both the anterior insula and the anterior cingulate cortex were activated not only during the experience of physical pain but also when imagining the pain of loved ones (Singer et al., 2004). An fMRI study done by Osborn and Derbyshire (2010) also found that participants who reported feeling pain when observing injury images, demonstrated significant activation in brain regions associated with both the sensory and emotional aspects of pain. These regions include anterior cingulate cortex, particularly the anterior midcingulate cortex, the insula, and the somatosensory cortices. In contrast, participants who did not report feeling pain exhibited minimal activation in these areas when viewing the same injury images compared to non-injury emotional images. The study concluded that for some people who observe someone else in pain, both an emotional and sensory sense of pain can be elicited. This emphasizes a "shared" physical pain sensation and a close relationship between emotional empathy and sensory processing in the brain.

There are two primary approaches to explain the mechanisms underlying the vicarious pain phenomenon: one focuses on shared processes in the brain, while the other emphasizes cognitive reflection. The first approach proposes that vicarious pain results from a shared experience in which the brain circuits responsible for somatic pain in the observer are activated when observing another person in pain (Decety & Jackson, 2004; Singer et al., 2004). The dorsal anterior cingulate cortex, anterior insular (Corradi-Dell'Acqua et al., 2011, 2016; Fan et al., 2011; Jackson et al., 2005, 2006; Lamm et al., 2007, 2011; Singer et al., 2004) and primary and secondary somatosensory areas (Jackson et al., 2005; Keysers et al., 2004; Lamm et al., 2011; Singer et al., 2004) are implicated in both direct pain experiences and pain perception in others. According to Langford et al. (2006) observing others in pain can even increase one's own pain sensitivity even in mice. Moreover, Rütgen et al. (2015) demonstrated that placebo therapies can reduce the vicarious experience of pain, indicated by decreased activation of the affective aspect of pain-related neural components such as P2

event-related potential and reduced empathy ratings. This suggests that placebo analgesia may reduce both subjective and neural responses to observing others' pain. This finding suggests that empathy and direct pain experiences activate similar neural mechanisms. The activation of the dorsal anterior cingulate cortex and the anterior insula is commonly referred to as neural resonance, a type of shared pain experience that occurs naturally and is an essential component of empathy (Singer et al., 2004; Zaki et al., 2012). According to Iacoboni (2009), empathy is based on fundamental mechanisms that link perception to action and serve as the foundation for vicarious experiences. In contrast, the cognitive reflection approach suggests that vicarious pain is essentially a cognitive experience rather than a direct imitation of physical pain (Chartrand & Bargh, 1999; Hooker et al., 2008; Levenson et al., 1990). This approach is also associated with perception–action models of empathy (Preston and de Waal, 2002; Meltzoff & Decety, 2003). The cognitive reflection approach proposes that it is difficult to adequately replicate or recreate another person's subjective experience of pain (Hooker et al., 2008; Zaki, 2014). Therefore, individuals simulate the experiences of others in order to better understand what others are feeling (Gallese & Goldman, 1998)

There are notable conflicts between these two main approaches to vicarious pain. According to Krishnan et al. (2016), vicarious pain and somatic pain rely on two different neural mechanisms rather than shared neural processes. The main regions that are involved for somatic pain are anterior insula, dorsal anterior cingulate cortex, dorsal posterior insula, and secondary somatosensory cortex (Horing & Büchel, 2022; Kaplan et al., 2020; Tso et al., 2015; Wang et al., 2019). On the other hand, vicarious pain is linked to the dorso-medial prefrontal cortex, amygdala, posterior cingulate cortex, and temporo-parietal junction, which are regions involved in mentalization and cognitive reflection processes. In contrast, a meta-analysis further supports that adopting different emotional perspectives, including others' pain, fear, happiness, disgust, and anxiety consistently engages the dorsal anterior cingulate

cortex, the anterior midcingulate cortex, the supplementary motor area, and the anterior insula (Fan et al., 2011). Another study suggests that the anterior midcingulate cortex and the anterior insula are activated when individuals observe others in pain, and even participants who had never personally experienced physical pain, displayed similar hemodynamic responses to those of control subjects when observing pain in others (Danziger et al., 2009). In addition to these approaches, other researchers state that vicarious pain may reflect processes such as valence (the emotional value of a stimuli), arousal (the intensity of an emotional reaction), or basic behavioral impulses like approach and withdrawal (Barrett & Wager, 2006). A study involving physicians provides evidence to support this alternative approach. Cheng et al. (2007) demonstrated that when physicians observed body regions being poked by a needle, which is generally unpleasant for most individuals, there was no activation in the anterior insula or anterior cingulate cortex which are the regions typically involved with reactions to vicarious pain. This alternative approach concludes that the absence of activation may indicate that when a situation is not personally distressing or aversive, typical pain-related circuits may not be activated, even when observing another person's pain. In conclusion, although the shared neural representation concept of vicarious pain remains an influential framework, emerging evidence suggests that further multifaceted approaches may provide a more comprehensive understanding of how the brain processes the vicarious pain.

Recent studies suggest that empathy for pain is also influenced by neurochemical factors in addition to neural pathways. In this regard, several studies have been conducted to comprehend the connection between painkillers and their effect on empathy for others' pain. For example, acetaminophen, commonly known as paracetamol, not only alleviated physical pain but also has also been shown to reduce empathy towards others' pain. Even though particular neurochemicals as oxytocin (Barraza & Zak, 2013), endogenous opioids (Rütgen et

al., 2015 a, b) and serotonin (Kuypers et al., 2014) have been associated with empathy, the precise link between neurochemical processes of empathy and physical pain remains unclear (Mischkowski et al., 2016).

To summarize, the perception of pain has a profound connection in the human brain, involving complex neural pathways that extend beyond direct experience with physical stimuli. Observing another person's pain activates an area of the brain involved with firsthand pain sensation, such as the somatosensory cortex. Vicarious pain perception activates brain regions that frequently correspond with direct pain experience, particularly the primary and secondary somatosensory cortex (Keysers et al., 2010). Also, single-neuron recording indicates that the anterior cingulate cortex plays a role in both direct and indirect pain (Hutchison et al., 1999). Furthermore, from a neuroanatomical point of view, possible pathways for integrating visual and somatosensory information could explain somatosensory cortices' vicarious activity. Particularly, Brodmann area 2, a subdivision of the primary and secondary cortices, in non-human primates is linked to visual processing regions such as the ventral intraparietal area and the inferior parietal lobule, suggesting a potential substrate for visual-somatosensory integration in humans (Banati et al., 2000; Lewis & Van Essen, 2000; Pandya & Seltzer, 1982). This integration may facilitate the activation of somatosensory regions simply by observing touch or pain which contributes to the suggested somatosensory mirror systems. The existence of such systems is consistent with the discovery of mirror neurons for action and touch in monkeys, which activate during both execution and observation of similar behaviors (Lewis & Van Essen, 2000; Rozzi et al., 2005). Besides, functional neuroimaging studies have reported overlapping regions of activation within these cortices when people are in pain or see others in pain (Blakemore et al., 2005; Ebisch et al., 2008; Keyser et al., 2004). Similarly, EEG studies have indicated that observing touch or pain in others modulates somatosensory evoked potentials (SEPs) (Bufalari et al., 2007;

Deschrijver et al., 2016). In addition, Galang et al. (2019) used visual stimuli consisted of images of a hand being pricked by a needle or touched by a Q-tip. Images were presented from two perspectives: first-person (upright) and third-person (inverted) to investigate the role of visual perspective (first-person vs. third-person) influences event-related potential (ERP) components when observing painful stimuli. They reported that when individuals experienced pain from a first-person perspective, the N2 component (early automatic component) showed higher activation. This finding implies that N2 could be an affective component of empathy when pain is more easily misattributed to oneself. In contrast, the P3 component (late cognitive component), previously used to discriminate between stimuli depicting someone in pain and those depicting someone not in pain (Fan & Han, 2008), was more pronounced during third-person observation of pain. This result suggests that the P3 component can be interpreted as the perception of an individual's pain state from a third-person perspective. Moreover, individuals who observed painful stimuli indicated right lateralization of the theta band, whereas the control group showed a left lateralization of the theta and beta bands when observing non-painful stimuli (Balconi & Angioletti, 2021). Frontal cortical regions in both groups were substantially sensitive to social scenarios. On the other hand, multi-voxel pattern analysis (MVPA) findings revealed distinctive neural hallmarks for self and other-pain perception, implying that although there is an overlap, the brain representations may not be completely identical (Krishnan et al., 2016). In addition, MEG study suggested that observing others' pain facilitates neuronal synchronization and involves dynamic communication between somatomotor regions rather than isolated neural activity. Specifically, observing a needle penetrate a stranger's hand resulted in a rapid and transient increase in functional connectivity between primary somatosensory and motor cortices, without detectable changes in neural activity in either area (Betti et al., 2009). In brief, the overlapping activity in somatosensory cortices during firsthand and observed pain, in combination with individual

variability in vicarious experience, highlights the complexity of these connected processes and the need for additional investigation into the specific pathways and mechanisms that underpin vicarious pain. Understanding how pain affects motor behavior is necessary, especially in social situations when consuming others in pain might trigger automatic responses.

1.4 Pain and Motor Control

Pain is a multifaceted phenomenon with profound impacts on motor control. Pain can impair our capacity to move, maintain muscular function and complete tasks. Pain can affect everything from the strength of muscle contractions to the variability of our movements. Rohel et al. (2021) stated that different pain types (tonic and phasic pain) have been shown to produce distinct effects on corticospinal excitability.

Our understanding of motor adaptation in response to pain has evolved profoundly over the last few decades, as evidenced by the development of numerous fundamental theories (Hodges & Tucker, 2011; Peck et al., 2008; Lund et al., 1991; Roland, 1986). Advances in pain theories are crucial to the development of more effective treatments for pain-related motor dysfunction, with a focus not only on pain management but also the underlying adaptations that contribute to chronic pain problems. Originally, the Vicious Cycle Theory (Roland, 1986) stated that pain causes a uniform increase in muscular activity (i.e., muscle spasms), resulting in muscle ischemia and the accumulation of pain-inducing substances, sustaining a cycle of increased tension and suffering. However, this idea was found to be overly simplistic, which led Lund and his colleagues to propose the Pain Adaptation Theory (Lund et al., 1991). This theory introduced that muscle activity during pain is not uniform, but rather varied based on the task at hand. Muscles engaged in the painful action decrease activity, whereas antagonist muscles increase activity to slow the movement and protect the

injured area (Lund et al., 1991). Most recently, the Redistribution of activity approach (Hodges & Tucker, 2011) expands on this by suggesting that pain causes a flexible redistribution of activity within and between muscles. This adaptive process permits the body to continue functioning while preventing further harm, but it can also result in changed movement patterns that contribute to chronic pain over time (Hodges & Tucker, 2011). When these theories are taken together, they highlight a shift from viewing pain responses as uniform and reflexive to recognizing them as highly individualized and context-dependent, providing deeper insights into how the body copes with pain and informing more effective approaches to managing pain-related motor dysfunction.

1.4.1 TMS Studies on Vicarious Pain

Pain is not an isolated sensory experience, it is closely tied to the brain's action systems that drive observational learning and imitation. When we witness someone in pain, our brain's motor regions are automatically engaged, reflecting the sensory experience of the observed pain (Avenanti et al., 2005; Avenanti et al., 2006). Notably, when a person observes another person in pain, a modulation of the motor system occurs by increasing finger withdrawal movements and slowing down approach movements (Morrison et al., 2007). One possible cause of these changes can be attributed to a decrease in corticospinal excitability or in the responsiveness of neural circuits that connect the motor cortex to the spinal cord and muscles. The relationship between vicarious pain and motor system implies that vicarious pain goes beyond a mere emotional response, but also activates sensorimotor systems. These mechanisms are significant for social threat learning since they enable us to recognize and anticipate activities that may cause harm by simulating others' painful experiences within our own motor system (Avenanti et al., 2005).

Transcranial Magnetic Stimulation (TMS) is a technique that allows us to obtain critical information about how pain affects the nervous system's ability to regulate movement (Rohel et al., 2021). TMS applied to the primary motor cortex (M1) can lead depolarization in the underlying cortical tissue, which activates corticomotor pathways and produces a motor evoked potential (MEP) in targeted muscles. The magnitude of the MEP serves as an index of corticospinal excitability (Bank et al., 2013; Rohel et al., 2021). Studies in which TMS was used to measure MEPs following acute experimental pain have shown an inhibitory effect on the motor cortex (Kofler et al., 2001; Valeriani et al., 1999). Furthermore, research demonstrated that both tonic and phasic pain can lead to a decrease in motor responses elicited by TMS (Farina et al., 2001; Urban et al., 2004). Collectively, these findings imply that pain may affect with M1 activity (Dubé & Mercier, 2011). This decrease in MEP amplitude is hypothesized to be an adaptive mechanism that limits movement in the painful region, so safeguarding it from additional pain and injury (Hodges & Tucker, 2011). In this respect, MEPs may make a substantial contribution to understanding the complicated interactions between behavioral, neural mechanisms and other important factors such as genetic and environmental factors. These factors are critical to understanding aspects such as fear avoidance, pain catastrophizing, pain intervention and pain management (Fullwood et al., 2021). In line with this, the study by Minio-Paluello et al. (2009) showed that individuals with Asperger Syndrome, unlike neurotypical subjects, did not show a decrease in MEPs when observing a needle penetrated deeply into a hand muscle, indicating that they did not physically mimic the pain of others. This absence of embodiment implies that their difficulties in empathy are not only cognitive, but also involve a lack of sensorimotor resonance.

Several TMS studies on pain observation indicate an inhibition in corticospinal excitability and decreased MEP amplitude in individuals who observe another person in pain (Avenanti et al., 2005, 2006, 2009a, 2009b, 2010; De Coster et al. 2014; Minio-Paluello et al., 2006, 2009).

A pioneering study by Avenanti and colleagues (2005) aimed to determine if observing painful events in others activates the observers' motor system similarly to when they experience pain directly. TMS was used to measure MEPs in participants as they observed different stimuli, such as a needle piercing a human hand or a non-corporeal object like a tomato. As a result, when participants observed someone being pricked, a significant reduction in the MEP amplitude emerged in the same hand muscle affected by the observed painful stimulation. Essentially, inhibition of MEPs was then specific to the muscle corresponding to the body part in pain and indicated a precise motor response associated with the observed experience. For example, observing pain referred to a foot did not result in decreased activity in the observer's hand muscles. Furthermore, the degree of motor inhibition was directly correlated to the observer's subjective assessment of the sensory characteristics of pain associated with the model, instead of to their emotional reaction. This shows that pain observation is associated with sensorimotor processes rather than just emotional responses. This also implies that automatic sensorimotor mapping may contribute to social learning by allowing individuals to respond to prospective threats by observing the pain of others. These findings point to a somatosensory mirror system that reflects the sensory experiences of others, helping to prepare for similar threats.

Research suggests that the left hemisphere can more effectively represent the sensory characteristics of others' pain. A fMRI study demonstrated activation in the left infero-parietal cortex, left precentral gyrus, and left anterior cingulate cortex, as well as bilateral activation in the anterior insula, when participants observed images of facial expressions demonstrating pain (Saarela et al., 2006). For instance, individuals who watched different video clips (e.g., static view of the dorsal surface of a hand and needle deeply penetrating the FDI muscle of a hand) demonstrated a significant reduction in MEP amplitudes and stronger inhibitory effects after stimulation of the left motor cortex for the muscle targeted by the model (Minio-Paluello

et al., 2006). In addition, according to the literature, the right hemisphere might be primarily engaged in the emotional dimensions of empathy for pain, whereas the left hemisphere appears to be more dominant in simulating the sensory characteristics of others' pain (Minio-Paluello et al., 2006). This aligns with pain studies indicating more pronounced right-sided alterations in BOLD fMRI signals within cortical regions associated with attentional and emotional processing of pain stimuli (Coghill et al., 2001; Symonds et al., 2006), as well as the left hemisphere's predominance in laser-evoked potential sources linked to the sensory-discriminative aspects of pain processing (Schlereth et al., 2003). Prior TMS research demonstrates that the left somatomotor cortex specifically encodes the sensory characteristics of others' pain (Avenanti et al., 2005, 2006). Moreover, Avenanti and colleagues (2009a) revealed not only a distinctive decrease in corticospinal excitability in the muscle that individuals observed being punctured, but also that corticospinal excitability was more inhibited among participants with high trait-cognitive empathy while it decreased less in participants with high personal distress and high aversion to the observed videos (Avenanti et al., 2009a).

Taken together, the vicarious pain studies summarized here emphasize the intricate reciprocal interaction between body representations and pain. The current findings indicate that our bodily representations can influence our perception of pain, and also pain can affect these representations (Beccherle & Scandola, 2024).

The research presented in this thesis builds on a research by Betti et al. (2024) that combined Pavlovian threat learning with transcranial magnetic stimulation (TMS) to explore changes in corticospinal excitability when subjects anticipate pain. In this research, participants were conditioned to identify certain colored dots with painful shocks in different parts of their bodies such as extensor carpi radialis (ECR) and right first dorsal interosseous (FDI). Participants underwent classical conditioning with either two colored dots (CS+)

followed by an electro cutaneous shock to specific side of the body (left, right) and body regions (forearm in experiment 1 and hand in experiment 2), or a third dot (CS−) presented without shock. Single-pulse TMS was applied over left M1 during the task to measure the amount of corticospinal excitability, whereas MEPs were recorded from the right ECR and FDI muscles. The results indicated that corticospinal inhibition was modulated according to the threatened muscle; specifically, pain threat to the forearm inhibited both the forearm and hand muscles, while pain threat to the hand inhibited only the hand muscle. Anticipating pain then caused topographically organized corticospinal inhibition, which means that the motor system inhibits responses based on the expected location of harm. Besides, this inhibition was stronger for individuals with higher levels of trait anxiety, indicating a relationship between anxiety and motor responses. The outcomes of this research underscore the strong relationship between our motor control systems and emotional states, particularly in the setting of fear and pain.

1.4 Aim of My Thesis

This thesis aims to investigate motor and autonomic response in response to stimuli that may acquire different values through learning. This study builds on the work of Betti et al. (2024) who examined the changes in corticospinal excitability as individuals learned to anticipate muscle-specific pain localized to the upper limb through a Pavlovian threat conditioning task. They used single-pulse TMS to measure corticospinal excitability during stimulus presentation that coud anticipate an electrotactile painful stimulation. The results revealed that corticospinal inhibition was elicited by the threat of pain, particularly in the limb where pain was anticipated. Here, we tested whether a reduction of MEP amplitude also occurs during vicarious learning, therefore by observing a person receiving a painful

electrotactile stimulation paired with a stimulus presentation. This thesis indeed focuses on the involvement of the motor and autonomic system in socially transmitted fear learning by measuring corticospinal excitability as well as skin conductance response in anticipation of an potential threat.

Here, we tested whether corticospinal excitability responses in vicarious fear conditioning are modulated similarly to Pavlovian fear conditioning in which pain is directly experienced by the individual (Betti et al., 2024). In line with this, we then expect that MEP for CS+ are reduced compared to the CS-; otherwise, if classical Pavlovian conditioning and vicarious fear conditioning differently affect the motor system, and if direct experience of pain is required to achieve this modulation, then no such difference in MEP amplitude between CS+ and CS- is expected. As regards autonomic responses, we expect greater SCR for CS+ than CS- according to the previous literature on vicarious fear conditioning (e.g., Haaker et al., 2017).

Overall, this thesis aims to provide new insights into the roles of the motor and autonomic systems in vicarious fear learning, to expand on previous research, and to clarify the contributions of the motor system to this complex learning process.

CHAPTER 2

METHODS

2.1 Participants

Twenty right-handed volunteers (15 women, aged between 19 and 38 years, mean age 24.55 ± 4.15 years) participated in the experiment. All participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971) with normal or corrected-to-normal visual acuity. They had no contraindication to TMS stimulation and no recent history of trauma affecting the upper limbs, nor were they currently suffering from any pain or taking any analgesic medication. The study followed the American Psychological Association Ethical Principles of Psychologists and Code of Conduct and the Declaration of Helsinki and was approved by the Ethical Committee for the Psychological Research of the University of Padova (protocol number 467-b). All participants were naïve to the purposes of the experiment and gave their written informed consent for their participation.

2.2 Experimental paradigm

Participants were tested individually in a single experimental session lasting approximately two hours. They were comfortably seated in a silent room in front of a computer screen (1440 × 900 pixels; refresh rate: 60 Hz), at ~80 cm viewing distance (see Fig. 1). Participants were initially introduced to the equipment present in the laboratory, namely the TMS stimulator, the Digitimer stimulator which it was explained is used to deliver mild electrotactile shocks, and the equipment for psychophysiological data recording. During the experiment, a PC running the OpenSesame software (Mathôt, 2012), connected to a Magstim BiStim^2 stimulator (Magstim Co., Whitland, UK) and a BIOPAC MP-160 System (Goleta, CA), controlled the flow of the task and data recordings. At the beginning and at the end of the experimental session, baseline corticospinal excitability was measured by acquiring MEPs

while participants passively observed a fixation cross on a screen to check for any basal CSE change during the experiment (15 repetitions per block). An inter-pulse interval of 10000-12000 ms was adopted, thereby avoiding changes in CSE due to repeated TMS pulses. This was followed by an Observational learning and Direct-expression tasks. In particular, in the Observational learning task, participants were shown video clips of an actress observing colored dots (blue or yellow) on a computer screen and received a painful shock based on the color of the dots. When the shock was received, the actress's exhibited painful facial expressions. The conditioned stimulus (CS+; e.g. blue dot) was associated with shock delivery in 70% of the trials, whereas the neutral stimulus (CS-; e.g. yellow dot) was never associated with shock. In the Direct expression phase, participants were only shown the colored dots (blue or yellow). For each experimental phase, the first two stimuli were a CS+ and a CS- presented to participants in a random order; in the Observational learning phase, the first CS+ was always associated with a model's pain expression. A total of 20 CS+ and 20 CS- were presented to the participant in each experimental phase, for a total of 80 trials. Before the start of the experimental task, two electrodes connected to the Digitimer stimulator, which were attached to the participant's right arm as in the video clip they would soon watch, but no shock was never administered. At the beginning of the Observational learning phase the istructions given to participants were as follows: "We ask you to pay attention to what happens on the screen. You will see a person sitting in front of a computer screen, connected to equipment similar to the one you are connected to. This person will be presented with colored circles, and occasionally, this person may receive painful electrotactile stimulations on their arm. Your task is to carefully observe the scene and try to figure out which color of the circle is associated with the shock". A clarification regarding the difference between the actress's electro tactile shock and the TMS pulse that participants will receive and have experienced was also provided. Then, before the start of the Direct expression phase,

participants were instructed to still to pay attention to what happens on the screen, “where the same colored circles that the person in the videos was looking at will be presented”. During the task, participants were also instructed to try to stay still and keep their hands and arms relaxed. At the end of the experimental task, the two CSs (blue and yellow dots) and all the video clips were rated by participants (see par. 2.4 on self-report measures). Then, a post-baseline phase with 15 MEPs was completed. At the end of the whole experiment, participants were debriefed about the experimental hypotheses.

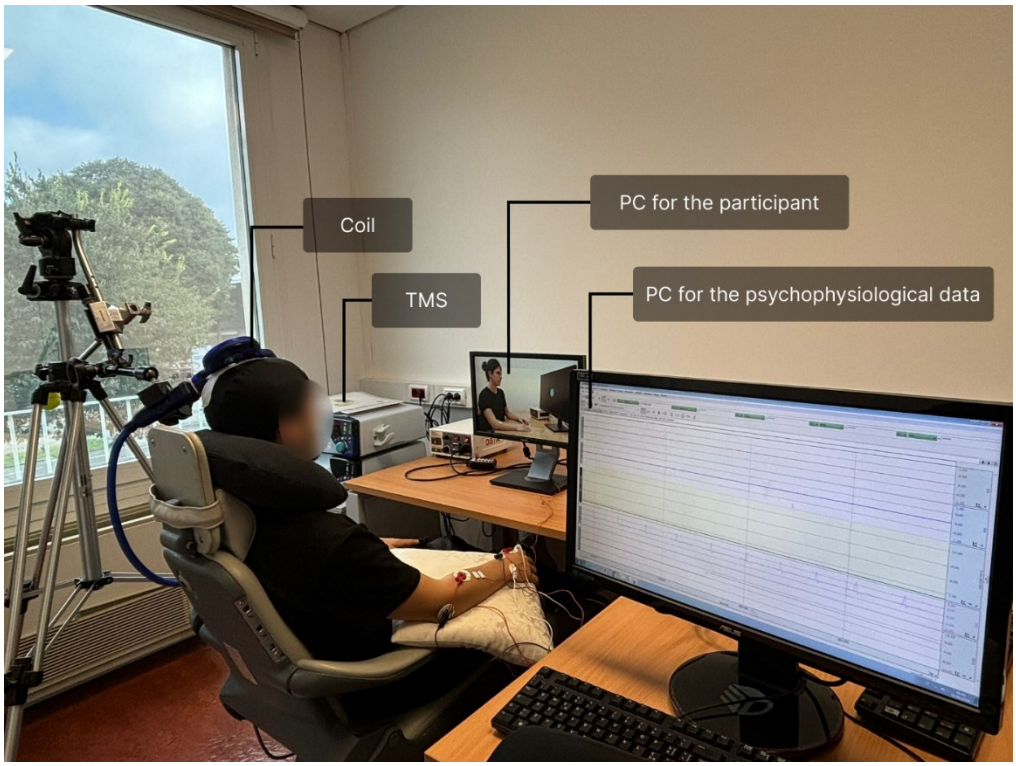

Figure 1. Experimental setup. TMS laboratory equipped with a Magstim BiStim^2 stimulator connected with a figure of eight coil to measure corticospinal excitability in hand (FDI) and arm (ECR) muscles. Stimuli were presented on a monitor placed in front of the participant and connected to a PC; psychophsyiological data were acquired in another PC connected to a BIOPAC MP-160 System. Participants confortably sat on a chair with electrodes for electromyography attached to their right hand and arm, and the elecrodes for electrodermal activity recording connected to the tip of the left index and middle fingers. Two elecrodes connected with a Digitimer Stimulator were also attached to the participant’s right arm, proximal to the ECR muscle.

2.3 Stimuli

2.3.1 Validation of video clip stimuli

The video clips used in the experiment were selected through a prior online validation study conducted on the Qualtrics platform (Qualtrics, Provo, UT). Three non-professional models (two female, one male) were filmed and the video clips were evaluated by a total sample of 147 participants (96 women, aged 18-71, mean age 31.82 ± 11.47 years). Each participant was randomly assigned to the videos from one of the three models. The validation focused on three main aspects: the intensity, unpleasantness, and genuineness of the pain experienced by the person in the video clip. Specifically, participants rated the intensity of the observed pain on a scale from 0 (no pain) to 10 (worst possible pain), the unpleasantness of the pain from 0 (not at all) to 10 (extremely), and the genuineness of the pain from 0 (not at all) to 10 (extremely). Additionally, participants were asked to indicate which sources of information (face, body, hands, arms, or computer screen) they used to interpret the models' experience, with faces being the most frequently reported source. All models received comparable ratings on perceived pain intensity, unpleasantness and genuineness; however, a female model was selected for the main experiment based on the higher scores obtained across these three aspects in the pain videos.

2.3.2 Experimental stimuli

Observational learning phase

The stimuli used in the observational learning phase featured a non-professional actress sitting in front of a computer screen with her right arm visible and resting on the table. Two electrodes were attached to her right arm and connected to a Digitimer stimulator device placed next to the screen (see Figure 2). This person was initially presented with a black screen for 3000 ms, followed by a colored dot (blue or yellow) for 4500 ms. At 4480 ms, 20 ms before stimulus disappeared, a TMS pulse was delivered and MEPs were recorded from the participant's target muscles. For CS+ trials, a painful electric shock was delivered to the actress in 70% of cases (14 trials) upon stimulus disappearance (Pain videos; Figure 2A), resulting in a painful expression on her face. In the remaining 30% of CS+ trials (6 trials), she did not express any pain (No-Pain videos). After stimulus disappearance, the video lasted other 3500 ms, allowing time for a potential pain reaction to be observed in CS+ reinforced trials. For CS- trials (20 trials), the same trial structure was adopted, but the actress never received a shock and maintained a neutral expression throughout (Figure 1B).

The colored dots in the video clips were edited in post-production to produce identical videos with the stimulus shown in either blue and yellow; color assignment to each CS was counterbalanced among participants.

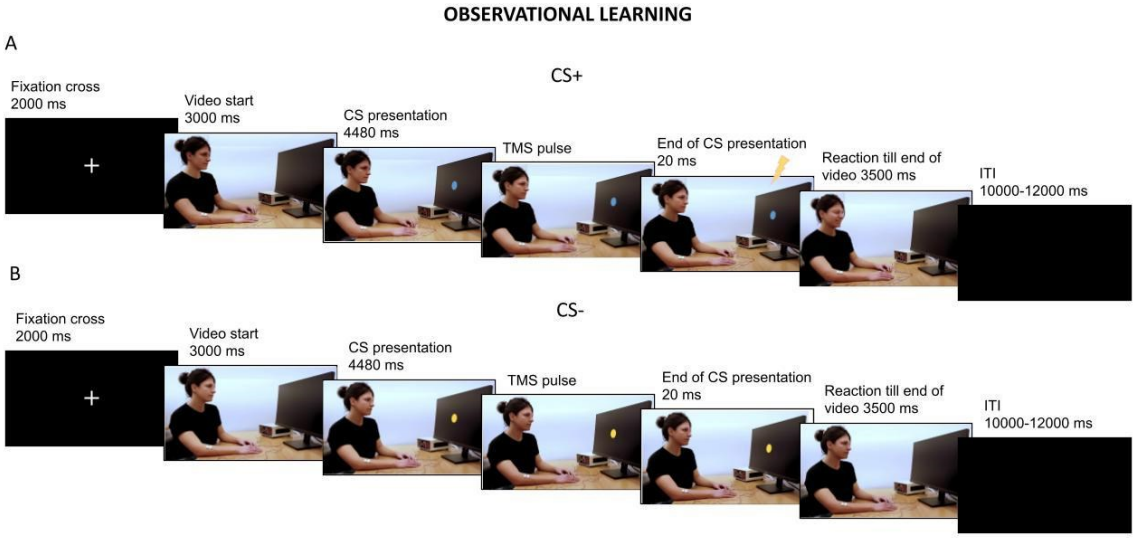

Figure 2. Trial structure for the observational learning task. Participants first observed a fixation cross (2000 ms), followed by a video clip showing a person seated in front of a computer screen, with electrodes attached to her right arm and connected to a Digitimer stimulator. The video began with a black screen for 3000 ms, after which a colored dot was displayed (in this example, blue for CS+ and yellow for CS-). The colored dot was presented for 4500 ms, with a TMS pulse applied 20 ms before it disappeared. The video then continued for an additional 3500 ms, during which the model displayed a painful expression in CS+ reinforced trials (panel A) or maintained a neutral expression for CS- trials (panel B). An intertrial interval (ITI) of 10000–12000 ms was used.

Direct expression phase

In the Direct expression phase, participants were presented with stimuli consisting of two-colored dots (71 pixels diameter) colored blue or yellow, presented in the center of the screen. Similarly to the Observational learning phase, each trial began with the presentation of a fixation cross lasting 2000 ms. After the fixation cross, a colored dot appeared on the screen. These dots were alike those presented to the model in the Observational learning phase, namely a CS+, e.g. colored in blue (Figure 3A), and a CS-, e.g., colored in yellow (Figure 3B). CSs presentation lasted 4500 ms and a TMS pulse was delivered 20 ms before stimulus disappearance. An inter-trial interval of 10000-12000 ms was adopted.

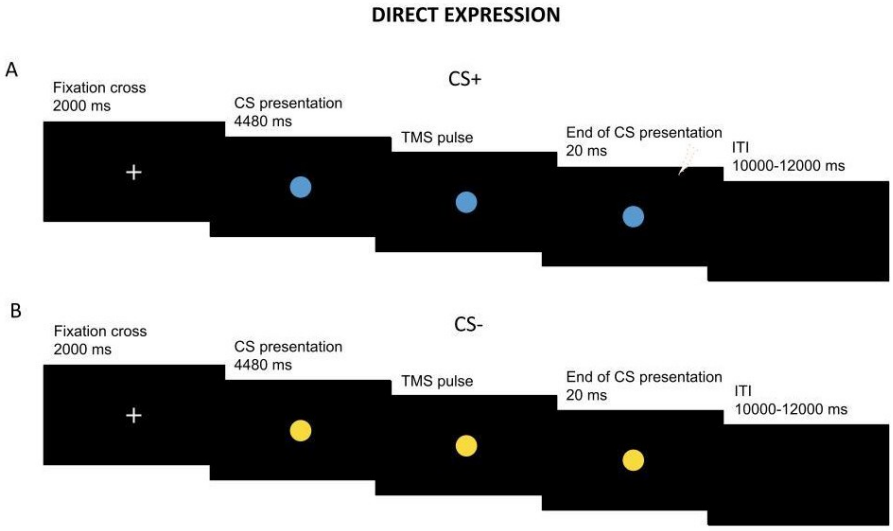

Figure 3. Trial structure for the direct expression task. Participants observed a fixation cross for 2000 ms, followed by the presentation of a blue dot for CS+ trials (panel A) or a yellow dot for CS- trials (panel B), which lasted 4500 ms. A TMS pulse was applied 20 ms before the dot disappeared. An intertrial interval (ITI) of 10000–12000 ms was used.

2.4 Self-report measures

Participants were asked to evaluate the video clips and colored dots they observed during the experiment using a 11-point Likert scale (ranging from 0 to 10), after completing the Observational learning and Direct expression phases. For each colored dot, participants were requested to respond to the questions "*The feeling I had when the dot was this color was*" (Valence; ranging from "unpleasant" to "pleasant") and "*When the dot was this color, I expected to receive the shock in my right arm*" (Expectancy; ranging from "never" to "always"). The purpose of this evaluation was to explicitly determine whether participants developed a fear conditioning toward the CS+ stimuli, compared to the CS- stimuli.

Besides, also the potential unpleasantness of TMS stimulation was evaluated asking participants *"How unpleasant was the TMS stimulation on the head?"* (ranging from "not at all" to "extremely").

Participants also rated the video clips they had previously watched during the Observational learning phase of the experiment. They were shown each video clip presented in a random order, then they were asked to rate each video clip according to the intensity, unpleasantness, and genuineness of the pain experienced by the person in the video clip as it was done in the video validation phase (see par. 2.3.1). Finally, participants indicated the source of information (face, body, arms, hands, computer screen) they used to understand what the model was experiencing in the video clips.

2.5 Stimulation and recordings

2.5.1 Transcranial magnetic stimulation

Single-pulse TMS was administered using a 70 mm figure-of-eight coil connected to a Magstim BiStim^2 stimulator (Magstim Co., Whitland, UK). Pulses were delivered to the left primary motor cortex (M1) of participants, in correspondence with the target muscles' representation. The coil was placed on the head at a 45-degree angle relative to the interhemispheric fissure, with the handle pointing laterally and caudally (Brasil-Neto et al., 1992; Mills et al., 1992). The best position for the coil on the scalp at which the lower intensity of stimulation elicits the largest MEP of both first dorsal interosseous (FDI) and extensor carpi radialis (ECR) muscles (optimal scalp position, OSP) was determined by moving the coil in approximately 0.5 cm steps around the presumed hand motor area. The OSP was then marked on a tight-fitting cap worn by the participants, ensuring a correct coil placement throughout the experiment. For each participant, the intensity of TMS stimulation was set at 120% of the individual resting motor threshold (rMT), that is, the lowest stimulation intensity inducing MEPs with at least ≥ 50 μV peak-to-peak amplitude in a relaxed muscle was found in 5 of 10 trials (Rossini et al., 1994). rMT ranged from 38 to 70% (mean = 55.10%, SD = 7.39) of the maximum stimulator output.

2.5.2 Electromyography (EMG) recording

Surface EMG activity was recorded simultaneously from the FDI and ECR muscles of the participant's right hand and forearm, respectively. Two pairs of Ag/AgCl electrodes placed in a belly-tendon montage and connected to an EMG100C module of the BIOPAC MP-160 System (Goleta, CA) were adopted. The active electrode was placed over the muscle belly, determined by palpation during maximum voluntary contraction. The reference and ground electrodes were placed over the proximal interphalangeal juncture and the radial styloid process for the FDI muscle and over the ulnar styloid process and the lateral epicondyle for the ECR muscle.

2.5.3 Skin conductance response (SCR) recording

Skin conductance was recorded throughout each phase at 5000 Hz, with a 20 Hz low-pass filter, from two Ag/AgCl electrodes (TSD203; BIOPAC Systems) filled with isotonic hypo saturated conductive gel (GEL101 model; BIOPAC System) attached to the distal phalanges of the first and second fingers of participants' left hands, connected to an EDA100C module of the BIOPAC MP-160 System (Goleta, CA).

2.6 Dependent variables

2.6.1 Motor evoked potential (MEP)

EMG data were imported and analyzed offline in MATLAB using custom-made scripts. Individual peak-to-peak MEP amplitudes (mV) for the FDI and ECR muscles were considered as a proxy for corticospinal excitability. Trials in which peaks of EMG activity in the 100 ms window preceding the TMS pulse exceeded 2 SD from the mean background EMG activity were discarded to prevent contamination of the MEP measurements (a total of

3.88% and 3.31% of MEPs were excluded for FDI and ECR, respectively). In addition, values exceeded ± 2 SD of the mean amplitude for each experimental condition were excluded as outliers (CS-: 2.38% and 1.81%; CS+: 2.31% and 1.56% for FDI and ECR, respectively). To control for interindividual variability in MEP amplitudes, separately for each participant and each muscle, the raw MEP amplitudes were z- transformed. The FDI MEP data for one subject could not be analyzed due to technical issues during data registration.

2.6.2 Skin conductance response (SCR)

The digitalized electrodermal activity signal was processed using Autonomate 2.8 (Green et al., 2014) running in MATLAB (The Mathworks) to obtain trough-to-peak SCR values. The digitalized signal was down-sampled at 625 Hz, a SCR was considered valid if the trough-to-peak response occurred between 500 to 4500 ms following the stimulus onset, lasted for a maximum of 5000 ms, and was greater than 0.02 μS. Raw SCR data were z-transformed, and values exceeded ± 2 SD of the sample mean were excluded as outliers (CS-: 2.63%; CS+: 2.50%).

2.7 Statistical analysis

Analyses were performed with JASP 0.19.1.0 (JASP Team, 2022). Repeated-measures ANOVAs (rmANOVA) were used to investigate differences between more than 2 conditions. For SCR data, experimental phase (observational learning, direct expression) and stimulus type (CS+, CS-) were considered as a within-subject factors in the analysis, whereas for MEP data, the additional muscle (FDI, ECR) factor was also considered. For the evaluation of the video clips, a rmANOVA was conducted to examine the effect of condition (Control, Pain, and No pain) on pain intensity, unpleasantness, and genuineness ratings. Paired samples t-

tests were performed to compare the CS+ to the CS- in the valence and expectancy ratings. In the presence of significant interactions, post-hoc comparisons were performed using the Bonferroni correction. Degrees of freedom and p-values were Greenhouse–Geisser corrected, whenever a violation of the sphericity assumption occurred. To test for any basal change in CSE during the experiment, the raw MEPs acquired during the initial and final baseline blocks were compared through paired t-tests. Partial eta-squared (η^2_p) was computed as estimates of effect sizes for the ANOVAs' main effects and interactions. A statistical significance threshold of $p < 0.05$ was adopted for all analyses.

CHAPTER 3

RESULTS

3.1 Corticospinal excitability

No significant differences emerged between the raw MEP amplitudes recorded during the initial and final baseline blocks, either for the FDI (t_{18} = 0.43, p = .676) and ECR (t_{19}= -0.961, p = .349) muscles. This indicates that TMS per se had not induced general changes in motor excitability during the experiment. The results of the rmANOVA performed on mean MEP amplitude (z-scores) revealed no significant main effect of stimulus type ($F_{1, 18}$ = .07, p = .80, η^2_p = .004), indicating that MEP amplitudes were not significantly different for CS+ compared to CS- stimuli. Additionally, there was no significant main effect of phase ($F_{1, 18}$ = .72, p = .41, η^2_p = .04), suggesting no significant difference in MEP amplitude between the observational and direct phases. The interaction between phase and stimulus type was also not significant ($F_{1, 18}$ = .19, p = .67, η^2_p = .01), as well as the interaction between muscle and stimulus type ($F_{1, 18}$ = 2.49, p = .13, η^2_p = .12) and the interaction between phase, muscle and stimulus type ($F_{1, 18}$ = .03, p = .86, η^2_p = .002), as shown in Figure 4.

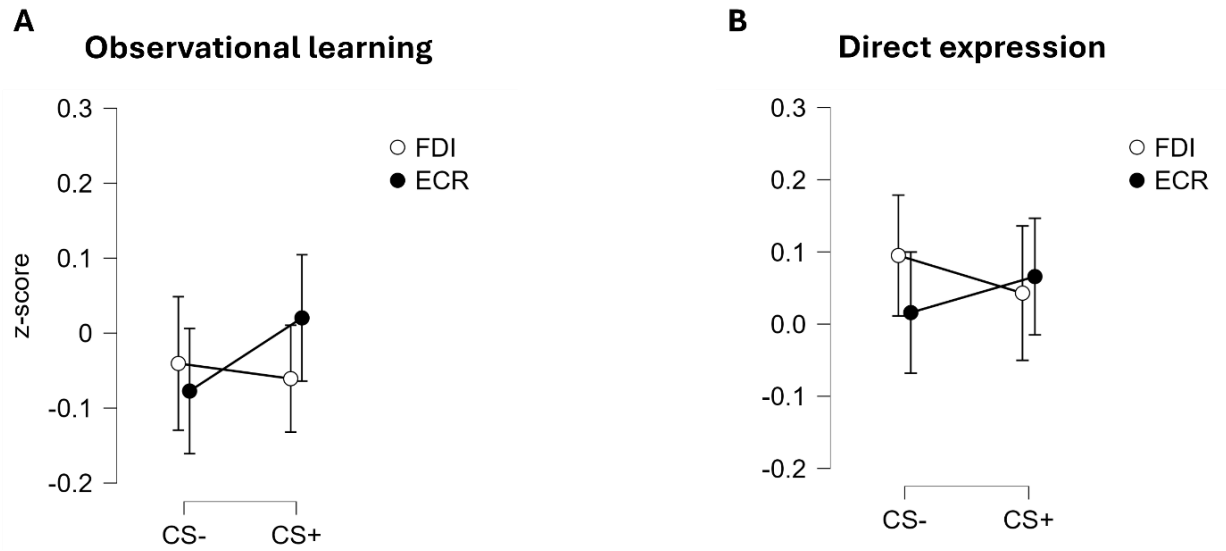

Figure 4. Corticospinal excitability during vicarious fear conditioning. Group estimate marginal means of motor evoked potential (MEP) amplitudes (z-score) for the FDI and ECR muscles as a function of the CS types (CS-, CS+) in (A) observational learning phase and (B) direct expression phase. FDI, first dorsal interosseous; ECR, extensor carpi radialis.

3.2 Skin conductance response

The results of the rmANOVA on SCR data showed a significant main effect of stimulus type ($F_{1,19} = 5.08$, $p = .04$, $\eta^2_p = .21$), indicating that SCR was significantly higher for CS+ stimuli in comparison to CS- stimuli (see Figure 5). As shown in the Figure 5A, although higher SCR values appear to characterize the CS+ in the Direct experience phase compared to the Observational learning phase, the results do not reveal a main effect of the experimental phase ($F_{1,19} = .77$, $p = .39$, $\eta^2_p = .04$), nor an interaction between experimental phase and stimulus type ($F_{1,19} = 0.66$, $p = .43$, $\eta^2_p = .03$).

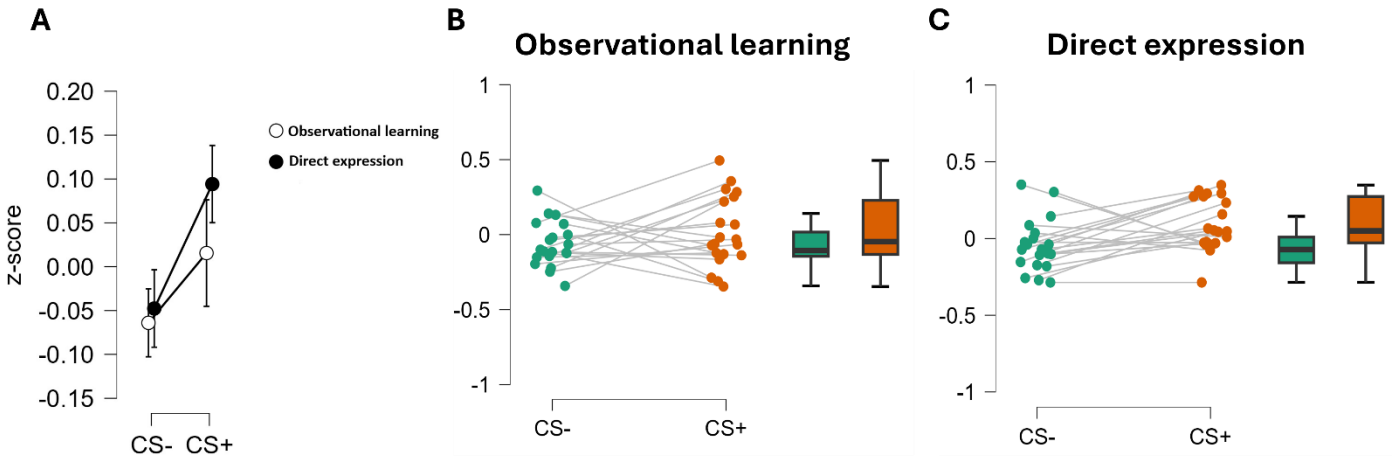

Figure 5. Skin conductance response during vicarious fear conditioning. Group estimate marginal means of skin conductance response (SCR) amplitudes (z-score) for the CS types (CS-, CS+) (A). raincloud plots for bservational learning and expression phase.

3.3 CS Valence and shock expectancy

A significant difference in valence ratings between CS+ (M = 3.95, SD = 1.90) and CS- (M = 5.30, SD = 1.49) emerged (t_{19} = 3.18, p = .005, Cohen's d = .71), indicating that participants rated the CS+ as significantly more unpleasant than the CS- (see Figure 6A). In addition, when participants were requested to rate if they expected to receive the shock in their right arm following CS+ or CS- presentation, the results show that the expectancy ratings differed significantly between CS+ (M = 6.85, SD = 2.52) and CS- (M = 2.85, SD = 3.28) (t_{19} = -4.69, p < .001, Cohen's d = -1.05) (see Figure 6B). This indicates that participants had a stronger expectation of receiving a shock after the CS+ presentation compared to the CS- presentation.

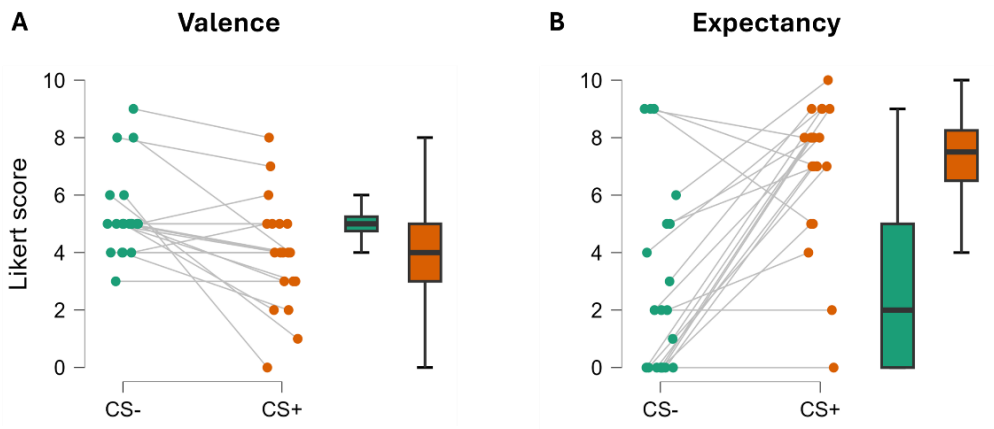

Figure 6. Subjective ratings. Raincloud plots of likert-scale ratings for stimuli valence (A), CS-US expectancy (B). Raw individual data are presented on the left and and boxplots on the right.

3.4 Pain intensity

At the end of the experimental session, participants were also requested to evaluate the observed videos based on the pain expression manifested by the model. The results indicate a significant main effect of condition on pain intensity ($F_{2,38} = 116.9$, $p < .001$, $\eta^2 = 0.86$). Participants reported significantly higher pain intensity in the pain videos (M = 6.24, SD = 1.19) compared to control (M = 0.46, SD = 1.18) and no pain (M = 1.00, SD = 2.05) videos (see Figure 7A). Post-hoc comparisons using Bonferroni correction indicated that there was a significant difference between the control and pain conditions ($t_{20} = -13,74$, $p < .001$), and between the pain and no pain conditions ($t_{20} = 10.11$, $p < .001$), indicating that pain intensity was significantly higher in the pain condition compared to control and no pain conditions. However, there was not a significant difference between the control and no pain conditions ($t_{20} = -1,94$, $p = .20$) in which two different stimuli were shown on the computer screen in front of the model (i.e., CS- and CS+, respectively), but the model remained neutral in both conditions.

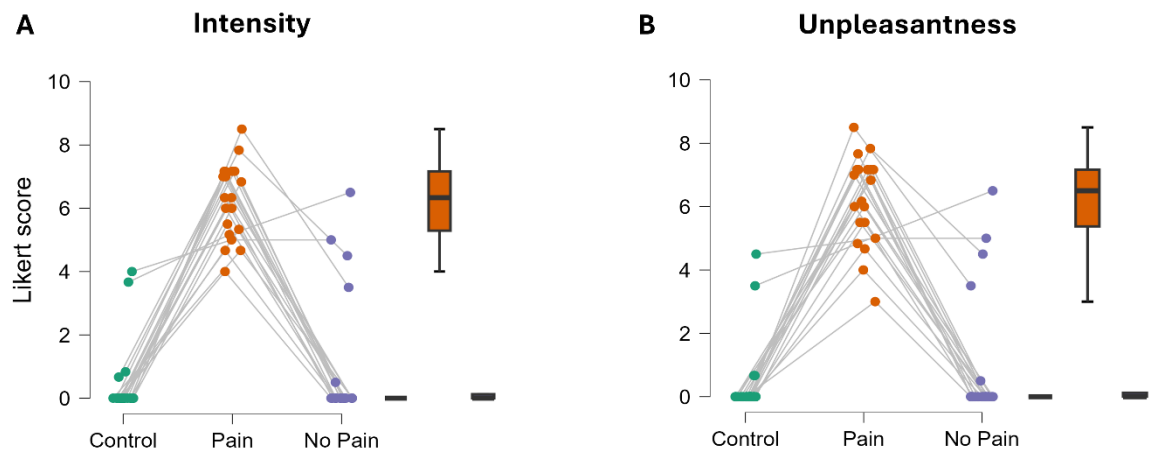

Figure 7. Pain subjective ratings. Raincloud plots of likert-scale ratings for stimuli intensity (A), unpleasantness (B). Raw individual data are presented on the left and and boxplots on the right.

3.5 Pain unpleasantness

Similarly to what emerged for the pain intensity ratings, the statistical analysis revealed a significant main effect of condition on pain unpleasantness ($F_{2, 38} = 99.37$, $p < .001$, $\eta^2_p = 0.83$). Indeed, higher scores of pain unpleasantness were given in pain videos (M = 6.21, SD = 1.40) compared to the control (M = 0.46, SD = 1.23) and the no pain videos (M = 1.00 SD = 2.05). Post-hoc comparisons using Bonferroni correction indicated that there was a significant difference between the control and pain conditions (M = -5.75; $t_{20} = -12.22$, $p < .001$), and between the pain and no pain conditions (M = 5,22; $t_{20} = 9.43$, $p < .001$), but the difference between the control and no pain conditions was not significant (M = -0.53; $t_{20} = -1,86$, p = .24) (see Figure 7B). In addition, the participants rated the genuineness of the actress's facial expressions in the video clips with a mean±SD of 6.33±2.05 in the pain condition (Min = 2, Max = 10). This suggest participants perceived the actress's facial expressions as moderately genuine in expressing pain.

Finally, Likert-scale scores were also acquired to check for a possible unpleasantness associated to the TMS stimulation applied to the head region. The mean response was 3.60±2.33, with the minimum score of 0 and a maximum score of 7, indicating that participants reported mild discomfort from TMS.

CHAPTER 4

DISCUSSION

This study investigates the role of the motor and autonomic systems in vicarious fear learning, emphasizing the impact of observing another individual in pain on the sensorimotor system. The findings provide insights into corticospinal excitability and skin conductance response in vicarious fear conditioning in which pain expression is observed in response to shock. We hypothesized a reduction in MEP amplitude in reaction to CS+ stimuli in line with previous research showing the threat of pain induces corticospinal inhibition prior to any actual harm, specifically targeting the body area where pain is anticipated (Betti et al., 2024). The results suggested that, although participants had a higher shock expectancy for the CS+ compared to the CS-, there was no significant main effect of stimulus type, as the MEP amplitude did not differ significantly between the CS+ and CS- stimuli. This implies that, in our vicarious fear conditioning paradigm, the corticospinal excitability did not decrease significantly when CS+ was observed in comparison to CS-. Furthermore, the main effect of phase was not significant, indicating that the MEP amplitudes were not significantly different between the observational learning and direct expression phases. This suggests that the motor system did not exhibit distinct responses based on whether corticospinal excitability was probed during observational learning or during the sole stimuli presentation as in the direct expression phase. This implies that the response of the motor system to threat-associated stimuli did not change significantly depending on whether participants observed another person in pain or were directly shown a threat associated with the previously pain-inducing stimulus. The lack of significant interactions between phase and stimulus type, as well as the lack of significant differences in motor-evoked potential amplitude between the observational and direct phases could be attributed to a variety of factors. One possible explanation is the

intensity, unpleasantness, and perceived genuineness of the pain exhibited by the actress in the video clips. Participants indicated moderate levels of unpleasantness, pain intensity, and genuineness for the pain videos; however, these features of the stimuli used in the study may not have been robust enough to elicit the expected modulation in the motor system. It is essential to note that the emotional impact of observing pain may depend on the genuineness of the pain reaction that has been observed. After the experiment, some participants reported that the actress's pain reactions appeared not genuine enough, even if overall the genuineness was rated as moderate. This perception possibly diminished the degree of emotional engagement that might be required to elicit a robust activation of the motor system during vicarious fear conditioning. Another explanation is that the passive nature of the task, in which participants did not experience any actual shock, may have influenced these results. Additionally, despite participants were clearly instructed that the shock that the person observed in the videos were different to the TMS stimulation they were experiencing, and that the shock stimulation was delivered through the two electrodes that were attached to their arm as well as to the model's arm, the distinction between TMS pulses, which produce muscle activation eliciting motor evoked potentials, and electric shocks may still have been ambiguous. It is also important to consider that the video clips presented during the experiment did not include TMS and its equipment. Another alternative explanation for the lack of significant findings in MEP amplitude in our study may be related to the characteristics of the stimuli used. Previous studies which measured corticospinal excitability during pain observation, but not in the context of vicarious fear learning, have used pain-inducing objects, such as needles, to target specific body parts (Avenanti et al., 2005; Avenanti et al., 2006; Minio-Paluello et al., 2009). These stimuli may have elicited more intense emotional and physiological responses due to their direct and unambiguous threat presentation. Conversely, the pain stimulation used in our video clips delivered through

electrodes attached to the model's arm, and the visual complexity of the scene, might have affected the perceived intensity of the threat. This, in turn, may have influenced the motor responses observed in this study.

In contrast to the findings related to the motor system activation, skin conductance response, used as a proxy of autonomic system activation, showed differentiation between CS+ and CS- stimuli. Specifically, a main effect of stimulus type emerged, with skin conductance responses significantly higher for CS+ than for CS- stimuli. According to classical conditioning theories, CS+ stimuli produce higher physiological responses due to increased arousal and pain anticipation (Marin et el., 2020; Sevenster et al., 2014; Starita et al., 2023; Tabbert et al., 2006). Besides, also in the literature regarding vicarious fear learning, the CS+ elicits a significantly greater SCR compared to the CS- (Golkar & Olsson, 2016; Haaker et al., 2017; Olsson et al., 2007). Participants appear to better discriminate the CS+ relative to the CS- during the direct expression phase compared to the observational learning phase, despite the absence of significant statistical differences. The higher skin conductance responses for CS+ stimuli suggest that participants learned to associate the CS+ with shock despite no shock being administered. On the other hand, there was no significant main effect of phase, suggesting that participants' autonomic responses were not significantly different in the observational learning and direct expression phases. The phase of stimulus presentation, that is, learning to anticipate pain vicariously or being directly presented with the conditioned stimulus, did not significantly impact participants' physiological arousal.

One limitation of this study is that there was no direct shock administration to participants, potentially influencing the strength of vicarious fear conditioning. This suggests that the somatosensory experience of pain might be necessary to modulate the motor system. According to Schabrun and her colleagues (2015), pain severity is a subjective feature influenced by various factors, including the threat value of the stimulus and an individual's

prior experiences with pain. Therefore, absence of shock administration to the participants, although it is a standard procedure in the literature on vicarious learning (Haaker et al. (2017), may have affected both the perception of the genuineness of the actress' pain expression and the intensity of pain during the observational learning phase, as well as the possible modulation of the motor system.

While participants observed an actress experiencing painful stimuli, direct exposure to threats may elicit stronger motor and autonomic responses. To overcome this limitation, future studies might examine motor system modulation in vicarious fear conditioning by administering shock to participants to provide somatosensory experience prior to the vicarious fear conditioning task.

CONCLUSION

This study expands our understanding of the relationship between motor function and autonomic responses in vicarious fear conditioning. The findings suggest that the corticospinal inhibition in anticipation of shock does not occur in vicarious fear conditioning, and the role of the motor system in this process remains unclear. In contrast, skin conductance responses reflect heightened physiological arousal for conditioned compared to neutral stimuli. The lack of significant findings in corticospinal excitability might suggest a different involvement of the motor and autonomic systems in vicarious fear conditioning, with only the latter distinguishing between stimuli and their potential aversive value. The passive nature of the task and the lack of a direct experience of the pain that the observed model was experiencing, that is the lack of any actual shocks delivered to participants, might have affected corticospinal excitability responses. Also, the complexity and broad context of the video clips may have dispersed participants' attention, thereby restricting the motor system's engagement with the threat-related stimuli. Finally, a potential confusion in the distinction between TMS pulses and shock may have obscured any potential differences in motor response. However, despite the absence of direct shock application, skin conductance responses and the explicit ratings on stimulus valence and pain expectancy showed that participants effectively linked the CS+ stimuli to an aversive event.

Overall, this research provides new insights into the processing of vicarious fear learning in sensorimotor and autonomic systems. The research work presented in the thesis highlights the methodological challenges in eliciting robust motor responses using an observational learning paradigm. Future research could attempt to use more specific and unambiguous pain-associated stimuli to better clarify the specific conditions that might activate the motor system during vicarious fear learning.

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