Effects of long-lasting and intensive physical exercise regime on experimental pain response and sensitization, and their EEG GABAergic correlates: a case-control study

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Abstract

Introduction: Chronic pain (CP) is a major public health problem affecting millions worldwide. Current literature expresses the beta (β) oscillation, indicating GABA-dependent inhibition, as a potential objective pain biomarker and regular physical exercise as an attractive analgesic strategy. Thus, a better understanding of the underlying mechanisms of physical exercise analgesic effect could improve treatment decisions. This preliminary investigation comparatively assessed central sensitization (CS) clinical features, pain responses and the GABA-dependent inhibition dynamics during cold-induced pain in athletes and non-athletes.

Methods: This case-control study investigated 26 healthy right-handed, highly trained athletes (at least 7 h/week) and 24 age-and sex-matched non-athletes, all submitted to a cold pressor test (CPT) protocol consisting of hand immersion in ice-cold water at 4°C and concomitant high-density (64 electrodes) EEG recording (BIOSEMI). The numerical rating scale (NRS) for the sensory and affective (unpleasantness) dimensions measured pain perception at onset (threshold) and when it became unbearable (tolerance), reflecting pain sensitivity; the immersion time from pain threshold to tolerance (i.e. pain perception time, PPT) indicated resistance to pain; while the CS index (CSI) evaluated CS features.

Results: Pain indicators tend to be lower in athletes than non-athletes but did not reach significance. When comparing the low (Lβ, 13-20Hz) and the high (Hβ, 21-30Hz) β global power spectrum (GPS) computed during cold and pain perceptions, athletes showed a decrease in both sub-bands. In contrast, non-athletes witnessed an increase (Lβ p=.014). During PPT, Hβ GPS further dropped in athletes (p=.008) and raised in non-athletes, while the Lβ GPS increased in both groups. This period also witnessed a negative correlation between Hβ GPS and PPT (R=-0.434, p=.028) in athletes and between Lβ GPS and CS scores (R=-0.438, p=.032), which correlated with PPT (R=-0.492, p=.015) in non-athletes. No EEG marker correlated to NRS scores.

Discussion: As hypothesized, there is a trend of decreased pain sensitivity and CS but increased resistance to pain under the intensive physical exercise regime. Furthermore, compared to non-athletes, athletes display different GABAergic EEG markers modifications during pain and associations with pain indicators, affecting CS and resistance to pain. Indeed, it dissociates CS from resistance to pain and Lβ while reinforcing the link between Hβ and pain resistance.

Conclusion: This first insight into physical exercise-induced GABAergic modifications and their clinical correlates could mediate physical exercise's beneficial effect and participate in analgesia in CP patients, even if further investigations must confirm these preliminary results.

1 Introduction

1.1 Topic

Pain is defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Williams & Craig, 2016). Pain constitutes a significant clinical, social and health problem that dramatically affects the patients' quality of life and life expectancy (Todd, 2017; Torrance et al., 2010). Acute pain is a physiological warning mechanism essential for survival, preserving well-being (Malcangio, 2018; Pak et al., 2018). As such, it should disappear with the healing of the causing lesion. However, for reasons not yet fully understood, some individuals will develop chronic pain (CP) regardless of the disappearance of the causing lesion (Fregoso et al., 2019; Glare et al., 2019).

CP, defined by the International Association of the study of pain (IASP) as pain lasting over three months (Treede et al., 2019), cannot, however, solely refer to a protracted duration of acute pain (Treede et al., 2015). Indeed, CP is currently considered as a pathology on its own and corresponds to dramatic and long-lasting changes within structural and functional nervous system pathways involved in nociception (Baliki et al., 2014; Henderson et al., 2013; Nicholas et al., 2019; Treede et al., 2015). Moreover, prolongation of pain through time results in several adverse consequences in patients' life, like unemployment, early retirement, depression, family issues, socioeconomic distress (Bushnell et al., 2015; Domenichiello & Ramsden, 2019; Dueñas et al., 2016; Kawai et al., 2017; Müller et al., 2017; Torrance et al., 2010; West et al., 2012), in addition to multifaceted health deterioration (Fine, 2011; Turk & Dworkin, 2004).

Despite the progress achieved within the field of analgesia, pain management remains a challenging and complex issue often addressed with unsatisfactory success, since complete pain relief is rarely reached (Finnerup et al., 2018; Todd, 2017). Indeed, insufficient pain alleviation in about one-third of CP patients makes CP a neglected disease (Raffaeli & Arnaudo, 2017), leading to a significant burden on individuals and enormous costs for the society (Goldberg & McGee, 2011), unequivocally overtaking the costs of cardiovascular disease, diabetes and cancer combined, due to health care and lost productivity (Phillips, 2006). Finally, the health-related quality of life level is sadly comparable, if not inferior, to the palliative care stage of neoplastic disease patients (Fredheim et al., 2008).

The exceptional abilities of trained athletes to modulate pain is of particular interest in the field of analgesia. In particular, the way they cope with pain resulting from their intensive training (considered as a non-adverse feeling (Garland, 2012; Geisler et al., 2021; Pettersen et al., 2020))

ultimately questions the way they perceive pain and is worth paying attention to, when seeking for strategies to help patients dealing with CP. Furthermore, current literature points to a potential analgesic effect of physical exercise through central desensitization ((Nijs et al., 2016; Nijs et al., 2014; Senba & Kami, 2020; Sluka et al., 2018).

From a mechanistic point of view, the GABAergic signaling, owing to his crucial role both in maintaining brain homeostasis and regulating pain, and given measurable dysfunction observed in CP situation, is a pathway deserving attention when attempting to improve pain management. Indeed, changes of GABAergic markers have already been highlighted in CP patients (Pinheiro et al., 2016; Teixeira et al., 2021), as well as in healthy volunteers submitted to experimental pain (Zis et al., 2022). Furthermore, preliminary observations suggest GABAergic restoration corresponding to measurable analgesia upon balance training (Mory et al. 2022, under redaction).

Altogether, these observations emphasize not only on the potential role of physical exercise in modifying pain perception, behavior towards pain, and reducing pain, but also a possible mediation of the GABAergic neurotransmission in induced analgesia. From this perspective and having potential therapeutic applications in mind, this research project investigated differences between healthy volunteers with different physical exercise profiles regarding their responses to experimental pain, their pain sensitization features and related modifications in the GABAergic signaling, in order to understand potential advantages of intensive physical training in pain modulation and its GABAergic correlates.

In this background chapter, we will selectively review the most important concepts in the field, leading to our research questions and working hypotheses.

1.2 Nociception and Pain

1.2.1 The anatomical basis of nociception and pain perception: the pain matrix

It is crucial to differentiate pain, a conscious psychophysical perception, from nociception representing the whole nervous system processing following noxious stimulation, which does not necessarily lead to pain. On the other hand, pain can occur in the absence of nociceptive input, like in CP (Cortelli et al., 2013; Lee et al., 2009; Nikolajsen & Jensen, 2001). Pain perception describes a biopsychosocial phenomenon that involves multiple neuroanatomic and neurochemical pathways and processes (Garland, 2012). Pain pathways (Figure 1) represent a complex regulatory system implying the central nervous system (CNS) and the peripheral nervous system (PNS).

Noxious stimuli, which can be chemical, mechanical or thermal in nature, activate peripheral nociceptors specialized in detecting and transforming noxious stimuli into electrical signals (Cortelli et al., 2013; Marchand, 2008). The latter propagate along poorly myelinated Aδ and unmyelinated C fibers of the dorsal root ganglion (DRG), making the first synapse to the dorsal horn of the spinal cord (Marchand, 2008; Schug et al., 2011; Woller et al., 2017). The second-order dorsal horn nociceptive neurons constitute the spinothalamic (lateral) and spinoreticular (medial) tracts to thalamic nuclei. The second synaptic contact for a large proportion of sensory afferents is encountered in the lateral and medial nuclei of the thalamus, the central "relay station" for sensory information to the cerebral cortex. It is important to emphasize that the second order neurons also synapse with neurons in different brainstem nuclei (including the periaqueductal grey (PAG), the rostroventromedial medulla (RVM), etc), also involved in descending endogenous pain modulation (see below). The third-order neurons convey pain information from thalamic nuclei to pain-regulating cortical and subcortical areas, including the amygdala, hypothalamus, basal ganglia and specific regions of the cerebral cortex (Garland, 2012; Legrain et al., 2011; Marchand, 2008; Woller et al., 2017).

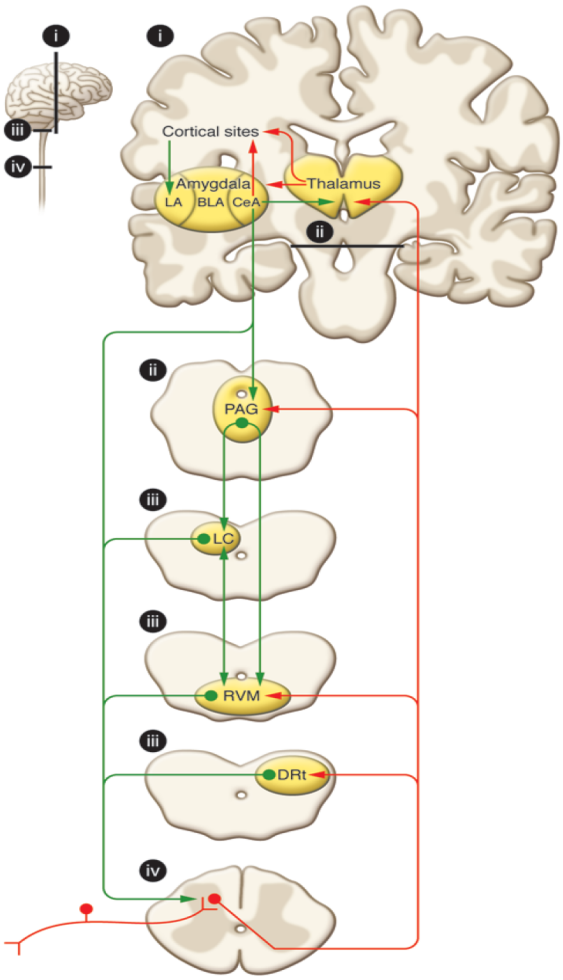
Among targets of the third order sensory neurons, the primary somatosensory cortex (S1) is the first level of conscious pain perception, while the secondary somatosensory cortex (S2) discriminates the location and intensity of painful stimuli. Together, the S1 and S2 constitute the lateral pain system (Brooks & Tracey, 2005; Bushnell et al., 1999; Kanda et al., 2000; Marchand, 2008), while the medial system (anterior cingulate cortex (ACC)) is involved in the affective regulation of pain (Brooks & Tracey, 2005; Rainville et al., 1997; Vogt et al., 2003). Thalamocortical and corticolimbic structures constitute the "pain matrix" that processes somatosensory input and related neural output regulating nociception (Garcia-Larrea & Bastuji, 2018; Garland, 2012; Legrain et al., 2011; Mansour et al., 2014).

The descending pain modulatory system regulates nociceptive response and behavior and plays a critical role in determining the experience of pain (Heinricher et al., 2009; Staud, 2013). This system, composed of the PAG in the midbrain and its projections to the RVM and the spinal cord dorsal horn, receives inputs from higher brain centers (mainly constituents of the "pain matrix"). It regulates the interplay between facilitatory and inhibitory nociceptive and non-nociceptive inputs (RVM) (Baliki et al., 2012; Henderson et al., 2013; Ossipov et al., 2010; Ossipov et al., 2014; Reddi et al., 2013; Staud, 2013), resulting in either facilitatory or inhibitory neural and behavioral nociceptive response (through dorsal reticular nucleus (DRt) and ventrolateral medulla (VLM)) and even producing analgesia (via the PAG, for example in emergencies or high priority situations where the survival reflex and/or necessity outbalance

pain perception (Heinricher et al., 2009)). In adverse situations, however, descending nociceptive can contribute to pain maintenance and chronification.

Figure 1

Schematic representation of pain circuitry according to Ossipov et al. (2010)



Note. The main structures implicated in the pain modulation are represented schematically in addition to the ascending (red) and descending tracts (green). "i–iv" shows site correspondence between the small and larger diagrams. Nociceptive inputs propagate to the spinal dorsal horn via primary afferent fibers synapsing onto transmission neurons. The ascendant projection fibers, which constitute the spinothalamic tract, target the thalamus, while collateral projections brainstem nuclei, including the DRt (dorsal reticular nucleus), the RVM (rostroventromedial medulla), and the midbrain PAG (periaqueductal grey) (Ossipov et al., 2010).

How the balance between analgesia and aberrance pain perception or their determinants are regulated, remains incompletely understood (Heinricher et al., 2009; Vanegas & Schaible, 2004). Thus, pain perception, depending not only on the physical characteristics of the stimulus but also on the individual cognitive and affective state, finally results from a dynamic interaction between sensory and contextual (cognitive, emotional and motivational) processes (Garland, 2012; Lumley et al., 2011; Ploner et al., 2017).

1.2.2 Illustrative psychological factors influencing pain perception

Several cognitive and emotional factors, including attention, cognitive appraisal, and the subsequent emotional and psychophysiological reaction, contribute to pain perception (Bustan et al., 2018; Garland, 2012; Linton & Shaw, 2011). Due to its threatening nature, pain automatically and involuntarily captures attention and disrupts cognitive activities non-related to it or to survival (Ahmad & Abdul Aziz, 2014; Assa et al., 2019; Garland, 2012; Legrain et al., 2009; Moore et al., 2013; Oliva et al., 2021). This attentional modulation impacts pain experience and correlates with modifications within the pain matrix (Tracey & Mantyh, 2007). For example, attentional distraction reduces pain-related activations in somatosensory cortices, among other brain regions and, at the same time, increases brain activations in the prefrontal and anterior cingulate cortex and periaqueductal grey nucleus, suggesting an interaction between the pain attentional modulation system and the descending pain modulatory system. (Garland, 2012; Tracey & Mantyh, 2007; Wiech et al., 2008).

Among pain-modulating psychological processes, cognitive appraisal, in its primary form, refers to the conscious or unconscious subjective emotional assessment regarding the personal significance of a situation for the well-being, while the secondary appraisal is the evaluation of how the situation can be managed (Garland, 2012; Khera & Rangasamy, 2021; Ramírez-Maestre et al., 2008). Thus, cognitive appraisal provides an emotional valence given to a situation, leading to its positive or negative interpretation (Kim & Hamann, 2012).

Finally, a powerful adverse emotional reaction, such as anxiety and fear, often accompanying physically painful situations, modulates pain perception (Cimpean & David, 2019; Garland, 2012; Kelley et al., 2018) in a way that can bias attention toward pain (Li et al., 2020) and reduce capacity to regulate pain through higher-order cognitive strategies, which are normally helpful to cope with pain and view it as controllable. This capacity is referred to as reappraisal (Garland, 2012; Kelley et al., 2018; Lawrence et al., 2011).

1.2.3 Pain perception assessment

Pain assessment is, so far, based exclusively on subjective scales (Haefeli & Elfering, 2006), prone to be influenced by several factors (see above), that could limit their reliability. The most commonly valid and reliable pain scale is the Visual Analogue Scale (VAS), usually consisting of a ten centimeters horizontal line with endpoints describing outer limits such as "no pain at all" and "the worst pain ever possible" and its numeric equivalent, the Numerical Rating Scale (NRS). In the latter, numbers between 0 and 10, 0 and 20 or 0 and 100 constructs the scale. In contrast to the VAS, only numbers themselves are valuable answers, thus allowing less-subtle discrimination of pain levels. These scales are easy to administer and record, and reliably represent the patient's feeling (Haefeli & Elfering, 2006; Hjermstad et al., 2011; Williamson & Hoggart, 2005).

Both the VAS and the NRS can simply assess the sensory and the emotional dimensions of pain, using respectively pain intensity (the sensory aspect of pain) and unpleasantness (the emotional aspect of pain), thus providing a general estimation without further characterization or details (Karcioglu et al., 2018; Williamson & Hoggart, 2005). They are easier to administrate than the McGill pain questionnaire (Haefeli & Elfering, 2006; Scrimshaw & Maher, 2001) and can apply precisely to the evaluation time, while the McGill questionnaire refers to the whole week before. Thus, they are more suitable for experimental settings to assess these two pain perception modalities in response to a stimulus. Because pain evaluating scales are subject to non-controllable variability due to their subjective nature, objective criteria are warranted for a more comprehensive pain evaluation, in complement to assessment through subjective scales. Several attempts to find reliable and accurate markers of pain using functional and imaging techniques, although promising, are not yet consistent enough to be applicable in clinical practice (Barr et al., 2013; Fallon et al., 2018; Favilla et al., 2014; Harris & Clauw, 2012; Lim et al., 2016; Mane et al., 2018; Mhalla et al., 2010; Pinheiro et al., 2016; Teixeira et al., 2021). Electrophysiological methods (including EEG) are, among non-invasive and cost-effective methods, used in this perspective.

1.3 Sensitization

1.3.1 Central and peripheral sensitization mechanisms

Beyond acute pain, noxious stimulation from tissue damage results in release of inflammatory mediators (prostaglandins, histamine, bradykinin, substance P), activating peripheral nociceptors and further generating action potentials transmitted to the cerebral cortex.

Descending nociceptive pathways, in normal conditions, simultaneously impedes this signal by triggering inhibitory neurotransmitter (i.e. noradrenaline and serotonin) release over the dorsal horn to hyperpolarize ascending neurons, providing endogenous analgesia (De Ridder et al., 2021; Pak et al., 2018; Yam et al., 2018).

However, repeated and/or persistent peripheral noxious inputs lead to further excitatory release of chemicals, triggering a transduction cascade that enhances nociceptor excitability and lowers the latter's threshold, which results in overall hyperexcitability at the level of the nociceptive PNS called peripheral sensitization. (De Ridder et al., 2021; Greenwald & Shafritz, 2018; Pak et al., 2018). Continuous transmission of these nociceptive aberrant signals from the PNS may subsequently trigger a central sensitization (CS) in the spinal cord and upper brain structures (De Ridder et al., 2021; Ji et al., 2018).

Pain sensitization is mediated both by upregulation of excitatory neurotransmission (mostly driven by glutamatergic receptor activation) and downregulation of the inhibitory system (mainly depending on GABAergic receptor activation) (Latremoliere & Woolf, 2009; Yang & Chang, 2019). Sodium and potassium channel modifications, as well as specific changes in transporter activity (e.g. KCC2 and NKCC1) further feed up neuronal hyperexcitability respectively through increased excitability (Curatolo et al., 2006; Du & Gamper, 2013; Hasbargen et al., 2010; Yam et al., 2018) and a switch of the GABAergic activity from inhibitory through a more excitatory input (Curatolo et al., 2006).

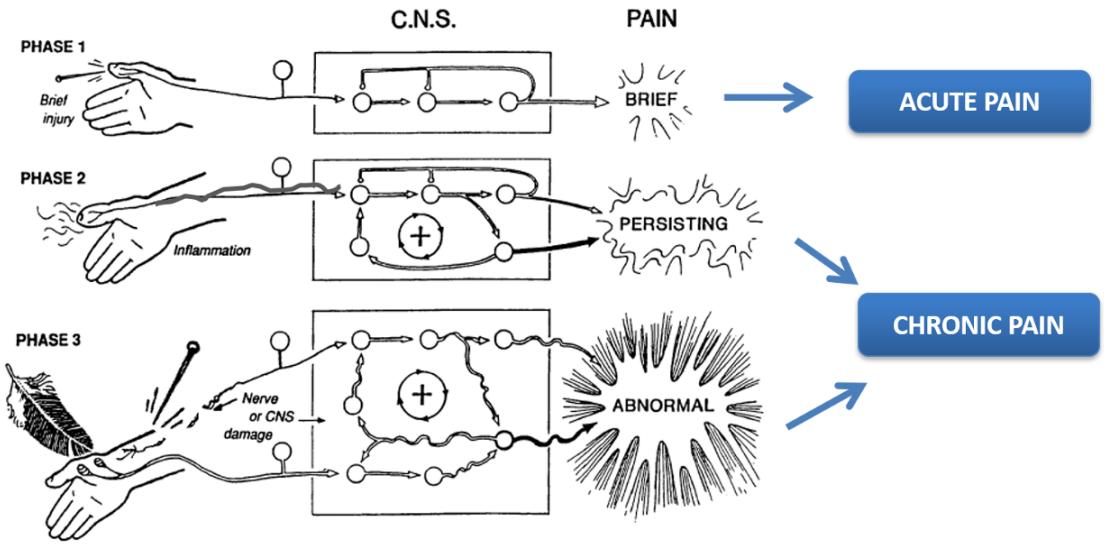
Overall, increased excitatory input and decreased inhibitory signaling result in central and peripheral nervous system hyperexcitability, even after stimulus removal (Latremoliere & Woolf, 2009). Thus, nociceptive neurons respond at a lower threshold to peripheral inputs, but also increase their receptive fields and their spontaneous firing rates (Greenwald & Shafritz, 2018), setting a new physiological equilibrium characterized by overexcitation (Harris & Clauw, 2012; Parker et al., 2016; Schaible, 2007) illustrated in figure 2. In addition, in CP situation, descending nociceptive pathways do not play anymore their inhibiting, pain-limiting role, but participate now to pain maintenance (Lv et al., 2019; Ossipov et al., 2010).

Peripheral sensitization and CS are key mechanisms and even considered to be the hallmarks of CP (Harris & Clauw, 2012; Neblett et al., 2013), even if mechanisms subtending pain chronification are not yet fully understood. Nevertheless, the progressive modification of the nervous system structure and function (illustrated in figure 2), as well as changes in pain perception and related behavior are more and more enlighten (Schaible, 2007; Yang & Chang, 2019). Knowing better determinants of these modifications would constitute a great progress not only in enlightening mechanisms involved in CP occurrence, but also in settling preventive

and therapeutic strategies counteracting CP. Among promising therapeutic approaches against CP, physical exercise is being more and more cited (Nijs et al., 2015; Senba & Kami, 2020). Proposed mechanisms underlying physical exercise-induced analgesia include reduction of CS, even if involved pathways are still to be disclosed.

Figure 2

Pain chronification process



Note. Schematic representation of pain chronification according to Cervero et Laird (1996) adapted by Dr. Joëlle N. Chabwine. Three-phase model of pain: from phase 1) normal nociception (processing of brief noxious stimuli) to normal nociceptive system under prolonged noxious stimulation resulting in tissue damage and inflammation (phase 2) to neurological damage, including peripheral and central pain states (phase 3). CNS, central nervous system (Cervero & Laird, 1996).

From a behavioral perspective, sensitization is characterized by exaggerated responses to noxious (hyperalgesia) or non-noxious (allodynia) stimuli (Neblett et al., 2017), two phenomena observed in CP, and involving all nociceptive pathways and beyond (Baliki et al., 2012; De Ridder et al., 2021; Greenwald & Shafritz, 2018; Ji et al., 2018; Pak et al., 2018). However, it should be noted, as stated above, that CS primarily represents a virtuous adaptive mechanism. Indeed, activity-dependent CS boosts pain sensitivity by increasing nociceptive neurons' activity in response to standard or sub-threshold input (Latremoliere & Woolf, 2009), creating a situation in which innocuous stimuli elicit pain. This change in pain sensitivity

participates to the healing process by limiting the use of the injured body part and by restoring homeostasis when nociceptive stimuli last longer, such as in subacute pain (Neblett et al., 2017). In case no healing occurs and pain persists, CS becomes a maladaptive mechanism contributing to the pathological process, namely within CP context (Guler et al., 2020; Ji et al., 2018; Latremoliere & Woolf, 2009; Lluch et al., 2014; Nijs et al., 2016), with reduced brain inhibitory input.

In summary, CS can occur under normal circumstances (limiting pain extension) or/and in pathological conditions, resulting in pain exacerbation and persistence (Latremoliere & Woolf, 2009) due to functional, chemical and structural plasticity within nociceptive pathways. Several determinants and associated behavioral pain responses participate to maladaptive CS, which constitutes one path towards pain chronification (Baliki & Apkarian, 2015) (Mayer et al., 2012).

1.3.2 Contextual factors contributing to central sensitization

Factors preexisting to the original pain-related injury and others following pain appearance contribute to CS. Prior history of anxiety, physical and psychological traumatism, and depression constitute predisposing factors for pain chronification (Afari et al., 2014; Häuser et al., 2013; McWilliams et al., 2003; Nahit et al., 2003; Rivat et al., 2010; Schmaling & Nounou, 2019). Following appearance of pain, existence of depression, fear-avoidance, anxiety, catastrophizing behavior or other stressors, may favor CS due to exacerbated CNS reactivity (Curatolo et al., 2006; Diatchenko et al., 2006; Hruschak & Cochran, 2018; Rivat et al., 2010). Sleep disturbance also play a role, as disrupted sleep following painful injury is associated with increased pain sensitivity and persistent pain (Campbell et al., 2015; Gupta et al., 2007; Smith et al., 2008).

1.3.3 Central sensitization assessment

Quantitative sensory testing (QST) comprises a battery of somatosensory tests among which hyperalgesia (increased pain sensitivity induced by lowering of the nociceptor threshold level) and allodynia (pain response to stimuli that does not normally elicit pain due to an altered balance of signals) correlates to CS, in addition to temporal summation which also constitutes a good CS indicator. In addition, an easily applicable questionnaire, the central sensitization inventory (CSI) validated as a screening tool and for treatment outcome measure (Neblett et al., 2013; Scerbo et al., 2018; van Wilgen et al., 2018), was introduced to better assess symptoms related to CS, as a help for clinicians in syndrome categorization, sensitivity and severity identification, as well as treatment planning and evaluation (Mayer et al., 2012; Neblett et al.,

2013). However, although the CSI questionnaire is widely used in clinical and experimental settings (den Boer et al., 2019), its appraisal and predictive value over pain sensitivity have never been evaluated in a healthy population so far, to our best knowledge.

On the other hand, overexcitation due to CS and leading to apoptosis and atrophy in higher centers such as RVM, thalamus and amygdala, can as such be measured using brain MRI. In addition, functional imaging methods such as fMRI and PET allow detecting an increased signal in the thalamus, insula and cingulate cortex associated with CS (den Boer et al., 2019). Some biological markers like increased blood and urine cytokines or neurotrophine level, possibly reflect CS. However, these functional imaging and laboratory markers constitute general indicators, none of them being specific to CS (den Boer et al., 2019).

1.4 Gamma-aminobutyric acid (GABA) in the mechanistic approach of pain

1.4.1 GABA in the inhibitory/excitatory brain balance

The optimal functioning of the nervous system depends, among other factors, on the balance between the excitatory (mainly glutamate-dependent) and the inhibitory system (predominantly driven by GABA in the CNS). The neurotransmitter GABA, synthesized by glutamic acid decarboxylase (GADs), is widely distributed in the central nervous system. It acts as an essential mediator of synaptic inhibition and is required to control the synaptic excitation/inhibition equilibrium and optimal neuronal oscillation (Lee et al., 2019). The broad expression of GABAergic neurons in many brain cortical and subcortical structures indicates the crucial role of this inhibitory neurotransmitter in regulating behaviour, motor control, mood, sleep (de Leon & Tadi, 2021; Mele et al., 2019; Plante et al., 2012), but also cognitive functions such as memory and attention (Edden et al., 2012; Porges et al., 2017). Furthermore, the GABAergic system plasticity provides extensive flexibility in neural circuits allowing adaption to diverse homeostatic and other demands (C. Li, Y. Lei, et al., 2019).

A disruption in the excitation/inhibition balance is a prominent CP hallmark (Harris & Clauw, 2012; Parker et al., 2016), pointing to excitatory and inhibitory neurotransmitters as meaningful targets in the mechanistic approach of CP. In this work, we will focus on the GABAergic neurotransmission.

1.4.2 The GABAergic signaling in nociception and in CP

GABAergic receptors are present at most levels of nociceptive pathways, starting from the dorsal root ganglion (DRG) neurons, that constitute the primary afferent fibers to the spinal

cord, and express necessary proteins for GABA synthesis, transport and release. The contribution of GABA-mediated primary afferent inhibition is crucial to the nociception gate control (Wang et al., 2021). In the spinal cord, GABAergic neurons are present as well, although glycinergic pathways also contribute to inhibitory inputs. Within the brain, GABAergic signaling predominates (including in nociceptive pathways) and is thus the main provider of inhibition contributing, participating among other functions, to nociception (Barr et al., 2013; Enna & McCarson, 2006; Yam et al., 2018).

As stated above, a reduced GABAergic inhibitory function (Teixeira et al., 2021; Wang et al., 2021) is associated to CP conditions. Decreased GABA level in the spinal horn (Wang et al., 2021) originates from GABA-synthesizing enzyme (Moore et al., 2002) downregulation and subsequent reduction in pre- and postsynaptic GABA receptors activation (Polgár & Todd, 2008). Additionally, primary afferent and dorsal horn Cl^- cotransporters dysregulation (i.e. KCC2 downregulation and/or NKCC1 upregulation (Hasbargen et al., 2010) shifts GABAergic equilibrium towards depolarizing potentials, leading to the so-called primary afferent depolarization (Chen et al., 2014). Overall, reduction in GABA-dependent inhibition (regardless of the mechanism engaged) results in spinal cord (dorsal horn in particular) hyperexcitability lowering pain perception threshold (causing hyperalgesia) and aberrant pain response to non-noxious stimuli (corresponding to allodynia (Comitato & Bardoni, 2021)). Whether reduced inhibition contributes to CP pathology or constitutes rather its consequence, remains still an open question. However, in this thesis, we will only be interested in the GABAergic neurotransmission, as a pathway involved in nociception and CP, without studying the type and direction of relationship existing between them.

1.4.3 The GABAergic system in the mechanistic approach of pain

The mechanistic approach of pain consists in disentangling nociception and pain in relation with involved neurophysiological mechanisms, with the idea that a mechanism-based classification CP syndromes or CP patients could contribute not only to further understand pathological mechanisms engaged, but also to a more successful CP management (Teixeira et al., 2021). In this perspective, diverse neurotransmitter pathways are currently being the object of intense research interest (e.g. the dopaminergic system (C. Li, S. Liu, et al., 2019), the GABAergic system (Enna & McCarson, 2006; C. Li, Y. Lei, et al., 2019), etc).

There are a number of reasons that make GABA a suitable pathway in the mechanism-based approach of pain (Ossipov et al., 2010; Price et al., 2006; Rudomin & Schmidt, 1999; Schaible, 2007; Teixeira et al., 2021). Firstly, as stated above, GABA is the main inhibitory pathway

maintaining brain homeostasis, and more specifically the balance between excitation and inhibition (Lee et al., 2019). Secondly, GABAergic signaling is crucial for nociception and pain regulation, while being objectively disturbed in a measurable way in CP situation (Schaible, 2015; Teixeira et al., 2021). Likewise, GABAergic neurotransmission also plays a crucial role in mood (de Leon & Tadi, 2021) and sleep (Plante et al., 2012) regulations, these two functions being tightly linked with pain regulation and their dysfunction being associated with CP (Blågestad et al., 2016).

Thus, targeting the GABAergic signaling in pain investigation should yield not only physiologically, but also clinically meaningful information. In addition, because GABA is not implicated in neuronal metabolism, its brain concentration may reliably reflect neural activity and, that way, be related to the GABAergic neurotransmission (Harris & Clauw, 2012; Teixeira et al., 2021).

1.4.4 Assessment of brain GABAergic activity

Brain GABAergic neurotransmission can be measured either through electrophysiological markers (as indicators of cortical inhibition (Christian et al., 2015)) or by GABA concentration in various brain areas (Ke et al., 2000).

GABA concentration in the brain is measured using magnetic resonance spectroscopy (Ke et al., 2000). Among electrophysiological methods, paired-pulse TMS protocols assess either short-interval intracortical inhibition (SICI), or long-interval intracortical inhibition (LICI) (Premoli et al., 2014), both related to different GABAergic receptor activation (Barr et al., 2013; Kuhn et al., 2017; Stagg et al., 2011). On the other hand, using EEG, brain GABAergic activity can reliably be assessed by beta (β, 13-30 Hz) and gamma (γ, 30-80 Hz) waves, which are driven by GABAergic interneurons (Baumgarten et al., 2016; Christian et al., 2015; Gaetz et al., 2011). Although most existing pain studies have evaluated γ waves, showing some correlation with perceived pain (Barr et al., 2013; Schulz et al., 2012; Zhang et al., 2021), β oscillations, of which reports remain scarce (Sarnthein et al., 2006; Stern et al., 2006), are more reliably measured by scalp EEG than deeply generated γ waves, and correlate well with cortical GABA concentration (Baumgarten et al., 2016; Teixeira et al., 2021). For this reason, this study will be interested in measuring EEG β oscillations as indicators of brain GABAergic signaling (Barr et al., 2013; Teixeira et al., 2021).

Although several studies using TMS, MRS and EEG measurements indicate a decreased cortical inhibition in CP patients (Arendt-Nielsen et al., 2007), especially within the pain matrix (Barr et al., 2013; Baumgarten et al., 2016; Henderson et al., 2013; Parker et al., 2016; Teixeira

et al., 2021), others report opposite results, in particular concerning EEG GABAergic markers (Lim et al., 2016; Sarnthein et al., 2006). Therefore, there is a need for further studying these GABAergic markers to better understand how they are related to nociception and to pain. Experimental studies constitute one way to do so. Among existing human experimental pain models, those inducing tonic pain constitute the closest mimics of CP, owing to slow adaptation of pain response (Arendt-Nielsen et al., 2007; Petersen-Felix & Arendt-Nielsen, 2002).

1.5 Effects of physical exercise

1.5.1 Impact of physical exercise in the CNS

Nowadays, the benefits of physical exercise on health in general, but in particular in functional ability (defined as the capacity to carry out everyday activities) and mental health (such as reduced anxiety, improved sleep and mood outcomes), as well as in cognitive functions and in CP, are widely demonstrated. Indeed, physical exercise impacts factors that positively influence brain homeostasis, including increased blood flow through higher vascularization and angiogenesis resulting into better oxygen supply to several cortical regions, modulation of the immune system, and finally, increased brain-derived neurotrophic factors (BDNF), a protein promoting neuronal survival, differentiation, and neuronal growth (McAllister et al., 1999; Petzinger et al., 2013).

These factors facilitate structural and functional changes (Etnier et al., 2016) related to physical exercise beneficial effects on the brain (and thus, on cognitive functioning) and well-being (physical and mental health) (Mandolesi et al., 2018). Human studies using magnetic resonance imaging (MRI) to track structural changes after physical exercise report increased grey matter volume in frontal and hippocampal regions (Colcombe et al., 2006), which represent the two most impacted brain areas by physical exercise (Erickson et al., 2013). The frontal cortex is responsible for many cognitive functions, such as inhibitory control, decision-making, attention, emotion regulation, and other higher-level processes, while the hippocampus is responsible for memory consolidation, learning, and overall mood and cognition regulation.

In addition, recent evidence suggests that physical exercise induces motor cortex (M1) plasticity resulting in increased cortical facilitation and reduced inhibition respectively due to increased glutamatergic facilitation and reduction in GABA transmission, which lead to enhanced M1 and corticospinal excitability (El-Sayes et al., 2020; Hendy et al., 2022; Monda et al., 2017; Moscatelli et al., 2021; Nicolini et al., 2021). Furthermore, owing to use-dependent plasticity, repetitive physical training elicits cortical motor representational changes (Moscatelli et al.,

2021), which is an important component of normal motor learning and recovery after neural injury (Conner et al., 2005)

Exercise-induced neuronal adaptation in the CNS is also linked to the monoamine system regulation, including dopaminergic, noradrenergic and serotonergic systems leading to improved physical and mental adaptative abilities to cope with external and internal challenges and maintain homeostasis (Lin & Kuo, 2013). Dopamine regulates motivation, reward and attention, while serotonin mood, emotion, sleep and appetite and norepinephrine are involved in various cognitive processes (Basso & Suzuki, 2017).

However, mechanisms underlying the beneficial effects of physical exercise are far from being elucidated. Thus, taking into account all above-mentioned impacts on the CNS (possibly related health improvement), further understanding related neural mechanisms could constitute a promising domain to better tailor therapeutic strategies for improved health conditions, including CP (Morgan et al., 2015).

1.5.2 Behavioral responses to exercise-induced neuroplasticity

Usual exercise is associated with increased cognitive control, such as inhibitory, attentional and emotional control (Cox et al., 2016). For example, enhanced inhibitory control is applied to displeasing sensation reduction, allowing people with greater inhibitory control to engage longer in unpleasant physical activity (Padilla et al., 2014). Furthermore, physical exercise is related to lower depression and anxiety symptoms and reduced stress reactivity due to better emotional regulation, flexible attention shifting and focusing through conscious or non-conscious processes. Cognitive reappraisal, which involves reconsidering emotional stimuli to downregulate their emotional impact, is one among these processes (Giles et al., 2017; Gross, 2002). Thus, physical exercise is associated with higher cognitive and behavioural flexibility allowing appropriate adaptations of thoughts and behaviours in response to changing environments, such as under pain stimulation.

1.5.3 Potential analgesic effect of physical exercise

Because pain is omnipresent in sports, athletes constitute a population of great interest in studies tracking the potential advantages of physical exercise in pain modulation. Indeed, athletes' ability to perceive and tolerate pain is essential to success (Scott & Gijsbers, 1981). In that perspective, higher cognitive and behavioral flexibility related to intensive physical activity allows interpreting pas as an ally, not a threat, which positively impacts pain perception and thus, participates in the analgesic effect of physical exercise (Baker & Kirsch, 1991; Geva &

Defrin, 2013; Gorczyca et al., 2013; Jones et al., 2014; Kakiashvili et al., 2016; Meyers et al., 1996). In addition, acceptance, lower harm avoidance and pain catastrophizing are characteristic traits of athletes, who are more able to forget themselves in order to pursue a goal, meaning they are keen to control their physical and emotional needs and complaints for higher goal (Freund et al., 2013). This constitutes a kind of reappraisal process.

The beneficial pain-related effect of physical exercise goes beyond psychological aspects. Indeed, in the field of analgesia, CS has recently emerged as an interesting target owing to its prominent contribution to CP mechanisms (Fine, 2011; Schaible, 2007). Thus, analgesic therapies promoting central desensitization appear to have high success potential. Among them, physical activity is a harmless and cost-effective measure easy to implement, with beneficial effects going well beyond analgesia, as stated above (Nijs et al., 2015). The analgesic effect of physical exercise seems to occur through positive impact on pain modulation (Geva et al., 2017; Sluka et al., 2018), resulting in reduced pain and unpleasantness ratings (Ellingson et al., 2012; Naugle & Riley, 2014; Sluka et al., 2018).

While acute exercise bouts lead to a temporary reduction in pain sensitivity, a phenomenon called exercise-induced hypoalgesia (Koltyn et al., 2014; Naugle et al., 2012), regular physical activity could prevent the development of CP, possibly, among other mechanisms, through maintenance of the balance between excitatory and inhibitory neurotransmission due to GABAergic neurotransmission improvement ((Fitzgerald & Carter, 2011). One suggested mechanism is the expression and activity increase of the GAD, which is an enzyme responsible for catalyzing the decarboxylation of glutamate into GABA (Fitzgerald & Carter, 2011). As a result, glutamatergic signaling decreases (in parallel with increase of the GABAergic input) in parallel with attenuated pain response (Fitzgerald & Carter, 2011; Koltyn et al., 2014; Naugle & Riley, 2014). In support to this assumption, in the partial sciatic ligation (PSL) neuropathic pain experimental model (Seltzer et al., 1990), physical exercise allowed preservation of neuronal GABA content, positively correlated with the threshold of mechanical hypersensitivity on one side, and with GABA and GAD65/67 levels, as well as with the number of involved GABAergic interneurons on the other side, in the dorsal horns (Naugle & Riley, 2014; Senba & Kami, 2020).

Intriguingly, intensive physical exercise reduces GABAergic transmission and increases glutamatergic facilitation, resulting in increased M1 and corticospinal excitability (El-Sayes et al., 2020; Hendy et al., 2022; Monda et al., 2017; Nicolini et al., 2021). Existing data state that M1 increased excitability has an inhibitory effect on experimental pain through activation of limbic, cortical and subcortical regions associated with antinociception and depression of the

noxious inputs at the spinal cord level (Granovsky et al., 2019; Pagano et al., 2012; Tang et al., 2009), all this resulting in increased pain threshold (Moloney & Witney, 2014) and reduced pain perception in healthy populations (Granovsky et al., 2016). However, in CP condition, enhanced M1 excitability loses its pain inhibitory function (Granovsky et al., 2019), probably due to altered organization and function in M1 occurring in CP situation (Jodoin et al., 2020; Schabrun et al., 2016).

Overall, these observations appear contradictory regarding the effect of physical exercise on CNS excitability in healthy versus CP populations, in acute versus regular intensive exercise practice. Nevertheless, there appears to be an indication for the implication of GABAergic signaling in exercise-induced analgesia, including in CP. Whether the GABAergic activity is also involved in central desensitization obtained through physical exercise, remains still a question. Furthermore, the effect of exercise on EEG oscillations remains controversial, especially regarding the direction of changes in GABAergic electrophysiological markers (Gramkow et al., 2020), while the impact of a long-lasting and intensive physical exercise regime on pain (particularly on CS) in clinical and experimental settings and its GABAergic counterpart remain poorly studied.

1.6 Aim of the work and working hypotheses

The objective of the present work is to comparatively assess the response to cold-induced pain stimulation, as well as CS clinical features, and related EEG β oscillation changes, in healthy volunteers with two different profiles of physical activity, to better understand how intensive physical exercise impacts pain perception, CS and associated GABAergic signaling. Our results should give more insight into pain regulating (GABA-dependent-) mechanism and thus, contribute to improve pain management through a GABA-base mechanistic approach.

Concretely, this study will investigate the following questions:

1) Are there significant changes in EEG-recorded β oscillations throughout cold-induced pain stimulation?
2) Will a long-lasting intensive physical training regime influence pain sensitivity and its EEG correlates?
3) Will a long-lasting intensive physical training regime impact CS component?
4) Are noticed differences in CS associated with modifications in pain sensitivity and their EEG correlates?

The following hypotheses have been formulated to examine our research questions. All hypotheses are numbered following the research questions. For clarity, we only state below

non-null hypotheses (null hypotheses should be considered as denying differences or associations assumed in non-null hypotheses):

1. The impact of cold-induced pain on EEG-recorded β oscillation

   H_1: EEG GABAergic markers will show changes throughout cold-induced pain stimulation

   In particular:

   H_1a: There will be EEG differences between cold and pain perception

   H_1b: There will be EEG differences according to the participant's pain perception at critical experimental time points (i.e. pain threshold and pain tolerance)

2. The impact of a long-lasting intensive physical training regime on cold induced-pain sensitivity and its EEG correlates

   H_2a: A long-lasting intensive physical training regime reduces pain sensitivity

   H_2b: A long-lasting intensive physical training regime modifies GABAergic EEG markers.

3. The impact of a long-lasting intensive physical training regime on CS

   H_3: A long-lasting intensive physical training regime reduces CS.

4. The link between CS components and pain sensitivity and related GABAergic markers

   H_4a: Lower CS features are associated with reduced pain sensitivity

   H_4b: Lower CS features and reduced pain sensitivity are associated with higher brain GABAergic input.

2 Methods

2.1 Participants

This monocentric prospective experimental case-control study targeted healthy right-handed men aged 18 to 60 years, with two different sports activity profiles: on one side, highly trained participants (athletes), and on the other side, their non-trained age-adjusted i.e. similar age (+/- 7 years) without performing a one-to-one age-matching controls (non-athletes). Athletes practiced mainly endurance sports such as triathlon, running or cycling and had to train at least 7 hours/week for the last 6 months, while non-athletes had at most 2.5 hours of sports activity/week. Exclusion criteria were presence of acute or chronic pain, existence of neurological dysfunction or lesion of any kind, significant cognitive or psychiatric disorders, documented severe sleep disorders, and potential local lesion risk (e.g. limb ischemia), symptom aggravation or complication due to the experimental procedure (Pienimäki, 2002) in relation with vascular dysfunction (diabetes, respiratory and cardiovascular disease, presence of Raynaud phenomenon (Musa & Qurie, 2022) or existing musculoskeletal lesion or diseases. The study fulfilled all requirements regarding international ethical standards (including the Declaration of Helsinki) and was approved by the Ethics Committee of Vaud under the number 2019-00442. Accordingly, all participants had to sign an informed consent before inclusion and evaluation. Participants were screened and recruited through social networks and clubs dedicated to the most popular sports in Fribourg and the neighborhood.

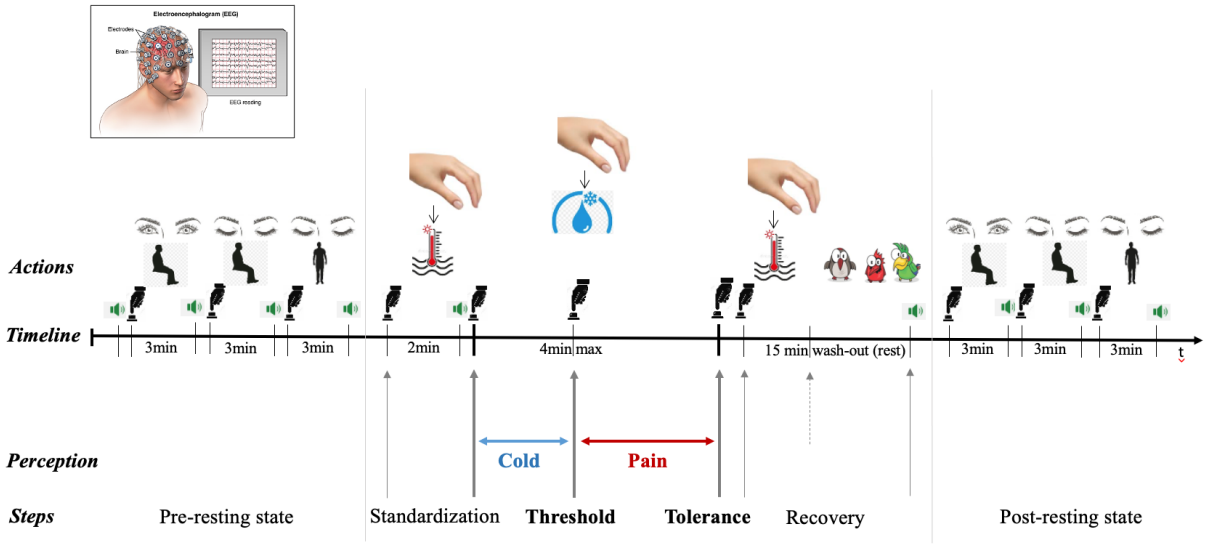
2.2 Experimental procedure

Participants were submitted to a single experimental session (see below) at the Laboratory of the Neurology Unit at the University of Fribourg before noon (between 08 and 12 am) to avoid any bias due to circadian variation of pain (Strian et al., 1989) and of GABAergic signaling (Vogt, 2015). In addition, they were requested not to consume any psychoactive products in the form of beverages (e.g. coffee, tea, energy drinks, soda, chocolate) or drugs potentially interacting with the GABAergic neurotransmission (Isokawa, 2016; Landolt et al., 2004). Furthermore, they were invited to avoid unusual physical activities 48 hours before the experimental sessions to exclude unwanted influence on pain response and electrophysiological data, but also for preventing appearance of musculoskeletal pain excluding them from the study. The complete experimental procedure was explained to the participant in addition to explanations provided in the informed consent form, at the time of inclusion and again the day of evaluation before the experimental procedure started.

The experiment consisted of cold-induced pain stimulation through ice-cold water. Throughout the experiment, the participant was asked to report perceived pain. Experimental conditions (room temperature, noise and lighting levels, the participant position and posture, the hand position for immersion, water temperatures, experiment steps and reporting) were rigorously standardized and controlled. The participant remained in a standing position with eyes open, in front of water trays. The latter were disposed on a table adjustable to the participant's height. The participant was allowed to feel the cold-water temperature prior to the experiment with his left hand (not submitted to the experiment, see below). These precautions contributed to his comfort and minimized his anxiety about the experiment. Acoustic beeps served as warnings to announce the main experimental steps. Figure 3 illustrates the whole experimental procedure.
The cold pressor test (CPT) is an easy, cost-effective, and reliable cold-induced pain experimental procedure. The obtained potent tonic cold pain constitutes, as said above, a suitable CP experimental model (Gram et al., 2015; Hansen et al., 2017; Terrighena et al., 2017). In our setting, the cold stimulation temperature and duration (see below) minimized lesion risk, in addition to exclusion criteria listed above. Thus, this approach can be considered as safe in healthy volunteers as in chronic pain patients.
The CPT consisted of right-hand immersion in ice-cold water at 4°C (mean ± SD: 4.18 ± 0.49 °C), with the palm in a flat position up to the wrist, until pain became unbearable, with a maximal immersion time of 4 minutes allowed, in order to limit the risk of tissue injury (MacLachlan et al., 2016). Prior to the experiment, the participant was informed of the existence of a maximal immersion time but was left blind to the value of this maximal duration to avoid targeting. The key steps of the experiments were *pain threshold* (i.e. the time point when pain appeared) and *pain tolerance* (when pain became unbearable to the participant, reason why he was requested to remove immediately his hand from the cold water).
Before and after CPT, warm (non-noxious) water immersion was allowed respectively during 2 minutes at 32 °C (means ± SD: 31.82 ± 0.92 °C) for standardization and for the participant's comfort (after CPT, warm immersion elapsed until the pain disappeared). The post-stimulation recovery step included the second warm-water immersion (maximum 2 minutes) and additional 13 minutes of relaxing time; thus lasted 15 minutes, which is considered to be the optimal wash-out period for effects of cold-induced pain (Kennedy et al., 2016). During this period, the participant watched a neutral cartoon in order to standardize the resting condition. As shown in Figure 3, the total duration of the experiment was ~ 40 minutes.
This thesis focused solely on the experimental step elapsing between pain threshold and pain tolerance (i.e. pain perception time, PPT).

Figure 3

Overview of the experimental procedure



Note. The experiment is started with a baseline resting-state EEG measurement in three randomized conditions for three minutes each (seated position eyes open and closed and standing position) followed by cold-induced pain stimulation including two minutes warm water immersion, a maximal cold-water immersion time for 4 minutes and the recovery time (again warm water immersion and cartoon watching), with continuous EEG. The cold-water immersion consisted of two crucial steps, the onset of pain (threshold) and the moment when the pain was unbearable (tolerance). The last experimental step was again a resting-state EEG measurement.

2.3 Data collection

2.3.1 Formal interview, clinical and psychophysical data

All recruited participants underwent a formal interview (in paper form), including general information (date of birth, residence, marital status, profession and sleep, alcohol, nicotine and caffeine habits) and relevant medical history (mainly oriented towards medication and any other information likely to influence our data recording and interpretation). In addition, their sports practice (type of exercise, frequency of training, number of hours, and participation in a competition) were reported for the last 6 months. Finally, when available, objective training data (smartwatches) were collected from the athletes from a typical training week to confirm the self-report. For the purpose of this thesis, these data will not be detailed.

Pain was evaluated using the Numerical Rating Scale ("sensory" NRS, rated from 0 to 10), which was easier to record than the Visual Analog Scale (VAS) in our experimental settings, but has similar validity (Ferreira-Valente et al., 2011). The NRS recorded pain intensity and unpleasantness in order to document respectively the sensory and the affective pain components (Haefeli & Elfering, 2006). Thus, the participant was instructed to report the number corresponding to his pain perception from both points of view (i.e. intensity and unpleasantness) as quickly as possible upon pain threshold (by reporting the appropriate number to the investigator, who wrote it on the participant experimental datasheet) and pain tolerance (by saying the number when he removed his hand from the cold-water tray).

CS components were assessed using the CSI questionnaires (Neblett et al., 2013). In addition, clinical scores related to pain catastrophizing (Pain Catastrophizing Scale (PCS) (Sullivan et al., 2001)) and fear (Fear of Pain Questionnaire-9 (FPQ-9) (McNeil et al., 2018)) were administrated to inform the participant's behavior towards pain (Hermans et al., 2016; Parr et al., 2012). Finally, because mood and sleep disorders can influence pain perception (Klyne et al., 2018), mood states and the existence of insomnia were respectively evaluated via the Hospital Anxiety and Depression Scale (HADs (Zigmond & Snaith, 1983)) and the Insomnia Severity Index (ISI (Morin et al., 2011; Omachi, 2011). However, only pain intensity (NRS) and CS components (CSI) were analyzed for this thesis work.

2.3.2 Electroencephalographic recordings

This study is part of a larger project on EEG GABAergic markers of pain. Without any task additional to the experiment, a continuous high density (64 electrodes) EEG recording occurred all through the CPT. In addition, before and after the CPT, a resting-state EEG recording was performed in 3 randomized positions (seated position eyes open and eyes closed, and standing position with eyes closed) lasting 3 minutes each. After the post-stimulation resting-state recording (i.e. during the additional 13 minutes of recovery time), the EEG session was definitely stopped so that the participant could relax and move around in his seat as he wished. Position randomization was performed to avoid systematic position-related bias.

The EEG recording was performed at a sampling rate of 1,024 Hz using a BIOSEMI Active Two recording system referenced to the built-in CMS-DRL ground in a quiet room with all possibly interfering devices (e.g. smartphones) turned off or left outside the room. During the EEG recording, the participant was requested to remain quiet and to minimize eye blinks and unnecessary body movements. Before the recording phase, each electrode was visually controlled and improved as necessary and possible.

2.4 Data analysis

All collected data were recorded in REDCap after being coded (i.e. each participant was attributed a code not allowing his identification for confidentiality purposes and as requested by the Ethical Commission) and prior to any analysis. The REDCap database was constructed as closely as possible to the original paper format. Upon encoding in RedCap, useful data to this thesis work were exported for statistical analyses. EEG data were cut into two main categories; the resting state and the CPT. During the CPT, warm water immersions were further segregated from the cold pain stimulation. For this thesis, we only considered data related to the cold stimulation step.

2.4.1 EEG data preprocessing

Raw EEG data were preprocessed offline, using in-house Matlab scripts (EEGpalCS program by Dr. De Pretto M) within the EEGlab Toolbox (Delorme et al., 2011). First, they were bandpass filtered by a high pass of 1 Hz and a low pass of 60 Hz using Finite Impulse Response (FIR) filters. Automated artefacts rejection algorithms (EEGlab plugin) were used to withdraw sinusoidal noise stemming like 50 Hz AC powerline fluctuation noise and their harmonics (CleanLine (Mullen, 2012), https://www.nitrc.org/projects/cleanline) or to remove high amplitude eyes movements, muscle artefacts, and electrode drifts (ASR; (Chang et al., 2018; Mullen et al., 2015). In addition, the Flag Bad Channel EEGlab plugin was used to detect flawed electrodes. Bad EEG channels were further excluded by visual inspection using the Cartool software (Brunet et al., 2011) for data visualization (limited to a maximum of 7 rejected electrodes). Then, selected channels were interpolated using spherical splines (Perrin et al., 1989) (median ± IQR = 3.1 ± 24.7 % interpolated electrodes). Obtained preprocessed data were segmented in 1-sec epochs using EEGpalCS. To eliminate remaining artefacts, all epochs containing one channel or more above the threshold, were automatically rejected from the final analysis. In this study, the artefactual signals threshold was set to 100 µV according to our laboratory standard.

2.4.2 Spectral EEG analysis

Finally, retained epochs were recomputed into the frequency domains using the Fast Fourier Transform (FFT) with a frequency resolution of 1 Hz. The frequency bands of interest were Delta (2-4 Hz), Low Beta (13-20 Hz) and High Beta (20-30 Hz), the two latter being considered as GABAergic markers (see the introduction above) and the first as a control band supposedly not related to pain regulation (Pinheiro et al., 2016). The spectral power of each frequency was

divided by the average power of all epochs for that given frequency to remove 1/f noise. Frequency bands were obtained by averaging all frequency bins within the range of interest. Further analysis was conducted on the global power spectrum (GPS, i.e., the frequency power within the band averaged across all electrodes) considered in this study as the quantitative indicator of the power for a given frequency band.

For this thesis work, the GPS within each frequency was computed respectively during the cold stimulation period (i.e. from the beginning of cold stimulation until pain threshold) and the pain perception time (from pain threshold until pain tolerance). In addition, information about pain threshold and pain tolerance time-points were crucial. Because epochs containing movement artefacts due to pain rating at pain threshold and hand removal from the cold water at pain tolerance (see above) were rejected, EEG data retained for these analyses were collected the closest to the exact time points of interest in the cleaned signal.

2.4.3 Statistical Analysis

Statistical analyses were performed using the Jamovi Statistical Software, version 2.2.5 (Sydney, Australia) and all data were tested for normality (Shapiro-Wilk). Comparative, as well as correlation analyses were selected according to the normality of data distribution. Since most of them were not normally distributed, and unless otherwise specified, data are expressed as median (IQR). Graphics were designed using Python (version 3.9.7).

The two groups of participants (i.e. athletes and non-athletes) were compared regarding their CSI and their NRS scores at pain threshold and pain tolerance, as well as β (high and low) GPS at the primary time points of interest for this study (i.e. during the PPT, at pain threshold and pain tolerance. Differences between athletes and non-athletes groups were evaluated using the Student's t-test (normal distribution) and the Mann-Whitney U test (non-normal distribution) when comparing only two variables. The mixed design and repeated non-parametric ANOVAs allowed multiple comparisons, further analyzing the interaction between experimental steps/time points (within groups effect) and between participants groups (between groups effect). The Kruskal-Wallis test was used for multiple comparisons with a simple design. Significance threshold was set at $p < .05$ (95 % confidence interval), while $.05 < p < 0.1$ was assimilated to a significance trend (Ganesh & Cave, 2018; Greenland et al., 2016).

Given the small sample and difficulties defining a power for this sample size in such an exploratory investigation, the effect size was computed to complete data interpretation beyond the significance test (of which interpretation can be subject to some limitations in identifying meaningful observations (Greenland et al., 2016; Serdar et al., 2021). That way, we could also

avoid dismissing interesting trends not reaching significance, but deserving further confirmation or investigations. In summary, this stepwise analysis procedure first evaluated significance (and trends for significance) and thereafter assessed the effect size in order to identify additional trends (define restrictively at moderate or larger effect in order to remain rigorous).

For multiple comparisons by non-parametric ANOVA, the effect size was defined by generalized eta^2 (η^2G) classification as follows: small effect $\eta^2G < 0.3$, moderate effect if $\eta^2G < 0.5$ and large effect if $\eta^2G > 0.5$. Concerning the Kruskal-Wallis test, the effect size was computed using ε^2: small effect if $\varepsilon^2 < 0.04$, moderate effect if $\varepsilon^2 < 0.16$, large effect if $\varepsilon^2 < 0.64$ and very large effect if $\varepsilon^2 < 1.0$. The Tukey post-hoc test corrected the level of significance of multiple comparisons. For the Student's t test, the effect size was computed using the Cohen's d: small effect if d = 0.2, moderate effect if d = 0.5 and large effect if d = 0.8.

Correlations were assessed using the Spearman's Rho correlation coefficient and the effect size estimated as following: small correlation if r_s between -0.5 and 0 or 0 and 0.5, large correlation if r_s between -1.0 and -0.5 or 0.5 and 1.0. In order to avoid the risk of type 1 error (false positive conclusion), the level of statistical significance for correlation coefficient was adjusted by dividing α=.05 by the number of tests performed according to the Bonferroni method (Andrade, 2019). Finally, normalized differences (i.e. differences between athletes and no-athletes reported to athletes values, expressed in %) were used to indicate the magnitude of differences in pain perception delays between the two groups. All significance tests were performed as two-tailed for more robust interpretation, and regardless of the direction in which the difference or the correlation was hypothesized.

2.4.4 Operationalized non-null hypotheses, applied analyses and interpretation plan

Table 1

Summarizes operationalized hypotheses, as well as specific tests used to demonstrate them and the effect size computation method.

N°	Hypotheses	Tests	Effect size
H_1a H_1b	β GPS (cold) ≠ β GPS (pain) β GPS (threshold) ≠ β GPS (tolerance)	Repeated ANOVA	η^2G <0.3 (small); 0.3 < η^2G < 0.5 (medium); η^2G > 0.5 (large)
H_2a	NRS_{s+a} (A) < NRS_{s+a} (NA)	Kruskal-Wallis	ε2 < 0.04 (small); 0.4 < ε2 < 0.16 (moderate); 0.16 < ε2 < 0.64 (large); 0.64 < ε2 < 1.0 (very large)
H_2b	β GPS (A) ≠ β GPS (NA): ○ pain threshold/tolerance ○ pain cold/pain	Repeated ANOVA	η^2G <0.3 (small); 0.3 < η^2G < 0.5 (medium); η^2G > 0.5 (large)
H_3	CSI (A) < CSI (NA)	Students' t	d = 0.2 (small); d = 0.5 (moderate); d = 0.8 (large)
H_4a H_4b	CSI >* correlated with NRS_{s+a} and <* PPT CSI & NRS_{s+a} <* and PPT >* correlated with β GPS	Spearmann Rho	r_s < 0.5 or -0.5 < r_s < 0 (small) -1.0 < r_s < -0.5 or 0.5 < r_s < 1.0 (large)

Note. A= athletes; NA = non-athletes. *Negative or positive correlation respectively labeled as < or >. NRS_{s+a}= sensory and affective NRS

3 Results

3.1 General data and pain indicators

In total, 27 athletes and 27 non-athletes were screened for the study. Out of them, 26 athletes and 24 non-athletes were finally included (participant exclusion was due to insufficient EEG data quality). Therefore, unless otherwise specified, analyses were performed in selected athletes (n=26) and/or non-athletes (n=24) as appropriate. Their demographic and general characteristics are summarized in Table 2. Data are shown as median (IQR), unless otherwise specified.

Non-athletes were overall significantly older (despite adjustment attempts) than athletes. In accordance with inclusion criteria, athletes had indeed more than 7 hours of training per week and non-athletes less than 2.5 hours weekly training. Non-athletes showed higher weight and as expected, higher BMI than athletes.

Table 2

Participants' characteristics

	Athletes	Non-athletes	Statistics
n	26	27	
Age [years]*	35 (8.02)	42.1 (10.3)	t(48)=-2.73 p=.009
Exercise/week [hours]	10 (4.5)	1.5 (2.0)	U=0.0 p<.001
Height [cm]*	180 (5.87)	179 (5.58)	t(48)=0.673 p=.504
Weight [kg]	72 (10.5)	81 (10.3)	U=123 p<.001
BMI [kg/m^2]	22.9 (3.13)	26.1 (2.96)	U=90 p<.001

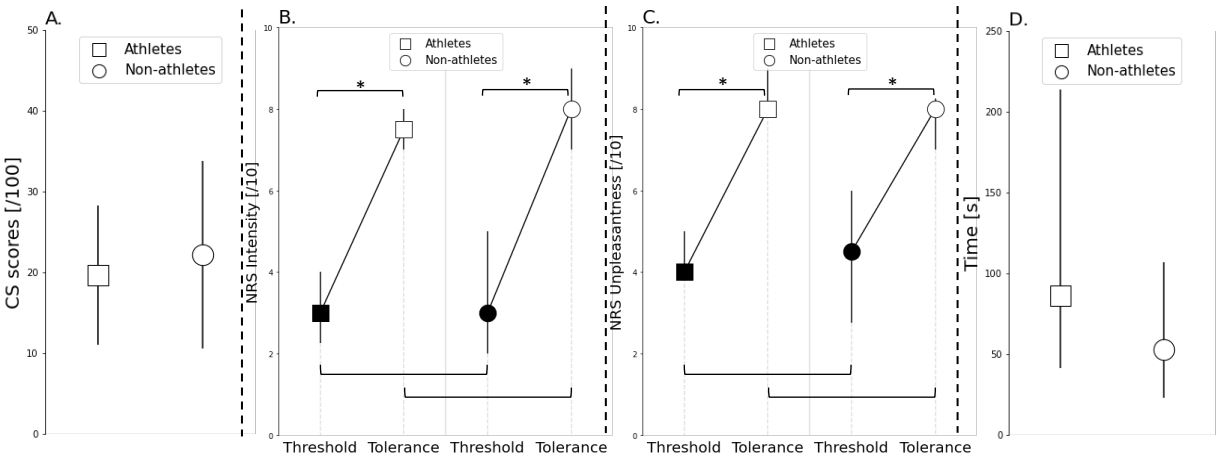
*Note. *:* Age and height are shown as mean (SD)

Clinical and psychophysical pain indicators (Figure 4) showed trends to be lower in athletes than in non-athletes (differences did not reach significance): CSI (p=.389 d=-0.246), sensory NRS at pain tolerance (p=.280 $\varepsilon^2 = 0.023$) and affective NRS at pain threshold (p=.890 ε^2=3.9e-4). In contrast, the sensory NRS at pain threshold (NRS = 3.0/10 p=.835 ε^2=8.82e-4), and the affective NRS at pain tolerance (NRS = 8.0/10 p=.128 ε^2=0.047) were similar between the two groups. As expected, both NRS scores (i.e. sensory and affective) were higher at pain tolerance than at pain threshold both in athletes (p<.001 and p<.001) and in non-athletes (p<.001 and p<.001).

The immersion time while perceiving pain (PPT) was considered to be similar (p=.123) in athletes and in non-athletes although longer (38.4 %) in the first group. In addition, pain perception started at the same time in athletes and in non-athletes (2.6% p=.907). It should be noted that 50 % of the athletes and 20 % of the non-athletes reached the maximal immersion time of 4 minutes.

Figure 4

Clinical and psychophysical pain indicators



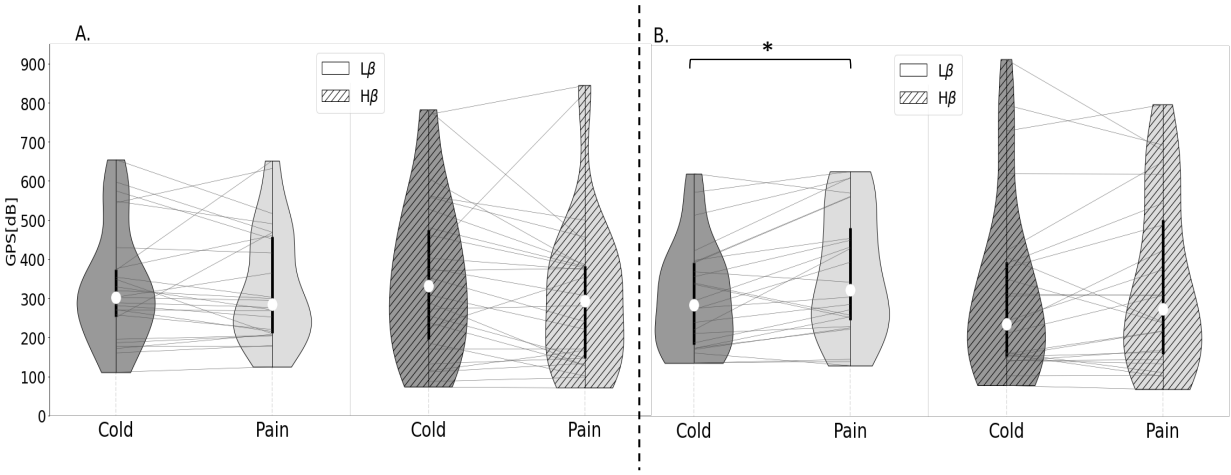
Note. Clinical and psychophysical pain indicators scores in athletes (squares) and non-athletes (circles). **(A)** On the y-axis, the central sensitization (CS) index questionnaire scores [/100] are represented. A = athletes, NA = non-athletes. No significant CS scores difference was observed between A and NA (mean 19.6 (8.83) vs 22.2 (11.8), Student t-test: t(48)=-0.868 p=0.389). **(B) (C)** The y-axis shows the numeric rating scale (NRS) scores in the sensory (intensity) (B) and affective (unpleasantness) (C) dimensions of pain at the threshold (black square and circle) and tolerance (white square and circle) time points represented on the x-axis. No significant differences were showed between A and NA in both dimensions at the pain threshold (intensity 3.0 (1.75) vs 3.0 (2.0) p.835; unpleasantness 4.0 (1.0) vs 4.5 (3.25) p=.890) and at the pain tolerance (intensity 7.5 (1.0) vs 8.0 (2.0) p=.280; unpleasantness 8.0 (1.0) vs 8.0 (1.25) p=.128). Significant differences in both populations and both dimensions between the pain threshold and tolerance were demonstrated (intensity: A<.001 NA<.001; unpleasantness: A<.001 NA<.001). Kruskal-Wallis results. **(D)** The immersion time in seconds achieved perceiving pain is on the y-axis. No significant difference was observed between A and NA (86.2 (172) vs (53.1 (83.9); Mann-Whitney U=232 p=.123). *= p<0.05 significant.

3.2 GPS in Lβ and Hβ sub-bands and δ band and correlation with pain indicators

When comparing Lβ and Hβ frequency sub-bands powers computed during cold and pain perceptions (figure 5) in different groups, there was a significant interaction ($F_{1,48}$=5.55 p=.023 η^2G=0.011) in the Lβ GPS sub-band, with a significant difference for the factor steps (within groups) ($F_{1,48}$ = 4.9 p = .032 η2G = 0.009) but not for the factor groups (between groups) ($F_{1,48}$=0.017 p=.895 η^2G=0.0). The Tukey post hoc shows a significant effect for the Lβ only in non-athletes (p=.014) for the factor steps.

Figure 5

GPS differences between the two main experimental steps



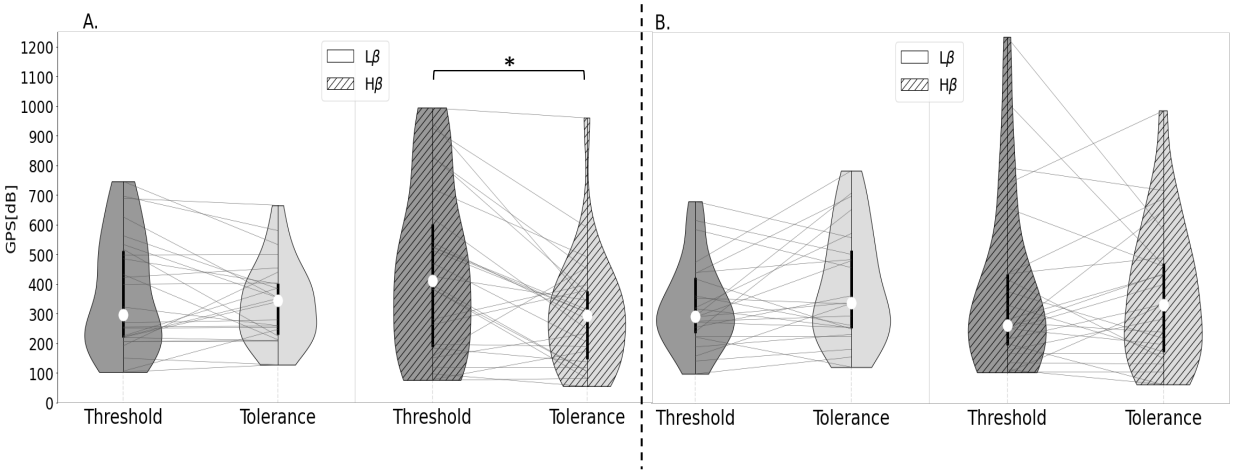
Note. The global power spectrum (GPS [dB]) on the y-axis in Lβ (13-20Hz) (light and dark grey) and Hβ (20-30Hz) (hatched light and dark grey) frequency sub-bands in the two main experimental steps (cold/pain), represented on the x-axis. The violin plots show the median (white circle) ± IQR (thick black vertical line), the GPS correspondence (thin light grey line) for each participant between cold and pain steps and the distribution for both populations. Pain step is related to PPT. Athletes **(A)** displayed higher Lβ and Hβ GPS in the cold compared to the pain step (Lβ 302.18 (122.2) to 285.36 (247.5) [dB], p=1.0 / Hβ 331 (280.5) to 294.03 (235.2) [dB], p=.318), while non-athletes **(B)** showed lower Lβ and Hβ GPS in the cold than in the pain steps (Lβ: 286.9 (208.6) to 325.4 (235.1) [dB], p=.014 / Hβ: 237.1 (241.8) to 276.3 (344.5), p=.903). *= p<0.05 significant. Results of the repeated measures ANOVA followed by the Post hoc Tukey.

Concerning the Hβ sub-band, there was neither a significant interaction ($F_{1,48}$=2.871 p=.097 η^2G=0.005) nor a within ($F_{1,48}$=0.502 p=.482 η^2G=0.001) or a between groups ($F_{1,48}$=3.39e-4 p=.985 η^2G=0.0) effect.

In the δ frequency GPS, only a within groups effect was seen ($F_{1,48}$=5.42 p=.024 η^2G=0.017), but no interaction ($F_{1,48}$=2.0 p=.164 η^2G=0.007) or a between groups effect ($F_{1,48}$=0.141 p=.709 η^2G=0.002).

Figure 6

GPS differences between the two critical experimental time points



Note. The global power spectrum (GPS [dB]) on the y-axis in Lβ (light and dark grey) and Hβ (hatched light and dark grey) frequency sub-bands at the two critical experimental time points (threshold/tolerance), represented on the x-axis. The violin plots show the median (white circle) ± IQR (thick black vertical line), the GPS correspondence (thin light grey line) for each participant between threshold and tolerance time points and the distribution for both populations. Athletes **(A)** displayed lower Lβ GPS at pain threshold than at pain tolerance (296 (293) to 346 (172) [dB], p=.741), while Hβ GPS was higher (411 (414) to 293 (231) [dB], p=.008). Non-athletes **(B)** demonstrated lower Lβ (293 (188) to 339 (263), p=.153) and Hβ GPS (265 (241) to 334 (300), p=.985) at pain threshold compared to pain tolerance. *= p<0.05 significant. Results of the repeated measures ANOVA followed by the Post hoc Tukey.

Comparison of Lβ GPS computed at pain threshold and at pain tolerance time points between athletes and non-athletes (Figure 6), showed a significant interaction (F1,48=5.073 p=.029 η2G=0.096), even if the time point factor (within groups effect, F1,48=0.713 p=.403

η2G=0.015) and the groups factor (between groups effect, F1,48=0.074 p=.786 η2G=0.002) were not significant. Regarding Hβ GPS, there was a significant interaction ($F_{1,48}$=4.36 p=.042 η^2G=0.083), with significant time points factor (within groups effect, $F_{1,48}$=6.74 p=.012 η^2G=0.123), but no groups factor (between groups effect, $F_{1,48}$=0.002 p=.961 η^2G=0.0). The Tukey post hoc shows a significant effect for the Hβ (p=.008) only in athletes for the time point factor.

There was neither interaction in the δ GPS ($F_{1,48}$=1.051 p=.031 η^2G=0.006) when comparing athletes and non-athletes at threshold and tolerance time points, nor significant time points ($F_{1,48}$=0.999 p=.322 η^2G=0.006) or groups ($F_{1,48}$=0.098 p=.755 η^2G=0.001) factors.

Table 3

Results consistency with our hypotheses

N°	Hypotheses	Consistency
H_1a	β GPS (cold) ≠ β GPS (pain)	V
H_1b	β GPS (threshold) ≠ β GPS (tolerance)	V
H_2a	NRS_{s+a}(A) < NRS_{s+a} (NA)	V
H_2b	β GPS (A) ≠ β GPS (NA):	
	○ pain threshold/tolerance	V
	○ pain cold/pain	V
H_3	CSI (A) < CSI (NA)	V
H_4a	CSI >* correlated with NRS_{s+a} and <* PPT	V**
H_4b	CSI & NRS_{s+a} < and PPT > correlated with β GPS	V**
Additional H	PPT <* NRS_{s+a}	V**

Note. A= athletes; NA = non-athletes. * Negative or positive correlation respectively labeled as < or >. NRS_{s+a} = sensory and affective NRS. Green V = significant results consistent with our hypothesis, orange V = non-significant results, but trends compatible with our hypothesis, orange V** = compatible trends observed only in one group, red V = non-significant results, small effect size.

The Lβ GPS during pain was significantly negatively correlated with CS score (r_s = -0.438 p=.032) in non-athletes, similar as Hβ and PPT (r_s = -0.434 p=.028) in athletes. No correlation was found with the EEG marker at pain threshold. In athletes, Lβ and Hβ computed at pain tolerance correlated negatively with the PPT (respectively r_s = -0.526 p=.006, r_s = -0.436 p=.027), but not in non-athletes.

Finally, in non-athletes, the CS score correlated negatively with PPT (r_s = -0.492 p=.015), and the threshold time (cold immersion to pain onset) positively correlated with the affective NRS score reported at pain threshold (r_s = 0.486 p=.016). Conversely, in athletes, the PPT correlated significantly negatively with the sensory NRS scores reported at pain tolerance (r_s = -0.483 p=.012).

In order to further examine the relationship between sensitization components, pain perception, and EEG markers, the cohort was divided into two groups according to CSI scores cutoffs (subclinical [0 to 29], (n=41) and mild/moderate [30 to 49], n=9), regardless of the training profile, with the assumption that CS would be negatively associated with resistance to pain and to possibly to EEG markers. A high negative correlation was found in the mild/moderate group (n=9) between the CS scores and the PPT (r_s =-0.792 p=0.011), but not in the subclinical group. No correlation was observed with the EEG markers in both groups.

4 Discussion

The purpose of this experimental case-control study was to comparatively assess responses to cold-induced pain stimulation and related EEG β oscillations, as well as CS clinical features in healthy volunteers with two different physical training profiles. The hypothesis was that a long-lasting and intensive physical exercise regime (at least 7 hours/week for 6 months) would positively impact pain perception and CS components due to central nervous system adaptations. Additionally, we expected GABA-dependent cortical inhibition (quantitatively measured through EEG β GPS), to change, in association with decreased pain perception and CS features in athletes.

4.1 Pain responses in athletes vs non-athletes

There was no statistical difference in pain appearance time and in PPT between athletes and non-athletes, although it is widely demonstrated in the literature that athletes have a higher pain tolerance than those who do not exercise (Assa et al., 2019; Geisler et al., 2021; Pettersen et al., 2020; Tesarz et al., 2012). Accordingly, we would expect the PPT to be longer in athletes than in non-athletes. This non-significant observation in our study could be explained by the fact that non-negligeable number of participants reached the maximum cold immersion time, which most probably induced an artificial ceiling effect vanishing potential differences, especially if we consider that the proportion of athletes reaching the maximal immersion time was more than the double of non-athletes.

There was a trend for lower affective pain rating at pain threshold in athletes than in non-athletes. This finding, although not significant, is consistent with the current literature. Indeed, the feeling of unpleasantness belongs to the initial feeling of the noxious sensation (Kong et al., 2006; Mercer Lindsay et al., 2021). Furthermore, according to Talbot et al. (2019), people who associate pain with a more significant threat, rate higher the feeling of unpleasantness related to pain. In contrast, for many athletes, due to regular intensive training, pain is a daily experience essential to endure for success. Thus, athletes develop various semantic constructs based on multiple pain experiences and finally view pain as an ally they can successfully deal with (Geisler et al., 2021; Hyland, 1979). Therefore, it is not surprising that their affective pain sensitivity is lower than in non-athletes. Intriguingly, the affective pain score at pain threshold positively correlated with the threshold time in non-athletes. It might mean that non-athletes in whom pain appears later tend to perceive higher unpleasantness level.

The sensory NRS tended to be lower in athletes at pain tolerance. During longer-lasting pain, the pain encoding shifts from sensory brain areas to emotional-motivational areas (Ploner et al., 2017). This modulation reduces pain's emotional valence (Salomons et al., 2015). Accordingly, athletes will tend to experience pain more sensorial than affective and, as said above, cope better with it than non-athletes. The negative correlation observed between the sensory pain score at pain tolerance and the PPT in athletes reinforces this statement, suggesting that resistance to pain (of which PPT represents a good estimate) constitutes a strategy to deal with the sensory perception of pain.

In summary, although there is a trend for athletes to be less sensitive to cold-induced pain than non-athletes, the threshold time point appears to be crucial regarding the affective valence given to pain by non-athletes, while intensive exercise would have shifted pain perception focus towards the sensory pain dimension in athletes, tailoring their limits (tolerance) and ability to deal with (or resist to) pain. *These observations support the hypothesis stating that a long-lasting intensive physical training regime reduces pain sensitivity, although not significant. They therefore need confirmation in larger settings*.

The CS score tended to be lower in athletes than in non-athletes. However, it should be noted that only 2 athletes reached a clinically meaningful level of the CS score, suggesting that there was a floor effect in athletes that could have affected the comparison with non-athletes. Nevertheless, when segregating participants with clinically significant CS traits from those at sub-clinical level (Neblett et al., 2017) regardless of their training regime, a negative correlation appeared between the CS score and the PPT, suggesting that CS components are associated with lower resistance to pain. This association was most probably due to the non-athlete group, which predominantly displayed clinically significant CS scores and in which a negative correlation between the CS score and PPT was also shown, suggesting that CS traits reduces resistance to pain in non-trained individuals. *Thus, the hypothesis associating lower CS features to reduced pain sensitivity is not confirmed, rather association to higher resistance to pain in the non-athletes group.*

Overall, CS elements appear to play a role in resistance to pain in non-athletes, while the link is lost in the athlete group, *supporting the assumption that intensive physical exercise minimizes CS features, but would need further investigation to reach significance*.

4.2 EEG marker changes

When analyzing EEG markers during cold and pain perception in athletes versus non-athletes, an interaction was found, but only the factor step (within) finally appeared to be significant,

suggesting the difference was mostly due to the difference between cold and pain perception steps, but not between the two groups. In addition, Lβ GPS increased in non-athletes between non-noxious (cold) and noxious (pain) steps and further with pain increase (from pain threshold to pain tolerance). This linear increase probably indicates a GABA-dependent inhibition increase to counteract pain and would reflect the major role played by the GABAergic neurotransmission in nociception and pain regulation (Barr et al., 2013; Enna & McCarson, 2006; Yam et al., 2018), more remarkably in non-athletes. In contrast, a decrease of GABAergic markers was observed in CP patients compared to healthy controls (Barr et al., 2013; Baumgarten et al., 2016; Teixeira et al., 2021), implying that CP patients had lost the ability to counteract pain. Such assumptions would only be confirmed by submitting CP patients to cold-induced pain. The fact that Lβ GPS during pain perception negatively correlated with CS components in non-athletes supports the hypothesis that the GABAergic system is involved in counteracting CS, *partially confirming the link between low CS features and high brain GABAergic input only in non-athletes.*

Although the pain threshold time appeared as a key time in non-athletes, no correlation was found between Lβ GPS at threshold and any of the clinical variables. Additionally, and despite the interaction found when comparing the threshold and tolerance steps in the two groups, no within and between group effect appeared to be significant. This observation seems in contradiction with the linear increase of the GABAergic input stated earlier but could be due to the way Lβ GPS was computed at pain threshold (leaving out data closest to the time point of interest).

The Hβ GPS, while showing no interaction nor within and between group effect regarding cold and pain perception steps comparing athletes to non-athletes, showed a significant interaction when comparing pain threshold to pain tolerance between the two groups, with however a more prominent experimental step factor (i.e. threshold versus tolerance). Furthermore, in athletes, the Hβ GPS (and to a lower extent the Lβ GPS) at pain tolerance was negatively correlated with PPT, emphasizing once more on the crucial role of pain tolerance and, also the role of GABA in resistance to pain, in athletes. However, the negative correlation would suggest a decrease in the GABAergic input, rather than the increase noticed in non-athletes.

In summary, our results suggest that Lβ increase in response to pain stimulation, negatively associated to CS, and would participate to the non-athlete strategy to counteract pain (especially at pain threshold). These findings are in accordance with the study by Bismuth et al. (2020) in which neuropathic pain could be relieved by increasing brain Lβ over Hβ activity.

In contrast, Hβ to be more involved in athletes, decreasing with higher resistance to pain, especially at pain tolerance. According to current literature, excess of fast beta waves (which corresponded to Hβ frequency in our study) is associated with stress, anxiety, muscle tension and overthinking as well as in adults with Attentional-Deficit/Hyperactivity Disorder in whom the emotional control impairment is lost (Bismuth et al., 2020; Engel & Fries, 2010; H. Li et al., 2019; Ribas et al., 2018; Wang et al., 2019). Thus, Hβ reduction in athletes associated with increased pain could be related to a better emotional control and lower anxiety level when facing pain, yielding a higher pain resistance. Another possible explanation could be that athletes display decreased GABA-dependent inhibition as an adaptation to their long-lasting and intensive physical training regime (El-Sayes et al., 2020; Hendy et al., 2022; Monda et al., 2017; Moscatelli et al., 2021; Nicolini et al., 2021). The primary motor cortex (M1) higher excitability also resulting from intensive training would therefore exert a higher order "descending" inhibitory effect on the lower pain regulatory pathways via activation of limbic, cortical and subcortical regions associated with anti-nociception (Granovsky et al., 2019; Pagano et al., 2012). The fact that M1 is a privileged target for non-invasive brain stimulation as an analgesic therapy could be an additional indication supporting this hypothesis. This could be a kind of exercise-induced reinforcement of descending pathways (subsequent to observed inhibition?). An alternative hypothesis of this adaptation would be that, similar to physiological modifications athletes witness consecutively to their physical training, such as low heart rate (Bjørnstad et al., 1993), they could reduce their brain inhibitory input in order to be able to reach higher magnitudes of GABAergic increase during intensive exercise (possibly accompanied by pain). If this is true, then we should be able to observe a higher increase of Hβ GPS, which was not the case in our study measuring cold-induced pain out of exercise context.

Thus, there appears to be EEG GABAergic markers modifications, although different in each participants' group, at different experimental time point and related to different clinical variables, all nevertheless confirming our hypothesis that long-lasting intensive physical training regime modifies GABAergic EEG markers.

It should be noted that no meaningful modification was observed in the δ frequency band, except an increase from cold to pain perception, most probably witnessing overall brain modifications following this change of perception. However, absence of other changes and lack of correlation with any of the clinical variables support the specificity our results to EEG GABAergic markers.

5 Conclusion, study limitations and future directions

In this study, we investigated differences between highly trained athletes and non-athletes regarding their response to cold-induced pain as well as their CS features and EEG GABAergic markers. Beyond strict significance (which should not solely be considered to point meaningful results in exploratory studies), we could confirm interesting trends coherent with our hypotheses. Namely, it appears from our results that athletes develop different strategies to cope with pain and show different modifications in GABAergic markers compared to non-athletes. Precisely, observed adaptations in athletes, not only occur at different pain response time (pain tolerance), but relate to difference clinical variables (sensory pain, resistance to pain) and differently affect (decrease) specific EEG GABAergic markers (Hβ power). In non-athletes, modifications occur at pain threshold, are associated to the affective pain and CS features, and are seen as an increase in Lβ power.

Despite rigorous and standardized experimental procedure and clear selection and exclusion criteria, and although these interesting preliminary results gave more insight into the clinical and electrophysiological effect of exercise, our study bears some limitations. The study sample was small, the power could not be appropriately computed, and correction were not made for multiple testing. Age difference was not fully controlled for, which could have at least partially accounted for the observed differences between the two compared groups. This study analyzed the effect of a long-lasting physical training regime out of the exercise context. In addition, it was sometimes difficult for participants to assess pain and differentiate between the sensory and the affective pain dimensions. Setting the maximal immersion time at 4 minutes to limit the risk of tissue injury may have biased our results. Finally, lack of comparison with CP patients limits the interpretation of our data in a more therapeutic perspective. Although needing to be confirmed and specified, these preliminary results open the possibility for better integration of exercise among analgesic treatments.

In the future, it would be interesting to perform the same study during or just after intense training in athletes and in non-athletes. In addition, CP patients' response patterns in the same setting would further enlighten GABA-dependent modifications occurring in CP situation and how they impact patients' pain response in relation with CS.

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Appendix

Case report form (CRF)

INDIVIDUAL DATA SHEET PARTICIPANT

A. GENERAL AND MEDICAL DATA

I. GENERAL DATA

Code: _____ Name/Surname: _____/_____

Birthdate: ___/___/____ Sex: F / M

Marital Status: _____Profession: _____ Ed. level:_____

Address (n°/street): ___/_____Zip/Town: _____/_____

Height: _____cm; Weight: _____kg; BMI: _____kg/m^2

Smoking: No / Yes (_____)

Alcohol: No / Yes (_____)

Caffeine: No / Yes (_____)

Drugs: No / Yes (_____)

Medication: No / Yes (_____)

II. EVALUATION DATES AND GENERAL REMARKS/INFORMATION:

Oral interview : ____/____/____

Formal interview : ____/____/_____

Cold pain stimulation: ____/____/_____

III. EXISTENCE OF PAIN

The day of cold pain stimulation: Yes / No

IV. CURRENT ANALGESIC OR OTHER TREATMENTS

V. OTHER RELEVANT NEUROLOGICAL, PSYCHIATRIC OR OTHER DISEASES (not included among exclusion criteria)

B. SLEEP INFORMATION AND PAIN SCALES

I. COMPLEMENTARY INFORMATION ABOUT SLEEP

Sleep diary

Usual time to bed: _____; wakeup time:_____ ; sleep duration: _____hours

Before cold pain stimulation: time to bed: _____; wakeup time:_____; sleep duration: _____hours

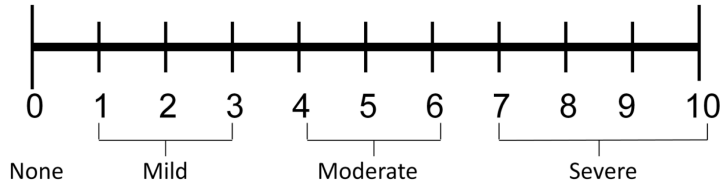
Sleep medication:

No / Yes

Specify if Yes:

II. NUMERICAL RATING SCALE FOR PAIN INTENSITY:

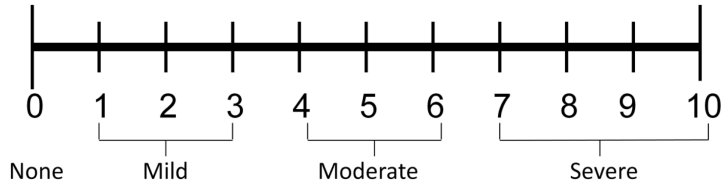
The scale will be presented in analog form. When the participant is submitted to the scale, descriptors will be hidden.



Ref: McCaffery, M., Beebe, A., et al. (1989). Pain: Clinical manual for nursing practice, Mosby St. Louis, MO.

III. EQUIVALENT OF NUMERICAL RATING SCALE FOR UNPLEASANTNESS:

The scale will be presented in analog form. When the participant is submitted to the scale, descriptors will be hidden.



Ref: McCaffery, M., Beebe, A., et al. (1989). Pain: Clinical manual for nursing practice, Mosby St. Louis, MO.

C. SPORTS TRAINING INFORMATION

Type of exercise: _____

Number of trainings/weeks: _____

Number of hours trainings/weeks: _____

Participation in competition for the last 6 months minimum: No / Yes

If yes, which and when? (_____)

Smartwatches data: No / Yes

D. PAIN, SLEEP, MOOD QUESTIONNAIRES AND CENTRAL SENSITIZATION INVENTORY

The questionnaires will be presented separately and encoding in the REDcap system. The scores are then automatically calculated.

Questionnaires	Abbreviations	Score (computed by Redcap)	Assessment date
Central sensitization score	CSI		
Mood status	HAD		
Sleep status	ISI		
Fear of pain	FPQ-9		
Catastrophizing	PCS		

E. DATA FROM THE COLD-INDUCED PAIN EXPERIMENT

I. BASELINE CONDITIONS

The baseline conditions will be recorded at rest in different positions, which will be randomized.

	Sitting position		Standing position
	Eyes open	Eyes closed	Eyes closed
Pre-experiment (1-2-3)			
Post-experiment (1-2-3)	Same order as pre-experiment		

II. EXPERIMENT

a) Pressure pain threshold (PPT)

Until the participant experienced the stimulus as annoying (gênant) and uncomfortable.

	Threshold		Threshold			
	First measure		Second measure		Average	
Time	**[N]**	**NRS**	**[N]**	**NRS**	**[N]**	**NRS**
1						
2						

b) Cold pain stimulation (CPT)

Water temperature

- Warm: .....
- Cold:.....

	Warm water 2 min	**Cold pain stimulation** Max. 4 min		**Wash-out period** Max. 2 min	
		Threshold	**Tolerance**	**Painful**	**Disappearance of pain**
Start time of immersion					
Time in [s]					
NRS intensity					
NRS unpleasantness					

c) EEG recording

Head circumference (cm): …….

Cap size: …….

Electrodes sets: ……

Central sensitization index

Inventaire de sensibilisation Centrale.

INVENTAIRE DE SENSIBILISATION CENTRALE: PARTIE A

Veuillez indiquer pour chaque situation la proposition la plus adaptée	Jamais	Rarement	Parfois	Souvent	Toujours
1. J'ai la sensation d'un sommeil non récupérateur quand je me réveille le matin	☐	☐	☐	☐	☐
2. Je ressens des raideurs et des douleurs musculaires	☐	☐	☐	☐	☐
3. Je fais des crises d'angoisse	☐	☐	☐	☐	☐
4. Je grince ou serre les dents	☐	☐	☐	☐	☐
5. J'ai des problèmes de diarrhée et/ou de constipation	☐	☐	☐	☐	☐
6. J'ai besoin d'aide pour effectuer mes activités quotidiennes	☐	☐	☐	☐	☐
7. Je suis sensible aux fortes lumières	☐	☐	☐	☐	☐
8. Je me fatigue très facilement lorsque je suis actif physiquement	☐	☐	☐	☐	☐
9. Je ressens des douleurs partout dans le corps	☐	☐	☐	☐	☐
10. J'ai des maux de tête	☐	☐	☐	☐	☐
11. Je ressens une gêne à la vessie et/ou des brûlures lorsque j'urine	☐	☐	☐	☐	☐
12. Je ne dors pas bien	☐	☐	☐	☐	☐
13. J'ai des difficultés de concentration	☐	☐	☐	☐	☐
14. J'ai des problèmes de peau tels que sécheresse, démangeaisons ou éruption cutanées	☐	☐	☐	☐	☐
15. Le stress aggrave mes symptômes physiques	☐	☐	☐	☐	☐
16. Je me sens triste ou déprimé	☐	☐	☐	☐	☐
17. J'ai peu d'énergie	☐	☐	☐	☐	☐
18. Je ressens des tensions musculaires dans la nuque et dans les épaules	☐	☐	☐	☐	☐
19. J'ai mal à la mâchoire	☐	☐	☐	☐	☐
20. Certaines odeurs, comme des parfums, me donnent des nausées et des étourdissements	☐	☐	☐	☐	☐
21. Je dois uriner fréquemment	☐	☐	☐	☐	☐
22. J'ai la sensation désagréable des jambes sans repos lorsque j'essaye de dormir le soir	☐	☐	☐	☐	☐
23. J'ai des difficultés à me souvenir de certaines choses	☐	☐	☐	☐	☐
24. J'ai eu des traumatismes au cours de mon enfance	☐	☐	☐	☐	☐
25. Je ressens des douleurs dans la région du bassin	☐	☐	☐	☐	☐

INVENTAIRE DES SYMPTOMES ASSOCIES A LA SENSIBILISATION CENTRALE: PARTIE B

Un médecin vous a-t-il diagnostiqué l'un des troubles suivants? *Pour chaque diagnostic, veuillez cocher **Oui** ou **Non** dans la colonne de droite et indiquer l'année du diagnostic*	OUI	NON	Année du diagnostic
1. Syndrome des jambes sans repos	☐	☐	
2. Syndrome de fatigue chronique	☐	☐	
3. Fibromyalgie	☐	☐	
4. Trouble de l'articulation temporo-mandibulaire (ATM)	☐	☐	
5. Migraines ou céphalées de tension	☐	☐	
6. Syndrome du côlon irritable	☐	☐	
7. Hypersensibilité chimique multiple	☐	☐	
8. Lésion de la nuque (y-compris le syndrome du coup du lapin, ou « whiplash syndrome »)	☐	☐	
9. Troubles anxieux ou attaques de panique	☐	☐	
10. Dépression	☐	☐	

(Pitance, L., Piraux, E., Lannoy, B., Meuus, M., Berquin, A., Eeckhout, C., ... & Roussel, N. (2016). Cross cultural adaptation, reliability and validity of the French version of the central sensitization inventory. *Manual therapy*, *25*, 83.)

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