UCLouvain

Faculté de pharmacie
et des sciences biomédicales

Investigating the nociceptive neural responses under focused hypnotic analgesia: local and remote effects

Auteure : Clara Bourgy
Promoteur : Valéry Legrain
Lecteurs : André Mouraux et Marcus Missal
Année académique 2023-2024
Master en sciences biomédicales, à finalité approfondie

Remerciements

Ce mémoire de Master est le fruit de 5 ans d'études en sciences biomédicales. Durant cette année de stage, je me suis enrichie à la fois d'un point de vue théorique mais également personnel. C'est pourquoi je tiens à remercier les personnes qui ont contribué de près ou de loin au bon déroulement de mon stage et à la rédaction de mon mémoire.

Tout d'abord, je tiens à remercier Valéry Legrain, mon promoteur et maître de stage, de m'avoir accompagné durant cette année de stage et de m'avoir permis de m'ouvrir au monde de la recherche. Je voudrais également le remercier pour le temps qu'il a consacré à la relecture de mon mémoire et pour ses conseils.
Merci également à Amélie Van Caekenberghe, d'avoir été présente pour moi tout au long de mon stage et pour avoir répondu à mes questions tout en me permettant de développer ma réflexion scientifique.
Merci à Gabrielle, Marine et Cécile, pour m'avoir accompagné et aidé durant ce stage.
Merci à Sorenza pour nous avoir aider et d'être venue en tant que cobaye pendant ces longues sessions de testing.
Merci à l'équipe NOCIONS d'avoir créé une ambiance de stage agréable et de m'avoir aidé à préparer mes défenses orales.
Merci à André Mouraux et Marcus Missal, mes lecteurs, pour le temps qu'ils allloueront à la lecture de mon mémoire.
Merci à Tiffany de m'avoir soutenu tout au long de ces 5 années d'études tant dans les bons moments que dans les périodes de stresse et de doute.
Merci à Rémy d'avoir cru en moi et de m'avoir soutenu moralement pendant cette année de stage.
Merci à mes parents de tout avoir mis en œuvre pour que je puisse réaliser tous mes rêves.

Résumé

La douleur est un problème de santé majeur et une meilleure compréhension des mécanismes physiologiques qui la sous-tendent et des facteurs psychologiques et cognitifs qui peuvent la moduler est nécessaire pour aider à diagnostiquer celle-ci et la traiter. Il a été prouvé qu'une analgésie hypnotique focalisée utilisant la suggestion d'un gant de protection sur un bras peut réduire la perception de la douleur et ses réponses physiologiques. Néanmoins, les expériences utilisant l'analgésie hypnotique focalisée n'ont pas encore étudié l'effet sélectif potentiel de cette technique sur le traitement de la douleur en comparant la réponse cérébrale nociceptive provoquée par des stimuli nociceptifs appliqués sur les deux bras, le bras protégé par la suggestion, le bras local, et l'autre bras considéré comme contrôle, le bras périphérique. Par conséquent, le but de cette étude est d'étudier l'effet de l'analgésie hypnotique focalisée sur la perception de la douleur et les ERPs nociceptifs par stimulation thermique de contact. Pour cela, deux expériences ont été menées. Lors de la première, 40 sujets sains ont participé. Cela consistait en la récolte des évaluations de douleur et de désagrément après chaque stimulation nociceptive délivrée soit sur l'avant-bras protégé, soit sur l'avant-bras non protégé. Pour la deuxième, des ERPs ont été enregistrés chez 15 volontaires sains en réponse à des stimuli nociceptifs délivrés soit sur l'avant-bras protégé soit sur l'avant-bras non protégé. Pour la première expérience, les ANOVAs a mesures répétées effectuées sur les évaluations de douleurs ont montré une diminution significative des évaluations pendant la suggestion comparée à avant celle-ci. De plus, il y a aussi une différence significative entre les deux bras, avec des évaluations plus basses lorsque les stimulations sont reçues sur le bras soumis à la suggestion en comparaison au bras non protégé, ce qui confirme l'efficacité du gant sur le bras où il a été construit. Pour la deuxième, il n'y a pas de résultats significatifs que ce soit au niveau de difference d'amplitudes ou de latences des composantes ERPs lorsque des stimuli nociceptifs sont appliqués sur les deux bras et que l'hypnotisation est focalisée sur un membre par la méthode du gant de protection, principalement parce que l'expérience est encore en cours et d'autres sujets doivent être testés.

Abstract

Pain is a major healthcare issue and a better understanding of the physiological mechanisms underlying it and the psychological and cognitive factors that can modulate it is necessary to help diagnose and treat pain. There is evidence that focused hypnotic analgesia using the suggestion of a protective glove on one arm can reduce the perception of pain and its physiological responses. Nevertheless, experiences using focused hypnotic analgesia have not yet investigated the potential selective effect of this technique on pain processing by comparing the nociceptive brain response elicited by nociceptive stimuli applied on the two arms, the arm concerned by the focused hypnotic analgesia, the local arm, and the other arm considered as the control arm, the remote arm. Therefore, the aim of this study is to investigate the effect of focused hypnotic analgesia on pain perception and nociceptive ERPs using contact heat stimulation. For this, two experiments were conducted. In the first one, 40 healthy subjects participated. This consisted of collecting pain and unpleasantness evaluations after each nociceptive stimulation delivered either to the protected forearm or to the unprotected forearm. For the second one, ERPs were recorded for 15 healthy volunteers in response to nociceptive stimuli delivered either to the protected forearm or to the unprotected forearm. For the first experiment, repeated measures ANOVAs performed on the pain ratings showed a significant decrease in the ratings during the suggestion as compared to before. There is also a significant difference between the two arms, with lower ratings when the stimulations were applied on the suggested arm compared to the unprotected arm, confirming that the protective glove was efficient on the arm on which it was built. For the second one, there are no significant results, either for differences in amplitudes or latencies of the ERPs components when nociceptive stimuli have been applied on both arms and hypnotization was focused on one limb by the method of the protective glove, mainly because the experiment is still in progress and that more subjects have to be tested.

Table of contents

List of abbreviations

CNS	Central nervous system
fMRI	functional Magnetic resonance Imaging
EEG	Electroencephalography
ERP	Event-related potential
LEP	Laser-evoked potential
TCS	Thermal Cutaneous Stimulator
NRS	Numerical Rating Scale
CHEP	Contact Heat Evoked Potential

Introduction

1) General introduction

Pain is a natural phenomenon, a warning mechanism through which the individual becomes aware of a danger to his physical integrity from the inside of his body or the environment. Such protective behavior had already been discovered in single-celled eukaryotes such as protozoans, suggesting that this defensive behavior appeared early during evolution as described by Jennings in 1906. Moreover, it has been shown that congenital insensitivity to pain is an extremely dangerous condition (Daneshjou et al., 2012). Unfortunately, this detection system can be defective, leading to chronic pain, which is a major healthcare issue since it affects the quality of life of about 20% of the European population and is a financial burden for society as explained by van Hecke in 2013. Therefore, a better understanding of the physiological mechanisms underlying pain and the psychological factors, that can modulate it, such as hypnosis, is necessary to help diagnose and treat chronic pain.

This introduction will be divided into four sections. The first section will distinguish pain and nociception and their physiological mechanism. The second section will be on the effect of attention on pain perception supported by behavioral, neuroimaging, and neurophysiological studies. Indeed, attention is a physiological factor already known to modulate pain (Legrain et al., 2002), so the mechanisms underlying the modulation of pain by attention can be used as a comparison to what could be found studying the effect of hypnosis on pain. The third section will be an explanation of neutral hypnotic analgesia to alleviate pain supported by behavioral, neuroimaging, and neurophysiological studies. Finally, the last section will introduce the use of focused hypnotic analgesia to alleviate pain.

1.1) Nociception and pain

First, a distinction between nociception and pain must be made. On one hand, nociception is defined by the International Association for the Study of Pain (IASP) as the neural process of encoding noxious stimuli (Loeser et al., 2008). A nociceptive stimulus has the particularity to threaten the body's integrity and activates a discrete set of sensory organs, the nociceptors. Nociceptors are polymodal receptors characterized by high activation thresholds and therefore respond to high-intensity

stimuli. Nociception is then considered as an alarm system that protects the organism by triggering responses such as a reflex or a behavioral response to eliminate the cause of the threat and limit its consequences (Le Bars and Plaghki, 2009).

On the other hand, according to the International Association for the Study of Pain (IASP), pain is defined as an unpleasant sensory and emotional experience associated with or resembling actual or potential tissue damage (Raja et al., 2020). Indeed, pain is more than just a discriminative sensory experience because it is also characterized by an aversive emotional state driving action. That is why pain is inherently « unpleasant », has the capacity to drive attention, interfere with any ongoing activity, and mobilize resources and individual defense strategies (Le Bars and Plaghki, 2009).

Moreover, a nociceptive stimulus can cause brain responses without causing pain and pain can be felt even when a non-nociceptive stimulus is applied (Legrain et al., 2010).

1.2) Physiology

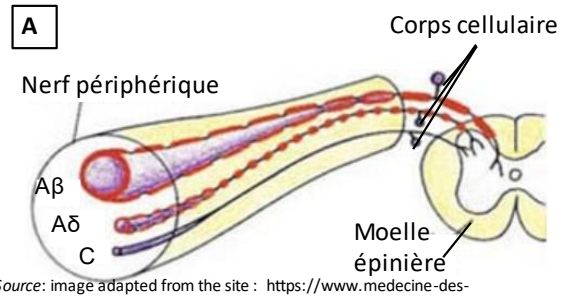
Nociceptive inputs are generated at the level of epidermal free nerve endings, the nociceptors, that detect potentially damaging stimuli by activating different receptors that are specific for a stimulus and depolarise the membrane of the nociceptors. For example, the Transient Receptor Potential (TRP) receptor family is mostly activated by thermal stimuli and the Acid Sensing Ion Channel (ASIC) family by acidity. When nociceptors are activated, they release chemicals that will activate or sensitize more nociceptors, such as substance P, histamine, bradykinin, and serotonin. (Le Bars and Plaghki, 2009).

There are two types of nociceptive fibers, the Aδ and C fibers. The main difference between them is their conduction velocity, as Aδ fibers are thinly myelinated and C fibers are unmyelinated (**figure 1A**). Aδ fibers conduct information at a speed of 4-30 m/s and are responsible for a brief and well-localized sting feeling. C fibers conduct nerve impulses at a speed of 0,4-2 m/s and are responsible for slow pain appearing

in the form of a prolonged and diffuse burn. Moreover, the activation threshold of Aδ fibers is higher than that of C fibers. In conclusion, these two groups of fibers constitute a “double” alarm system threshold. Indeed, when the first is reached, the brain is warned only enough belatedly, but going beyond the second results in the setting of a faster warning system. (Le Bars and Plaghki, 2009).

Figure 1

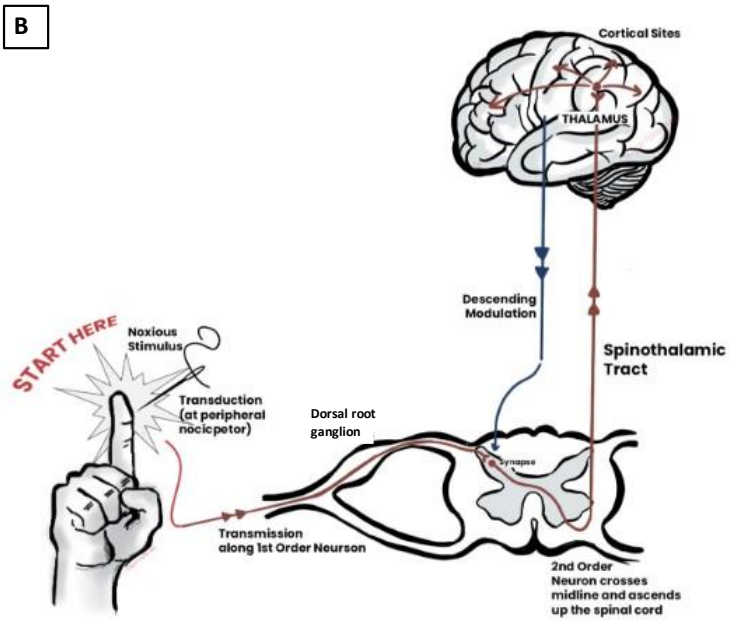
A



Source: image adapted from the site : https://www.medecine-des-arts.com/fr/article/douleur-et-pratiques-artistiques/qu-elle-est-la-regulation-de-la-douleur.php

Type of fiber	Aβ	Aδ	C
Information	non-nociceptive	nociceptive	nociceptive
Thermal activation threshold	Not activated by thermal stimuli	± 46°C	± 41°C
Myelin sheath	myelinated	thinly myelinated	unmyelinated
Diameter (µm)	6-20	1-5	0,3-1,5
Velocity (m/s)	30-120	4-30	0,4-2

B



Source: Pain and Placebo Physiology | PM&R KnowledgeNow (aapmr.org)

Figure 1: The nociceptive system. A) Representation of the type of fibers that carry the signal to the spinal cord. Nociceptive fibers (Aδ or C) will transmit the message to the spinal cord, when a specific activation threshold is reached, at different speeds as described in the table. The speed of conduction depends on the diameter of the fiber and the presence of a myelin sheath. (Le Bars and Plaghki, 2009). **B)** The ascending pathway. Noxious stimuli activate nociceptors associated with the nociceptive fibers (Aδ or C). Then, in the dorsal horn of the spinal cord, the nociceptive signal reaches the second-order neuron, and the first relay takes place. In the spinal cord, fibers cross the midline and, through the spinothalamic tract, convey information to the third-order neuron in the thalamus that conveys the signal to cortical structures like the somatosensory cortex, the insula, the anterior cingulate cortex, or the prefrontal cortex, where nociceptive information is processed. (Parikh et al., 2015). The descending pathway from the brain, there is a descending modulatory signal modulating spinal cord activity (Gebhart et al., 2004).

As explained by Parikh in 2015 (Parikh et al. 2015), when a noxious stimulus activates a nociceptor, it is transduced into electrical signals. These signals are transmitted along three neurons from the periphery to the central nervous system (CNS). The first-order afferent neuron conveys the signals from the spinal cord dorsal horn to its synapses with the second-order neuron. There, neurotransmitters such as glutamate and aspartate are released. It is on those synapses that painkillers such as opioids can act, by regulating the release of neurotransmitters. The second-order neuron in the dorsal horn can be either Nociceptive-specific (NS) or Wide Dynamic Range (WDR) receiving signals from Aβ fibers or the nociceptive Aδ and C fibers. Following the spinothalamic tract, the second-order neuron then projects toward the thalamus where the third-order neuron is located and conveys the signals to be processed to various cortical sites such as the somatosensory cortex, the insula, the anterior cingulate cortex, and the prefrontal cortex. (**Figure 1B**).

Moreover, descending from these cortical structures, there is a modulatory signal modulating spinal cord activity (**Figure 1B**). Early studies established that descending influences were tonically active and principally inhibitory with GABA, glycine, enkephalin, and noradrenaline as key inhibitory neurotransmitters found at the supraspinal and spinal levels (Gebhart et al., 2004). There is also evidence suggesting that descending facilitatory influences may contribute to chronic pain states (Gebhart et al., 2004). On those synapses, painkillers such as opioids can act by regulating the release of neurotransmitters. Furthermore, cognitive manipulations such as attention or hypnosis can also access this modulatory system (Villemure & Bushnell, 2002).

Thus, the pain pathway produces an individual's perception of pain and their overall pain experience, and the descending pathway constitutes an internal system on which we could act to modulate pain.

2) Effects of attention on pain perception

Several pain modulatory mechanisms exist in the nervous system such as the descending pathway, and these modulatory systems can be accessed through contextual and cognitive manipulation (Villemure & Bushnell, 2002). Indeed,

experimental evidence supports the role that cognitive functions such as selective attention play in nociceptive processing (Legrain et al., 2015).
Attention is the ability to concentrate on the perception of an object present in the environment or a behavior. More precisely, selective attention prioritizes the processing of some inputs and then facilitates their perception and responses at the expense of other inputs (Legrain et al., 2015). It is largely admitted that paying attention to a nociceptive stimulus can increase pain perception and, on the contrary, focusing attention either on another perceptual object or another task reduces it (Legrain et al., 2012; Villemure & Bushnell, 2002).

2.1) Behavioral studies

As human cognition is presented as a limited system, the selection of sensory information is a necessity as multiple events arise from our environment and compete for processing. Some inputs must be prioritized over others to maintain behavioral coherence, promote or sustain action, and to serve a super-ordinate goal of survival (Legrain et at., 2009). This could be explained by the existence of an involuntary capture of attention but also a voluntary attentional control which can be explained by two modes of attentional selection, the bottom-up and top-down models (Legrain et al., 2009). Bottum-up selection corresponds to unintentional stimulus-driven capture of attention by events themselves. This attentional capture often depends on the saliency of the stimulus in the environment, which is defined by the ability of a stimulus to distinguish itself from others due to its features such as its novelty, intensity, or threat to the body's integrity (Legrain et al., 2009). Top-down selection is an intentional and goal-directed process that prioritizes information relevant for current actions. This intentional capture is acting through the attentional load, which is the amount of attention that the participant has to deploy to achieve a task, and the attentional set, which is the task-relevant stimulus feature (Legrain et al., 2009). Those processes are based on a dynamic model in which the attentional modulation of pain depends on a balance between bottom-up and top-down influences and it needs to be systematically investigated (Legrain et al., 2009).

For example, when subjects are paying attention to noxious stimuli, it has been demonstrated that both the speed and accuracy of detecting changes in noxious heat stimuli are increased as compared to when attention is focused on another stimulus

modality (Miron et al.,1989), it could be that attention on pain is captured by the load and the set when it is asked to pay attention to noxious stimuli. Moreover, this study demonstrated that the direction of attention affects the perceived intensity and unpleasantness of nociceptive stimuli as they were indeed increased when subjects had their attention focused on the stimuli (Miron et al.,1989). Similar results were obtained by another study (Dunckley et al., 2007), which reported that the subjects provide lower pain ratings when their attention is distracted from the painful stimulus. In addition, in a clinical context, a report showed that in post-operative conditions, where the participant had to report his pain perception more often, he reported it as more intense than patients who were less frequently asked to report their pain (Levine et al., 1982).

Since pain has the evolutionary purpose of escaping danger, threatening stimuli will inherently attract an organism's attention. The purpose of this directed attention is to allocate necessary neuronal resources to address and, if necessary, plan and execute a response, directed attention can then heighten or improve the relevant senses and speed up that response (Dunckley et al., 2007). To the extreme, some patients with chronic pain diseases constantly have their attention involuntarily captured by pain, resulting in a hypervigilance state. Such attentional hypervigilance occurs when people pay excessive attention to all signals related to their pain, such as their symptoms, and is linked to a fear of pain leading individuals to avoid situations likely to increase their pain and lead them into a vicious circle of hypervigilance, fear, and pain avoidance. This cycle would contribute to exaggerated pain perception and the maintenance of pain (Crombez et al, 2005). This amplification of pain can also be observed in healthy subjects because people who tend to catastrophize pain have indeed more difficulty disengaging from pain once their attention has been captured (Van Damme et al., 2004). Thus, it is important to find ways to interact with the top-down process, with distraction tasks, for example, to decrease this saliency of pain.

2.2) Neuroimaging studies

As explained above (*cfr section 1.2*), painful stimuli can elicit responses in a wide array of cortical and subcortical sites such as the somatosensory cortex, the insula, the anterior cingulate cortex, or the prefrontal cortex (Parikh et al. 2015). Studies on

attentional modulation of pain have demonstrated that directing or distracting attention from nociceptive stimuli can alter the activation of this network (Dunckley et al., 2007). A study using functional Magnetic Resonance Imaging (fMRI) has shown that distracting attention from noxious stimuli decreased the pain perception of participants, confirming the results obtained in behavioral studies. This pain reduction was also accompanied by a reduction in the activity of the cortical network implicated in pain perception, including the dorsolateral prefrontal cortex, suggesting a modulation in the activity of those areas by cognitive processes such as attention (Dunckley et al., 2007).

2.3) Neurophysiological studies

First, an introduction on electroencephalography (EEG) must be made as it will be discussed and used all along. EEG is a non-invasive technique recorded directly from the participant's scalp. EEG can provide information about the neurophysiological activity with a precise temporal resolution, in the order of milliseconds (Roberts et al., 2008). Nociceptive event-related potentials (ERPs) correspond to time-locked EEG responses elicited by the phasic activation of peripheral skin nociceptors, they can be obtained by applying brief pulses of heat stimuli to the skin. In pain research, ERPs can be elicited by stimuli specifically activating skin nociceptors such as contact or radiant heat. For instance, laser-evoked potentials (LEPs) are transient cortical responses elicited by laser-induced radiant heat stimuli applied on the skin allowing a preferential and phasic activation of heat-sensitive Aδ and C fiber free nerve endings without co-activating non-nociceptive mechano-sensitive Aβ fibers (Lejeune et al., 2023). Alternative methods can be used to obtain ERPs, such as intra-epidermal electrical stimulation and contact heat stimulation using thermodes (Lejeune et al., 2023).

Nociceptive ERPs reflect the sequential activation of an extensive cortical network, which is mainly expressed on the scalp by the occurrence of three successive waves: N1, N2, and P2. The first to appear is the N1 negative component which is maximal at the temporal electrode contralateral to the body site on which the eliciting nociceptive stimulus is applied. Next, the negative N2 and positive P2, which are evoked with maximal amplitude at the vertex electrode (**figure 2**).

Figure 2

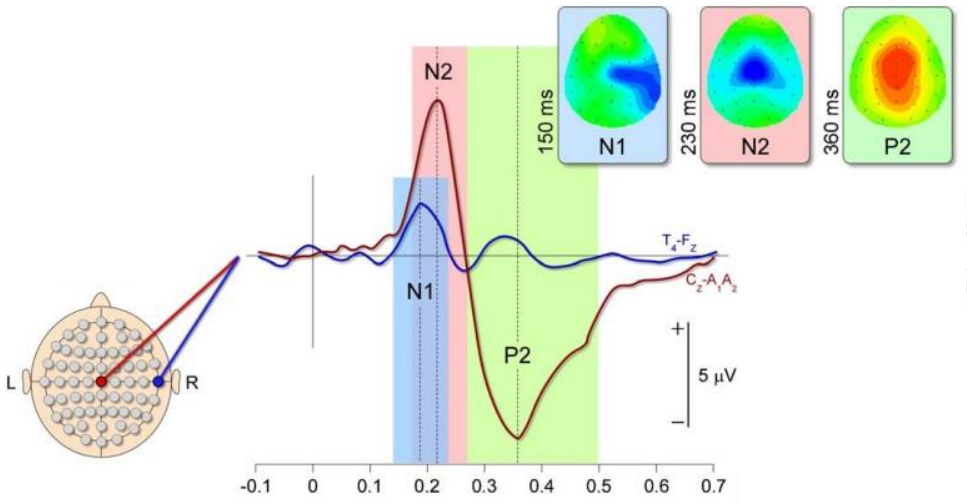


Figure 2: Nociceptive ERPs elicited by laser-induced radiant heat stimuli. Nociceptive ERPs were recorded at the scalp vertex electrode (red waveform) and at the contralateral temporoparietal electrode (blue waveform). The ERPs components are shown in their respective time windows represented by colored boxes: N1 (blue), N2 (red), and P2 (green). The time 0 sec corresponds to the onset of the stimulus. The upper right part of the figure represents the scalp distribution maps of nociceptive ERP magnitude at the latency of the N1, N2 and P2 waves respectively. (Legrain et al., 2010).

Those components are characterized by their amplitude, measured in µV, and their latencies, being the time between the stimulus onset and the recording of the component, measured in seconds. (Legrain et al., 2010). The latencies of the ERPs components change between the modalities of stimulation, for example, the responses elicited by contact heat are slightly delayed relative to the latencies elicited by radiant heat, due to the heating mechanism which relies on thermal conduction and is therefore limited by the intrinsic thermal inertia of the skin (Lejeune et al., 2023). Moreover, some pain research suggests that the early component, N1, is more sensory in nature and that the late components, N2 and P2, are more emotional or evaluative in nature (De Pascalis and Ray, 2003). However, Legrain et al. in 2001 have shown that all nociceptive ERPs components can be modulated by cognitive factors. Furthermore, the estimated sources of those ERPs components are mainly the primary and secondary somatosensory cortex, the insula, and the anterior cingulate cortex (Legrain et al., 2010).

Then, concerning the literature, experimental manipulation that modulates pain can also modulate the magnitude of the brain responses triggered by nociceptive stimuli. Indeed, paying attention to or discarding attention from the stimulus can modulate the activity of the cortical network processing nociceptive inputs (Miltner et al., 1989;

Garcia-Larrea et al, 1997; Legrain et al., 2002; Bentley et al, 2004). For instance, directing subjects' attention away from the nociceptive stimulus may result in a decrease in pain rating and a decrease in the magnitude of the elicited brain responses as compared to the control condition without distraction (Legrain et al., 2011). The most common result is a reduction of the magnitude of the vertex positivity of the ERPs, the P2 component, which is supposed to mainly reflect the activity of the anterior cingulate cortex when attention is distracted from the pain. This P2 amplitude reduction was accompanied by a reduction in pain ratings (Legrain et al., 2012). Results were shown to be less consistent regarding the temporoparietal negative signal reflecting the earliest cortical processing in the somatosensory cortices, the N1 component (Legrain et al., 2012). Some studies found no significative modulation and these results were interpreted as evidence that the early N1 component reflected sensory processing impervious to cognitive stimulation, whereas the late P2 reflected perceptual processing under the influence of attention (Miltner et al., 1989; Garcia-Larrea et al, 1997). However, other studies found a clear modulation of the N1 component, specifically during spatial attention modulation of nociceptive processing (Legrain et al., 2002; Bentley et al. 2004), confirming the conclusion of neuroimaging studies showing that almost all cortical areas processing nociceptive inputs may have their activity modulated by attention and since the earliest stage of the nociceptive processing (Legrain et al., 2012).

Two main propositions of biological mechanisms were made to explain the selective attention effects of the ERPs. Firstly, the sensory gain control hypothesis postulates that the flow of information is efferently gated in cortical areas in such ways that the processing of the attended stimuli is facilitated in comparison to unattended stimuli. Since the nociceptive ERPs under attention only differ by their amplitude and not their latency and topographic waveform, it is suggested that attention can directly act by amplifying the neural responses evoked by the stimuli, acting as a gate facilitating the processing of stimuli in the attended modality, modality on which the attention is focused, in comparison to the non-attended stimuli (Legrain et al., 2002). Secondly, attention could also act through the descending modulatory pathway (*cfr section 1.2*) (**Figure 1B**). This pathway is connected to different brain areas involved in cognitive processes such as the somatosensory cortex, the insula, the anterior cingulate cortex, and the prefrontal cortex. Cognitive manipulations such as attention or

hypnosis access this modulatory system at the level of those brain areas (Villemure & Bushnell, 2002) to modulate the nociceptive input. This could be one way to explain how attention modulates nociceptive stimuli and therefore, pain. It has even been demonstrated in an fMRI study that there is an inhibition of the nociceptive signal in the spinal cord when attention is distracted from the nociceptive stimulation (Sprenger et al., 2012).

3) Neutral hypnotic analgesia to alleviate pain

Hypnosis is defined as a state of focused attention, involving concentration and inner absorption with a relative suspension of peripheral awareness (Vanhaudenhuyse et al., 2019). For several years it has been increasingly clear that hypnosis allows a better understanding of the neurophysiological bases of human consciousness, the effects of suggestion, and the resulting biopsychological dimensions. By knowing the mechanisms of hypnosis and by having more experiments to study how it could act on pain, hypnotic analgesia could then be integrated into medical practice.

The hypnotic process has three main components as explained by Rousseaux et al. from the University Liège in 2018 (Rousseaux et al., 2018). Firstly, absorption is the ability to become fully involved in an imaginative experience. Secondly, dissociation is the mental separation from behaviors that usually go hand in hand. Finally, there is suggestibility, the ability to accept and follow instructions or suggestions. Under hypnosis, it is also possible to observe an alteration in the perception of time, accompanied by a decrease in the ability to discern and censor, spontaneous thoughts, as well as printing automatic responses. In other words, the subjects under hypnosis remain collaborators with the experimenter while in an altered state of consciousness. It is recognized that hypnosis is an innate talent and, in the population, about 25% of subjects are qualified as highly hypnotizable because of their ability to quickly slip into a trance state. Even though everyone has the innate talent to be hypnotizable, three fundamental conditions must be met to induce hypnosis. Indeed, without motivation, cooperation and trust, hypnosis is not possible (Virot and Bernard, 2018). First, there is the motivation, hypnosis is only practiced with subjects who wish it and understand the benefits of it. Then, there is the cooperation, the subjects must participate in the success of the treatment. Finally,

there is the trust, subjects have to be able to trust the therapist created in maintaining the relationship, it can only appear if the therapist has confidence in himself.

In clinical practice, the interests of hypnosis are multiple. For example, hypnosedation, used during a surgical procedure by an anesthetist to sedate the patient using hypnosis rather than traditional anesthetics offer many advantages. Hypnosedation increases patient comfort before and after the operation, offers better surgical conditions for the healthcare team, a reduction in emotional distress, a reduction of medication and post-operative fatigue, as well as a faster return to work (Rousseaux et al., 2018). Furthermore, hypnosis is easily administered and has few or no side effects (Thompson et al, 2019).

3.1) Behavioral studies

Hypnoanalgesia represents a process aiming to reduce pain through the delivery of hypnotic suggestions (Lanfranco et al, 2014). It is already efficiently used in clinical practice however, the underlying mechanisms of its effect on pain are still unclear. Thompson et al. showed in 2019 that being under hypnosis is effective to procure pain relief by analyzing pain ratings compared to no-intervention control conditions. Moreover, they demonstrated that efficacy was strongly influenced by hypnotic suggestibility and the use of direct analgesic suggestion. However, minimal benefits were found for people with low hypnotic suggestibility. In fact, suggestibility can be based on different scales scoring the behavioral responses to a series of individual suggestions. For example, suggestions of heaviness or tiredness in the arm producing lowering of the hand are scored in those scales (Kekecs et al., 2016). Indeed, it is hypnotized that highly hypnotizable persons can partition their attentional resources more effectively than can low hypnotizable individuals as explained by Crawford et al. in 1998. Because of these abilities to control unwanted stimuli, such as pain, there is a relationship between hypnotic susceptibility and pain reduction using hypnotic analgesia. Similar results were obtained by other studies (De Pascalis et al., 1999; Valentini et al., 2013; Houzé et al., 2021), which reported that the participants provided lower pain ratings when they were under hypnosis while receiving painful stimuli. Furthermore, in a clinical context, a study by Nowak et al. in 2020 showed that, in post-operation conditions, patients operated on while receiving therapeutic suggestions during general anesthesia reported a reduction in the use of

postoperative opioids compared to patients only under general anesthesia. These findings suggest that hypnotic intervention can deliver pain relief for most people and therefore may be an effective and safe alternative to pharmaceutical intervention.

3.2) Neuroimaging studies

To study the cerebral mechanisms that characterize variations in the state of consciousness in hypnosis several neurophysiological studies had already been carried out. For example, using functional Magnetic resonance Imaging (fMRI) to learn about the processes of consciousness modified during hypnosis made it possible to discover that consciousness is made up of two main components, self-awareness and awareness of the environment, each linked to a specific cerebral network, the precuneus and mesiofrontal regions and the fronto-lateral parietal regions respectively (Rousseaux et al. 2018). During hypnosis, the activity observed in internal and external consciousness networks is modified with an increase in the activity of the self-awareness cerebral regions and a decrease in the awareness of the environment cerebral network (Rousseaux et al., 2018). Moreover, fMRI to evaluate the influence of hypnosis on pain perception shows a modification of the activation of the primary and secondary somatosensory cortex, the thalamus, the insula, and the anterior cingulate cortex. This induces changes in the cognitive and behavioral mechanisms involved in information processing (Rousseaux et al., 2018).

3.3) Neurophysiological studies

Numerous studies have shown that the magnitude of the nociceptive ERPs can be modulated by hypnotic analgesia, confirming that hypnosis can modulate the activity of the cortical network processing nociceptive inputs (De Pascalis et al., 1999; Friederich et al, 2001; Valentini et al., 2013; Perri et al., 2020; Rousseaux et al. 2022). Contact heat stimulation was used in none of these studies but rather, electrical stimulation (De Pascalis et al., 1999; Perri et al., 2020; Rousseaux et al., 2022) and radiant heat stimulation using a laser (Friederich et al., 2001; Valentini et al., 2013). The most common results of these studies are that late ERPs show a significant modulation in response to nociceptive stimulation during hypnotic analgesia as compared to a control condition and this change in the amplitude of the ERPs was greater for highly hypnotizable subjects as compared to low hypnotizable

subjects. This change in the amplitude of the late ERPs was accompanied by a reduction in pain ratings as compared to a control condition. However, there are contradictions in the literature regarding the amplitude of these potentials and these could be explained by the different ways used to induce a noxious stimulus.

For instance, the study of De Pascalis et al. in 1999, showed a decrease in late ERPs components N2 and P3 (at 280 and 405 msec after the stimulus onset), in response to nociceptive electrical stimulation during hypnotic analgesia. Moreover, those reductions in ERPs amplitudes, as compared to a control condition, were associated with less recruitment of the somatosensory and prefrontal cortex and less engagement from the thalamocortical radiations, anterior insula, and cingulate gyrus (Perri et al. 2020). Furthermore, the influence of hypnosis on the EEG components seems to be more associated with later components that carry with them cognitive and emotional information (De Pascalis and Ray, 2003). According to these, it has been concluded that hypnotic analgesia is the expression of an active process that requires inhibitory effort, dissociated from conscious awareness (De Pascalis et al., 1999). Taken together, these findings suggest that hypnotic hypoalgesia acts through a combination of top-down and bottom-up mechanisms as attentional modulation (*cfr section 2.1*). However, one could argue that electrical stimulations are not selective of the nociceptive Aδ and C fibers as they also activate deeper large-diameter non-nociceptive Aβ fibers (Mouraux et al., 2010).

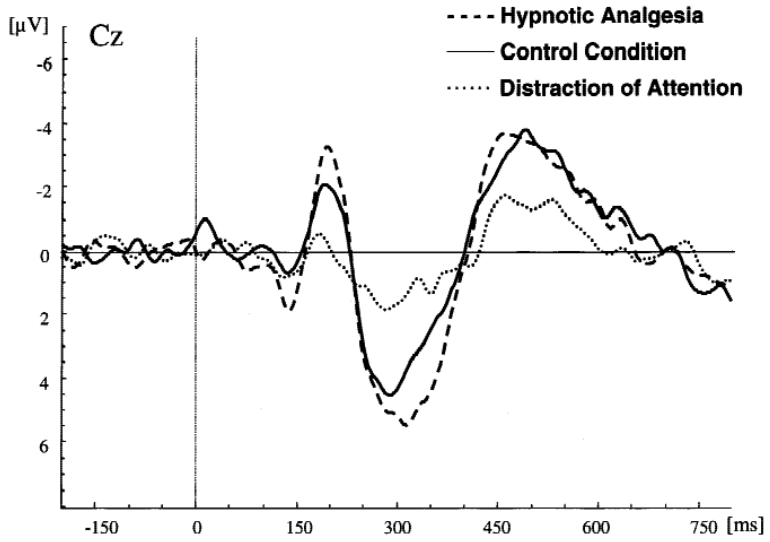
Indeed, studies using selective activation of nociceptive fibers using radiant heat stimulation with a laser (Mouraux et al., 2010) rather showed that late LEPs, the N2-P2 components (at 200 and 320 msec after the stimulus onset), tended to show larger magnitude during hypnotic analgesia as compared to the control condition (Friederich et al., 2001). Moreover, the early-stage sensory processing activity, represented by the N1 component, is not significantly modulated by hypnosis as explained by Valentini et al. in 2013.

3.4) Comparison between attention and hypnosis

Studies on the effect of attention on pain perception can be used to study the effect of hypnosis to alleviate pain. Indeed, it is hypothesized that hypnotic suggestions act as verbal stimuli that distract a person's attention from processing noxious inputs and

then represent an extensive state of reduced attention. This process would involve simultaneously increasing attentional resources for the processing of hypnotic suggestions while decreasing attentional resources for the processing of noxious information (Friederich et al., 2001). This shift of attention from the somatosensory input channel to the auditory channel is thought to be one of the most significant mechanisms of hypnosis-induced pain control (Friederich et al., 2001). Moreover, both experimental and clinical studies have shown that psychological manipulations, such as hypnosis and modulation of attention can reduce reports of pain (De Pascalis et al., 1999; Friederich et al., 2001). However, in the study of Friederich et al. in 2001 it was shown that the amplitudes of the late components were significantly smaller during distraction of attention as compared to a control condition, but these amplitudes tended to show larger magnitude when subjects were exposed to suggestion of hypnotic analgesia as compared to the control condition (**Figure 3**) (Friederich et al., 2001).

Figure 3



<u>Figure 3:</u> Grand averages of the LEPs at Cz for the control condition (CC), distraction of attention (DA), and hypnotic analgesia (HA). For the DA condition, there is a decrease of amplitude for the late LEPs components, N200 and P320, as compared to the CC condition, indicating the effectiveness of attentional diversion to modulate pain. For the HA condition, however, there is an increase of amplitude for the late components, N200 and P320, indicating that HA and DA represent different mechanisms of pain control and involve different brain mechanisms. (Friederich et al., 2001).

It was then concluded that the difference between the effect of hypnotic analgesia and distraction of attention in electrophysiological parameters reflects different mechanisms of pain control and involves different brain mechanisms (Friederich et al., 2001). A possible explanation for the reduced pain ratings under suggestions of hypnotic analgesia is that the somatosensory features of noxious stimuli are still evaluated properly during hypnotic analgesia as they are in the nonhypnotic control condition, but the output of this processing is not communicated appropriately to other brains areas that complete the evaluation of these stimuli as being painful and are responsible for the organization of proper behaviors to pain (Friederich et al., 2001).

4) Focused hypnotic analgesia to alleviate pain

As explained before, hypnosis can alter the state of consciousness, and the effect on the perception of pain is global over the body. By showing that it is possible to protect only one part of the body by using focused hypnotic analgesia, it would be likely to know if hypnotic analgesia selectively influences how nociceptive stimuli are processed in the brain. Indeed, studies already demonstrated that attention could selectively prioritize information (Legrain et al., 2015), henceforth by referring to the mechanisms demonstrated for attention, it could be thought that hypnoanalgesia could also selectively impacts nociceptive processing and pain perception.

To perform focused hypnotic analgesia, the technique of the protective glove is usually used (De Pascalis et al., 1999; De Pascalis et al., 2007; Paqueron et al., 2019). The hypnotic glove analgesia is a suggestive method to induce a unilateral short hypnotic focal trance allowing hypnotic analgesia of the hand and forearm. During this method, the investigator suggests the subject to build his own hypnotic glove over the chosen hand, which requires focusing attention on the hand receiving painful stimulation (De Pascalis et al., 1999; Paqueron et al., 2019, Virot C. and Bernard F., 2019).

4.1) Behavioral studies

Studies have shown that after the subject had installed the analgesic hypnotic glove, the perceived intensity of pain, given by pain ratings, was decreased as compared to a control condition without hypnotic suggestion (De Pascalis et al., 1999; De Pascalis et al., 2007; Paqueron et al., 2019). With this, patients report frequent sensations of numbness and warmth or swelling occurring during hypnotic suggestion of analgesia. Furthermore, this method induces thermal changes within the area of hypnotic protection compared to the contralateral forearm serving as the control side, bringing some evidence that the technique is a selective method (Paqueron et al., 2019). As well as for the condition of neutral hypnosis, in focused hypnotic analgesia, high hypnotizable subjects display greater reductions in pain ratings than low hypnotizable subjects compared to a no-intervention control condition (Zachariae and Bjerring, 1994; De Pascalis et al., 2007). Moreover, focused hypnotic analgesia induces the largest reduction in pain ratings as compared to neutral hypnosis, even more in high than low hypnotizable subjects (Zachariae and Bjerring, 1994; De Pascalis et al., 2001; Sharav and Tal, 2006). Finally, the reduction of pain perception is more important over the limb under focused hypnotic analgesia as compared to the remote limb, with no intervention, bringing more evidence that it is a selective method. This effect of relative location, local versus remote of the site of analgesia, is also greater for highly hypnotizable subjects (Sharav and Tal, 2006).

4.2) Neurophysiological studies

Neurophysiological studies reported that focused hypnotic analgesia, which requires attention on the hand receiving painful stimulations decreases the amplitude of the late ERPs components, N140 and P200 (at 139 and 196 msec after the stimulus onset), in response to nociceptive electrical stimulation as compared to a control condition (De Pascalis et al. 2007). This reduction is greater for highly hypnotizable subjects compared to low hypnotizable subjects, as for the general hypnotic analgesia explained before (Zachariae and Bjerring, 1994, De Pascalis et al. 2007). However, arguments in favour of the selectivity of hypnosis are lacking as no experiment compares electrophysiological responses of a local and remote localization of the suggestion of analgesia.

To summarize, hypnotic analgesia has been proven to decrease pain perception. However, we don't know if focused hypnotic analgesia can be selective over the way that nociceptive inputs are processed in the brain. Therefore, the aim of this study is to investigate the effect of focused hypnotic analgesia on pain perception and nociceptive ERPs using contact heat stimulation. For that two experiments were conducted. The first experiment was only behavioral and allowed us to know if the experimental design was allowing us to obtain an effect of the protective glove. For the second experiment we aimed to investigate the effect of focused hypnotic analgesia by comparing the nociceptive ERPs elicited by contact heat stimuli delivered on the arm on which the protective glove suggestion has been applied and the other arm, considered as a control. It is already hypothesized that when nociceptive stimuli are applied on both arms and that hypnotization is focused on one limb by the method of the protective glove, a decrease in pain ratings as well as a decrease in the magnitude of the ERPs elicited by nociceptive stimuli in the hypnotized forearm will be observed in comparison to unhypnotized forearm during the protective glove suggestion.

Material and methods

1) Experiment 1: behavioral experiment

1.1) Participants

40 healthy volunteers aged between 18 and 36 (M ± SD = 24 ± 4) took part in this study (11 men and 29 women, 2 left-handed and 38 right-handed). Participants were recruited through advertisements on social networks and by word of mouth. The exclusion criteria were not speaking French fluently, having psychiatric and neurologic disorders, having chronic pain disorder, having regular use of psychotropic drugs or intake of analgesic drugs within the 12 hours before the experiment, having traumatic injury of the forearms at the present or in the past 6 months and having a dermatological disease or recent tattoo at the forearms.
The experimental procedure was approved by the local ethic committee (Comité d'Ethique hospitalo-facultaire, Saint-Luc University Hospital & UCLouvain) in agreement with the Declaration of Helsinki. Before the experiment, all volunteers signed an informed consent and received financial compensation for their participation.

1.2) Apparatus and stimuli

Thermo-nociceptive stimuli were delivered by two Peltier thermodes, contained in the probe of the TCS (Thermal cutaneous Stimulator II, QST.Lab, France), on the participant's volar forearms (**Figure 4**). Each thermode measures 3.2 by 2.4 mm placed on a round stimulation probe of 12 cm2 divided into 5 zones of 3 thermodes each. Despite each zone can be activated independently, the five zones have been activated at the same time for each stimulation trial during this experiment.
TCS with Peltier elements has some advantages compared to other devices such as laser stimulation devices. Firstly, it can generate steep cooling and heating ramps of up to 300°C/sec allowing brief and sharp onset thermal stimuli, which is required for the recording of time-locked EEG responses such as nociceptive ERPs. Secondly, it is also a lightweight device, easy to manipulate. Finally, the temperature of the stimulations can be controlled (Lejeune et al., 2023). The two TCS were remotely controlled by a computer with the software MATLAB. Each probe of the two TCS devices was manipulated by an experimenter who then produced thermal stimulation

on one of the two forearms. The experimenters in charge of the TCS kept the same probe during all sessions and they changed sides between each participant while keeping their assigned probe to counterbalance the TCS and avoid bias due to technical issues such as difference in temperature stimulation between the two TCS. Moreover, the probes were moved on the forearm between each stimulation to not always stimulate the same zone in order to avoid a spatial summation effect (Lejeune et al., 2023). The basal temperature of the thermodes was set at 32°C, and the stimulations had to go up from 38°C to 70°C depending on the sensitivity specific for each subject which was determined during a familiarization task before the experiment, the stimulations had to be painful but not intolerable. The thermodes actively cooled the skin to return to the baseline temperature after each stimulation and a total stimulus duration was set to 200ms. The ramp of heating and cooling was set at 300 °C/sec.

Figure 4

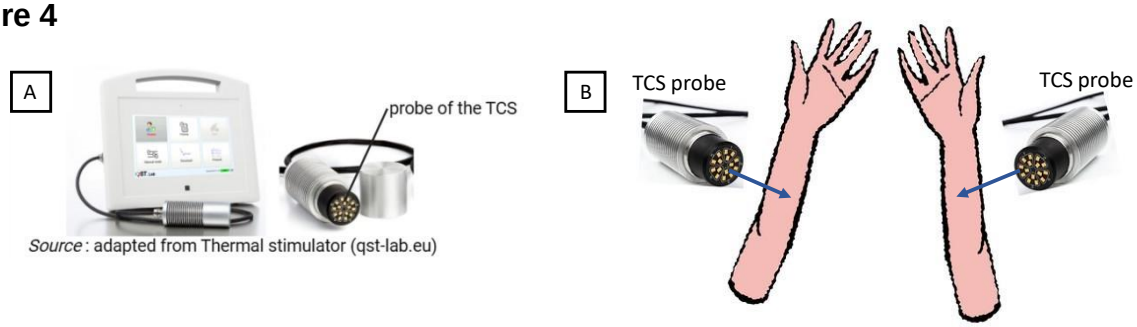


Figure 4 : Apparatus and stimuli. A) Pictures showing a TCS and its probe. **B)** Schema of the two probes of the TCS applied at the same time to deliver contact heat stimulation on the volar forearms.

1.3) Procedure

Three experimenters conducted the study, one in charge of the hypnosis and two in charge of the stimulations. First, the participant arrived and after signing the consent papers, the explanations of the experiment were given by the experimenter in charge of the hypnosis. It is important that it is the role of the hypnotist to have the most contact with the participant so he can install a trusting relationship with the subject who will be hypnotized and thus, improve the quality of hypnosis (Virot and Bernard, 2018). Then, the subject is asked to sit comfortably on a deck chair and to place his arms on the armrests with his sleeves to his elbow so the experimenters giving the

stimulations have access to his volar forearms. Each session lasted for about one hour and forty minutes.

Next, participants were presented with a familiarization task for approximately 7 minutes, consisting of nine contact heat stimulations for each forearm respectively at 38°C, 48°C, 58°C, 60°C, 62°C, 64°C, 66°C, 68°C, 70°C. The temperature of the stimulations for this task was given in ascending order and scales of pain and unpleasantness were asked after each stimulus to familiarize the subject with their use. The scale of pain consisted of giving a number from 0 to 100, 0 when nothing was perceived, 100 was the most painful sensation imaginable and 50 is the pain threshold. The scale of unpleasantness consisted in giving a number from 0 to 100, 0 was not unpleasant at all and 100 was the most unpleasant sensation imaginable. By the end of the familiarization task, a single temperature of stimulation was arbitrarily chosen for the experimental phase, a temperature perceived the same way by both arms and as painful as possible without being unbearable. A stimulation was considered unbearable when the score for the scale of pain or unpleasantness corresponding to this stimulus was maximal.

Then, the experimental phase was performed (**Figure 5**)**.** It consisted of three conditions, a control condition before focused hypnotic analgesia, an experimental condition during focused hypnotic analgesia with the suggestion of the protective glove on the chosen arm (Paqueron et al., 2019) (**Annex 1**), and a condition after focused hypnotic analgesia with a post-hypnotic suggestion where the participants could remove the glove in an imaginary way and put it somewhere in their mind to use it later when needed. To ensure blinding, the two experimenters in charge of the stimulations were not aware of where the participant decided to build the protective glove. To this end, they were never present in the lab during the administration of the suggestion of the protective glove. Each condition consisted of a block of twenty stimuli, ten for each arm, sent in a randomized order and with a temperature of stimulation determined at the end of the familiarization task (**Figure 5**). During each block, participants were again asked to rate the perceived pain and the unpleasantness of the stimulation after each stimulation. Each block lasted approximately 5 minutes. After a block, by the end of each condition, subjects were asked four scales to predict hypnotizability (Vanhaudenhuyse et al., 2019). Those

scales concern absorption, dissociation, perception of time, and automaticity. Breaks were also done between each condition to avoid habituation of nociceptive fibers due to repetitive painful stimulation (Rennefeld et al., 2010), with a break of 18 minutes after the first condition including the four questions and the induction of the hypnotic suggestion, and a break of approximatively 10 minutes after the second condition including the four questions and the post-hypnotic suggestion.

Figure 5

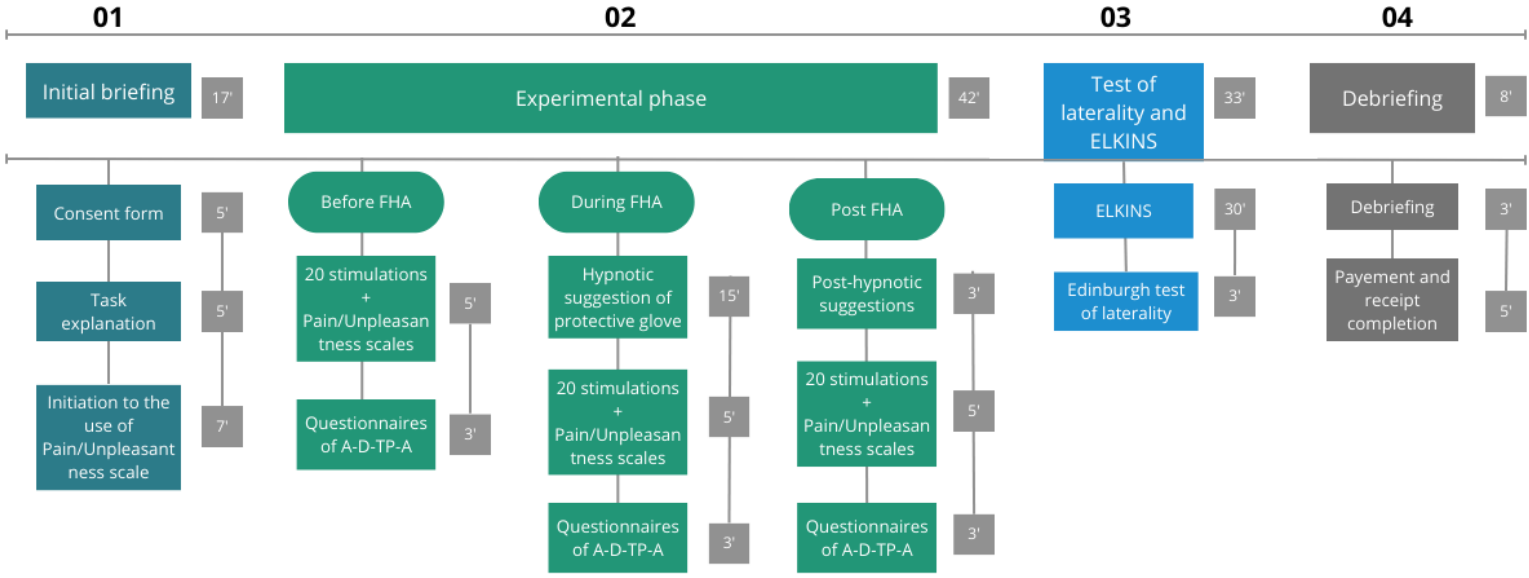


Figure 5 : Time course of the behavioral experiment. First, it was the initial briefing and the familiarization task. Then, there was the experimental phase with the three conditions: before, during, and after focused hypnotic analgesia. Each condition was followed by the question of absorption (A), dissociation (D), time perception (TP), and automaticity (A). Next, there were the Edinburgh test of laterality and the ELKINS hypnotizability scale. Finally, subjects received a debrief and were reimbursed for their participation.

Following that, subjects were submitted to the Edinburgh test of laterality (Oldfield, 1971) which assesses the dominance of a person's right or left hand in everyday activities, referred to as laterality. Participants were also submitted to the scale of suggestibility, the ELKINS hypnotizability scale (Kekecs et al., 2016), scoring the behavioral responses to a series of individual suggestions, and they were categorized into three groups, low hypnotizable, moderately hypnotizable, and highly hypnotizable. Finally, once the experiment was over, subjects were debriefed and reimbursed for their participation.

1.4) Measures

After each stimulation, subjects had to give two numerical rating scales (NRS) to rate the pain and the unpleasantness of the stimulations. The pain scale consists of giving a number from 0 to 100, 0 when nothing is perceived, 100 when it is the most painful sensation imaginable and 50 is the pain threshold (Lejeune et al., 2023). The scale of unpleasantness consists of giving a number from 0 to 100, 0 when it is not unpleasant at all and 100 when it is the most unpleasant sensation imaginable (Rainville, 2002).

After each condition, four questions to predict hypnotizability were asked to the participants (Vanhaudenhuyse et al., 2019). The first one was a question of absorption where participants were asked to estimate on a scale of 0, not at all to 10, fully, how deeply they felt absorbed and felt their attention focalized and focused on the experience they have just lived. The second question was on dissociation, participants were asked to estimate on a 0 to 10 scale if they felt a dissociation between their bodily sensations and the actual environment. Zero means they were in the reality, in the room, and 10 means that they completely escaped in their subjective experience, totally disconnected from the here-and-now reality. The third question was on automaticity, participants were asked to rate on a scale of 0 to 10 how much control they had over their actions and thoughts. 10 signifies a sense of perfect control, where they felt like they were the driving force behind their actions and thoughts. 0 means a state where they were the passive witness of their actions and thoughts, where they occur and follow each other naturally without them having the impression of being at the origin of one or the other. The last question was for time perception where participants were asked to estimate the duration of stimulation.

At the end of the experiment, subjects did the ELKINS hypnotizability scale. The ELKINS scale is a standardized scale scoring the behavioral responses to a series of individual suggestions, and they have been categorized into three groups, low hypnotizable, moderately hypnotizable, and highly hypnotizable (Kekecs et al., 2016). This scale has been carried out by the experimenter in charge of the hypnosis, a trained female hypnotist.

1.5) Analyses

All data analyses were conducted using the JASP program (version 0.17.2.0). All statistical tests were considered as significant with a $p < .05$. To estimate the effect size partial eta squared (η^2p) was used for the repeated measures ANOVA analysis and Cohen's d was used for paired t-Test analysis. Assumptions of normality, equality of variance, and sphericity were tested with their respective tests: Shapiro-Wilk, Levene's, and Mauchly's. The Greenhouse-Geisser or the Huynh-Feldt corrections were applied when needed.

Preliminary analysis has been conducted to determine the number of subjects in each category of hypnotisability (high, medium, low) using the ELKINS scale, as well as the number of subjects that protected either their right or left arm while being suggested to build a protective glove over one of their arms. Additionally, Pearson's correlations between pain ratings and unpleasantness ratings were assessed for each period of time (before, during, after).

Then, to compare the efficacity of the suggestion of the protective glove measured before, during, and after focused hypnotic analgesia between the two arms and between the different groups of hypnotizability, a repeated measures ANOVA on pain ratings was conducted with "TIME" (before, during and after) and "ARM" (local vs remote) as within factors and "GROUP" (high, medium and low hypnotizable) as between-subject factor. We hypothesized a significant TIME x ARM x GROUP interaction suggesting an impact of the level of hypnotizability on the development of the protective glove during focused hypnotic analgesia on the local arm, being the arm receiving the suggestion of the protective glove. We also expected a significant TIME x ARM interaction that would confirm that the reduction of pain perception is more important over the local arm, as compared to the remote arm, with no suggestion of a protective glove, during focused hypnotic analgesia and verify the reliability of our results by validating our controls (before and remote arm). When significant interactions were observed, post-hoc analyses were carried out using the Holm correction in order to locate those differences.

Next, a supplementary analysis has been made on ratings of pain to verify that the difference in ratings between the two arms was not already significant before and after the suggestion of the protective glove. For that, a paired samples t-test has been performed by pairing the ratings of pain for each time (before, during, after) for the local arm, which has been under the suggestion of the protective glove, with the remote arm, where no suggestion was made.

Finally, exploratory analysis has been made on the four questions of absorption, dissociation, time perception, and automaticity. For that, a repeated measures ANOVA was conducted with “TIME” (before, during, and after) as within factors to predict hypnotizability. Another repeated measures ANOVA was conducted with “TIME” as within factor and “GROUP” (high, medium, and low hypnotizable) as a between-subject factor, we hypothesized a significant TIME x GROUP interaction suggesting an impact of hypnotizability on the responses given for those questions. We also expected a significant TIME x ARM interaction. When significant interactions were observed, post-hoc analyses were carried out using the Holm correction in order to locate those differences.

2) Experiment 2: Neurophysiological experiment

2.1) Participants

Based on the first experiment (*cfr* section 1.1) using a similar design, we ran a power analysis using PASS Software (NCSS Statistical Software) that indicated that 15 participants had to be included, when an effect size of d = 0.9 with a power of 80% was set, and a 2 × 3 (ARM x TIME) within-subject design was used. 12 healthy volunteers aged between 35 and 20 (M ± SD = 26 ± 5) took part in this study (3 men and 9 women, all right-handed), the experiment is still in progress. As the first experiment showed an effect of focused hypnotic analgesia on all levels of hypnotizability, the recruitment of participants wasn't based on their hypnotizability level. Participants were recruited under the same criteria as the first experiment with the addition of exclusion criteria due to the EEG recording. The added exclusion criteria were not being aged between 18 and 35, and consuming coffee excessively. Due to issues with the quality of the EEG signal, participants with frizzy hair or bold were also excluded. Moreover, having participated in the previous experiment including hypnosis was also an exclusion criterion.

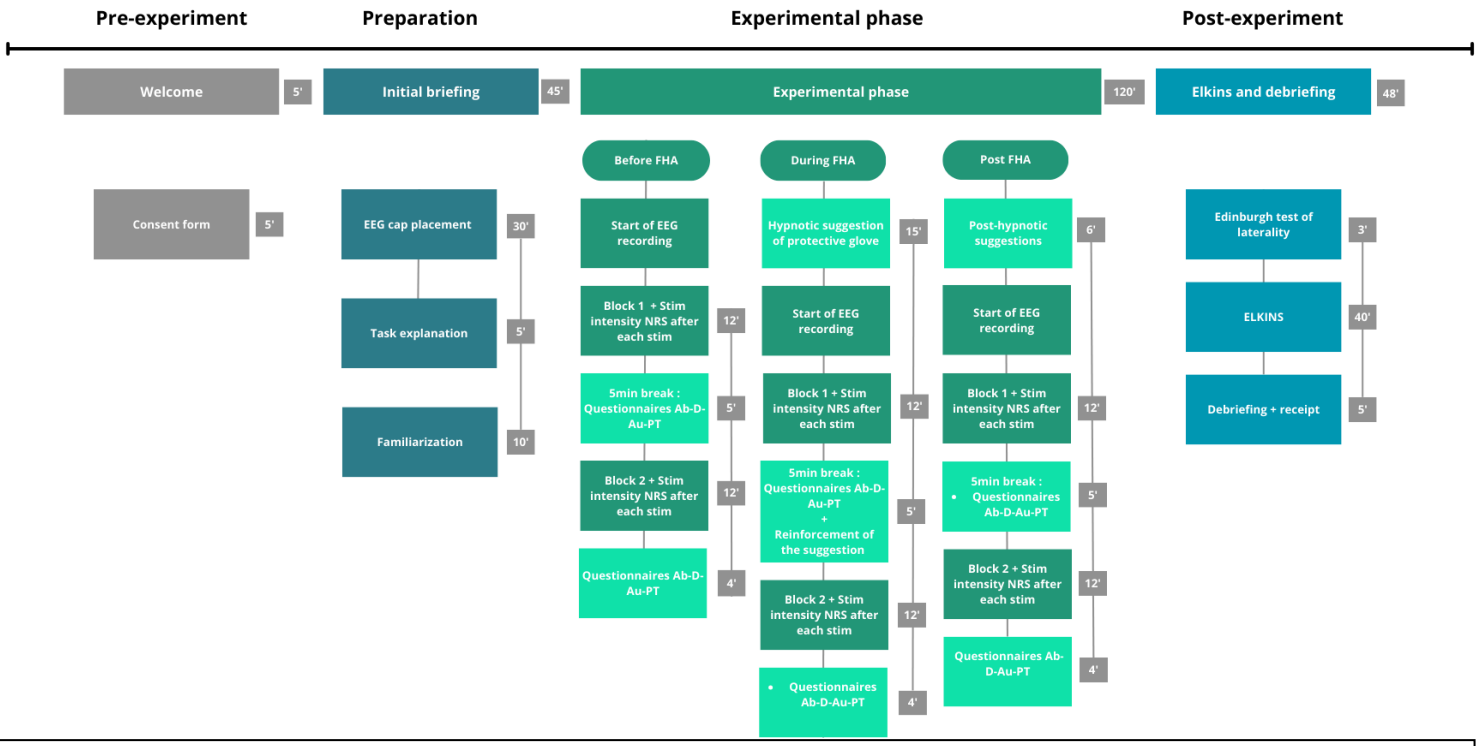
2.2) Apparatus and stimuli

Thermo-nociceptive stimuli were, as for the first experiment, delivered by two Peltier thermodes, contained in the probe of the TCS (Thermal cutaneous Stimulator II, QST.Lab, France), on the participant's volar forearms (**Figures 4**). The two experimenters in charge of the TCS changed sides between the different blocks while keeping their assigned probe to avoid a bias linked to technical issues, such as a difference in temperature stimulation between the two TCS. The thermodes were again moved on the forearm between each stimulation to avoid a spatial summation effect (Lejeune et al., 2023). The profile of stimulation was the same as for the first experiment except for the temperature of stimulation which was fixed at 62° (Lejeune et al., 2023) to avoid variability between subjects and avoid calculating a threshold of pain to simplify the experiment. With a ramp of heating and cooling set at 300 °C/sec and a total duration of 200ms, the duration of the plateau for each stimulation was about 120ms.

2.3) Procedure

Three experimenters conducted the study, one in charge of the hypnosis and two in charge of the stimulations. First, the participant arrived and after signing the consent papers he was asked to sit comfortably on a deck chair and to place his arms on the armrests with his sleeves to his elbow so the experimenters giving the stimulations have access to his volar forearms. Then, the experimenter in charge of the hypnosis explained the experiment while the two other experimenters placed the EEG cap on the participant's scalp. External electrodes were also placed, one was on the upper left side of the right eye (EX1), one was on the right lower side of the same eye (EX2), the two others were placed on the right and left earlobes (EX3 and EX4 respectively) for future re-referencing. The experiment lasted for about four hours (**Figure 6**).

Figure 6



<u>Figure 6:</u> Time course of the EEG experiment. First, the participant signed the consent papers. Then, there is the preparation of the experiment, it is the installation of the EEG device, the task explanation to the subject and the familiarization. Next, there is the experimental phase with the three conditions, before, during and after hypnotic suggestion. Each condition is made of two blocks composed of forty stimulations and after each stimulation, the participant was asked to rate the intensity of the stimulation using an NRS. The breaks between each block are represented in light green. During those breaks, the subject was asked questions on absorption (Ab), dissociation (D), time perception (PT) and automaticity (Au) (Vanhaudenhuyse et al., 2019). Finally, subjects were submitted to the Edinburgh test of laterality (Oldfield, 1971) and the ELKINS hypnotizability scale (Kekecs et al., 2016).

Before the experimental phase, the participant was presented with a familiarization task where the participant was introduced to contact heat stimulations. Therefore, they first received 1 stimulation at 58°C and then 60 °C on each forearm to get familiarized with the thermic stimulations gradually. Then he received stimulations, four at each forearm sent in a randomized order, of 62°C, the temperature used during the experiment. The familiarization task was simplified as compared to the first experiment because there is only one temperature of stimulation during this one so that each participant is in the same condition for the EEG recording and to avoid variability between sessions. After each stimulation at 62°C, the participant was asked to rate the intensity of the stimulation using an intensity scale from 0 to 100 (0=no sensation, 100=the most intense stimulation imaginable). The participant was also asked to give the best description of sensation felt during the stimulation after each stimulation according to 1 or 2 adjectives presented on a list of words (not perceived, light touch, tickling, prickling, warm, burning) and to notify if the stimulation was painful (yes or no answer) to have a trace of perception for all participants as for this experiment participants were all stimulated at the same temperature and so their perception was not matched.

The experimental phase was then performed with EEG recording (**Figure 6**). As the first experiment, it consisted of three conditions, a control condition before focused hypnotic analgesia, an experimental condition during focused hypnotic analgesia with the suggestion of the protective glove on the chosen arm (Paqueron et al., 2019) (**Annex 1**), and a condition after focused hypnotic analgesia with a post-hypnotic suggestion. To ensure blinding, the two experimenters in charge of the stimulation were not aware of where the participant decided to build the protective glove. To this end, they were never present in the lab during the administration of the suggestion of the protective glove. Each condition consisted of two blocks and each block was composed of forty trials in total, twenty for each arm in a randomized order. A trial is composed of one stimulation and is followed by the rating of the intensity of this stimulation by the participant using the same scale as during the familiarization task. Breaks were also done between each condition to avoid habituation of nociceptive fibers due to repetitive painful stimulation (Rennefeld et al., 2010). During those breaks, subjects were asked four questions to predict hypnotizability (Vanhaudenhuyse et al., 2019), questions on absorption, dissociation, time

perception, and automaticity. There were 5 minutes breaks after the first blocks of each condition, a break of approximately 19 minutes after the first condition was also made in order to include the induction of the hypnotic suggestion and a break of 10 minutes was made after the second condition to include the post-hypnotic suggestion. Moreover, during the break after the first block of the second condition, a reinforcement of the hypnotic suggestion was made.

Finally, subjects were submitted to the Edinburgh test of laterality (Oldfield, 1971) which assesses the dominance of a person's right or left hand in everyday activities, referred to as laterality. Participants were also submitted to the scale of suggestibility, the ELKINS hypnotizability scale (Kekecs et al., 2016), scoring the behavioral responses to a series of individual suggestions, and they were then categorized into three groups, low hypnotizable, moderately hypnotizable, and highly hypnotizable. At the end of the experiment, subjects were debriefed and reimbursed for their participation.

2.4) Measures

Participants were asked to rate the intensity of each stimulation using a numerical scale (NRS) to rate the intensity from 0 to 100, 0 being when nothing was perceived and 100 being when it was the most intense imaginable stimulation.

After each condition, four questions to predict hypnotizability were asked to the participants (Vanhaudenhuyse et al., 2019). The first one was a question of absorption where participants were asked to estimate on a scale of 0, not at all to 10, fully, how deeply they felt absorbed and felt their attention focalized and focused on the experience they have just lived. The second question was on dissociation, participants were asked to estimate on a 0 to 10 scale if they felt a dissociation between their bodily sensations and the actual environment. Zero means they were in the reality, in the room, and 10 means that they completely escaped in their subjective experience, totally disconnected from the here-and-now reality. The third question was on automaticity, participants were asked to rate on a scale of 0 to 10 how much control they had over their actions and thoughts. 10 signifies a sense of perfect control, where they felt like they were the driving force behind their actions and thoughts. 0 means a state where they were the passive witness of their actions

and thoughts, where they occur and follow each other naturally without them having the impression of being at the origin of one or the other. The last question was for time perception where participants were asked to estimate the duration of stimulation.

At the end of the experiment, subjects did the ELKINS hypnotizability scale. The ELKINS scale is a standardized scale scoring the behavioral responses to a series of individual suggestions, and they have been categorized into three groups, low hypnotizable, moderately hypnotizable, and highly hypnotizable (Kekecs et al., 2016). This scale has been carried out by the experimenter in charge of the hypnosis, a trained female hypnotist.

Nociceptive ERPs were recorded with 64 Ag-AgCl electrodes placed on the scalp according to the 10/20 system using an Active Two amplifier (BIOSEMI, Amsterdam, The Netherlands) at a sampling rate of 1024Hz. Impedances were kept under 20 kΩ and signals were referenced to the CMS electrode. Eye movements and blinks were tracked using electro-oculography with additional electrodes (EX1 and EX2) and two more additional electrodes were attached to the ear lobes for off-line referencing (EX3 and EX4). EEG recording started before each block and was stopped after each block.

The EEG recordings were analyzed offline using Matlab R2021b (the MathWorks) and the Letswave 6 toolbox for EEG data analysis (https://1etswave.org) (Mouraux and Iannetti, 2008). Bad electrodes were interpolated to the signal of the neighboring electrodes and signals were downsampled at a rate of 512 Hz. Then, the continuous EEG recordings were filtered using a 0,1-30 Hz bandpass 4^{th} degree Butterworth filter and a 50 Hz notch filter. EEG recordings were next rereferenced a first time by rereferencing all electrodes together, except the external electrodes, and a linear detrend has been applied to the signals. Then, EEG signals were first segmented in epochs of 2 seconds, starting 0,5 before stimulus onset, and an Independent Component Analysis using the FastICA algorithm was used to remove eye movement and eye blink artifacts. Next, signals were rereferenced to the ear lobes to increase the signal-to-noise ratio. EEG recordings were then segmented in epochs of 2 seconds, starting 0,5 before stimulus onset again, but based on the arm stimulated

to have one event per code, one for stimulations sent to the right arm and one for stimulations sent to the left arm. Then, to remove remaining artifacts, epochs with an amplitude signal above 100 µV were excluded. Finally, before averaging the epochs of the same condition, that is averaging two segments corresponding to the right or left arm stimulated for each condition, signals were baseline-corrected regarding the time interval -0.5 to 0 seconds relative to the stimulus onset. Once it is done, 6 signals are obtained, one for each arm and for the three conditions.

Next, the identification of the main components of the nociceptive ERPs (N1, N2 and P2) was based on their scalp topography, their morphology, and their latency. Their latency will be delayed compared to latencies of laser-evoked potentials (LEPs) as contact heat-evoked potentials (CHEPs) and LEPs use different processes to heat the skin and thus it takes more time to heat the skin using contact heat stimulation than laser (Lejeune et al., 2023). The method to identify ERPs components was therefore based on the morphology and topography as described by Legrain et al. in 2010 (Legrain et al., 2010) knowing that the latencies were going to be delayed. The N2 component was first identified at the vertex electrode (Cz) as a negative component peaking between 200 and 400ms after thermal stimulus onset. The P2 was identified similarly at Cz as the positive component following the N2 around 350-550ms after thermal stimulus onset. The N1 was isolated by rereferencing to the frontal Fz electrode and identified as a negative component peaking at the contralateral temporal electrode at 200-350ms after thermal stimulus onset. Peak amplitudes and latencies of the three components were used for analyses. Additionally, the amplitude difference between the N2 and P2 was also analysed.

2.5) Analyses

All data analysis were conducted using the JASP program (version 0.17.2.0). All statistical tests were considered as significant with a $p < .05$. To estimate the effect size partial eta squared (η^2p) was used for the repeated measures ANOVA analysis and Cohen's d was used for paired t-Test analysis. Assumptions of normality, equality of variance, and sphericity were tested with their respective tests: Shapiro-Wilk, Levene's, and Mauchly's. The Greenhouse-Geisser or the Huynh-Feldt corrections were applied when needed.

Preliminary analysis has been conducted to determine the number of subjects in each category of hypnotisability (high, medium, low) using the ELKINS scale, as well as the number of subjects that protected either their right or left arm while being suggested to build a protective glove over one of their arms.

Then, to compare the efficacity of the suggestion of the protective glove measured before, during, and after focused hypnotic analgesia between the two arms, a repeated measures ANOVA was conducted with “TIME” (before, during and after) and “ARM” (local vs remote) as within factors using the ratings of intensity. A significant TIME x ARM interaction is expected and that would confirm that the reduction of perception of the intensity of the stimulation is more important over the local arm, as compared to the remote arm, with no suggestion of a protective glove, during focused hypnotic analgesia and verify the reliability of our results by validating our controls (before and remote arm).

Next, exploratory analysis will be made on the four questions of absorption, dissociation, time perception, and automaticity. For that, a repeated measures ANOVA was conducted with “TIME” (before, during, and after) as within factors to predict hypnotizability). When significant interactions were observed, post-hoc analyses were carried out using the Holm correction in order to locate those differences.

Finally, supplementary analyses will be done on the questions asked during the familiarization, by using the description of sensation felt during the stimulation according to 1 or 2 adjectives presented on a list of words (not perceived, light touch, tickling, prickling, warm, burning), and responses on painfulness (yes or no answer) in order to make different groups depending on the perception of the stimulations for each subject.

Results

1) Experiment 1: Behavioral experiment

40 participants were tested for this experiment, 11 were categorized as highly hypnotizable, 22 as medium hypnotizable, and 7 as low using the ELKINS scale (Kekecs et al., 2016). 20 subjects decided to build the protective glove over their right arm and the other 20 built it over their left arm. Participants were not pre-selected according to their hand laterality assessed by the Edinburgh test of laterality (Oldfield, 1971) since no literary evidence showed an effect of this laterality on the effectiveness of the protective glove. Moreover, stimulations during the experimental phase, after a temperature was chosen during the familiarization task, were going from 62°C to 70°C. Additionally, Pearson's correlation revealed significative correlations between the ratings of pain and unpleasantness. Indeed, before the suggestion of the protective glove, the correlation between ratings of pain and unpleasantness was significant ($r=0,929$, $p<0,001$) as well as during the suggestion ($r=0,822$, $p<0,001$) and after removing the glove ($r=0,901$, $p<0,001$). As results for unpleasantness ratings (**Annex 2**) are very similar to those of pain ratings and unpleasantness ratings are highly correlated with pain ratings, only pain ratings will be described.

The ANOVA for repeated measures performed on pain ratings did not show a significant TIME x ARM x GROUP interaction ($F(4,74)=0,146$, $p=0,964$, $\eta^2p=0,008$) suggesting that the hypnotisability did not significantly influence the effect of the suggestion of the protective glove. However, the results revealed a significant TIME x ARM interaction ($F(2,74)=8,770$, $p<0,001$, $\eta^2p=0,192$) indicating that there is a selective effect of the protective glove regardless of the classification of hypnotisability. Indeed, post hoc tests, using the Holm correction, showed that pain ratings before focused hypnotic analgesia did not significantly differ between the stimuli applied on the local arm and those applied on the remote arm (Mean difference = - 0,440, $p=1$, Cohen's $d= - 0,024$) confirming that there is no difference in ratings between both arms before the hypnotic suggestion. Pain ratings following stimuli applied on the local arm, with the protection, significantly decreased during the suggestion as compared to before (Mean difference = -8,001, $p<0,001$, Cohen's $d= -0,439$) but it was not the case for the remote arm (Mean difference = -3,358

p=0,092, Cohen's d= -0,188) confirming that the protective glove has been built on the local arm. Furthermore, pain ratings following stimuli applied on the local arm, are significantly decreased during the suggestion as compared to after focused hypnotic analgesia (Mean difference = -5,167, p=0,001, Cohen's d=-0,289) but again it was not the case for the remote arm (Mean difference = 0,156 p=1, Cohen's d=0,009), confirming that the protective glove has been removed from where it was built, the local arm. Finally, pain ratings during focused hypnotic analgesia following stimuli applied on the local or the remote arm significantly differ (Mean difference = - 5,019, p=0,007, Cohen's d= - 0,275) with pain ratings for the local arm being lower as compared to those of the remote arm, confirming that the protective glove is effective over the arm where it has been built. (**Figure 7**).

Figure 7

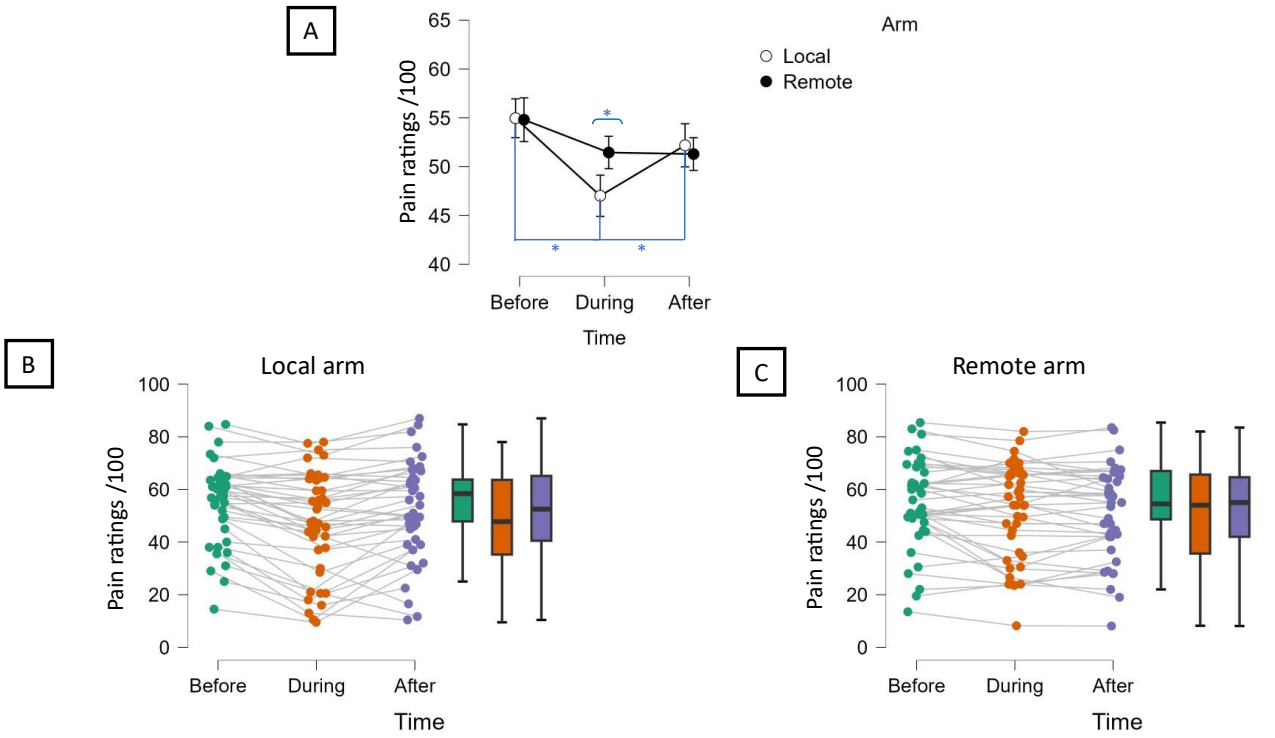
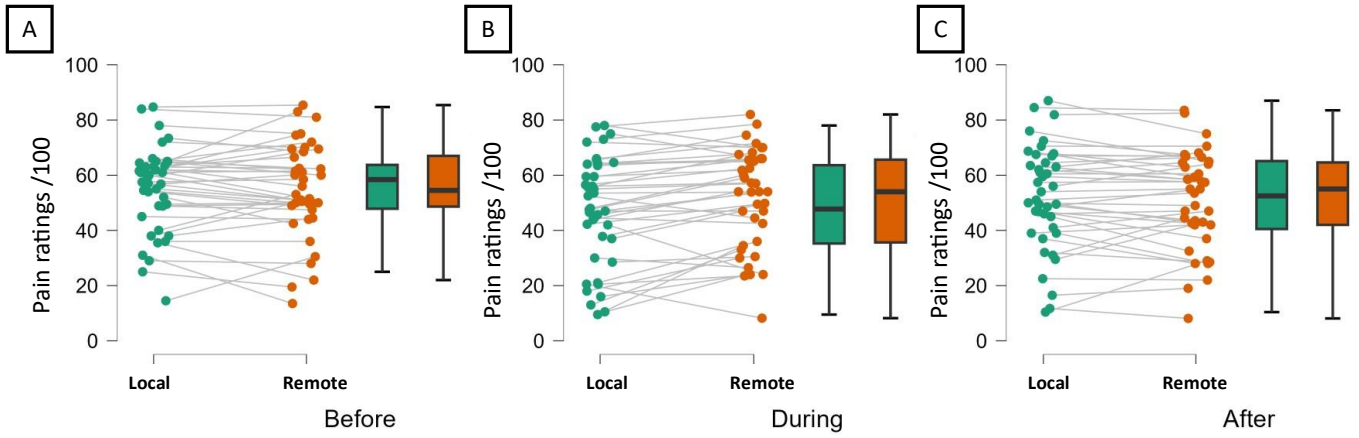


Figure 7: Participants' mean pain ratings. Pain ratings were given on a scale from 0 to 100 over the different conditions (TIME) corresponding to the before, during, and after focused hypnotic analgesia. **A)** Descriptive plot with different lines corresponding to the mean pain ratings for the different conditions when stimuli have been applied to the local or remote arm. *p<0,05. The error bars represent the 95% confidence interval. **B)** Raincloud plots for the mean pain ratings during the different conditions when stimuli have been applied to the local arm, where the protective glove has been built. **C)** Raincloud plots for the mean pain ratings during the different conditions when stimuli have been applied to the remote arm, where the protective glove has not been built.

The paired samples t-test revealed no significant difference either between the pain ratings of the local and remote arm before the suggestion of the protective glove (p=0,901, Cohen's d=0,020) but also after removing the glove (p=0,425, Cohen's d=0,127) (**Figure 8A et C**). However, there was a significant difference between the local and remote arms during the suggestion (p=0,002, Cohen's d=-0,523) with pain ratings being lower on the local arm which received the suggestion (**Figure 8B**). This confirms that there is only a difference in pain ratings between the two arms during the suggestion of the protective glove, confirming again that the protective glove is effective on the arm where it has been built.

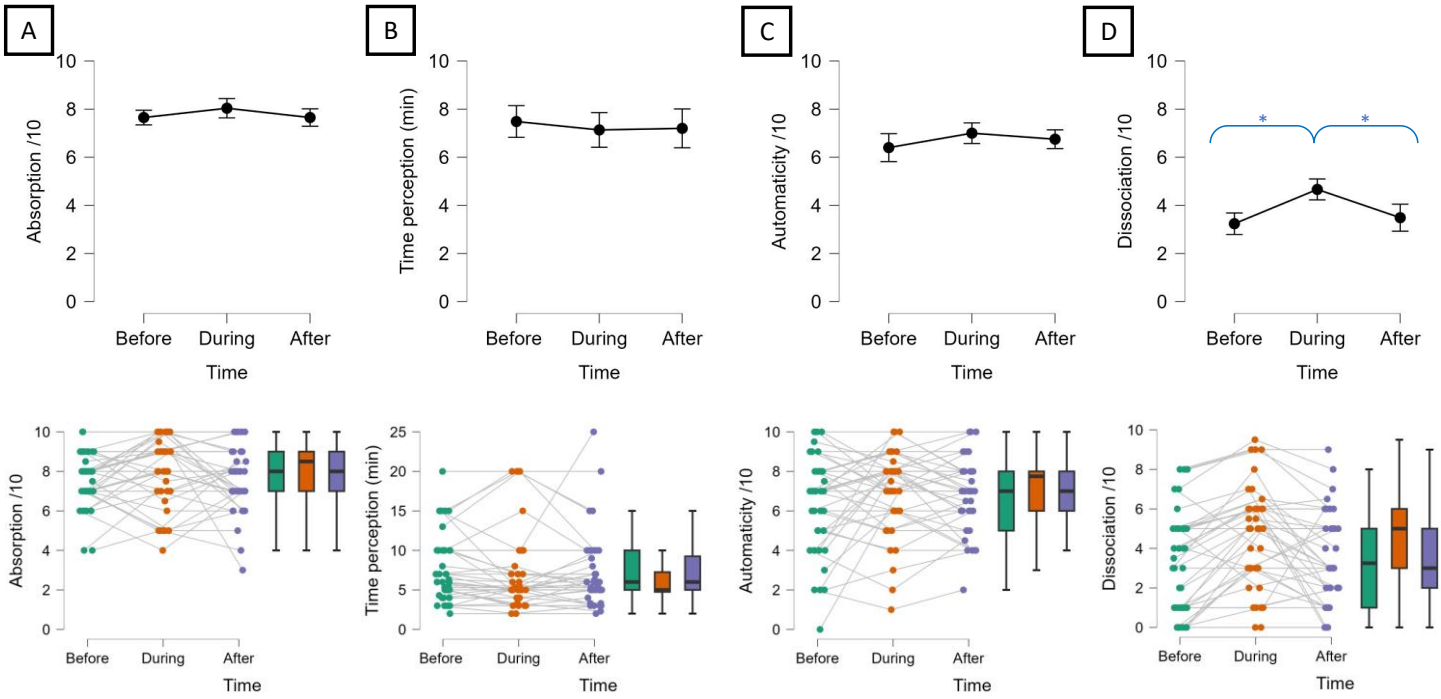
Figure 8



<u>Figure 8:</u> Participants' ratings of pain for the local and remote arms. Ratings were given on a scale from 0 to 100. **A)** Scatter plot of the paired samples t-test of the pain ratings between le local and remote arms before the suggestion of the protective glove. **B)** Scatter plot of the paired samples t-test of the pain ratings between le local and remote arms during the suggestion of the protective glove **C)** Scatter plot of the paired samples t-test of the pain ratings between le local and remote arms after removing the glove.

The ANOVA for repeated measures performed on the four questions did not show a significant TIME interaction for the questions of absorption ($F(2,78)=1,591$, $p=0,210$, $\eta^2p=0,039$), time perception ($F(2,78)=0,265$, $p=0,768$, $\eta^2p=0,007$) and automaticity ($F(2,78)=1,666$, $p=0,201$, $\eta^2p=0,041$) suggesting that those questions did not significantly predict hypnotisability. However, the results revealed a significant TIME interaction ($F(2,78)=10,090$, $p<0,001$, $\eta^2p=0,206$) for the question of dissociation indicating, in agreement with the literature, that dissociation would be the best parameter to predict hypnotizability (Vanhaudenhuyse et al., 2019). Indeed, post hoc tests, using the Holm correction, showed that the ratings of dissociation between the conditions before and during focused hypnotic analgesia differ (Mean difference = - 1,425, $p<0,001$, Cohen's d= - 0,573) confirming that dissociation increased during focused hypnotic analgesia. Ratings of dissociation before and after focused hypnotic analgesia did not significantly differ (Mean difference = - 0,250, $p=0,463$, Cohen's d= - 0,101) confirming that the glove has been removed after the suggestion. Moreover, ratings of dissociation between the conditions during and after focused hypnotic analgesia significantly differ (Mean difference = 1,175, $p=0,002$, Cohen's d=0,474) with ratings for the condition after focused hypnotic analgesia, after the subjects had removed the protective glove, increasing again to go back to the same ratings as before focused hypnotic analgesia. (**Figure 9**). However, the ANOVA for repeated measures performed on the four questions did not show a significant TIME x GROUP interaction for any of the questions. Absorption ($F(4,74)=1,575$, $p=0,190$, $\eta^2p=0,078$), time perception ($F(4,74)=0,278$, $p=0,891$, $\eta^2p=0,015$), dissociation ($F(4,74)=1,085$, $p=0,370$, $\eta^2p=0,055$) and automaticity ($F(4,74)=1,291$, $p=0,285$, $\eta^2p=0,020$). This suggests that there is no impact of hypnotizability on the responses given to those questions either.

Figure 9



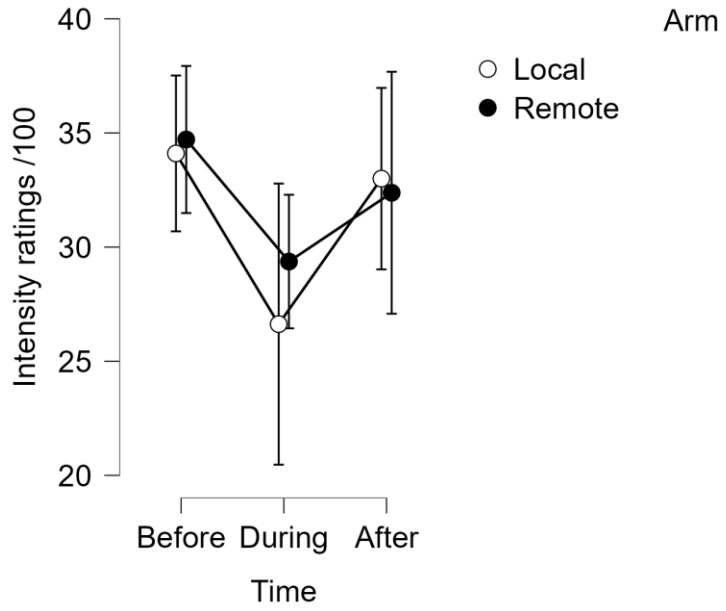
<u>Figure 9:</u> Participants' ratings of absorption, time perception, automaticity, and dissociation. Ratings were given on a scale from 0 to 10, except for time perception where subjects had to estimate the duration in minutes, for the different conditions (TIME) corresponding to the before, during, and after focused hypnotic analgesia. **A)** Descriptive plot of the mean ratings of absorption across all participants and raincloud plots of the ratings of absorption for each participant. **B)** Descriptive plot of the mean perception of time across all participants and raincloud plots of the time perception for each participant. **C)** Descriptive plot of the mean ratings of automaticity across all participants and raincloud plots of the ratings of automaticity for each participant. **D)** Descriptive plot of the mean ratings of dissociation across all participants and raincloud plots of the ratings of dissociation for each participant.
*p<0,05. The error bars represent the 95% confidence interval.

2) Experiment 2: Neurophysiological experiment

12 participants were tested for this experiment, 4 were categorized as highly hypnotizable, 6 as medium hypnotizable, and 2 as low using the ELKINS scale (Kekecs et al., 2016). 7 subjects decided to build the protective glove over their right arm and the other 5 built it over their left arm. As in the first experiment, participants were not pre-selected according to their hand laterality assessed by the Edinburgh test of laterality (Oldfield, 1971).

The ANOVA for repeated measures performed on intensity ratings did not show a significant TIME x ARM interaction ($F(2,18)=0,400$, $p=0,676$, $\eta^2p=0,043$) indicating that there is not a selective effect of the protective glove. However, even if this is not significant, a slight decrease in the mean ratings of intensity can be observed during the suggestion of the protective glove as compared to before and after the suggestion, and this decrease seems to be even greater for the local arm as compared to the remote arm. Also, after removing the glove, it seems that intensity ratings go back to what they were before the suggestion (**Figure 10**).

Figure 10



<u>Figure 10:</u> Participants' mean intensity ratings. Intensity ratings were given on a scale from 0 to 100 over the different conditions (TIME) corresponding to the before, during, and after focused hypnotic analgesia. The lines correspond to the mean intensity ratings for the different conditions when stimuli have been applied to the local or remote arm. The error bars represent the 95% confidence interval.

The nociceptive contact heat stimulations evoked a clear N2-P2 complex (**Figure 11**) and a weaker N1 component (**Figure 12**). The topographies of the N1 components were contralateral to the stimuli and, as expected, the topographies of the N2-P2 components were maximal at the vertex electrode (Cz).

Figure 11

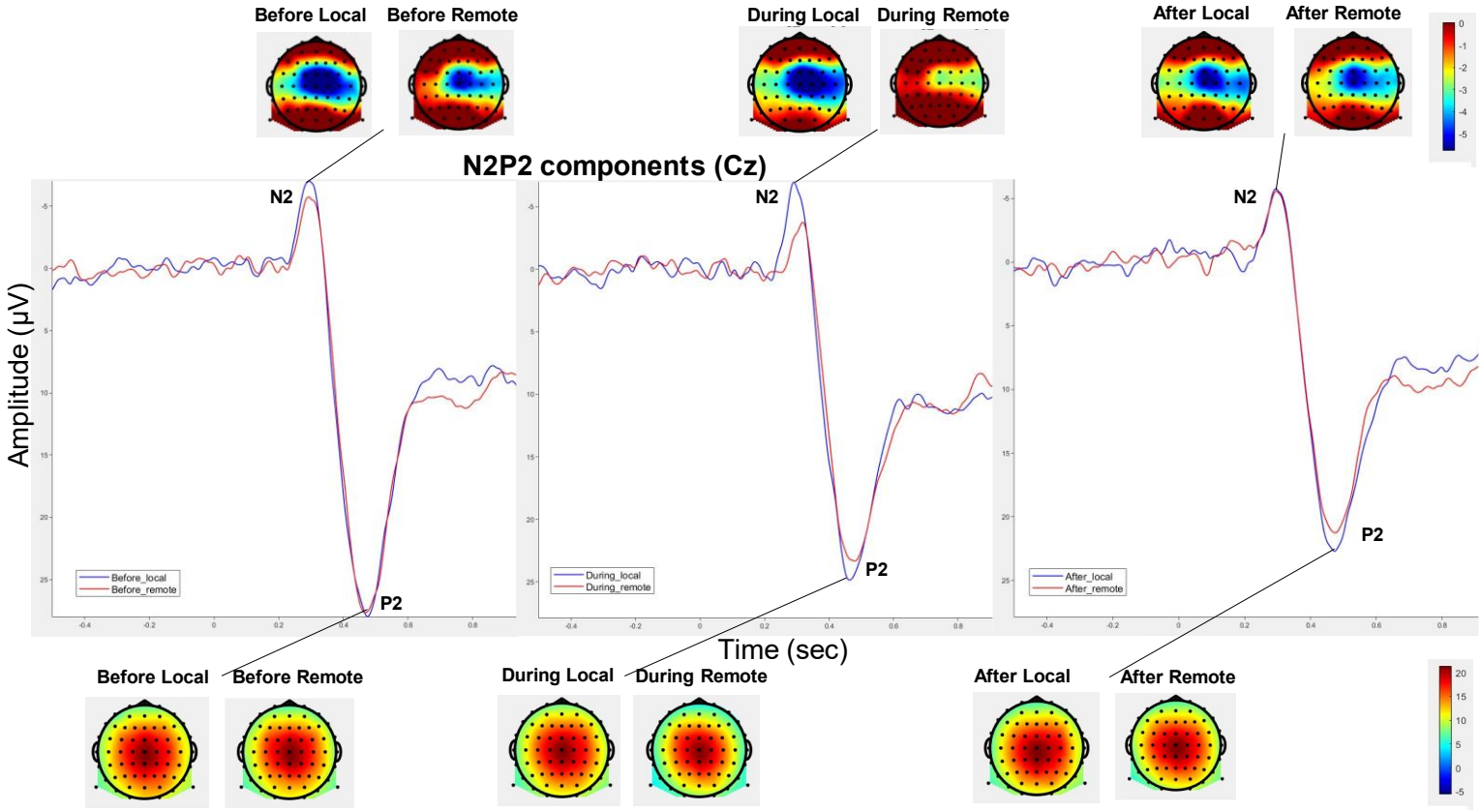
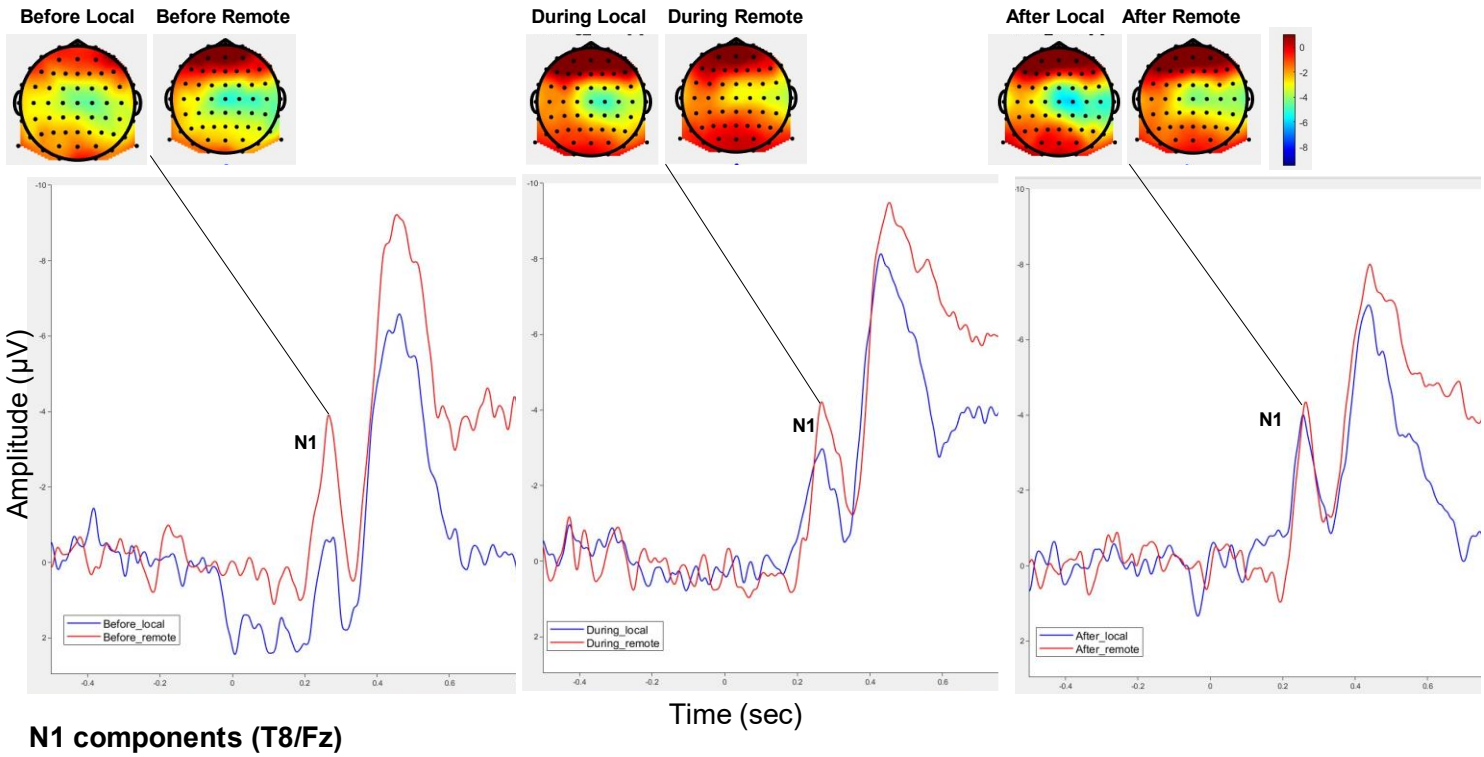


Figure 11: N2-P2 components at Cz and their topography. The across-participant grand-averaged ERPs obtained for each condition, before, during, and after hypnotic suggestion for the local and the remote arm. The N2-P2 component is maximal at the vertex electrode (Cz). The N2 component is the negativity peaking at 200-400ms after the stimulus onset and the P2 component is the positivity peaking between 350-550ms after the stimulus onset.

Figure 12



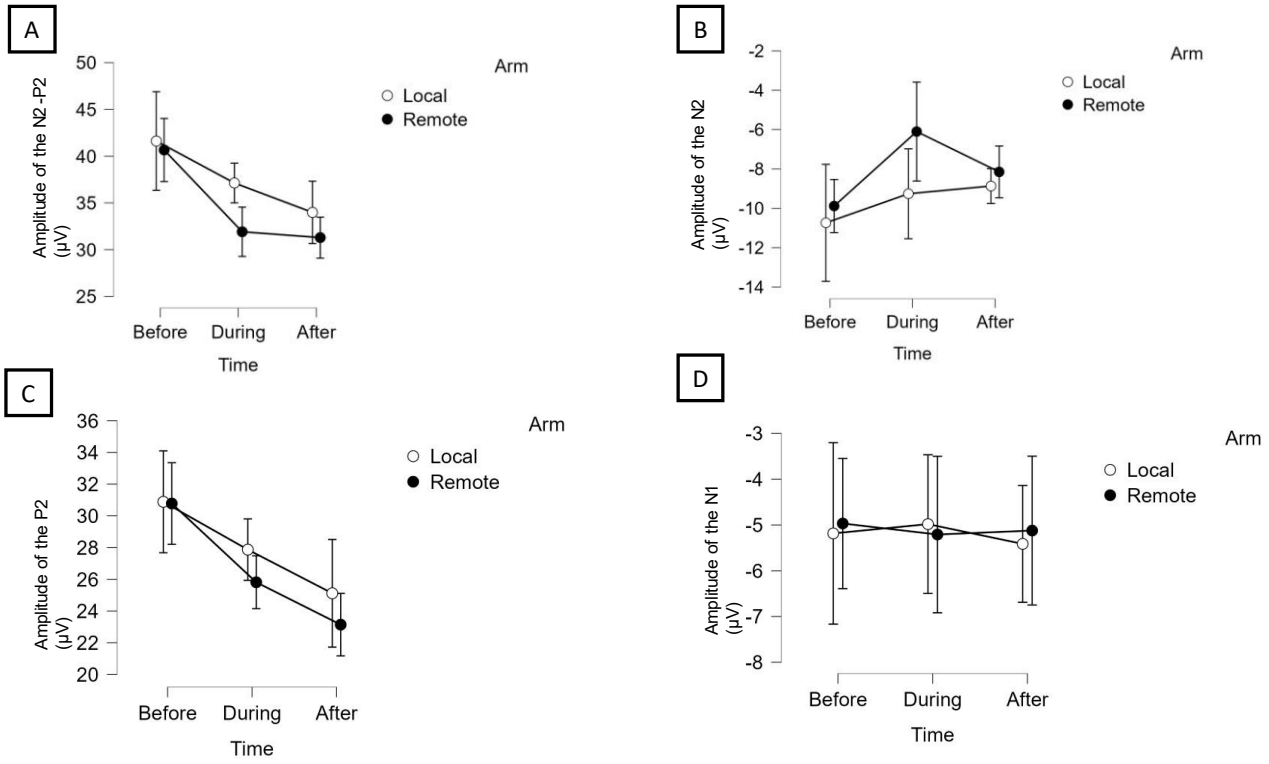
N1 components (T8/Fz)

<u>Figure 12:</u> N1 components at T8 and their topography. Signals have been rereferenced to the Fz electrode and the ERPs obtained for each subject have been averaged per condition, before, during and after the hypnotic suggestion for the local and remote arms. The N1 component has been identified as the negative component peaking between 200 and 350 ms after the stimulus onset.

The ANOVA for repeated measures performed on the amplitudes of the N2-P2 component did not show a significant TIME x ARM interaction ($F(2,22)=2,769$, $p=0,085$, $\eta^2p=0,201$). However, even if this is not significant, a slight decrease in the mean amplitudes of the N2-P2 component can be observed during the suggestion of the protective glove as compared to before, this decrease seems to be even greater for the remote arm as compared to the local arm and to continue after the suggestion for the local arm (**Figure 13A**). The ANOVA for repeated measures performed on the amplitudes of the N2 component did not show a significant TIME x ARM interaction ($F(2,22)=1,448$, $p=0,257$, $\eta^2p=0,116$). However, even if this is not significant, a slight decrease in the mean peak amplitudes of the N2 component can be observed during the suggestion of the protective glove as compared to before, this decrease seems to be even greater for the remote arm as compared to the local arm (**Figure 13B**). The ANOVA for repeated measures performed on the amplitudes of the P2 component

did not show a significant TIME x ARM interaction (F(2,22)=0,832, p=0,448, Ƞ²p=0,070). However, even if this is not significant, a slight decrease in the mean amplitudes of the P2 component can be observed during the suggestion of the protective glove as compared to before, this decrease even continues after the protective glove has been removed. Moreover, this decrease seems to be even greater for the remote arm as compared to the local arm (**Figure 13C**). The ANOVA for repeated measures performed on the amplitudes of the N1 component did not show a significant TIME x ARM interaction either (F(2,22)=0,110, p=0,896, Ƞ²p=0,010) (**Figure 13D**).

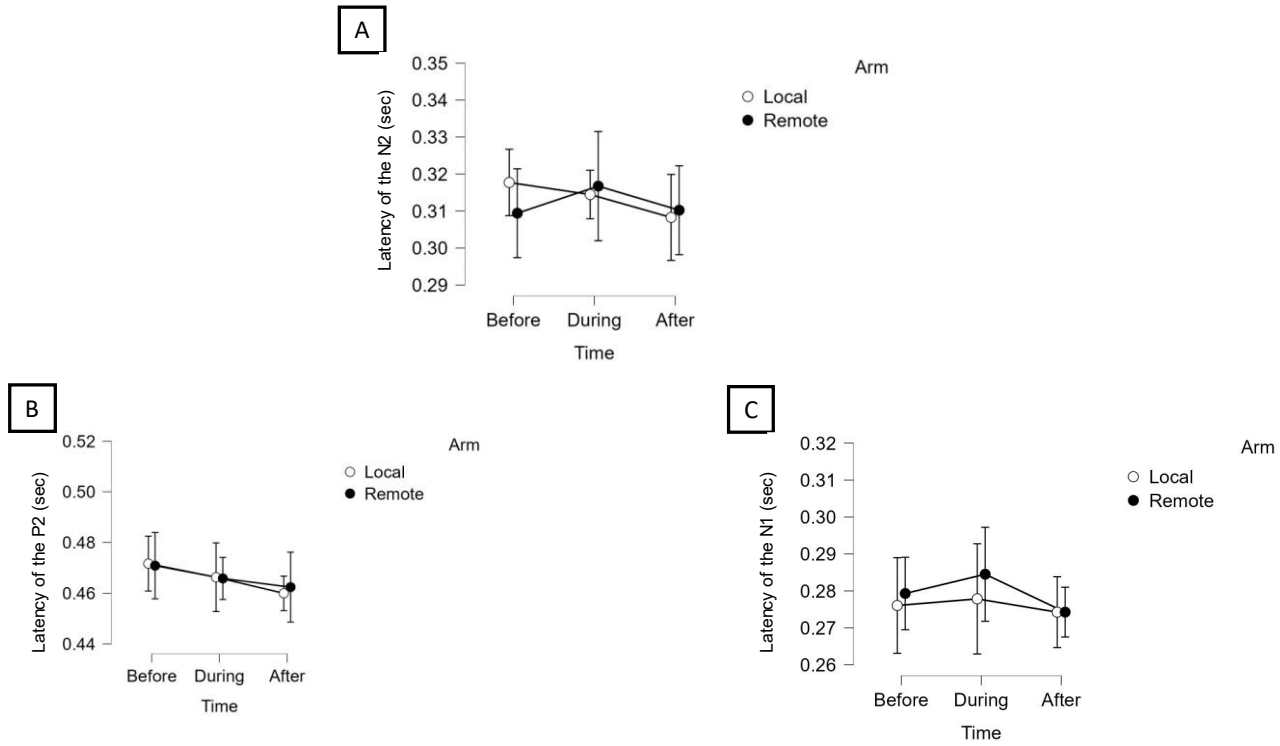
Figure 13



<u>Figure 13:</u> Mean amplitudes of ERPs components for the three conditions and for each arm. A) Mean amplitude of the N2-P2 component. **B)** Mean amplitude of the N2 component. **C)** Mean amplitude of the P2 component. **D)** Mean amplitude of the N1 component. No significative differences in the amplitudes of the different ERPs components were highlighted by the statistical analysis.

The ANOVA for repeated measures performed on the latencies of the N2 component did not show a significant TIME x ARM interaction (F(2,22)=0,650, p=0,532, η^2p=0,056) (**Figure 14A**). The ANOVA for repeated measures performed on the amplitudes of the P2 component did not show a significant TIME x ARM interaction (F(2,22)=0,078, p=0,929, η^2p=0,007) (**Figure 14B**). The ANOVA for repeated measures performed on the amplitudes of the N1 component did not show a significant TIME x ARM interaction either (F(2,22)=0,410, p=0,669, η^2p=0,036) (**Figure 14C**).

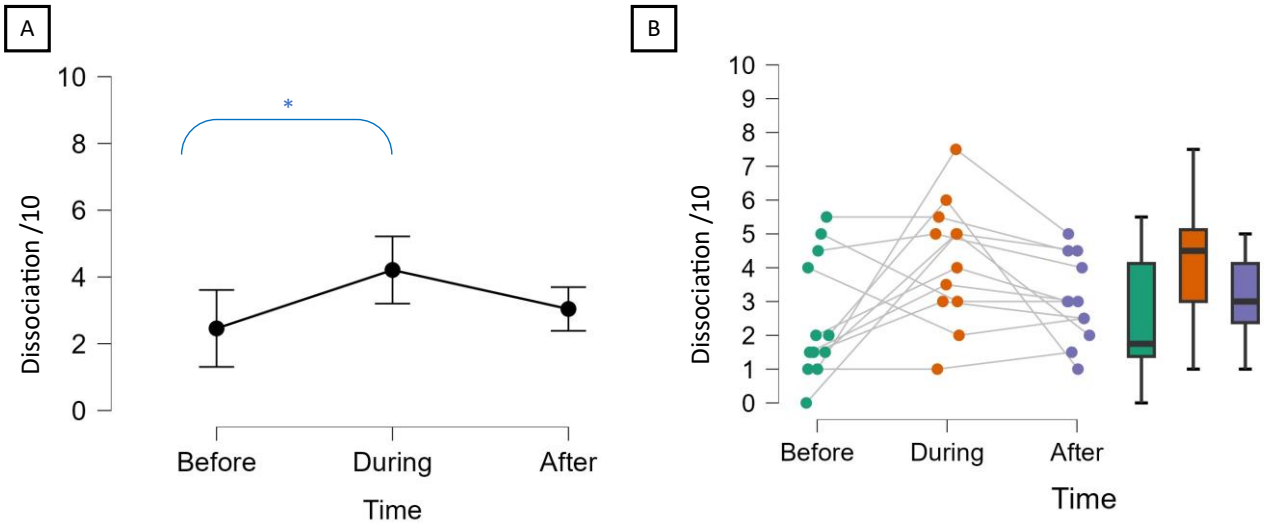
Figure 14



<u>Figure 14:</u> Mean latencies of ERPs components for the three conditions and for each arm. A) Mean latency of the N2 component. **B)** Mean latency of the P2 component. **C)** Mean amplitude of the N1 component. No significative differences in the latencies of the different ERPs components were highlighted by the statistical analysis.

The ANOVA for repeated measures performed on the four questions did not show a significant TIME interaction for the questions of absorption ($F(2,22)=1,793$, $p=0,202$, $\eta^2p=0,135$), time perception ($F(2,22)=0,047$, $p=0,954$, $\eta^2p=0,004$) and automaticity ($F(2,22)=0,022$, $p=0,978$, $\eta^2p=0,002$) suggesting that those questions did not significantly predict hypnotisability. However, the results revealed a significant TIME interaction ($F(2,22)=4,169$, $p=0,029$, $\eta^2p=0,275$) for the question of dissociation (**Figure 15**) indicating, that dissociation would be the best parameter to predict hypnotizability. Indeed, post hoc tests, using the Holm correction, showed that the ratings of dissociation between the conditions before and during focused hypnotic analgesia significantly differ (Mean difference = - 1,750 $p=0,029$, Cohen's d= - 1,064) confirming that the ratings of dissociation increased during focused hypnotic analgesia as compared to before. Ratings of dissociation before and after focused hypnotic analgesia did not significantly differ (Mean difference = - 0,583, $p=0,355$, Cohen's d= - 0,355) confirming that the glove has been removed after the suggestion.

Figure 15



<u>Figure 15:</u> Participants' ratings dissociation. Ratings were given on a scale from 0 to 10, with the different conditions (TIME) corresponding to the before, during, and after focused hypnotic analgesia. *p<0,05. The error bars represent the 95% confidence interval. **A)** Descriptive plot of the mean ratings of dissociation across all participants. **B)** raincloud plots of the ratings of dissociation for each participant.

Finally, supplementary analyses on questions asked during the familiarization, by using the description of sensation felt during the stimulation according to 1 or 2 adjectives presented on a list of words (not perceived, light touch, tickling, prickling, warm, burning), and responses on painfulness (yes or no answer) in order to make different groups depending on the perception of the stimulations for each subject allowed us to make a classification in two groups. The first group of subjects perceived 62°C stimulations mostly as non-painful and mostly used adjectives such as light touch, tickling, and warm to describe the simulations. The second group of subjects perceived 62°C stimulations mostly as painful and mostly used adjectives such as prickling and burning (**Annex 3**). However, this classification cannot be used for further analyses on pain ratings and ERPs components yet, by using CLASSIFICATION as a between-subject factor. Indeed, there are not enough participants in each group to be able to make these analyses, as 8 participants are classified in the first group and only 4 in the second one.

Discussion

This study aimed to investigate if our experimental design allows showing an effect of the suggestion of the protective glove and to investigate the effect of the hypnotic suggestion on pain processing by studying nociceptive ERPs elicited by nociceptive stimuli applied on the local arm, receiving the hypnotic suggestion, and the remote arm with no intervention. It was hypothesized that pain perception would be significantly decreased for the condition during focused hypnotic analgesia for the local arm, where the protective glove has been built, as compared to pain perception of the remote arm, where no suggestion has been made (De Pascalis et al., 1999; Houzé et al., 2021; Thompson et al. 2019; Valentini et al., 201). Moreover, it was also hypothesized that a decrease in the amplitude of the late ERPs evoked by contact heat stimuli at the level of the local arm would be observed in comparison to those from the remote arm, based on previous work (Zachariae and Bjerring, 1994, De Pascalis et al. 2007). Added to this is the fact that the efficacy of the glove should be influenced by hypnotic suggestibility. Indeed, more effect of the protective glove should be found in subjects with a higher score of hypnotizability and minimal benefits should be found for subjects with low hypnotic suggestibility as described by previous studies (Zachariae and Bjerring, 1994; De Pascalis et al., 2007).

Consistent with previous studies, the results showed a significant decrease in pain perception on the local arm during focused hypnotic analgesia compared with the other conditions, before and after focused hypnotic analgesia. Even more importantly, pain perception for the local arm, under the suggestion, was significantly different from that of the remote arm, the control arm, during the hypnotic suggestion. Indeed, pain ratings were lower for the local arm than the remote arm during the suggestion, confirming that the protective glove was efficient on the arm on which it was built. As for attention, this phenomenon could be explained by the processing of cognitive resources. In fact, as mentioned in the introduction, selective attention is the ability to prioritize the processing of some inputs and then facilitate their perception and responses at the expense of other inputs (Legrain et al., 2015). In the same way, focused hypnotic analgesia requires focusing attention on the hand receiving painful stimulation (Paqueron et al., 2019, Virot C. and Bernard F., 2019). Therefore, inputs from the local arm could be prioritized over those from the remote arm to maintain the effect suggested by the protective glove. Then, this could mean

that hypnotic and attentional mechanisms are different but share similarities. Indeed, hypnosis seems to decrease pain perception where attention is focused whereas if this was explained only by attentional mechanisms it would be by directing subjects' attention away from the nociceptive stimulus that a decrease in pain perception should be observed as compared to a control condition (Miron et al.,1989; Dunckley et al., 2007).

Surprisingly, no significative results were shown on the amplitudes of the different ERPs components generated for both arms during the three conditions, indicating there is no effect of focused hypnotic suggestion on the amplitudes of the ERPs components. However, even if this is not significant some tendencies can be observed on the amplitudes of the ERPs components. First, a slight decrease in the mean amplitudes of the late N2-P2 components can be observed during the suggestion of the protective glove as compared to before, this decrease seems to be even greater for the remote arm as compared to the local arm and continues for the local arm which is surprising. Then, a slight decrease in the mean peak amplitudes of the N2 component can be observed during the suggestion as compared to before, this decrease seems to be even greater for the remote arm as compared to the local arm which is surprising too. Finally, a slight decrease in the mean amplitude of the P2 component can be observed during the suggestion as compared to before. What is surprising is that this decrease continues after the protective glove has been removed and seems to be even greater for the remote arm than the local arm.

Moreover, no significant differences were found between the latencies of the different ERPs components, indicating that focused hypnotic analgesia does not act on speed conduction.

Even more surprisingly, the analyses of the triple interaction with the between-subject factor GROUP (low, medium, and high hypnotizable) show that there is no significant effect of the classification of hypnotisability either for pain perception or for the four questions of hypnotisability (absorption, dissociation, time perception, automatic).

In the following section, different hypotheses will be addressed. First, on the absence of an effect of focused hypnotic analgesia on the ERPs components. Next, on the

absence of the effect of the classification of hypnotisability. It will then be followed by a general conclusion and the perspectives of this experiment will be evoked.

1) Why no effect on ERPs components?

Firstly, it is important to note that the second experiment is still in progress so more participants will be tested, and analyses will be redone with the whole sample. Indeed, power analyses using PASS Software (NCSS Statistical Software) indicated that at least 15 participants had to be included, using a similar design as for the first experiment, in order to observe a different effect of the protective glove on the local arm than on the remote arm during the suggestion. Nevertheless, we only tested 12 participants for now. Furthermore, because for the second experiment an effect on ERPs components is expected rather than only an effect on pain perception as in the first experiment, it could be expected that more participants must be included. In fact, as 15 participants are the minimum required, the next analyses will be redone on 30 participants as done in previous experiments using hypnoanalgesia and EEG recordings (De Pascalis et al., 1999; De Pascalis et al., 2007; Friederich et al., 2001).

Secondly, a tendency of decrease is already noticeable as the mean amplitudes of the late N2-P2 components can be observed during the suggestion of the protective glove as compared to before, this tendency could become significant with the whole set of participants required. This decrease would be expected and would confirm what has already been shown in previous experiments in which a decrease in the late components has been demonstrated for subjects receiving nociceptive stimuli under hypnosis as compared to subjects with no intervention (De Pascalis et al., 1999; Perri et al., 2020). However, this decrease during the suggestions seems to continue even after removing the protective glove which is surprising. This could be explained by habituation to the repetitive painful stimulation (Rennefeld et al, 2010). Indeed, with this phenomenon of habituation, an effect of time is expected. Because for our experiments the three conditions were required to be always given in the same order, we expected to have a decrease in the magnitude of the ERPs component after each condition and thus to observe smaller magnitudes during the suggestion as compared to before and even smaller magnitudes after the

suggestion. The tendency observed here could then not be specific to hypnosis but rather due to this habituation.

Moreover, even if this is not significant, it can be observed that this decrease seems to be even greater for the remote arm as compared to the local arm. This is surprising as we hypothesize that the decrease in the amplitude of the late ERPs evoked by contact heat stimuli at the level of the local arm would be observed in comparison to those from the remote arm based on previous work although there is also a non-specific general hypnosis effect that is expected in both arms (Zachariae and Bjerring, 1994, De Pascalis et al. 2007). If this result is maintained while more subjects will have been tested, it could indicate that the technique of the protective glove is not effective enough to affect ERPs components. Other controls may be needed in order to measure the proportion of the effect which would be due to general hypnosis and therefore present on both arms. For example, by changing the conditions. Indeed, the condition before focused hypnotic suggestion could include a phase of neutral hypnotic suggestion, nociceptive stimulations would then still be sent on both arms. After that, the second condition could still be the one where the suggestion of the protective glove is made, again nociceptive stimulations would then be sent on both arms, the local arm that received the suggestion and the remote arm, without suggestion. By Doing that we could then compare the effect of neutral hypnosis with the specific effect of the glove suggestion.

Finally, in this second experiment, all participants did not perceive the stimulations as painful as the temperature of stimulation was fixed at 62°C and was not perceived the same way for all participants, as was observed during the familiarization task. This could be a problem because all participants did not have the same motivation to build the protective glove, yet motivation is a fundamental requirement for hypnosis (Virot and Bernard, 2018). Thus, there could be a negative bias of the effect of the suggestion on the ERPs components due to participants that were not motivated enough to build the glove compared to the one that were more motivated to do it. For this reason, when all participants will have been tested, the classification with subjects perceiving 62°C stimulations as painful or not could be used as a between-subject factor for the ANOVAs repeated measure analyses.

Why no effect of hypnotisability?

Studies have shown an effect of hypnotisability on pain ratings (De Pascalis et al., 1999; Houzé et al., 2021; Valentini et al., 2013), in those studies, pain ratings are shown to decrease even more for highly hypnotizable persons than for low hypnotizable persons as compared to a control condition without hypnosis.
It is hypnotized that highly hypnotizable persons can partition their attentional resources more effectively than can low hypnotizable individuals as explained by Crawford et al. in 1998. Because of these abilities to control unwanted stimuli, such as pain, there should be a relationship between hypnotic susceptibility and pain reduction using hypnotic analgesia. However, our experiment showed an effect of the protective glove for all groups, suggesting that the hypnotisability did not significantly influence the effect of the suggestion of the protective glove.

This could be explained by the fact that the suggestion of the protective glove required little effort and thus worked on everyone. Indeed, even though only 25% of the population is categorized as highly hypnotizable (Rousseaux et al., 2018), three fundamental conditions must be met to induce hypnosis as without motivation, cooperation and trust, hypnosis is not possible (Virot and Bernard, 2018). Those three conditions were easily fulfilled so that the suggestion could worked on everyone. First, subjects were motivated to be protected as stimulations were unpleasant. Then, subjects were cooperative as they came voluntarily to advance Science and they knew that hypnosis would only do them good. Finally, they had trust in the experimenter in charge of the hypnosis as knew he was trained.

Another hypothesis could be that the hypnotizability scale used, the ELKINS (Kekecs et al., 2016) was not reliable enough to cluster the different groups of hypnotizability. Indeed, the ELKINS is a recent scale, and it was not used in many studies yet and further studies must still be carried out to establish its role as a surrogate for the Stanford Hypnotic Susceptibility Scale: Form C used in most studies (De Pascalis et al., 1999; Houzé et al., 2021; Kekecs et al., 2016; Valentini et al., 2013). However, the Stanford Hypnotic Susceptibility scale: Form C takes longer to administer than the ELKINS, approximately one hour (Kekecs et al., 2016), which is long considering that our experiment already took a lot of time.

A study also showed, concerning the four questions of hypnotizability, that ratings were not significantly different between high and low hypnotizable persons for the question of absorption, time perception, and automaticity (Vanhaudenhuyse et al., 2019) as it was found in our study. However, in the study by Vanhaudenhuyse et al. in 2019, dissociation ratings differed when comparing low to high and medium to high hypnotizable subjects. Moreover, a positive correlation was found between dissociation ratings and the Stanford Hypnotic Susceptibility Scale: Form C. In our study, only a significant TIME interaction has been found for the question of dissociation indicating, in agreement with the literature, that dissociation would be the best parameter to predict hypnotizability (Vanhaudenhuyse et al., 2019). However, in our study, none of these ratings differed when comparing groups of hypnotizability. This could also be linked to the scale of hypnotizability in our study, the ELKINS, that differ from the study of Vanhaudenhuyse et al., 2019.

However, considering all groups of hypnotisability is more representative of the hypnosis effect on the population. Given that, although it is recognized that hypnosis is an innate talent, there is only about 25% of the population qualified as highly hypnotizable (Rousseaux et al., 2018) and by only considering them we would reject a large part of the population. Moreover, another study showed an effect of hypnosis on ERPs components without clustering by groups of hypnotizability either (Perri et al., 2020), this demonstrated that the effect of hypnotic suggestion could be present for every subject.

3) Conclusion and perspectives

To conclude, our hypotheses were only partially highlighted in this study. Pain perception is indeed different for the local arm that received the suggestion and the remote arm without intervention. Indeed, pain ratings for the local arm were lower than those from the remote arm, bringing evidence that focused hypnotic analgesia could be selective over the way that nociceptive inputs are processed in the brain. However, the selective effect of focused hypnotic analgesia on pain processing has not been shown as there is no significant difference in amplitudes or latencies of the ERPs components when nociceptive stimuli have been applied to the local or remote arms during the hypnotic suggestion as compared to before and after, probably because more subjects must be recruited. Moreover, there is no significant effect of

the classification of hypnotisability on the four questions to predict hypnotisability, but there is a significant increase in dissociation during hypnotic suggestion compared to before and after the suggestion suggesting that dissociation would be the best parameter to predict hypnotizability (Vanhaudenhuyse et al., 2019).

Perspectives would first be to do the EEG analyses again when all subjects will be tested. Then, if still no selective effect of focused hypnotic analgesia on pain processing will be shown, modification of the experiment could be done. For example, by using the questions we asked during the familiarization task of the second experiment, the best description of sensation felt during the stimulation after each stimulation according to 1 or 2 adjectives presented on a list of words (not perceived, light touch, tickling, prickling, warm, burning) and asking if the stimulation was painful (yes or no answer). By using these questions, it would be possible to make two groups of subjects. A first group of subjects who perceived 62°C stimulations mostly as non-painful and by using adjectives such as light touch, tickling, and warm to describe the simulations. A second group of subjects who perceived 62°C stimulations mostly as painful and by using adjectives such as prickling and burning. With this classification, we could see if there is more effect on this second group of subjects than in the first one, as they could have more motivation to build the protective glove making it more effective. We could then do the analyses again by using this classification as a between-subject factor in the ANOVAs repeated measures.

Bibliography

Bentley D.E, Watson A, Treede R.-D, Barrett G, Youell P.D, Kulkarni B, Jones A.K.P. (2004) Differential effects on the laser evoked potential of selectively attending to pain localisation versus pain unpleasantness. *Clinical Neurophysiology,* volume 115, Issue 8, Pages 1846-1856, ISSN 1388-2457. https://doi.org/10.1016/j.clinph.2004.03.010.

Crawford H.J, Knebel T., Kaplan L., Vendemia J., Xie M., Jamison S. & Pribram K.H. (1998) Hypnotic analgesia: 1. somatosensory event-related potential changes to noxious stimuli and 2. transfer learning to reduce chronic low back pain. *International Journal of Clinical and Experimental Hypnosis, 46:1, 92-132*. https://doi.org/10.1080/00207149808409992

Crombez, G., Van Damme, S., & Eccleston, C. (2005). Hypervigilance to pain: an experimental and clinical analysis. *Pain*. https://doi.org/10.1016/j.pain.2005.03.035

Daneshjou K., Jafarieh H., Raaeskarami S.R. (2012) Congenital Insensitivity to Pain and Anhydrosis (CIPA) Syndrome; A Report of 4 Cases. *Iran J Pediatr. Vol* 22 (No 3) 412-416. PMID: 23400697; PMCID: PMC3564101.

De Pascalis V., Cacae I., Massicolle F. (2007) Focused analgesia in waking and hypnosis: Effects on pain, memory, and somatosensory event-related potentials. *Pain*. 134(1-2):197-208. PMID: 18023535. https://doi.org/10.1016/j.pain.2007.09.005

De Pascalis V., Margurano M.R., Bellusci A. (1999) Pain perception, somatosensory event-related potentials and skin conductance responses to painful stimuli in high, mid, and low hypnotizable subjects: effects of differential pain reduction strategies. *Pain.* 1999 Dec;83(3):499-508. PMID: 10568858. https://doi.org/10.1016/S0304-3959(99)00157-8

De Pascalis V., Margurano M.R., Bellusci A., Chen A.C.N. (2001) Somatosensory event-related potential and automatic activity to varying pain reduction cognitive strategies in hypnosis. *Clin Neurophysiol.* 2001 Aug;112(8):1475-85. PMID: 11459688. https://doi.org/10.1016/s1388-2457(01)00586-7

De Pascalis V., Ray W.J. (2003) Temporal Aspects of Hypnotic Processes. *International Journal of Clinical and Experimental Hypnosis,* 51:2, 147-165. https://doi.org/10.1076/iceh.51.2.147.14615

Dunckley, P., Aziz, Q., Wise, R. G., Brooks, J., Tracey, I., & Chang, L. (2007). Attentional modulation of visceral and somatic pain. *Neurogastroenterol Motil,* 19(7), 569-577. https://doi.org/10.1111/j.1365-2982.2007.00908.x

Friederich M., H. Trippe R., Özcan M., Weiss T., Hecht H., H.R. Miltner W. (2001) Laser-evoked potentials to noxious stimulation during hypnotic analgesia and distraction of attention suggest different brain mechanisms of pain control. *Psychophysiology.* 2001 Sep;38(5):768-76. PMID: 11577900. https://doi.org/10.1111/1469-8986.3850768

García-Larrea L., Peyron R., Laurent B., Mauguière F. (1997) Association and dissociation between laser-evoked potentials and pain perception. *NeuroReport* 8(17):p 3785-3789. https://doi.org/10.1097/00001756- 199712010-00026

Gebhart G.F. (2004) Descending modulation of pain*.* *Neuroscience & Biobehavioral Reviews, Volume 27,* Issue 8, Pages 729-737. ISSN 0149-7634. https://doi.org/10.1016/j.neubiorev.2003.11.008

Houzé B., Streff A, Piché M., Rainville P. (2021) Spinal and supraspinal modulation of pain responses by hypnosis, suggestions, and distraction. *American Journal of Clinical Hypnosis,* 63:4, 329-354*.* https://doi.org/10.1080/00029157.2020.1863184

Jennings H.S. (1906) Behaviour of the lower organisms.

Kekecs Z., Bowers J., Johnson A., Kendrick C. & Elkins G. (2016) The Elkins Hypnotizability Scale: Assessment of Reliability and Validity. *International Journal of Clinical and Experimental Hypnosis,* 64:3, 285-304. https://doi.org/10.1080/00207144.2016.1171089

Lanfranco R.C., Canales-Johnson A., Huepe D. (2014) Hypnoanalgesia and the study of pain experience: from Cajal to modern neuroscience. *Front Psychol*.30;5:1126. PMID: 25324822; PMCID: PMC4179709. https://doi.org/10.3389/fpsyg.2014.01126

Le Bars D., Plaghki L. (2009). Physiologie et physiopathologie de la douleur, In "Le livre de l'interne : Médecine de la douleur " (F. Médecine-Sciences, Ed.), Chapitre 1.

Legrain V., Guérit J.-M., Bruyer R., Plaghki L. (2002) Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. *PAIN,* Volume 99, Issues 1–2, Pages 21-39. ISSN 0304-3959. https://doi.org/10.1016/S0304-3959(02)00051-9

Legrain V., Iannetti G.D., Plaghki L., Mouraux A. (2011) The pain matrix reloaded: a salience detection system for the body. *Prog Neurobiol*.; 93(1):111-24. PMID: 21040755. https://doi.org/10.1016/j.pneurobio.2010.10.005

Legrain V., Mancini F., Sambo C.F., Torta D.M., Ronga I., Valentini E. (2012) Cognitive aspects of nociception and pain. Bridging neurophysiology with cognitive psychology. *Neurophysiologie Clinique/Clinical Neurophysiology*, Volume 42, Issue 5, Pages 325-336. https://doi.org/10.1016/j.neucli.2012.06.003

Legrain V. and Torta D. (2015) Cognitive Psychology and Neuropsychology of Nociception and Pain. In: Pickering, G., Gibson, S. (eds) Pain, Emotion and Cognition. Springer, Cham. https://doi.org/10.1007/978-3-319-12033-1

Legrain V., Van Damme S., Eccleston C., Davis K.D., Seminowicz D.A, Crombez G. (2009) A neurocognitive model of attention to pain: Behavioral and neuroimaging evidence. 144(3), 0–232. https://doi.org/10.1016/j.pain.2009.03.020

Lejeune N., Petrossova E., Frahm K.S., Mouraux A. (2023) High-speed heating of the skin using a contact thermode elicits brain responses comparable to CO_2 laser-evoked potentials. *Clin Neurophysiol; 146:1-9.* PMID: 36473333. https://doi.org/10.1016/j.clinph.2022.11.008
Levine, J. D., Gordon, N. C., Smith, R., & Fields, H. L. (1982). Post-operative pain: effect of extent of injury and attention. *Brain Research,* 234(2), 500-504. https://doi.org/10.1016/0006-8993(82)90894-0

Loeser, J. D., & Treede, R. D. (2008). The Kyoto protocol of IASP basic pain terminology. *PAIN*, *137*(3), 473-477.

Miltner W., Johnson R., Braun C., Larbig W. (1989) Somatosensory event-related potentials to painful and non-painful stimuli: effects of attention. *Pain,* Volume 38, Issue 3, Pages 303-312, ISSN 0304-3959. https://doi.org/10.1016/0304-3959(89)90217-0.

Miron, D., Duncan, G. H., & Bushnell, C. M. (1989). Effects of attention on the intensity and unpleasantness of thermal pain. *Pain,* 39(3), 345-352. https://doi.org/10.1016/0304-3959(89)90048-1

Mouraux A., Iannetti G.D., Plaghki L. (2010) Low intensity intra-epidermal electrical stimulation can activate Aδ-nociceptors selectively. *PAIN,* Volume 150, Issue 1,Pages 199-207,ISSN 0304-3959. https://doi.org/10.1016/j.pain.2010.04.026.

Nowak H., Zech N., Asmussen S., Rahmel T., Tryba M., Oprea G., Grause L., Schork K., Moeller M., Loeser J., Gyarmati K., Mittler C., Saller T., Zagler A., Lutz K., Adamzik M., Hansen E. (2020) Effect of therapeutic suggestions during general anaesthesia on postoperative pain and opioid use: multicentre randomised controlled trial. *BMJ* 371 :m4282. https://doi.org/10.1136:bmj.m4281

Oldfield R.C. (1971) The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia,* Volume 9, Issue 1, Pages 97-113, ISSN 0028-3932, https://doi.org/10.1016/0028-3932(71)90067-4

Paqueron X., Musellec H., Virot C. & Boselli E (2019) Hypnotic Glove Anesthesia Induces Skin Temperature Changes in Adult Volunteers: A Prospective Controlled Pilot Study*. International Journal of Clinical and Experimental Hypnosis, 6*7:4, 408-427*.* https://doi.org/10.1080/00207144.2019.1649544

Parikh S.S., Chiu E., Taborda R. (2015) Pain and placebo physiology. *PM&R Knowledge NOW.*

Perri R.L., Facco E., Quinzi F., Bianco V., Berchicci M., Rossani F., Di Russo F. (2020) Cerebral mechanisms of hypnotic hypoesthesia. An ERP investigation on the expectancy stage of perception. *Psychophysiology.* (11):e13657. PMID: 32748968. https://doi.org/10.1111/psyp.13657

Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K (2020) The revised International Association for the Study of Pain definition

of pain: concepts, challenges, and compromises. *Pain.* 161(9):1976-1982. PMID: 32694387; PMCID: PMC7680716. https://doi.org/10.1097/j.pain.0000000000001939

Rainville P. (2002) Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology*, Volume 12, Issue 2, Pages 195-204, ISSN 0959-4388, https://doi.org/10.1016/S0959-4388(02)00313-6

Rennefeld C., Wiech K., Schoell E.D., Lorenz J., Bingel U. (2010) Habituation to pain: Further support for a central component. *PAIN*®, Volume 148, Issue 3, Pages 503-508, ISSN 0304-3959. https://doi.org/10.1016/j.pain.2009.12.014

Roberts K., Papadaki A., Gonçalves C., Tighe M., Atherton D., Shenoy R., McRobbie D., Anand P. (2008) Contact heat evoked potentials using simultaneous EEG and fMRI and their correlation with evoked pain. *BMC Anesthesiol* 8, 8. https://doi.org/10.1186/1471-2253-8-8

Rousseaux F., Faymonville M-E., Nysses A-S., Grégoire C., Bicego A., Vanhaudenhuyse A. (2018) Hypnose et recherche : que se passe-t-il à Liège ? *Hegel* N° 3(3):214-217. https://doi.org/10.4267/2042/68730

Rousseaux F., Panda R., Toussaint C., Bicego A., Niimi M., Faymonville M.E., Nyssen A.S., Laureys S., Gosseries O., Vanhaudenhuyse A. (2022) Virtual reality hypnosis in the management of pain: Self-reported and neurophysiological measures in healthy subjects. *Eur J Pain.* 148-162. PMID: 36196745; PMCID: PMC10091709. https://doi.org/10.1002/ejp.2045

Sharav Y., Tal M. (2006) Focused hypnotic analgesia: Local and remote effects. *Pain.* 124(3):280-286. PMID: 16750295. https://doi.org/10.1016/j.pain.2006.04.016

Sprenger C, Eippert F, Finsterbusch J, Bingel U, Rose M, Büchel C. (2012) Attention modulates spinal cord responses to pain. *Curr Biol ;*22(11):1019-22. PMID: 22608507. https://doi.org/10.1016/j.cub.2012.04.006

Thompson T., Terhune D.B., Oram C., Sharangparni J., Rouf R., Solmi M., Veronese N., Stubbs B. (2019) The effectiveness of hypnosis for pain relief: A systematic review and meta-analysis of 85 controlled experimental trials. *Neuroscience & Biobehavioral Reviews,* volume 99, pages 298-310. ISSN 0149-7634, https://doi.org/10.1016/j.neubiorev.2019.02.013

Valentini E., Betti V., Hu L., Aglioti S.M. (2013) Hypnotic modulation of pain perception and of brain activity triggered by nociceptive laser stimuli. *Cortex*, Volume 49, issue 2, pages 446-462,ISSN 0010-9452, https://doi.org/10.1016/j.cortex.2012.02.005

Van Damme, S., Crombez, G., & Eccleston, C. (2004). Disengagement from pain: the role of catastrophic thinking about pain. *Pain*, 107(1-2), 70-76. https://doi.org/10.1016/j.pain.2003.09.023

Vanhaudenhuyse A, Ledoux D, Gosseries O, Demertzi A, Laureys S, Faymonville ME. (2019) Can subjective ratings of absorption, dissociation, and time perception

during “neutral hypnosis” predict hypnotizability? An exploratory study. *Int J Clin Exp Hypn*. PMID: 30702397. https://doi.org/10.1080/00207144.2019.1553765

Van Hecke O., Torrance N., Smith B.H. (2013) Chronic pain epidemiology and its clinical relevance. *Br J Anaesth. ;*111(1):13-8*.* PMID: 23794640. https://doi.org/10.1093/bja/aet123

Villemure C, Bushnell CM. (2002) Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain*. PMID: 11839418. https://doi.org/10.1016/S0304-3959(02)00007-

Virot C., Bernard F. (2018) Hypnose, douleurs aiguës et anesthésie. *Arnette*

Wagenmakers, EJ., Love, J., Marsman, M. *et al.* (2018) Bayesian inference for psychology. Part II: Example applications with JASP. *Psychon Bull Rev*. https://doi.org/10.3758/s13423-017-1323-7

Zachariae R. & Bjerring P. (1994) Laser-Induced Pain-Related Brain Potentials and Sensory Pain Ratings in High and low Hypnotizable Subjects During Hypnotic Suggestions of Relaxation, Associated Imagery, Focused Analgesia, and Placebo. *International Journal of Clinical and Experimental Hypnosis,* 42:1, 56-80*.* https://doi.org/10.1080/00207149408409341

Appendix

<u>Annex 1:</u> Induction of focused hypnotic analgesia using the method of the protective glove (Paqueron et al., 2019, Virot & Bernard, 2018).

The protocol was based on the guidelines of Virot & Bernard, 2018. This technique was originally based on the construction of a protective glove, but it was adapted to a protection applied on the forearm in order to protect the zone stimulated by the contact-heat stimulation.

First, the experimenter asked the subject if a forearm preferred to be protected. If no preference was expressed, the experimenter in charge of the hypnosis chose the arm so the number of subjects protecting the right or left arm was equivalent. Once the protected arm was determined, the experimenter sat next to the subject and the arm to be protected and started the procedure by applying a slight nociceptive stimulation by pinching the skin of the volar forearm in order to make the participant feel pain to show that it would be interesting to protect it. Then, the subject was invited to mentally recall in of an object in her or his home that could be used to protect their forearm from pain. No restriction was given beside the fact that this object had to exist in their home and be familiar. Once the object was chosen, the experimenter asked what it was and a detailed description of it (size, colour, utility, material, texture, thickness). After taking a deep breath and visual and auditory references in the room, the experimenter asked the authorization to the participant to lift her or his forearm by taking it by the wrist and placed it in catalepsy. The participant was then invited to wrap the protective object around her or his forearm. No instruction was given regarding eye closure, and subjects were free to decide to close them or not. While the subject was putting the protection on, the experimenter gave some suggestions to feel the materiel and texture on the skin and remembering the details of its colour that they just mentioned before. Once the participants confirmed that the protection was correctly settled, the next step consisted in reinforcing it by adding a layer of cotton, such as used to build a cast. The experimenter started by asking what colour the cotton layer was and invited the subject to wrap it around the forearm, on top of the protection put on before. For this procedure, the experimenter helped the subject by virtually wrapping the band around its forearm and giving some suggestions of increased protection and analgesia. After passing two times completely on the forearm, the experimenter

stopped the movement and asked to the subject if enough cotton had been added to form an efficient protection against pain. Eventually, more cotton was virtually added at some places pointed out by the subject. The last step consisted in adding a layer of resin over the cotton one. The experimenter explained that the resin was initially soft, and progressively dried when put around the arm, until it became as hard as concrete. The explanation was accompanied by a sound of a hard surface by knocking on a table. The experimenter then asked the subject to take the time to feel the resin drying and becoming as hard as concrete, again by accompanying this explanation by a knock on the table. It was also specified that the harder and stiffer the protection became, the more protective and efficient it would be. Once the participant felt that the layer was dry and hard enough, she or he was asked to keep it well in place as it would be useful for the next step of the experiment. To end the procedure, the experimenter tested the evolution of sensitivity to pain by applying the same pinch as made before the procedure. In addition, another pinch was administered on the control arm to observe if a difference of pain perception was present between the protected and unprotected arm. Finally, it was explained that the protection they had built could be re-used every time they would need to protect themselves from pain.

Annex 2: Analyses made on unpleasantness ratings. Repeated measures ANOVAs on unpleasantness ratings with “TIME” (before, during and after) and “ARM” (local vs remote) as within factors and “GROUP” (high, medium, and low hypnotizable) as between-subject factor. Highlighted in green is the significant TIME x ARM interaction. When significant interactions were observed, post-hoc analyses were carried out using the Holm correction in order to locate those differences. Significant differences for the post-hoc analyses are highlighted in blue.

Within Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Time	1019.970 [a]	2 [a]	509.985 [a]	8.157 [a]	< .001 [a]
Time ✻ Group	97.961 [a]	4 [a]	24.490 [a]	0.392 [a]	0.814 [a]
Residuals	4626.822	74	62.525		
Arm	93.438	1	93.438	1.686	0.202
Arm ✻ Group	47.274	2	23.637	0.426	0.656
Residuals	2050.778	37	55.426		
Time ✻ Arm	341.783	2	170.891	12.727	< .001
Time ✻ Arm ✻ Group	26.566	4	6.642	0.495	0.740
Residuals	993.614	74	13.427		

Post Hoc Comparisons - Time ✻ Arm

			95% CI for Mean Difference					95% CI for Cohen's d		
		Mean Difference	Lower	Upper	SE	t	Cohen's d	Lower	Upper	p_{holm}
Before, Local	During, Local	8.012	3.400	12.623	1.535	5.219	0.372	0.113	0.630	< .001
	After, Local	2.368	-2.244	6.980	1.535	1.543	0.110	-0.115	0.334	0.756
	Before, Remote	-0.269	-4.228	3.690	1.305	-0.206	-0.012	-0.200	0.175	1.000
	During, Remote	2.953	-2.426	8.331	1.796	1.644	0.137	-0.126	0.400	0.719
	After, Remote	3.525	-1.853	8.904	1.796	1.963	0.164	-0.102	0.429	0.416
During, Local	After, Local	-5.644	-10.255	-1.032	1.535	-3.677	-0.262	-0.502	-0.022	0.005
	Before, Remote	-8.280	-13.659	-2.902	1.796	-4.611	-0.384	-0.678	-0.091	< .001
	During, Remote	-5.059	-9.018	-1.100	1.305	-3.878	-0.235	-0.441	-0.029	0.003
	After, Remote	-4.486	-9.865	0.892	1.796	-2.498	-0.208	-0.477	0.061	0.152
After, Local	Before, Remote	-2.637	-8.015	2.742	1.796	-1.468	-0.122	-0.385	0.140	0.756
	During, Remote	0.585	-4.794	5.963	1.796	0.326	0.027	-0.232	0.286	1.000
	After, Remote	1.157	-2.802	5.116	1.305	0.887	0.054	-0.135	0.243	1.000
Before, Remote	During, Remote	3.221	-1.390	7.833	1.535	2.099	0.150	-0.078	0.377	0.344
	After, Remote	3.794	-0.818	8.406	1.535	2.472	0.176	-0.054	0.406	0.152
During, Remote	After, Remote	0.573	-4.039	5.184	1.535	0.373	0.027	-0.195	0.248	1.000

Annex 3: **Data from the familiarization**. Description of sensation felt during the stimulation according to 1 or 2 adjectives presented on a list of words (not perceived, light touch, tickling, prickling, warm, burning) for each arm (L = left and R = right), responses on painfulness (yes or no answer) (L = left and R = right), and classification (1 = first group and 2 = second group). The first group was made of subjects perceiving 62°C stimulations mostly as non-painful and who mostly used adjectives such as light touch, tickling, and warm to describe the simulations. The second group was made of subjects perceiving 62°C stimulations mostly as painful and who mostly used adjectives such as prickling and burning. For subject 5 one stimulation was not sent.

Subject	L-Adjective	L-Adjective	L-Adjective	L-Adjective	R - Adjective	R - Adjective	R - Adjective	R - Adjective
1	Tickling	Prickling	Prickling	Prickling	Tickling	Light touch	Warm	Warm
2	Tickling	Prickling - Warm	Prickling	Prickling	Tickling	Prickling	Prickling - Warm	Prickling
3	Tickling	Prickling	Warm	Tickling	Prickling	Prickling	Tickling	Light touch
4	Tickling	Tickling	Prickling	Light touch	Prickling	Prickling	Tickling	Tickling
5	Tickling	Prickling	/	Burning	Tickling	Prickling	Prickling	Burning
6	Prickling	Prickling	Burning	Warm	Warm	Prickling	Warm	Warm
7	Prickling	Burning	Burning	Prickling	Prickling	Prickling	Warm	Warm
8	Light touch	Light touch	Light touch	Light touch	Tickling	Light touch	Tickling	Light touch
9	Burning	Warm	Burning	Warm	Warm	Burning	Warm	Warm
10	Warm	Warm	Warm	Prickling/Warm	Prickling/Warm	Tickling/Prickling	Warm	Prickling
11	Tickling	Light touch	Light touch	Tickling	Light touch	Light touch	Light touch	Light touch
12	Tickling	Prickling	Prickling	Warm	Tickling	Prickling	Prickling	Prickling

Subject	L - Pain	L - Pain	L - Pain	L - Pain	R - Pain	R - Pain	R - Pain	R- Pain	Classification
1	NO	NO	NO	NO	NO	NO	NO	NO	1
2	NO	YES	NO	NO	NO	YES	YES	NO	1
3	YES	YES	NO	YES	YES	YES	NO	NO	1
4	NO	NO	NO	NO	YES	YES	YES	NO	1
5	NO	NO	/	YES	NO	NO	NO	YES	1
6	YES	YES	YES	YES	YES	YES	YES	YES	2
7	YES	YES	YES	YES	YES	YES	NO	NO	2
8	NO	NO	NO	NO	NO	NO	NO	NO	1
9	YES	YES	YES	YES	YES	YES	YES	YES	2
10	YES	YES	NO	NO	NO	NO	YES	NO	1
11	NO	NO	NO	NO	NO	NO	NO	NO	1
12	YES	YES	YES	YES	YES	YES	YES	YES	2

Pain is a major healthcare issue and a better understanding of the physiological mechanisms underlying it and the psychological and cognitive factors that can modulate it is necessary to help diagnose and treat pain. There is evidence that focused hypnotic analgesia using the suggestion of a protective glove on one arm can reduce the perception of pain and its physiological responses. Nevertheless, experiences using focused hypnotic analgesia have not yet investigated the potential selective effect of this technique on pain processing by comparing the nociceptive brain response elicited by nociceptive stimuli applied on the two arms, the arm concerned by the focused hypnotic analgesia, the local arm, and the other arm considered as the control arm, the remote arm. Therefore, the aim of this study is to investigate the effect of focused hypnotic analgesia on pain perception and nociceptive ERPs using contact heat stimulation. For this, two experiments were conducted. In the first one, 40 healthy subjects participated. This consisted of collecting pain and unpleasantness evaluations after each nociceptive stimulation delivered either to the protected forearm or to the unprotected forearm. For the second one, ERPs were recorded for 15 healthy volunteers in response to nociceptive stimuli delivered either to the protected forearm or to the unprotected forearm. For the first experiment, repeated measures ANOVAs performed on the pain ratings showed a significant decrease in the ratings during the suggestion as compared to before. There is also a significant difference between the two arms, with lower ratings when the stimulations were applied on the suggested arm compared to the unprotected arm, confirming that the protective glove was efficient on the arm on which it was built. For the second one, there are no significant results, either for differences in amplitudes or latencies of the ERPs components when nociceptive stimuli have been applied on both arm and hypnotization was focused on one limb by the method of the protective glove, mainly because the experiment is still in progress and that more subjects have to be tested.

UNIVERSITÉ CATHOLIQUE DE LOUVAIN
Faculté de pharmacie et des sciences biomédicales
Avenue Mounier, 73 bte B1.73.06, 1200 Woluwe-Saint-Lambert, Belgique | **www.uclouvain.be/fasb**