Université de Montréal

Modulation ascendante et descendante de l'intégration supraspinale d'inputs nociceptifs bilatéraux

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Résumé

La nociception est un système d'alarme spécialisé dans la détection d'évènements potentiellement nocifs pour l'organisme. Les informations nociceptives sont traitées en priorité par le cerveau et captent l'attention involontairement (un mécanisme ascendant). Cependant, l'information sensorielle à laquelle nous portons attention volontairement est sélectionnée pour être priorisée (un mécanisme descendant). Ainsi, le traitement de l'information nociceptive est déterminé par une balance attentionnelle résultant de la compétition entre les signaux ascendants et descendants. Or, des situations où plusieurs stimuli nociceptifs ont lieu simultanément se produisent couramment. Mais quels mécanismes permettent au système nerveux central de s'adapter à de telles situations? Cela demeure méconnu à ce jour.

L'objectif principal de cette thèse était de mieux comprendre les mécanismes d'intégration cérébrale de l'information nociceptive. Cette thèse inclut quatre études examinant l'intégration cérébrale de l'information nociceptive bilatérale dans différentes conditions expérimentales. Dans ces études, nous avons investigué comment l'intégration de l'information nociceptive est affectée par 1) la latéralisation hémisphérique présumée distincte entre les droitiers et les gauchers, 2) la modalité utilisée pour induire la douleur (stimuli laser sélectifs aux nocicepteurs et stimuli électriques non spécifiques), 3) l'attention spatiale et 4) la proximité des régions corporelles stimulées. Dans chaque étude, au moins vingt participants furent recrutés et reçurent soit des stimuli électriques (étude 1 et 3) ou lasers (étude 2 à 4) douloureux. L'activité du cerveau fut enregistrée avec l'électroencéphalographie. Les stimulations unilatérales et bilatérales furent appliquées sur les chevilles (étude 1) et sur les mains (études 2 à 4). Les variables d'intérêts étaient la perception de la douleur, les potentiels évoqués, et les oscillations cérébrales évoquées entre 2 et 100 Hz.

Nos résultats indiquent que l'effet le plus reproductible lors d'une stimulation laser ou électrique bilatérale comparée à une stimulation unilatérale, est une augmentation de l'amplitude des réponses cérébrales (potentiels évoqués et oscillations cérébrales dans certaines bandes de fréquences). De plus, la comparaison entre les gauchers et les droitiers indique que ces effets sont comparables malgré la latéralisation hémisphérique présumée. Par ailleurs, l'augmentation des réponses cérébrales est modulée par la proximité des régions corporelles stimulées. Quant à la perception de la douleur, elle augmente pour les stimuli bilatéraux lorsque ces derniers sont

appliqués sur les chevilles ou les mains. Pour les mains, cet effet dépend toutefois de la distance entre les mains et de l'attention spatiale, étant observé seulement lorsque les mains sont rapprochées l'une de l'autre ou lorsque l'attention spatiale est dirigée vers les deux mains plutôt qu'une seule. Ces résultats montrent que l'intégration cérébrale de l'information nociceptive bilatérale est modulable, et nous proposons que l'augmentation des réponses cérébrales lors d'une stimulation bilatérale reflète une augmentation de la saillance et de la capture attentionnelle. Cette intégration et sa modulation par différents facteurs permettraient au système nerveux central de produire des réponses adaptées selon les sources de nociception et la balance attentionnelle.

Mots-clés : douleur, nociception, électroencéphalographie, potentiels évoqués, oscillations cérébrales évoquées, intégration sensorielle, stimuli bilatéraux, laser, attention spatiale, proximité spatiale, dominance motrice.

Abstract

Nociception is an alarm system specialized in the detection of events that are potentially harmful to the body. Nociceptive processing is prioritized in the brain and is particularly adept at capturing attention automatically and involuntarily (i.e., a bottom-up mechanism). However, the sensory information to which we voluntarily pay attention (a top-down mechanism) is also prioritized. Thus, the processing of nociceptive information is subject to a bottom-up and top-down attentional balance. However, situations where several nociceptive stimuli take place simultaneously are common. The mechanisms that allow the nervous system to manage this attentional balance in such situations remain poorly understood.

The main objective of this thesis was to better understand the integration of nociceptive information. This thesis presents four studies examining the cortical integration of bilateral nociceptive stimuli. These studies investigated the role of 1) the hemispherical lateralization of pain that is presumed to be different between left- and right-handed individuals, 2) the modality (a bottom-up mechanism) used to induce pain, 3) spatial attention (a top-down mechanism), and 4) between-limb proximity in the integration of bilateral painful stimuli. In each study, at least twenty participants were recruited and received either painful but tolerable electrical (Studies 1 and 3) or laser (Studies 2 to 4) stimulation. Brain activity was recorded via electroencephalography. Unilateral and bilateral stimulations were delivered to the ankles (Study 1) and to the hands (Studies 2 to 4). The variables of interest were pain perception, evoked potentials (ERP), and event-related spectral perturbations (ERSP) from 2 to 100 Hz.

In the first study, the impact of the hemispherical lateralization of pain processing (located mainly in the right hemisphere) on the integration of pain stimuli was examined by comparing left-handed and right-handed participants. In the second study, lasers selectively activating nociceptors were used to study the integration of bilateral nociceptive stimuli specifically. The third study sought to explain the observed discrepancies between laser and electrical modalities in Studies 1 and 2 by comparing these modalities in the same participants and in two separate experiments. The fourth study explored the role of spatial attention and limb proximity in the integration of bilateral nociceptive stimuli.

The results show that bilateral painful stimuli led to increases in ERP and some ERSP frequencies compared to unilateral stimuli. These results were similar between left-handed and right-handed people. More variability was noted for laser compared to electrical stimuli with the most reproducible response being an increase in ERP and ERSP. Finally, this increase was modulated by limb proximity. Pain perception was increased for bilateral stimuli to the ankles. It was also increased for bilateral stimuli to the hands, but only when the limbs were in close proximity or when spatial attention was global. These results suggest that bilateral painful stimuli are integrated, which possibly reflects an increase in salience and attentional capture. This would allow the central nervous system to produce adapted responses in the face of increased danger.

Keywords: pain, nociception, electroencephalography, event-related potentials, event-related spectral perturbations, sensory integration, bilateral stimuli, spatial attention, limb proximity, hand dominance.

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LEP : Laser-evoked potentials- Potentiels évoqués laser

SEP : Somatosensory evoked potentials- Potentiels évoqués somatosensoriels

ERP : Event-related potentials- Potentiels évoqués

ERSP : Event-related spectral perturbations- Oscillations

EEG : Électroencéphalographie

EMG : Électromyographie

SI : Primary somatosensory cortex – Cortex somatosensoriel primaire

SII : Second somatosensory cortex – Cortex somatosensoriel secondaire

ACC : Cortex cingulaire antérieur (Anterior cingulate cortex)

MCC : Cortex cingulaire moyen (Midcingulate cortex)

VAS : Visual analogue scale – Échelle visuelle analogue

NRS : Numerical rating scale – Échelle d'évaluation numérique

WDR : Wide dynamic range – Neurone à large gamme dynamique

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Chapitre 1 Présentation de la thèse

Le phénomène de la douleur est défini comme une expérience sensorielle et émotionnelle désagréable, associée à une lésion tissulaire réelle ou potentielle[1]. Dans notre quotidien, la douleur est fortement associée à l'activation de neurones, les nocicepteurs, qui sont spécialisés dans la détection d'évènements potentiellement nocifs pour l'intégrité des tissus de l'organisme (Perl, 1968; Sherrington, 1906; Woolf & Ma, 2007). Si la présence d'activité dans les nocicepteurs mène souvent à de la douleur, les deux phénomènes sont néanmoins fortement dissociables, et la douleur n'est qu'une des possibilités suivant la nociception (Beecher, 1946; Ossipov et al., 2010; Sneddon, 2018). Cela s'explique en partie par des interactions entre deux formes de mécanismes attentionnels impliqués dans le contrôle du traitement de l'information sensorielle : les mécanismes ascendants (« *bottom-up* », provenant de l'environnement, involontaire et automatique) et descendants (« *top-down* », provenant de nos objectifs ou buts cognitifs, du contrôle volontaire de l'information, de nos attentes et de notre expérience antérieure). Le système nerveux central doit en tout temps équilibrer les priorités environnementales qui se présentent automatiquement (p. ex., un prédateur) avec celles personnelles et volontaires (p. ex., besoins à prioriser).

L'activité des nocicepteurs est en soi intrinsèquement saillante (un paramètre ascendant), soit la caractéristique d'un stimulus à être clairement distinct de son environnement (Itti & Koch, 2001; Menon & Uddin, 2010). La nociception, et la douleur qui peut en résulter sont particulièrement aptes à capturer notre attention involontairement et automatiquement, à interrompre nos objectifs en cours et à forcer une réorientation de notre attention sur l'endroit du corps potentiellement blessé (Eccleston & Crombez, 1999; Van Ryckeghem et al., 2013). D'un autre côté, il est bien documenté que des facteurs cognitifs comme l'attention sélective (un paramètre descendant), tel un projecteur qui illumine une partie de la scène sensorielle (Posner et al., 1980), peuvent affecter quelle information sera traitée en priorité. Ainsi, l'information nociceptive doit être intégrée au niveau cortical afin de produire des comportements élaborés et adaptés au contexte et à l'environnement (Tabor et al., 2017).

[1] Définition tirée de l'*International Association for the Study of Pain*

Dans la vie de tous les jours, les nocicepteurs peuvent être activés sur différentes régions corporelles simultanément comme lorsque nous manipulons un plat très chaud à deux mains. Cela présente une situation où le système nerveux central fait face à plusieurs stimuli particulièrement saillants et aptes à capturer l'attention. Afin de produire des réponses adéquates dans un tel contexte, le système nerveux central doit être en mesure d'intégrer ces stimuli nociceptifs. Par exemple, une fusion perceptuelle plus douloureuse et saillante pourrait permettre à l'organisme de réagir plus promptement et vigoureusement à la situation qui présente une plus grande menace à l'intégrité de l'organisme.

Nos connaissances sur des mécanismes centraux qui permettraient d'intégrer des stimuli nociceptifs simultanés sont très limitées. Des études ont démontré qu'en présence de deux stimuli douloureux, la douleur peut être plus élevée lorsque la sensation globale produite par les stimuli simultanés est évaluée par rapport à l'évaluation de l'un des deux stimuli (Algom et al., 1986; Lautenbacher et al., 2007; Nielsen & Arendt-Nielsen, 1997b; Quevedo & Coghill, 2007, 2009; Quevedo et al., 2017). Cependant, ces travaux ont uniquement mesuré les changements au niveau de la perception de la douleur, ce qui ne permet pas de comprendre quels mécanismes neurophysiologiques pourraient sous-tendre ces changements.

Une étude de notre laboratoire a mesuré les changements au niveau de l'activité électrique corticale entre une stimulation douloureuse sur une cheville, et une stimulation sur les deux chevilles ou sur une cheville et une main (Rustamov et al., 2019). Cette étude a démontré une augmentation de l'activité électrique mesurée par un électroencéphalogramme en présence de deux stimuli, suggérant que les deux stimuli douloureux pouvaient être intégrés. Cependant, certains facteurs qui seront détaillés dans l'introduction n'ont pas pu être contrôlés. Cela limite notre capacité à comprendre les mécanismes sous-jacents à cette intégration.

Cette thèse tente de répondre à ces questions à l'aide d'une série de quatre études. Le chapitre 2 de la thèse présente tout d'abord les phénomènes de la nociception et de la douleur. Cela est suivi d'une définition de l'intégration sensorielle et de facteurs importants de type descendant et ascendant pouvant la moduler. Par la suite, une section *Considérations Méthodologiques* présente les outils et les mesures utilisées dans le cadre de la thèse. La problématique est ensuite présentée, suivie de la présentation des quatre études réalisées dans le cadre de la thèse. Le chapitre 3 à 6 contient les quatre articles publiés. Finalement, le chapitre 7 présente une discussion visant à synthétiser les travaux et à expliquer comment ceux-ci s'inscrivent dans la littérature actuelle tout en proposant des avenues futures sur des questions connexes.

Chapitre 2 Introduction

La protection de l'intégrité de l'organisme

Deux systèmes nous permettent de protéger l'intégrité des tissus de notre organisme et ainsi promouvoir la survie de l'organisme: la nociception et la douleur (Dubin & Patapoutian, 2010; Middleton et al., 2021; Smith & Lewin, 2009). La nociception est la capacité à détecter des évènements nocifs pour les tissus (Sneddon, 2018, 2019; Woolf & Ma, 2007) et est plus ancienne évolutivement que la douleur (Burrell, 2017; Smith & Lewin, 2009), se retrouvant notamment chez les nématodes. En effet, la nociception a émergé de la nécessité des organismes à éviter des stimuli menaçant leur intégrité comme des stimuli de haute intensité de nature mécanique, chimique ou thermique (Sneddon, 2019). Cette capacité dépend grandement de la présence d'activité dans des neurones spécialisés appelés nocicepteurs (Burgess & Perl, 1967; Perl, 1968; Sherrington, 1903).

Les différents récepteurs du système somesthésique

La peau est un organe sensoriel situé à la frontière entre notre organisme et l'environnement extérieur et fait partie du système somesthésique. Elle est riche en récepteurs sensoriels nous permettant de percevoir notre environnement sensoriel immédiat, c.-à-d. la portion extéroceptive du système somesthésique. Si les nocicepteurs se retrouvent dans presque tous les tissus du corps humain, ce sont ceux au niveau de la peau qui servent un rôle extéroceptif. De façon générale, il est possible de diviser le traitement de l'information somesthésique en quatre étapes : la transduction, la transmission, la perception et la modulation du message nociceptif (Mertens et al., 2015). Par le mécanisme de transduction, ces récepteurs transforment en potentiels d'actions des stimuli de différentes natures comme la pression ou la vibration (mécanorécepteurs), la température (thermorécepteurs) ou la présence de certaines molécules (chémorécepteurs). Ces récepteurs peuvent répondre spécifiquement à une seule modalité ou au contraire être polymodaux (Sneddon, 2019). L'intensité minimale pour produire un potentiel d'action, le seuil d'excitation d'un neurone, peut également être très différente d'un récepteur à l'autre.

Ces potentiels d'action sont générés soit au niveau de récepteurs spécialisés (encapsulés ou non) ou au niveau de terminaisons nerveuses libres. La transmission de ces potentiels d'action se réalise ensuite via des fibres nerveuses vers le corps du neurone, situé dans le ganglion de la racine dorsal (Haberberger et al., 2019). Un tel neurone est ainsi considéré comme un neurone de 1er ordre, ou neurone afférent primaire. Les fibres nerveuses de la portion extéroceptive du système somesthésique peuvent être catégorisées en trois groupes principaux: les fibres Aβ, Aδ et C (Abraira & Ginty, 2013; Smith & Lewin, 2009). Ces catégories ont été déterminées selon des critères anatomiques, notamment leur calibre, et la présence d'une gaine de myéline qui isole électriquement le neurone et augmente la vitesse de conduction, et d'autres critères fonctionnels (Abraira & Ginty, 2013). Par fonctionnel, notons la modalité des stimuli qui évoquent une réponse (p. ex., mécanique, thermique, chimique) et les caractéristiques de la réponse aux stimuli (p. ex., seuil du neurone).

Les fibres Aβ sont fortement myélinisées ce qui leur confère une vitesse de conduction très élevée variant de 16 à 100 mètres par seconde (Abraira & Ginty, 2013; Rogart & Ritchie, 1977; Tran et al., 2001). Les neurones associés à ces fibres sont encapsulés, possèdent un seuil d'excitation très faible, et sont surtout impliqués dans la détection de stimuli mécaniques à bas seuil et non nocifs. En effet, leur réponse tend à être maximale à des intensités ne pouvant générer des dommages tissulaires. Lorsque l'activité dans ces fibres est traitée dans le cerveau, elle est associée à la sensation du toucher (Abraira & Ginty, 2013). Des travaux récents suggèrent néanmoins l'existence d'un sous-groupe spécialisé de fibres Aβ pouvant être associé à la douleur via un système ultrarapide de détection de danger (Nagi et al., 2019). Les fibres Aδ sont légèrement myélinisées et leur vitesse de conduction varie de 5 à 30 mètres par seconde (Perl, 1968; Tran et al., 2001). Les récepteurs associés aux fibres Aδ sont des terminaisons nerveuses libres (non encapsulés) (Burgess & Perl, 1967). Ces fibres sont considérées comme des nocicepteurs puisque leurs potentiels d'action se produisent à des intensités assez élevées pour potentiellement induire des dommages tissulaires (Basbaum et al., 2009). Ces stimuli peuvent être de différentes modalités et associés à une augmentation importante notamment au niveau de l'acidité des tissus, de la pression mécanique, ou de la température. L'activation sélective des fibres Aδ est associée à une sensation de piqûre intense et douloureuse, brève et facile à localiser. Pour ce qui est des fibres C, elles sont non-myélinisées, de petit calibre et leur vitesse de conduction atteint environ 1 mètre par seconde (Tran et al., 2001). Tout comme les fibres Aδ, les

récepteurs sont situés au niveau de terminaisons nerveuses libres. La population des fibres C est plus variable que les Aδ, et seulement un sous-groupe peut être considéré comme nocicepteurs, les autres étant notamment des mécanorécepteurs à faible seuil, des thermorécepteurs ou des pruritocepteurs. L'activation sélective des fibres C nociceptives est associée à une sensation de chaleur désagréable ou de brûlure diffuse et plus difficile à localiser précisément que la piqûre associée aux fibres Aδ.

Cette distinction importante au niveau de la vélocité de conduction et de la sensation suivant l'activation de fibres Aδ et C se traduit par le phénomène de double douleur : leur co-activation mène à une sensation initiale de piqûre très circonscrite (précise) suivie, presque une seconde plus tard, d'une sensation de brûlure désagréable et diffuse (Bishop et al., 1958; Lewis & Pochin, 1937; Price, 1977). Également, le faible seuil mécanique des fibres Aβ fait en sorte que la plupart des méthodes pour induire de la douleur expérimentalement mènent à une co-activation de nocicepteurs et de fibres Aβ. Cette co-activation complexifie l'interprétation des données issues de stimulations douloureuses puisque cela ouvre la possibilité à de nombreuses interactions entre les différentes fibres. Dans trois des quatre études présentées dans cette thèse, nous avons utilisé des lasers qui nous permettent de recruter sélectivement les fibres Aδ et C sans co-activation des fibres Aβ. Cela nous a ainsi permis de documenter les interactions se produisant au niveau du système nociceptif spécifiquement. Les avantages et les inconvénients à l'utilisation de lasers par rapport à d'autres modalités sont présentés dans la section *Considérations méthodologiques*.

De la périphérie à la moelle épinière

Les neurones associés aux fibres Aβ, Aδ et C provenant du tronc et des membres ont leurs corps neuronaux au niveau des ganglions de la racine dorsale. Suite à la transduction de l'énergie mécanique, chimique ou thermique en influx nerveux, la transmission se poursuit jusqu'au noyau du neurone, puis vers les neurones au niveau de la moelle épinière et du cerveau (Todd, 2010; Urch, 2007; Wall & Melzack, 2013). La moelle épinière, relais obligatoire pour le message nociceptif, peut être grossièrement séparée en corne dorsale, intermédiaire et ventrale (voir Figure 2.1. Vue d'une section horizontale de la moelle épinière). Plus spécifiquement, les travaux de Bor Rexed dans les années 1950 ont démontré l'existence d'une organisation structurelle et histologique dans la moelle épinière (Rexed, 1952). En effet, sur cette base, il est possible de séparer la moelle épinière en dix lames : six lames dans la corne dorsale, deux dans la corne latérale et deux dans la corne antérieure.

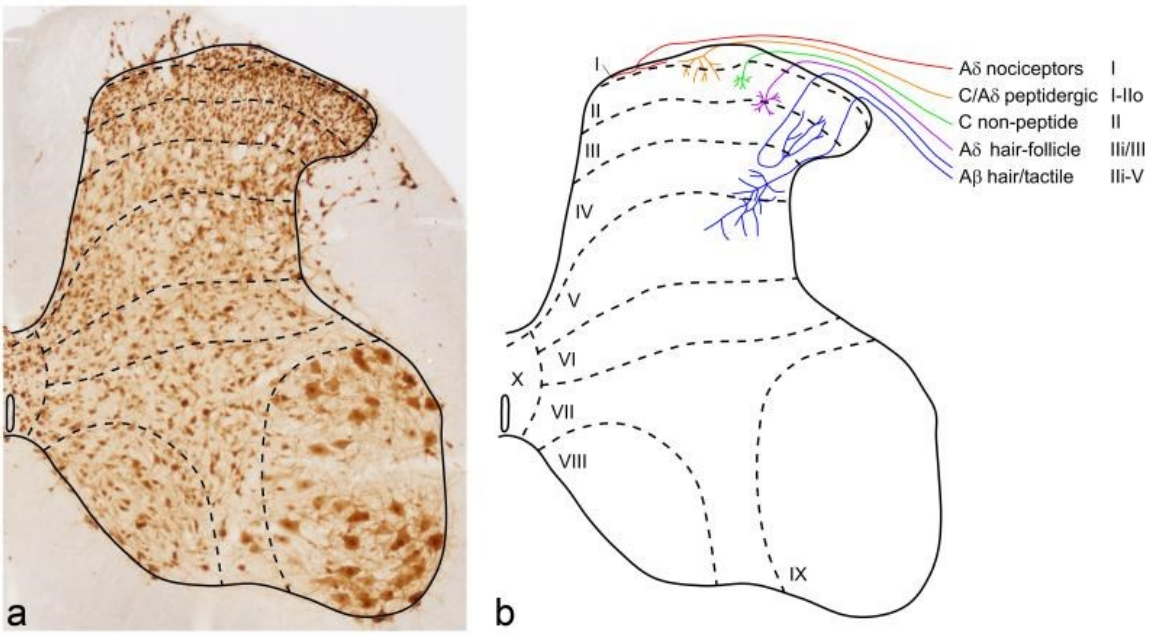

Figure 2.1. Vue d'une section horizontale de la moelle épinière

Image tirée de Todd A., Nat Rev Neurosci 2010 (Todd, 2010)

En ce qui concerne la transmission des messages sensoriels au niveau de la corne dorsale de la moelle épinière, quatre composantes neuronales peuvent être observées: 1) les axones des neurones des ganglions de la racine dorsale qui se dirigent vers les interneurones et les neurones intrinsèques de la moelle, 2) les interneurones ou neurones intrinsèques à la moelle qui représentent la majorité des neurones dans la corne dorsale (Abraira & Ginty, 2013; Haberberger et al., 2019), 3) les axones des neurones des ganglions de la racine dorsale qui se dirigent directement vers les structures supraspinales, et 4) les axones des voies descendantes provenant des structures supraspinales. Les nocicepteurs (fibres Aδ et C) font principalement synapse avec des neurones de projection au niveau des lames I, II et V de la corne dorsale (Wall & Melzack, 2013). Ces neurones sont considérés comme des neurones de 2^{e} ordre. Leurs axones passent ventralement et controlatéralement vers le cadran antérolatéral de la moelle épinière avant de se projeter vers les structures supraspinales dont le tronc cérébral et le thalamus. Les neurones des fibres Aβ se dirigent principalement vers les structures supraspinales ipsilatérales dès leur entrée dans la moelle épinière. Ces neurones ont néanmoins des axones collatéraux qui donnent des connexions des neurones non nociceptifs de la corne dorsale dans la lame III à VI.

La moelle épinière n'est pas simplement un relais passif de l'information provenant de la périphérie et ascendant vers les structures supraspinales. Il s'agit également d'un site où se produit une intégration de l'information sensorielle et motrice, et une forte modulation de l'information est possible grâce aux voies descendantes provenant de structures supraspinales. En effet, la moelle épinière isolée chirurgicalement peut encoder plusieurs paramètres sensoriels comme l'intensité des stimuli et la localisation des stimuli (Coghill, 2020; Weng & Schouenborg, 1996). C'est d'ailleurs au niveau de la moelle épinière que sera d'abord traitée l'information somesthésique pour initier des réflexes autonomiques (p. ex., changement de débit sanguin) et des réflexes moteurs (p. ex., le réflexe de retrait). Pour l'initiation des différents réflexes moteurs, l'information des fibres Aβ, Aδ et C est transmise à des neurones moteurs, les motoneurones, impliqués dans la contraction des muscles et situés dans la corne ventrale de la moelle épinière. Ces réflexes moteurs peuvent avoir différents degrés de complexité en termes de nombre de synapses, allant d'une synapse directe (simple boucle monosynaptique) à des synapses indirectes (boucles polysynaptiques) impliquant plusieurs interneurones. Le réflexe de retrait nociceptif, par

exemple, est un réflexe polysynaptique et représente la première réponse disponible face à une menace potentielle à l'intégrité de l'organisme (Gandhi et al., 2017). Ce réflexe induit une action motrice qui a comme but premier le retrait de la source de nociception. Par exemple, si nous marchons sur un objet pointu, une flexion réflexe du membre inférieur affecté permet de réduire la mise en charge sur ce membre inférieur et ainsi protéger la région affectée. Lorsqu'isolés de l'influence des régions supraspinales par des lésions complètes de la moelle épinière, les réflexes spinaux peuvent être considérés comme « stéréotypés » et fixes (Schouenborg & Kalliomäki, 1990; Sherrington, 1910). Cela étant dit, les structures supraspinales ont un rôle crucial dans la modulation notamment des réflexes spinaux (Defrin et al., 2007), des réponses autonomiques (Mischkowski et al., 2018) et des réponses comportementales à la douleur (Defrin et al., 2007; Tracey & Mantyh, 2007; Wall & Melzack, 2013). Ceci nous permet de produire des comportements qui sont adaptés à la situation (Tabor et al., 2017), comme d'inhiber le réflexe de retrait lorsque nous manipulons un plat très chaud, ou d'amplifier la réponse lorsqu'une menace est perçue comme crédible (Tabor et al., 2017).

Les voies ascendantes somatosensorielles

Transmission des influx somatosensoriels au thalamus

Le principal relais des influx nerveux du système somesthésique à des fins de traitement de l'information par le cortex est le thalamus. Les influx nerveux provenant de stimuli somatosensoriels sont propagés différemment vers le thalamus selon si ceux-ci proviennent initialement de fibres Aβ, Aδ ou C. Les neurones des fibres Aβ cheminent vers les structures supraspinales du même côté (ipsilatéral) de leur entrée dans la moelle épinière, formant collectivement la voie ou colonne dorsale. Cette voie est associée notamment au traitement de l'information reliée au tact fin, la vibration et la position des régions corporelles dans l'espace. Une première synapse est établie au niveau de neurones des noyaux graciles et cunéiformes du tronc cérébral. Ces neurones projettent ensuite leurs axones du côté controlatéral (une décussation), avant d'établir une synapse sur les neurones du noyau ventro-postéro-latéral du thalamus.

Les neurones des fibres Aδ et C ont des axones qui font une décussation du côté controlatéral de la face antérolatérale de la moelle épinière préalablement à leur ascension vers les structures supraspinales. Ceux-ci forment collectivement le système antérolatéral qui est impliqué dans la perception de la douleur, la température et le tact brut (Urch, 2007; Wall & Melzack, 2013); en effet, les lésions du système antérolatéral mènent à une perte de la discrimination thermique et de la douleur associée à une stimulation nociceptive de l'endroit desservi par la moelle épinière et de tous les étages situés caudalement. Ce système peut être séparé en plusieurs faisceaux distincts selon leurs projections supraspinales: spino-mesencéphalique, spino-réticulaire, spino-parabrachiale et spinothalamique (ou spino-thalamo-cortical) (Millan, 1999). Les deux premiers faisceaux (spino-mesencéphalique et spino-réticulaire) sont impliqués notamment dans les réflexes autonomiques reliés à la nociception (Mischkowski et al., 2018), la modulation du système réticulaire d'activation et la modulation de l'information nociceptive atteignant les structures corticales via le système inhibiteur descendant (Ossipov et al., 2010; Willis & Westlund, 1997).

Les deux derniers faisceaux (spinoparabrachial et spinothalamique) forment les deux voies principalement impliquées dans la transformation de l'information nociceptive en une expérience consciente de douleur. Pour la voie spinoparabrachiale, une première synapse est établie au niveau du noyau parabrachial, suivie de synapses au niveau notamment de l'amygdale et de l'hypothalamus (Chiang et al., 2019; Dum et al., 2009). Cette voie est ainsi indirectement impliquée dans la composante affective-motivationnelle de la douleur – composante responsable de l'aspect désagréable de la douleur, et au besoin impératif de réagir afin de mettre fin à la sensation – et dans certains réflexes autonomiques reliés à la douleur, au changement de température (Morrison & Nakamura, 2019), et à la douleur (Chiang et al., 2019; Gauriau & Bernard, 2002). Finalement, tout comme les deux voies précédentes, des synapses sont présentes sur les structures du tronc cérébral impliquées dans la modulation descendante de la douleur (Roeder et al., 2016; Willis & Westlund, 1997).

La voie spinothalamique établie des synapses au niveau de plusieurs noyaux du thalamus, notamment le complexe ventro-postérieur (inférieur et latéral) et les noyaux intralaminaires (Dum et al., 2009; Hong et al., 2010; Sherman & Guillery, 1996). Décrite en plus de détails dans la section suivante, cette voie est impliquée dans la composante sensori-discriminante de la douleur, c.-à-d. la capacité à évaluer l'intensité, la qualité, la durée et la localisation sur le corps d'une stimulation nociceptive (Wall & Melzack, 2013; Willis & Westlund, 1997). Les connexions de la voie spinothalamique avec certains noyaux du thalamus lui confère également un rôle très important dans la composante affective-motivationnelle de la douleur à l'instar de la voie spinoparabrachiale.

Le réseau cortical impliqué dans la perception de la douleur

Du thalamus aux structures corticales

Le thalamus est généralement considéré comme une barrière dirigeant l'information sensorielle (de la périphérie) vers le cortex pour un traitement ultérieur (Sherman & Guillery, 1996). Le thalamus peut être séparé en noyaux qui sont regroupés selon leur position anatomique (p. ex., antérieurs, ventraux, dorsaux, intralaminaires, postérieurs, réticulaire). À l'exception de l'olfaction, chaque modalité sensorielle forme une connexion privilégiée avec certains noyaux thalamiques avant de faire le relais vers l'aire corticale primaire associée à la modalité. Les noyaux recevant davantage d'information sensorielle soit de la périphérie (p. ex., de la moelle épinière) sont dénommés les « noyaux de premier ordre ». Lorsque la majorité de l'information provient des structures corticales, nous parlons plutôt de « noyaux d'ordre supérieur ». Ainsi, le thalamus agit aussi comme relais sensoriel entre la périphérie et le cortex, et aussi entre les différentes régions corticales via de nombreuses boucles (p. ex., réticulo-thalamo-corticales et cortico-thalamo-corticales). Tout comme la moelle épinière, le thalamus n'est pas qu'un simple relais passif de messages sensoriels: les neurones thalamo-corticaux peuvent modifier la nature des messages sensoriels, notamment en alternant entre deux modes de transfert d'information, tonique et en rafales, lui permettant d'être très sensible à la présence d'un changement dans la régularité des informations sensorielles provenant de nos sens (Ahissar & Oram, 2013; Ramcharan et al., 2005; Sherman & Guillery, 1996).

Les neurones du thalamus dans les noyaux ayant reçu des synapses des neurones de la voie spinothalamique sont les neurones de 3^{e} ordre dans la transmission du message nociceptif. Ceux-ci ont des axones qui se projettent vers de nombreuses structures du cerveau. Les avancements technologiques des techniques d'imagerie médicale nous ont permis de mieux définir où et quand se produisent les changements dans le système nerveux central lors du traitement de l'information nociceptive. Les méta-analyses de centaines d'études ont retrouvé une modulation de l'activité très robuste et constante dans un réseau étendu du cerveau (voir Figure 2.2. Principales structures supraspinales activées par un stimulus nociceptif), et ce, quelle que soit la technologie employée (imagerie par résonance magnétique fonctionnelle, tomographie par émission de positron, électroencéphalographie, magnétoencéphalographie) ou la modalité utilisée (p. ex. thermique ou mécanique) pour induire la douleur expérimentale (Apkarian et al., 2005;

Derbyshire, 2000; Duerden & Albanese, 2013; Farrell et al., 2005; Jensen et al., 2016; Jones et al., 2002; Peyron et al., 2000; Porro, 2003; Schnitzler & Ploner, 2000; Tracey, 2008; Tracey & Mantyh, 2007; Treede et al., 2000; Treede et al., 1999; Xu et al., 2020). Ces régions du cerveau sont l'insula, le cortex somatosensoriel secondaire (SII) et le cortex cingulaire antérieur (ACC) et moyen (MCC) bilatéralement, ainsi que le thalamus et le cortex somatosensoriel primaire (S1) du côté controlatéral à la stimulation, et le cortex préfrontal gauche (Farrell et al., 2005).

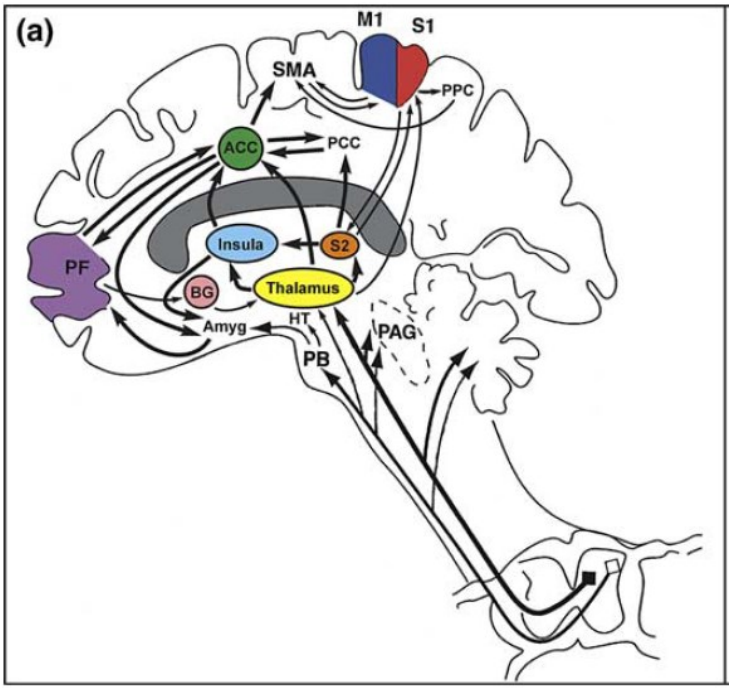

Figure 2.2. Principales structures supraspinales activées par un stimulus nociceptif

Image tirée de Apkarian et al., Eur J Pain 2005 (Apkarian et al., 2005)

Cependant, la transformation de l'information nociceptive en une expérience perceptuelle de douleur est complexe et très variable (Morrison et al., 2013). Plusieurs facteurs (p. ex., contextuels, culturels, et reliés au passé et à l'apprentissage d'un individu) peuvent grandement affecter la relation entre les deux, ce qui augmente considérablement la variabilité interindividuelle (Iannetti et al., 2008; Mouraux & Iannetti, 2009; Ronga et al., 2013; Torta et al., 2012; Valentini et al., 2011; Wang et al., 2010). Ainsi, ces méta-analyses sont généralement peu sensibles aux différences interindividuelles.

La douleur : définition et théories

Intensité, spécificité, pattern, gate control

Avant l'émergence de théories modernes sur la douleur, plusieurs théories ont tenté d'expliquer la douleur (Moayedi & Davis, 2013; Perl, 2007). Plusieurs de ces théories coexistaient au 19e et 20e siècle : la théorie de la spécificité, de l'intensité, du patron d'activation et du portillon. Brièvement, la théorie de la spécificité suggérait que chaque modalité possède des récepteurs et des fibres nerveuses spécifiques, et que la douleur est une modalité comme la vision et le tact. L'existence de neurones spécifiquement associés à une perception de douleur a dû attendre les travaux de Sherrington sur les nocicepteurs (Sherrington, 1903) et particulièrement ceux de Perl (1967) sur les terminaisons nerveuses libres et les fibres afférentes myélinisées ne répondant qu'à des stimuli de haute intensité potentiellement nocifs (Burgess & Perl, 1967). D'autres chercheurs préconisaient la théorie de l'intensité où tous les sens (ou récepteurs) peuvent produire de la douleur dans la mesure où ceux-ci sont activés par un stimulus suffisamment intense (Dallenbach, 1939). La découverte d'une catégorie de neurones dans la corne dorsale de la moelle épinière répondant à des stimuli tant nociceptifs que non nociceptifs, les neurones à large gamme dynamique (« *wide dynamic range* »), semblait supporter cette théorie. Parallèlement à ces deux théories, la théorie du patron d'activation (« *pattern theory* ») (Nafe, 1929) et la théorie du portillon, avancée dans l'article de Melzack et Wall (Melzack & Wall, 1965), proposaient que le patron d'activation (p. ex. spatial, temporel) des neurones dicte la sensation résultante. La théorie du portillon ajouta le concept important de convergence des fibres somesthésiques fines et larges sur des neurones communs dans la moelle épinière; l'activité résultant de ces neurones communs peut ainsi « ouvrir » ou « fermer » le portillon (Melzack & Wall, 1965).

Malgré les lacunes de la théorie du portillon (Mendell, 2014), notamment l'absence de nocicepteurs dans le modèle, un ajout important était la postulation d'un contrôle inhibiteur descendant provenant des structures supraspinales et pouvant directement moduler l'ouverture ou la fermeture du portillon (Melzack et al., 1958). Ce postulat a mené de nombreux chercheurs à s'intéresser notamment à l'influence des structures supraspinales sur la transmission du message

nociceptif et sur la douleur. La neuromatrice de la douleur (Melzack, 1999, 2001) formalise de telles idées en proposant que la douleur soit une expérience multidimensionnelle produite par un réseau neuronal étendu (la « *neurosignature* de la douleur ») qui s'inscrit dans un système nerveux central dynamique. Dans ce modèle, l'information nociceptive active différents « centres neuronaux » qui collectivement sont interprétés comme la *neurosignature*. Ces centres neuronaux interagissent constamment, et l'information nociceptive est intégrée notamment avec des éléments perceptuels, homéostatiques, et moteurs; cela rend l'expérience fortement modulable et unique à l'individu.

La neuromatrice de la douleur a été redéfinie récemment comme un système à trois niveaux (Garcia-Larrea & Peyron, 2013b), soit la matrice nociceptive, la matrice perceptuelle et la matrice de niveau supérieur. Dans ce modèle, la matrice nociceptive (de 1er ordre) correspond aux premières régions du cerveau recevant des informations de la voie spinothalamique du système nociceptif : l'insula postérieure, l'operculum pariétal, le cortex cingulaire moyen et le cortex somatosensoriel primaire. Cette matrice constitue ainsi le relais obligatoire de l'information nociceptive au cerveau pour éventuellement générer une expérience douloureuse physiologique. Cependant, l'activation de cette matrice est préservée pendant le sommeil, le coma et les états végétatifs et est ainsi insuffisante pour expliquer la douleur. La matrice perceptuelle (de 2^{e} ordre) est associée à de l'activité neuronale de structures ne recevant pas d'informations directement de la voie spinothalamique. Ces structures sont l'insula antérieure, le cortex cingulaire antérieur, le cortex préfrontal et le cortex pariétal postérieur. Ces régions sont non spécifiques à la nociception et sont plutôt impliquées dans l'attention, l'anticipation, le contrôle cognitif, l'intéroception et la détection de stimuli saillants. Cette matrice est fortement influencée par le contexte et elle peut, à son tour, fortement influencer l'activité dans la matrice de 1er ordre – menant à de potentielles dissociations importantes entre l'activité nociceptive et la douleur. Par exemple, l'attention et le contrôle cognitif peuvent directement moduler le gain des neurones recevant les informations nociceptives, et ce, même au niveau de la moelle épinière (Sprenger et al., 2012). Finalement, la matrice de 3^{e} ordre est associée à l'activation de structures supramodales comme le cortex orbitofrontal, périgénual et préfrontal antérolatéral. Cette matrice serait associée notamment aux croyances, à l'effet placebo, et à la capacité à contrôler les stimuli causant la douleur.

Ainsi, la neuromatrice de la douleur (Melzack, 1999, 2001) et les modèles s'en inspirant (Garcia-Larrea & Peyron, 2013b; Legrain et al., 2011) s'éloignent des concepts historiques voulant que 1) la douleur soit entièrement reliée à l'information nociceptive et 2) qu'un centre de la douleur unique existe dans le cerveau. Plutôt, ils reconnaissent le rôle important que joue l'intégration de facteurs cognitifs, attentionnels, affectifs, sensorimoteurs, émotionnels et autonomiques dans la modulation de l'information nociceptive et, au final, de l'expérience douloureuse.

Définition de l'intégration sensorielle

L'intégration sensorielle est le processus par lequel l'information sensorielle de différentes sources est combinée, offrant une réponse émergente avec des propriétés différentes des informations entrantes respectives (Calvert et al., 2004; Stein & Meredith, 1993; Stein et al., 2009, 2014). Il s'agit d'un processus critique pour la perception de notre environnement sensoriel et pour l'adoption de réponses et de comportements adaptés. Par exemple, en combinant le signal de différentes sources, l'incertitude et l'ambiguïté inhérente aux systèmes sensoriels sont grandement réduites. Cette stratégie de communication neuronale est omniprésente à travers le système nerveux central : elle est observée au niveau de la moelle épinière (Nielsen, 2004), du tronc cérébral (Stein & Meredith, 1993), des structures corticales (Passarelli et al., 2021) et entre les différentes structures du système nerveux central comme, par exemple, le cortex moteur et la moelle épinière (Nielsen, 2004; Vahdat et al., 2020). La modification de l'information nociceptive originale peut être telle, que certains auteurs vont jusqu'à suggérer que le terme « traitement sensoriel nociceptif » est inapproprié dans le contexte de la douleur:

« *By the time a pain-relevant signal reaches the cortex, if not before, the terms of "nociceptive processing" become inadequate to describe pain representation, just as the terms of "auditory processing" become inadequate to describe music* » (Morrison et al., 2013)

L'intégration sensorielle peut faire référence à l'intégration d'information sensorielle provenant d'un stimulus unique qui chemine vers les aires corticales supérieures et où des

connexions convergent vers les mêmes neurones. Elle peut aussi faire référence à l'intégration de plusieurs informations sensorielles qui cheminent et interagissent sur des neurones communs, le plus souvent aux aires corticales supérieures puisque ces dernières reçoivent davantage de convergence d'informations. Des travaux récents ont démontré que de telles interactions peuvent se produire dans les régions corticales généralement caractérisées comme ne répondant qu'à une seule modalité (Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007).

Ces informations peuvent provenir de différentes modalités (intégration multisensorielle) ou de la même modalité (unisensorielle). Par exemple, un neurone peut ne répondre que peu à deux stimuli individuels, mais répondre vigoureusement lorsque ces deux stimuli sont appliqués simultanément (facilitation multi- ou unisensorielle) (Stein et al., 2009); à l'inverse, une inhibition ou dépression de la réponse en présence de plusieurs stimuli simultanés peut également être observée. Au niveau perceptuel, plusieurs exemples démontrent l'importance de l'intégration sensorielle : la contribution du système visuel à notre compréhension du langage parlé (Ross et al., 2007; Sumby & Pollack, 1954), ou l'orientation et l'épaisseur d'un objet manipulé avec les deux mains (Jung et al., 2012). L'intégration d'information de différentes sources peut même mener à des illusions perceptuelles comme l'effet McGurk, où l'information auditive et visuelle n'est pas congruente. Dans cet exemple, le son « ba – ba » est joué par-dessus une vidéo d'une personne articulant « ga – ga », menant à une perception d'un son « da – da » (McGurk & Macdonald, 1976). Dans le contexte de la nociception, ce mécanisme d'intégration nous permet d'adapter nos comportements de défense (nocifensifs) en combinant le message nociceptif (danger potentiel aux tissus) avec l'information sensorielle disponible quant au contexte (p. ex., situation nouvelle ou connue, possibilité de se sauver ou non) et l'environnement (p. ex., visuel, auditif, proprioceptif, ou autre stimulation nociceptive concurrente).

Physiologie et mesures de l'intégration sensorielle

La présence d'intégration uni- et multisensorielle est confirmée par des mesures d'activité des neurones. Cependant, des mesures psychophysiques comme le temps de réaction ou le seuil de détection peuvent également être utilisées afin d'inférer la présence de mécanismes sous-jacents. L'intégration sensorielle se produit dans une fenêtre temporelle très courte (voir section *Synchronisation temporelle et oscillations neuronales*), et une mesure de celle-ci doit idéalement capturer le phénomène en temps réel; les mesures d'activité électriques et électromagnétiques répondent à un tel besoin grâce à une résolution temporelle amplement suffisante (Hari & Puce, 2017). Ces mesures d'activité neuronale peuvent être 1) locales, via les potentiels de champ locaux, 2) globales, via notamment l'activité électrique ou magnétique mesurée au niveau du scalp, ou 3) à mi-chemin, via l'activité enregistrée par-dessus la dure-mère via l'électrocorticographie. Dans un contexte expérimental usuel chez l'humain, les potentiels de champ locaux et l'électrocorticographie ne sont pas accessibles puisqu'ils requièrent une chirurgie invasive afin d'implanter des électrodes (p. ex., une craniotomie afin d'exposer la région d'intérêt).

Pour les mesures au niveau du scalp, l'électroencéphalographie (EEG) et la magnétoencéphalographie (MEG), décrites à la section *Considérations méthodologique*, sont deux outils de choix pour mesurer l'activité de large population de neurones en temps réel. L'activité électrique ou magnétique provenant de ces outils est généralement mesurée en comparant l'activité suivant un stimulus à celle précédant le stimulus, une approche dénommée les potentiels évoqués (« event-related potentials », ERP). En comparant l'amplitude des potentiels évoqués induits par les deux stimuli individuels et lorsqu'ils sont appliqués simultanément (réponse combinée), il est possible de parler de réponse superadditive (l'amplitude combinée est plus grande que la somme des informations), subadditive (l'amplitude combinée est plus grande qu'une seule information, mais plus petite que la somme), et suppressive (l'amplitude combinée est moindre qu'une seule information). L'intégration multisensorielle tend à produire des réponses superadditives tandis que celle unisensorielle produit davantage de réponses subadditives (Alvarado et al., 2007). Cela peut s'expliquer en partie par le fait que les stimuli d'une même modalité tendent à contenir une plus grande quantité de covariance comparativement

à des stimuli de deux modalités différentes (Ernst & Banks, 2002). Les principaux facteurs favorisant l'intégration sensorielle d'un point de vue physiologique et anatomique sont la synchronisation spatiale – l'information sensorielle provenant de différentes structures doit converger vers les mêmes neurones (Stein & Meredith, 1993) – et la synchronisation temporelle – l'information doit converger dans un laps de temps très rapproché pour produire un effet.

Synchronisation spatiale

Au niveau de la synchronisation spatiale, il y a davantage de convergence de l'information sensorielle dans les niveaux supérieurs de la hiérarchie corticale, et donc davantage d'opportunités pour de l'intégration sensorielle, au niveau des aires corticales supérieures (associatives) qu'inférieures. Cela ne veut pas pour autant dire que l'intégration est réservée aux structures cérébrales, comme démontré par la littérature exhaustive sur l'intégration multisensorielle dans une structure du tronc cérébral, le colliculus supérieur (Stein & Meredith, 1993). Cependant, l'analyse de l'activité électrique de structures sous-corticales via des mesures non invasives chez l'humain est complexifiée par la faiblesse du signal atteignant les électrodes de surface et la difficulté à identifier les générateurs menant à l'activité enregistrée (Krishnaswamy et al., 2017).

Pour le traitement de l'information nociceptive, certaines régions présentent une grande convergence de l'information sensorielle provenant autant de régions différentes que des régions homologues du côté de l'hémisphère opposé (Bastuji et al., 2018; Bastuji et al., 2016; Khoshnejad et al., 2014) (Figure 2.3. Connexions entre les aires corticales dont l'activité change suivant un stimulus nociceptif). Tel que mentionné dans la section *Le réseau cortical impliqué dans la perception de la douleur*, plusieurs structures cérébrales sont activées bilatéralement (p. ex. le cortex somatosensoriel secondaire), ou bilatéralement avec activation préférentielle dans l'hémisphère droit (p. ex. l'insula et le cortex cingulaire antérieur). Cela suggère qu'une forte convergence des informations nociceptives peut se produire dans ces régions en présence de multiples stimuli nociceptifs. À contrario, certaines régions comme le cortex somatosensoriel primaire démontrent de l'activité quasi exclusivement contralatérale.

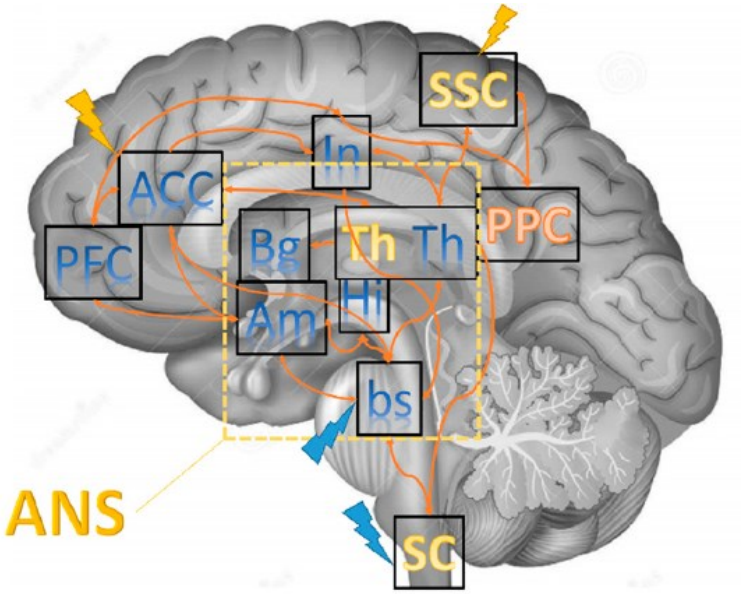

Figure 2.3. Connexions entre les aires corticales dont l'activité change suivant un stimulus nociceptif (ACC : cortex cingulaire antérieur, In : insula, Th : Thalamus)

Image adaptée de Calàbro et al., Brain Sciences 2021. (Calabrò et al., 2021)

Cette convergence spatiale permet de transformer l'information nociceptive en une expérience perceptuelle cohérente de douleur où de nombreuses caractéristiques sont unifiées. Ces caractéristiques sont notamment la modalité, la localisation et l'intensité du stimulus nociceptif (caractère sensori-discriminant), la position du corps et des régions corporelles dans l'espace (proprioceptif et spatial), l'aspect désagréable associé au besoin impératif de mettre fin à la douleur (caractère affective-motivationnel et moteur), et l'orientation du focus d'attention sur le stimulus et l'élaboration d'un comportement adapté à la situation (caractère cognitif) (Bustan et al., 2015; Melzack & Casey, 1968; Singh et al., 2020; Tracey, 2016). Cette idée d'intégration est reprise dans le modèle de neuromatrice de la douleur redéfinie par Garcia-Larrea en 2013 (Garcia-Larrea & Peyron, 2013a), où la matrice nociceptive, la matrice perceptuelle et la matrice de niveau supérieur sont intégrées pour donner lieu à un *qualia*, ou expérience perceptuelle possédant des propriétés uniques pour une personne. La douleur vécue par un individu peut donc être amplifiée ou inhibée en fonction de l'information sensorielle disponible dans son environnement (contexte) immédiat et de celle stockée dans le passé (expérience, croyances, etc.). Cela explique en partie la nature très variable de la douleur tant d'un individu à l'autre que d'une situation à l'autre.

Synchronisation temporelle et oscillations neuronales

Malgré un environnement sensoriel en perpétuel changement, ce dernier nous apparait comme étant continu, ou en temps réel. Cela suggère un paradoxe au niveau de la sensibilité et la stabilité de notre perception (Wutz et al., 2016) : notre système nerveux central doit posséder une résolution temporelle très élevée pour être sensible aux changements rapides se produisant dans l'environnement qui pourraient menacer notre survie (p. ex., l'apparition d'un prédateur), mais doit également posséder une fenêtre d'intégration temporelle suffisamment grande pour que les représentations perceptuelles soient stables afin que nous puissions identifier et localiser un stimulus (Wutz et al., 2016). Des études récentes suggèrent que le cerveau ne traite pas l'information de façon continue, mais plutôt discrète, un phénomène dénommé les cycles perceptuels (ou fenêtres d'intégrations temporelles) (Baumgarten et al., 2015; VanRullen & Koch, 2003). Lorsque plusieurs stimuli tombent dans le même cycle perceptuel, ceux-ci tendent à être perçus comme étant un seul évènement. La fenêtre d'intégration pour la synchronisation temporelle de ces cycles perceptuels est courte : de l'ordre de quelques dizaines de millisecondes (Baumgarten et al., 2015; Buzsáki, 2006; Wutz et al., 2016). Elle dépend cependant de la modalité du stimulus et des aires corticales visées. Par exemple, deux stimuli successifs sont rapportés de façon erronée comme étant unique lorsque le délai entre chaque image est inférieur à 50 ms (Samaha & Postle, 2015) et de 250 ms pour deux sons consécutifs (Horváth et al., 2007; Näätänen et al., 2011). Lorsque deux stimuli sont appliqués successivement sur les deux mains, un délai de 25 à 50 ms pour les stimulations tactiles (Baumgarten et al., 2015; Sambo et al., 2013) et de 80 à 100 ms pour les stimulations nociceptives (Lee et al., 2009; Sambo et al., 2013) est requis pour rapporter quelle main fut stimulée en premier, et ce, avec un taux de succès au-delà du hasard. Au niveau somatosensoriel, cette fenêtre d'intégration est non seulement sensible à l'aspect temporel, mais également à l'aspect spatial : un deuxième stimulus appliqué à proximité du premier réduit grandement les chances de le percevoir (Mouraux et al., 2004).

Un mécanisme permettant d'intégrer l'information de plusieurs informations sensorielles doit ainsi se produire avec très peu de latence afin d'augmenter les chances que le neurone visé décharge à son tour. De nombreux travaux ont démontré l'importance des rythmes oscillatoires, particulièrement à haute fréquence (gamma, >30 Hz), dans la synchronisation temporelle des

décharges neuronales de groupes de neurones (Fries, 2009, 2015; Fries et al., 2007; Gray et al., 1989). De tels rythmes offrent une fenêtre d'intégration avec des cycles variant le plus souvent de 25 ms (oscillation gamma à 40 Hz) à 12 ms (oscillations gamma à 80 Hz) mais parfois aussi à 50 ms (oscillations bêta à 20 Hz), ce qui est suffisamment rapide pour permettre une synchronisation temporelle (Baumgarten et al., 2015; Fries, 2009). La présence de telles oscillations gamma a été confirmée dans de nombreuses régions du cortex et dans de nombreux processus cognitifs et perceptuels dont l'attention, la mémoire, la perception de stimuli somatosensoriels et plus récemment la nociception et la douleur (Bassez et al., 2020; Hauck et al., 2015; Heid et al., 2020; Kim & Davis, 2020; Liberati et al., 2018b; Liberati et al., 2020; Michail et al., 2016; Rustamov et al., 2019; Schulz et al., 2015; Tiemann et al., 2015; Tu et al., 2016; Yue et al., 2020; Zhang et al., 2012). Il a également été proposé que la présence d'oscillations gamma soit associée à la communication neuronale à longue distance, puisque la présence de telles oscillations peut être observée dans plusieurs régions du cortex simultanément, ou dans la même région corticale de chaque hémisphère (Buzsáki & Schomburg, 2015; Buzsáki & Wang, 2012; Steinmann et al., 2014). Cela suggère que ces oscillations gamma sont, à la base, une forme de communication neuronale et permettent un couplage entre différents groupes neuronaux ou nodules neuronaux (Doesburg et al., 2008). Cependant, l'amplitude de ces oscillations gamma est fortement modulée par les oscillations à plus basse fréquence (Buzsáki & Wang, 2012), et celles-ci contribuent également à la communication à longue distance. Par exemple, les oscillations à basse fréquence sont associées à des fluctuations de l'excitabilité neuronale, créant des fenêtres où l'excitabilité est maximale (ou minimale, selon la phase des oscillations) (Palva & Palva, 2017). De plus, de nombreux travaux ont démontré des rôles fonctionnels distincts entre les fréquences gamma, surtout associées au traitement ascendant de l'information sensorielle, et les fréquences plus lentes au contrôle cognitif descendant (Hipp et al., 2011; Richter et al., 2017).

Cela suggère qu'il est important d'explorer la modulation de l'activité oscillatoire à différentes fréquences pour mieux comprendre le traitement et l'intégration de l'information nociceptive. Comme il sera détaillé dans la section *Considérations méthodologique*, les stimuli nociceptifs mènent à des changements d'activité oscillatoires dans des fréquences allant de 2 à 100 Hz. Ces fréquences sont le plus souvent regroupées en bandes : delta (2 – 3 Hz), thêta (4 – 6

Hz), alpha (7 – 12 Hz), bêta (13 – 30 Hz), et gamma (> 30 Hz) (Figure 2.4. Oscillations cérébrales séparées en bandes de fréquences). Puisque la comparaison de l'activité oscillatoire est le plus souvent réalisée entre le moment suivant un stimulus et la période précédente, la terminologie pour une telle analyse est l'oscillation cérébrale évoquée (« *event-related spectral perturbations* » ERSP) (Makeig, 1993; Pfurtscheller & Lopes da Silva, 1999). Au final, l'analyse des potentiels évoqués reliés à l'évènement (ERP) et les oscillations évoquées (ERSP) s'avèrent complémentaires dans la mesure de l'intégration sensorielle.

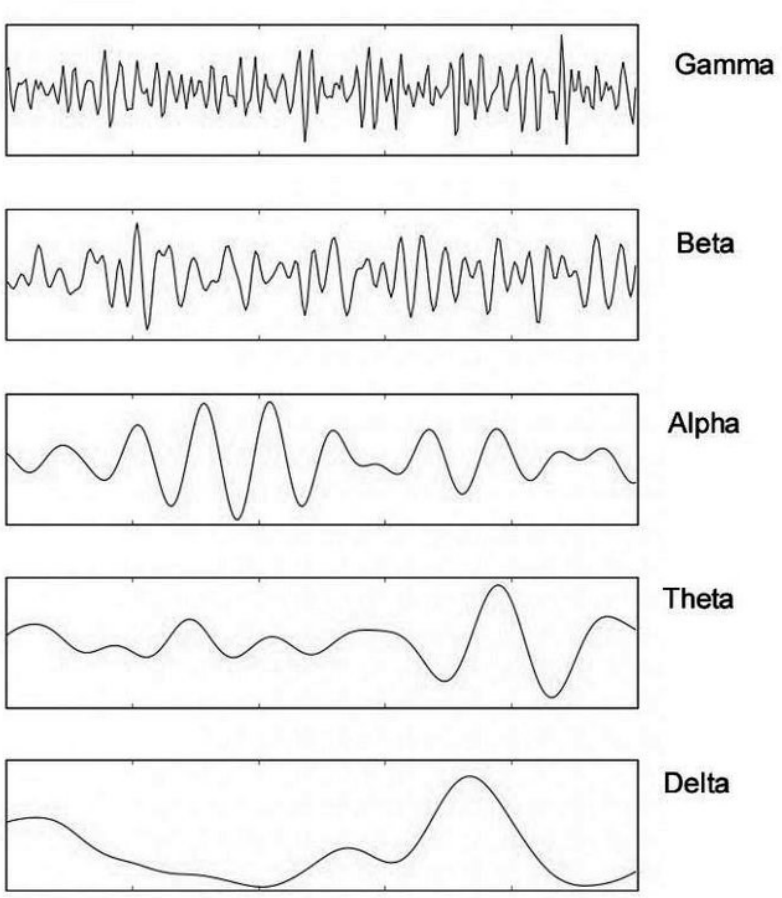

Figure 2.4. Oscillations cérébrales séparées en bandes de fréquences

Image tirée de Chatterjee et al., Machine Learning in Bio-Signal Analysis and Diagnostic Imaging (Chatterjee et al., 2019)

Modulation de l'intégration sensorielle par l'attention

L'intégration sensorielle peut être fortement modulée par l'attention (Fagioli & Macaluso, 2009; Fairhall & Macaluso, 2009; Koelewijn et al., 2010; Santangelo et al., 2009), une fonction cognitive complexe comportant trois macrosystèmes (Coubard, 2015; Pashler, 2000). Un de ces trois « macrosystèmes » est l'attention sélective, qui nous permet d'orienter et maintenir le focus sur l'information sensorielle pertinente à la réalisation d'une tâche ou à l'adoption d'un comportement adapté à une situation. Le modèle neurocognitif de la douleur (Legrain et al., 2009a) et le modèle de détection de saillance (Legrain et al., 2011) formalisent le rôle clé que jouent deux mécanismes d'attention sélective dans le traitement de l'information nociceptive, soit la sélection ascendante (*bottom-up*) et descendante (*top-down*). L'attention ascendante correspond à la capture attentionnelle involontaire et automatique associée à des stimuli saillants (p. ex., nouveaux, potentiellement dangereux, inattendus, et intenses). Les évènements saillants comme les stimuli nociceptifs tendent à capturer automatiquement et involontairement notre attention (Desimone & Duncan, 1995) afin d'être traités en priorité dans le cerveau, et ce, aux dépends des autres activités mentales (Corbetta & Shulman, 2002). L'attention descendante correspond plutôt à la priorisation volontaire et délibérée de certaines informations en fonction de nos objectifs ou buts cognitifs (Corbetta & Shulman, 2002; Melloni et al., 2012). Cela se démontre notamment avec l'effet « cocktail party » où la détection et la sélection de stimuli pertinents demeurent possibles même dans un environnement très bruyant (Bronkhorst, 2015; Cherry, 1953).

Les premiers modèles de l'attention sélective décrivaient l'attention comme un filtre (Broadbent, 1958) ne laissant passer que certains stimuli, notamment ceux auxquels nous portons activement attention. Les modèles subséquents abandonnèrent le filtre sélectif pour parler plutôt d'un atténuateur qui réduit le gain des stimuli qui sont ignorés (Treisman, 1969). Ces modèles ont inspiré les modèles subséquents sur les capacités limitées (« *limited-capacity models* ») qui stipulent que le système nerveux central fait constamment face à plus d'information sensorielle qu'il ne peut en traiter, et un tri via l'attention doit avoir lieu (Lachter et al., 2004; Lavie & Tsal, 1994). Kahneman (1973) décrit l'attention comme une ressource qui peut être allouée à différentes informations jusqu'à ce que sa limite soit atteinte, un modèle à la base de plusieurs

travaux sur l'attention divisée ou globale et à la base de nombreux modèles sur les capacités limitées. Le modèle de capacités limitées de Lavie (Lavie & Tsal, 1994) reprend les éléments majeurs de Treisman (1964) et ajoute la notion de « charge perceptuelle ». Cette notion dépend notamment de la quantité de stimuli à traiter en même temps, et la charge perceptuelle respective de chaque stimulus. La charge perceptuelle influence notre capacité à allouer notre attention à un stimulus distracteur : plus la charge perceptuelle est élevée, moins le système est apte à allouer son attention à d'autres stimuli concurrents. Considérant la forte charge perceptuelle des stimuli nociceptifs, cela pourrait suggérer qu'un effet plafond existe lorsque plusieurs stimuli nociceptifs sont concurrents.

En présence de stimuli concurrents, l'attention sélective peut également « accélérer », ou favoriser le traitement d'une information au détriment de l'autre, un phénomène, dénommé la loi d'entrée préalable (« *Law of prior entry* ») (Spence & Parise, 2010; Titchener, 1908). Ce phénomène peut être démontré notamment en présentant deux stimuli avec des intervalles interstimulus très courts mais variables, et en demandant aux participants de rapporter si les deux stimuli étaient simultanés, ou de rapporter l'ordre de présentation des stimuli. Comme mentionné dans la section *Synchronisation temporelle*, les cycles perceptuels sont des fenêtres d'intégration temporelle dans lesquelles deux stimuli seront perçus comme étant un seul stimulus unique. Or, selon cette loi, l'attention peut moduler cette fenêtre d'intégration : afin de percevoir deux stimuli comme étant simultanés, un stimulus ignoré doit être appliqué légèrement plus tôt que celui auquel nous portons attention (Titchener, 1908). Ce phénomène attentionnel a été documenté tant pour les stimuli visuels (Shore et al., 2001), auditifs (Kanai et al., 2007), tactiles (Yates & Nicholls, 2009) et, plus récemment, nociceptifs. Cela suggère qu'il s'agisse d'un mécanisme généralisable et supramodal (Spence & Parise, 2010; Yates & Nicholls, 2009).

Finalement, d'autres travaux font plutôt appel à la notion d'attention en tant que système de supervision – nos comportements quotidiens (des schémas) seraient généralement déclenchés automatiquement par notre environnement, mais un système de supervision permet d'adapter le comportement face à des situations nouvelles, dangereuses ou des situations où la réponse usuelle

automatique serait contextuellement inappropriée (Cieslik et al., 2015; Norman et al., 1986). Par exemple, le schéma usuel et automatique face à un stimulus nociceptif est le retrait de la source de nociception, comme dans l'exemple mentionné précédemment de la manipulation d'un plat très chaud. Dans ce modèle, une compétition a lieu entre le schéma automatique et les buts intentionnels supraordinaux (p. ex., éviter un dégât en inhibant le réflexe de retrait).

Ainsi, la littérature sur l'attention est vaste et complexe. De façon générale, il est possible de conclure que l'attention nous permet de mettre l'accent sur l'information qui sera traitée ultérieurement, de réduire la probabilité de traiter l'information ignorée, et d'adapter nos comportements en concordance avec nos objectifs actuels et avec le contexte.

Intégration d'information bilatérale

Le système nerveux central fait régulièrement face à des situations où deux organes sensoriels (p. ex., oreille gauche et droite) captent de l'énergie simultanément comme un son qui se propage aux deux oreilles. Ces stimuli peuvent interagir à différents niveaux du système nerveux central, notamment les régions recevant de l'information sensorielle bilatéralement (voir section *Synchronisation spatiale*). De telles zones possédant des champs récepteurs bilatéraux se retrouvent communément dans les aires corticales supérieures comme le cortex. Elles sont également observées dans des zones du cerveau comme le cortex inféro-temporal pour la vision (Gross et al., 1972; Tootell et al., 1998), le cortex auditif au niveau du gyrus de Heschl pour l'audition (Bilecen et al., 2002; Chang et al., 2016; Heggdal et al., 2019; Pantev et al., 1998; Uppenkamp & Behler, 2016), le cortex somatosensoriel secondaire (Iwamura, 2000; Petit et al., 1990) pour le domaine somatosensoriel, et le cortex somatosensoriel secondaire, l'insula et le cortex cingulaire antérieur pour la nociception (Coghill et al., 2001; Duerden & Albanese, 2013).

La capacité à intégrer des stimuli bilatéraux procure un avantage indéniable à l'organisme, notamment au niveau de la localisation des sons (Bell, 1880) ou de leur intensité (« *binaural loudness* ») (Baker et al., 2020; Marks, 1978; Shaw et al., 1947; Uppenkamp & Behler, 2016), de

la localisation tridimensionnelle et de l'identification des objets par la vision binoculaire (« *binocular summation* ») (Baker et al., 2018) ou de l'identification et la manipulation d'objets à l'aide des deux mains (Glowania et al., 2020). Cependant, le système nerveux central semble avoir développé une stratégie pour éviter la surreprésentation d'évènements (et potentiellement la perte d'énergie) dans l'environnement appartenant à la même modalité. En effet, lorsque deux stimuli d'une même modalité sont appliqués, la réponse la plus commune est celle d'une réponse non linéaire et subadditive, suggérant une suppression partielle de l'information combinée (Ernst & Banks, 2002; Stein & Meredith, 1993). Cette suppression partielle dépend cependant de plusieurs facteurs, dont le sens étudié (audition, vision, somatosensation), l'intensité des stimuli et la direction de l'attention. Par exemple, la suppression de stimuli auditifs bilatéraux est moindre que celle au niveau visuel (Baker et al., 2020), où la non-linéarité de sommation binoculaire est estimée à 1,53, démontrant une suppression importante de l'information redondante (Baker et al., 2018). De telles estimations de suppression ne sont pas disponibles pour le domaine somatosensoriel, mais des études ont documenté des effets de suppression en présence de stimuli tactiles bilatéraux. La présence d'un stimulus vibrotactile au membre supérieur droit augmente le seuil de détection d'un autre stimulus similaire au membre supérieur gauche (D'Amour & Harris, 2014a, 2016b). Cet effet est grandement amplifié lorsque le même endroit est stimulé de chaque côté du corps (D'Amour & Harris, 2014b), et lorsque les deux bras sont à proximité (D'Amour & Harris, 2014a, 2016b). L'intensité, la saillance et les caractéristiques respectives de chaque stimulus peuvent également jouer un rôle dans cette suppression. Par exemple, en présence de stimuli vibrotactiles bilatéraux de fréquence différente pour chaque main, des effets d'assimilation peuvent être observés puisque la fréquence estimée se situe entre les deux fréquences appliquées (Kuroki et al., 2017), suggérant que la perception peut être globale. Le système nerveux central tente ainsi de trouver une solution ou réponse optimale en estimant une fréquence de vibration qui n'existe pas dans le monde externe. De plus, la loi de l'efficacité inverse suggère que les stimuli ambigus, peu intenses, ou qui mènent à des réponses de faible amplitude gagnent le plus à être intégrés avec d'autres informations accessibles (Stein & Meredith, 1993) afin de maximiser la probabilité de leur détection (Ernst & Banks, 2002).

Lors du traitement de stimuli somatosensoriels bilatéraux simultanés, il y a davantage d'interactions, tel que mesuré par les ERP, dans les processus tardifs (Disbrow et al., 2001; Disbrow et al., 2003; Okajima et al., 1991; Shimojo et al., 1996; Tame et al., 2016) que précoces (Schnitzler et al., 1995). Cela est en accord avec la plus grande convergence spatiale des informations vers les régions corticales supérieures qui possèdent des champs récepteurs bilatéraux.

Intégration d'information nociceptive bilatérale

Nos connaissances sur l'intégration d'information nociceptive bilatérale dans le système nerveux central sont très limitées. À l'instar des autres modalités sensorielles, cette intégration apparaît nécessaire à l'adoption de comportements adaptés au contexte. Cela est particulièrement important considérant la relation étroite entre la nociception, le danger imminent et l'impératif biologique de la survie de l'organisme. L'intégration d'information nociceptive bilatérale permettrait l'émergence de stratégies de défense (comportementales) plus élaborées pour faire face à un danger pour l'organisme. En reprenant l'exemple de la manipulation d'un plat très chaud à deux mains, notre première ligne de défense, le réflexe de retrait nociceptif, tendra à immédiatement retirer la source de nociception. Pour éviter un dégât, il nous est possible d'inhiber ce comportement. Pourtant, une telle situation suggère que le système nerveux central fait face à davantage d'information nociceptive et que la situation pourrait ainsi représenter un plus grand danger à l'organisme, mais cela demeure méconnu. Les structures supraspinales pourraient permettre d'intégrer l'information nociceptive provenant des deux mains (bilatérales) afin d'évaluer le contexte et d'offrir une réponse adaptée : la source de nociception provenant de deux structures anatomiques suggère-t-elle un plus grand danger?

Davantage de travaux ont regardé l'effet de stimuli douloureux simultanés. Des études ont exploré l'effet d'avoir deux stimulations douloureuses appliquées simultanément, soit au même endroit du corps (Nielsen & Arendt-Nielsen, 1997b; Quevedo & Coghill, 2007), à différents dermatomes du même côté du corps (Douglass et al., 1992; Nielsen & Arendt-Nielsen, 1997b; Staud et al., 2004), au même dermatome du même côté du corps (Douglass et al., 1992), ou au

même dermatome de deux côtés du corps (bilatérale) (Nielsen & Arendt-Nielsen, 1997b; Quevedo et al., 2017). Pour les stimuli concurrents sur des régions corporelles différentes, une sommation, où « deux douleurs sont plus douloureuses qu'une » (Lautenbacher et al., 2007) fut observée pour les stimuli au même dermatome des deux côtés du corps (Nielsen & Arendt-Nielsen, 1997b) et à différents dermatomes du même côté du corps (Douglass et al., 1992; Staud et al., 2004) suggérant qu'une intégration spatiale de la douleur peut dépendre au moins partiellement de mécanismes supraspinaux. Pour les stimuli concurrents sur la même région corporelle, un phénomène d'inhibition latérale, où un neurone excité inhibe les neurones l'avoisinant, a pu être confirmé en observant les évaluations de douleur entre un et deux stimuli douloureux. En effet, l'augmentation de la douleur en présence de multiples stimuli douloureux ne se produit que lorsque la distance entre les deux stimuli est supérieure à environ 5 cm (Oshiro et al., 2007) et est maximale entre 10 et 20 cm (Oshiro et al., 2007; Quevedo & Coghill, 2007, 2009; Quevedo et al., 2017). Il est important de noter que dans toutes ces études, l'augmentation de la douleur par la stimulation concurrente est modeste et non-linéaire. Ensemble, cela suggère qu'une intégration spatiotemporelle complexe se produit en présence de plusieurs stimuli douloureux. La similitude entre les stimuli concurrents à différentes régions corporelles tend à démontrer que cette intégration dépend davantage de mécanismes centraux sans égards à la localisation des stimuli douloureux. Ces études se sont cependant intéressées exclusivement à l'aspect perceptuel de la douleur (Defrin et al., 2010; Douglass et al., 1992; Lautenbacher et al., 2007; Nielsen & Arendt-Nielsen, 1997b; Quevedo & Coghill, 2007, 2009; Quevedo et al., 2017; Staud et al., 2004). Des données électrophysiologiques permettraient potentiellement d'isoler les mécanismes en jeu. De tels mécanismes permettraient de procurer une meilleure estimation du niveau de danger pour l'organisme et ainsi d'adopter des comportements adaptés à la situation et au contexte.

Dans une étude récente de notre laboratoire, les changements au niveau de l'activité électrique au niveau cortical furent comparés entre des stimuli unilatéraux et bilatéraux (Rustamov et al., 2019). Les stimuli douloureux furent présentés sur le nerf sural droit (stimulations unilatérales), sur le nerf sural droit et gauche (stimulations bilatérales homosegmentaires), et sur le nerf sural droit et ulnaire gauche (stimulations bilatérales

hétérosegmentaire). Une augmentation des ERP et ERSP furent observées pour les stimuli bilatéraux comparativement à ceux unilatéraux, suggérant que les deux stimuli douloureux pouvaient être intégrés. La douleur augmenta également, mais seulement pour les stimuli bilatéraux homosegmentaires. Cependant, cette étude présente certaines limites, et des facteurs reliés à l'attention descendante et ascendante n'ont pas pu être contrôlés. Plusieurs facteurs sont présentés dans la section suivante.

Modulation ascendante et descendante de l'intégration nociceptive bilatérale

La latéralité ou dominance motrice

Les participants de notre étude antérieure (Rustamov et al., 2019) étaient tous droitiers, ce qui est usuel dans les études sur la douleur afin de limiter la variabilité interindividuelle. Or, la latéralisation de la douleur dans le cerveau demeure méconnue, et les méta-analyses sur les régions du cerveau qui sont activées en présence de stimuli douloureux ne présentent pas un portrait clair de l'influence de la dominance motrice. Il est intéressant de noter que chez les droitiers, les stimulations nociceptives à la main gauche ou à la main droite mènent à une activation cérébrale bilatérale pour de nombreuses structures (p. ex., thalamus, insula, ACC, cortex somatosensoriel secondaire, aires sensorimotrices, et amygdale), et sont pratiquement l'image miroir pour celles activées controlatéralement (p. ex., cortex somatosensoriel primaire) (Farrell et al., 2005; Xu et al., 2020). La réponse du cortex somatosensoriel secondaire – putatif cortex thermoréceptif (Ye et al., 2021) impliqué « dans des fonctions d'ordre supérieur, notamment l'intégration sensorimotrice, l'intégration de l'information bilatérale, l'apprentissage et la mémoire » (Chen et al., 2008) – est bilatérale, mais plus robuste du côté contralatéral (Xu et al., 2020). Également, certaines régions impliquées dans le traitement de la douleur et des émotions négatives dont l'insula, l'ACC et l'amygdale semblent préférentiellement activées du côté de l'hémisphère droit (Coghill et al., 2001; Duerden & Albanese, 2013; Gainotti, 2021; Symonds et al., 2006), et forment la base de l'hypothèse de la latéralisation du côté de l'hémisphère droit du traitement des émotions négatives (Gainotti, 2021). Plusieurs autres fonctions chez l'humain, et également chez certains vertébrés et invertébrés (Gainotti, 2021),

semblent être associées à un hémisphère en particulier – une spécialisation hémisphérique – comme le langage dans l'hémisphère gauche (Broca, 1861; Broca, 1863) et l'attention spatiale dans l'hémisphère droit (Marshall & Fink, 2001). Cependant, ces résultats ont été confirmés majoritairement chez des participants droitiers.

Les gauchers sont sous-représentés dans la littérature neuroscientifique (Bailey et al., 2020) et sont régulièrement exclus des études sur la douleur par crainte d'introduire de la variabilité. En effet, les spécialisations hémisphériques tendent à être plus variables chez les gauchers (Corballis, 2020a; Corballis, 2009a, 2014a; Corballis & Häberling, 2017). Par exemple, la spécialisation de l'hémisphère gauche pour le langage (Knecht et al., 2000) et l'hémisphère droit pour l'attention spatiale est très stable et reproductible chez les droitiers, mais beaucoup plus variable chez les gauchers (O'Regan & Serrien, 2018). Au niveau de la perception de la douleur chez les droitiers, une stimulation à intensité égale est évaluée comme plus douloureuse sur la main non dominante, et le seuil de la douleur est plus bas sur la main non dominante (Brennum et al., 1989; Buchanan & Midgley, 1987; Haslam, 1970; Jensen et al., 1992; Lugo et al., 2002a; Pud et al., 2009). Chez les gauchers, une telle différence est rarement observée, et la perception et le seuil de douleur sont souvent équivalents sur les deux mains (Haslam, 1970; Jensen et al., 1992; Long, 1994; Lugo et al., 2002a; Pud et al., 2009). Il demeure méconnu si des réponses cérébrales à la douleur différentes existent entre les droitiers et les gauchers. Ainsi, il est important de mieux caractériser l'impact potentiel de la dominance motrice sur le traitement et l'intégration de l'information nociceptive.

La modalité

La modalité utilisée pour induire la douleur dans l'étude de Rustamov et coll. (Rustamov et al., 2019) était la stimulation électrique transcutanée. Cette modalité recrute des neurones nociceptifs (fibres Aδ et C) et non nociceptifs (p. ex. Aβ) (voir section *Considérations méthodologiques*), limitant ainsi notre capacité à inférer si les mécanismes identifiés dans l'étude sont spécifiques au système nociceptif. Ainsi, il est important de corroborer ces résultats avec d'autres modalités de stimulation douloureuses qui sont complémentaires aux stimuli électriques transcutanés.

La première étude présentée dans le cadre de la thèse a utilisé des stimuli au laser. Brièvement, cet outil permet d'irradier à distance (sans contact) un endroit sur la peau et produire de la chaleur. À une intensité suffisante, cette énergie produit une chaleur suffisante pour activer les nocicepteurs Aδ et C sans activation concomitante des fibres Aβ. Une telle stimulation est perçue comme une piqûre locale douloureuse suivie d'une sensation de brûlure diffuse (Plaghki & Mouraux, 2003, 2005). L'étude a eu recours à un paradigme expérimental similaire à l'étude de Rustamov et coll. (Rustamov et al., 2019), avec comme différence majeure la modalité (laser plutôt qu'électrique) et la localisation des stimuli (mains plutôt que chevilles). Les résultats, présentés au Chapitre 4, étaient différents de ceux obtenus dans l'étude de Rustamov et coll. (Rustamov et al., 2019), suggérant que l'intégration d'information nociceptive bilatérale dépend crucialement soit de la modalité (électrique vs laser), de la localisation de stimuli (mains vs pieds), ou d'une combinaison des deux.

La saillance

Toujours dans l'étude de Rustamov et coll., les stimuli sur la cheville droite étaient toujours douloureux (120% du seuil du réflexe de retrait), tandis que ceux sur la cheville gauche étaient soit intenses, mais non douloureux (70% du seuil du réflexe), douloureux (120% du seuil) ou très douloureux (140% du seuil), et l'attention était toujours dirigée sur la cheville droite. Deux choses intéressantes peuvent être observées : 1) une augmentation de certains ERP suivants les stimulations bilatérales, et 2) une tendance à avoir une augmentation plus importante pour les stimuli douloureux (120% et 140% seuil) que non douloureux (70% du seuil), mais une absence d'effet additionnel entre les stimuli douloureux (120%) et très douloureux (140%). Ainsi, cela soulève deux questions additionnelles : cette intégration est-elle sensible à la douleur, ou un stimulus somatosensoriel saillant suffit? Existe-t-il un effet plafond au-delà duquel aucun effet supplémentaire n'est obtenu? Par exemple, un stimulus est évalué comme plus douloureux lorsqu'un stimulus nociceptif additionnel est appliqué en même temps, et ce, même si ce dernier est légèrement sous le seuil de douleur (Lautenbacher et al., 2007). Or, cet effet est moins robuste lorsque le premier stimulus est déjà très douloureux, suggérant aussi un effet plafond (Lautenbacher et al., 2007).

La forte contribution de la saillance aux ERP associés à des stimuli douloureux a été mise en évidence par un paradigme utilisant une répétition de trois stimulations douloureuses très rapprochées dans le temps (Iannetti et al., 2008). Dans ce paradigme, la première stimulation du triplet survient à des intervalles irréguliers tandis que les deux stimulations subséquentes sont toujours espacées d'une seconde. Cela rend la première stimulation beaucoup plus imprévisible que les deux suivantes. Les résultats démontrent que la perception douloureuse demeure similaire pour les trois stimuli, mais que les ERP sont fortement atténués entre la première et la deuxième stimulation, sans réduction subséquente entre la deuxième et la troisième (Iannetti et al., 2008).

La prévisibilité des stimuli

Toujours dans l'étude de Rustamov et coll. (Rustamov et al., 2019), les stimuli unilatéraux et bilatéraux étaient appliqués dans des blocs séparés. Les participants avaient comme instructions de porter attention à la cheville droite. Spéculativement, il est possible que de savoir à l'avance qu'un bloc de stimuli contiendra des stimuli bilatéraux biaise involontairement nos mécanismes attentionnels. Par exemple, la prévisibilité des stimuli affecte l'allocation de l'attention (Alink & Blank, 2021; Baluch & Itti, 2011; Desimone & Duncan, 1995). Il est ainsi important de comparer ces résultats sur l'intégration d'information nociceptive bilatérale avec des paradigmes utilisant des stimuli moins prévisibles. Par exemple, les conditions expérimentales unilatérales et bilatérales « peuvent être variées au sein d'un même bloc plutôt qu'entre les blocs » (Luck, 2014).

L'attention spatiale

Dans l'étude de Rustamov et coll. (Rustamov et al., 2019), les participants avaient comme instructions de rapporter la sensation ressentie à une seule cheville. Ceci permet de comparer directement l'effet de l'information additionnelle tout en contrôlant pour l'attention spatiale. Il n'est donc pas possible de conclure si les résultats rapportés sont reliés à une capture attentionnelle involontaire et automatique (mécanisme ascendant) par le stimulus ignoré. Ainsi, il

est important d'examiner le rôle de l'attention spatiale dans l'intégration d'information nociceptive bilatérale.

Au niveau perceptuel, l'intégration de multiples informations somatosensorielles douloureuse et non douloureuse peut être fortement modulée par l'attention spatiale (Kuroki et al., 2017; Lautenbacher et al., 2007; Quevedo & Coghill, 2007). Par exemple, l'attention spatiale peut induire des changements (expansions ou contractions) dans la grosseur des champs récepteurs de neurones nociceptifs (Coghill, 2020); cela est également observé pour l'attention globale, où les participants rapportent la sensation globale créée par deux stimuli, qui nécessite d'intégrer de l'information nociceptive sur une large surface du corps (Nielsen & Arendt-Nielsen, 1997b; Oshiro et al., 2007; Quevedo & Coghill, 2007). Il est possible d'abolir ou d'amplifier la sommation spatiale de la douleur en changeant les instructions attentionnelles. L'additivité de la douleur, où « deux douleurs sont plus douloureuse qu'une » (Lautenbacher et al., 2007), est amplifiée par l'attention globale, mais abolie par l'attention divisée (Quevedo & Coghill, 2007). Au niveau somatosensoriel, l'effet d'assimilation associé à la présence de fréquences vibrotactiles différentes sur chaque main (menant à une perception de vibration à mi-chemin entre les deux fréquences) est amplifié par l'attention spatiale globale (Kuroki et al., 2017).

La proximité des régions corporelles

L'étude de Rustamov et coll. (Rustamov et al., 2019) a démontré qu'en dirigeant l'attention à la cheville droite, une augmentation de la douleur se produisait en présence de stimuli bilatéraux homosegmentaires (cheville droite et gauche), mais pas pour les stimuli hétérosegmentaires (cheville droite et main gauche). Dans la première étude de cette thèse (Northon et al., 2019), un tel effet homosegmentaire ne fut pas trouvé pour des stimuli laser appliqués sur les deux mains (Northon et al., 2019). Plusieurs hypothèses furent soulevées, notamment 1) une plus grande capacité à maintenir l'attention spatiale à l'endroit requis pour les membres supérieurs qu'inférieurs, 2) une différence reliée à la modalité de stimulation, 3) ou à la plus grande proximité des pieds dans l'espace comparativement aux mains.

Tout comme pour le toucher, la nociception se trouve à la frontière entre notre corps et le monde externe. Pour remplir un rôle de protection du corps en guidant nos réponses motrices au

niveau spatial et ainsi faire face aux dangers potentiels de notre environnement, le système nerveux central doit intégrer plusieurs systèmes de références spatiales (Haggard et al., 2013; Legrain & Torta, 2015) : l'endroit sur le corps qui fut stimulé (aspect *somatotopique*), la position des différents régions corporelles du corps dans l'espace (aspect *spatiotopique*), et la position du corps par rapport à l'environnement immédiat (aspect *péripersonnel*). L'espace péripersonnel peut également être défini selon plusieurs références spatiales centrée sur la position du corps (« *body-centered space representation* ») (Serino, 2019; Serino et al., 2015), le plus souvent centrée sur la position de segments du corps, dont le visage, le tronc, ou les membres supérieurs et inférieurs (Cléry & Hamed, 2018; De Paepe et al., 2015, 2016).

Les stimuli saillants et potentiellement dangereux comme la nociception tendent non seulement à capturer notre attention, mais également à biaiser notre attention spatiale à l'espace péripersonnel autour de l'endroit stimulé (Filbrich et al., 2017a; Filbrich et al., 2016). Par exemple, une stimulation nociceptive accélère le traitement de l'information visuelle à proximité de l'endroit stimulé (Filbrich et al., 2017a; Filbrich et al., 2017b).

De nombreux travaux ont également démontré l'influence de la proximité des mains dans le traitement de l'information somatosensorielle. Par exemple, lorsque deux stimuli tactiles sont appliqués sur chaque main avec un court délai entre chaque stimulus plus de temps est nécessaire entre les deux stimuli pour rapporter correctement quelle main fut stimulée en premier lorsque les mains sont très rapprochées (Shore et al., 2005). Également, la capacité à percevoir et à discriminer un stimulus vibrotactile est réduite par la présence d'un autre stimulus vibrotactile sur la région corporelle opposée, et cet effet est drastiquement augmenté lorsque les mains sont à proximité l'une de l'autre (D'Amour & Harris, 2014a; Soto-Faraco et al., 2004; Tamè et al., 2011). Cela suggère que les stimuli douloureux bilatéraux pourraient mener à un chevauchement de l'espace péripersonnel centré sur les deux mains lorsque les mains sont à proximité l'une de l'autre, en accord avec la règle de la coïncidence spatiale dans l'intégration sensorielle. Cette règle stipule que l'intégration est plus robuste lorsque les stimuli sont appliqués au même endroit dans l'espace (Spence, 2013). Un effet synergétique entre l'attention spatiale et la proximité des

régions corporelles sur la modulation des ERP somatosensoriels associés a également été démontré (Eimer et al., 2004); l'effet de l'attention spatiale à l'un de deux stimuli tactiles sur les ERP fut grandement modulé par une posture avec les mains rapprochées comparativement aux mains éloignées.

Considérations méthodologiques

Choix de la modalité pour induire de la douleur

Cette thèse présente des études ayant eu recours à deux modalités de stimulations pour la douleur : les stimulations électriques transcutanées et les stimulations laser. Ces deux méthodes présentent des similitudes et des différences, et donc des avantages et des inconvénients.

Stimulations électriques transcutanées

Les stimulations électriques transcutanées font passer un courant à la surface de la peau via des électrodes de surface. La stimulation électrique transcutanée est utilisée couramment dans la littérature puisqu'elle 1) permet d'obtenir des réponses électrophysiologiques reproductibles et de grande amplitude en induisant une réponse neuronale extrêmement synchronisée, et ce, tant au niveau spinal (p. ex., réflexe de retrait) que supraspinal (p. ex., potentiels évoqués), 2) présente un faible coût, est facile d'installation et ne produit aucun dommage tissulaire pour les paramètres utilisés, et 3) permet d'augmenter et diminuer l'intensité des stimulations de façon très précise, et les appareils contrôlent de façon très précise l'intensité du courant transmis aux électrodes. Cela permet notamment de mesurer les réflexes comme le réflexe de retrait nociceptif (Sandrini et al., 2005) de façon stable. Lorsque l'intensité de tels stimuli augmente graduellement, une faible sensation tactile émerge (le seuil de perception) qui se transforme en piqûre douloureuse et désagréable (le seuil de douleur).

Cependant, ces stimuli présentent certaines particularités, limites et désavantages. Premièrement, puisque les fibres nociceptives Aδ et C ont une résistance au courant plus grande

que les fibres Aβ, une stimulation d'intensité suffisante pour recruter les fibres Aδ et C recrutera obligatoirement des fibres Aβ (Fox & Kenmore, 1967; Magladery et al., 1951). Cela complexifie inévitablement l'interprétation des données provenant de ces stimuli considérant les interactions entre ces deux systèmes même au niveau spinal (Garcia-Larrea, 2006). Une série de travaux de Dowman propose que l'information spécifique aux nocicepteurs puisse être isolée en soustrayant les ERP provenant de stimuli électriques douloureux à ceux non douloureux (le « *difference potential* ») (Dowman, 1994a; Dowman, 1994b; Dowman, 2002; Dowman & Bridgman, 1995; Dowman & Darcey, 1994). Or, une telle approche est vivement critiquée puisqu'il demeure impossible de mesurer la contribution de chaque fibre aux différents potentiels mesurés (Garcia-Larrea, 2006). Un deuxième point important est que le courant électrique contourne les mécanismes qui permettent la transduction de l'énergie (mécanique, chimique, thermique) en influx nerveux. Les stimulations électriques induisent de la douleur en dépolarisant directement les axones, ce qui élimine l'information reliée à la transduction au niveau des récepteurs sensibles à la pression (mécanorécepteurs) et à la température (thermorécepteurs) (Garcia-Larrea, 2006; Plaghki & Mouraux, 2003). Finalement, les stimuli sont toujours produits exactement au même endroit puisque les électrodes sont attachées à la peau, annulant la variabilité spatiale. Ce dernier point peut être un avantage ou un inconvénient selon ce qui est étudié.

Stimulations au laser

Brièvement, les stimulations au laser (acronyme de *Light Amplification by Stimulated Emission of Radiation*) émettent une lumière pulsée dans une direction très spécifique (un aspect spatial) et dans une fréquence, ou longueur d'onde, très restreinte (p. ex., 1341 mm ou rayonnement infrarouge, un aspect fréquentiel). Cela confère aux lasers une très grande densité d'énergie par unité de temps et par unité de surface. Ainsi, dans le contexte de la recherche sur la douleur, cette technique comporte plusieurs avantages : 1) il n'y a pas de contact avec la peau ce qui évite le recrutement de fibres mécanoréceptrices à faible seuil (Aβ), et la nature du stimulus laser permet une transduction physiologique et sélective des fibres thermoréceptrices Aδ et C (Iannetti et al., 2004; Plaghki & Mouraux, 2003). Les lasers utilisés couramment en recherche sur la douleur permettent théoriquement d'augmenter la température de la peau de quelques milliers de degrés Celsius par seconde; il est donc possible de recruter les nocicepteurs en seulement

quelques millisecondes, résultant en des réponses neuronales suffisamment synchronisées pour obtenir des ERP robustes. Finalement, les stimulations peuvent être présentées sur une surface de peau variable (le plus souvent de 2 à 20 mm) selon les besoins du protocole expérimental.

Cette méthode n'est pas sans danger pour les tissus et plusieurs précautions doivent être observées. À l'inverse des stimuli électriques, il est fortement recommandé de bouger légèrement le laser entre chaque stimulus pour éviter la fatigue des récepteurs ainsi que les dommages tissulaires par accumulation de chaleur (Iannetti et al., 2004; Leandri et al., 2006). Cela introduit cependant de la variabilité spatiale, et la densité des champs récepteurs peut varier légèrement d'un endroit à l'autre sur une même région corporelle. Selon le laser utilisé, l'énergie peut être entièrement déposée à la surface de la peau (laser au CO2), augmentant les risques de brûlure, ou être absorbée plus en profondeur dans le derme (Nd:YAP et Nd:YAG) (Plaghki & Mouraux, 2003, 2005).

Choix de l'outil et des mesures pour l'intégration sensorielle

Les différents outils pour mesurer l'activité cérébrale en présence de douleur ont soit une grande résolution spatiale, comme l'imagerie par résonance magnétique fonctionnelle et la tomographie par émission de positron, ou une grande résolution temporelle, comme l'électroencéphalographie (EEG) et la magnétoencéphalographie (MEG). La mesure de l'intégration sensorielle requiert une méthode qui mesure l'activité des neurones en temps réel et donc une grande résolution temporelle comme l'EEG et la MEG. Des travaux récents ont néanmoins démontré la complémentarité des deux approches en combinant les outils avec grande résolution spatiale et temporelle (p. ex., EEG et IRMf) (Wirsich et al., 2017). Cette approche demeure cependant irréaliste pour la majorité des laboratoires de recherche en matière d'espace, de coût et de personnel qualifié requis.

L'activité électrique (EEG) ou magnétique (MEG) mesurée suite à un stimulus nociceptif est de faible amplitude et difficile à dissocier de l'activité se produisant en tout temps dans le cerveau. Ces outils requièrent plusieurs essais pour dissocier l'activité constante et aléatoire à celle associée aux stimuli d'intérêt. Cette activité constante provient d'éléments physiologiques et non physiologiques (Luck, 2014; Nunez & Srinivasan, 2006): des fluctuations d'activité électrique dans le cerveau non associées aux stimuli d'intérêt (historiquement considérées comme du *bruit de fond* sans intérêt), et des artéfacts contaminant notre signal d'intérêt provenant de l'activité électrique de structures adjacentes (principalement des yeux et des muscles à proximité dont le muscle cardiaque) ou du bruit électrique dans l'environnement immédiat. Suite à la répétition des stimuli, ces fluctuations aléatoires tendent à s'estomper, et seule l'activité reliée à l'évènement demeure. Des déflexions typiques émergent ainsi des courbes moyennes : les potentiels évoqués (*event-related potentials*, ERP) (Luck, 2014). La même approche est utilisée lorsque le signal est décomposé en temps-fréquences, et l'analyse résultante est l'oscillation cérébrale évoquée (*event-related spectral perturbations*, ERSP) (Makeig, 1993).

Suite à une stimulation électrique douloureuse, de nombreuses modulations de l'activité neuronale (des ERP) peuvent être identifiées par un EEG. Les ERP les plus souvent rapportés sont la P45, la N100 et la P260. La P45 est un potentiel positif maximal entre 30 et 50 ms post-stimulus et est générée par le cortex somatosensoriel primaire et est controlatérale à l'endroit stimulé (Allison et al., 1996). Son amplitude sature avant qu'un stimulus électrique devienne douloureux (Dowman, 1994a; Dowman, 1994b), et est réduite en amplitude avec un bloc nerveux des fibres Aβ (Dowman & Bridgman, 1995). La N100 est un potentiel négatif apparaissant entre 90 et 120 ms post-stimulus qui est généré en partie par le cortex somatosensoriel supplémentaire (Dowman et al., 2007) et somatosensoriel secondaire (Thees et al., 2003) bilatéralement avec possibles contributions de l'operculum pariétal (Dowman & Darcey, 1994), et est maximal au niveau du vertex (Dowman, 1994a). Son amplitude augmente en fonction de l'intensité du stimulus et de l'intensité de la douleur (Dowman, 1994b). Le cortex somatosensoriel secondaire est d'ailleurs impliqué dans l'intégration d'information provenant de chaque côté du corps et l'attention (Van der Lubbe et al., 2012). Finalement, la P260 est un potentiel positif apparaissant entre 280 et 350 ms post-stimulus et est générée en partie par le cortex cingulaire et le cortex

pariétal inférieur, et est maximale au niveau du vertex et parfois centropariétal. Ce potentiel est notamment impliqué dans la capture attentionnelle de stimuli en dehors du focus d'attention (Swider et al., 2017).

Suite à une stimulation laser douloureuse, les ERP les plus souvent rapportés sont la N1, la N2 et la P2. La N1, un potentiel négatif, est maximale entre 140 et 200 ms post-stimulus, est générée par le cortex somatosensoriel primaire et l'operculum pariétal, et est controlatérale à l'endroit stimulé (Chen et al., 1998; Garcia-Larrea et al., 2003). Son amplitude représente en quelque sorte l'information nociceptive arrivant au cortex somatosensoriel primaire (Mancini et al., 2015). Elle varie en fonction de l'intensité de la stimulation, et est quelque peu sensible à la saillance et aux stimuli rares et nouveaux (Iannetti et al., 2008; Ronga et al., 2013). Cependant, son amplitude est similaire entre les stimuli perçus et non perçus (Lee et al., 2009). La N2 est un potentiel négatif apparaissant entre 160 et 280 ms post-stimulus qui est généré en partie par le cortex somatosensoriel secondaire, l'operculum pariétal et l'insula postérieure bilatéralement, et est maximal au niveau du vertex (Chen et al., 1998; Garcia-Larrea et al., 2003). L'amplitude de la N2 est particulièrement sensible à la composante sensori-discriminante de la douleur; notamment, elle est fortement modulée par la saillance et la prévisibilité des stimuli nociceptifs (Iannetti et al., 2008; Ronga et al., 2013). Des travaux récents ont démontré que l'amplitude de cette composante est également sensible à la détection de changements spatiaux importants (en termes de danger potentiel accru) dans l'environnement sensoriel (Moayedi et al., 2016), et permet l'élaboration de réactions de retrait appropriées face au danger (Moayedi et al., 2015). Finalement, la P2 est un potentiel positif apparaissant entre 280 et 350 ms post-stimulus et, tout comme la P260 suivant un stimulus électrique douloureux, est générée en partie par le cortex cingulaire et le cortex pariétal inférieur, et est maximale au niveau centropariétal. L'amplitude de la P2 est associée à une orientation de l'attention vers le stimulus potentiellement dangereux, une urgence de réagir, et la préparation d'une éventuelle réaction motrice. Il convient de mentionner que les réponses suivant les stimuli au laser sont largement dominées par les fibres Aδ. Les réponses associées aux fibres C sont plus difficiles à détecter, et ne se produisent qu'à des latences beaucoup plus tardives (>700 ms) (Hu et al., 2014).

Ces stimulations électriques et lasers peuvent également moduler l'activité oscillatoire dans le cerveau, tel que mesuré par les oscillations cérébrales évoquées (ERSP) (Makeig, 1993). Les ERSP les plus souvent rapportés se retrouvent entre 2 et 100 Hz, et, selon la modalité utilisée, de 50 ou 150 ms à 1000 ms suivant la stimulation (Gross et al., 2007; Hauck et al., 2007; Mouraux et al., 2003; Ploner et al., 2006; Ploner et al., 2017; Tiemann et al., 2010; Zhang et al., 2012). Les oscillations à basse fréquence (principalement delta et thêta) entre 2 et 10 Hz augmentent au niveau du vertex à la suite d'un stimulus douloureux, et correspondent en grande partie au même phénomène que les ERP. Cependant, cette analyse peut s'avérer complémentaire aux ERP grâce à son meilleur ratio signal-bruit; en effet, la puissance des oscillations, surtout à basses fréquences, est moins sensible à la variation de latence se produisant naturellement d'un stimulus à l'autre (le « *latency jitter* ») qui peut affecter les ERP (Mouraux & Iannetti, 2008). Les oscillations entre 8 et 29 Hz (alpha et bêta) sont atténuées au niveau des électrodes centropariétales entre 300 et 1000 ms après un stimulus douloureux (Hauck et al., 2007; Ploner et al., 2006; Raij et al., 2004; Rustamov et al., 2019). Ces oscillations incluent le rythme mμ et sont générées par le cortex sensorimoteur (≈10 Hz : cortex sensorimoteur (Hari & Salmelin, 1997; Mouraux et al., 2003; Neuper et al., 2006; Pfurtscheller & Lopes da Silva, 1999); ≈20 Hz : cortex moteur (Neuper et al., 2006; Pfurtscheller & Lopes da Silva, 1999; Raij et al., 2004)). Ce rythme inhibiteur est tonique et représente le « *statu quo sensorimoteur* » en étant présent au repos, mais supprimé lors de mouvements (réels ou imaginaires) et de stimuli somatosensoriels non douloureux et douloureux (Cheyne et al., 2003; Ploner et al., 2017; Raij et al., 2004). Cela suggère ainsi que les stimuli somatosensoriels ont un accès privilégié au cortex sensorimoteur pour supplanter cette inhibition et préparer un mouvement en réponse aux stimuli. Finalement, une augmentation des oscillations à haute fréquence (>30 Hz) au niveau du vertex et du cortex somatosensoriel primaire a été rapportée entre 50 et 350 ms suivant une stimulation électrique douloureuse (Hauck et al., 2007; Rossiter et al., 2013; Rustamov et al., 2019) et entre 150 et 400 ms suivant le laser douloureux (Bassez et al., 2020; Hauck et al., 2015; Heid et al., 2020; Tiemann et al., 2015; Tiemann et al., 2010; Yue et al., 2020; Zhang et al., 2012). Cette augmentation est associée à la capture attentionnelle (Rustamov et al., 2019), à l'aspect saillant du stimulus (Hauck et al., 2007), ou encore à l'intensité du stimulus somatosensoriel (Rossiter et al., 2013) ou de la douleur (Zhang et al., 2012).

Problématique et manque aux connaissances

Les stimuli nociceptifs représentent un potentiel danger pour les tissus et sont de la plus grande importance pour l'organisme. Ces signaux étant particulièrement saillants, et capturant ainsi automatiquement notre attention, qu'arrive-t-il en présence de nombreux stimuli nociceptifs identiques? Le système nerveux central doit être en mesure de s'adapter pour adopter un comportement approprié en fonction de la situation. Nos connaissances sur les mécanismes cérébraux nous permettant d'intégrer des stimuli nociceptifs bilatéraux sont très limitées. Seules quelques études ont exploré de près cette question, et présentent toutes une ou plusieurs limites importantes énumérées précédemment. Notons principalement l'utilisation de stimuli toniques et non spécifiques aux nocicepteurs, ou l'absence de mesures neurophysiologiques.

La seule étude ayant eu recours à des mesures neurophysiologiques a démontré que l'information nociceptive bilatérale était intégrée au niveau du cortex. Cependant, plusieurs questions demeurent, notamment si cette intégration corticale est 1) sensible à la latéralisation hémisphérique de la douleur située partiellement à l'hémisphère droit, 2) spécifique au système nociceptif et à la perception douloureuse (des mécanismes ascendants), et si elle est sensible à différents paramètres comme l'attention spatiale (des mécanismes descendants) et la proximité des régions corporelles dans l'espace. Cette thèse présente une série de quatre études répondant à ces questions.

Présentation des études de la thèse

La première étude visait à explorer l'impact de la latéralité (dominance motrice) sur l'intégration d'information nociceptive bilatérale. L'information nociceptive est préférentiellement traitée dans l'hémisphère droit (une latéralisation, ou spécialisation hémisphérique), et la latéralité (la dominance motrice) a un impact sur ses spécialisations hémisphériques. Une différence dans l'intégration nociceptive était donc attendue entre les individus droitiers et gauchers. Des participants droitiers et gauchers ont été recrutés, et les réponses EEG ont été mesurées à la suite de stimulations douloureuses unilatérales (nerf sural

droit, nerf sural gauche, nerf ulnaire gauche) et bilatérales (nerfs suraux droit et gauche, nerf sural droit et ulnaire gauche). Les résultats démontrent une augmentation sous-additive des potentiels évoqués négatifs (la N100) et des oscillations cérébrales gamma lors de stimulations bilatérales comparativement aux stimulations unilatérales. De plus, une augmentation de la douleur fut observée lorsque les stimuli bilatéraux étaient homosegmentaires (membres inférieurs droit et gauche) et non hétérosegmentaire (membre inférieur droit et membre supérieur gauche). Cependant, aucune différence ne fut observée entre les gauchers et les droitiers.

La deuxième étude visait à explorer si l'intégration sous-additive de stimuli douloureux bilatéraux est présente lorsque des stimuli spécifiques aux fibres Aδ et C (lasers) sont utilisés. Les réponses EEG furent mesurées à la suite de stimuli laser unilatéraux (main droite seule et main gauche seule) et bilatéraux (main gauche et droite avec attention à la main droite ou attention à la main gauche). Au contraire des résultats sur les stimuli douloureux électriques, cette deuxième étude démontre une réduction des potentiels évoqués et des perturbations gamma lors de stimulations bilatérales comparativement aux stimulations unilatérales (intégration suppressive).

Les troisièmes et quatrièmes études ont été réalisées en parallèle et visaient à mieux comprendre l'origine des divergences entre notre première étude (intégration subadditive) et notre deuxième étude (intégration suppressive).

La troisième étude a eu recours à deux expérimentations dans lesquelles les réponses cérébrales à des stimuli électriques et lasers sur les mains furent comparées chez les mêmes participants. Cela nous a permis d'isoler le facteur *Modalité* sans égards à la localisation des stimuli (pieds ou mains) et à la variabilité interindividuelle. La première expérience a utilisé un paradigme expérimental où les stimuli unilatéraux et bilatéraux étaient présentés de façon aléatoire afin de réduire les effets de séquence qui pourraient potentiellement influencer les mesures de nos études antérieures. L'ordre de présentation des modalités était contrebalancé. Trois modalités de stimuli furent utilisées, soit des stimuli électriques douloureux, des stimuli électriques non douloureux, et des stimuli laser douloureux. Les résultats obtenus dans cette

première expérience suggèrent que les stimuli somatosensoriels, qu'ils soient sélectifs aux nocicepteurs ou non (laser ou électrique douloureux), douloureux ou non (électrique douloureux ou non douloureux), sont intégrés de façon similaire dans le cerveau. Cette intégration se manifeste par une augmentation des ERP et de la perception de l'intensité des stimuli non douloureux sans effet sur la perception de la douleur. Cependant, suite aux stimuli laser, quelques participants ont démontré une absence d'effet et même une réduction des ERP suivant les stimuli bilatéraux comme dans la deuxième étude. La seconde expérience a été réalisée afin de mieux comprendre les disparités entre les résultats de la première expérience de la troisième étude et nos résultats antérieurs. La méthodologie de la deuxième étude fut répliquée tout en ajoutant la modalité électrique douloureuse. Cette seconde expérience démontre à nouveau que l'effet le plus commun suivant des stimuli bilatéraux douloureux électriques ou laser est une augmentation des ERP. Encore une fois, certains sujets démontrent un effet contraire suivant des stimuli bilatéraux au laser, ce qui contribue à une certaine variabilité qui n'est pas présente pour les stimuli électriques. De plus, les résultats entre la première et la deuxième expérience sont comparables et suggèrent que le fait de savoir à l'avance si les stimuli seront unilatéraux ou bilatéraux n'est pas un facteur important dans l'intégration d'information nociceptive bilatérale.

La quatrième étude a évalué l'effet de la proximité des membres dans l'espace ainsi que l'attention spatiale dans l'intégration d'information nociceptive bilatérale. L'augmentation de la douleur pour les stimuli électriques bilatéraux au niveau des membres inférieurs rapportés par Rustamov et coll. (2019) (Rustamov et al., 2019) et répliqués dans notre première étude (Northon et al., 2021c) n'a pas été retrouvée pour les stimuli aux membres supérieurs, et ce, peu importe la modalité. Puisque la proximité entre deux régions corporelles (p. ex., les mains) affecte le traitement de l'information somatosensorielle (voir section *La proximité des régions corporelles*), nous avons fait l'hypothèse que ce facteur pouvait expliquer au moins en partie cette différence; en effet, les pieds sont plus rapprochés que les mains tant dans l'espace (spatiotopique) que dans le cerveau (somatotopique) – les pieds sont très proches de chaque côté de leur hémisphère respectif. De plus, afin de contrôler l'attention spatiale dans nos travaux précédents, les participants rapportaient leur perception des stimuli sur le membre droit seulement (attention spatiale focale). Or, l'attention spatiale globale peut altérer la perception et l'intégration spatiale

de stimuli nociceptifs (tel que décrit à la section *L'attention spatiale*). Dans cette étude, les stimuli unilatéraux et bilatéraux au laser étaient présentés de façon aléatoire dans chaque bloc de stimuli. L'impact de la proximité des régions corporelles et l'attention spatiale fut mesuré à l'aide de deux facteurs : *Attention* (focale vs globale) et *Proximité* (mains rapprochées vs éloignées) pour un total de quatre conditions. L'ordre de présentation des conditions était contrebalancé. Les résultats démontrent à nouveau une augmentation des ERP pour les stimuli bilatéraux comparativement aux stimuli unilatéraux. Cette augmentation fut également modulée par la proximité des mains. Cependant, une grande variabilité est encore notée, et 30% des participants présentent un effet quasi nul ou une réduction. Finalement, une augmentation de la douleur fut observée lorsque les mains étaient rapprochées, et lorsque l'attention était globale. Aucun effet synergétique entre l'attention spatiale et la proximité des mains ne fut observé.

Chapitre 3 Article 1. Spinal and cerebral integration of noxious inputs in left-handed individuals.

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Contribution des auteurs

Stéphane Northon : Récension des écrits, collecte de données, analyses statistiques, rédaction de l'article, révision de l'article.

Zoha Deldar : Récension des écrits, analyses statistiques, rédaction de l'article, relecture de l'article.

Mathieu Piché : Supervision de l'étude

Abstract

Some pain-related information is processed preferentially in the right cerebral hemisphere. Considering that functional lateralization can be affected by handedness, spinal and cerebral pain-related responses may be different between right- and left-handed individuals. Therefore, this study aimed to investigate the cortical and spinal mechanisms of nociceptive integration when nociceptive stimuli are applied to right -handed vs. left -handed individuals. The NFR, evoked potentials (ERP: P45, N100, P260), and event-related spectral perturbations (ERSP: theta, alpha, beta and gamma band oscillations) were compared between ten right-handed and ten left-handed participants. Pain was induced by transcutaneous electrical stimulation of the lower limbs and left upper limb. Stimulation intensity was adjusted individually in five counterbalanced conditions of 21 stimuli each: three unilateral (right lower limb, left lower limb, and left upper limb stimulation) and two bilateral conditions (right and left lower limbs, and the right lower limb and left upper limb stimulation). The amplitude of the NFR, ERP, ERSP, and pain ratings were compared between groups and conditions using a mixed ANOVA. A significant increase of responses was observed in bilateral compared with unilateral conditions for pain intensity, NFR amplitude, N100, theta oscillations, and gamma oscillations. However, these effects were not significantly different between right- and left-handed individuals. These results suggest that spinal and cerebral integration of bilateral nociceptive inputs is similar between right- and left-handed individuals. They also imply that pain-related responses measured in this study may be examined independently of handedness.

Introduction

The concept of brain lateralization was first described by Paul Broca, who found that language appeared to be a specific function of the left hemisphere, particularly in right-handed patients (Broca, 1863). Since then, the concepts of functional specialization and of cerebral hemispheric functional and structural asymmetries have been studied extensively in humans and animals (Corballis, 2014b; Corballis & Häberling, 2017; Duboc et al., 2015; Ehret, 1987; Neubauer et al., 2020; Serrien et al., 2006; Souza et al., 2018). The study of these asymmetries led to the concept of brain lateralization, where some specific sensory, motor, or cognitive functions are localized in one hemisphere or the other (Cykowski et al., 2008; Gazzaniga, 2005; Geschwind & Levitsky, 1968; Karolis et al., 2019; Mangin et al., 2004; Manning & Thomas-Antérion, 2011; Neubauer et al., 2020; Rogers et al., 2004; Toga & Thompson, 2003; White et al., 1994). Brain lateralization seems to be particularly relevant in humans because of hemispheric specialization for complex cognitive abilities (Corballis, 2014b; Duboc et al., 2015; Gazzaniga et al., 1962; Gotts et al., 2013; Neubauer et al., 2020; Nicholls et al., 2010; Ocklenburg et al., 2013).

Functional asymmetries have been associated with handedness, i.e., the preference for using one hand over the other when performing skilled movements (Cazzoli & Chechlacz, 2017; Corballis & Häberling, 2017; Gonzalez et al., 2018; Mazoyer et al., 2014; McManus, 1985; Ocklenburg et al., 2013; Serrien et al., 2006; Souza et al., 2018; Sun et al., 2012; White et al., 1994; Woytowicz et al., 2018). The majority of the population shows a right-hand preference, implying a left hemispheric dominance for hand use (Corballis, 2009b; Corballis & Häberling, 2017; Geuze et al., 2012; Gilbert & Wysocki, 1992; Neubauer et al., 2020; Ocklenburg et al., 2013). Handedness also tends to reflect the degree to which the nervous system is lateralized (Corballis, 2020b; Duboc et al., 2015; Pool et al., 2015). Indeed, in the ten percent of the population that is left-handed or ambidextrous (Neubauer et al., 2020), brain asymmetries are more often reversed or less pronounced compared with those of right-handed individuals (Corballis, 2009b; Corballis & Häberling, 2017; Geuze et al., 2012; Gilbert & Wysocki, 1992; Neubauer et al., 2020; Ocklenburg et al., 2013; Souza et al., 2018).

In addition to handedness, the processing of most sensory information is highly lateralized (Coghill et al., 2001; Greenspan et al., 1993; Lugo et al., 2002b; Sarlani et al., 2003; Youell et al., 2004). For example, somatosensory information such as nociception is preferentially integrated

into the contralateral hemisphere (Coghill et al., 2001). However, the processing of negative emotions and of some pain-related information appears to be processed preferentially in the right hemisphere, at least in right-handed individuals (Brooks et al., 2002; Coghill et al., 2001; Duerden & Albanese, 2013; Fouché et al., 2017a; Ocklenburg et al., 2013; Pauli et al., 1999; Symonds et al., 2006; Youell et al., 2004). In addition, pain thresholds were reported to be lower and pain perception higher on the non-dominant compared with the dominant body side in right-handed individuals (Brennum et al., 1989; Buchanan & Midgley, 1987; Haslam, 1970; Jensen et al., 1992; Lugo et al., 2002b; Pauli et al., 1999; Petersen et al., 1992; Pud et al., 2009; Sarlani et al., 2003; Spernal et al., 2003), although not always (Chéry-Croze, 1983; Greenspan & McGillis, 1994; Long, 1994; Meh & Denislic, 1994; Taylor et al., 1993). These discrepancies may stem from the tested body sites (Antonaci et al., 1992; Bingel et al., 2003; Brooks et al., 2002; Buchanan & Midgley, 1987; Coghill et al., 2001; Fischer, 1987; Petersen et al., 1992; Schlereth et al., 2003; Youell et al., 2004) and the stimulus modality used to induce pain (Greenspan et al., 1993; Long, 1994; Pauli et al., 1999; Vierck et al., 2001). Lastly, studies assessing the effect of handedness on pain have produced conflicting evidence (Haslam, 1970; Jensen et al., 1992; Long, 1994; Lugo et al., 2002b; Murray & Safferstone, 1970; Pauli et al., 1999). Considering that functional lateralization might be different in left-handed people, hand dominance should be studied to further characterize individual variations in nociceptive processing (Greenspan et al., 1993; Pud et al., 2009).

Nociception is known to evoke protective responses at the spinal and supraspinal levels. Supraspinal responses evoked by transcutaneous electrical stimulation of the sural nerve include event-related potentials (ERPs: the P45, N100 and P260) and event-related spectral perturbations (ERSPs: changes in oscillatory power in different frequency bands, including theta, alpha, beta, and gamma oscillations) (Rustamov et al., 2019). These responses must be adapted according to where and how noxious stimuli are applied. For example, concurrent noxious inputs from two body sites must be integrated in order to produce an appropriate response. Indeed, recent studies showed that concurrent painful stimuli are integrated in the brain as measured by the modulation of ERPs and ERSPs (Northon et al., 2021a; Northon et al., 2019; Rustamov et al., 2019). Since handedness impacts functional specializations, and some nociceptive information is preferentially processed in the right hemisphere, a different pattern of integration would thus be expected between right- and left-handed individuals. This effect could also be reflected at the spinal level,

which can be assessed using the nociceptive flexion reflex (NFR) (Arendt-Nielsen et al., 2000; Hagbarth, 1960; Sandrini et al., 2005; Willer, 1977). A previous study using concurrent painful stimuli showed that the NFR was increased by concurrent bilateral painful stimulation compared with unilateral stimulation and that this involved descending motor facilitation (Rustamov et al., 2019). The difference in motor cortex organization between right- and left-handed individuals suggests that the sensorimotor processing of unilateral and bilateral noxious inputs between right- and left-handed individuals may affect spinal processes (Hammond, 2002).

The aim of the present study was to investigate the cortical and spinal mechanisms of nociceptive integration when bilateral nociceptive stimuli are applied to the limbs in right-handed vs. left-handed individuals. We expected an increase in the spinal NFR and cerebral pain-related responses for bilateral stimulation compared with unilateral stimulation. We also expected these increases to be different between right- and left-handed participants. The results indicate spinal and cerebral responses are increased during bilateral stimulation compared with unilateral stimulation. However, no differences were observed between right- and left-handed individuals.

Materials and Methods

Participants

Twenty-six healthy volunteers were recruited by advertisements on the campus of the Université du Québec à Trois-Rivières. All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of the Université du Québec à Trois-Rivières. Participants were included in the study if they were between 18 and 45 years old. They were excluded if they had taken any medication affecting the nervous system or pain perception within two weeks prior to the experiment, including antihypertensives, pain killers, anxiolytics, antidepressants, and other psychotropic medication. They were also excluded if they had acute or chronic pain or a diagnosed neurologic or psychiatric disorder. Six participants could not complete the experimental procedures because the stimulus intensity required to produce a reliable NFR was not tolerable. Therefore, data from these six participants were not collected, leaving a sample of 20 participants (11 women and 9 men; range 20-34 years old; mean ± SD: 22.95 ± 6.61). These 20 participants were divided into two groups according to their hand dominance: right-handed (5 women and 5 men; range: 21-29 years old; mean ± SD: 24.4 ± 3.5 years old) and left-handed (6 women and 4 men; range: 20-34

years old; mean ± SD: 24.3 ± 6.8 years old). Hand dominance was measured using the Edinburgh handedness inventory questionnaire, which provides a spectrum of handedness with score from -100 to 100, from pure left-handed to pure right-handed individuals, and 0 for ambidextrous individuals (Oldfield, 1971). The average handedness scores in the present study were -73.0 ± 23.5 for left-handed individuals and 76.6 ± 25.9 for right-handed individuals.

Experimental design

The present study relied on a mixed design. The experimental protocol comprised three conditions in which electrical stimuli were applied on one limb (unilateral) and two conditions in which electrical stimuli were applied on two limbs (bilateral) for a total of five conditions. The three unilateral conditions consisted of 1) right lower limb stimulation, 2) left lower limb stimulation, and 3) left upper limb stimulation; the two bilateral conditions consisted of 1) concurrent stimulation of right and left lower limbs, and 2) concurrent stimulation of right lower limb and left upper limb. The order of conditions was counterbalanced to avoid sequence order effects. Each condition included 21 stimuli with an inter-stimulus interval varying between 11000 and 18000 ms (with a geometric distribution). The experiment lasted approximately 90 minutes, including preparation, the determination of thresholds (NFR and pain), and the recording of NFR and brain activity in the five conditions (see Figure 1).

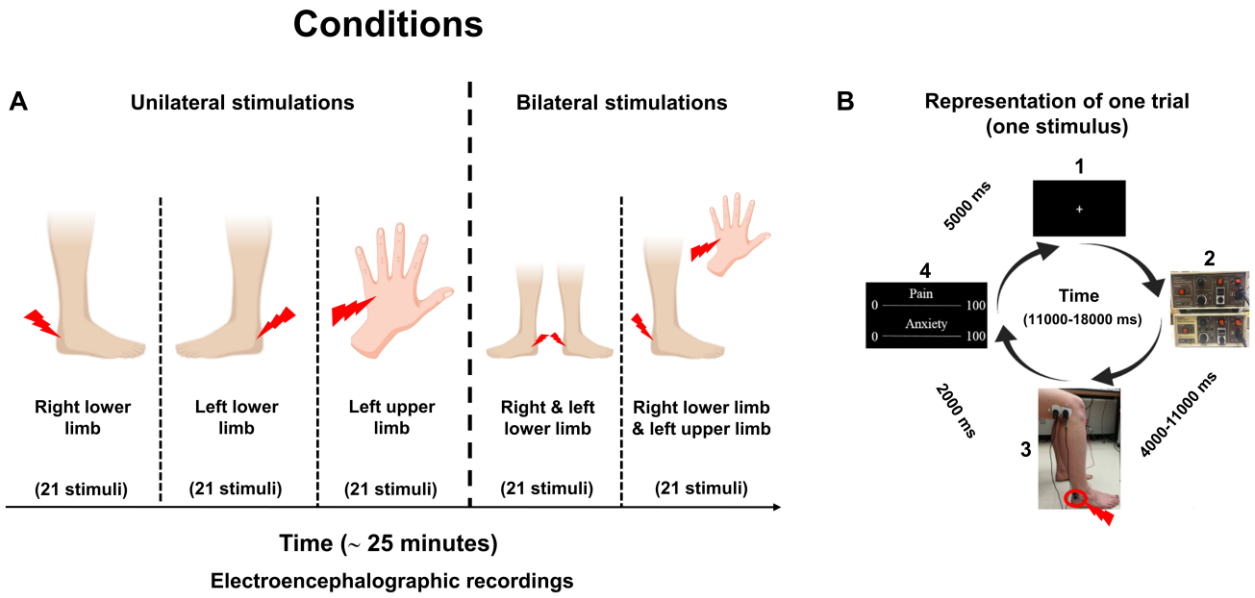

Figure 3.1 Experimental design

Left panel (A) is a depiction of the five conditions. The three unilateral conditions consisted of right lower limb stimulation, left lower limb stimulation, and left upper limb stimulation; the two bilateral conditions involved the right and left lower limbs, and the right lower limb and left upper limb (each condition included 21 stimuli). Right panel (B) is a depiction of one trial (one stimulus). Each trial lasted between 11000 and 18000 ms (geometric distribution). Participants rated pain and pain-related anxiety 5000 ms after each stimulus using a visual analog scale with left (0) and right (100) anchors indicating "no pain" and "worse pain imaginable," respectively. Participants were informed that stimuli would be delivered unilaterally on the right hand or bilaterally on both hands.

Electrical stimulation

Transcutaneous electrical stimulation (trains of 10 x 1 ms pulses at 333 Hz) was delivered with two isolated DS7A constant current stimulators (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) triggered by a Grass S88 train generator (Grass Medical Instruments, Quincy, MA, USA). Scripts running in stimulus presentation programs (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA and Spike 2 data analysis software, Cambridge Electronic Design, Ltd., Cambridge, UK) were used to control the stimulators. The skin over the retromalleolar path of the right and left sural nerves (lower limbs) and over the ulnar nerve territory of the left-hand dorsum (upper limb) was shaven, degreased, and rubbed with alcohol. The skin was stimulated by two adjacent pairs of custom-made surface electrodes (1 cm2; 2 cm inter-electrode distance). The right and left NFR thresholds were determined separately using the staircase method including three series of stimuli of increasing and decreasing intensity, as in our previous studies (Ladouceur et al., 2018; Rustamov et al., 2019). Stimulus intensity was then adjusted individually and for each lower limb to 120% of the NFR threshold. For the left hand, pain threshold was determined using a staircase method starting from a low intensity and was defined as the lowest stimulus intensity evoking pain. Stimuli were then adjusted individually to 120% of pain threshold.

Nociceptive flexion reflex measure and analysis

Electromyography (EMG) of the short head of the biceps femoris was recorded with a pair of surface electrodes (EL-508, Biopac Systems, Inc., Goleta, CA, USA). The signal was amplified 2000 times, high-pass filtered with the low edge at 10 Hz, low-pass filtered with the high edge at 500 Hz, sampled at 1000 Hz (Biopac Systems, Inc., Goleta, CA, USA), and stored

on a personal computer for off-line analyses. These EMG recordings were full wave rectified and the resulting signal was used to quantify the amplitude of NFR to each shock by extracting the integral value between 90 and 180 ms after stimulus onset. This amplitude was standardized within each subject for each shock in each condition using T scores, mean-centered at 50. The mean T scores of the 21 responses were then calculated for each of the three conditions (stimulation of the right lower limb, the right and left lower limbs, and the right lower limb and left upper limb) for comparisons.

Pain and pain-related anxiety ratings

Participants verbally rated pain intensity and pain-related anxiety for the stimulated limb during unilateral stimulation. For bilateral conditions, participants were asked to rate the right lower limb only. The prompt for ratings appeared two seconds after stimulation using a verbal numerical rating scale (NRS) with the 0 and 100 pain and pain-related anxiety anchors representing "no pain/no anxiety" and "worse pain imaginable/worse anxiety imaginable". These scales were displayed horizontally on a computer screen after each stimulus (see Figure 1).

Electroencephalographic recordings

Electroencephalographic activity (EEG) was recorded using a 64-channel BrainVision system with active electrodes mounted on an actiCAP in an International 10–20 System montage (Brain Products, Gilching, Germany). The electrodes were referenced to the nose and the ground electrode was placed on the forehead at FPz. To record electrooculographic activity, a pair of electrodes was placed at the suborbital ridge (vertical electrooculogram, vEOG) and the external ocular canthus (horizontal electrooculogram, hEOG) of the right eye. Electrode impedance was kept below 10 kΩ. Electroencephalographic and electrooculographic signals were filtered with a 0.01–100 Hz bandpass, a notch filter (60 Hz), and were sampled at 500 Hz for offline analyses.

Event-related potentials analyses

EEG data were analyzed in the MATLAB (Mathworks, Nattick, MA, USA) environment using EEGLAB version 14.1.0. Data were filtered offline with FIR filters using the in-built automatic filter function in EEGLAB, with the lower edge of high-pass filter at 0.5 Hz and the higher edge of the low-pass filter at 30 Hz. Data were then screened for infrequent and non-

stereotyped artifacts, including electrode failure, cable movement, or body movement. For further artifact attenuation, Infomax independent component analysis (ICA) was applied. Artifacts were identified using the EEGLAB-Runica function, and independent components found to reflect blinks, eye movements, muscle-related artifacts, cardiac artifacts and electric noise were removed from the data. Following ICA-based artifact attenuation, ERPs were time-locked to the stimulation, baseline-corrected between -100 and 0 ms prior to the electrical stimulus, and averaged for each condition. The amplitude of the N100 and P260 components was quantified using the mean amplitude between fixed latencies (N100: 90–120 ms post-stimulus; P260: 280–350 ms post-stimulus) (Dowman, 1994a). These components are maximal at the vertex (Dowman, 1994a; Dowman, 2004c; Rustamov et al., 2019), so they were calculated at the Cz electrode after confirming the expected topography.

To examine non-linear interactions between unilateral and bilateral conditions, the sum of unilateral conditions ERPs (summed ERPs) were compared to the ERPs obtained for bilateral conditions. The two summed ERPs were computed from the right and left lower limb in unilateral conditions, and from the right lower limb and left upper limb in unilateral conditions. In addition, a differential ERP was generated by subtracting ERPs in bilateral conditions from the summed ERPs.

To examine potential differences in lateralization, the P45 was measured for the left upper limb condition using the mean amplitude between fixed latencies (30–45 ms post-stimulus). This early response, generated by the primary somatosensory cortex, is clearly lateralized following hand stimuli. Subject-averaged scalp topoplots from 30 to 45 ms post-stimulus clearly showed a lateralized potential with a maximal value at CP6.

Time-frequency analysis

Event-related spectral perturbations (ERSP) were analyzed separately for each condition. Data were filtered with FIR filters using the in-built automatic filter function in EEGLAB, with the edge of the high-pass filter at 1 Hz and the edge of the low-pass filter at 100 Hz. Data were segmented into stimulus-locked epochs from -1600 to 2600 ms, with time 0 corresponding to the electrical stimuli. An independent component analysis was applied to remove artifacts, in the same way as described for the ERPs above. A Morlet wavelet convolution was computed using the time-frequency options available in EEGLAB v.14.1.0. Four hundred time points were

generated and 100 linearly spaced frequencies were computed from 4 to 100 Hz. Variable cycles were used for low and high frequencies, with three cycles for lowest frequencies and up to fifteen cycles for the highest frequencies. This approach allows the wavelet convolution method to optimize frequency resolution at lower frequencies and temporal resolution at higher frequencies (Delorme & Makeig, 2004). ERSP data were computed in decibels relative to the -700 to -200 ms baseline. Computations were performed for all electrodes separately. For each participant, the time-frequency data of all trials were averaged for each condition and electrode separately, resulting in five average time-frequency maps for each electrode.

From these maps, the mean power in four regions of interest (time-frequency) was extracted from the Cz electrode based on previous studies: from 4 to 10 Hz between 50 and 400 ms, from 8 to 29 Hz between 250 and 1000 ms, from 30 to 60 Hz between 50 and 350 ms, and from 61 to 100 Hz between 100 and 350 ms (Hauck et al., 2007; Ploner et al., 2017; Rustamov et al., 2019). The gamma band was separated into low and high gamma as previous work has identified components in both (Heid et al., 2020; Rustamov et al., 2019). The ERSP values for each time-frequency point included in the regions of interest were extracted from each subject. A mean ERSP value was then obtained for each subject and region of interest by selecting and averaging the values with the 20% highest amplitude (for power increases relative to the baseline) or 20% lowest amplitude (for power decreases relative to the baseline in the case of suppression). This procedure has been used in previous studies for EEG data processing with the main advantage of allowing for the selection of wide regions of interests to account for variability across subjects while reducing the regression to the mean problem with near-zero values (Mouraux & Iannetti, 2008).

Statistical analyses

Data analysis was conducted using Statistica v13.1 (Dell, Inc, Tulsa, OK). All results are expressed as mean ± standard deviation, and the statistical threshold was set to $p \leq 0.05$ (two-tailed). Data distribution was assessed for normality with the Kolmogorov–Smirnov test. Sphericity was assessed with Mauchly test and corrected with the Greenhouse–Geisser correction when appropriate. To examine the interactions of concurrent noxious inputs, pain intensity, pain-related anxiety, NFR amplitude, ERP amplitude, and ERSP values were compared using a mixed ANOVA with GROUP (right-handed vs. left-handed individuals) as a between-subject factor and

CONDITION (unilateral stimulation: right lower limb vs. bilateral stimulation: right lower limb and left lower limb; right lower limb and left upper limb) as a within-subject factor. To examine non-linear interactions between concurrent bilateral inputs reflected in ERPs, a mixed ANOVA was used with GROUP (right-handed vs. left-handed individuals) as a between-subject factor and INTERACTION (Summed vs. Bilateral ERPs) as a within-subject factor. For changes in P45 amplitude following left upper limb stimulation, an independent *t*-test was performed between right-handed and left-handed individuals. Effect sizes are reported based on partial eta-squared (η_p^2). A priori hypotheses were tested with planned contrasts.

Results

Pain intensity

Pain ratings are presented in Figure 2A. Right- and left-handed individuals were comparable in terms of mean pain intensity (main effect of handedness: $F_{1,18} = 0.26$, $p = 0.60$, $\eta_p^2 = 0.01$), but pain intensity was significantly different between the bilateral stimulation compared with the unilateral stimulation (main effect of condition: $F_{2,36} = 9.05$, $p = 0.0006$, $\eta_p^2 = 0.33$). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{2,36} = 0.002$, $p = 0.99$, $\eta_p^2 = 0.0001$). Planned contrast for the main effect of condition revealed that pain intensity was significantly increased by the bilateral stimulation of the right and left lower limbs compared with the unilateral stimulation of the right lower limb ($p = 0.004$). In contrast, pain intensity for the bilateral stimulation of the right lower limb and left upper limb were not significantly different compared with unilateral stimulation of the right lower limb ($p > 0.6$).

Pain-related anxiety

Pain-related anxiety ratings are presented in Figure 2B. In parallel with the results for pain intensity, right- and left-handed individuals were comparable in terms of mean pain-related anxiety (main effect of handedness: $F_{1,18} = 1.65$, $p = 0.21$, $\eta_p^2 = 0.08$), whereas a significant effect of condition was observed (main effect of condition: $F_{2,36} = 3.96$, $p = 0.02$, $\eta_p^2 = 0.18$). However, this effect was not significantly different between right-handed and left-handed individuals (interaction: $F_{2,36} = 2.87$, $p = 0.06$, $\eta_p^2 = 0.13$). Planned contrast for the main effect of condition revealed that pain-related anxiety was significantly increased by bilateral stimulation of the right

and left lower limbs compared with unilateral stimulation of the right lower limb (p = 0.03). Besides, pain-related anxiety for the bilateral stimulation of the right lower limb and left upper limb was not significantly different compared with unilateral stimulation of the right lower limb ($p > 0.2$).

Nociceptive flexion reflex

The comparison of NFR amplitude between groups and conditions is presented in Figure 2C. Right- and left-handed individuals were comparable in terms of mean NFR amplitudes (main effect of handedness: $F_{1,18}$ = 0.18, p = 0.66, η_p^2 = 0.01), but the NFR was significantly modulated by the bilateral stimulation compared with the unilateral stimulation (main effect of condition: $F_{2,36}$ =13.82, $p < 0.001$, η_p^2= 0.43). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{2,36}$ =0.9, p = 0.41, η_p^2= 0.04). Planned contrasts for the main effect of condition revealed that the right NFR was significantly increased by bilateral stimulation of the right and left lower limbs (p = 0.0003) and by bilateral stimulation of the right lower limb and left upper limb (p = 0.003) compared with unilateral stimulation of the right lower limb.

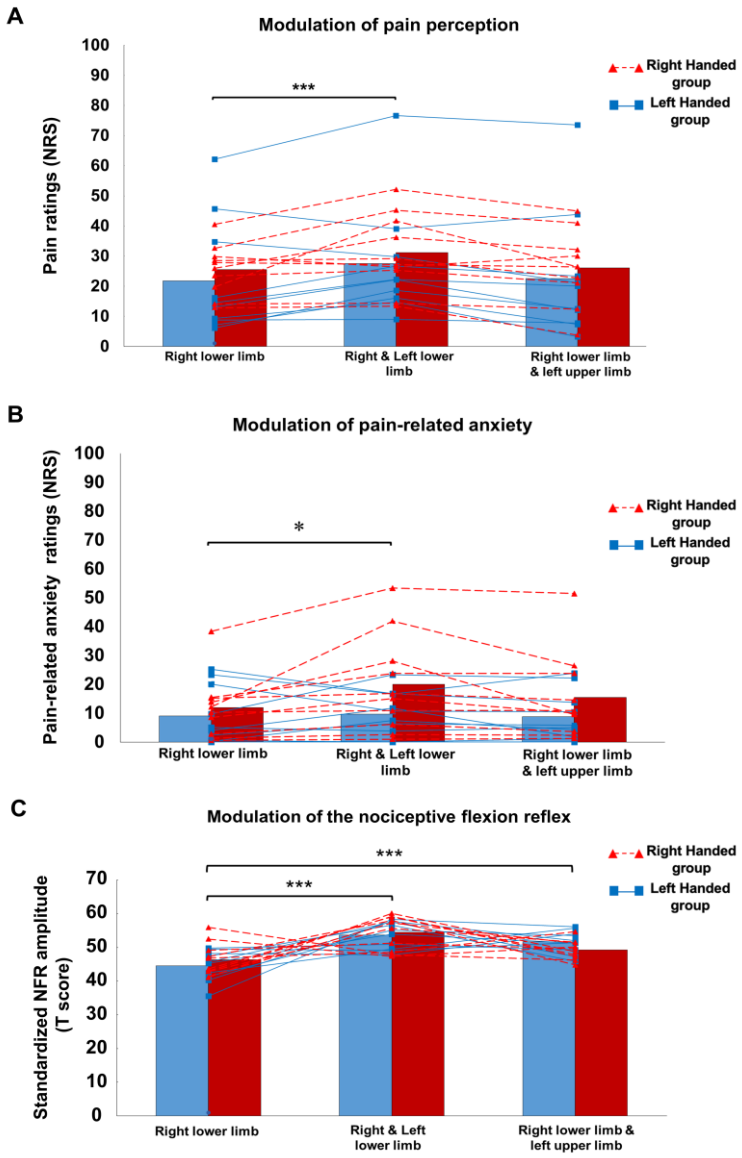

Figure 3.2 Modulation of pain, pain-related anxiety and the nociceptive flexion reflex.

(A) Modulation of pain perception (NRS: 0–100). Triangle and square icons represent right-handed and left-handed individual data, respectively. Red dashed lines indicate the right-handed group and blue lines indicate the left-handed group. ***: Planned contrasts for the main effect of CONDITION: $p < 0.001$. (B) Modulation of pain-related anxiety (NRS: 0–100). Triangle and square icons represent right-handed and left-handed individual data, respectively. Red dashed lines indicate the right-handed group and blue lines indicate the left-handed group. *: Planned contrasts for the main effect of CONDITION: $p < 0.05$. (C) Modulation of nociceptive flexion reflex (NFR) (T score). Triangle and square icons represent right-handed and left-handed individual data, respectively. Red dashed lines indicate the right-handed group and blue lines indicate the left-handed group. ***: Planned contrasts for the main effect of CONDITION: $p < 0.001$.

Event-related potentials

Electrical stimulation produced robust vertex ERPs, with notable N100 and P260 components in all conditions (see Figure 3). The mean N100 amplitude was comparable between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.01$, $p = 0.88$, $\eta_p^2 = 0.001$), but was significantly different between conditions (main effect of condition: $F_{2,36} = 40.11$, $p < 0.0001$, $\eta_p^2 = 0.69$). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{2,36} = 1.2$, $p = 0.31$, $\eta_p^2 = 0.06$). Planned contrast for the main effect of condition revealed that the amplitude of the N100 evoked by bilateral stimulation of the right and left lower limbs ($p < 0.0001$) and by bilateral stimulation of the right lower limb and left upper limb ($p < 0.0001$) was significantly increased compared with unilateral stimulation of the right lower limb (see Figure 3).

The mean amplitude of the P260 was not significantly different between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.21$, $p = 0.64$, $\eta_p^2 = 0.01$), between conditions (main effect of condition: $F_{2,36} = 3.09$, $p = 0.05$, $\eta_p^2 = 0.14$), or between groups across conditions (interaction: $F_{2,36} = 0.3$, $p = 0.69$, $\eta_p^2 = 0.01$; see Figure 3).

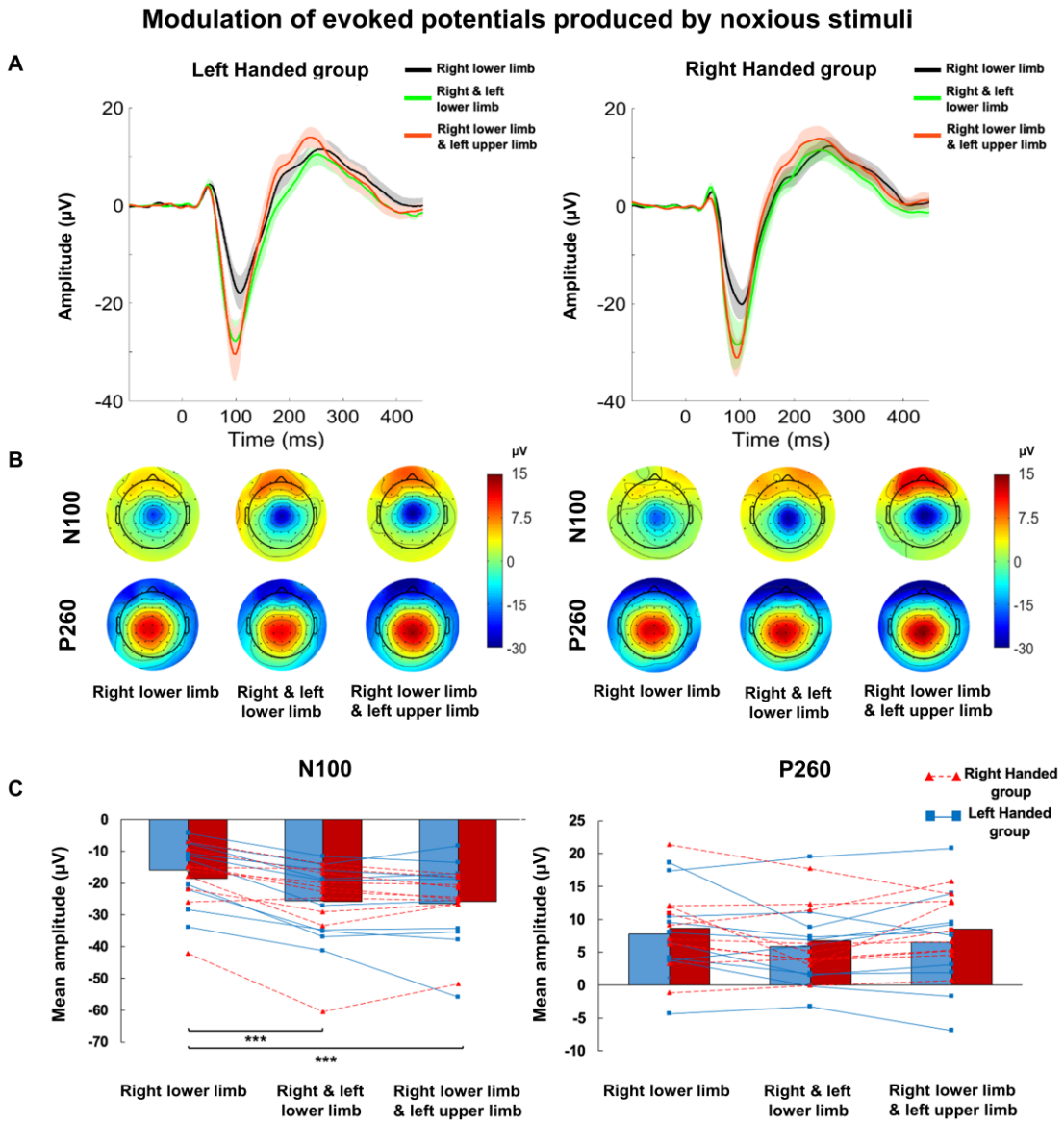

Figure 3.3 Modulation of evoked potentials produced by noxious stimuli.

(A) Average ERPs recorded at the central electrode (Cz) evoked by unilateral and bilateral stimulation in right-handed and left-handed groups. Black lines represent unilateral stimulation of the right lower limb, green lines represent bilateral stimulation of the right and left lower limbs, orange lines represent bilateral stimulation of the right lower limb and left upper limb. The shaded color above and below the lines represent the standard error of the mean. (B) Scalp topography for the first major negative N100 (top) and positive P260 (bottom) deflection for uni- and bilateral conditions in right-handed and left-handed groups. (C) Average N100 and P260 mean values for the right lower limb, right and left lower limbs, right lower limb and left upper limb conditions in right-handed and left-handed groups. Triangle and square icons represent right-handed and left-handed individual data, respectively. Red dashed lines indicate the right-handed group and blue lines indicate the left-handed group. *** Planned contrasts for the main effect of CONDITION: $p < 0.001$.

The comparison of summed ERPs and ERPs evoked in bilateral conditions is presented in Figure 4. For the lower limbs summed ERP (Figure 4A-B, left panel), the N100 amplitude was comparable between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.004$, $p = 0.94$, $\eta_p^2 = 0.0002$), but was significantly greater for the summed ERP compared with the ERP evoked in the bilateral condition (main effect of condition: $F_{1,18} = 23.38$, $p = 0.0001$, $\eta_p^2 = 0.56$). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{1,18} = 0.01$, $p = 0.91$, $\eta_p^2 = 0.0007$). Similarly, the P260 amplitude was not significantly different between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.11$, $p = 0.74$, $\eta_p^2 = 0.006$), but was significantly greater for the summed ERP compared with the ERP evoked in the bilateral condition (main effect condition: $F_{1,18} = 30.9$, $p < 0.0001$, $\eta_p^2 = 0.63$). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{1,18} = 0.09$, $p = 0.77$, $\eta_p^2 = 0.005$).

For the right lower limb and left upper limb summed ERPs (Figure 4A-B, right panel), the N100 amplitude was comparable between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.008$, $p = 0.93$, $\eta_p^2 = 0.0004$), but was significantly greater for the summed ERP compared with the ERP evoked in the bilateral condition (main effect of condition: $F_{2,36} = 26.87$, $p < 0.0001$, $\eta_p^2 = 0.60$). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{1,18} = 0.55$, $p = 0.47$, $\eta_p^2 = 0.03$). Similarly, the P260 amplitude was not significantly different between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.12$, $p = 0.73$, $\eta_p^2 = 0.006$), but was significantly greater for the summed ERP compared with the ERP evoked in the bilateral condition (main effect condition: $F_{1,18} = 44.24$, $p < 0.0001$, $\eta_p^2 = 0.71$). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{1,18} = 0.22$, $p = 0.64$, $\eta_p^2 = 0.012$).

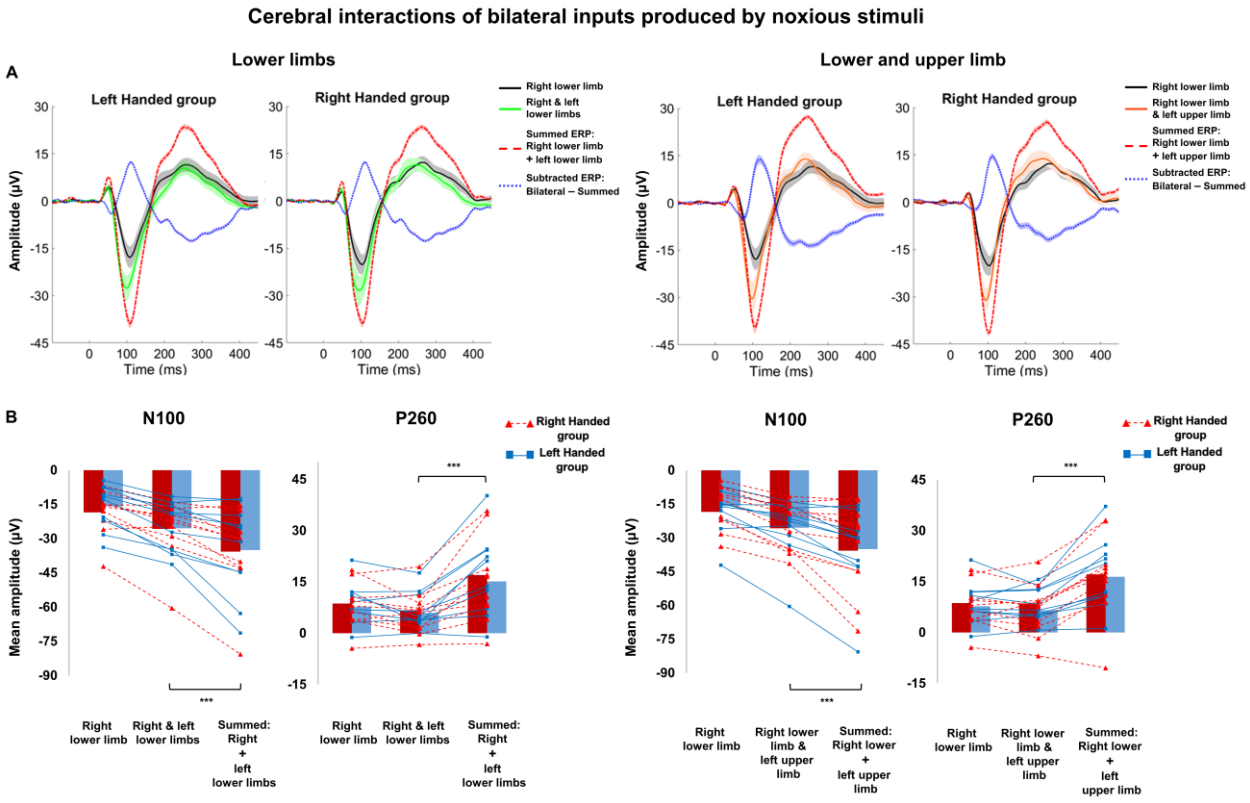

Figure 3.4 Cerebral interaction of bilateral inputs produced by noxious stimuli.

(A) Average ERPs recorded at the central electrode (Cz) evoked by unilateral and bilateral stimulation along with the sum of unilateral conditions ERPs (summed ERPs) and the differential ERP (ERPs evoked by bilateral stimulation subtracted from summed ERPs) in right-handed and left-handed groups. Left panel: black lines represent unilateral stimulation of the right lower limb, green lines represent bilateral stimulation of the right and left lower limbs, red dashed lines represent the sum of unilateral conditions (summed ERPs), and dotted blue lines represent the differential ERPs. Right panel: black lines represent unilateral stimulation of the right lower limb, orange lines represent bilateral stimulation of the right lower limb and left upper limb, red dashed lines represent the sum of unilateral conditions (summed ERPs), and dotted blue lines represent the differential ERPs. The shaded color above and below the lines represent the standard error of the mean. (B) Mean N100 and P260 (Left panel: right lower limb, right and left lower limbs, summed right and left lower limb; Right panel: right lower limb, right lower limb and left upper limb, summed right lower limb and left upper limb) in right-handed and left-handed groups. Triangle and square icons represent right-handed and left-handed individual data, respectively. Red dashed lines indicate the right-handed group and blue lines indicate the left-handed group. *** Main effect of INTERACTION: $p < 0.001$.

Electrical stimulation also produced a clear contralateral P45 following left upper limb stimulation (see Figure 5A-B). The P45 was maximal between 30 and 45 ms at the CP6 electrode for both groups (see Figure 5B). The values at CP5 (electrode ipsilateral to stimulation) are also shown for visual appreciation. The P45 amplitude was not significantly different between right- and left-handed individuals ($t(18) = 0.06$, $p = 0.95$, $\eta_p^2 < 0.01$; see Figure 5C).

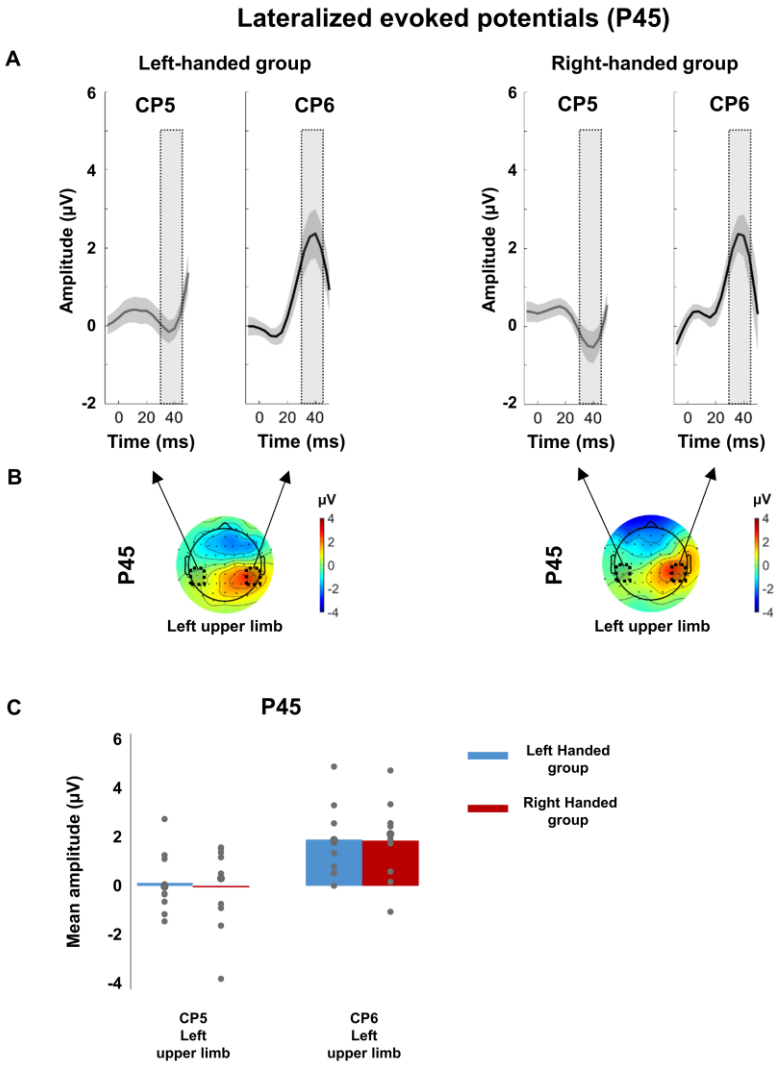

Figure 3.5 Lateralized evoked potentials (P45).

(A) Average ERPs recorded at the left hemisphere electrode (CP5) and right hemisphere electrode (CP6) for the left-hand stimulation in the right- and left-handed groups. The shaded color above and below the lines represent the standard error of the mean. (B) Scalp topography representation for the P45 in right-handed and left-handed groups, (C) Average P45 value extracted at CP5 and CP6 following left upper limb stimuli in right-handed and left-handed groups. Dots represent individual data.

Event-related spectral perturbations (ERSP)

ERSPs evoked by electrical stimulation are presented in Figure 6A. The mean power of ERSPs at 4–10 Hz was not significantly different between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.04$, $p = 0.83$, $\eta_p^2 = 0.002$), but was significantly different between conditions (main effect of condition: $F_{2,36} = 47.46$, $p < 0.001$, $\eta_p^2 = 0.72$). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{2,36} = 0.31$, $p = 0.73$, $\eta_p^2 = 0.01$). Planned contrasts for the main effect of condition revealed that 4–10 Hz oscillations were significantly increased for the bilateral stimulation of the right and left lower limbs ($p < 0.001$) and for the bilateral stimulation of the right lower limb and left upper limb ($p < 0.001$) compared with unilateral stimulation of the right lower limb.

The mean power of ERSPs at 8–29 Hz was not significantly different between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.31$, $p = 0.57$, $\eta_p^2 = 0.01$), between conditions (main effect of condition: $F_{2,36} = 0.18$, $p = 0.82$, $\eta_p^2 = 0.01$), or between groups across conditions (interaction: $F_{2,36} = 0.51$, $p = 0.60$, $\eta_p^2 = 0.02$).

The mean power of ERSPs at 30–60 Hz was not significantly different between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.03$, $p = 0.85$, $\eta_p^2 = 0.001$), but was significantly different between conditions (main effect of condition: $F_{2,36} = 7.66$, $p = 0.001$, $\eta_p^2 = 0.29$). However, this effect was not significantly different between left- and right-handed individuals (interaction: $F_{2,36} = 0.68$, $p = 0.50$, $\eta_p^2 = 0.03$) (see Figure 6B, bottom row, and 6C left panel). Planned contrasts for the main effect of condition revealed that 30–60 Hz oscillations were significantly increased by bilateral stimulation of the right and left lower limbs ($p < 0.001$) and by bilateral stimulation the right lower limb and left upper limb ($p = 0.01$) compared with unilateral stimulation of the right lower limb (see Figure 6C, left panel).

The mean power of ERSPs at 60-100 Hz was not significantly different between right- and left-handed individuals (main effect of handedness: $F_{1,18} = 0.0003$, $p = 0.98$, $\eta_p^2 = 0.00002$), but was significantly different between conditions (main effect of condition: $F_{2,36} = 7.01$, $p = 0.002$, $\eta_p^2 = 0.28$). However, this effect was not significantly different between right- and left-handed individuals (interaction: $F_{2,36} = 0.14$, $p = 0.86$, $\eta_p^2 = 0.007$) (see Figure 6B, top row, and 6C right panel). Planned contrasts for the main effect of condition revealed that the 60–100 Hz

oscillations were significantly increased for the bilateral stimulation of the right and left lower limbs (p = 0.009) and for bilateral stimulation of the right lower limb and left upper limb (p = 0.005) compared with unilateral stimulation of the right lower limb (see Figure 6C, right panel).

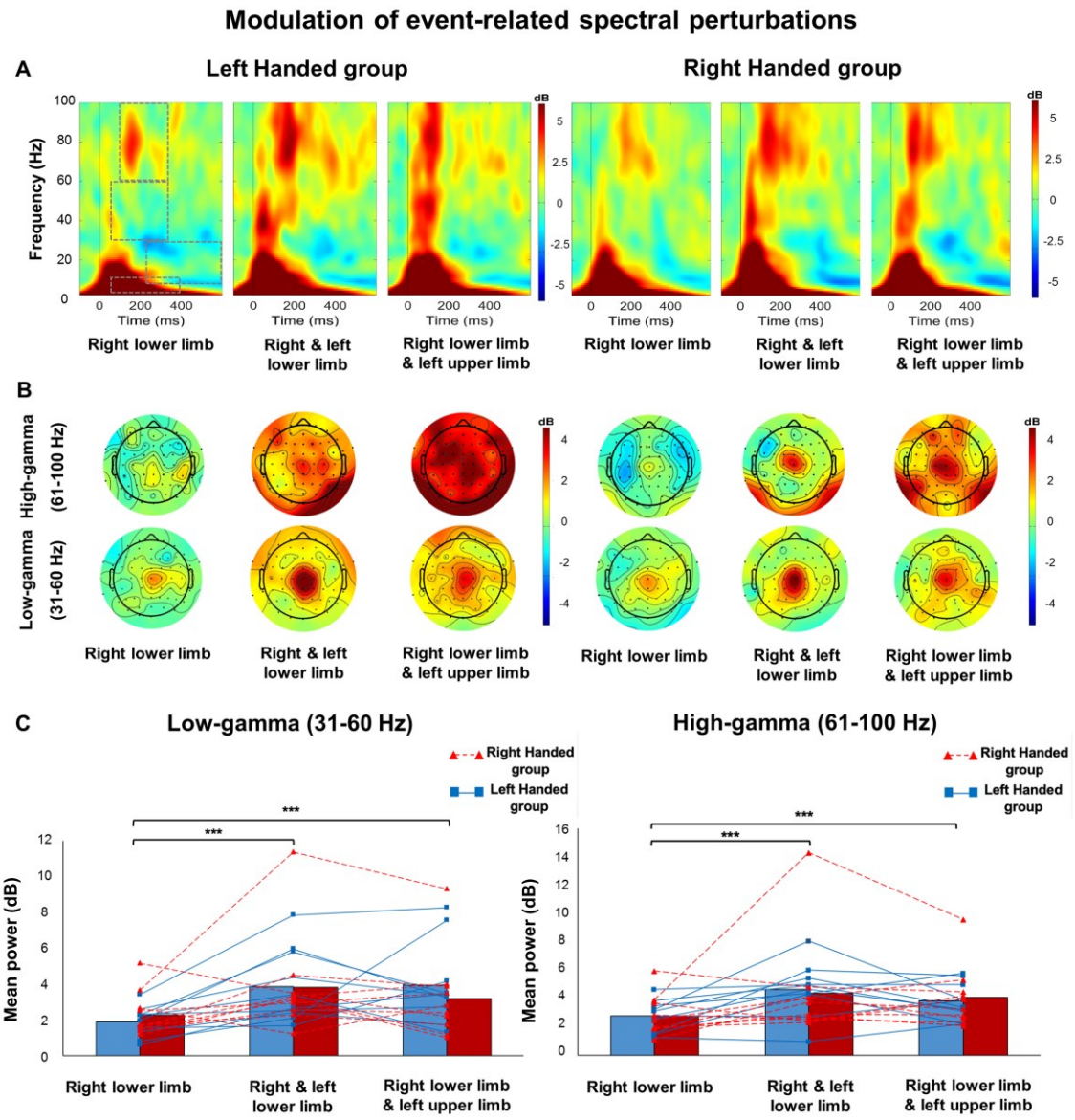

Figure 3.6 Modulation of event-related spectral perturbations.

(A) Average ERSPs from central electrode (Cz) for each condition in right-handed and left-handed groups. Units are in decibels (dB) relative to baseline. Positive and negative power changes are represented by red and blue colors, respectively. Regions of interest for the 4 frequency bands are represented by rectangles on the left time-frequency map. (B) Topographic representation of brain activity for time-frequency points representing the maximal activity at frequency ranges that were statistically different between conditions according to top 20% approach (theta, low gamma, and high gamma bands) for uni- and bilateral stimuli in right-handed and left-handed groups. (C) Average

low-gamma (31–60 Hz) and high-gamma (61–100 Hz) values extracted for the right lower limb, right and left lower limb, right lower limb and left upper limb conditions in the right-handed and left-handed groups. Triangle and square icons represent right-handed and left-handed individual data, respectively. Red dashed lines indicate the right-handed group and blue lines indicate the left-handed group. Power values in dB. *** Planned contrasts for the main effect of CONDITION: $p < 0.001$.

Lastly, to further examine the potential impact of handedness, pain intensity, pain-related anxiety, NFR amplitude, ERP amplitude and ERSP values were compared between conditions using a one-way repeated-measures ANCOVA with the handedness scores as a continuous predictor instead of GROUP as a binary categorical factor. The results indicate that the differences between conditions for all variables were not significantly modulated by handedness (all $p > 0.2$). This further support the lack of difference in pain and pain-related responses between right- and left-handed individuals.

Discussion

In the present study, we examined the impact of handedness on pain and pain-related responses in a paradigm with unilateral and bilateral stimulation. Spinal and cerebral responses were not significantly different between right- and left-handed individuals. Moreover, spinal and cerebral interactions of bilateral noxious inputs during concurrent bilateral stimulation was not significantly different between right- and left-handed individuals. These findings indicate that the pain-related responses measured in the present study may be examined independently of handedness.

Pain-related cerebral responses

The spinal and cerebral pain-related responses analyzed in this study have been shown to be sensitive to different aspects of the pain experience and offer complementary information. Regarding cerebral responses, the N100 was proposed to reflect the involuntary orientation of attention towards painful stimuli (Dowman, 2004a). Accordingly, the increase in N100 amplitude with concurrent bilateral noxious stimuli could be interpreted as an increase in saliency and attentional capture (Rustamov et al., 2019). However, this increase was smaller compared with the summed ERPs, suggesting that the increase in N100 amplitude may saturate when two salient stimuli are applied concurrently. This may be tested in future studies by manipulating stimulus

saliency (Iannetti et al., 2008). The P260 reflects, at least in part, top-down voluntary direction of attention to relevant somatosensory stimuli (Dowman, 2004b; Dowman et al., 2007). During concurrent bilateral stimulation, participants were instructed to pay attention to the right lower limb. This may explain the lack of difference in P260 amplitude between unilateral and bilateral conditions, and consequently, the stark difference between the bilateral and summed ERPs. This suggests that goal-oriented attention was not affected by the concurrent bilateral stimulation. This could be confirmed by manipulating attention direction in future studies. Notwithstanding, both right- and left-handed groups showed a similar pattern when comparing the bilateral with the summed waveforms.

Pain-related cerebral oscillations allow dynamic and flexible information flow to integrate sensory and contextual factors into a unique percept (Ploner et al., 2017). In particular, gamma band oscillations are related to nociceptive processing and pain perception (Hauck et al., 2015; Heid et al., 2020; Rustamov et al., 2019; Tiemann et al., 2015; Tiemann et al., 2010) as well as to the involuntary capture of attention by pain (Tiemann et al., 2010). The gamma power increase during concurrent bilateral stimulation is consistent with an increase in nociceptive processing to allow integration into a coherent percept and in an increase in involuntary attentional capture by pain due to increased saliency.

Lastly, while NFR, N100 and gamma oscillations power all increased following bilateral stimulation, pain only increased with segmental stimulation (both lower limbs) and not with heterosegmental stimulation (right lower limb and left upper limb). In addition to the convergence of segmental but not heterosegmental noxious inputs on the same spinal sensory neurons, this may be related to the physical distance between the two stimulated limbs. In the present study, the two feet were in closer proximity than the foot and the hand. When limbs are in close proximity, this may increase the likelihood of both inputs originating from a common event in the environment. This could lead to more perceptual fusion or increase attentional capture (Driver & Grossenbacher, 1996; Heed & Röder, 2010; Soto-Faraco et al., 2004). This indicates a partial dissociation between the pain-related responses and pain perception, consistent with previous findings (Rustamov et al., 2019). Most relevant to the present study, however, this dissociation was not significantly different between left- and right-handed individuals.

Cerebral responses and handedness

The present results indicate that right- and left-handed individuals exhibit similar painful shock-related brain responses. The lack of group difference in the present study may be explained by at least three possibilities: 1) functional integration, 2) adaptation of left-handed individuals to a right-handed world, and 3) methodological limitations.

Functional integration

Two main theories have been suggested to explain the dynamics of cortical processing for motor control and how it may be affected by handedness: functional specialization, and functional integration (Serrien et al., 2006). Functional specialization (e.g., brain lateralization) implies that specific neuroanatomical regions are responsible for specialized tasks (Serrien et al., 2006; Sperry, 1974). This theory initially relied on observations from patients with brain injury (Broca, 1863), but was confirmed, updated, and expanded through findings from neuroimaging studies (Goldberg et al., 1994; Serrien et al., 2006). This theory is consistent with the preferential processing of pain-related information in the right hemisphere. Accordingly, a large meta-analysis of neuroimaging studies conducted in right-handed individuals suggested that nociceptive information is processed bilaterally, but tends to be processed preferentially in the right hemisphere, especially in the right anterior cingulate cortex and insula (Duerden & Albanese, 2013).

The present results, however, appear more consistent with the functional integration theory (Friston, 2005; Serrien et al., 2006). This theory implies that sensory processing for successful task performance requires complex intra- and inter-hemispheric interactions between specialized neural loci in both hemispheres (Friston, 2005; Serrien & Brown, 2002; Serrien et al., 2006). For example, although specific motor functions are lateralized to one hemisphere, information processing requires integration from different areas of both hemispheres (McIntosh, 2004; Tononi et al., 1998). Thus, while lateralization seems necessary to perform specific tasks, goal-directed behaviors are produced through interactions between several brain areas in both hemispheres (McIntosh, 2004; Serrien et al., 2006; Tononi et al., 1998). This is consistent with pain-related brain activity, which is bilateral with some degree of lateralization in the right hemisphere (Duerden & Albanese, 2013). This raises the question of whether handedness may really affect pain-related brain activity since functional integration would produce widespread

and bilateral activity. The present results indicate that at least for event-related responses, no difference is observable between right- and left-handed individuals.

Adaptation to the right-handed world

The lack of group difference in pain-related responses may be explained by the fact that left-handed individuals must adapt to an environment designed for right-handed individuals. Indeed, environmental factors may influence cerebral asymmetries -related to handedness (Haaland et al., 2000; Karni et al., 1995; Klöppel et al., 2007; Pool et al., 2015). Left-handed individuals use both hands more frequently for their daily activities (Bryden et al., 2011; Vaid et al., 1989), which may explain why their motor system is less lateralized. This is consistent with the reduced functional asymmetry in experienced pianists that were trained to play with both hands (Landau & D'Esposito, 2006). However, it remains unclear whether exposure to bimanual tasks has an impact on lateralization of somatosensory and pain processing in left-handed individuals. If so, it would be more difficult to detect differences in pain-related brain activity, consistent with the present findings.

Methodological limitations

It should be noted that left-handed individuals have been underrepresented in neuroimaging studies, limiting our understanding of the effects of handedness on pain-related brain lateralization. Most studies on lateralization of pain-related processes have included right-handed individuals only, which could lead to the conclusion that pain-related information is preferentially processed by the right hemisphere (Duerden & Albanese, 2013). To our knowledge, the present study is the first to compare pain-related brain responses between right- and left-handed individuals. More studies are needed to replicate the present findings and to examine the whole brain with brain imaging methods that allow precise localization of pain-related brain activity, like functional magnetic resonance imaging. Also, our limited sample size does not allow identifying effects that may be related to sex and gender, two factors that may affect nociceptive processing (Aloisi, 2017) and it remains unclear whether these effects may be different between right- and left-handed individuals. For the purpose of the experiment, however, the sample size is adequate based on the observed effect sizes. To obtain significant effects between right- and left-handed individuals for most variables, a large number of

participants would be needed and the results may not be physiologically meaningful. Therefore, the conclusion on the lack of difference between right- and left-handed individuals for the responses and conditions examined in the present study is unlikely to change in future studies.

The lack of group difference in the present study could also be due to the stimulus properties. The stimulation site and modality in the present study were chosen because they allow the measurement of spinal cord responses to pain through the NFR. However, some authors have suggested that superficial painful stimuli (e.g., electrical or heat pain), compared to deep stimuli (e.g., pressure pain), may show smaller differences between the right and left hands (Greenspan et al., 1993; Pud et al., 2009; Sarlani et al., 2003). Therefore, the choice of noxious stimuli might impact the results.

Handedness and lateralization in other sensory systems: insight for the nociceptive system?

Sensory systems other than the nociceptive system are also lateralized (Cazzoli & Chechlacz, 2017; Corbetta & Shulman, 2002; Gilmore et al., 2009; Kinsbourne, 1987; Mesulam, 1981; Tervaniemi & Hugdahl, 2003) so handedness may also affect their underlying processes. The effect of handedness on these systems (e.g., visual and auditory) is also not well understood.

Visuospatial attention depends on processes in both hemispheres but relies predominantly on the right hemisphere (Cazzoli & Chechlacz, 2017; Corbetta & Shulman, 2002; Kinsbourne, 1987; Mesulam, 1981). Thus, if handedness affects lateralization, differences in visuospatial attention should be observed between right- and left-handed individuals. However, the current literature does not support this hypothesis (Bryden et al., 1983; Cai et al., 2013; Cazzoli & Chechlacz, 2017; Chechlacz et al., 2015; Flöel et al., 2005; Mazoyer et al., 2014; Petit et al., 2015; Somers et al., 2015; Szczepanski & Knight, 2014; Whitehouse & Bishop, 2009; Willems et al., 2014).

In the auditory system, speech sounds are processed preferentially in the left hemisphere, whereas musical sounds predominantly activate the right hemisphere (Tervaniemi & Hugdahl, 2003). Auditory evoked potentials are also higher in the contralateral hemisphere (Palomaki et al., 2005; Pantev et al., 1986; Reite et al., 1981; Salminen et al., 2010; Ungan et al., 2001). However, studies have found no difference between right- and left-handed individuals for sound localization (Burke et al., 1994) or the processing of a periodic auditory stimulation at 40 Hz

(Melynyte et al., 2018). Thus, as for other sensory modalities, there is insufficient evidence regarding the influence of handedness.

Findings on the interaction between handedness and somatosensory input related to performance on manual tasks are also inconsistent. The dominant hand performs better in movement processing and visually guided grasping, while the non-dominant hand performs better in spatial detection and movement tasks and object recognition guided by touch (De Renzi, 1978; De Renzi, 1982; Millar & Al-Attar, 2003). However, when using tactile searches to detect salient stimuli such as sharp objects (Plaisier et al., 2008), no difference in number estimation is observed between the right and left hands (Ittyerah, 2017; Plaisier et al., 2010). Other experiments have shown that dominance effects disappear depending on the task characteristics. (De Renzi, 1978; De Renzi, 1982; Ittyerah, 2017; Millar & Ai-Attar, 2003; Millar & Al-Attar, 2003). Considering these results, it is unclear whether handedness would have any impact on hand ability (Ittyerah, 2013) or tactile discriminative skills (Ittyerah, 1993).

In summary, findings regarding the interaction between sensory responses, handedness, and lateralization are mixed. These contradictory findings suggest that right -handed and left-handed individuals are more alike than dissimilar. The findings on cerebral processing of different sensory modalities might also support the functional integration hypothesis, in which the brain integrates information for the successful performance of tasks independently of lateralization.

Is integration of bilateral nociceptive inputs affected by handedness?

The results of the present study replicate findings from a previous study (Rustamov et al., 2019) in which bilateral noxious stimulation produced greater NFR, N100, and pain-related gamma oscillations compared with unilateral stimulation. This study indicated that the NFR facilitation is likely due to activation of descending motor pathways (Rustamov et al., 2019). The NFR was expected to be regulated differently under the hypothesis that the motor system is lateralized differently between right-and left-handed individuals. For example, a previous study showed different recovery characteristics of the H-reflex between right- and left-handed individuals; this finding was interpreted as reflecting differences in supraspinal influence over this spinal reflex (Nativ et al., 1989). However, unilateral brain lesions also produce bilateral changes in single-joint spinal reflexes (Thilmann et al., 1991; Trumbower et al., 2013).

Interestingly, right-handed but not left-handed individuals show a side-dependent difference in the responsiveness of the stretch reflex induced mechanically, but no such difference is observed when the reflex is induced electrically (H-reflex) (Aimonetti et al., 1999). In another study, NFR threshold appeared slightly lower for the dominant compared with the non-dominant limb (Neziri et al., 2010), although handedness was not clearly stated in this study. These findings seem consistent with a mostly bilateral modulation of spinal responses to pain, with little or no influence from lateralization and handedness, in line with our findings regarding the lack of group differences.

To understand how the brain processes input arising from both sides of the body, the theory of functional integration might provide some clues about how both hemispheres are engaged in the processing of both unilateral and bilateral nociceptive stimulation (Friston, 2005; McIntosh, 2004; Serrien et al., 2006; Tononi et al., 1998). For example, behavioral studies on split-brain or acallosal patients suggest that both hemispheres are involved in the processing of unilateral nociceptive stimuli (Coghill et al., 2001; Stein et al., 1989), which would allow the comparison of innocuous thermal information arising from one side of the body to information arising from the other side (Coghill et al., 2001; Lepore et al., 1997). Interestingly, callosotomized patients show bilateral activation of pain-related brain areas, suggesting that the bilateral hemispheric involvement is independent of callosal integrity (Duquette et al., 2008). Our findings indicate that increased spinal and cerebral responses during painful bilateral stimulation compared with unilateral stimulation is independent of handedness. They also suggest a bilateral integration of nociceptive stimulation, independent of handedness, which may be a protective strategy when facing multiple threats.

Clinical evidence and neuroimaging studies suggest that the right hemisphere plays a more important role in pain (Coghill et al., 2001; Fouché et al., 2017b; Otto et al., 1989; Symonds et al., 2006; Youell et al., 2004) and that the right anterior cingulate cortex seems to be more active during chronic pain, regardless of which side of the body pain (Hsieh et al., 1995; Hsieh et al., 1996). Additionally, activation of the amygdala during nociceptive processing has been shown to be highly lateralized (Neugebauer et al., 2020). These findings suggest that there is certainly some degree of lateralization concerning pain processing in the brain. What remains unknown is whether left-handed individuals show a reversal or modification of this lateralization.

Our study was not designed to answer this question, and future neuroimaging studies should help clarify this.

Conclusion

In summary, the present study is the first to examine the effect of handedness on spinal and cerebral responses to noxious stimulation. The results suggest that the integration of bilateral noxious inputs is not affected by handedness. Indeed, some spinal and cerebral pain-related responses were increased during bilateral stimulation compared with unilateral stimulation, but these effects were not significantly different between right- and left-handed individuals. The present results contribute to fill the gap of knowledge on pain perception in left-handed individuals, shedding new light on the interplay between handedness and pain. The extent of hemispheric lateralization involved in pain perception is likely more complex than a simple functional asymmetry. Increasing evidence suggests that pain processing requires dynamic inter- and intra-hemispheric interactions in multiple areas, at specific timescales, and with a significant degree of coherence. The inclusion of both right- and left-handed participants in future neuroimaging studies is essential in order to better understand these dynamics.

Declarations

Funding

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Conflict of interest

The authors declare no competing interests and no relationship that may lead to any conflict of interest.

Ethics approval

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of the Université du Québec à Trois-Rivières.

Consent to participate

All participants received written informed consent, acknowledged their right to withdraw from the experiment without prejudice, and received a compensation of $25 for their travel expenses, time, and commitment.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated during the current study are available from the corresponding author on reasonable request.

Code availability

The codes generated during the current study are available from the corresponding author on reasonable request.

Authors' contribution

All authors contributed significantly to this study and has read the final version of the manuscript. Stéphane Northon and Zoha Deldar contributed equally to this work. S.N. contributed to data collection and analyses and manuscript writing. Z.D contributed to data collection and wrote the first version of the manuscript. M.P. contributed to study design, data collection, analyses and interpretation, wrote the final version of the manuscript and obtained funding.

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Chapitre 4 Article 2. Cortical integration of bilateral nociceptive signals: when more is less.

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Stéphane Northon : Récension des écrits, collecte de données, analyses statistiques, rédaction de l'article, révision de l'article.
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Mathieu Piché : Supervision de l'étude

Abstract

Integration of nociceptive information is essential to produce adapted responses, to promote body integrity and survival. However, how the brain integrates nociceptive inputs from different body areas remains unknown. The aim of this study was to examine the cortical integration of bilateral nociceptive inputs evoked by laser heat stimuli. Sixteen healthy volunteers (8 F, 8 M; age: 25.5 ± 4.3) were recruited to participate in one session during which painful laser stimuli were applied to their hands with 2 Nd:YAP laser systems. Electroencephalographic activity was recorded to measure laser-evoked potentials and event-related spectral perturbations. Twenty nociceptive stimuli were applied in each of the 4 counterbalanced conditions: (1) right hand, (2) left hand, and both hands with (3) attention to the right or (4) attention to the left. Compared with unilateral conditions, N2 and P2 peak amplitude as well as gamma oscillation power were decreased in bilateral conditions ($p < 0.05$), but these effects were not affected by the direction of attention ($p > 0.1$). By contrast, pain was not significantly different in any condition ($p > 0.05$). These findings show that although more nociceptive inputs reach the brain with multiple nociceptive stimuli, their sensory representation is decreased while pain perception remains unchanged. These interactions between cerebral processing of nociceptive information from different body regions could support coordinated behavioral responses when pain origins from multiple sources.

1. Introduction

Cerebral integration of sensory information is critical for perception and behavior. This was shown for the visual (Saija et al., 2017a), auditory (Saija et al., 2014; Saija et al., 2017a) and somatosensory (Tame et al., 2016) systems. Although integration of multiple nociceptive inputs is essential to produce adapted responses and promote body integrity and survival, this has been largely overlooked.

Laser heat stimulation is an established method to investigate the nociceptive system (Treede, 2003). Nd:YAP lasers produce laser-evoked potentials (LEPs), including the N1, N2, and P2 (Hullemann et al., 2013; Perchet et al., 2008; Terhaar et al., 2011; Truini et al., 2010; Valentini et al., 2013). They also produce event-related spectral perturbations (ERSPs), including increased power below 10 Hz and in the gamma range between 150 and 400 ms, as well as suppression of alpha and beta power between 300 and 1000 ms (Ploner et al., 2017). While LEP may not reflect pain-related activity per se, but rather stimulus saliency (Iannetti et al., 2008; Mouraux & Iannetti, 2009; Ronga et al., 2013), they are a useful tool to examine the cerebral integration of nociceptive inputs. As for ERSPs evoked by painful stimuli, it was suggested that gamma synchronization is related to pain intensity (Ploner et al., 2017), attentional capture by pain (Legrain et al., 2009b; Tiemann et al., 2010) and may modulate the impact of spiking neurons on their target (Fries, 2009).

Both LEPs and ERSPs can be modulated by bottom-up (e.g. stimulus saliency) and top-down processes (e.g. selective attention). For instance, increasing stimulus intensity leads to increases in both the N2 and P2 peak amplitude (Legrain et al., 2011). In contrast, distraction away from the painful stimulus leads to reduced N2 (Beydoun et al., 1993; Franz et al., 2015; Legrain et al., 2002) and P2 (Beydoun et al., 1993; Legrain et al., 2002) peak amplitude. Besides, stimulus intensity and selective attention influence responses in alpha and gamma bands, while responses in delta and beta bands are affected by stimulus intensity only (Hauck et al., 2015). However, how the integration of nociceptive information induced by concurrent bilateral stimulation would be reflected in these brain responses remains unknown.

Studies on somatosensory integration indicate that responses to non-painful somatosensory stimulation in the somatosensory cortex are modulated when multiple

stimuli are applied concurrently (Brodie et al., 2014; Hoechstetter et al., 2001; Pang & Mueller, 2015; Shimojo et al., 1996; Tame et al., 2016). For instance, suppressive interference was reported in SI when tactile, electrical, or vibrotactile stimuli were applied bilaterally on both upper limbs compared with unilateral stimulation (Tame et al., 2016). From a behavioral perspective, studies have shown that concurrent stimuli to homologous body parts increase the detection threshold of tactile stimuli (D'Amour & Harris, 2014a). These findings may also apply to pain perception and pain-related behaviors, but this remains to be investigated.

The aim of the present study was to examine the cortical mechanisms of nociceptive integration when nociceptive stimuli are applied concurrently. Based on the literature on somatosensory processing of non-painful somatosensory stimuli, we hypothesized that LEPs and ERSPs would be attenuated in bilateral compared with unilateral conditions, consistent with a decrease in their relative sensory representation. In accordance with this idea and based on results from a previous study showing that decreased LEP amplitude by saliency manipulation was not associated with a significant change in pain perception (Iannetti et al., 2008), we anticipated that pain intensity would remain unaffected, in spite of the increase in nociceptive inputs arising from the periphery.

2. Materials and methods

2.1 Participants

Nineteen healthy volunteers were recruited by an advertisement on the campus of the Université du Québec à Trois-Rivières. All participants gave written informed consent and acknowledged their right to withdraw from the experiment at any time without prejudice. The procedures were approved by the institutional ethical committees and were in accordance with the declaration of the revised version of Helsinki. Participants were recruited if they were right-handed and between 18 and 50 years old. They were excluded if they reported chronic pain, had a diagnosed psychiatric or neurologic disorder, or took any medication during the 2 weeks prior to their participation. From the 19 participants recruited, only those who felt a clear pricking pain

at or before the maximal laser fluence were retained (n=16; 8 women; range 18–35 years; mean: 25.3, SD: 4.4).

2.2 Experimental procedures

Room temperature was kept constant at 23 °C. Participants sat in a chair with both arms on an armrest (inter-limb distance of 70 cm) with hands in a comfortable and stable pronation position. Participants and experimenters wore safety glasses designed for a 1340 nm wavelength laser during the entire duration of the experiment. Participants were instructed to avoid excessive head and body movement.

The experimental paradigm is illustrated in Figure 1. All participants were submitted to four experimental conditions in a counterbalanced order. For two conditions, stimuli were applied unilaterally to the right or left hand while participants were asked to direct their attention towards the stimulation side (unilateral with attention to right hand: UR, unilateral with attention to left hand: UL). For the other two conditions, both hands were stimulated concurrently while participants were asked to direct their attention to the right hand (bilateral stimulation with attention to the right hand: BR) or left hand (bilateral stimulation with attention to the left hand: BL). Each condition included a series of 20 laser stimuli delivered with an inter-stimulus interval of six seconds. To ensure that selective attention was directed to the right or left hand as instructed, participants provided verbal pain ratings after each stimulus, for the attended hand only.

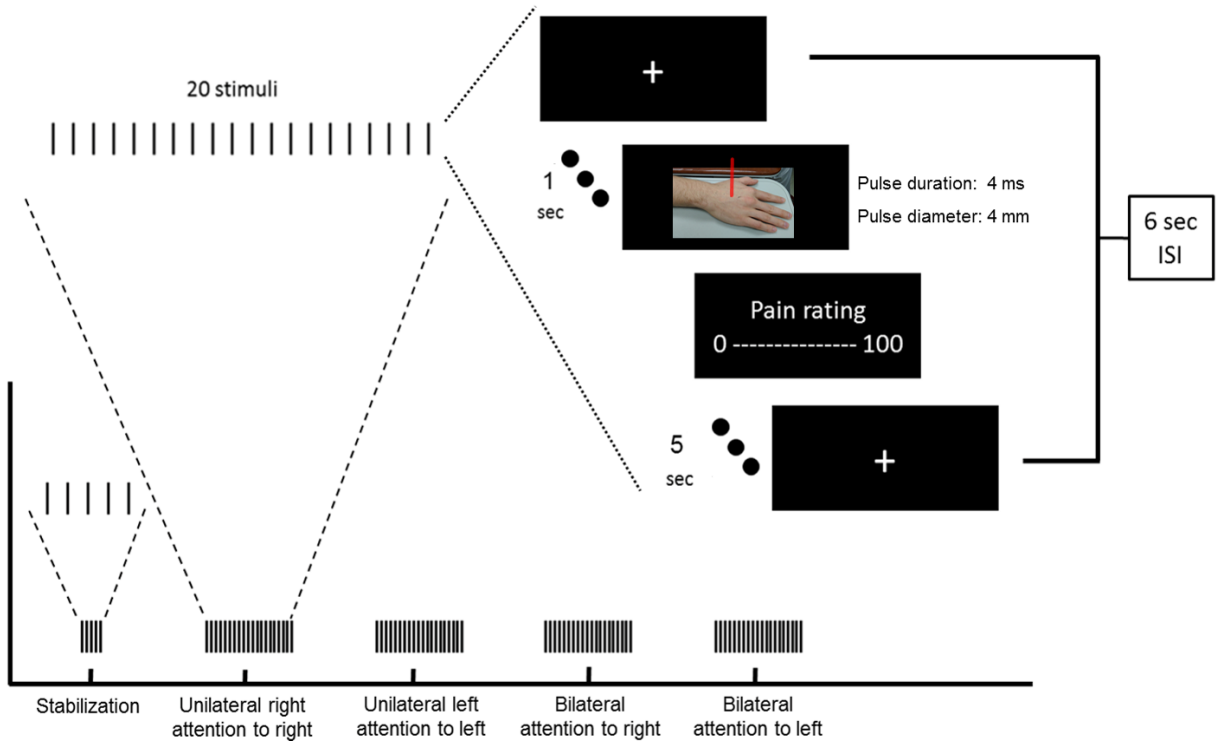

Figure 4.1 Experimental paradigm.

The four conditions are presented at the bottom of the figure, along with the stabilization procedure. Condition order was counterbalanced. Each condition included 20 stimuli and each trial lasted 6 seconds, during which laser-heat stimuli were applied and pain was rated. The painful laser stimulus is represented by the lightning symbol. Pain ratings were prompted immediately after each stimulus using a visual analogue scale with left (0) and right (100) anchors indicating "no pain" and "worse pain imaginable," respectively. ISI, interstimulus interval.

2.3 Pain ratings

A fixation cross was displayed on a computer monitor in front of participants to minimize eye movements. It remained visible for the duration of the experiment, except when pain ratings were prompted by a visual analogue scale with left (0) and right (100) anchors indicating "no pain" and "worse pain imaginable", respectively. Participants were instructed to rate the attended painful stimulus verbally from 0 to 100 when prompted by this scale. The scale always appeared outside the time window of interest for brain activity analyses.

2.4 Painful Laser Stimulation

Painful stimuli were produced by laser heat pulses using 2 infrared neodymium yttrium aluminum perovskite lasers (Nd:YAP, DEKA 1380, Electronical Engineering, Florence, Italy), one for each hand. This type of stimulation has been shown to activate nociceptors selectively (Iannetti et al., 2006; Plaghki & Mouraux, 2003). The laser beam was transmitted through a 10-meter fiber-optic cable. Laser pulse duration was set at 4 ms and the diameter at 4 mm (≈12.5 mm^2 area). Based on safety recommendations for repeated laser stimuli (Madden et al., 2016), a maximum fluence limit was set at 20 J/cm^2 (i.e. a 2.25 J upper limit for a 4 mm diameter). The lasers were triggered externally using a stimulus presentation software (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA). To avoid stimulating the same area more than once per condition, ink markers were drawn on the hand dorsum in the superficial radial nerve territory. The in-built helium-neon laser was used for aiming purpose and stimulation distance was kept constant using the mounted guides on the laser probe.

The pain threshold was determined using a staircase method for each hand separately. Before the beginning of the staircase assessment, participants were told to focus on the pinprick (bee sting) sensation and to report pain intensity verbally. Energy output started at the lowest possible level (0.5 J) and increased sequentially by 0.25 J increments until pain was reported, or up to the 2.25 J upper limit. The energy at which pain was first reported was repeated three times to obtain a reliable pain threshold. To induce a clear painful pinprick sensation, the energy was then adjusted to two increments (0.5 J) over threshold, or to 2.25 J if this upper limit was reached. For each hand, the participant was then familiarized with the selected stimulus intensity using a sequence of five consecutive stimuli with an inter-stimulus interval of six seconds. Pain intensity was reported after each stimulus and averaged for comparison between hands. Pain intensity discrepancies between hands were corrected by adjusting laser intensity to have comparable ratings (increasing or reducing energy output if already at the security threshold). Another series of three consecutive stimuli were then delivered for each hand at the adjusted stimulus intensity to confirm that pain ratings were comparable between hands.

2.5 Electroencephalographic recordings

Electroencephalographic activity (EEG) was measured using a 64-channel BrainVision system with active electrodes mounted on an actiCAP (Brain Products, Gilching, Germany). Electrodes were nose-referenced and the ground was set at FPz. Signals were digitized at 500 Hz with a hardware band-pass filter of 0.01–100 Hz. Eye movements and blinks were recorded using right eye electrooculography (EOG) with electrodes placed at the suborbital ridge and just lateral to the outer canthus.

2.6 Laser-evoked potentials

EEG data were analyzed offline using EEGLAB v.13.5.4b (Delorme & Makeig, 2004). Data were filtered using a finite impulse response (FIR) band pass filter (0.1–30 Hz), down sampled to 250 Hz, and re-referenced to the common average. Data were segmented into stimulus-locked epochs from -100 ms to 800 ms, with time 0 corresponding to the onset of laser stimuli. Baseline correction was made using the -100 to 0 ms window. An Infomax independent component analysis (ICA) was applied using the inbuilt EEGLAB function *Runica* to identify and remove components associated with noise (e.g. eye movement, eye blinks, cardiac and muscle artifacts). Baseline corrected epochs were then averaged for each condition separately to extract LEP components of interest, including the N2 and P2 (Franz et al., 2015; Hullemann et al., 2013; Legrain et al., 2009b; Perchet et al., 2008; Ronga et al., 2013). The N1 component could not be clearly identified in all subjects after re-referencing to electrode Fz and looking at central electrodes. It is therefore not reported. The N2 was defined as the first major negative deflection occurring between 140 and 220 ms with a maximum amplitude at the vertex (Cz) and the P2 was defined as the first major positive deflection occurring between 230 and 350 ms with a maximum amplitude at the vertex (Cz). From the 16 participants that reported pricking pain, three did not have clear N2 and P2 peaks from their average waveforms. The N2 and P2 calculations were thus performed on data from the remaining 13 subjects.

2.7 Time-frequency analysis

Event-related spectral perturbations (ERSPs) (Makeig, 1993; Pfurtscheller & Lopes da Silva, 1999) were analyzed for each condition. Data were filtered using a FIR

band pass filter (1–100 Hz). Data were segmented into stimulus-locked epochs from -2000 to 2600 ms, with time 0 corresponding to the onset of laser stimuli. As for LEPs, an ICA was applied to remove artifacts as described above. A Morlet wavelet convolution (Mouraux & Iannetti, 2008) was computed using the channel time-frequency options available in EEGLAB v.13.5.4b (Delorme & Makeig, 2004). Two hundred time points were generated, and 100 linearly spaced frequencies were computed from 1 to 100 Hz. Variable cycles were used for low and high frequencies, with 3 cycles for lowest frequencies and up to 15 cycles for highest frequencies. This variable number of cycles allows the wavelet convolution method to provide a better frequency resolution at lower frequencies and a better temporal resolution at higher frequencies (Delorme & Makeig, 2004). ERSP data were computed in decibels relative to the -400 to -100 ms baseline.

ERSPs were computed for all electrodes separately. For each participant, the time-frequency data of all trials were averaged for each condition separately, resulting in four average time-frequency maps for each electrode. From these maps, two types of analyses were conducted. In the first analysis, the mean power in four time-frequency maps were extracted from the Cz electrode in regions of interest (*time* X *frequency*) based on previous studies (Ploner et al., 2017): from 2 to 10 Hz between 150 and 400 ms, from 8 to 29 Hz between 300 and 1000 ms, from 30 to 60 Hz between 100 and 350 ms, and from 61 to 100 Hz between 150 and 350 ms. As some previous work has identified components in lower gamma frequencies (Babiloni et al., 2002; Croft et al., 2002), the gamma band was separated as low and high gamma. The ERSP values for each time-frequency point included in the regions of interest were extracted from each subject. A mean ERSP value was then obtained for each subject and regions of interest by selecting and averaging the values with the 20% highest amplitude (for power increases relative to the baseline) or 20% lowest amplitude (for power decreases relative to the baseline in the case of suppression). This procedure has been used in previous studies for EEG data processing (Hu et al., 2013; Iannetti et al., 2008; Mouraux & Iannetti, 2008; Valentini et al., 2013) and its main advantage is to allow the selection of wide regions of interests to account for variability across subjects, while reducing the regression to the mean problem with near-zero values.

For the second analysis, a data-driven approach was used to test for differences across all time-frequency points between 0 and 1000 ms for the Cz electrode. As no attention effect was observed in previous analyses, this analysis compared unilateral (UR and UL) and bilateral (BR and BL) conditions. Specific spectral bands were defined as follows: delta (2 to 3 Hz), theta (4 to 7 Hz), alpha (8 to 12 Hz), beta (13 to 29 Hz), low gamma (30 to 60 Hz) and high gamma (61 to 100 Hz). To that end, the cluster correction method was used (Maris & Oostenveld, 2007). Cluster correction is a non-parametric method that limits the multiple comparison problems without being overly conservative. Firstly, for each specific spectral band, the differences between unilateral and bilateral conditions were computed in *t*-values at each time-frequency point. A Monte Carlo permutation analysis with 2000 permutations was used to create a permutation distribution, with the null hypothesis being that the data from both conditions are drawn from similar probability distributions. For a two-tailed *t*-test at alpha-level 0.05, all *t*-values lower or greater than the 2.5^{th} and 97.5^{th} percentile on the permutation distribution were selected. From this selection, temporally and spectrally adjacent *t*-values with similar magnitude and sign were clustered. All the *t*-values comprised in a cluster were summed, and the largest cluster-level statistic was taken as test statistic. Its *p*-value was then calculated under a permutation distribution obtained using the procedure just described. Since the *p*-values for smaller clusters are calculated under the same distribution, this approach reduces the false alarm rate at the expense of reduced sensitivity for smaller clusters. Time-frequency clusters were then explored on a time-frequency-electrode level. Within a given time-frequency cluster, the time and frequency pair with the highest *t*-value was selected for time and frequency plotting across all electrodes. Permutation analysis was performed again, by clustering adjacent electrodes with similar magnitude and sign. The grand average time-frequency map for the group was also obtained for each condition by averaging data across subjects, for illustration purposes.

2.8 Statistical Analysis

Data analysis was conducted using Statistica v13.1 (Dell Inc., Tulsa, OK, USA). All results are expressed as mean ± SEM and statistical threshold was set at $p \leq 0.05$ (two-

tailed). Data distribution was assessed for normality with the Kolmogorov-Smirnov test. Sphericity was assessed with Mauchly's test and corrected with the Greenhouse-Geisser correction when appropriate. Pain intensity, N2 and P2 peak amplitude, and ERSP values were compared between conditions using repeated-measures ANOVA with two within-subject factors, including *Stimulation* (unilateral vs. bilateral) and *Attention* (left vs. right). Effect sizes are reported based on partial eta-squared (η^2_p).

3. Results

3.1 Laser-evoked potentials

Laser heat stimuli produced the expected LEPs in all conditions, including the N2 and P2 components, with a central scalp distribution and a maximum at Cz (see Figure 2). The latencies of N2 and P2 peaks were also as expected and are reported in Table 1.

Tableau 4.1 N2 and P2 peak latencies

	Unilateral right stimulation	Unilateral left stimulation	Bilateral stimulation attention to the right	Bilateral stimulation attention to the left
N2 latency (mean ± SEM)	185.2 ± 6.7	180.9 ± 5.7	179.4 ± 7.1	174.5 ± 7.1
P2 latency (mean ± SEM)	292.3 ± 9.3	295.4 ± 9.5	289.8 ± 10.6	288.3 ± 12.1

N2 peak amplitude was strongly decreased in the bilateral compared with unilateral conditions (*main effect:* $F_{1,12} = 14.0$, $p = 0.003$, $\eta^2_p = 0.54$). However, selective attention did not modulate N2 peak amplitude for unilateral and bilateral conditions combined (*main effect:* $F_{1,12} = 0.2$, $p = 0.7$, $\eta^2_p = 0.02$) or between unilateral and bilateral conditions (*interaction:* $F_{1,12} = 2.5$, $p = 0.14$, $\eta^2_p = 0.17$). As for N2 peak latency, it was not significantly different between unilateral and bilateral conditions (*main effect:* $F_{1,12} = 1.3$, $p = 0.3$, $\eta^2_p = 0.10$) and not significantly affected by selective attention for unilateral and bilateral conditions combined (*main effect:* $F_{1,12} = 1.6$, $p = 0.3$, $\eta^2_p = 0.11$) or between unilateral and bilateral conditions (*interaction:* $F_{1,12} < 0.01$, $p = 0.9$, $\eta^2_p < 0.01$).

Similar effects were observed for P2 peak amplitude that was strongly decreased in the bilateral compared with unilateral conditions (*main effect:* $F_{1,12} = 19.5$, $p < 0.001$, $\eta^2_p = 0.62$). Also, selective attention did not modulate P2 peak amplitude for unilateral and bilateral conditions combined (*main effect:* $F_{1,12} = 2.1$, $p = 0.17$, $\eta^2_p = 0.15$) or between unilateral and bilateral conditions (*interaction:* $F_{1,12} = 0.1$, $p = 0.8$, $\eta^2_p < 0.01$). As for P2 peak latency, it was not significantly different between unilateral and bilateral conditions (*main effect:* $F_{1,12} = 0.5$, $p = 0.5$, $\eta^2_p = 0.04$), not significantly affected by selective attention for unilateral and bilateral conditions combined (*main effect:* $F_{1,12} = 0.2$, $p = 0.9$, $\eta^2_p < 0.01$) or between unilateral and bilateral conditions (*interaction:* $F_{1,12} = 0.1$, $p = 0.7$, $\eta^2_p = 0.01$).

Together these results indicate that cortical integration of concurrent bilateral laser heat stimuli is reflected in decreased N2 and P2 peak amplitude while latency is unaffected.

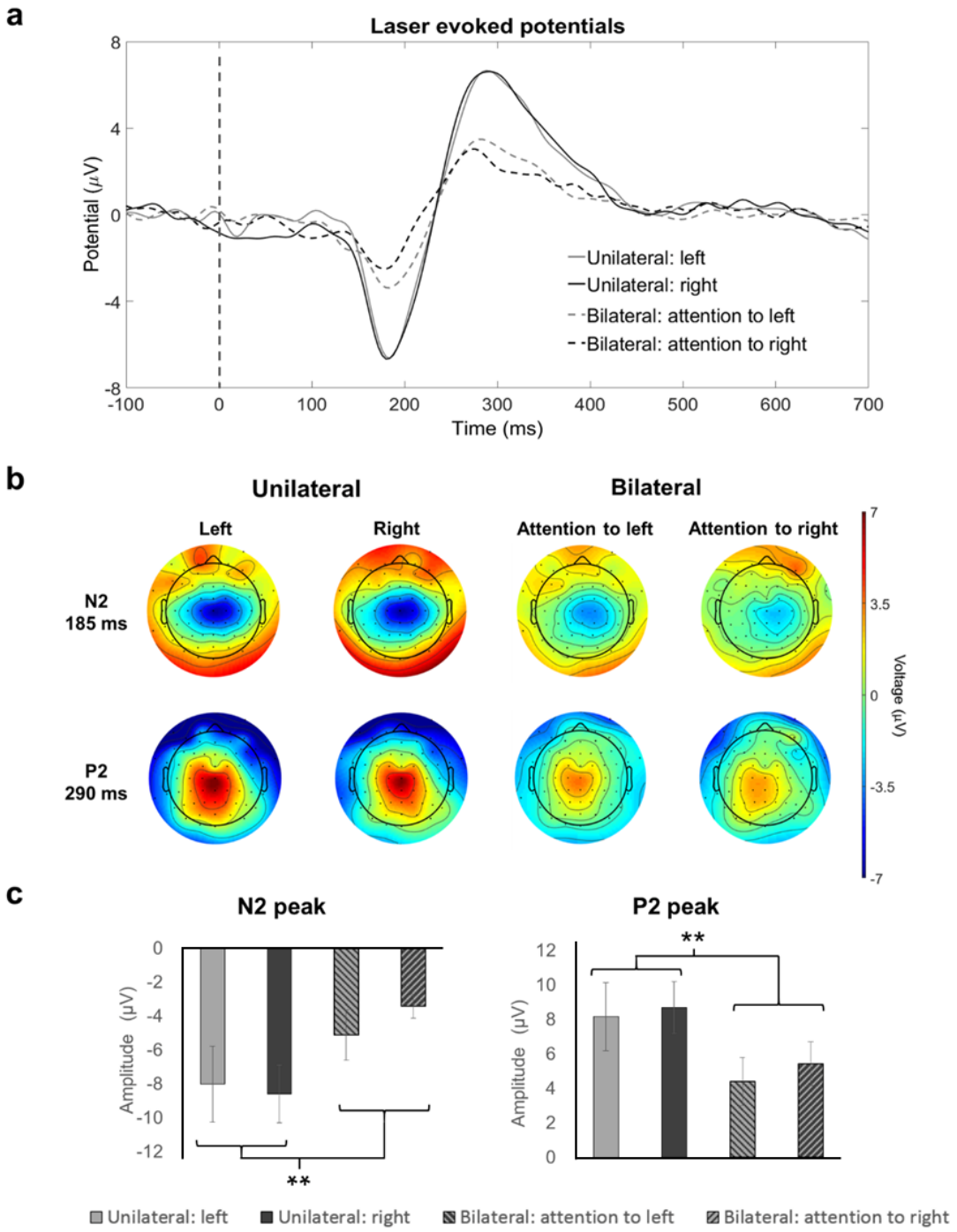

Figure 4.2 Laser-evoked potentials.

a: time course of the average laser-evoked potentials for the four conditions. Unilateral conditions are depicted as full lines and bilateral conditions as dashed lines. **b**: scalp topography for the average N2 (top) and P2 (bottom) peaks for all four conditions. **c**: average N2 and P2 peak values for all four conditions. Unilateral conditions are depicted as unicolor bars and bilateral conditions as dashed bars. ** $p<0.01$ for the main effect of STIMULATION (unilateral vs. bilateral).

3.2 Event-related spectral perturbations

Laser heat stimuli evoked robust event-related spectral perturbations in all conditions (see Figure 3a). The mean power increase in the regions of interest of 2–10 Hz or 8–29 Hz was not significantly different between the unilateral and bilateral conditions (*main effect:* $F_{1,15} = 0.5$, $p = 0.5$, $\eta^2_p = 0.03$ and $F_{1,15} = 2.5$, $p = 0.13$, $\eta^2_p = 0.14$, respectively). Similarly, selective attention did not modulate power for unilateral and bilateral conditions combined (*main effect:* $F_{1,15} = 0.05$, $p = 0.82$, $\eta^2_p = 0.004$ and $F_{1,15} = 1.14$, $p = 0.3$, $\eta^2_p = 0.07$, respectively) or between unilateral and bilateral conditions (*interaction:* $F_{1,15} = 0.24$, $p = 0.63$, $\eta^2_p = 0.02$ and $F_{1,15} = 0.22$, $p = 0.64$, $\eta^2_p = 0.01$, respectively). In contrast, low-gamma (30–60 Hz) power was decreased in the bilateral compared with unilateral conditions (*main effect:* $F_{1,15} = 4.4$, $p = 0.05$, $\eta^2_p = 0.23$; see Figure 3b). This low-gamma suppression in the bilateral condition affected several scalp regions with a marked difference at central electrodes (see Figure 3c, top row). Besides, selective attention did not produce significant effects for unilateral and bilateral conditions combined (*main effect:* $F_{1,15} = 1.81$, $p = 0.2$, $\eta^2_p = 0.11$) or between unilateral and bilateral conditions (*interaction:* $F_{1,15} = 1.77$, $p = 0.2$, $\eta^2_p = 0.11$). Lastly, high-gamma (61–100 Hz) power was strongly suppressed in bilateral compared with unilateral conditions (*main effect:* $F_{1,15} = 14.13$, $p = 0.002$, $\eta^2_p = 0.48$; see Figure 3b). This suppression also affected several scalp regions with a marked difference at central electrodes (see Figure 3c, bottom row). Again, selective attention did not produce significant effects for unilateral and bilateral conditions combined (*main effect:* $F_{1,15} = 0.94$, $p = 0.34$, $\eta^2_p = 0.06$) or between unilateral and bilateral conditions (*interaction:* $F_{1,15} = 0.6$, $p = 0.45$, $\eta^2_p = 0.04$). Considering these significant effects, it may be expected that the 8 to 29 Hz oscillations also be modulated. Since the 8-to 29-Hz suppression usually originates, in part, from electrodes over the sensorimotor cortices, further analyses were performed by clustering electrodes in hemispheres ipsilateral (CP2, CP4, C2, and C4) and contralateral (CP1, CP3, C1, and C3) to stimulation, to confirm the results. No main effects of *Hemisphere* (ipsilateral vs contralateral), *Stimulation* or *Attention*, and no interactions were observed (all $p > 0.3$, all $\eta^2_p<0.07$). The permutation analysis with cluster-correction revealed differences between unilateral and bilateral

conditions in the alpha, beta and high-gamma frequency bands (see Figure 4a). While alpha power was tonically suppressed from 300 to 1000 ms during unilateral stimulation, an opposite and significantly different pattern emerged from 575 to 825 ms for bilateral stimulation ($p = 0.01$). For beta power, bilateral stimulation produced a stronger and tonic power suppression at frequencies neighboring 20 Hz from 270 to 570 ms compared with unilateral stimulation ($p = 0.006$). For high-gamma power, two widespread clusters corresponding to decreased power for bilateral compared with unilateral conditions were observed between 75 and 85 Hz: one centered at 190 ms ($p = 0.002$), and the other extending between 340 and 575 ms ($p = 0.007$). Permutations with cluster corrections at the electrode level revealed that the differences were mostly distributed at Cz and adjacent electrodes over the sensorimotor cortex (see Figure 4b).

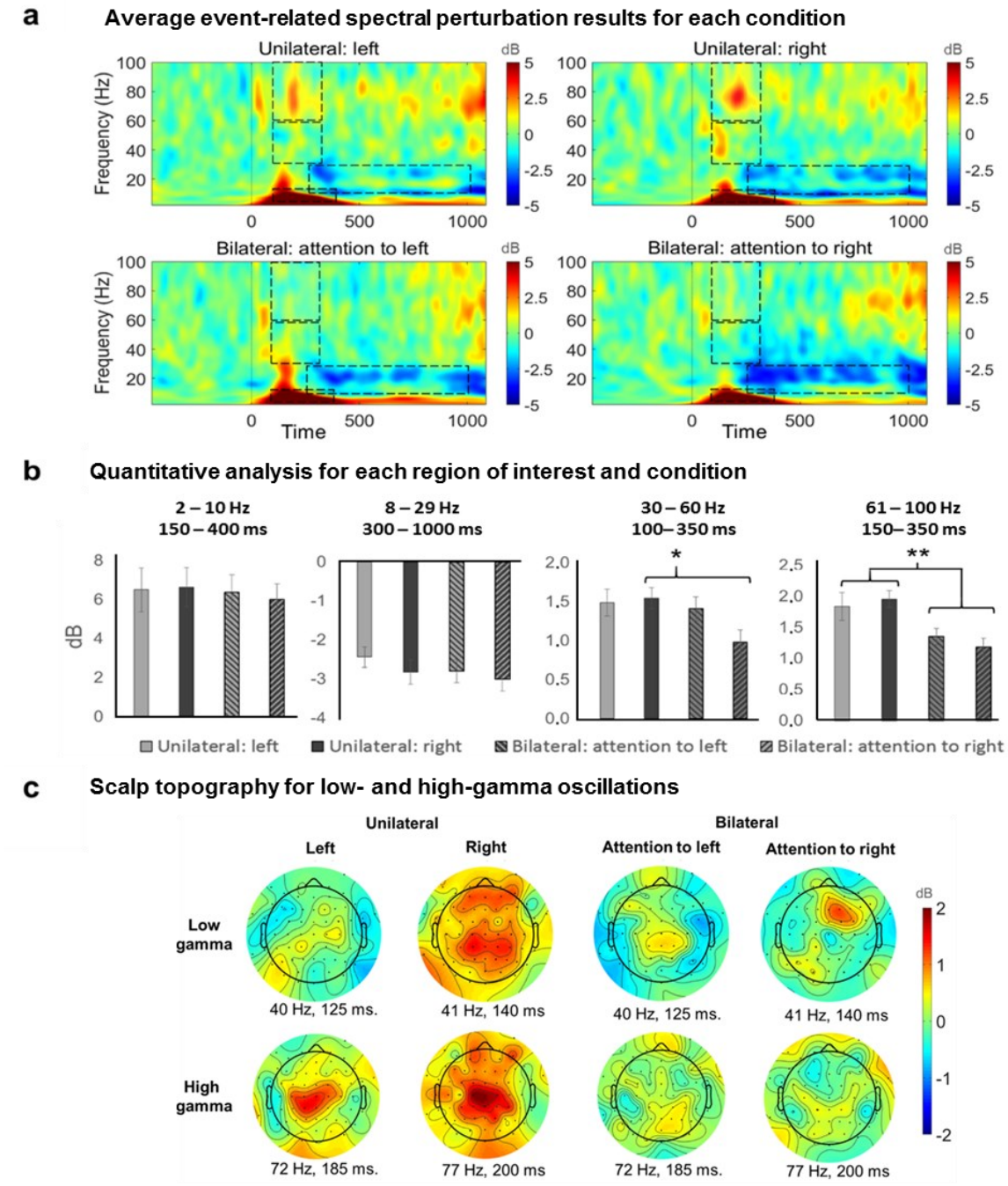

Figure 4.3 Event-related spectral perturbations in regions of interest.

a: average event-related spectral perturbation analysis for each condition. Units are in decibels relative to baseline (-400 to -100 ms). Dashed areas represent the four regions of interests: 2–10 Hz (150 to 400 ms), 8–29 Hz (300 to 1000 ms), 30–60 Hz (100–350 ms), and 61–100 Hz (150–350 ms). b: average results from the top 20% values within the region of interest for event-related synchronization and lowest 20% values for event-related desynchronization for the four conditions. * $p<0.05$; ** $p<0.01$ for the main effect of STIMULATION (unilateral vs. bilateral). c: scalp topography for the low—and high gamma (30–60 Hz and 61–100 Hz) at the time X frequency peak.

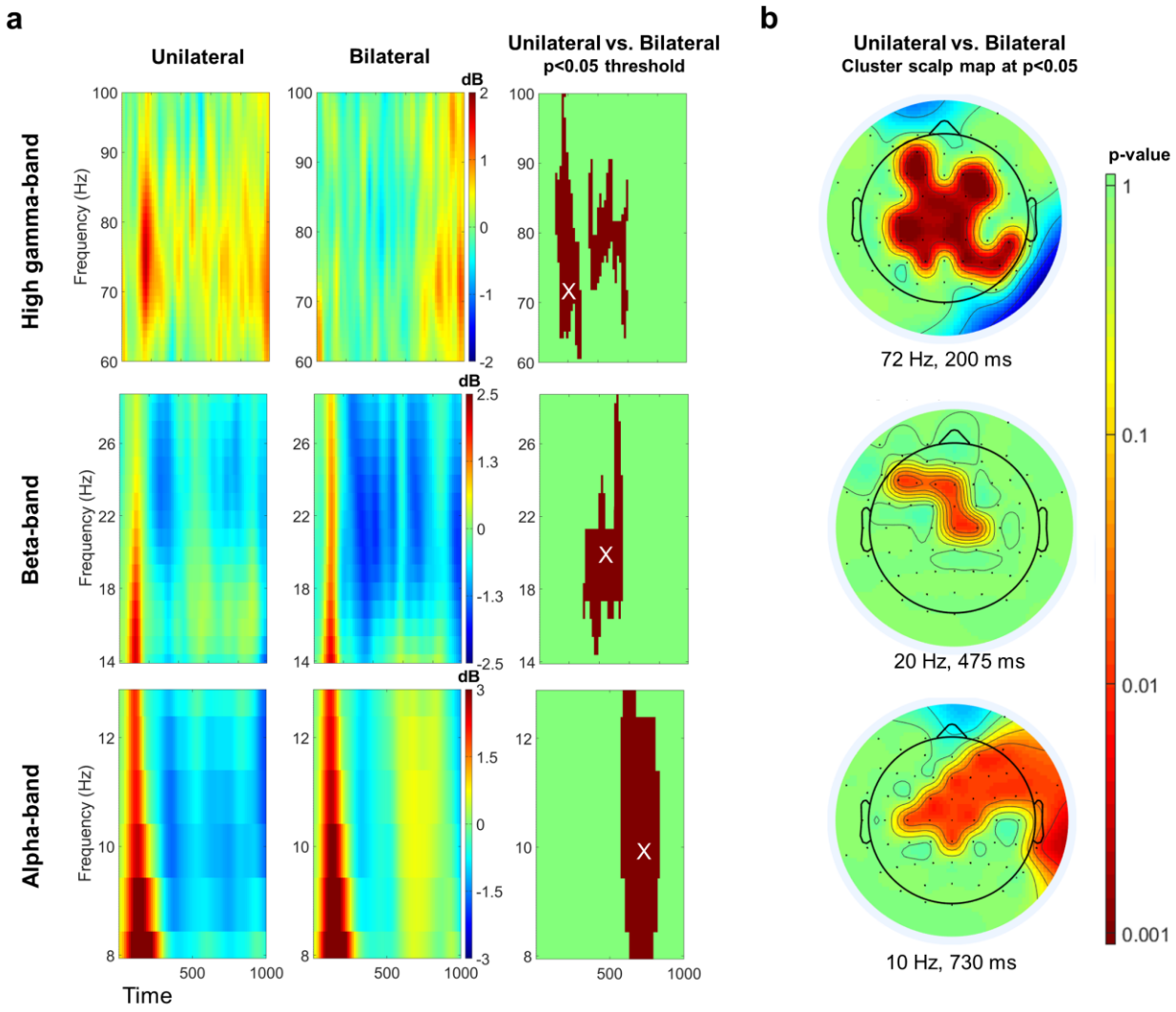

Figure 4.4 Event-related spectral perturbations across all time points.

a: average event-related spectral perturbation analysis shown from 0 to 1000 ms and for frequency bands with significant differences at p<0.05 after 1000 permutations with cluster correction between unilateral (left and right merged together) and bilateral conditions (attention to left hand and right hand merged together): high-gamma (61–100 Hz), beta (13–29 Hz) and alpha (8–12 Hz). Units are in decibels relative to baseline (-400 to -100 ms). The white cross on each plot depicts the time-frequency point with the highest *t* value. Data from this point is used for scalp topography, for illustration purposes. b: scalp topography of electrodes with significant differences between unilateral and bilateral conditions at the time-frequency point represented by a white cross in (a) for high-gamma, beta and alpha frequency bands.

3.3 Pain intensity ratings and stimulus intensity

Participants reported light pain during unilateral (right hand: 8.1 ± 2.0; left hand: 15.5 ± 4.3) and bilateral (attention to right: 8.2 ± 1.6; attention to left: 10.3 ± 2.5) laser stimulation. Mean pain ratings were not significantly different between bilateral compared with unilateral conditions (*main effect:* $F_{1,12}$ = 3.7, p = 0.08, η^2_p = 0.24). Moreover, pain ratings were not significantly affected by selective attention (main effect: $F_{1,12}$ = 1.8, p = 0.2, η^2_p = 0.13). In addition, selective attention did not significantly modulate pain ratings for bilateral compared with unilateral conditions (interaction: $F_{1,12}$ = 3.0, p = 0.11, η^2_p = 0.20). These results are consistent with the individual adjustment of stimulus intensity to produce comparable pain perception on both hands and they indicate that selective attention did not modulate pain. To confirm that stimulus intensity was comparable for each hand although individual adjustment was made using pain ratings, laser power was compared using a paired T-test. Stimulus intensity was not significantly different between the left and the right hands (1.72 ± 0.12 and 1.78 ± 0.11 J, respectively; T(15) = 1.0, p = 0.33), consistent with the lack of pain rating difference between unilateral conditions and ruling out the possibility that the effects reported above may be due to different stimulus intensity.

4. Discussion

The novel finding of this study is that cortical integration of bilateral nociceptive inputs is reflected in decreased nociceptive brain activity. To explain this reduction, several mechanisms will be considered below. Nonetheless, these findings suggest that although more nociceptive inputs reached the brain, the sensory representation of stimuli was decreased. These interactions between cerebral processing of nociceptive information from different body regions could support coordinated behavioral responses when pain origins from multiple sources.

4.1. Changes in saliency

The specificity of LEPs to pain perception or to activation of the "pain neuromatrix" was revised in recent years (Legrain et al., 2009a; Legrain et al., 2011). It was proposed that LEPs most likely reflect a saliency detection system (Legrain et al., 2011). In this study, the 2 nociceptive stimuli were temporally aligned and matched in

terms of pain perception. Stimulus intensity, another determinant of stimulus saliency, was also comparable. Considering that LEP amplitude was proposed to represent stimulus saliency (Iannetti et al., 2008; Legrain et al., 2011), we suggest that both stimuli were of comparable saliency, based on their comparable LEP amplitude. Accordingly, we propose that the relative saliency of one stimulus was lower when applied concurrently with the second stimulus. Indeed, saliency depends on how much a stimulus stands out from the sensory background. Thus, the unilateral hand stimulus stood out from a sensory background that was controlled to be minimal. When presented concurrently to the other stimulus, we propose that the saliency of this stimulus was reduced because its sensory background comprised a competing stimulus. To test this hypothesis, future studies could manipulate the saliency of the competing stimulus and thus the sensory background. Thus, we propose that concurrent nociceptive information arising from both hands is integrated in the brain, resulting in a weaker sensory representation of each nociceptive stimulus. We also propose that this is critical to generate coordinated behavioral responses to nociceptive inputs from both hands without giving priority to 1 of the 2 pain sources. In accordance with this interpretation, repeated application of a nociceptive stimulus with a short interstimulus interval leads to decreased LEP amplitude (Iannetti et al., 2008). In this study, series of 3 laser stimuli were applied on the hand with a 1-second interstimulus interval. Laser-evoked potential reduction was observed from the second stimulus, with no further reduction for the third stimulus. This is consistent with the idea that the stimulus was less salient when preceded by the same sensory input. As in this study, decreased LEP amplitude was not associated with significant changes in pain perception. Another factor that should be considered is the stimulated body region. This was examined in previous studies using repeated laser stimuli to test whether saliency is spatially specific. In the repeated laser stimulus paradigm mentioned above, when the location of the third stimulus was changed from one hand to the other, no dishabituation of LEPs was observed (Torta et al., 2012), suggesting that saliency is not spatially specific. Conversely, when the third stimulus changed from the foot to the hand, dishabituation was observed, arguing for spatial specificity (Moayedi et al., 2016). However, this dishabituation was not observed when changing the third stimulus from the hand to the foot, which argues against spatial specificity. To reconcile these

discrepancies, we suggest that there is a saliency gradient, where a stimulus with the same characteristics has a different saliency depending on the body region on which it is applied.

4.2. Response suppression

Previous findings indicate that bilateral somatosensory stimuli applied to homologous body parts produce response suppression (Hoechstetter et al., 2001; Pang & Mueller, 2015), increase tactile detection threshold (D'Amour & Harris, 2014a, 2016b), and decrease tactile discrimination abilities (reviewed in (Tame et al., 2015)). Accordingly, some brain areas may integrate information from a body part, regardless of the body side (D'Amour & Harris, 2014a). If so, a suppression of redundant information is expected during bilateral stimulation. This is consistent with the reduction of LEPs during bilateral stimulation in this study. Coherent with this interpretation, dishabituation does not occur in the repeated stimulus paradigm, if the third stimulus of the series is applied on the contralateral hand (Torta et al., 2012), as if it was the same body region. By contrast, when 2 foot stimuli are followed by a hand stimulus, dishabituation occurs (Moayedi et al., 2016). Response suppression alone is unlikely to explain LEP reduction observed in this study. Other mechanisms such as those presented above likely contribute to this effect as well.

4.3. Top-down inhibition

Nociceptive inputs could be modulated in the spinal cord by segmental processes. Although this cannot be ruled out, to the best of our knowledge, no mechanism was shown to produce such inhibition with concurrent bilateral A-d fibre inputs. Nociceptive activity could also be modulated by descending pathways from the cortex or the brainstem. Diffuse noxious inhibitory controls (Le Bars et al., 1979) or conditioned pain modulation (Yarnitsky, 2015) and cortical projections to brain stem regions involved in these mechanisms (Desbois et al., 1999) produce such inhibition. These mechanisms are unlikely to explain the present findings because diffuse noxious inhibitory controls and conditioned pain modulation are triggered by tonic stimuli that activate a spino-bulbo-

spinal loop (Le Bars et al., 1979; Villanueva & Le Bars, 1995). Indeed, this inhibitory system cannot be effective when short concurrent stimuli are applied, because nociceptive inputs are already ascending when inhibitory feedback reaches their spinal origin. Other top-down mechanisms from cortical to subcortical regions involved in expectations and cognitive control, such as the dorsolateral prefrontal cortex (Seminowicz & Moayedi, 2017), may contribute to the present reduction of LEPs. For example, spatial integration of pain can be dynamically altered by top-down attentional control as shown by the reduction in pain when dividing attention between 2 painful stimuli delivered 10 cm apart and by the increase in pain when directing attention to only 1 of the 2 stimuli (Quevedo & Coghill, 2007). However, this possibility also seems unlikely considering that pain ratings were unaffected in this study.

4.4. Brain oscillations

Two approaches were used to compare brain oscillations in bilateral and unilateral conditions. The first one, using predetermined time–frequency regions of interest, revealed a suppression of low and high gamma oscillations during bilateral stimulation. The second one, a permutation analysis applied on the whole time–frequency range revealed suppression of beta oscillations from 270 to 570 ms and of high gamma oscillations between 180 and 200 ms and between 340 and 575 ms during bilateral stimulation. Considering that oscillations below 10 Hz correspond to the LEPs (Ploner et al., 2017), a decrease of 2 to 10 Hz oscillations was expected in the time window of LEPs. However, it is likely that the hypothesis-driven method, based on a broader time window (150-400 ms), was less sensitive than peak assessment. Also, although gamma and theta oscillations often act as coupled oscillators, previous studies show that gamma oscillations are unaffected by repeated laser stimuli while theta power decreases (Zhang et al., 2012). Moreover, when comparing attended and unattended painful laser stimuli, gamma power increases while delta/theta power remains similar (Hauck et al., 2015). The present findings are consistent with these results, indicating a gamma–theta dissociation. The gamma power decrease may reflect changes in processes related to selective attention and sensory processing as suggested previously (Fries, 2009). As for the beta suppression, it most likely reflects changes in the motor cortex (Raij et al., 2004),

possibly to prevent movement during the task, as instructed to participants. In contrast to these suppressions, a late alpha power increase between 575 and 825 ms was observed during bilateral stimulation. This may reflect alerting and task-related processing (Hu et al., 2013).

4.5. Special considerations for gamma oscillations

Recent studies have explored the significance of pain-related gamma oscillations evoked by phasic pain (reviewed in (Ploner et al., 2017)). Using 3 consecutive laser stimuli, a study reported that gamma oscillations, as opposed to LEPs, are insensitive to habituation. Based on these findings, it was proposed that gamma oscillations reflect the encoding of pain intensity (Zhang et al., 2012). However, pain reduction by placebo is not associated with changes in gamma oscillations (Tiemann et al., 2015), suggesting that gamma oscillations do not simply encode pain intensity but also possibly context-dependent sensory processing (Tiemann et al., 2015). Furthermore, gamma oscillations recorded intracranially in the insula, an important region of the saliency network (Menon & Uddin, 2010), strongly habituate after 3 consecutive laser stimuli (Liberati et al., 2018a), suggesting in this case that gamma oscillations reflect saliency. It is likely that the multidimensional pain experience is associated with gamma oscillations from multiple subsystems that possibly overlap in time and space, leading to conflicting results. Future studies are needed to reconciliate these diverging views and provide a better understanding of what represent gamma oscillations and their modulation in specific regions. Besides, pain-induced gamma oscillations over central areas were reported to be negatively associated with visually induced gamma oscillations over occipital areas (Tiemann et al., 2010). Because gamma oscillations are associated with attentional processes, this effect suggests a transient and involuntary attentional capture of attention by pain (Hauck et al., 2007). In this study, attenuation of gamma power in the bilateral condition may be due to a transient shift in the attended body location. This could reflect a way of reducing the impact of neurons activated by nociceptive inputs on their target (Fries, 2009) to take into account the bilateral origin of nociceptive inputs and thus promote an adapted behavior.

5. Conclusion

In summary, concurrent bilateral nociceptive stimulation leads to reduced LEPs and high gamma oscillation power compared with unilateral stimulation. We propose that this cerebral integration may be essential for coordinated behavioral responses.

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Chapitre 5 Article 3. Cortical interaction of bilateral inputs is similar for noxious and innocuous stimuli but leads to different perceptual effects

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Contribution des auteurs

Stéphane Northon : Récension des écrits, collecte de données, analyses statistiques, rédaction de l'article, révision de l'article.

Zoha Deldar : Collectes de données, aide à la rédaction de l'article, relecture de l'article.

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Abstract

The cerebral integration of somatosensory inputs from multiple sources is essential to produce adapted behaviors. Previous studies suggest that bilateral somatosensory inputs interact differently depending on stimulus characteristics, including their noxious nature. The aim of this study was to clarify how bilateral inputs evoked by noxious laser stimuli, noxious shocks, and innocuous shocks interact in terms of perception and brain responses. The experiment comprised two conditions (right-hand stimulation and concurrent stimulation of both hands) in which painful laser stimuli, painful shocks and non-painful shocks were delivered. Perception, somatosensory-evoked potentials (*P45*, *N100*, *P260),* laser-evoked potentials (*N1*, *N2* and *P2*) and event-related spectral perturbations (delta to gamma oscillation power) were compared between conditions and stimulus modalities. The amplitude of negative vertex potentials (N2 or N100) and the power of delta/theta oscillations were increased in the bilateral compared with unilateral condition, regardless of the stimulus type ($P < 0.01$). Gamma oscillation power increased for painful and non-painful shocks as well as for painful laser stimuli ($P < 0.01$). Despite the similarities in terms of brain activity, bilateral inputs interacted differently for painful stimuli, for which perception remained unchanged, and non-painful stimuli, for which perception increased. This may reflect a ceiling effect for the attentional capture by noxious stimuli and warrants further investigations to examine the regulation of such interactions by bottom-up and top-down processes.

Introduction

Nociception is the encoding of noxious stimuli by nociceptors (Sherrington, 1906; Woolf & Ma, 2007). These nociceptive inputs are then processed in the spinal cord and may produce nociceptive reflexes that are independent of volition (Sandrini et al., 2005; Willer, 1977). Nociceptive inputs are then processed in the brain, which may result in pain and defensive responses that prevent tissue damage (Sandrini et al., 2005; Sherrington, 1910; Willer, 1977). Further cortical processing and integration of nociceptive inputs lead to elaborated behaviors that are adapted to the context and environment (Tabor et al., 2017), which may be particularly needed when noxious stimuli are complex or occur in a dynamic environment.

Sensory integration of concurrent stimuli has been explored for visual (Beume et al., 2015; Girard et al., 2013; Liu et al., 2009; Saija et al., 2017b), auditory (Bidet-Caulet et al., 2007a; Bidet-Caulet et al., 2007b), tactile (Girard et al., 2013; Hoechstetter et al., 2001; Kakigi & Jones, 1986; Ragert et al., 2011; Simões et al., 2002) and vibrotactile (D'Amour & Harris, 2014a, 2016b; Harris et al., 2006; Kuroki et al., 2017; Tame et al., 2015) modalities. For example, integration of different vibration signals from distinct locations leads to assimilation or averaging effects, indicating that tactile perception can be global although information arises from different sensory channels (Kuroki et al., 2017). Accordingly, tactile stimulation on two locations produced suppression of cortical responses in the somatosensory cortex, which was proposed to contribute to better coordination of manipulative actions (Tame et al., 2015). Recent studies also indicate that concurrent bilateral noxious inputs lead to modulation of pain and electroencephalographic (EEG) responses compared with unilateral inputs, although these effects seem to vary depending on stimulus properties (Northon et al., 2019; Rustamov et al., 2019).

Noxious stimuli are intrinsically salient and threatening and thus capture attention (Legrain et al., 2011). But what happens when more than one noxious stimulus occurs? Concurrent noxious stimuli may be more salient and their information may interact and lead to the perception of greater threat compared with a single stimulus. Such interaction of noxious inputs from different locations also imply coordination to produce an adapted

behavior. In a recent EEG study, a sub-additive increase of N100 amplitude and gamma oscillation power was reported for bilateral painful shocks applied to sural nerves compared with a unilateral shock (Rustamov et al., 2019). In contrast, a reduction of vertex potentials and gamma oscillation power was reported for bilateral laser stimuli applied to the hands compared with unilateral stimulation (Northon et al., 2019). Thus, bilateral noxious inputs may lead to different responses, but it remains unclear whether the direction of these effects (increase vs. decrease) are due to stimulus properties (laser heat pain vs. shock pain), stimulus location (hand vs. ankle) or other factors such as individual differences, which may vary between studies.

The objective of this study was to examine the cortical integration of noxious and innocuous inputs. In a first experiment, event-related potentials (ERPs) and event-related spectral perturbations (ERSPs) were compared between unilateral and bilateral hand stimulation (painful laser stimuli, noxious shocks and innocuous shocks). In a second experiment, which was a replication of a previous study (Northon et al., 2019), ERPs and ERSPs were compared between unilateral and bilateral stimulation for painful laser stimuli and noxious shocks. A within-subjects design was used in order to prevent the influence of individual differences between stimulus modalities. Based on previous reports (Northon et al., 2019; N. Rustamov et al., 2019), we expected that the interactions resulting from bilateral stimulation would produce opposite effects for painful shocks and painful laser stimuli (increase and decrease, respectively). Considering that these differences may be due to individual differences between studies and that painful shocks and laser stimuli may activate different brain regions (Dowman, 2004c), this may result in different cortical responses between stimulus modalities. In addition, considering that the behavioral responses related to painful and non-painful stimuli are different (e.g., withdrawal reflex for painful, but not non-painful stimuli), we examined whether bilateral non-painful shocks would produce an increase in cortical responses, similarly to what is observed for painful shocks.

Methods

Experiment 1

Participants

Twenty-five participants were recruited on the campus of Université du Québec à Trois-Rivières. Participants gave their written informed consent and acknowledged their right to withdraw at any time without prejudice. Procedures were accepted by the institutional ethical committee and were in accordance with the declaration of the revised version of Helsinki. Participants were included if they were right-handed and aged between 18 and 45 years old. They were excluded if they had chronic pain, a diagnosed neurologic or psychiatric disorder, or if they were taking medication two weeks prior to the experiment. Three participants were excluded because of technical issues leaving a total of 22 participants (11 females, 11 males; age range 20 – 38 years; mean ± SD: 25 ± 5.3).

Experimental procedures

Room temperature was kept constant at 23°C. Participants were seated comfortably in a chair, with both arms on an armrest with hands in pronation. The inter-limb distance was 70 cm and the viewing distance from the computer monitor was approximately 100 cm. Both participants and experimenters wore safety glasses designed for a 1340 nm wavelength laser, during the entire experiment.

The experimental paradigm is illustrated in Figure 1. Before the experiment, participants were instructed to refrain from excessive head and body movement and were instructed to look at a fixation cross. The experiment included three counterbalanced conditions containing one modality each: painful laser stimulation, painful transcutaneous electrical stimulation and non-painful transcutaneous electrical stimulation. Each condition included a total of 66 stimuli with a 9 to 11 s inter-stimulus interval. The fixation cross appeared 4 to 6 seconds before a stimulus was delivered. Following the stimulus, a visual numerical rating scale appeared on the screen 1.5 second later. After 3.5 seconds, the fixation cross reappeared. A rest period of up to 120 s was allowed every 21 to 23 stimuli. Participants were informed that stimuli would be delivered unilaterally

on the right hand or bilaterally on both hands with a 50:50 ratio. There were no more than two identical stimuli in a row.

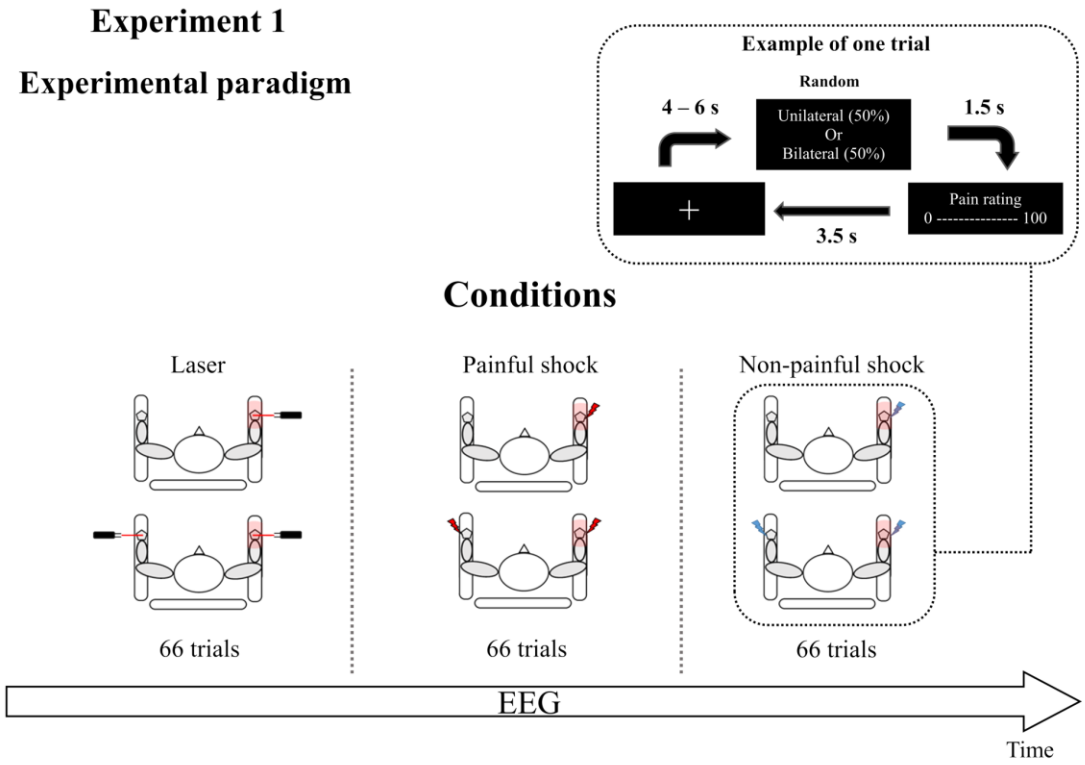

Figure 5.1 Experimental paradigm

The three modalities are presented. Condition order was counterbalanced. The pictograms in the first row represent the unilateral conditions (one input) for each modality, and in the second row, the bilateral conditions (two inputs). The red circle overlying the hand is the side on which attention had to be deployed. Top-right: temporal depiction of a single trial. Participants were informed that stimuli would be delivered unilaterally on the right hand or bilaterally on both hands with a 50:50 ratio. Pain (for laser and painful shocks) or tactile intensity (for non-painful shocks) were rated 1.5 s after each stimulus. EEG: electroencephalography.

Pain and tactile intensity ratings

Participants were instructed to pay attention to the right hand and to rate tactile intensity (for non-painful shock) or pain intensity (for painful shocks and laser) perceived on the right hand, following each stimulus. This rating ensured that participants attended

the right hand prior to each stimulation. They were prompted to report pain verbally on a 0 – 100 numerical rating scale that appeared on the screen 1.5 seconds after each stimulus. The scale anchors were "no pain" and "most intense pain imaginable", respectively. For non-painful electrical stimuli, participants were asked to report the intensity of the stimulation between 0 (no sensation) and 100 (intense enough to be painful). This ensured that the stimulation was always perceived, but not painful. During each rest period, participants also provided an average rating for the unattended left-hand stimuli to ensure that the stimuli were perceived. Following each rest period, participants were reminded to attend and rate the right hand.

Noxious and innocuous transcutaneous electrical stimulation

Noxious and innocuous transcutaneous electrical stimulation was delivered as train pulses (10 x 1 ms pulses at 333 Hz) from an isolated DS7A constant current stimulator (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK). The device was triggered by a Grass S88 train generator (Grass Medical Instruments, Quincy, MA, USA) and controlled by a computer with a stimulus presentation program (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA). The skin in the innervation territory of the left and right dorsal ulnar nerve was stimulated using a pair of custom-made surface electrodes (1 cm^2) separated by 2 cm.

Pain thresholds were determined for the left and right hands using the staircase method beginning from a low stimulus intensity and increasing progressively. Thresholds were defined as the lowest stimulus intensity evoking pain. To confirm the reliability of the pain threshold, the intensity that first produced pain was applied 5 times. Stimulus intensity was then adjusted individually to 120% or 70% of pain threshold for noxious and innocuous electrical stimuli, respectively. A series of five stimuli were then delivered to ensure that the selected intensity produced a stable and tolerable sensation. Perception was matched between hands by slightly increasing or decreasing one of the two stimulus intensities. Innocuous shocks were rated using a non-painful scale, and all participants confirmed that the stimuli produced a tactile sensation and did not evoke pain.

Painful laser stimulation

Painful radiant heat stimuli were produced by laser pulses using two infrared neodymium yttrium aluminum perovskite lasers (Nd:YAP, DEKA 1340; Electronical Engineering, Florence, Italy) each held by one experimenter. Nd:YAP laser pulses have been shown to activate Aδ and C fiber nociceptors selectively (Plaghki & Mouraux, 2003). Laser beams were transmitted through a 10 m fiber-optic cable. The pulse duration was set at 4 ms and the diameter at 5 mm (≈20 mm^2 area). Following safety recommendations for repeated laser stimuli to a 0.4 mm ink-marked skin, a maximal output was fixed at 3.75 Joules (maximal fluence < 20 J / cm^2) (Madden et al., 2016). The lasers were controlled by a computer with a stimulus presentation program (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA). Ink markers were drawn on the superficial radial nerve territory of each hand dorsum to avoid stimulating the same area more than once before each pause. The in-built helium neon laser was used for aiming purposes and the mounting guides allowed a constant stimulating distance.

Pain thresholds were determined for each hand separately using the staircase method. Participants were instructed to focus on the pinprick sensation and to report pain intensity on the 0 – 100 scale. Laser energy output was set at 0.5 J and was increased by 0.25 J increments until pain was reported, or up to the 3.75 J upper limit. To confirm the reliability of the pain threshold, stimulation at the energy that first elicited a painful pinprick was repeated 5 times. To obtain a sharp and painful pinprick sensation for the experiment, stimulation was adjusted individually by increasing the output by one or two increments. For each hand, a sequence of 5 consecutive stimuli at the selected intensity was delivered to familiarize participants. Pain intensity was then compared between hands and laser intensity was adjusted to match perception between hands. Hand temperature was monitored for both hands using an infrared thermometer before and after the threshold and was within a range of 27 to 34°C.

Electroencephalographic recordings

Brain activity was measured with electroencephalography (EEG). EEG was recorded with 64 active electrodes positioned on the scalp in accordance with the international 10-20 system (Brain Products, Gilching, Germany). The ground electrode

was set at FPz and all electrodes were nose-referenced. The signals were digitized at 2000 Hz with a hardware band-pass filter set from 0.01 – 500 Hz. Eye blinks and movements were monitored using electrooculography (EOG) with electrodes placed on the right suborbital ridge and region lateral to the outer canthus.

Event-related potentials

EEG data were exported to Matlab and processed in EEGLab v14.1.0 to examine event-related potentials (ERPs) and event-related spectral perturbations (ERSPs). For ERPs, data were processed with a finite impulse response band-pass filter (0.5 - 30 Hz), down sampled to 500 Hz, and re-referenced to the common average. Prior to re-referencing, noisy channels were interpolated using the spherical interpolation method available in EEGLab. Data were time-locked to the stimulus and segmented in epochs from -100 to 700 ms. The -100 to 0 window was used for baseline correction. Epochs were screened for non-stereotyped artifacts and removed if necessary. An Infomax independent component analysis (*Runica* function) was used to identify and remove components that were associated with noise based on their spectral, temporal and topographical characteristics (eye blinks or movements, muscle and cardiac artifacts). Epochs were averaged separately for bilateral and unilateral stimuli and for each modality.

ERP components were examined for each modality, by extracting their peak amplitude (laser stimulation) or mean amplitude within a fixed time window (electrical stimulation) as in previous studies (Dowman, 1994a; Perchet et al., 2008; Rustamov et al., 2019). The peak and mean amplitude were calculated for both modalities and lead to similar results. Thus, only the peak amplitude is reported, consistent with the current literature. For laser ERPs, this included the N2 peak (first major negative deflection maximum at Cz between 160 – 280 ms) and P2 peak (first major positive deflection maximum at Cz between 250 – 400 ms) (Perchet et al., 2008). Following re-referencing to the Fz electrode, the N1 peak (first negative deflection at contralateral central electrodes between 140 – 200 ms) was also extracted. Only participants that felt a clear pricking pain at or before the maximal laser fluence were retained. Due to a technical issue with the lasers, the first three participants had to be excluded (n= 19; 8 women;

range 18-35 years; mean: 25.2, SD: 1.9). From these 19 subjects, 5 did not have clear N2 and P2 deflections from their average waveforms. Thus, N2 and P2 components were computed with data from the remaining 14 subjects.

For noxious and innocuous electrical stimulation, ERP components included the P45 (first positive deflection at contralateral centro-parietal electrodes from 45 to 55 ms), the N100 (first major negative deflection maximum at Cz between 90 and 120 ms), and the P260 (second positive deflection maximum at Cz between 240 and 300 ms) (Dowman, 1994a; Dowman, 1994b). All 22 subjects had a clear N100 and P260 potential.

Event-related spectral perturbations

For ERSPs, data were processed with a finite impulse response band-pass filter (1 - 100 Hz, down sampled to 500 Hz and re-referenced to the common average. Noisy channels were interpolated using the spherical interpolation method available in EEGLab. Data were time-locked to the stimulus and segmented in epochs from -2000 to 2000 ms. The -700 to -200 window was used for baseline correction. The baseline period was different from that of ERPs to avoid edge artifacts that occur at lower frequencies. Epochs were screened for non-stereotyped artifacts and removed if necessary. An Infomax independent component analysis (*Runica* function) was used to identify and remove noisy components. Time-frequency analysis was computed using a Morlet wavelet convolution with variable cycles for low and high frequencies (from 3 to 15 cycles). This flexibility allows a better frequency resolution at low frequencies and better temporal resolution at higher frequencies (Delorme & Makeig, 2004). ERSPs were computed in decibels (dB) relative to the -700 -200 ms baseline period. The ERSP values were first computed for all electrodes separately and for each trial. For each subject, all trials were averaged separately for unilateral and bilateral trials and for each modality, resulting in 6 time-frequency maps for each electrode.

From these time-frequency maps, values were extracted from predetermined *time X frequency* regions of interests based on previous EEG studies (Gross et al., 2007; Schulz et al., 2012; Tiemann et al., 2015; Tiemann et al., 2010; Zhang et al., 2012) (also see (Ploner et al., 2017) for a general overview). The timing for these regions was

adapted to the expected latency differences between responses to laser and electrical stimuli (Dowman, 1994a; Perchet et al., 2008). For laser stimulation, this included the frequency content of evoked potentials (delta and theta oscillations at 2 – 10 Hz from 150 to 400 ms), alpha-beta oscillations (8 – 29 Hz from 300 to 1000 ms), low-gamma oscillations (30 – 60 Hz from 100 to 350 ms) and high-gamma oscillations (61 – 100 hz from 150 to 350 ms). For electrical stimulation, this included oscillations in the range of 2 – 10 Hz (50 – 400 ms), 8 – 29 Hz (250 – 1000 ms), 30 - 60 Hz (50 – 350 ms) and 61 – 100 hz (100 – 350 ms). The low-frequency (delta and theta) and gamma responses were maximal at the Cz electrode. As the 8 – 29 Hz response likely originates from the sensorimotor cortices bilaterally (Ploner et al. 2006), a cluster of four electrodes was created for both hemispheres (left: C3, C5, CP3 and CP5; right: C4, C6, CP4 and CP6) and the values were averaged across the four electrodes (Raij et al., 2004). For each subject and region of interest, the values were extracted, sorted from lowest to highest, and a mean value was obtained by taking the top 20% (for increases relative to baseline) or lowest 20% (for decreases relative to baseline). This approach allows selecting a wide time-frequency region, thus accounting for between-subject variability while minimizing the problem associated with near-zero values (Mouraux & Iannetti, 2008).

Experiment 2

The similar sub-additive integration between modalities obtained in *Experiment 1* was divergent from a previous study, where bilateral laser stimuli lead to a decrease in EEG responses (Northon et al., 2019). To address this issue, a separate experiment was conducted to replicate previous findings (Northon et al., 2019) and to examine if discrepancies may be explained by methodological differences. The main methodological differences were the design of the conditions (separate unilateral and bilateral conditions vs blocks with 50% unilateral 50% bilateral stimuli) and the inter-stimulus interval (fixed vs variable inter-stimulus interval), which may lead to predictability and habituation. For brevity, only the main results are presented in the manuscript and all Figures and Tables for this experiment are available in the Online Resource document.

Participants

Twenty participants were recruited at the campus of Université du Québec à Trois-Rivières. Selection criteria were the same as Experiment 1. One participant was excluded because of technical issues leaving a total of 19 participants (9 female, 10 male; age range 20 – 37 years; mean ± SD: 26 ± 8.3).

Experimental paradigm

The experimental paradigm of Experiment 2 is illustrated in the Online Resource (Figure 5). Two stimulus modalities were used for this experiment: painful laser stimulation and painful electrical stimulation. Participants underwent a total of 8 conditions, including four conditions per modality. The four conditions were counterbalanced between participants and included 1) unilateral left hand, 2) unilateral right hand, 3) bilateral with attention to the left and 4) bilateral with attention to the right hand. The conditions were counterbalanced similarly between modalities. Each condition included a total of 20 stimuli with a fixed inter-stimulus interval of 6 sec. Prior to each condition, participants received instructions for stimulus location, and for which hand they should direct their attention to. Participants were instructed to rate pain intensity following each stimulus. At the end of each bilateral condition, participants also provided an average rating for the unattended hand. Before each condition, participants were reminded of the hand that had to be attended.

Pain ratings and stimulus intensities

Participants fixated a cross presented on a computer monitor. They were prompted to report pain verbally on a 0 – 100 numerical rating scale that appeared on the screen after each stimulus. The scale anchors were “no pain” and “most intense pain imaginable”, respectively.

Painful electrical stimulation

Painful transcutaneous electrical stimulations were delivered using the same material and threshold methods as for Experiment 1.

Painful laser stimulation

Painful radiant heat stimuli were produced by the same lasers as in Experiment 1. The laser spot size was adjusted to 4 mm to replicate the methodology used in our previous study (Northon et al., 2019). As such, the maximal intensity in Joules was set at 2.25 for a maximum fluence of 20 J / cm^2.

Electroencephalographic recordings

As in Experiment 1, brain activity was measured with a BrainVision EEG system comprising 64 active electrodes.

Event-related potentials

EEG data were preprocessed as described in *Experiment 1*. For ERPs, the epochs were averaged separately for the four conditions and for the two modalities (laser stimuli and painful electrical shocks). For laser stimuli, the 19 participants reported a clear pricking pain at or before the maximal fluence. Three did not have clear N2 and P2 deflections from their average waveforms. Thus, these components were computed on the 16 remaining participants. For painful electrical stimuli, two participants did not show clear N100 and P260 potentials, so the two components were examined in 17 participants.

Event-related spectral perturbations

Data were analyzed as described in Experiment 1, with the only difference being a shorter time window used for time-frequency transformation (from -1500 to 1500 ms) to take into account the shorter interstimulus interval.

Statistical analysis

Statistical analyses were performed using Statistica v12 (Dell Inc, Tulsa, OK, USA). All results are presented as mean ± standard deviation (SD). Statistical threshold was set at $P \leq 0.05$ (two-tailed). All effect sizes are expressed as partial eta-squared (η^2_p).

Experiment 1: Paired t-tests were used to compare variables between unilateral and bilateral stimulation for each modality: ratings (pain and tactile intensity), ERPs (laser: N1, N2 and P2; electrical shocks: P45, N100, P260) and ERSPs (2 – 10 Hz, 8 – 29 Hz, 30 – 60 Hz, 61 – 100 Hz). The 8 – 29 Hz response was examined with an ANOVA with *Stimulation* and *Hemisphere* as within-subject factors, since it is observed bilaterally.

Experiment 2: Repeated-measures ANOVAs were computed with two within-subject factors: *Stimulation* (unilateral vs bilateral conditions) and *Attention* (attention to left-hand vs right hand). This approach was used to compare pain ratings, ERPs (laser: N1, N2 and P2; electrical shocks: P45, N100, P260) and ERSPs (2 – 10 Hz, 8 – 29 Hz, 30 – 60 Hz, 61 – 100 Hz). The *Hemisphere* (left vs. right) factor was also included in the model for the 8 – 29 Hz response, since it is observed bilaterally.

It should be noted that a systematic approach was used to include participants in EEG analyses as described above; only participants with clear deflections were included. For consistency, the ERSPs were calculated using the same participants. However, since the inclusion/exclusion of participants is still a debated issue, and that it is also possible to include all participants regardless of the deflections' observation, we also examined another possibility. For participants with no clear deflections, the most positive or negative value (depending on the deflection polarity) within a time window spanning one standard deviation before and after the grand average peak latency was attributed as peak amplitude. Although this increased the sample size, all statistical values were lower, including the effect size. Therefore, we only report the results from the systematic approach that excludes participants from EEG analyses when no clear deflections are observable.

Results

Experiment 1

Perception and stimulus intensity

The mean ratings for unilateral and bilateral stimuli and the mean stimulus intensity for all modalities are presented in Table 1. On average, unilateral and bilateral laser stimuli evoked similar pain, with no significant difference ($t(13) = 0.96$, $P = 0.35$,

η^2_p = 0.07). Laser intensity was not significantly different between right and left hands (t(13) = 0.71, P = 0.49, η^2_p = 0.04). Painful electrical stimuli evoked moderate pain, with a trend towards a significant difference between unilateral and bilateral conditions (t(21) = 2.0, P = 0.059, η2p = 0.16), while stimulus intensity was higher for the right compared with the left hand (t(21) = 2.2, P = 0.037, η2p = 0.19). Lastly, non-painful electrical stimuli evoked moderate tactile sensation and ratings were higher for the bilateral condition compared with the unilateral condition (t(21) = 4.0, P < 0.001, η^2_p = 0.43) while stimulus intensity was not significantly different between right and left hands (t(21) = 2.0, P = 0.064, η^2_p = 0.15).

These results indicate that bilateral painful stimulation (laser or electrical) did not evoke more pain compared with unilateral stimulation while tactile sensation was greater in the bilateral compared with unilateral condition. Stimulus intensity is unlikely to explain these results.

Tableau 5.1 Perceptual ratings and stimulus intensity (Experiment 1).

a. Perceptual ratings		
	Unilateral	Bilateral
Average ratings (0 – 100) (mean ± SD)		
Laser (pain)	12.4 ± 10.7	13.0 ± 9.7
Painful shock (pain)	31.0 ± 13.1	33.2 ± 14.9
Non-painful shock (tactile sensation)	28.5 ± 16.3	33.0 ± 18.5

b. Stimulus intensity		
	Left Hand	Right Hand
Stimulus intensity (mean ± SD)		
Laser (Joules)	3.0 ± 0.5	3.1 ± 0.5
Painful shock (mA)	9.4 ± 4.2	11.1 ± 6.5
Non-painful shock (mA)	3.8 ± 2.4	4.5 ± 3.1

Vertex evoked potentials

Group-average ERPs and topoplots are presented in Figure 2 and mean values are reported in Online Resource (Table 2).

For N2 and P2 components of laser-evoked potentials (LEPs), the scalp distribution was centered at Cz and they occurred at expected latencies (N2: 197.9 ± 14.0 ms, P2: 319.5 ± 40.1 ms). N2 and P2 peak amplitude was greater in the bilateral compared with unilateral condition ($t(13) = 4.3$, $P < 0.001$, $\eta^2_p = 0.59$ and $t(13) = 2.28$, $P = 0.04$, $\eta^2_p = 0.29$, respectively).

For N100 and P260 components of potentials evoked by painful shocks, the scalp distribution was centered at Cz as expected. N100 amplitude was greater in the bilateral compared with the unilateral condition ($t(21) = 6.39$, $P < 0.0001$, $\eta^2_p = 0.66$) while P260 amplitude was not modulated significantly between conditions ($t(21) = 0.53$, $P = 0.60$, $\eta^2_p = 0.01$).

For N100 and P260 components of potentials evoked by non-painful shocks, the scalp distribution was centered at Cz as expected. N100 amplitude was greater in the bilateral compared with unilateral condition ($t(21) = 5.42$, $P < 0.0001$, $\eta_p 2 = 0.58$), while P260 amplitude was not modulated significantly ($t(21) = 1.84$, $P = 0.08$, $\eta_p 2 = 0.14$).

These results indicate that bilateral stimulation increased late ERPs for laser stimuli, while only the negative component of the late ERPs was modulated for electrical stimuli, whether they were painful or non-painful.

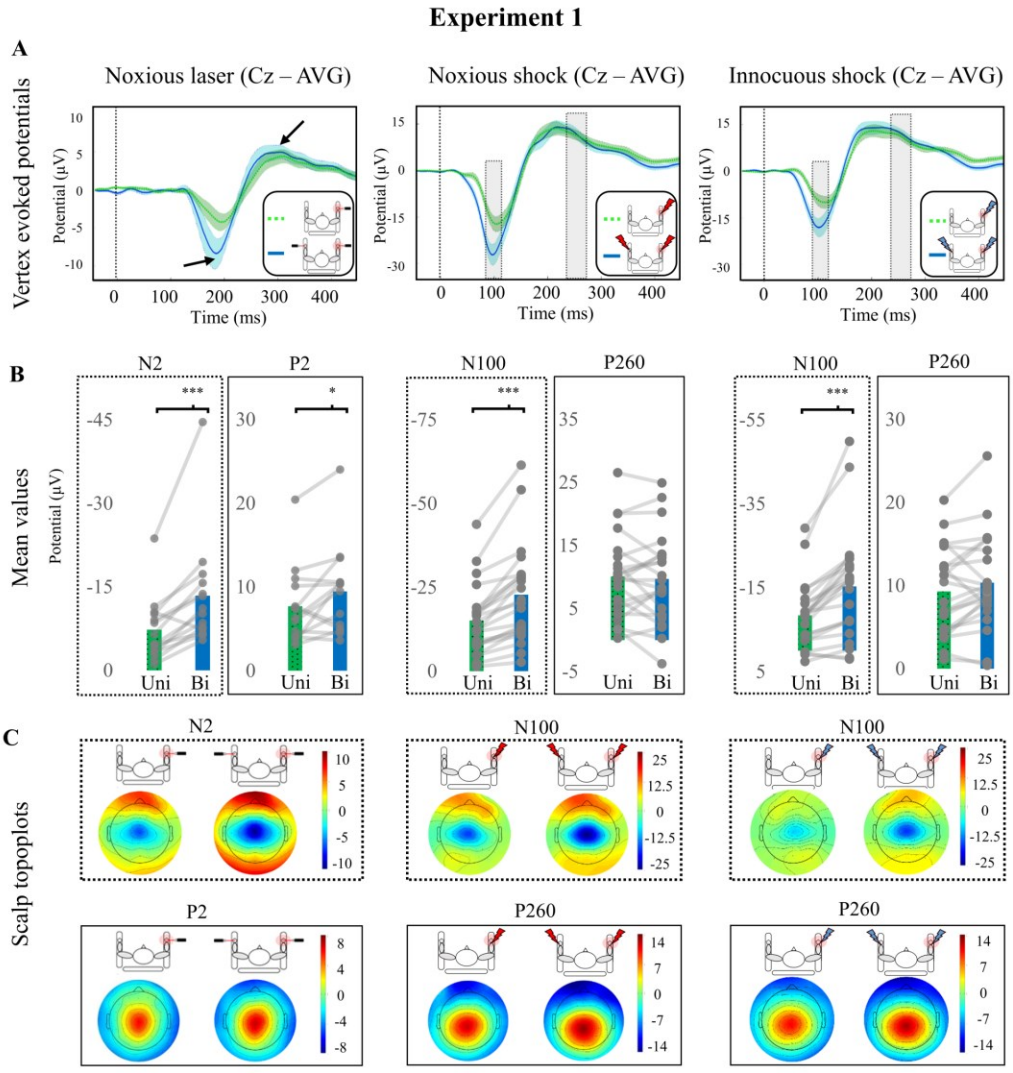

Figure 5.2 Event-related potentials for unilateral and bilateral conditions for each modality.

A: Time course of the event-related potentials for laser (left), painful shocks (middle), and non-painful shocks (right) for unilateral and bilateral stimuli. Unilateral stimuli are depicted as dashed lines and bilateral as full lines. The lightly colored areas above and below the event-related potentials time course represent the standard deviation. The black arrows (for Noxious laser) depict the peaks used for the analysis. The grey rectangles overlying the event-related potentials for noxious and innocuous shocks depict the time windows used to calculate the mean. The conditions are identified by the pictogram in the legend. The red circle overlying the hand is the side on which attention had to be deployed. B: Mean N2 and P2 (left) and N100 and P260 mean values (middle: painful shock; right: non-painful shocks) extracted for unilateral and bilateral conditions. The negative potentials are shown reversed (negative: up) for easier comparison with the positive potentials. Unilateral (Uni) are depicted as dotted bars and bilateral (Bi) as full bars. The dots represent individual data points. *, ***: P < 0.05 and < 0.001 for the *t*-test between

unilateral and bilateral conditions, respectively. C: Scalp topoplots for the vertex potentials (laser: N2, P2; painful and non-painful shocks: N100 and P260) for unilateral and bilateral conditions.

Lateralized evoked potentials

For laser stimuli, the lateralized N1 component was observed after re-referencing the signal to Fz. The measured temporo-central scalp distribution and latency (170.5 ± 16.0 ms) correspond to its usual characteristics (see Figure 3, and Online Resource Table 2). The N1 was maximal at central electrodes contralateral to the stimulation (C3 for measurements) for the unilateral condition and its amplitude was not significantly different between unilateral and bilateral conditions ($t(13) = 1.67$, $P = 0.12$, $\eta_p2 = 0.18$).

The lateralized P45 component was observed for painful and non-painful electrical shocks (see Figure 3). The temporo-parietal scalp distribution of the earliest observable positive deflection corresponds to its characteristics. It was maximal over contralateral parietal electrodes (P3 for measurements) for the unilateral condition and was not significantly different between unilateral and bilateral conditions ($t(21) = 0.37$, $P = 0.72$, $\eta_p2 = 0.01$ and $t(21) = 0.67$, $P = 0.51$, $\eta_p2 = 0.02$ for painful and non-painful stimulation, respectively).

These results indicate that early lateralized components were not modulated by inputs arising from the ipsilateral hand, whether the stimulus was painful or not and whether it was evoked by lasers or electric shocks.

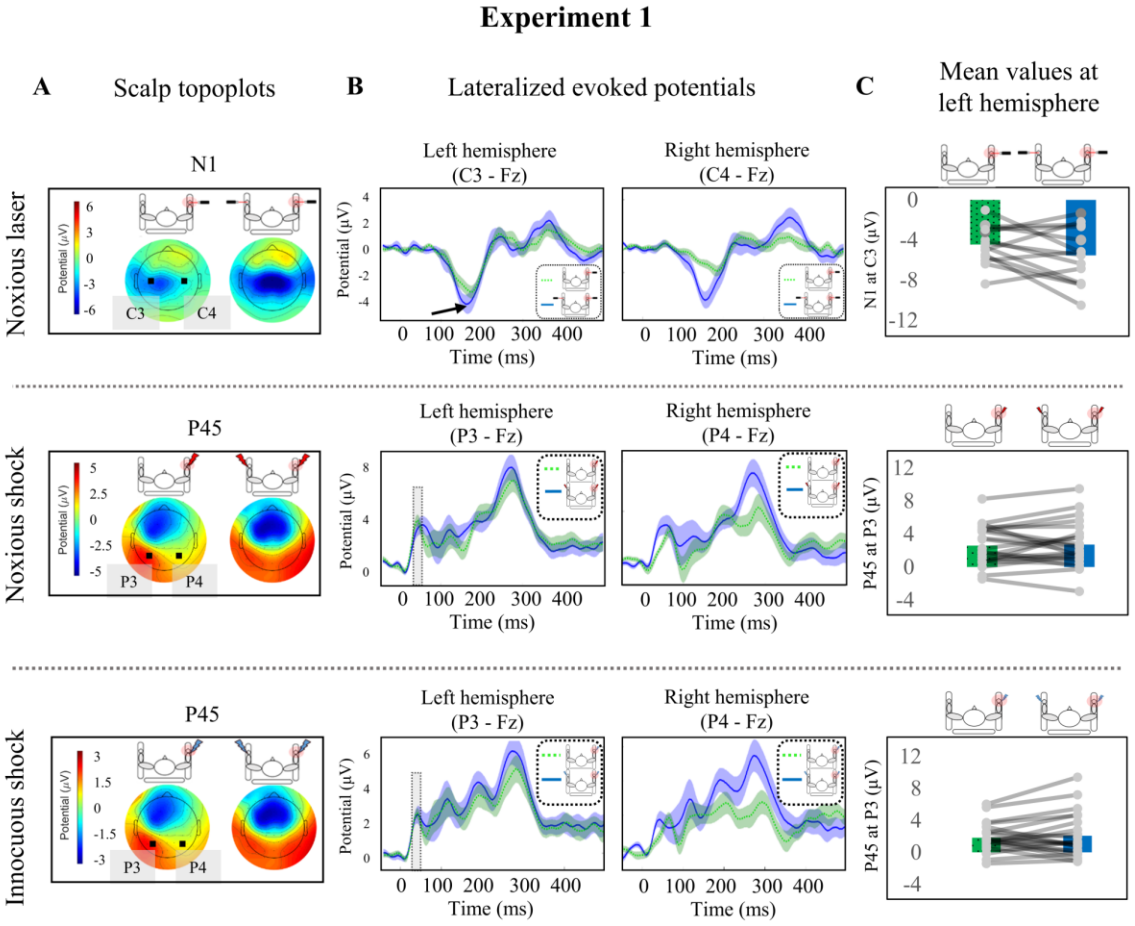

Figure 5.3 Lateralized event-related potentials for unilateral and bilateral conditions for each modality.

A: Scalp topoplots for the N1 (top: laser) and P45 (middle: painful shocks; bottom: non-painful shocks) for unilateral and bilateral conditions. The condition is identified by the pictogram. The red circle overlying the hand is the side on which attention had to be deployed. The contralateral (left hemisphere, C3) and ipsilateral (right hemisphere, C4) electrodes are depicted by dots. B: Time course of the lateralized evoked potentials at the contralateral and ipsilateral electrodes between unilateral and bilateral conditions for each modality (top: laser; middle: painful shocks; bottom: non-painful shocks). Unilateral condition is shown as dashed lines and bilateral as full lines. The lightly colored areas above and below the event-related potentials time course represent the standard deviation. The black arrows (for Noxious laser) depict the peak used for the analysis. The grey rectangles overlying the event-related potentials for noxious and innocuous shocks depict the time window used to calculate the mean. C: Mean values for the N1 (top: laser) and P45 (middle: painful shocks, bottom: non-painful shocks) extracted from the left hemisphere electrode for unilateral and bilateral conditions. Unilateral is depicted as dotted bars and bilateral as full bars. The dots represent individual data points.

Event-related spectral perturbations

Group-average ERSPs are presented in Figure 4A, topoplots along with mean and individual data points in Figure 4B, and mean values are reported in Online Resource (Table 3).

For laser stimuli, power was significantly greater in the bilateral compared with the unilateral condition for 2 – 10 Hz oscillations ($t(13) = 4.4$, $P = 0.0007$, $\eta_p2 = 0.60$) and 61 – 100 Hz oscillations ($t(13) = 2.7$, $P = 0.02$, $\eta_p2 = 0.35$), but not for 30 – 60 Hz oscillations ($t(13) = 1.03$, $P = 0.32$, $\eta_p2 = 0.07$). For the 8 – 29 Hz electrode clusters, oscillation power was significantly greater in the bilateral compared with unilateral condition (main effect: $F_{1,13} = 4.62$, $P = 0.05$, $\eta_p2 = 0.26$) and this effect was significantly different between hemispheres (interaction: $F_{1,13} = 6.49$, $P = 0.02$, $\eta_p2 = 0.33$). Planned comparisons revealed greater power for the bilateral compared with unilateral condition for the right ($P = 0.026$) but not the left ($P = 0.30$) electrode cluster.

For painful electrical stimuli, power was significantly greater in the bilateral compared with the unilateral condition for 2 – 10 Hz oscillations ($t(21) = 9.66$, $P < 0.0001$, $\eta_p2 = 0.82$), 30 – 60 Hz oscillations ($t(21) = 3.42$, $P = 0.0025$, $\eta_p2 = 0.36$) and 61 – 100 Hz oscillations ($t(21) = 3.7$, $P = 0.0013$, $\eta_p2 = 0.39$). The cluster analysis for 8 – 29 Hz power showed that oscillation power was greater in the bilateral compared with unilateral condition (main effect: $F_{1,21} = 6.5$, $P = 0.019$, $\eta_p2 = 0.24$), but this effect was not significantly different between hemispheres (interaction: $F_{1,21} = 0.72$, $P = 0.41$, $\eta_p2 = 0.03$).

Lastly, for non-painful electrical stimuli, power was significantly greater in the bilateral condition compared with the unilateral condition for 2 – 10 Hz oscillations ($t(21) = 7.1$, $P < 0.0001$, $\eta_p2 = 0.71$), 30 – 60 Hz oscillations ($t(21) = 3.76$, $P = 0.0013$, $\eta_p2 = 0.40$) and 61 – 100 Hz oscillations ($t(21) = 2.2$, $P = 0.036$, $\eta_p2 = 0.19$). For the 8 – 29 Hz cluster analysis, oscillation power was significantly greater in the bilateral compared with unilateral condition (main effect: $F_{1,21} = 18.78$, $P = 0.0003$, $\eta_p2 = 0.47$) and this effect was significantly different between hemispheres (interaction: $F_{1,21} = 9.94$, $P = 0.005$, $\eta_p2 = 0.32$). Planned comparisons revealed a stronger response (more negative) for the

bilateral compared with unilateral condition for both the right ($P = 0.0002$) and the left ($P = 0.006$) electrode cluster.

These results indicate that bilateral stimulation increased the power for 2 – 10 Hz oscillations and 8 – 29 Hz oscillations, whether the stimulus was painful or not, and whether it was evoked by lasers or electric shocks. Bilateral stimulation also increased the power for 30 – 60 Hz and 61 – 100 Hz oscillations for painful and non-painful electrical shocks, but not for laser stimulation.

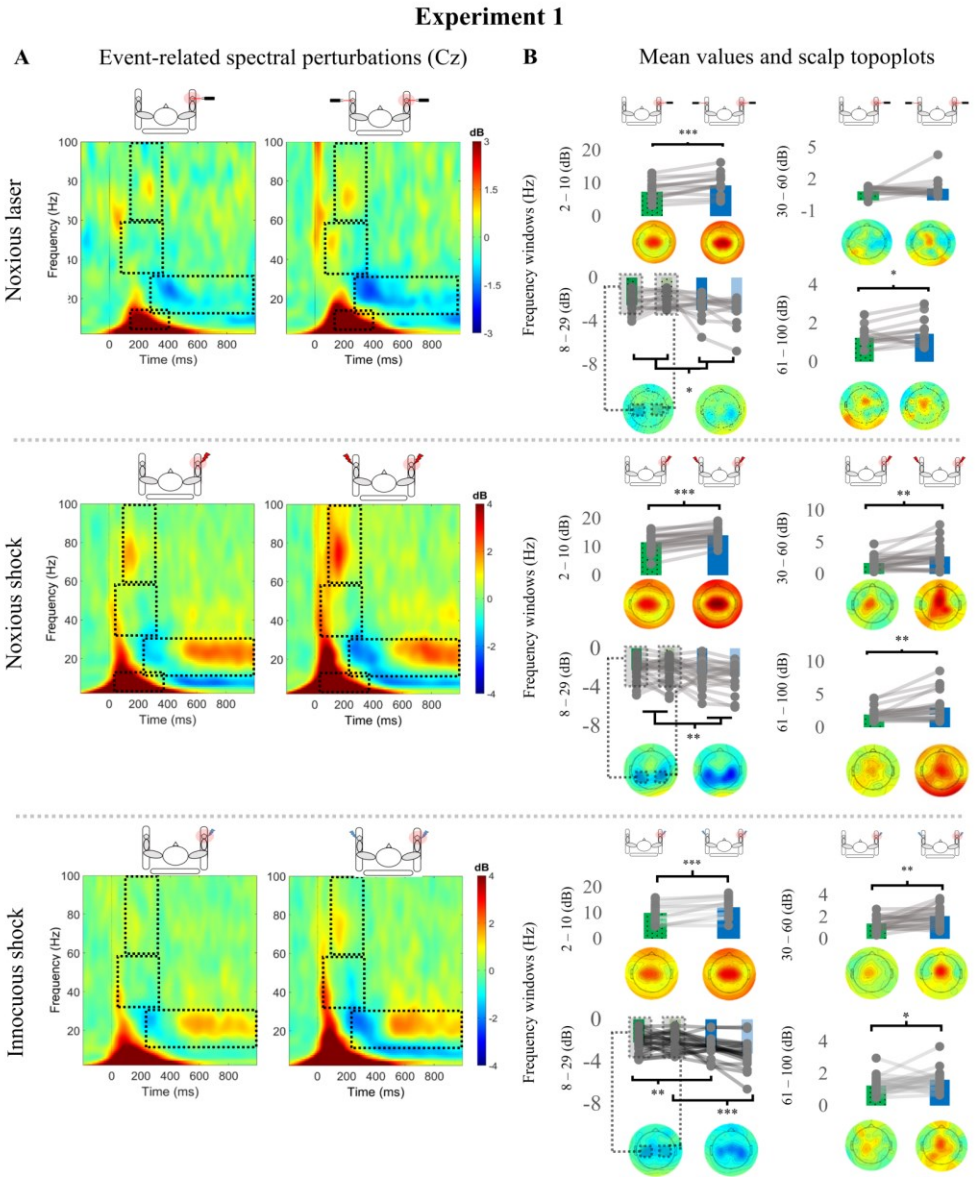

Figure 5.4 Event-related spectral perturbations for unilateral and bilateral conditions for each modality.

A: Average event-related spectral perturbation analysis for unilateral and bilateral conditions for each modality (top: laser, middle: painful shocks, bottom: non-painful shocks). The condition is identified by the pictogram. The red circle overlying the hand is the side on which attention had to be deployed. Units are in decibels (dB) relative to the baseline. Dashed areas represent the 4 regions of interests. B: Mean values extracted for unilateral and bilateral conditions for each modality. The dots represent individual data points. Below each graph: scalp topoplot of the time-frequency peak for each region of interest. For the 8 – 29 Hz region of interest the dashed area linking the bars to the topoplots represents the left and right electrode clusters. *: P< 0.05; **: P<0.01, ***: P < 0.001 for the *t*-test between unilateral and bilateral conditions. ‡‡, ‡‡‡: P<0.01 and P<0.001 for planned contrasts. ††: P < 0.01 for the main effect of unilateral vs bilateral.

Experiment 2

Pain ratings and stimulus intensities

Mean pain ratings and mean stimulus intensities are reported in Online Resources (Table 4). On average, laser stimuli evoked light pain, with no difference between unilateral and bilateral conditions (main effect: $F_{1,14} = 0.98$, $P = 0.34$, $\eta_p2 = 0.07$) and this was not affected by attention (interaction $F_{1,14} = 2.82$, $P = 0.11$, $\eta_p2 = 0.16$). Laser intensity was higher for the right compared with the left hand ($t(15) = 2.23$, $P = 0.041$, $\eta_p2 = 0.25$). Painful electrical stimuli evoked moderate pain with a significant difference between unilateral and bilateral conditions depending on attention direction (interaction: $F_{1,17} = 9.51$, $P = 0.007$, $\eta_p2 < 0.36$). Planned comparisons revealed that pain was greater in the bilateral condition when attention was focused on the left hand compared with the unilateral left hand stimulation ($P = 0.013$), but not when attention was focused on the right hand compared with the unilateral right hand stimulation ($P = 0.60$). For stimulus intensity, no difference was observed between right and left hands ($t(17) = 0.13$, $P = 0.89$, $\eta_p2 < 0.01$).

These results indicate that bilateral laser stimulation did not evoke more pain compared with unilateral stimulation. For electrical stimulation, the effects of bilateral stimulation were not consistent between hands.

Vertex evoked potentials

Group-average ERPs and topoplots are presented in Online Resource (Figure 6) and mean values are reported in Online Resource (Table 5).

For N2 and P2 LEPs, the scalp distribution was centered at Cz and occurred at the expected latencies (N2: 201.6 ± 25.6 ms, P2: 310.6 ± 27.8 ms).

N2 amplitude was significantly different between bilateral and unilateral conditions depending on attention direction (interaction: $F_{1,14} = 4.76$, $P = 0.046$, $\eta_p2 = 0.25$). Planned comparisons revealed an increase in N2 amplitude in the bilateral condition when attention was focused on the right hand compared with the unilateral

right hand stimulation ($P = 0.002$), but not when attention was focused on the left hand compared with the unilateral left hand stimulation ($P = 0.67$).

P2 amplitude was significantly different between bilateral and unilateral conditions depending on attention direction (interaction: $F_{1,14} = 14.17$, $P = 0.002$, $\eta_p 2 = 0.50$). Planned comparisons revealed a decrease in P2 amplitude for the bilateral condition when attention was focused on the left hand compared with the unilateral left hand stimulation ($P = 0.005$). In contrast, P2 amplitude was increased in the bilateral condition when attention was focused on the right hand compared with the unilateral right hand stimulation ($P = 0.013$).

For N100 and P260 components of potentials evoked by painful shocks, the scalp distribution was centered at Cz, as expected. N100 amplitude was greater in bilateral compared to unilateral condition (main effect: $F_{1,16} = 77.66$, $P < 0.0001$, $\eta_p 2 = 0.83$), but this effect was not modulated by attention (interaction: $F_{1,16} = 1.69$, $P = 0.21$, $\eta_p 2 = 0.10$). No significant effect was observed for the P260 (all $P > 0.59$).

These results indicate that bilateral stimulation increased the negative vertex potential for painful shocks. For laser stimuli, the effects of bilateral stimulation were not consistent between hands.

Lateralized evoked potentials

Group-average lateralized ERPs and topoplots are presented in Online Resource (Figure 7) and mean values are reported in Online Resource (Table 5).

For LEPs, the temporo-central scalp distribution and latency (166.0 ± 19.0 ms) correspond to usual characteristics of the N1. N1 amplitude was maximal at central electrodes contralateral to the stimulation for the unilateral stimulation (right hand: C3 for measurements, left hand: C4 for measurements). N1 amplitude was significantly different between unilateral and bilateral conditions depending on attention direction (interaction: $F_{1,14} = 7.91$, $P = 0.014$, $\eta_p 2 = 0.36$). Planned comparisons revealed that N1 amplitude decreased for the bilateral condition with attention to the left hand compared with unilateral left hand stimulation (measured at C4) ($P = 0.0013$), but not for the bilateral condition with attention to the right hand compared with unilateral right hand stimulation (measured at C3).

The P45 evoked by painful electrical stimuli was not consistently measurable between conditions so it is shown but not further analyzed.

These results indicate that the effects of bilateral stimulation on early lateralized potentials are not consistent either for laser or for electrical stimulation.

Event-related spectral perturbations

Group-average ERSPs and topoplots are presented in Online Resource (Figure 8) and mean values are reported in Online Resource (Table 6).

For laser stimuli, 2 – 10 Hz oscillation power was significantly different between bilateral and unilateral conditions depending on attention direction (interaction: $F_{1,14}$ = 11.75, P = 0.004, $\eta_p 2$ = 0.46). Planned comparisons revealed a power increase for the bilateral condition when attention was focused on to the right hand compared with unilateral right hand stimulation (P = 0.005), but not for the bilateral condition when attention was focused on to the left hand compared with unilateral left hand stimulation (P = 0.20). No power modulation was observed for 30 – 60 Hz oscillations (all P > 0.43), 61 – 100 Hz oscillations (all P > 0.08) or for the cluster analysis for 8 – 29 Hz oscillations (all P > 0.08).

For painful electrical stimulation, power was significantly increased in the bilateral compared with unilateral condition for 2 – 10 Hz oscillations (main effect: $F_{1,17}$ = 45.25, P < 0.0001, $\eta_p 2$ = 0.73), 30 – 60 Hz (main effect: $F_{1,17}$ = 13.51, P = 0.002, $\eta_p 2$ = 0.44) and 61 – 100 Hz (main effect: $F_{1,17}$ = 36.40, P < 0.0001, $\eta_p 2$ = 0.68), but these effects were not significantly modulated by attention (all P > 0.11). No significant modulation was observed for the 8 – 29 Hz cluster analysis (all P > 0.09).

These results indicate that bilateral stimulation increased power for 2 – 10 Hz, 30 – 60 Hz and 61 – 100 Hz oscillations evoked by painful shocks. For laser stimulation, the effects of bilateral stimulation were not consistent between hands.

Discussion

Previous work has shown that bilateral noxious inputs interact in the brain, as shown by a modulation of pain-related brain activity, although the limited number of studies led to divergent results (Northon et al., 2019; Rustamov et al., 2019). This could

be explained by differences in stimulation procedures, since the two available studies used either laser or electrical stimuli. Indeed, laser stimuli activate nociceptive fibers selectively while transcutaneous electrical stimuli activate nociceptive and other sensory fibers (Garcia-Larrea, 2006). Differences may also be due to stimulus location. The feet are closer to each other compared with the hands, both in space (in normal anatomical position) and in the cortical somatosensory map. In addition, the hands are closer to the face, the center of the defensive peripersonal space (Sambo et al., 2012), which may increase the modulation of defensive reflexes (Moayedi et al., 2015) and the behavioral relevance or threatfullness (Moayedi et al., 2016), especially when bilateral stimuli are applied. In experimental settings where participants are seated, participants may not see their feet and hands in the same way, a factor that modulates the perception and cortical responses of noxious and innocuous stimuli (Kennett et al., 2001; Torta et al., 2015). In the present study, vertex LEP and SEP data indicates that the interactions following bilateral inputs are generally not affected by the type of afferents activated by the stimuli. These results are consistent with those from a previous study showing that the amplitude of the N100 was greater for bilateral compared to unilateral electrical stimulation at the ankle (Rustamov et al., 2019). However, the results contrast with those of another study showing that LEP amplitude is decreased for bilateral compared with unilateral stimulation (Northon et al., 2019). To clarify this discrepancy, a second experiment was conducted with the same experimental design as in the previous study (Northon et al., 2019). Results from this second experiment confirm that the most common effect for bilateral laser stimulation is an increase in LEP amplitude. Nevertheless, it should be noted that some participants showed the opposite effect. Response suppression, as reported previously (Kuroki et al., 2017), may contribute to this effect. Notwithstanding, the present study clarifies that bilateral noxious inputs interact in the brain, and that this interaction is generally reflected in increased amplitude of vertex ERPs and is not affected by stimulus properties (shock vs laser) or stimulus location (hands in the present study and feet in a previous study [23]). Also, since the shock and laser stimuli were grouped in separate blocks, the results confirm that this observation is not affected by differences in the anticipated perception or threatfullness of the stimulus (shock vs laser).

In contrast to the vertex ERPs, lateralized ERPs were generally comparable between unilateral and bilateral stimulation. Lateralized ERPs measured in the present study mostly represent activity in the somatosensory cortex (Allison et al., 1996). The P45 is usually similar between painful and non-painful stimuli (Rustamov et al., 2016), as observed here. Likewise, the N1 is not different between perceived and unperceived laser stimuli (Lee et al., 2009). However, the N1 can be dissociated from pain ratings (Iannetti et al., 2008) and is sensitive to novelty and saliency (Ronga et al., 2013). Thus, the selective effects on vertex potentials cannot be fully explained by increased saliency, in which case N1 amplitude should also be increased. However, the signal to noise ratio of these lateralized responses is lower than that of vertex potentials and may preclude the detection of small effects.

ERSPs are other measures of interest from brain activity that were examined in the present study. Brain oscillations and how they synchronize or desynchronize are known to allow integration (Fries, 2015; Mejias et al., 2016; Schnitzler & Gross, 2005). Thus, they extend ERP findings and are especially well suited to study how noxious inputs interact in the brain.

Gamma oscillations are ubiquitous in the neocortex and are thought to reflect local cortical processing and long-range synchronization (Fries, 2009). An increase in gamma oscillation power evoked by phasic painful stimuli was reported in several studies (Chien et al., 2014; Hauck et al., 2015; Hauck et al., 2007; Heid et al., 2020; Northon et al., 2019; Ploner et al., 2017; Rossiter et al., 2013; Rustamov et al., 2019; Tan et al., 2019; Tiemann et al., 2010; Valentini et al., 2013; Yue et al., 2020; Zhang et al., 2012). Recent studies have shown that SI is an important contributor to the pain-related gamma oscillations evoked by laser stimuli (Heid et al., 2020; Tan et al., 2019; Yue et al., 2020). The present results show that bilateral laser stimuli did not increase pain or N1 amplitude, but increased high-gamma power, which may suggest that the interactions of concurrent bilateral inputs may be detectable at an early processing stage (SI) using ERSPs.

The degree to which gamma oscillations induced by painful laser and electrical stimuli can be compared remains unclear. It was reported that pain-related gamma oscillations in SI may reflect cortical activity that is specific to the processing of nociceptive information (Heid et al., 2020; Tan et al., 2019; Yue et al., 2020). However,

SI gamma oscillations evoked by transcutaneous electrical stimuli exhibit a monotonic relationship for intensities that evoke sensations ranging from light non-painful up to strongly painful (Rossiter et al., 2013), which argues against this idea and is consistent with the present findings showing gamma ERSPs with both non-painful and painful shocks. The power increase of gamma oscillations in the bilateral condition is reproducible and consistent with our previous study (Rustamov et al., 2019). In that previous study, the increase in gamma power in the bilateral condition was accompanied by an increase in pain ratings. The dissociation between gamma power and pain in Experiment 1 suggest that the gamma power increase is independent of changes in pain perception and thus reflects more than pain perception, at least in the present experimental conditions.

Previous studies have shown that homosegmental bilateral electrical stimulation, but not laser stimulation, increases pain compared with unilateral stimulation (Northon et al., 2019; Rustamov et al., 2019). The present results indicate that homosegmental bilateral electrical stimulation does not necessarily increase pain perception compared with unilateral stimulation, although a trend was observed. Other reports also showed that integration can occur between dermatomes from the ipsi- and contralateral limbs when concurrent tonic heat pain is used (Defrin et al., 2010; Nielsen & Arendt-Nielsen, 1997b). In these studies, spatial attention modulated perception: attention focusing on one of the two stimuli decreased spatial summation of pain, whereas dividing attention between both stimuli decreased pain compared with a single stimulus. Similarly, global rating of two painful stimuli modulates pain compared to the rating of a single stimulus (Lautenbacher et al., 2007; Quevedo & Coghill, 2007). However, these studies used tonic stimuli or a combination of tonic and phasic stimuli. Tonic painful stimuli activate a spino-bulbo-spinal loop that produce widespread inhibition of nociceptive activity in other body areas, a “pain-inhibits-pain” mechanism termed diffuse noxious inhibitory control (DNIC) (Le Bars et al., 1979) or conditioned pain modulation (CPM) (Yarnitsky, 2010). In the present study, since two short-duration concurrent stimuli were used, this mechanism is unlikely to be involved. Indeed, nociceptive inputs are already ascending when inhibitory feedback reaches their spinal origin. Besides, dividing attention between

concurrent painful and non-painful tonic stimuli also reduces pain perception (Quevedo & Coghill, 2007) suggesting that spatial attention is important in modulating the perception of concurrent stimuli. In the present study, participants always rated the right hand to control spatial attention and examine the effect of a concurrent contralateral input on perception and brain responses across different modalities. It should be noted that since participants rated average pain on the left hand (unattended) during each rest period, this may have prevented a complete attentional focus on the right hand. However, participants were reminded to attend and rate the right hand before the beginning of each stimulation block to limit this potential interference. Future studies should examine if different spatial attention sets (e.g. global, divided attention) can modulate the integration of concurrent phasic inputs.

For non-painful stimuli, we observed a significant increase in tactile sensation in the bilateral condition. One possibility to explain the discrepancy between painful and non-painful stimuli is a ceiling effect for the attentional capture by painful stimuli. Accordingly, the summation effects may not be linear and applying a concurrent stimulus to a non-painful or to a painful stimulus may not lead to proportional increases in perception. This could be examined in future studies with non-painful and painful stimuli of various intensities.

While perception and event-related brain activity tend to covary, dissociations are common (Iannetti et al., 2008; Legrain et al., 2011). An example is the stable pain perception but strong decrease in event-related potentials when a triplet of painful stimuli is presented with a 1-second interval (Iannetti et al., 2008). This and other investigations have led to the prevailing view that vertex potentials likely reflect a multimodal detection of salient stimuli (Legrain et al., 2011). Yet, both the N1 and N2 of the laser-evoked potentials tend to retain some somatosensory specificity whereas the late, multimodal P2 potential shares striking similarities with late potentials evoked by visual, tactile and auditory stimuli.

By changing stimulus-driven parameters of the 3rd stimulus in the triplet paradigm, N2 habituation was shown to be sensitive to changes in novelty and saliency (Ronga et al., 2013). Behaviorally relevant changes in stimulus location from the foot to the hand for the 3rd stimuli can also revert N2 habituation specifically (Moayedi et al.,

2016) and the trial-by-trial variability of the N2 predicts the reaction time of a defensive motor response to noxious stimuli (Moayedi et al., 2015). Thus, it was suggested that the N2 also reflects the detection of potential threats and initiation of defensive motor responses (Moayedi et al., 2016; Moayedi et al., 2015). This spatial-change effect is not observed when 3rd stimulus is displaced from one hand to the other (Torta et al., 2012). Thus, the effect observed in the present study is unlikely to be explained by the introduction of a spatial change (or addition of a spatial location) in the sensory stream. Based on these accounts, the selective effects on negative vertex potentials may be interpreted as an integration of bilateral inputs from individual stimuli into a more salient, threatening event. This may explain the similarity of results for painful and non-painful stimuli. These results would benefit from a multimodal approach combining methods that complement the high temporal but low spatial resolution of EEG such as functional magnetic resonance imagery (fMRI), to explore the brain areas in which such interactions may occur. Lastly, methodological studies on the selection of participants on the basis of the presence or absence of a physiological response are needed to clarify which approach is preferable in which context, and to standardize the methods between studies.

Conclusion

In summary, the present study clarifies that bilateral inputs lead to similar cortical interactions for noxious and innocuous stimuli, resulting in a subadditive increase of brain responses, but lead to different perceptual effects.

Abbreviations

ERP: Event-related potentials; LEP: Laser-evoked potentials; ERSP: Event-related spectral perturbations; EEG: Electroencephalography

Declarations

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Competing interests

The authors declare that they have no competing interests

Availability of data and material

The datasets generated during the current study are available from the corresponding author on reasonable request

Code availability

The custom code generated for the current study are available from the corresponding author on reasonable request

Authors' contributions

All authors contributed significantly to this study and has read the final version of the manuscript. S.N. contributed to data collection and analyses and wrote the first version of the manuscript. Z.D contributed to data collection. M.P. contributed to study design, data collection, analyses and interpretation, wrote the final version of the manuscript and obtained funding.

Ethics approval

All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the Research Ethics Board of the Université du Québec à Trois-Rivières.

Consent to participate

All participants received written informed consent, acknowledged their right to withdraw from the experiment without prejudice, and received a compensation of $25 for their time.

Consent for publication

Not applicable

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Article title: Cortical interaction of bilateral inputs is similar for noxious and innocuous stimuli but leads to different perceptual effects.

Supplementary material

Journal name: Experimental Brain Research

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Tableau 5.2 Evoked potentials for unilateral and bilateral stimuli for each modality (Experiment 1).

	Unilateral	Bilateral
Laser (mean ± SD)		
N1 peak – C3 (uV)	-4.4 ± 1.9	-5.5 ± 2.8
N2 peak (uV)	-7.3 ± 5.8	-13.4 ± 10.0
P2 peak (uV)	7.7 ± 4.6	9.5 ± 5.4
Painful shocks (mean ± SD)		
P45 mean – P3 (uV)	2.6 ± 2.4	2.7 ± 2.8
N100 mean (uV)	-15.2 ± 10.4	-22.8 ± 14.6
P260 mean (uV)	10.1 ± 6.7	9.7 ± 7.2
Non-painful shocks (mean ± SD)		
P45 mean – P3 (uV)	1.8 ± 1.8	2.1 ± 2.8
N100 mean (uV)	-8.4 ± 8.0	-15.4 ± 13.0
P260 mean (uV)	9.3 ± 5.3	10.4 ± 5.7

Tableau 5.3 Event-related spectral perturbations for unilateral and bilateral stimuli for each modality (Experiment 1).

	Unilateral	Bilateral
Laser (mean ± SD)		
2 – 10 Hz	7.4 ± 3.5	9.3 ± 4.0
8 – 29 Hz–		
Left SRM electrodes	-2.5 ± 1.1	-3.0 ± 1.6
Right SRM electrodes	-2.1 ± 0.9	-3.3 ± 1.5
30 – 60 Hz	0.9 ± 0.4	1.1 ± 0.9
61 – 100 Hz	1.3 ± 0.6	1.5 ± 0.8
Painful shocks (mean ± SD)		
2 – 10 Hz	11.6 ± 3.8	14.1 ± 3.9
8 – 29 Hz–		
Left SRM electrodes	-2.2 ± 1.2	-2.7 ± 1.4
Right SRM electrodes	-2.3 ± 1.3	-2.9 ± 1.5
30 – 60 Hz	1.7 ±1.1	2.7 ± 2.0
61 – 100 Hz	1.9 ± 1.0	3.0 ± 2.1
Non-painful shocks (mean ± SD)		
2 – 10 Hz	10.0 ± 3.9	12.2 ± 4.3
8 – 29 Hz–		
Left SRM electrodes	-2.2 ± 1.0	-3.3 ± 1.4
Right SRM electrodes	-2.2 ± 1.0	-2.7 ± 1.1
30 – 60 Hz	1.4 ± 0.6	2.1 ± 0.9
61 – 100 Hz	1.3 ± 0.6	1.6 ± 0.7

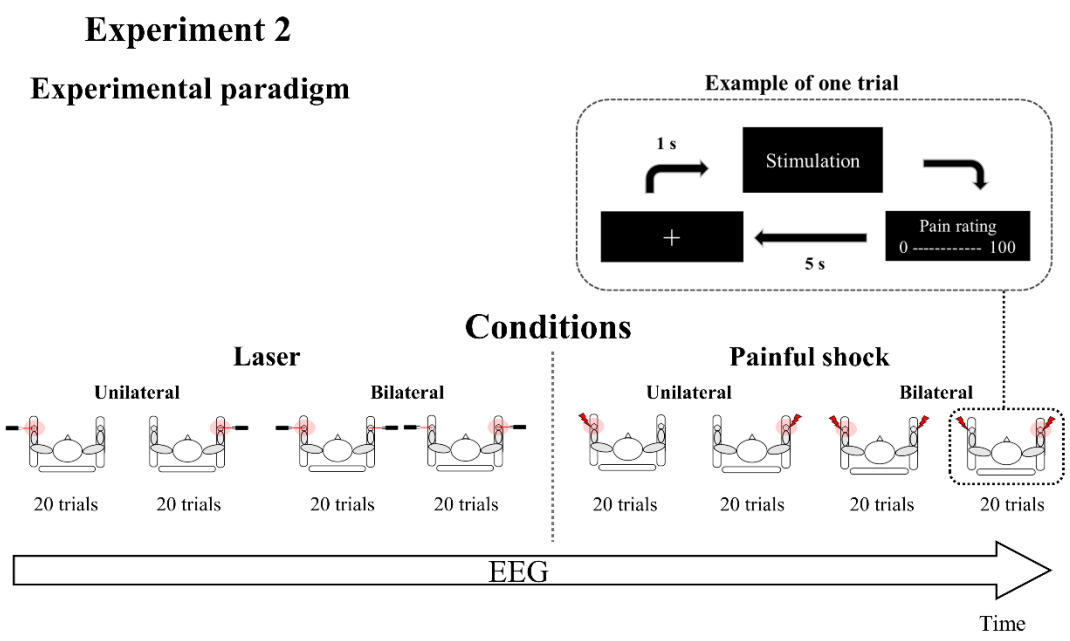

Figure 5.5 Experimental paradigm for experiment 2.

The 2 modalities (painful laser and painful electrical shocks) along with the four conditions (unilateral: left and right hand; bilateral: attention to right and left hand) are illustrated. Both modalities included the same four conditions. Condition order was counterbalanced. Pain ratings were prompted after each stimulus using a numerical scale with left (0) and right (100) anchors indicating "no pain" and "most intense pain imaginable," respectively. The red transparent circle overlying the pictogram's hand represents the side on which attention was directed. Top-right: temporal depiction of a single trial

Tableau 5.4 Pain ratings and stimulus intensities (Experiment 2).

	Unilateral left	Bilateral attention left	Unilateral right	Bilateral attention right
a. Pain ratings (numerical rating scores) (mean ± SD)				
Laser (0 – 100 pain)	11.4 ± 11.0	12.6 ± 12.6	16.0 ± 12.8	14.1 ± 11.7
Painful shock (0 – 100 pain)	15.1 ± 10.2	18.7 ± 11.4	19.5 ± 12.0	18.7 ± 10.6
b. Stimulus intensity (mean ± SD)				
	Left hand		Right hand	
Laser (Joules)	1.8 ± 0.5		1.9 ± 0.5	
Painful shock (mA)	5.1 ± 2.4		5.1 ± 3.2	

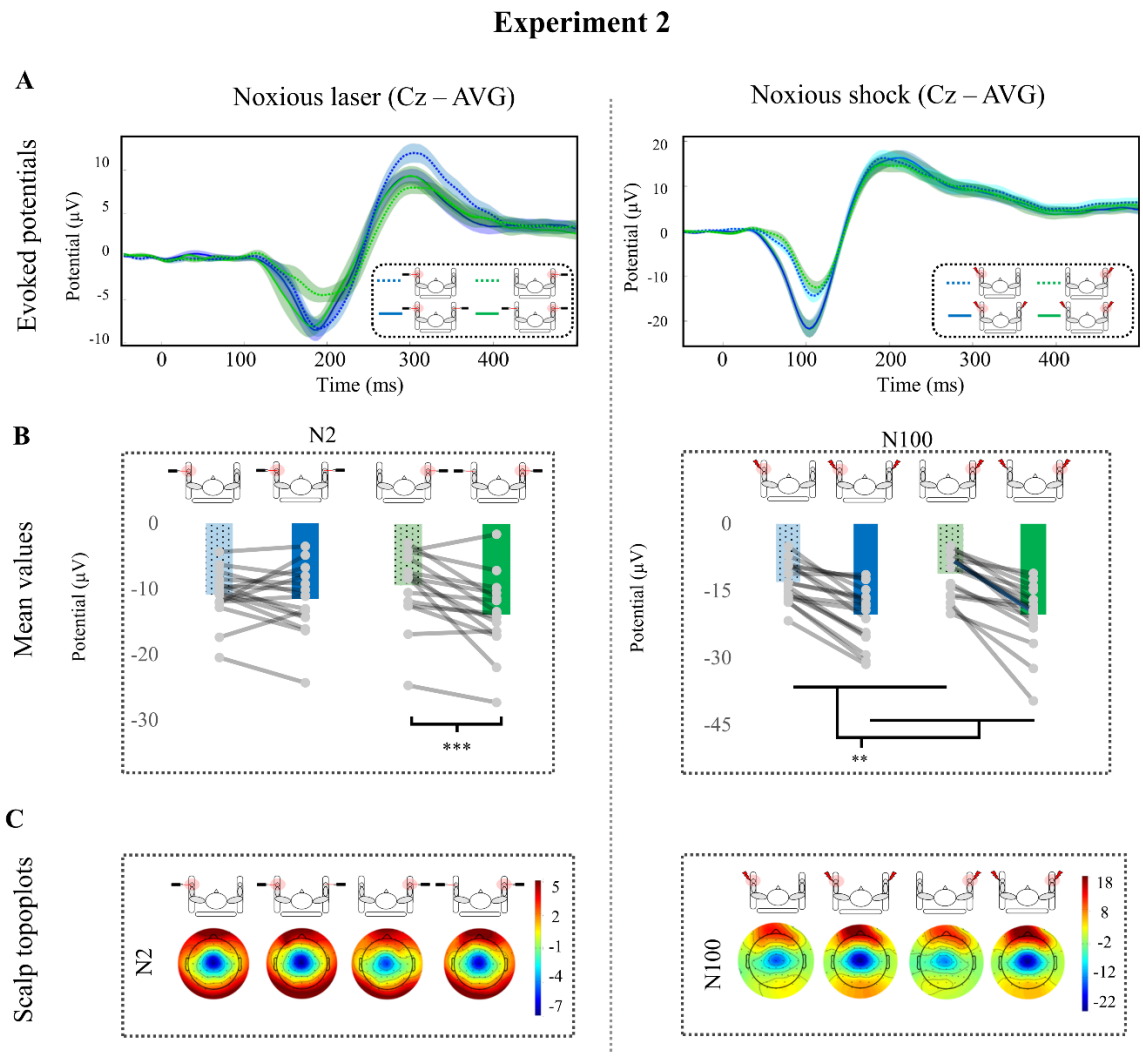

Figure 5.6 Event-related potentials for painful laser and painful shocks.

A: Laser-evoked potentials (left) and painful-shocks potentials (right) for the four conditions. Unilateral conditions are depicted as dashed lines and bilateral conditions as full lines. Attention to the left hand is illustrated in blue and attention to the right hand in green. B: Mean N2 (left) and N100 values (right) measured for the four conditions. Unilateral conditions are depicted as dotted bars and bilateral conditions as full bars. The dots represent individual data points. C: Scalp topoplots for the N2 (left) and N100 (right) for the four conditions. ††: $P < 0.001$ for bilateral conditions compared with unilateral conditions (main effect), ***: $P < 0.001$ for planned comparison. The red transparent circle overlying the hand represents attention direction

Tableau 5.5 Evoked potential amplitude (Experiment 2).

	Unilateral left	Bilateral attention left	Unilateral right	Bilateral attention right
Laser (mean ± SD)				
N1 peak – C4 electrode	-6.0 ± 3.4	-4.3 ± 2.8	-	-
N1 peak – C3 electrode	-	-	-5.4 ± 4.2	-5.7 ± 4.3
N2 peak	-10.9 ± 4.6	-11.5 ± 5.7	-7.8 ± 4.8	-11.6 ± 5.6
P2 peak	13.2 ± 4.7	11.3 ± 3.5	9.7 ± 3.5	11.8 ± 4.0
Painful shock (mean ± SD)				
P45 mean – CP4 electrode	0.7 ± 1.8	0.0 ± 2.4	-	-
P45 mean – CP3 electrode	-	-	0.9 ± 2.3	1.0 ± 2.6
N100 mean	-13.0 ± 5.3	-20.3 ± 7.9	-11.1 ± 5.5	-20.2 ± 8.4
P260 mean	10.6 ± 7.1	10.6 ± 7.8	10.6 ± 6.0	10.7 ± 6.7

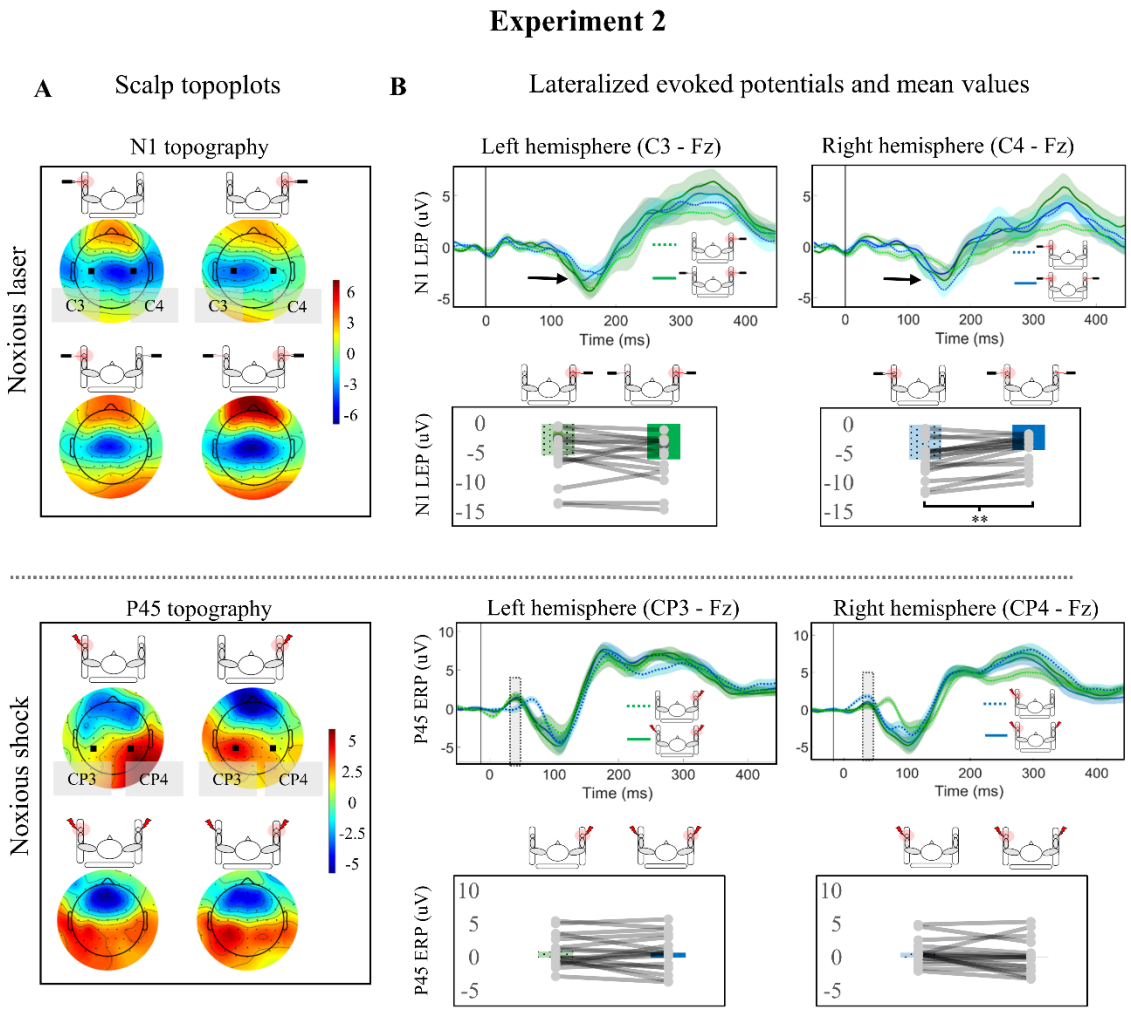

Figure 5.7 Lateralized event-related potentials for painful laser and painful shocks.

A: Scalp topoplots for the average N1 (top, laser stimuli) and P45 (bottom, painful shocks) for the four conditions. The contralateral (left for right-hand stimulation and vice-versa) and ipsilateral (right for right-hand stimulation and vice-versa) electrodes are depicted as dashed areas. B: Top: time course of the lateralized evoked potentials at the contralateral (left) and ipsilateral (right) electrodes. Laser-evoked potentials (top) and painful shocks potentials (bottom) are depicted for the four conditions. Unilateral conditions are shown as dashed lines and bilateral conditions as full lines. The dots represent individual data points. Underneath each evoked potential graph: N1 (top) and P45 (bottom) values measured at the contralateral electrode. Unilateral conditions are depicted as dotted bars and bilateral conditions as full bars. **: $P < 0.01$ for planned comparison. The red transparent circle overlying the hand represents attention direction

Experiment 2

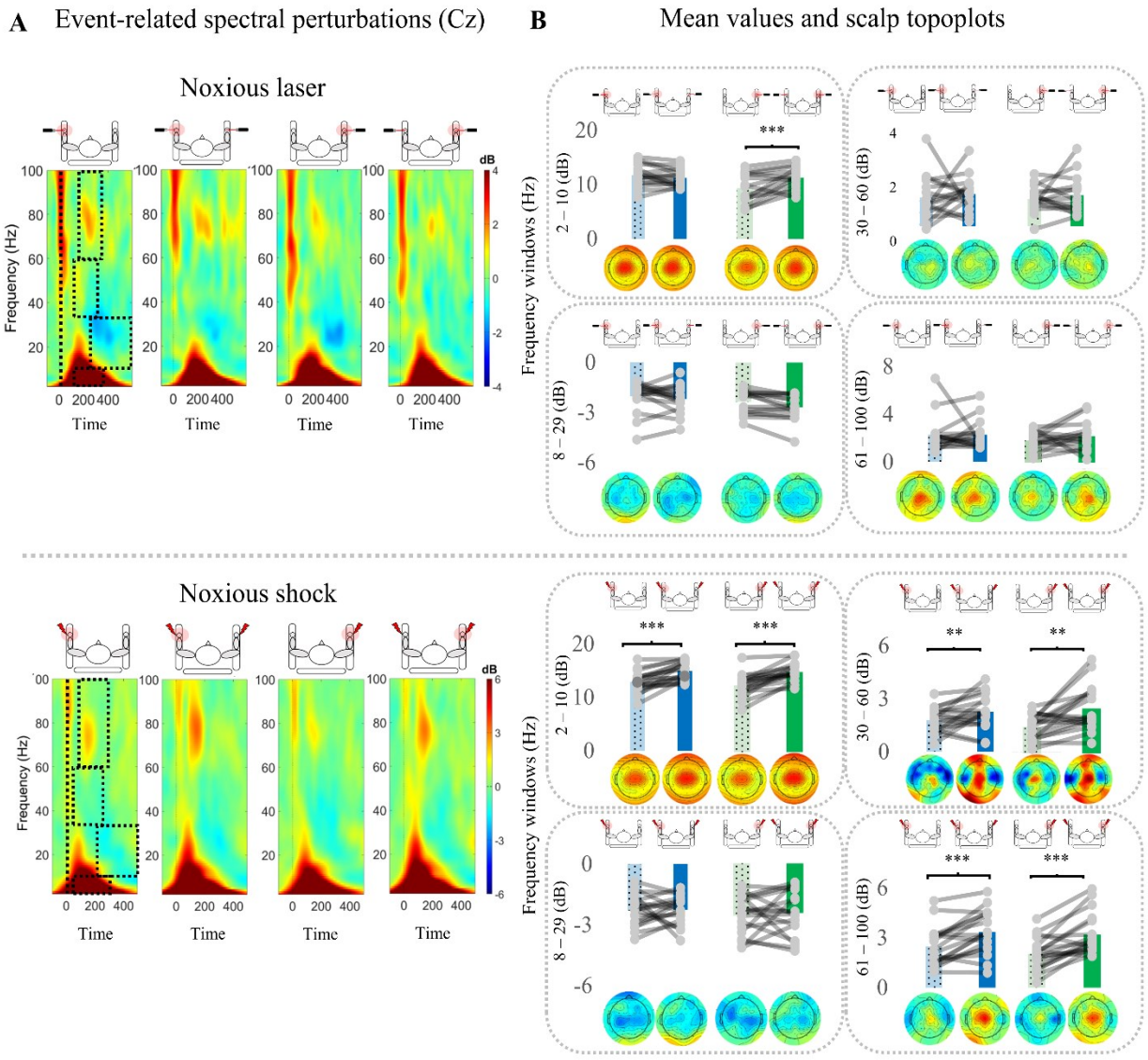

Figure 5.8 Event-related spectral perturbations in each region of interest for painful laser and painful shocks.

A: Average event-related spectral perturbation analysis for both modality (top: laser, bottom: painful shocks). Units are in decibels (dB) relative to baseline. Dashed areas represent the 4 regions of interests. B: Average results from the top 20% values within the region of interest for synchronization and lowest 20% values for desynchronization for unilateral and bilateral stimuli. The dots represent individual data points. Below each graph: scalp topography of the time-frequency peak for each region of interest. ††, †††: $P < 0.01$ and $P < 0.001$ for bilateral conditions compared with unilateral conditions (main effect), **: $P < 0.01$ for planned comparison. The red transparent circle overlying the hand represents attention direction

Tableau 5.6 Average event-related spectral perturbations (Experiment 2).

	Unilateral left	**Bilateral attention left**	**Unilateral right**	**Bilateral attention right**
Laser (mean ± SD)				
2 – 10 Hz	11.6 ± 2.1	11.2 ± 1.6	9.2 ± 2.6	11.1 ± 2.0
8 – 29 Hz–				
Left SRM electrodes	-2.3 ± 1.0	-2.7 ± 1.0	-2.2 ± 0.7	-2.3 ± 0.9
Right SRM electrodes	-2.2 ± 0.9	-2.5 ± 0.9	-2.3 ± 0.7	-2.1 ± 0.9
30 – 60 Hz	1.3 ± 1.0	1.5 ± 0.8	1.2 ± 0.6	1.4 ± 0.9
61 – 100 Hz	2.3 ± 1.5	2.3 ± 1.2	1.8 ± 0.7	2.1 ± 1.2
Painful shocks (mean ± SD)				
2 – 10 Hz	12.8 ± 2.0	14.9 ± 1.7	12.2 ± 2.1	14.6 ± 1.6
8 – 29 Hz–				
Left SRM electrodes	-2.3 ± 0.9	-2.1 ± 1.0	-2.2 ± 0.9	-2.0 ± 1.0
Right SRM electrodes	-2.3 ± 0.7	-2.4 ± 1.0	-2.7 ± 1.2	-2.1 ± 1.0
30 – 60 Hz	1.8 ± 0.7	2.3 ± 1.0	1.4 ± 0.6	2.4 ± 1.2
61 – 100 Hz	2.5 ± 1.2	3.3 ± 1.3	2.0 ± 1.0	3.2 ± 1.2

Chapitre 6 Article 4. Effects of spatial attention and limb position on the cortical interaction of bilateral noxious inputs.

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Impact statement:
The cerebral integration of noxious inputs is essential to produce adapted defensive responses. Here we show that increased brain responses and pain for bilateral compared with unilateral hand stimulation are modulated differentially by spatial attention and limb position. This suggests that the integration of noxious inputs occurs through partially independent pain-related processes, and that it is partially independent of pain perception. We propose that this is necessary to produce coordinated, flexible, and adapted defensive responses.

Contribution des auteurs

Stéphane Northon : Récension des écrits, collecte de données, analyses statistiques, rédaction de l'article, révision de l'article.

Zoha Deldar : Collectes de données, aide à la rédaction de l'article, relecture de l'article.

Mathieu Piché : Analyses statistiques, relecture de l'article, révision de l'article, supervision de l'étude

Abstract

Bilateral noxious inputs interact in the brain to provide a better representation of physical threat. In the present study, we investigated the effects of spatial attention and limb position on this interaction. Painful laser stimuli were applied randomly on the right hand or on both hands, while varying spatial attention (focal or overall) and limb position (hands near or far from each other). Pain perception and laser-evoked potentials (N1, N2, P2) were compared between conditions in 27 healthy volunteers. Compared with unilateral stimulation, bilateral stimulation increased pain (P=0.004), the N2 (P=0.0015) and P2 (P<0.001) amplitude. The effects on pain and the P2 were greater when hands were in the near compared with the far position (P<0.05). The effect on pain was also greater for overall compared with focal pain rating (P=0.003). In addition, the N1 amplitude was greater for bilateral stimulation when hands were in the far compared with the near position (P=0.01). These results show that increased brain responses and pain for bilateral compared with unilateral noxious stimulation are modulated differentially by spatial attention and limb position. This suggests that the integration of noxious inputs occurs through partially independent pain-related processes, that it is modulated by limb position, and that it is partially independent of pain perception. We propose that this is necessary to produce coordinated, flexible and adapted defensive responses.

1. Introduction

Noxious stimuli may elicit defensive behaviors and pain to prevent tissue damage (Sandrini et al., 2005; Sherrington, 1910). To provide a better estimate of potential bodily threat as well as defensive behaviors that are adapted to the context and the environment, the cerebral cortex integrates sensory inputs from different sources and modalities (Tabor et al., 2017). It has been shown that bilateral noxious inputs interact in the brain, leading to increased or decreased vertex evoked potential amplitude (Northon et al., 2021b; Northon et al., 2021c; Northon et al., 2019; Rustamov et al., 2019) . However, the factors that determine or influence this modulation remain unclear.

Previous studies indicate that vertex potentials evoked by noxious stimulation are influenced by spatial attention (Garcia-Larrea et al., 2003; Legrain et al., 2003; Lorenz & Garcia-Larrea, 2003). However, it is not clear how spatial attention may influence the interaction of noxious inputs produced by bilateral stimulation. When pain-related goals are prioritized, such as directing attention to the body region where noxious stimuli are applied, pain and pain-related brain activity are increased by top-down processes (Hauck et al., 2015; Hauck et al., 2007; Legrain et al., 2009a). Spatial attention can also modulate pain when concurrent noxious stimuli are applied. For example, pain is greater when the overall sensation produced by the concurrent stimuli is evaluated compared with the evaluation of one of the two stimuli (Algom et al., 1986, 1987; Lautenbacher et al., 2007; Nielsen & Arendt-Nielsen, 1997b; Quevedo & Coghill, 2007). Besides, according to the law of prior entry (Spence & Parise, 2010; Titchener, 1908), attending to a particular spatial location increases the processing of the attended compared with the unattended stimulus. Altogether, these studies suggest that spatial attention may modulate pain and the interaction of noxious inputs when bilateral noxious stimulation is applied, but this remains to be clarified.

Protecting the body against potential physical threats requires the discrimination of the body location where stimuli are applied (somatotopy), and the relative position of stimuli in space (spatiotopy) (De Paepe et al., 2014; Smania & Aglioti, 1995). It was also shown that pain-related brain activity is influenced by large spatiotopic changes with no

change in somatotopic coordinates (Moayedi et al., 2016). Behaviorally, the relative position of the hands affects the estimation of stimulus timing when two noxious stimuli are delivered almost simultaneously (De Paepe et al., 2015; Sambo et al., 2013). In addition, the cerebral cortex modulates the hand-blink reflex, a defensive reflex, as a function of the hand's proximity to the face or trunk (Sambo et al., 2012). Other insights on the relation between the relative position of the limbs and stimulus processing were reported for tactile stimuli. For example, when the hands are near, participants tend to make more errors when estimating which of the two tactile or vibrotactile stimuli was applied first, if the delay is relatively short (Shore et al., 2005). Similar effects were reported when participants were judging whether two vibrotactile stimuli were congruent or incongruent (Soto-Faraco et al., 2004). Moreover, the detection threshold of a tactile stimulus is increased by a concurrent tactile stimulus on the homologous body part (D'Amour & Harris, 2014a), and this increase is potentiated by the proximity of the two limbs (D'Amour & Harris, 2014a, 2016a). These findings indicate that the relative position of the limbs modulates the ability to detect and discriminate tactile stimuli. For concurrent bilateral noxious stimuli, the position of hands may modulate the interaction of noxious inputs in the brain. Although this is a fundamental question to understand how the brain produces defensive responses against complex physical threats, it has never been investigated.

Noxious stimuli bias attention to the peripersonal space and to the limb-centered peripersonal space (Filbrich et al., 2017b; Legrain & Torta, 2015; Van Damme et al., 2007; Vanderclausen et al., 2017). When the hands are near from each other, the limb-centered peripersonal space of each hand may overlap. This may modulate the integration of bilateral noxious inputs in the brain to generate a better representation of the physical threat, as the distance between hands affects the likelihood that both stimuli originate from a common source. This may partly explain why bilateral noxious stimuli applied on the feet (near from each other), but not on the hands (inter-limb distance of 70 cm) increase pain and pain-related brain activity compared with unilateral stimulation (Northon et al., 2021b; Northon et al., 2021c; Northon et al., 2019; Rustamov et al., 2019).

The aim of the present study was to examine how spatial attention and limb position modulate the interaction of bilateral noxious inputs in the brain and pain perception. Spatial attention was manipulated by instructing participants to focus on one hand to report pain intensity for that hand only or to attend stimuli on both hands to report the overall pain intensity for both hands. To manipulate limb position, hands were placed in front of the participant, 5 cm or 120 cm apart. Based on the studies mentioned above, we hypothesized that spatial attention and limb position would modulate pain as well as event-related potentials (ERPs) evoked by bilateral laser stimulation. More specifically, we expected that with the hands near from each other and attention to both hands (overall pain rating), brain responses and pain evoked by bilateral laser stimulation would be greater compared with the hands far from each other and attention to the right hand (focal pain rating).

2. Method

2.1 Participants

Thirty participants were recruited on the campus of the Université du Québec à Trois-Rivières. Participants gave written informed consent and acknowledged their right to withdraw from the experiment without prejudice. The experimental procedures were approved by the institutional ethics committee and conformed to the latest revision of the declaration of Helsinki. Participants were included if they were aged between 18 and 45 years old, and excluded if they had chronic pain, a diagnosed neurologic or psychiatric disorder, or if they were taking medication two weeks prior to the experiment. Participants above 45 years old were excluded to limit the potential confound of age, which may affect nociceptive processing (El Tumi et al., 2017; Lautenbacher et al., 2017; Quiton et al., 2007; Terrasa et al., 2021). Three participants were excluded because of technical failure, leaving a total of 27 participants (Age range: 20 – 37 years old; mean ± SD: 26.4 ± 5.2; Sex: 13 M; 14 F: seven in the 5th – 12th day of their menstrual cycle, five in the 18th -28th day of their menstrual cycle and 2 with no cycle due to contraceptives). Of the 27 participants, 25 were right-handed, one was ambidextrous, and one was left-handed. These two non-right-handed participants were included in the study since it was

shown that pain as well as cerebral responses and integration are comparable between right- and left-handed individuals (Northon et al., 2021c).

2.2 Experimental procedures

The experiment began two hours after ingestion of coffee and smoking. Room temperature was kept at 23°C. The viewing distance from the computer monitor was approximately 100 cm. Both the participant and experimenters wore safety glasses designed for a 1340 nm wavelength laser during the experiment. The experimental paradigm is shown in Figure 1. Prior to the experiment, participants were instructed to keep their gaze on a fixation cross and refrain from excessive body and head movements. The experiment comprised four conditions, including two different positions (hands far apart; hands near from each other) and two spatial attention conditions (Focal: attention to the right hand only with pain rating of the right hand stimulus; Overall: attention to both hands with an overall pain rating for stimuli on both hands). Each condition included 25 stimuli on the right hand and 25 on both hands for a total of 200 stimuli for the 4 conditions. Participants were informed that stimuli would be delivered with a 50:50 ratio. Identical stimuli (unilateral or bilateral) were never repeated more than once, the inter-stimulus interval varied randomly between 9 and 11 s and there was a rest period of 120 s every 16 to 18 stimuli.

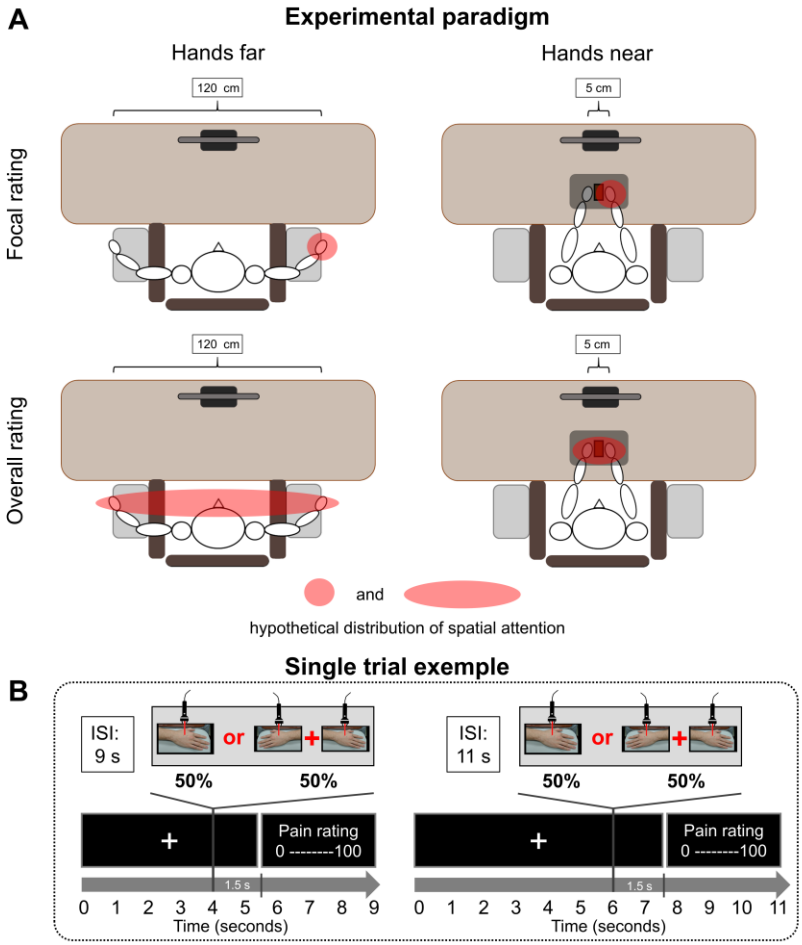

Figure 6.1 Experimental paradigm

2.3 Limb position

Position of the hands in the different conditions is shown in Figure 1. The distance between hands was either 120 cm or 5 cm. In the 120 cm position, the hands were not within eyesight. In the 5 cm position, the hands were placed under a panel that prevented the hands to be seen by the participant, as this may modulate brain responses to painful stimuli (Torta et al., 2015).

2.4 Spatial attention and pain rating instructions

Two pain rating instructions were given to participants: focal and overall pain intensity. For the focal rating condition, participants were instructed to rate pain intensity perceived on the right hand following each unilateral or bilateral stimulus. For the overall rating condition, they were instructed to rate pain intensity perceived overall for the two

concurrent stimuli, to assess the spatial summation of pain across body areas (Quevedo & Coghill, 2007). In all conditions, they were prompted to report pain verbally using a 0 – 100 numerical rating scale that appeared on the screen 1.5 seconds after each stimulus. The scale anchors were "no pain" and "most intense pain imaginable", respectively. Following rest periods, participants were reminded the pain rating instructions.

2.5 Painful laser stimulation

Painful radiant heat stimuli were produced by laser pulses using two infrared neodymium yttrium aluminum perovskite lasers (Nd:YAP, DEKA 1340; Electronical Engineering, Florence, Italy) each held by a different experimenter. Nd:YAP laser pulses activate Aδ and C nociceptors selectively (Plaghki & Mouraux, 2003). Laser beams were transmitted through a 10 m fiber-optic cable. The pulse duration was set at 5 ms and the diameter at 7 mm (≈38 mm^2 area). Safety recommendations for repeated laser stimuli were followed by moving to adjacent 0.4 mm ink-marked skin areas and by fixing a maximal output of 6 Joules (maximal fluence < 20 J / cm^2) (Madden et al., 2016). The lasers were controlled by a stimulus presentation program (E-Prime2, Psychology Software Tools, Sharpsburg, PA, USA). Ink dots (0.4 mm) were marked on the superficial radial nerve territory of both hand dorsum to avoid stimulating the same area more than once before reaching a pause. The mounting guides kept the stimulating distance constant and the in-built helium neon laser was used to aim the laser at the ink dots.

Pain thresholds were determined separately for each hand using the staircase method. Participants were instructed to focus on the pinprick sensation and to report pain intensity on the 0 – 100 scale. Laser energy output was first set at 1 J and was increased by 0.5 increments until heat was felt, and then by 0.25 J increments until pain was reported, or up to the 6 J upper limit. The reliability of the pain threshold was confirmed by stimulating at the energy that first elicited a painful pinprick sensation 5 times. To obtain a sharp and painful pinprick sensation, the energy was then adjusted individually by further increasing the output by one or two increments. For each hand, 5 consecutive stimuli at the selected intensity were delivered to familiarize participants. Pain ratings were compared between hands, and laser outputs were adjusted to match perception

between hands. Hand temperature was monitored using an infrared thermometer before and after thresholds and ranged between 27°C and 35°C.

2.6 Electroencephalographic recordings

Brain activity was measured using electroencephalography (EEG) with 64 active electrodes (Brain Products, Gilching, Germany). The electrodes were attached to a cap designed according to the international 10-20 system. The ground electrode was set at FPz and electrodes were nose-referenced. The signals were digitized at 1000 Hz with a hardware band-pass filter set from 0.01 to 500 Hz and a notch filter (60 Hz). Eye blinks and movements were monitored using electrooculography (EOG) with electrodes placed on the right suborbital ridge and the region lateral to the outer canthus.

2.7 Event-related potentials

EEG data were exported to Matlab and processed in EEGLab (v14.1.0) to extract and compute ERPs. ERP data were first filtered with FIR filters using the automatic filter function in EEGLAB, with the lower edge of the the high-pass set at 0.5 Hz and the higher edge of the low-pass set at 30 Hz. Data were then down sampled to 500 Hz and re-referenced to the common average. Prior to re-referencing, noisy channels were interpolated using the spherical method in EEGLab. Data were locked to the stimulus by segmenting epochs from -200 to 1000 ms, and data were baseline corrected using the -200 to 0 pre-stimulus window. Epochs were screened for non-stereotyped artifacts (e.g., cable or body movement and electrode failure) and removed if necessary. An Infomax independent component analysis (*Runica* function) was used to remove components associated with noise based on spectral and topographical characteristics (e.g., eye blinks, eye movements, muscle and cardiac artifacts). Epochs were then averaged separately for bilateral and unilateral stimuli and for each condition, leading to eight grand averages.

Laser-evoked potentials (LEPs) were examined by extracting the peak amplitude of each component. LEPs included the N2 (negative deflection between 170 – 230 ms) and P2 (positive deflection between 280 – 340 ms) (Perchet et al., 2008), which are maximal at the Cz electrode. When re-referencing to the Fz electrode, the N1 (negative deflection between 140 – 200 ms) is typically observable at the temporo-parietal

electrodes contralateral to the stimulated hand and precedes the N2 (Chen et al., 1998; Garcia-Larrea et al., 2003; Valeriani et al., 1996).

2.8 Statistical analyses

Statistical analyses were performed with Statistica v13 (Dell Inc, Tulsa, OK). All results are presented as mean ± standard deviation. Statistical threshold was set at $P \leq 0.05$ (two-tailed). All effect sizes are expressed as partial eta-squared (η^2_p) and reported with the observed power (OP). Distributions were assessed for normality using the Kolmogorov-Smirnov test and transformed using the log function as needed. Repeated-measures ANOVAs were computed with three within-subject factors: *Stimulation* (unilateral vs bilateral), *Limb position* (far vs near) and *spatial attention* (focal vs overall). This approach was used to compare pain and LEPs (N1, N2 and P2 potentials). Significant effects were decomposed using the Tukey's honestly significant difference test (HSD).

3. Results

3.1 Stimulus intensity and pain ratings

On average, the calibration procedure to produce comparable pain intensity on both hands at baseline required a slightly but significantly higher stimulus intensity on the right compared with the left hand (4.5 ± 0.6 J vs. 4.3 ± 0.5 J; $t(26) = 2.8$, $P = 0.009$, *OP= 0.78*).

The mean pain ratings (raw data) for all conditions are reported in Table 1 and log-transformed data is shown in Figure 2. On average, laser stimuli evoked light pain, with a significant increase in pain intensity for bilateral compared with unilateral stimulation (main effect: $F_{1,26} = 9.9$, $P = 0.004$, $\eta^2_p = 0.27$, $OP = 0.86$), and this effect was greater when hands were in the near compared with the far position (interaction: $F_{1,26} = 10.0$, $P = 0.004$, $\eta^2_p = 0.28$, $OP = 0.86$), or when ratings were reported for overall compared with focal pain intensity (interaction: $F_{1,26} = 11.1$, $P = 0.003$, $\eta^2_p = 0.30$, $OP = 0.89$). However, the interaction between spatial attention and the position of hands did not produce significant effects between unilateral and bilateral stimulation (interaction: $F_{1,26} = 0.1$, $P = 0.74$, $\eta^2_p = 0.004$, $OP = 0.06$).

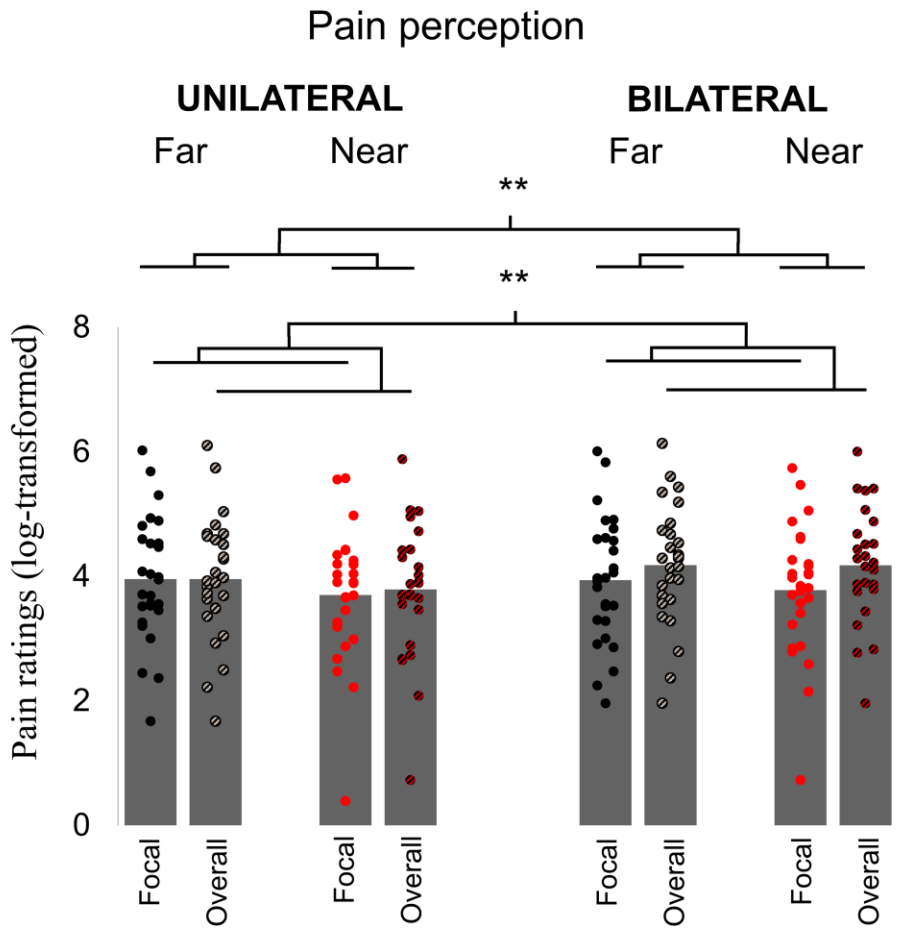

Figure 6.2 Pain ratings

3.2 Vertex laser-evoked potentials

Average vertex LEPs and the corresponding topoplots are presented in Figure 3. Both the N2 and P2 components showed a scalp distribution centered at Cz and occurred at expected latencies (N2: 211.0 ± 19.0 ms, P2: 323.6 ± 19.7 ms). The N2 peak amplitude was greater for bilateral compared with unilateral stimulation (main effect: $F_{1,26} = 12.6$, $P = 0.0015$, $\eta^2_p = 0.33$, $OP = 0.93$), but this effect was not significantly modulated by spatial attention (interaction: $F_{1,26} = 0.2$, $P = 0.7$, $\eta^2_p = 0.006$, $OP = 0.07$), the position of hands (interaction: $F_{1,26} = 1.4$, $P = 0.3$, $\eta^2_p = 0.05$, $OP = 0.21$) or the interaction of both factors (interaction: $F_{1,26} = 0.3$, $P = 0.6$, $\eta^2_p = 0.01$, $OP = 0.08$).

The P2 peak amplitude was greater for bilateral compared with unilateral stimulation (main effect: $F_{1,26} = 21.6$, $P < 0.001$, $\eta^2_p = 0.45$, $OP > 0.99$), and this effect was greater when hands were in the near compared with the far position (interaction: $F_{1,26} = 4.6$, $P = 0.041$, $\eta^2_p = 0.15$, $OP = 0.54$). However, the effect was not significantly modulated by spatial attention (interaction: $F_{1,26} = 1.5$, $P = 0.2$, $\eta^2_p = 0.06$, $OP = 0.22$) or by the interaction of spatial attention and the position of hands (interaction: $F_{1,26} = 2.0$, $P = 0.2$, $\eta^2_p = 0.07$, $OP = 0.28$).

In spite of these group effects, 30 % of participants (8/27) showed a decrease or no change in N2 and P2 amplitude for bilateral compared with unilateral stimulation.

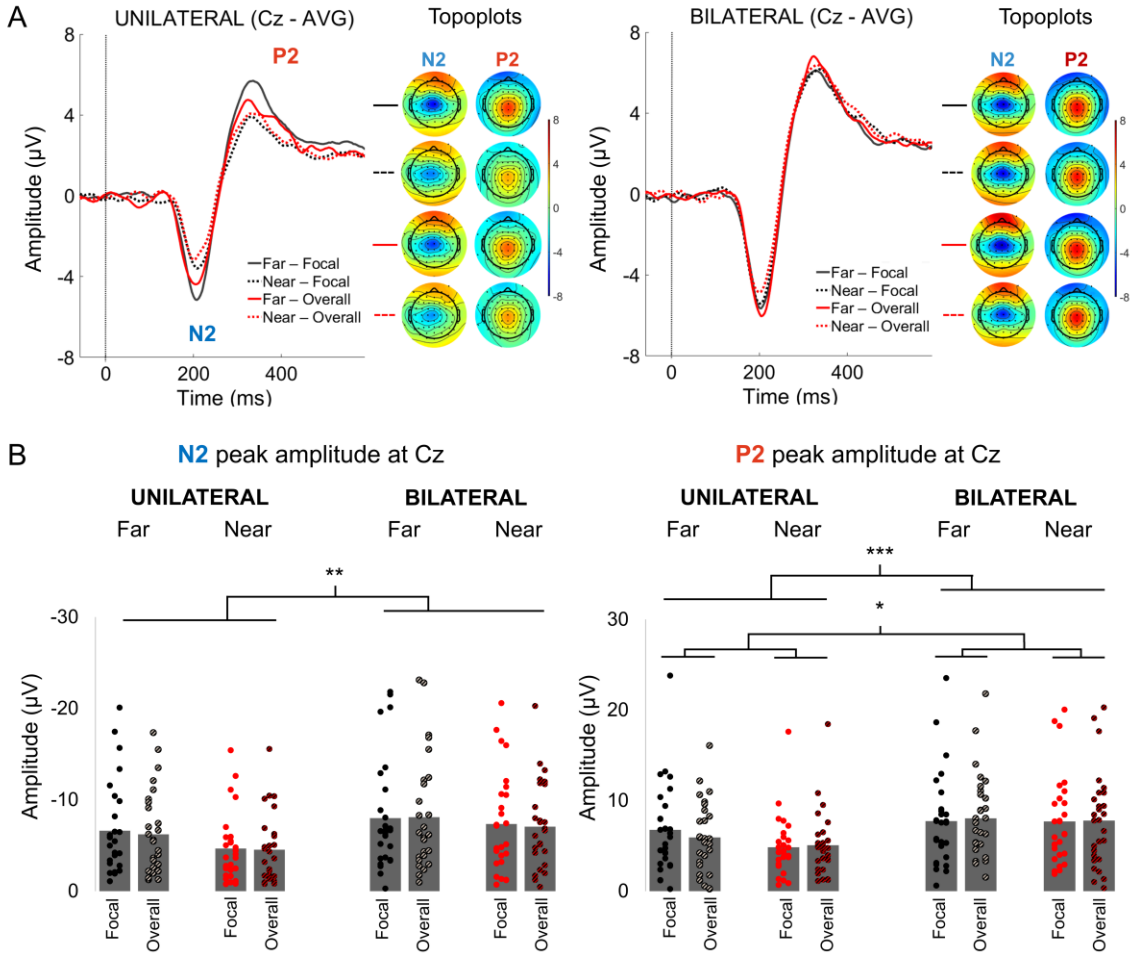

Figure 6.3 Vertex-evoked potentials

A: Time course of the laser-evoked potentials at Cz for unilateral stimulation (left) and bilateral stimulation (right) in each condition. Overall rating conditions are depicted in red and focal rating conditions in black. The hands far conditions are depicted as full lines and the hands near conditions as dotted lines. Scalp

topoplots at the N2 and P2 peak values are shown on the right of the laser-evoked potentials. B: Mean N2 peak amplitude (left) and mean P2 peak amplitude (right) for unilateral and bilateral stimulation in each condition (right). The N2 peak amplitude was greater for bilateral compared with unilateral stimulation ($P = 0.0015$), but this effect was not significantly modulated by spatial attention ($P = 0.7$), the position of hands ($P = 0.3$) or the interaction of both factors ($P = 0.6$). The P2 peak amplitude was greater for bilateral compared with unilateral stimulation ($P < 0.001$), and this effect was greater when hands were in the near compared with the far position ($P = 0.041$). However, the effect was not significantly modulated by spatial attention ($P = 0.2$) or by the interaction of spatial attention and the position of hands ($P = 0.2$). The dots represent individual data (n=27). *, **, ***: $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively.

3.3 Lateralized laser-evoked potentials

The lateralized N1 component could be observed at temporo-parietal electrodes after re-referencing the signal to Fz, with the expected scalp distribution and latency (178.2 ± 18.4 ms) (see Figure 4 and Table 1). For the right-hand unilateral stimulation, the N1 was maximal at the temporal electrode contralateral to the stimulation (T7, left). For bilateral stimulation, responses were maximal at both temporal electrodes (T7 and T8, left and right, respectively). The N1 amplitude at T7 was not significantly different between unilateral and bilateral stimulation (main effect: $F_{1,26} = 1.6$, $P = 0.21$, $\eta^2_p = 0.06$, $OP = 0.23$), but it was a greater in the bilateral compared with unilateral stimulation when the hands were in the far compared with the near position (interaction: $F_{1,26} = 7.4$, $P = 0.01$, $\eta^2_p = 0.22$, $OP = 0.75$). However, this effect, was not significantly modulated by spatial attention (interaction: $F_{1,26} = 1.0$, $P = 0.33$, $\eta^2_p = 0.04$, $OP = 0.05$). Also, spatial attention did not produce a significant difference in N1 amplitude at T7 between unilateral and bilateral stimulation (interaction: $F_{1,26} = 0.01$, $P = 0.97$, $\eta^2_p < 0.001$, $OP = 0.15$).

Since pain perception and brain responses to noxious stimuli may be influenced by sex, an ANCOVA was conducted with sex as a covariate for pain ratings, the N1, N2, and P2. No main effect of *Sex* and no significant interaction was observed for any variables (all $P > 0.13$).

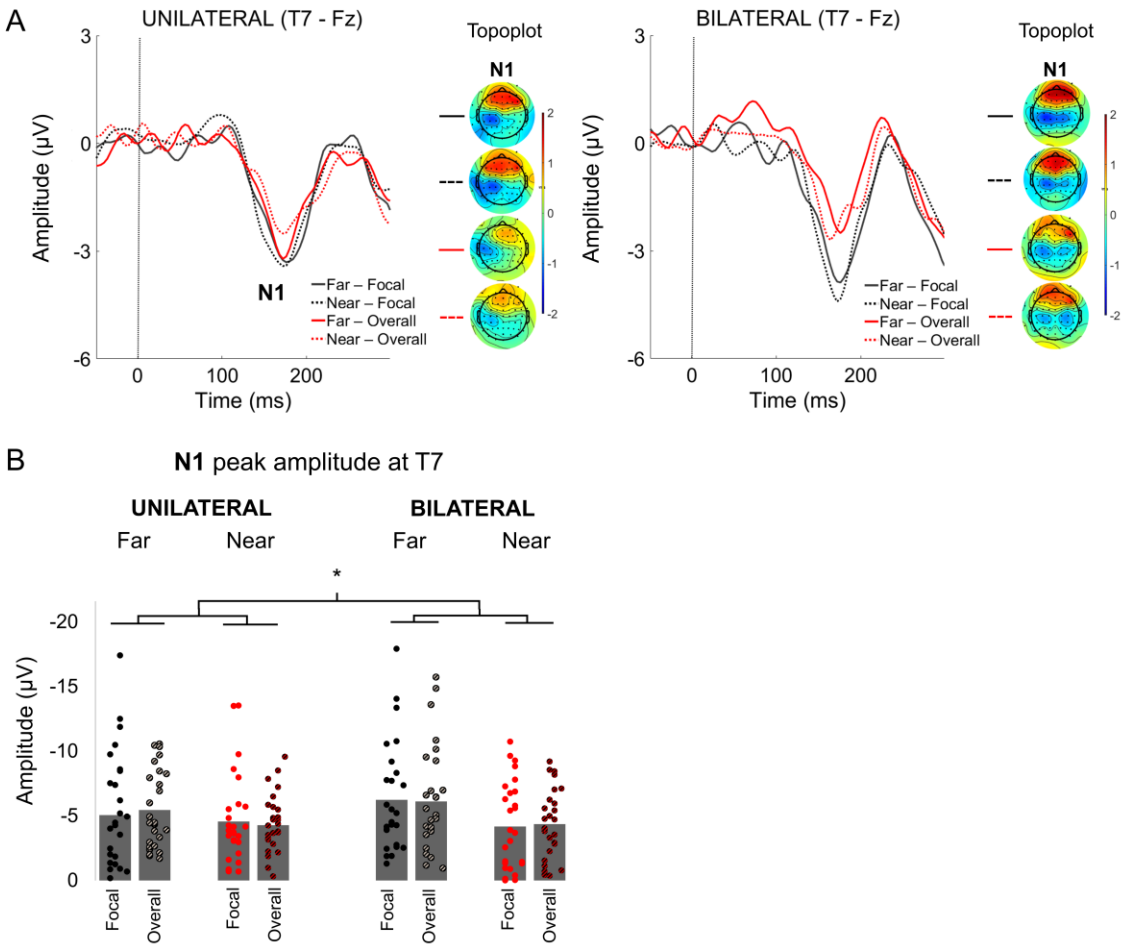

Figure 6.4 Lateralized event-related potentials.

A: Time course of the lateralized evoked potential at T7 for unilateral stimulation (left) and bilateral stimulation (right). Overall rating conditions are depicted in red and focal rating conditions in black. The hands far conditions are depicted as full lines and the hands near conditions as dotted lines. Scalp topoplots at the N1 peak values are shown on the right of the evoked potentials. B: Mean N1 peak amplitude for unilateral and bilateral stimulation in each condition. The N1 peak amplitude was not significantly different between unilateral and bilateral stimulation ($P = 0.21$), but it was a greater for the bilateral compared with unilateral stimulation when the hands were in the far compared with the near position ($P = 0.01$). However, this effect, was not significantly modulated by spatial attention ($P = 0.33$). Also, spatial attention did not produce a significant difference in N1 peak amplitude between unilateral and bilateral stimulation ($P = 0.97$). The dots represent individual data (n=27). *: $P < 0.05$

4. Discussion

In the present study, we examined the effects of spatial attention and limb position on pain and the interaction of bilateral noxious inputs in the brain. The results generally replicate previous findings and indicate that the cortical interaction of bilateral noxious inputs results in an increase of some LEPs. The novel findings of the present study are that these effects were not modulated by spatial attention but were partially and differentially modulated by limb position, where the N1 and P2 showed increased amplitude with bilateral stimulation when hands were far (N1), or near (P2). In addition, increased pain during bilateral compared with unilateral stimulation was greater when hands were near or when pain intensity was reported overall for both hands. Altogether, these results show that limb position and spatial attention differentially modulate brain responses and pain perception during bilateral noxious stimulation of the hands.

4.1 Increased pain-related brain responses for bilateral stimulation

The EEG results show that the N2 and P2 were increased for bilateral compared with unilateral stimulation. In previous studies, more variability was observed for LEPs compared to SEPs evoked by electrical stimulation (Northon et al., 2021b; Northon et al., 2019). For example, some participants showed a decrease in LEP amplitude for bilateral compared with unilateral stimulation, while all participants showed an increase in SEP amplitude evoked by electrical stimulation. Consistent with these findings, several participants of the present study (30 %) showed decreased N2 and P2 amplitude or no change, for bilateral compared with unilateral stimulation, although the group effect showed significantly increased N2 and P2 amplitude. Notwithstanding, the most common effect of bilateral compared with unilateral noxious stimulation (electrical or laser) on event-related potentials is an increase of the N2 and P2 (laser) as well as the N100 (electrical), but not the P260 (electrical) (Northon et al., 2021b; Northon et al., 2021c; Northon et al., 2019; Rustamov et al., 2019). Considering the view that event-related potentials are not specific to pain but mostly reflect a multimodal salience detection system (Iannetti et al., 2008), the results suggest that the integration of bilateral noxious inputs may serve to generate a representation of a more salient physical threat. However,

it should be noted that the N1 was not modulated, so the effect is more than a non-specific increase of brain activity.

The N1 was not significantly increased for bilateral compared with unilateral stimulation. This response occurs at an earlier latency and is partly generated by the somatosensory and insular cortex (Garcia-Larrea et al., 2003; Valeriani et al., 1996). Thus, this suggests that at early stages of cortical nociceptive processing, the interaction of noxious inputs is limited.

4.2 Effects of spatial attention on the interaction of bilateral noxious inputs

The increase in pain-related EEG responses for bilateral compared with unilateral stimulation was not modulated by spatial attention. In previous studies, it was shown that spatial attention can modulate pain-related brain responses, especially when the features of the concurrent stimulus are distinct from the attended stimulus (Torta et al., 2017; Van Ryckeghem et al., 2013). In contrast, it was shown that attending and rating the right or left noxious stimulus during bilateral stimulation does not modulate pain-related brain responses (Blöchl et al., 2015; Northon et al., 2019; Rustamov et al., 2019). In the present study, instructions for pain ratings were adapted from previous studies on the spatial integration of pain (Lautenbacher et al., 2007; Nielsen & Arendt-Nielsen, 1997a; Quevedo & Coghill, 2007, 2009). In these studies, participants reported one overall rating for the two noxious stimuli to integrate spatial information across large body areas, even within the same dermatome on both sides of the body (Nielsen & Arendt-Nielsen, 1997a). In the present study, the lack of effect of spatial attention on the increase of pain-related EEG responses for bilateral compared with unilateral stimulation may reflect an involuntary capture of attention by the concurrent stimulus, consistent with the representation of a more salient physical threat, as mentioned above. In other sensory modalities, including the visual system, it is only beneficial to integrate the information from two concurrent stimuli when both signals are very weak (around the detection threshold) and the signal-to-noise ratio is low (Baker et al., 2020). In the case of noxious stimuli used in the present study, they are salient and clearly above threshold, so it is possible that no further effect of could be observed by manipulating spatial attention. This could be tested in future studies by manipulating stimulus saliency. For example, the

saliency of nociceptive stimuli tends to decline with repetition and predictability (Iannetti et al., 2008; Ronga et al., 2013; Valentini et al., 2011). Thus, integration could be examined after one or both of the concurrent stimuli are applied repeatedly with intervals long enough to avoid temporal summation and short enough to produce a decline in saliency.

By manipulating spatial attention, pain additivity was expected, as in previous studies (Nielsen & Arendt-Nielsen, 1997b; Quevedo & Coghill, 2007). Accordingly, the present results show that bilateral stimulation increased pain compared with unilateral stimulation, but only with overall and not focal pain rating. This is consistent with previous studies in which no difference was observed in pain perception between unilateral and bilateral stimulation applied on the hands with focal pain rating (Northon et al., 2021b; Northon et al., 2019). Moreover, previous studies have shown that multiple tonic painful stimuli, or one tonic and one phasic stimulus, can increase pain intensity when an overall pain rating is reported for the two stimuli, compared with a pain rating of one of the two stimuli (Lautenbacher et al., 2007; Quevedo & Coghill, 2007). Such attentional tasks were suggested to require integration of pain-related information across large body regions, and this spatial summation has been shown even in dermatomes covering the two sides of the body (Nielsen & Arendt-Nielsen, 1997b). The present study extends these findings and show that additive effects occurs for bilateral phasic stimuli applied on homotopic areas.

4.3 Effects of limb position on the interaction of bilateral noxious inputs

Limb position is known to affect the processing of somatosensory stimuli (Eimer et al., 2004; Soto-Faraco et al., 2004) and noxious stimuli (Moayedi et al., 2016). The N2 was shown to be sensitive to large displacements in egocentric coordinates, but only when such a displacement was behaviorally relevant in terms of potential threat (Moayedi et al., 2016). Importantly, the sensitivity of the N2 to large displacements (100 cm) was observed only when the last stimulus of a triplet was displaced from the foot to the hand, and not the opposite. In the present study, increased N2 amplitude for bilateral compared with unilateral stimuli was not modulated by limb position. One possibility is that the

hand already represents a behaviorally relevant location and that this response is not modulated by another hand stimulus. Accordingly, another study found that the N2 was not sensitive to displacements when the last stimulus of a triplet is instead displaced from one hand to the other hand (Torta et al., 2012). Therefore, the effects of limb position on the integration of bilateral noxious stimuli may depend on the stimulated body region.

However, the N1 and P2 showed increased amplitude with bilateral compared with unilateral stimulation when hands were far (N1) or near (P2). The N1 is generated by the somatosensory and insular cortex and the P2 is generated by the anterior cingulate cortex (ACC) (Garcia-Larrea et al., 2003; Valeriani et al., 1996). These differential effects on the N1, N2 and P2 suggest that limb position selectively and differentially modulates distinct processes involved in the integration of noxious inputs. Most relevant to the present study, the generator of the P2 is located in an ACC region involved in motor control of the hand (Garcia-Larrea et al., 2003). Thus, limb position may enhance the integration to noxious inputs to allow the preparation and generation of a defensive response adapted to a more complex source of pain. For example, heat pain produced by a hot object held with both hands involves a more complex response than simple withdrawal; withdrawal occurs to prevent tissues damage, but the response is regulated (delayed) to avoid dropping the object. This warrants futures studies in which relevant and irrelevant motor responses are produced in relation to the noxious stimulus. Regarding the effect on the N1, it indicates that the integration of bilateral noxious stimuli occurs even at early stages of cortical processing. Moreover, the effect of limb position is opposite to that on the P2 so again, this suggests that integration of noxious inputs is reflected differentially on distinct processes. We propose that this allows the generation of coordinated, flexible and adapted defensive responses to threat. Conceptually, current approach/avoidance theories of personality describe defensive responses to threat to vary depending on the direction of the response, i.e., the engagement in escape behavior (fear-related avoidance of threat) or passively avoiding threat (anxiety-related cautious approach to threat)(Corr, 2008; Corr & McNaughton, 2012). These behaviors are related to personality traits and measures of fear and anxiety (Perkins & Corr, 2006). Future studies specifically designed to address this questions

could examine whether flexible and adapted defensive responses to pain are influenced by such personality traits.

In addition to these effects, limb position modulated pain perception. The results show that bilateral stimulation leads to a greater increase in pain perception when the hands are in the near compared with the far position, consistent with the effect on the P2 and previous studies (Lautenbacher et al., 2007; Quevedo & Coghill, 2007). The results may also explain why bilateral noxious stimuli increased pain when applied on both feet (close from each other), but not on both hands (70 cm apart) or on a foot and a hand (Northon et al., 2021b; Northon et al., 2021c; Northon et al., 2019; Rustamov et al., 2019). Although this should be examined in future studies, it could be speculated that this effect is related to perceptual fusion and to the overlap in the limb-centered peripersonal space of each limb (Legrain & Torta, 2015).

4.4 Interaction between spatial attention and limb position

The similarities between somatosensory and nociceptive stimuli on brain-evoked potentials (Mouraux et al., 2011), and the supramodal mechanisms related to stimulus-driven attention (Lakatos et al., 2009; Spagna et al., 2020) and proprioception (Maravita et al., 2003) suggest that spatial attention and limb position may have a synergistic effect on the interaction of bilateral noxious inputs. However, the present results indicate that the interaction of bilateral noxious inputs reflected in LEPs was not modulated by limb position as a function of spatial attention. Moreover, although limb position and spatial attention modulated the effect of bilateral stimulation on pain, they did not produce additive effects on pain, in contrast to our hypothesis. This may be due to a ceiling effect, where pain additivity can occur up to a certain level. However, this seems unlikely because the pain intensity was mild (between 8.5 and 13.3 on 100), even with bilateral stimulation. Thus, the effect may be too small to be detected when pain intensity is mild. It should be noted that the limited sample size may also preclude from finding small effects. However, the relevance of these small effects is not necessarily meaningful from a physiological point of view.

4.5 Conclusion

In summary, the novel findings of the present study are that the interaction of bilateral noxious inputs in the brain was not modulated by spatial attention, but was partially and differentially modulated by limb position, where the N1 and P2 amplitude increased with bilateral stimulation when hands were far (N1) or near (P2), while the N2 was not modulated. In addition, increased pain during bilateral compared with unilateral stimulation was greater when hands were near or when pain intensity was reported overall for both hands. Altogether, these results show that the integration of bilateral noxious inputs occurs through partially independent pain-related processes, that it is modulated by limb position, and that it is partially independent of pain perception. We propose that this is necessary to produce coordinated, flexible and adapted defensive responses.

5. References

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Chapitre 7 Discussion générale

Retour sur l'objectif de la thèse et résultats principaux

Cette thèse inclut quatre études visant à mieux comprendre les mécanismes d'intégration cérébrale de l'information nociceptive bilatérale décrits initialement dans une étude de notre laboratoire à laquelle j'ai collaboré (Rustamov et al., 2019). Plus spécifiquement, nous avons investigué comment l'intégration de l'information nociceptive est affectée par 1) la latéralisation hémisphérique présumée distincte entre les droitiers et les gauchers 2) la modalité utilisée pour induire la douleur, 3) l'attention spatiale, et 4) la proximité des régions corporelles stimulées. Cette section présente tout d'abord un bref rappel des résultats suivi d'une synthèse des résultats des quatre études en regard de la littérature actuelle. Finalement, la dernière section présente des limites aux travaux actuels et des perspectives de recherche futures afin de contourner ces limites.

Dans la première étude, nous avons investigué si l'intégration de l'information nociceptive bilatérale est affectée par la latéralisation hémisphérique présumée distincte entre les gauchers et les droitiers, sur la base de telles différences observées dans d'autres modalités sensorielles. Les résultats principaux ont démontré une augmentation des ERP au vertex (la N100) et des oscillations gamma pour les stimuli bilatéraux comparativement aux stimuli unilatéraux. Pour la douleur, une augmentation a été observée pour les stimuli bilatéraux aux chevilles (homosegmentaires) et non pour la cheville droite et la main gauche (hétérosegmentaire). Ces résultats concordent avec nos résultats antérieurs (Rustamov et al., 2019). Toutefois, aucune différence ne fut observée entre les gauchers et les droitiers.

Dans cette étude et une de nos études précédentes (Rustamov et al., 2019), nous avons utilisé des stimuli électriques douloureux, qui évoquent le réflexe nociceptif de flexion, mais qui activent les nocicepteurs de façon non sélective, ce qui complexifie légèrement l'interprétation des résultats. Dans la deuxième étude de la présente thèse,

afin de contourner cette limite, nous avons investigué l'intégration de l'information bilatérale nociceptive en utilisant des stimuli lasers, qui activent les nocicepteurs plus sélectivement. Les stimuli laser furent présentés sur les mains afin de comparer les réponses avec la littérature sur le laser, qui s'est majoritairement intéressée aux membres supérieurs. Contrairement aux résultats obtenus avec les stimuli électriques, nous avons observé une réduction des ERP au vertex (la N2 et la P2) et des oscillations gamma, sans effet sur la perception de la douleur.

Cette divergence dans l'intégration de l'information nociceptive bilatérale provenant de stimuli électriques et lasers (augmentation vs diminution) était présumée de provenir des différences méthodologiques, notamment la modalité utilisée (laser vs électrique), le site d'application des stimuli (chevilles vs mains) et la variabilité interindividuelle plus grande pour les stimuli lasers qu'électriques. La troisième étude a donc été conçue pour examiner l'effet de la modalité utilisée pour induire la douleur sur l'intégration cérébrale de l'information nociceptive bilatérale, et ce, chez un même groupe de participants. De plus, une limite de nos études précédentes (Northon et al., 2021c; Northon et al., 2019; Rustamov et al., 2019) était l'utilisation de blocs de stimuli séparés pour les conditions unilatérale et bilatérale, ce qui a rendu l'occurrence du type de stimulus prévisible. Ainsi, dans la première expérience de cette troisième étude, les stimuli unilatéraux et bilatéraux étaient présentés aléatoirement dans un même bloc de stimuli. Les résultats ont démontré qu'autant les stimuli lasers qu'électriques bilatéraux augmentent les ERP au vertex (la N100, la N2 et la P2) et les oscillations gamma, comparés aux stimuli unilatéraux. De plus, les stimulations électriques bilatérales ont augmenté les ERP qu'ils soient douloureux (120% du seuil de douleur) ou non (70% du seuil de douleur). Seules les stimulations non douloureuses bilatérales ont par ailleurs augmenté la perception du stimulus. Pour mieux comprendre la divergence des résultats et assurer leur reproductibilité, une seconde expérience a repris la méthodologie de la deuxième étude tout en ajoutant des blocs de stimuli avec la modalité électrique douloureuse. Cette expérience a permis de confirmer que l'effet le plus reproductible lors d'une stimulation laser ou électrique bilatérale comparée à une stimulation unilatérale est une augmentation de l'amplitude des réponses cérébrales au vertex (la N100, la N2 et la P2), sans effet sur la perception de la douleur.

Ainsi, les stimulations électriques bilatérales, comparativement aux stimulations unilatérales, ont augmenté l'amplitude des réponses cérébrales. Cela fut observé lorsque les stimulations étaient prévisibles ou non, sur les chevilles ou sur les mains, et lorsqu'elles étaient douloureuses ou non douloureuses. Cependant, la douleur n'a augmenté que lorsque les stimulations étaient présentées aux deux chevilles. Cela pourrait s'expliquer en partie par la plus grande proximité entre les pieds par rapport aux mains autant dans l'espace (spatiotopique) que dans le cerveau (somatotopique). De plus, dans toutes nos études précédentes, l'attention spatiale était dirigée sur une seule région du corps. Or, l'attention spatiale globale affecte le traitement de l'information somatosensorielle bilatérale (Kuroki et al., 2017), et la perception pour des stimuli douloureux appliqués à différents endroits du corps (Lautenbacher et al., 2007; Nielsen & Arendt-Nielsen, 1997a). Dans la quatrième étude, nous avons donc investigué le rôle de la distance spatiale (mains proches ou éloignées) et de l'attention spatiale (attention focale ou globale) dans l'intégration d'information nociceptive bilatérale. Les résultats ont démontré qu'une stimulation laser bilatérale comparée à une stimulation unilatérale augmente la N2 et la P2 des ERP au vertex. L'augmentation de la P2 fut modulée par la proximité des mains alors que la perception de la douleur augmenta pour les stimuli bilatéraux, mais seulement lorsque les mains étaient proches, ou que l'attention spatiale était globale.

Synthèse des résultats sur l'intégration d'information nociceptive bilatérale

Ensemble, les résultats de ces quatre études suggèrent que les informations nociceptives bilatérales sont intégrées au niveau du système nerveux central.

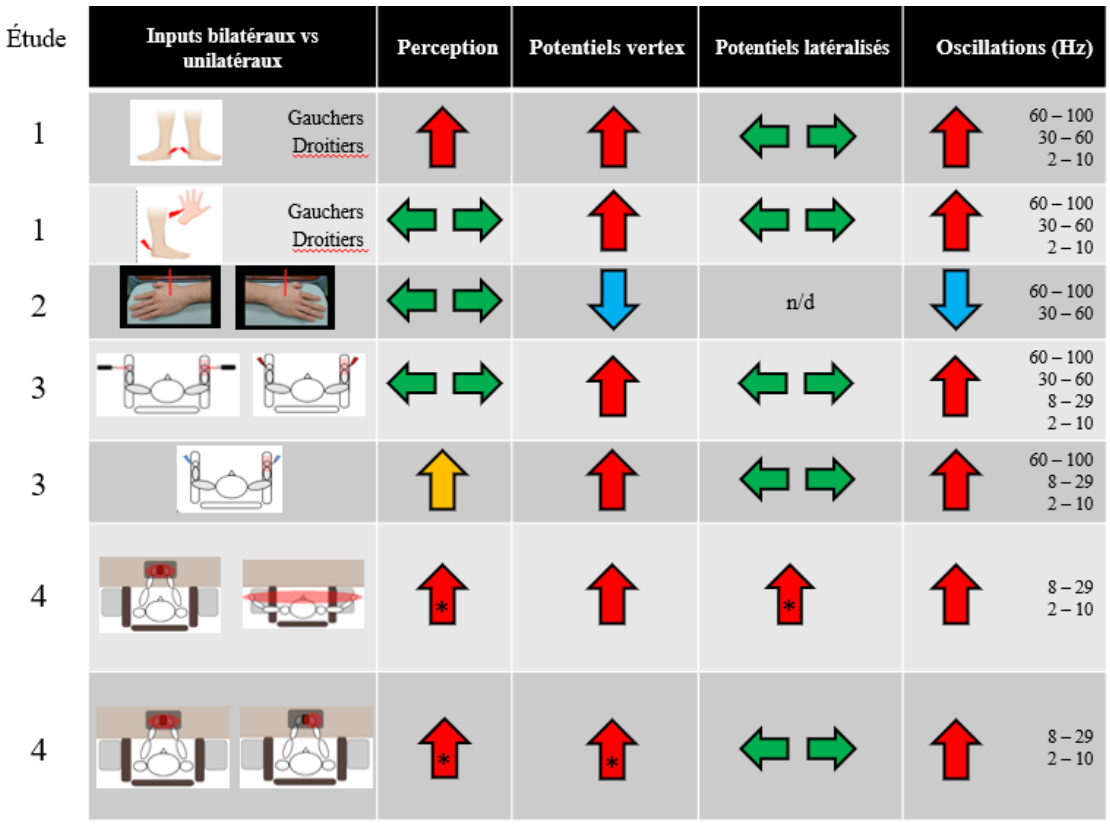

Figure 7.1 Tableau récapitulatif des résultats

Il est intéressant de noter que dans les études 2 et 3, la douleur est demeurée inchangée entre les stimuli laser unilatéraux et bilatéraux tandis que les ERP au vertex ont été modulés. Une telle dissociation entre la douleur et les ERP a déjà été démontrée dans des études antérieures. Un exemple éloquent d'un tel phénomène est le paradigme utilisant trois stimuli lasers (des triplets) très rapprochés dans le temps (Iannetti et al., 2008; Moayedi et al., 2016; Ronga et al., 2013; Torta et al., 2012; Valentini et al., 2011; Zhang et al., 2012). Plus précisément, dans ces études les triplets étaient séparés d'une pause de 20 secondes, alors que l'intervalle inter-stimulus à l'intérieur d'un même triplet était fixé à 1 seconde. Ainsi, l'occurrence temporelle du 1er stimulus était peu prévisible et plus saillante comparativement aux 2^{e} et 3^{e} stimuli. Les effets observés avec ce paradigme démontrent que la douleur demeure stable pour les trois stimuli, mais que les ERP (la N1, et surtout la N2 et P2 au vertex) sont fortement réduits entre le 1er et 2^{e} stimulus sans baisse supplémentaire pour le 3^{e}. Cette série d'études utilisant les triplets démontre que les ERP associés aux stimuli nociceptifs ne reflètent pas directement

l'intensité de la douleur. De plus, les ERP au vertex sont observés dans d'autres modalités que la nociception et tendent à être sensibles à des paramètres similaires (p. ex., la prévisibilité, la saillance, la nouveauté et l'intensité d'un stimulus). Cela a mené à la proposition par certains auteurs que ces ERP au vertex représentent plutôt un système multimodal relié à la détection d'évènements saillants d'intérêt pour la survie de l'organisme, qu'ils soient auditifs, visuels, somatosensoriels ou nociceptifs (Legrain et al., 2011; Mouraux & Iannetti, 2009), tel que résumé dans l'article de Su et al. (Su et al., 2019). En comparant ces modalités, il fut démontré que des stimuli de modalités différentes maintiennent une spécificité propre à la modalité lors du traitement précoce dans les aires sensorielles primaires (p. ex., la N1 des ERP laser ou la P45 des ERP électriques). Cependant, cette spécificité donne lieu à un traitement de plus en plus multimodal lors du décours temporel du traitement de l'information sensorielle (Young et al., 2004). Ainsi, la N2 et la N100 retiennent une certaine spécificité somatosensorielle, alors que la P2 et la P260 ont des similitudes frappantes avec les potentiels positifs tardifs évoqués par des stimuli visuels et auditifs.

Puisque le résultat principal de la thèse est une augmentation des ERP au vertex lors de stimulations bilatérales, une des interprétations possibles est que l'information nociceptive est intégrée en une représentation unique, davantage saillante, et représentant une menace potentiellement plus grande pour l'organisme (Corbetta & Shulman, 2002; Legrain et al., 2011; Legrain et al., 2009b; Menon & Uddin, 2010). D'ailleurs, le cœur du réseau neuronal de la saillance (« *salience network* ») est généralement considéré comme étant situé dans le cortex de l'insula. Ce système de saillance, en conjonction avec l'operculum pariétal et le cortex cingulaire antérieur (Corbetta & Shulman, 2002), est associé à la capture exogène de l'attention (mécanisme ascendant et automatique lié à l'environnement) portée aux stimuli saillants et à leur localisation dans l'espace. Cette interprétation d'intégration en une représentation unique et plus saillante semble plausible d'un point de vue neurophysiologique puisque l'insula et l'operculum pariétal sont deux des principaux générateurs de la N2 (Frot et al., 2007; Garcia-Larrea et al., 2003; Liberati et al., 2016; Liberati et al., 2020) et possiblement de la N100 (Dowman et al., 2007; Howland et al., 1995; Thees et al., 2003; Van der Lubbe et al., 2012), tandis que la P2 est

générée en grande partie par le cortex cingulaire antérieur (ACC) et l'aire motrice supplémentaire (SMA). Dans le contexte de la douleur, l'ACC est notamment impliqué dans l'orientation de l'attention vers l'endroit stimulé (Dowman, 2004b; Garcia-Larrea et al., 2003) et la préparation d'un mouvement en réponse à l'urgence de réagir (Bancaud et al., 1976). Cette préparation et élaboration de mouvement est possible notamment grâce à la présence de neurones corticospinaux dans la région cingulomotrice qui font synapses avec des motoneurones dans la corne ventrale de la moelle épinière (Paus, 2001). Cela est en accord avec une interprétation d'une intégration des deux stimuli en une représentation plus saillante et qui nécessite une réponse motrice unique. La modulation de l'augmentation de la P2 par la proximité des régions stimulées (étude 4) est également compatible avec une telle interprétation considérant que ces deux positions requièrent une réponse motrice de défense différente. L'absence de modulation des ERP par l'attention globale (étude 4) ou focale (étude 2 et expérience 2 de l'étude 3) suggère à son tour une intégration de bas niveau, possiblement reliée à une plus grande capture attentionnelle involontaire et automatique (Legrain et al., 2009a; Legrain et al., 2002; Legrain et al., 2011; Legrain et al., 2009b).

La composante positive P260 suivant les stimuli électriques ne fut pas modulée par les stimuli bilatéraux ni dans notre étude antérieure (Rustamov et al., 2019) ni dans les travaux de la présente thèse (étude 1 et 3), tandis que la P2 des ERP laser fut modulée (études 2, 3 et 4). Pourtant, les ERP produits par des stimuli laser et électriques douloureux ont une grande ressemblance en termes de distribution topographique et d'estimation des sources corticales générant la P2 et la P260, soit le cortex cingulaire antérieur (ACC) principalement (Dowman, 2004c; Kitamura et al., 1995; Thees et al., 2003; Van der Lubbe et al., 2012). Ceci étant dit, l'activation des fibres Aβ avec les stimuli électriques complexifie l'interprétation des résultats. Par exemple, une étude a utilisé des stimuli tactiles (recrutant des fibres Aβ sélectivement) dont l'intensité était calibrée afin que les stimuli soient perçus une fois sur deux. Comparativement aux stimuli non perçus, les stimuli perçus étaient associés à une augmentation importante de l'activité dans l'aire motrice supplémentaire, le cortex prémoteur et possiblement le

cortex cingulaire à des latences similaires à la P260 (Auksztulewicz & Blankenburg, 2013). Il reste à clarifier si une telle augmentation persisterait lorsque les stimuli sont largement au-dessus du seuil de perception. Cette composante semble sensible à l'augmentation de l'intensité de stimuli électriques non douloureux, mais une partie de la réponse sature en grande partie avant le seuil de douleur (Dowman, 1994b). Dans les études de la présente thèse, l'intensité des stimuli électriques douloureux est présumée saturer la réponse des fibres Aβ, et la réponse associée aux fibres Aβ pourrait masquer une modulation des réponses par les fibres nociceptives. En effet, dans l'étude 3 de la présente thèse, la P260 était d'amplitude comparable entre les stimuli douloureux (120% du seuil de douleur) et non douloureux (70% du seuil). De telles intensités (120% et 70%) furent choisies afin de pouvoir comparer deux conditions clairement perceptibles et saillantes tout en pouvant explorer la spécificité des résultats à la perception douloureuse. Il est cependant important de noter que les stimuli à 70% du seuil de douleur peuvent potentiellement recruter une faible portion de la population des fibres Aδ sans être toutefois douloureux (Garcia-Larrea, 2006). Cela pourrait donc contribuer à la similitude observée pour la P260 entre les deux conditions. Or, davantage de fibres Aβ sont recrutées dans la condition douloureuse que de fibres Aδ dans la condition non douloureuse.

Une étude a démontré que l'amplitude de la P260 augmente pour les stimuli ignorés, proposant que cette composante reflète un *appel à l'attention* (Van der Lubbe et al., 2012). Cette étude a eu recours à des stimuli électriques intra-cutanés permettant l'activation sélective de nocicepteurs à l'instar des lasers. Cependant, ces stimuli sont rarement douloureux, et à des intensités induisant de la douleur, recrutent également des fibres non nociceptives (de Tommaso et al., 2011; Hagiwara et al., 2017; Mouraux et al., 2013; Mouraux et al., 2010). Des travaux récents ont néanmoins démontré qu'il est possible de produire de la douleur à des intensités ne recrutant pas des fibres non nociceptives, en répétant le stimulus à cinq reprises afin de produire une sommation temporelle (van der Heide et al., 2009). Ainsi, dans nos travaux, il est possible que l'intensité utilisée pour les stimuli électriques ait mené à un effet plafond pour les mécanismes reliés notamment à l'urgence à réagir ou l'appel à l'attention. Cela pourrait

être clarifié en comparant des stimuli unilatéraux et bilatéraux à des intensités variables (p. ex. allant de tout juste perceptible à douloureux). À cet effet, il est bien documenté que l'intégration sensorielle est plus robuste lorsque les stimuli individuels sont peu saillants, de faibles intensités, et difficiles à détecter (voir même subliminaux) – le principe d'efficacité inverse (Stein & Meredith, 1993). De plus, les stimuli de différentes intensités pourraient être présentés aléatoirement dans un même bloc de stimuli afin de rendre moins prévisible leur intensité. En effet, si nos travaux de l'étude 3 ont contrôlé pour la prévisibilité de la principale variable d'intérêt (unilatéral vs bilatéral), l'intensité des stimuli (douloureux et non douloureux) était connue d'avance. Spéculativement, cela pourrait avoir affecté notamment la préparation de réponses de défense.

La perception douloureuse évoquée par des stimuli bilatéraux a augmenté pour les stimuli homosegmentaires aux membres inférieurs et, lorsque les mains sont rapprochées ou que l'attention spatiale est globale, pour les membres supérieurs. Une interprétation alternative est que l'attention focale peut au moins partiellement abolir la sommation spatiale de la douleur lorsque la distance entre les deux régions corporelles est suffisamment grande. En effet, comparativement à l'attention globale, l'attention focale réduit grandement la sommation spatiale de la douleur lorsque deux stimuli toniques et non spécifiques aux nocicepteurs sont présentés sur la même région corporelle (Quevedo & Coghill, 2007). Nos travaux suggèrent qu'une telle capacité est présente pour des stimuli phasiques et spécifiques aux nocicepteurs présentés bilatéralement sur des segments homosegmentaires. Cependant, la nature des stimuli utilisés entre les deux études (tonique et non spécifique aux nocicepteurs vs phasique et spécifique) rend la comparaison directe difficile. S'agit-t-il d'un mécanisme généralisable? Pour mieux comprendre l'interaction entre l'attention spatiale et la sommation spatiale de la douleur, il serait important d'investiguer la modulation des réponses provenant de deux stimuli laser présentés soit sur une seule région corporelle (p. ex. la main droite) ou sur les deux régions homosegmentaires.

Plusieurs hypothèses ont été soulevées pour expliquer la différence de perception entre les informations nociceptives bilatérales aux pieds et aux mains. Par exemple, des différences notables entre les membres supérieurs et inférieurs ont été observées au niveau de la performance proprioceptive (Han et al., 2013a; Han et al., 2013b), de la préparation motrice et du temps de réaction (Kato & Asami, 1998; Kato et al., 2005), et la capacité à rapporter quelle région fut stimulée en premier lorsque deux stimuli homosegmentaires successifs (main – main ou pied – pied) sont présentés avec un court délais (Schicke & Röder, 2006). De plus, l'espace péripersonnel, un espace centré autour d'un segment et permettant de préparer une réponse motrice de défense face à une menace potentielle (de Vignemont & Iannetti, 2015), est beaucoup plus petit au niveau des membres supérieurs (~30 cm) (Serino, 2019; Serino et al., 2015) que des membres inférieurs (~70 cm) (Stone et al., 2018). Ainsi, en position anatomique normale, il y aurait peu de fusion entre les deux membres supérieurs et, au contraire, une fusion importante pour les membres inférieurs. Cela pourrait suggérer une plus grande capacité du système nerveux central à « séparer » via l'attention focale les stimuli nociceptifs présentés aux membres supérieurs comparativement aux membres inférieurs; nos résultats suggéreraient ainsi que cette capacité accrue s'estompe en position rapprochée. Il serait important de tester cette hypothèse directement afin de mieux comprendre la relation entre l'attention spatiale et la proximité des régions corporelles. Par exemple, une expérience pourrait comparer l'effet de l'attention spatiale et de la proximité des régions corporelles entre les membres inférieurs et supérieurs dans une même étude.

Limites actuelles et perspectives futures

Ces travaux présentent l'effet de stimuli douloureux bilatéraux calibrés de telle façon à être perçus de façon comparable de chaque côté. Cela facilite l'interprétation des résultats en réduisant la possibilité qu'un des deux stimuli capte davantage l'attention par vertu de son intensité et de sa saillance accrues. Or, selon l'hypothèse des ensembles attentionnels (« *attentional set hypothesis* »), le contrôle attentionnel sera affecté différemment selon que les caractéristiques des deux stimuli douloureux sont distinctes ou non (Legrain et al., 2009a; Van Ryckeghem et al., 2013). Plus les stimuli sont similaires (p. ex. en termes d'intensité ou de modalité), plus la capture attentionnelle involontaire par le stimulus ignoré est grande. En ce sens, cela pourrait expliquer l'absence d'effet de l'attention sur les réponses électrophysiologiques dans les études de la présente thèse en favorisant une capture attentionnelle automatique. Pour valider notre interprétation d'une intégration reliée à une plus grande capture attentionnelle involontaire et automatique, deux expériences étaient prévues dans le cadre de cette thèse, mais le contexte pandémique n'a pas permis la réalisation de cette étude. En bref, ces expériences visaient à examiner l'intégration cérébrale nociceptive en modulant l'intensité des stimuli ou leur saillance.

Dans la première expérience, il était prévu de reprendre le paradigme des études 3 et 4 en utilisant des stimuli présentés aléatoirement sur la main droite et sur les deux mains à l'intérieur d'un même bloc de stimuli. L'intensité des stimuli à la main droite serait calibrée pour être modérément douloureux (~120% du seuil). Cependant, trois intensités seraient utilisées pour la main gauche : 100%, 120%, et 140%. Les participants ne rapporteraient que la sensation perçue à la main droite. Une telle expérience permettrait d'explorer si la capture involontaire dépend de l'intensité du stimulus ignoré, et si un effet plafond existe.

Dans la seconde expérience, il était prévu d'utiliser le paradigme du triplet de stimuli lasers (Iannetti et al., 2008; Moayedi et al., 2016; Ronga et al., 2013; Torta et al., 2012; Valentini et al., 2011; Zhang et al., 2012), tel que décrit précédemment. Brièvement, la répétition des trois stimuli rend la 2^{e} et la 3^{e} stimulation moins saillante que la 1ère, ce qui se reflète par une réduction importante des ERP. En modifiant les

caractéristiques du 3^{e} stimulus, la présence d'un « rebond » dans les ERP est interprétée comme une augmentation de la saillance associée à la caractéristique modulée. Dans cette expérience, il était prévu que des triplets de stimuli unilatéraux et bilatéraux soient appliqués, avec comme modification du 3^{e} stimulus l'ajout d'un stimulus bilatéral (pour les triplets unilatéraux) ou l'omission d'un stimulus bilatéral (pour les triplets bilatéraux). Cette expérience aurait permis d'investiguer le rôle de la saillance dans l'intégration de l'information bilatérale nociceptive.

Une limite inhérente à l'utilisation des lasers disponibles pour l'étude sur la douleur (et qui présentent un moindre risque de brûlures, p. ex. le Nd :YAP) est que, contrairement aux dispositifs utilisés pour les stimuli électriques, ils ne permettent pas d'ajuster l'intensité des stimuli de façon aussi précise. En effet, l'intensité du laser peut être fixée de 0.5 à 15 J et change par incréments de 0,25 J. Cependant, les lasers permettent également d'adapter le diamètre du faisceau, et ce faisant, affecte drastiquement la mesure de fluence soit l'énergie par aire de surface en J/cm^2 du laser. Ainsi, à énergie égale, plus le faisceau est grand, moins l'énergie est concentrée. Dans l'étude 2, un diamètre de 4 millimètres a été utilisé, tel que décrit couramment dans la littérature. Selon un article sur la sécurité des lasers, il est recommandé de garder la fluence sous 20 J/cm^2 soit environ 2.25 J à ce diamètre (Madden et al., 2016). Or, à ce diamètre, un niveau de stimulation induisant une douleur jugée tolérable et adéquate pour les objectifs de l'étude (p. ex. 2 J) peut parfois occasionner des réactions cutanées suggérant un risque de brûlure, et le niveau d'intensité plus bas (1.75 J), une douleur jugée trop faible ou nulle. Ainsi, pour les études 3 et 4, le diamètre fut augmenté à 5 mm (étude 3) et 7 mm (étude 4). Ce diamètre permet des intensités allant de 4 J (5 mm) à 7 J (7 mm) sans dépasser une fluence de 20 J/cm^2, sans affecter pour autant les réponses cérébrales. En ayant un meilleur contrôle sur la fluence des stimuli, cela réduit la possibilité de causer des brûlures à la peau tout en maintenant un niveau de douleur adéquat. Un tel contrôle est également nécessaire pour réaliser l'expérience décrite précédemment qui visait à moduler l'intensité de la douleur (100%, 120%, et 140% du seuil de la douleur).

Il est important de noter que les expériences de cette thèse, les résultats obtenus ainsi que leur interprétation sont présentés en fonction des réponses électroencéphalographiques pouvant être mesurées, qui sont particulièrement sensibles à l'activité corticale. Ceci n'implique pas pour autant que l'intégration de l'information nociceptive bilatérale est limitée aux structures corticales. En effet, nos travaux antérieurs (Rustamov et al., 2019) avaient démontré que l'information nociceptive bilatérale peut être intégrée à un niveau aussi précoce que la moelle épinière, tel que démontré par une augmentation de l'amplitude du réflexe de retrait spinal comparativement à de l'information nociceptive unilatérale. L'amygdale, tel que mentionné dans la section *Les voies ascendantes somatosensorielles* de l'introduction, est une structure très importante dans la régulation des émotions négatives comme la peur et l'anxiété (LeDoux, 2003) et est impliquée dans l'aspect motivo-affectif de la douleur (Simons et al., 2014). Certaines régions de l'amygdale, comme son noyau central, contiennent des neurones répondant exclusivement à des stimuli nociceptifs, et ces neurones présentent de vastes champs récepteurs bilatéraux (Bernard et al., 1992; Neugebauer et al., 2009; Neugebauer et al., 2004). Ainsi, il serait intéressant d'investiguer le rôle de l'amygdale dans l'intégration de l'information nociceptive provenant de stimuli douloureux bilatéraux. Cependant, l'analyse de l'activité électrique de structures profondes via des mesures non-invasives chez l'humain est complexifiée par la faiblesse du signal atteignant les électrodes de surface et la difficulté à identifier les générateurs menant à l'activité enregistrée (Krishnaswamy et al., 2017). L'ajout de méthodes complémentaires à l'électroencéphalographie comme la magnétoencéphalographie (Baillet et al., 2001; Lopes da Silva, 2013; Malmivuo, 2012), permettrait d'investiguer quelles autres régions du cerveau sont potentiellement impliquées dans l'intégration de l'information nociceptive bilatérale. En effet, la magnétoencéphalographie présente une meilleure résolution spatiale que l'électroencéphalographie, et n'est pas affectée par la conduction de volume, qui peut affecter les analyses de localisation de sources et de connectivité provenant des données électroencéphalographiques.

Il est également important de noter que comme dans la majorité des travaux sur la douleur (Garcia-Larrea, 2006), les participants avaient comme instructions de limiter leurs mouvements afin de prévenir les artéfacts dans les données. Ceci améliore bien sûr la qualité des données et facilite les analyses, mais affecte la validité écologique des résultats et donc la capacité à les généraliser à des situations de la vie de tous les jours. La capacité à limiter les mouvements de défense (nocifensifs) en présence de douleur est en soi un mécanisme descendant complexe (Garcia-Larrea, 2006; Perini et al., 2013; Zhuo, 2017). Des travaux ont démontré que l'exécution d'un mouvement de retrait suite à une stimulation laser, comparativement à un mouvement d'atteinte, est associé à une modulation des ERP au vertex (Moayedi et al., 2015). Ce mouvement de retrait étant la réponse habituelle à une stimulation douloureuse, cela la suggère que les ERP sont sensibles à des paramètres moteurs pertinents d'un point de vue écologique. D'ailleurs, nous ne réagissons pas tous de la même façon face à un danger imminent comme un stimulus nociceptif. En effet, selon les théories motivationnelle de la personnalité (Corr, 2008; Corr & McNaughton, 2012), de nombreux systèmes d'approche et d'évitement face au danger (p. ex. la réponse combat-fuite-gel) interagissent dans le cerveau en fonction des traits de personnalité d'un individu (Corr & Krupić, 2017). Ces traits sont à leur tour fortement relié à la notion de motivation (Corr & Krupić, 2017). Quoi que ceci n'ait pas été présenté dans la présente thèse, des chercheurs ont démontré que la sélection volontaire de l'information est non seulement régulée par la pertinence des stimuli comparés aux objectifs cognitifs, mais aussi en fonction de la motivation (Legrain et al., 2012; Van Damme et al., 2010). Une avenue intéressante pour nos travaux serait d'investiguer le rôle des traits motivationnel de personnalité (approche – évitement) face au danger dans l'intégration cérébral nociceptive.

Par ailleurs, près du tiers des sujets montrent un effet négligeable ou contraire lors des stimuli lasers bilatéraux, apportant une variabilité notable. Plusieurs hypothèses peuvent être énoncées pour expliquer la plus grande variabilité des réponses aux stimuli lasers par rapport aux stimuli électriques. Pour des raisons de sécurité, le même endroit ne doit pas être stimulé plus d'une fois par quelques minutes avec un laser (Leandri et al.,

2006). Ceci peut introduire de la variabilité spatiale d'une stimulation à l'autre en augmentant la variabilité des réponses et donc des effets observés, ce qui peut affecter la comparaison entre les conditions de stimulation unilatérale et bilatérale. Même si cela ne peut pas être exclu, la variabilité est possiblement similaire entre les différentes conditions bilatérales, et les comparaisons de deux conditions bilatérales sont probablement peu affectées par cette variabilité.

Conclusion

Les études présentées dans cette thèse démontrent que des mécanismes dans le système nerveux central permettent d'intégrer l'information nociceptive bilatérale. Cette intégration reflète au moins partiellement une plus grande capture attentionnelle involontaire. Finalement, la modulation de l'intégration par la proximité des régions corporelles stimulées suggère que cette intégration permet à l'organisme d'adapter les réponses comportementales de douleur en fonction de la situation.

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Annexe

I. Liste des publications durant mes études doctorales

1- Wagenaar A, Deldar Z, **Northon S**, Brisson B, Blanchette I, and Piché M. (2021) Disruption of working memory and contralateral delay activity by nociceptive stimuli is modulated by task demands. *Pain.* DOI: 10.1097/j.pain.0000000000002517.

2- Provencher B, **Northon S**, Piché M. (2021) Segmental chiropractic spinal manipulation does not reduce pain amplification and the associated pain-related brain activity in the capsaicin-heat pain model. *Frontiers in Pain Research.* DOI: doi.org/10.3389/fpain.2021.733727

3- **Northon S**, Deldar Z, Piché M. (2021) Effects of spatial attention and limb position on the cortical interaction of bilateral noxious inputs. *Psychophysiology.* DOI: 10.1111/psyp.13966.

4- **Northon S**, Deldar Z, Piché M. (2021) Spinal and cerebral integration of nociceptive inputs in left-handed individuals. *Brain Topography.* 34(5):568-586. DOI: 10.1007/s10548-021-00864-y

5- **Northon S**, Deldar Z, Piché M. (2021) Cortical integration of bilateral inputs is similar for noxious and innocuous stimuli but leads to different perceptual effects. *Experimental Brain Research.* 239(9):2803-2819. DOI: 10.1007/s00221-021-06175-9

6- Provencher B, **Northon S**, Gevers-Montoro C, O'Shaughnessy J and Piché M. (2021) Effects of chiropractic spinal manipulation on laser-evoked pain and brain activity. *Journal of Physiological Sciences.* 24;71(1):20. DOI: 10.1186/s12576-021-00804-2

7- Gevers-Montoro C, Provencher B, **Northon S**, Ortega A and Piché M. (2021) Chiropractic Spinal Manipulation Prevents Secondary Hyperalgesia Induced by Topical Capsaicin in Healthy Individuals. *Frontiers in Pain Research.* DOI:10.3389/fpain.2021.702429

8- Rustamov N, **Northon S**, Tessier J, Leblond H and Piché M. (2019) Integration of bilateral nociceptive inputs tunes spinal and cerebral responses. *Scientific Reports.* 9;9(1):7143. DOI: 10.1038/s41598-019-43567-y

9- **Northon S**, Rustamov N and Piché M. (2019) Cortical integration of bilateral nociceptive signals: when more is less. *Pain.* 160(3):724-733. DOI: 10.1097/j.pain.0000000000001451

10- **Northon S**, Boivin K, Laurencelle L, Hagemeister N, de Guise JA. (2018) Quantification of joint alignment and stability during a single leg stance task in a knee osteoarthritis cohort. *The Knee*. 25:1040-1050. DOI: https://doi.org/10.1016/j.knee.2018.08.011

II. Oscillations cérébrales évoquées pour l'étude 4