

Université de Montréal

**Mécanismes cérébraux de la régulation de la douleur**  
**Perception de la douleur et hypoalgésie induite psychologiquement**

par

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## Résumé

**Objectif :** Cette thèse a pour but de préciser les mécanismes neuropsychologiques de la douleur, de la régulation endogène de la douleur et de l'hypoalgésie induite psychologiquement (HIP) par la synthèse de près de trente ans de recherche imagerie cérébrale fonctionnelle. **Méthodologie :** Étant donné l'abondance des études sur le sujet et le manque d'intégration de leurs résultats, la technique de métaanalyse quantitative basée sur les coordonnées d'activation cérébrale fut privilégiée dans cette thèse, telle qu'implémentée dans l'algorithme ALE (*Activation Likelihood Estimate*). Une force supplémentaire de cette thèse repose sur la rigueur du processus de sélection des articles. En effet, les études incluses dans les métaanalyses devaient satisfaire des critères stricts d'inclusion, ceci dans le but de favoriser la précision et la validité des conclusions subséquentes. **Étude 1 :** Le premier article visait à identifier les aires cérébrales impliquées dans la réduction de la douleur par des méthodes psychologiques d'interventions. Les articles retenus portent sur une variété de méthodes d'intervention, telles que le placebo, l'hypnose, la méditation, la perception de contrôle sur la stimulation douloureuse et l'induction d'émotions. Les résultats indiquent que l'HIP implique un vaste réseau d'activation qui comprend le cortex cingulaire antérieur, l'insula antérieure, les zones orbitofrontale et préfrontale latérale, ainsi que les régions pariétale, temporale et sous-corticales. Ces activations reflèteraient l'implication des mécanismes neuropsychologiques cognitifs et émotionnels sous-tendant les interventions psychologiques ciblées par ces études, incluant la conscience de soi et la motivation. De plus, les divergences de patron d'activation entre les approches ont été explorées, notamment pour le placebo et la distraction. **Étude 2 :** Le deuxième article a identifié des patrons d'activations préférentiellement associés à la perception de la douleur, à l'HIP, ainsi que des activations communément associées à la douleur et l'HIP. Les résultats indiquent que 1) la perception de la douleur est associée à l'activation d'aires somatosensorielles et motrices, ce qui pourrait être le reflet de la préparation d'une action adaptative, 2) l'HIP est liée à l'engagement de régions préfrontales antéromédianes et orbitales, possiblement en lien avec des processus motivationnels et émotionnels, et 3) la douleur et l'HIP sont associés à l'activation d'aires préfrontales dorsolatérales, de l'insula antérieure et du cortex cingulaire moyen, ce qui pourrait refléter l'engagement spontané pendant la douleur de mécanismes endogènes de régulation descendante. **Conclusion :** Par ces études, cette thèse fait le point sur les mécanismes cérébraux impliqués différenciellement dans la perception de la douleur, dans sa régulation endogène et dans l'hypoalgésie induite psychologiquement.

**Mots-clés :** Douleur, Imagerie cérébrale, IRMf, TEP, métaanalyse, Analgésie cognitive, Hypoalgésie induite psychologiquement.

## Abstract

**Objective:** This thesis aims to clarify the neuropsychological mechanisms of pain, of the endogenous regulation of pain and of psychologically induced hypoalgesia (PIH), through the synthesis of almost thirty years of functional brain imaging research. **Methodology:** Given the abundance of studies in this domain and the lack of integration of their results, we used the quantitative meta-analysis technique based on brain activation using the ALE (Activation likelihood Estimate) statistic. The strength of this thesis lies in the globalized perspective of the literature, and in the rigor of the article selection process from which results were extracted. Indeed, the studies included in the meta-analyses needed to meet strict inclusion criteria in order to strengthen the accuracy and the validity of subsequent conclusions. **Study 1:** The first article is aimed at identifying brain areas involved in pain reduction through psychological methods of intervention. Chosen articles that covered a variety of approaches, such as placebo, hypnosis, meditation, perception of control over the stimulation, and induction of emotions. Analysis across these various studies indicated that PIH involves a broad network of activation that includes the anterior cingulate cortex, anterior insulae, orbital and lateral prefrontal and frontal areas, as well as parietal, temporal and subcortical regions. This activation network may reflect the involvement of diverse neuropsychological mechanisms in the various affective, self-awareness, cognitive and motivational processes underlying the psychological interventions targeted by these studies. In addition, we explored some specific patterns of brain activity related to placebo and distraction, in comparison to other approaches. We propose several hypotheses regarding the distinctive neuropsychological processes underlying these approaches. **Study 2:** The second article aimed at investigating patterns of brain activity preferentially associated with pain perception or with PIH. First we assessed patterns of increased and decreased activity during experimental pain in healthy volunteers. Second we determined the brain regions preferentially activated during pain perception or during PIH with subtraction analyses. Using a conjunction analysis, we also determined a set of brain regions possibly involved in regulatory processes activated spontaneously during acute of pain. Our results indicate that 1) somatosensory and motor areas are preferentially related to pain perception, which may reflect the preparation of a motor response, 2) dorsolateral prefrontal areas, anterior insula and the anterior midcingulate cortex were associated with both pain and PIH and may reflect the spontaneous activation of top-down regulation mechanisms during pain, and 3) antero-medial and orbital prefrontal regions were preferentially associated with PIH, which may indicate motivational and emotional processes associated with the engagement of an externally driven hypoalgesic procedure.

**Keywords :** Pain, brain imaging, fMRI, PET, meta-analyse, cognitive analgesia, psychologically induced hypoalgesia.

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## Liste des abréviations

ACC	<i>Anterior cingulate cortex</i> / Cortex cingulaire antérieur
ALE	<i>Activation likelyhood estimate</i> (estimation des plus probables activations)
BA	Aires de Brodmann / <i>Brodmann area</i>
BOLD	<i>Blood Oxygenation Level Dependant</i> / Taux d'oxygénation sanguin
CBMA	<i>Coordinate-based meta-analysis</i> /
DLPFC	<i>Dorsolateral prefrontal cortex</i> / Cortex préfrontal dorsolatéral
FDR	<i>False Discovery Rate</i> (taux de fausses découvertes)
fMRI	<i>Functional magnetic resonance imaging</i> / Imagerie par résonance magnétique fonctionnelle
FWER	<i>Family-wise error rate</i> (probabilité de fausses découvertes)
GLM	<i>General Linear Model</i> / Modèle général linéaire
IFG	<i>Inferior frontal gyrus</i> / Gyrus frontal inférieur
aINS	<i>Anterior insula</i> / Insula antérieur
pINS	<i>Posterior insula</i> / insula postérieure
MA	<i>Modeled activation</i> / Modélisation de l'activation
MCC	<i>Midcingulate cortex</i> / Cortex cingulaire moyen
MKDA	<i>Multilevel Kernel Density Analysis</i>
OFC	<i>Orbitofrontal cortex</i> / Cortex orbitofrontal
PAG	<i>Periaqueductal grey</i> / Substance grise périaqueductale
PET	<i>Positron emission tomography</i> / Tomographie par émission de positrons
PFC	<i>Prefrontal cortex</i> / Cortex préfrontal
PIH / HIP	<i>Psychologically induced hypoalgesia</i> / Hypoalgésie induite psychologiquement
PRISMA	<i>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</i>
rCBF	<i>Regional cerebral blood flow</i> / Débit sanguin cérébral
ROI	<i>Region of interest</i> / Région d'intérêt
RVM	<i>Rostroventromedial medulla</i> / Bulbe rostroventromédian
SI	<i>Primary somatosensory cortex</i> / Cortex somatosensoriel primaire
SII	<i>Secondary somatosensory cortex</i> / Cortex somatosensoriel secondaire
SMA	<i>Supplementary motor cortex</i> / Aire motrice supplémentaire
VPL	<i>Ventroposteriolateral nucleus of thalamus</i> / Noyaux thalamiques ventropostérieurs latéraux
VPM	<i>Ventroposteriomedial nucleus of thalamus</i> / Noyaux thalamiques ventropostérieurs médian

*Arielle et Gabriel,  
vous m'avez donné la vie,  
le courage et le bonheur.*

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## Chapitre 1. INTRODUCTION

"La douleur ne protège pas l'homme, elle le diminue" — René Leriche<sup>1</sup>, 1936

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<sup>1</sup> René Leriche était un célèbre chirurgien français reconnu pour son approche holistique du patient (Rangappa, 2008).

Lorsque la douleur aiguë se chronicise, l'incapacité qu'elle cause entraîne un fardeau socio-économique considérable. Malheureusement, la douleur chronique est souvent difficile à enrayer par des méthodes pharmacologiques traditionnelles. Par conséquent, le soulagement de la douleur, tout comme le traitement des conditions douloureuses, représente, même à ce jour, un véritable défi scientifique. Les mécanismes endogènes de régulation sont des alliés dans cette lutte. Or, ce potentiel d'autorégulation de la douleur est sous-exploité en raison de notre méconnaissance de leur entrée en action.

Plusieurs approches psychologiques visant l'hypoalgésie ont démontré leur efficacité pour réduire la perception de la douleur, notamment la distraction, le placebo, l'hypnose, la modulation des émotions et la méditation. *L'hypoalgésie induite psychologiquement* découlant de ces interventions serait potentiellement médiée par des systèmes endogènes de régulation de l'information nociceptive dans le système nerveux central.

Cette thèse a pour but de préciser les mécanismes neuropsychologiques de la douleur, de la régulation endogène de la douleur et de l'hypoalgésie induite psychologiquement. Découvrir les *fondements* de ces mécanismes endogènes servira subséquemment à soutenir la recherche clinique pour favoriser l'utilisation de ce remarquable potentiel d'autorégulation. C'est dans cette perspective que fut élaborée cette thèse.

Dans un premier temps, ce chapitre d'introduction définit la douleur ainsi que les substrats neuroanatomiques de sa perception et de sa modulation. Nous exposerons ensuite les principes élémentaires de la méthodologie utilisée dans cette thèse.

## 1.1. La douleur

La douleur n'est pas qu'un sens, ou qu'une émotion. Il s'agit d'une expérience émotionnelle et sensorielle désagréable associée à un dommage potentiel ou réel aux tissus, ou liée à une sensation décrite comme telle<sup>2</sup>. Sa complexité tient du fait qu'elle est hautement dépendante, et même conséquente, d'un amalgame de facteurs en constante interaction: des inputs sensoriels, des cognitions, des émotions et des processus physiologiques. À l'origine, la douleur résulte de multiples relais d'un influx nerveux nociceptif à travers le système nerveux central (Figure 1).

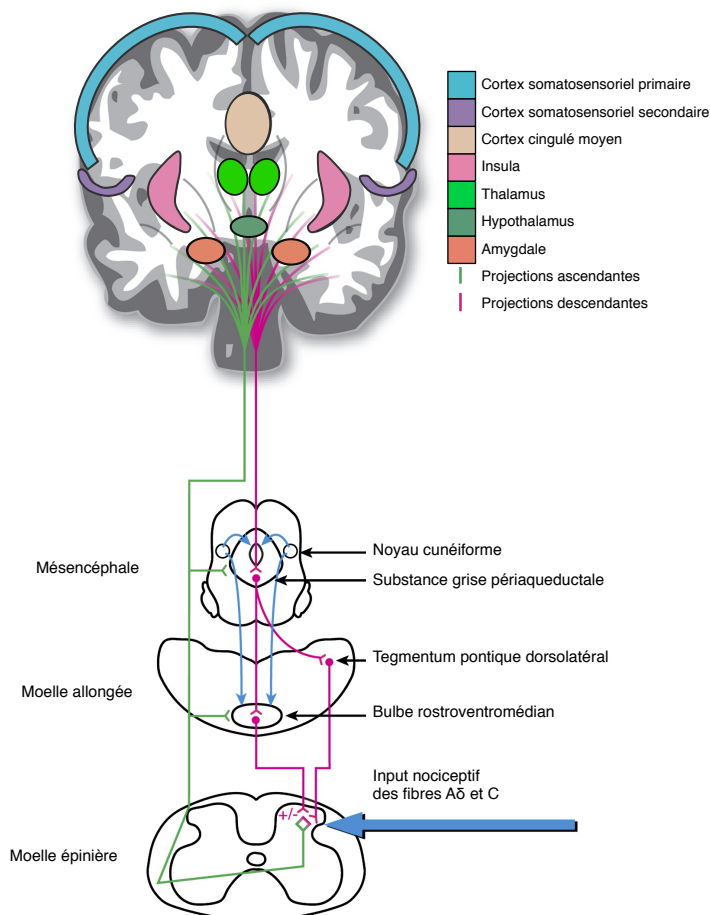
### 1.1.1. Ascension de l'influx nociceptif vers le cortex

Les processus physiologiques à la base de la transmission de l'influx nociceptif vers les centres cérébraux comportent divers relais (Dostrovsky & Craig, 2013; Ringkamp, Raja, Campbell, & Meyer, 2013). D'abord, ce signal est acheminé en périphérie par deux types de fibre nerveuse à conduction plus ou moins rapide : les fibres A $\delta$  et C. Les fibres A $\delta$  sont myélinisées et conduisent l'information (mécanique et thermique) nociceptive et non nociceptive de façon rapide (5 à 30 m/s) et précise. Elles sont responsables de la première sensation douloureuse brève et aiguë semblable à une piqûre. Les fibres C quant à elles ne sont pas myélinisées et conduisent l'information sensorielle nociceptive et non nociceptive moins rapidement (0,5 à 2 m/s). Il s'agit de fibres polymodales qui répondent à des stimulations thermiques, mécaniques et chimiques. Elles sont responsables de la deuxième douleur

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<sup>2</sup> Traduction de la définition formulée ainsi par l'*International Association for the Study of Pain (IASP)* : "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*".

caractérisée par une sensation plus diffuse de brûlure. Ces fibres entrent par la racine dorsale de la moelle épinière au segment correspondant à la localisation de la stimulation et font une première synapse au niveau de la substance gélatineuse de la corne dorsale à des niveaux plus ou moins élevés de couches laminaires. La majorité des axones de ce premier relai synaptique décussent et rejoignent leurs cibles de manière contralatérale au site de stimulation, mais une certaine proportion de ces fibres montent ipsilatéralement.



**Figure 1.** Voies ascendantes et descendantes de la douleur.

Figure traduite et adaptée de Tracey & Mantyh, 2007.



L'acheminement de l'information nociceptive reflète la multidimensionnalité de la douleur. Le système nociceptif est classiquement divisé en deux systèmes spino-cérébro-fonctionnels : les voies latérale et médiane (Melzack & Casey, 1968; Bouhassira & Calvino, 2009). La voie latérale, dite sensoridiscriminative, est responsable de la localisation du stimulus, de la discrimination de son intensité, ainsi que de la détection de ses propriétés physiques. Elle tire son origine dans les couches laminaires superficielles qui reçoivent principalement des afférences nociceptives provenant des fibres A $\delta$  et C. Ces neurones de la corne dorsale sont en grande partie spécifiques à la nociception ou la thermoception, ont de petits champs récepteurs et relaient l'information nociceptive sur les qualités sensorielles de la douleur. Leur influx nociceptif est acheminé par la voie spinothalamique vers plusieurs noyaux thalamiques postérieurs ventraux et latéraux.

La voie médiane, dite affective-motivationale, est associée à la valence de la sensation, à son interprétation, au désagrément qu'elle cause, ainsi qu'à la préparation d'une réponse comportementale. Elle provient de neurones des couches profondes de la substance gélatineuse de la moelle qui reçoivent principalement des afférences des fibres A $\beta$  (non nociceptives), mais qui font aussi synapse avec quelques fibres A $\delta$  et C. Ces neurones ont des champs récepteurs plus étendus et ont une large gamme dynamique (*wide dynamic range*), c'est-à-dire qu'ils ne répondent pas spécifiquement à des stimulations nocives. Ainsi, ils apportent, en quelque sorte, des informations relatives au contexte de la douleur. Leur axone suit la voie spinoréticulaire par laquelle le signal est acheminé vers les noyaux réticulaires qui s'étendent du bulbe rachidien à la protubérance. Certaines projections réticulaires subséquentes

atteignent ensuite le thalamus postérieur médian. Le noyau dorsomédian reçoit également une portion des projections spinales nociceptives, lesquelles joueraient un rôle dans la dimension affective-motivationnelle de la douleur (Dostrovsky & Craig, 2009).

Parallèlement aux voies spinothalamique et spinoréticulaire, l'input nociceptif est relayé à d'autres structures du tronc cérébral. Certaines afférences des couches laminaires profondes de la corne dorsale projettent vers le noyau raphé magnus du bulbe rostroventral (RVM) et vers la substance grise périaqueducatale (PAG), zones clés dans la régulation endogène descendante de la douleur. Ainsi, l'acheminement de l'information douloureuse n'est pas unidirectionnel, mais fait intervenir des mécanismes sous-corticaux bidirectionnels de régulation. C'est en effet ce qui se passe lorsque l'influx parvient au noyau parabrachial (situé à la jonction dorsale entre le mésencéphale et la protubérance), puisque celui-ci renvoie des efférences spinales modulatrices, en plus d'afférences vers l'hypothalamus, le thalamus et l'amygdale. L'amygdale est une structure limbique impliquée dans les processus émotionnels et associatifs (conditionnement) de la douleur (Neugebauer, Li, Bird & Han, 2004). Il s'agit donc de relais complémentaires à la voie spinoréticulaire. D'autre part, les collicules supérieurs mésencéphaliques sont également impliqués dans l'acheminement de l'information douloureuse, et seraient responsables du réflexe d'orientation des yeux, de la tête et du haut du corps vers la source de la douleur. Enfin, la voie spinothalamique (vers l'hypothalamus) serait quant à elle impliquée dans l'ajustement endocrinien et autonome en réponse au stimulus nociceptif (Dostrovsky & Craig, 2013).

En outre, l'information nociceptive provenant des viscères et de la tête emprunte des voies distinctes (du moins partiellement). Une portion des afférences viscérales nociceptives

est acheminée par la voie spinothalamique, mais la douleur viscérale repose en grande partie sur la voie postsynaptique des colonnes dorsales (Paleček, 2004; Willis Jr & Westlund, 2001). Les mécanorécepteurs viscéraux envoient leurs inputs sensoriels vers le ganglion de la racine dorsale, puis ce signal suit les colonnes dorsales de la moelle épinière et projettent vers les noyaux graciles et cunéiformes situés dans la portion caudale du bulbe rachidien. L'influx décusse, suit le lemniscus médian, puis se rend au noyau ventropostérolatéral du thalamus. Enfin, la voie trigéminothalamique est celle qui transporte l'information nociceptive en provenance du visage et de la tête. L'influx nociceptif se rend d'abord au noyau descendant du nerf crânien V (qui s'étend de la protubérance jusqu'au bulbe rachidien). De cette synapse, le signal décusse en grande partie, puis il rejoint la voie spinothalamique.

En dépit de son utilité conceptuelle, le modèle dichotomique à deux voies (latérale et médiane) s'avère maintenant trop simpliste pour tenir compte des connaissances actuelles sur l'existence d'autres voies ayant des rôles spécifiques et complémentaires (p.ex. la voie spino-parabrachiale, la voie postsynaptique des colonnes dorsales). Par leurs relais à différents niveaux du système nerveux central (Figure 1), ces multiples voies ascendantes permettent la transformation de l'influx nociceptif périphérique en de multiples réactions et réponses physiologiques. Ainsi, l'acheminement cérébral de cet influx et son traitement par un ensemble d'aires de bas et de haut niveau permettent l'émergence de la perception consciente, ou de l'expérience subjective de la douleur.

### 1.1.2. Traitement cérébral de l'influx nociceptif

Parallèlement au modèle dichotomique des voies latérale et médiane, différentes théories ont été proposées afin de conceptualiser la conversion de l'influx nociceptif en perception douloureuse dans le cerveau. Traditionnellement, deux points de vue opposés guident la compréhension de la douleur : la théorie de la spécificité et celle des patrons d'activation (Cervero, 2009; De Koninck, 1997).

#### *Spécificité versus convergence*

La théorie de la spécificité stipule que la douleur est un sens au même titre que la vision ou l'audition, et qu'il existe des éléments du système nerveux spécifiquement et exclusivement dédiés au traitement de la nociception. À l'opposé, la théorie des patrons soutient que la douleur émane d'une distribution spatiale et temporelle d'activations d'un ensemble de systèmes agissant en parallèle. Les données empiriques vont plutôt dans le sens d'une complémentarité de ces deux théories. Certes, il existe des neurones spécifiques à la nociception. Il en demeure toutefois que la douleur regroupe un éventail de processus spinaux et cérébraux qui, par leurs interactions, produisent sa multidimensionnalité (aspects sensoriels, affectifs, cognitifs, etc.). Cette vision dichotomique est pourtant tenace et continue d'influencer les hypothèses de recherche. En effet, le débat persiste quant à l'existence d'une région corticale, ou d'une matrice spécifique à la douleur (*Pain Matrix*). Il y a, d'un côté, les tenants d'une signature cérébrale spécifique à la douleur (Garcia-Larrea, 2012; Wager et al., 2013), et à l'autre extrême, ceux qui soutiennent que cette matrice n'est qu'un réseau multimodal reflétant la saillance non spécifique intrinsèque d'un stimulus douloureux (Legrain, Iannetti,

Plaghki & Mouraux, 2010). Notons par ailleurs la récente proposition d'un modèle hiérarchique de plusieurs niveaux de matrices de douleur, chacune plus ou moins spécifique et distribuée (Garcia-Larrea & Peyron, 2013).

### *La matrice de la douleur*

La théorie de la matrice de la douleur fut initialement proposée par Ronald Melzack (2005, 1989). Paradoxalement, elle s'apparente davantage au modèle en patrons d'activations qu'à la théorie de la spécificité. En fait, la "*body-self neuromatrix*" de Melzack serait le substrat neuroanatomique de la perception consciente de divers inputs, dont la douleur, constitué de boucles afférentes et efférentes entre le thalamus, le cortex et le système limbique (Melzack, 2005; Melzack, 1989). La perception consciente proviendrait d'une association de sous-modules neuronaux, chacun spécialisé dans un type particulier de traitement de l'information. De cette façon, le percept douloureux émanerait d'une neuromatrice de la douleur formée de l'intégration de multiples modules. La douleur serait donc le fruit d'interconnexions de sous-modules, chacun codant un aspect de la douleur (sensoriel, cognitif, émotionnel), et chacun supporté par divers processus génétiques, endocriniens, autonomiques, etc.

En d'autres mots, loin d'être formée de régions répondant *spécifiquement* à la nociception comme peut l'être l'aire visuelle primaire pour la vision, la matrice de la douleur consisterait en un ensemble de régions plus ou moins spécialisées dans un type de traitement (p.ex. aires primaires, aires associatives) qui, par leurs *associations*, engendreraient l'expérience de la douleur.

### *Activité cérébrale évoquée par la douleur*

Les études de neuroimagerie fonctionnelle démontrent une concordance robuste entre la perception de la douleur et l'activation d'un ensemble d'aires cérébrales. En outre, l'implication de ces aires varierait en fonction de l'interaction des dimensions sensorielle, émotionnelle et cognitive de l'expérience douloureuse (Bingel & Tracey, 2008). Les dernières revues de littérature et métaanalyse (Duerden & Albanese, 2013; Apkarian, Bushnell, Treede & Zubieta, 2005) sur le sujet convergent vers un réseau formé des cortex somatosensoriels primaire (SI) et secondaire (SII), de l'insula, du cortex cingulaire antérieur (ACC) et moyen (MCC<sup>3</sup>) et du thalamus. D'autres régions sont associées à la perception de la douleur, bien que moins systématiquement. Il s'agit du cortex préfrontal, de certaines aires motrices, du cortex pariétal postérieur, de l'amygdale et du cervelet (Treede & Apkarian, 2008). Chacune de ces structures semble jouer un rôle distinctif et complémentaire dans la perception de la douleur. Ainsi, les cortex somatosensoriels, avec l'insula postérieure sont associés l'aspect sensoridiscriminatif de la douleur, en continuité avec le système latéral, tandis que le ACC, le MCC et l'insula antérieure sont liés à sa dimension affective-motivationnelle émanant du système médian (Apkarian, Bushnell & Schweinhardt, 2013).

La prochaine section expose brièvement les rôles fonctionnels de chacune de ces régions dans le contexte de l'étude de la douleur, mais aussi dans une perspective neuropsychologique générale.

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<sup>3</sup> D'après la nomenclature de Vogt, Berger & Derbyshire, 2003 et Vogt, 2009.

## *Aires cérébrales liées à la douleur*

### **Cortex somatosensoriel primaire**

#### *Neuroanatomie*

SI est une région fonctionnelle somatosensorielle. Elle couvre anatomiquement le gyrus postcentral qui a une organisation somatotopique des différentes parties du corps. Ce gyrus est composé des aires cytoarchitectoniques de Brodmann (BA) 1, 2, 3a et 3b. Les aires 3b et 1 reçoivent des afférences tactiles cutanées, tandis que les aires 2 et 3a reçoivent des afférences proprioceptives (Treede & Apkarian, 2009). Du point de vue de la douleur, SI reçoit des afférences thalamiques nociceptives et non nociceptives (Treede & Apkarian, 2008).

#### *Rôle fonctionnel dans la douleur*

Près de 75 % des études d'imagerie par résonance magnétique fonctionnelle (fMRI) et par tomographie par émission de positrons (PET) rapportent une activation controlatérale de SI en lien avec des stimulations douloureuses chez les sujets humains normaux (Apkarian, Bushnell, Treede & Zubieta, 2005). Ce à quoi s'ajoute un riche historique d'études d'enregistrements cellulaires chez l'animal, ainsi que d'études de cas impliquant des individus cérébrolésés ou épileptiques (Duncan & Albanese, 2003). SI est impliqué dans la détection, la discrimination et la localisation du stimulus douloureux (Ploner, Freund & Schnitzler, 1999; Duncan & Albanese, 2003; Porro et al., 2007; Apkarian, Bushnell & Schweinhardt, 2013).

De par ses propriétés fonctionnelles, l'implication systématique de cette région sensorielle dans le traitement nociceptif s'inscrit en toute logique. Or, on note un manque de

constance dans l'observation de l'activation de SI parmi les études (Bushnell et al., 1999; Peyron, Laurent & García-Larrea, 2000), ce qui est par ailleurs illustré par une faible convergence, bien que présente, d'activations dans cette région lors d'une récente métaanalyse (Duerden & Albanese, 2013). Plusieurs facteurs peuvent expliquer une telle variabilité, comme la modulabilité de son activation par le degré d'engagement attentionnel vers le stimulus douloureux, la mixité des processus nociceptifs neuronaux excitateurs et inhibiteurs vers cette région, la sommation spatiale corticale plus ou moins suffisante de la stimulation douloureuse (Bushnell et al., 1999; Duncan & Albanese, 2003). Surtout, le peu d'afférences nociceptives spinothalamocorticales vers SI pourrait expliquer cette fluctuation (Dum, Levinthal & Strick, 2009). Dans le contexte d'une métaanalyse, la variété des sites de stimulation à travers les études peut avoir affaibli la convergence statistique des activations de SI (Duerden & Albanese, 2013).

### **Cortex somatosensoriel secondaire**

#### *Neuroanatomie*

SII est une aire fonctionnelle située anatomiquement dans la portion antérieure du lobe pariétal. Sa localisation anatomique précise est sujette à débat chez l'humain (p.ex. Craig, 2003; Eickhoff, Schleicher, Zilles & Amunts, 2006), mais il est généralement convenu qu'elle couvre l'opercule pariétal composé de BA 40 (Eickhoff et al., 2006a). La portion médiane de cet opercule est l'une des plus importantes cibles d'afférences nociceptives thalamocorticales de la voie spinothalamique, avec l'insula postéro-dorsale et le MCC (Dum et al., 2009).



### *Rôle fonctionnel dans la douleur*

La corrélation entre l'activation cérébrale de SII et le traitement de la douleur est beaucoup plus systématique que celle de SI. On observe généralement une activation bilatérale de cette région associative (Bushnell & Apkarian, 2006), ainsi qu'une forte convergence bilatérale des foyers d'activations en métaanalyse (Duerden & Albanese, 2013). Or, autant cette association peut être robuste, autant la compréhension du rôle fonctionnel de SII dans la douleur reste ambiguë. Ce rôle ne serait pas spécifique à la douleur (Treede, Kenshalo, Gracely & Jones, 1999), mais serait plutôt lié à l'intégration générale des afférences sensorielles, à l'orientation spatiale de l'attention vers les stimuli douloureux (Peyron et al., 2000), à la reconnaissance d'objet et à la mémoire tactile (Treede et al., 1999). En outre, SII possède une organisation cytoarchitectonique hétérogène, particulièrement sur l'axe rostro-caudal, avec des corrélats fonctionnels qui semblent suivre cette inhomogénéité (Eickhoff, Amunts, Mohlberg & Zilles, 2006b). En effet, sa portion postérieure est plus étroitement liée dans la douleur, tandis que sa zone antérieure est davantage associée aux stimuli non douloureux (Eickhoff et al., 2006b; Ferretti et al., 2003; Coghill et al., 1994).

L'activité de SII est liée à l'aspect sensoridiscriminatif de la douleur (Apkarian, Bushnell & Schweinhardt, 2013). En effet, les manipulations expérimentales de l'intensité de la stimulation (Moulton, Pendse, Becerra & Borsook, 2012), ou encore de certaines qualités physiques de la douleur (Maihöfner, Herzner, & Otto Handwerker, 2006) sont généralement associées à une variation de l'activité dans SII.

## **Cortex insulaire**

### *Neuroanatomie*

L'insula tient son nom de sa forme insulaire isolée au fond du sillon latéral. Elle est recouverte des opercules frontal, temporal et pariétal. L'insula est organisée en trois régions cytoarchitectoniquement distinctes : la zone granulaire postéro-dorsale, la zone agranulaire antéroventral, et entre les deux, une large zone intermédiaire dite dysgranulaire. La connectivité anatomique de l'insula suivrait d'ailleurs sa progression cytoarchitectomique rostro-caudale (Cerliani et al., 2012).

### *Connectivité*

D'abord, l'insula antérieure (aINS) aurait des connexions anatomiques avec les régions limbiques et paralimbiques, ainsi qu'avec le cortex orbitofrontal et le gyrus frontal inférieur antérieur (Cerliani et al., 2012). En revanche, l'insula postérieure (pINS) serait connectée davantage avec des régions sensorimotrices (les cortex pariétal et prémoteur latéral), avec le cortex temporal postérieur, ainsi qu'avec le gyrus frontal inférieur postérieur. Quant à la zone moyenne intermédiaire, elle présenterait un patron de connectivité hétérogène et peu spécifique, ce qui est cohérent avec son architecture cellulaire transitionnelle (Cerliani et al., 2012; Nieuwenhuys, 2012).

### *Rôles fonctionnels généraux*

L'activation de l'insula est concomitante à une multitude de tâches, et elle est associée à tout autant de processus mentaux : fonctions auditives, vestibulaires, olfactives, gustatives,

somatosensorielles, viscérales, somatomotrices et viscésomotrices, production de la parole, perception de la température, émotions sociales, état de manque de drogue, pour n'en citer que quelques-uns (Craig, 2009; Nieuwenhuys, 2012). Par conséquent, plusieurs efforts de synthèse ont été déployés récemment afin de préciser le ou les mécanismes unissant cet ensemble disparate d'observations (Mutschler et al., 2009; Kurth, Zilles, Fox, Laird & Eickhoff, 2010; Cauda et al., 2012; Kelly et al., 2012; Gu, Hof, Friston & Fan, 2013).

Les rôles fonctionnels de l'insula correspondent à sa connectivité anatomique. En effet, il existe de nombreuses évidences selon lesquelles l'aINS est impliquée dans des fonctions cognitivoémotionnelles, alors que l'pINS est associée à des processus sensorimoteurs (Nieuwenhuys, 2012; Klein, Ullsperger & Danielmeier, 2013; Christopher, Koshimori, Lang, Criaud & Strafella, 2014). Plus précisément, de récentes métaanalyses ont montré une association entre l'aINS dorsale et plusieurs processus cognitifs (attention, mémoire de travail, mémoire, langage), ainsi qu'une association entre l'aINS ventrale et des tâches de nature émotionnelle (Kurth et al., 2010; Kelly et al., 2012). En revanche, ces mêmes études ont révélé un rôle de l'pINS dans les perceptions somatosensorielles (la douleur, l'intéroception, les processus autonomiques et homéostatiques), ainsi que dans la motricité et l'action (Kurth et al., 2010; Kelly et al., 2012). La partie moyenne de l'insula afficherait également une certaine spécificité fonctionnelle (Kelly et al., 2012) se rapportant aux sens chimiques (gustation et olfaction), mais seulement dans l'hémisphère droit (Kurth et al., 2010).

### *Rôle fonctionnel dans la douleur*

Au niveau de l'étude de la douleur, la plupart des études PET et fMRI rapportent une activation bilatérale de l'insula (Bushnell & Apkarian, 2006). Avec SII et le MCC, l'insula postéro-dorsale est l'une des plus importantes cibles d'afférences nociceptives thalamocorticales de la voie spinothalamique (Dum et al., 2009). Des études électrophysiologiques auprès de patients épileptiques ont démontré la responsabilité de l'insula dans la production d'une sensation douloureuse, soit via une hyperactivation provoquée par des crises épileptiques (*ictal pain*), soit par des stimulations électriques intracérébrales (Afif, Minotti, Kahane & Hoffmann, 2010; Isnard, Guénot, Ostrowsky, Sindou & Mauguère, 2000; Mazzola, Isnard, Peyron, Guénot & Mauguère, 2009). De plus, une récente étude d'enregistrement cellulaire chez des patients épileptiques a mis en évidence une gradation postéro-antérieure temporelle de la réponse de l'insula causée par des stimulations douloureuses (Frot, Faillenot & Mauguère, 2014), suggérant que l'information nociceptive serait d'abord traitée dans l'pINS, puis dans l'aINS. Ces nouvelles données sont compatibles avec l'hypothèse selon laquelle l'pINS serait au premier plan du déclenchement de la réponse cérébrale à la douleur (Isnard, Magnin, Jung, Mauguère & Garcia-Larrea, 2011).

D'autre part, les Drs Craig et Garcia-Larrea, par leurs travaux approfondis sur l'insula, ont chacun développé leur point de vue sur le rôle de cette région. D'abord, Craig (2003, 2009, 2011) soutient que l'aINS serait le corrélat neuronal de la conscience corporelle, c'est-à-dire de la reconnaissance de nos sensations somatiques, viscérales, autonomiques, etc. (*self-awareness of bodily signals and feelings*). Cette sensation subjective "directement basée sur l'intégration homéostatique sensorielle" (Craig, 2011; p.74) proviendrait d'inputs sensorimoteurs de l'pINS.

Par ailleurs, les deux chercheurs considèrent que l'pINS et l'opercule pariétal médial adjacent<sup>4</sup>, devraient être considérés comme une seule entité anatomofonctionnelle plutôt que comme deux zones distinctes. Toutefois, leurs points de vue divergent quant aux rôles fonctionnels qu'ils attribuent à cette région (Garcia-Larrea et al., 2010 vs Craig, 2011). Alors que Craig (2003) la considère comme le "cortex intéroceptif", Garcia-Larrea (2012) soutient qu'il s'agit d'une aire somatosensorielle distincte de SI et SII, possiblement une nouvelle "S3" (Garcia-Larrea, 2012). Il appuie cette proposition, entre autres, sur la constatation que cette zone est la principale cible corticale des projections spinothalamiques nociceptives, et qu'elle répond à certains aspects sensoriels se rapportant aux signaux homéostatiques. En outre, sa revue d'études d'imagerie, d'électrophysiologies et de lésions l'amène à proposer que la région couvrant l'pINS et l'opercule pariétal médian puisse être considérée comme une aire nociceptive primaire (Garcia-Larrea, 2012; il s'agit de sa proposition initiale et l'argumentaire penche vers un rôle associatif essentiel dans l'expérience de la douleur).

## **Cortex cingulaire**

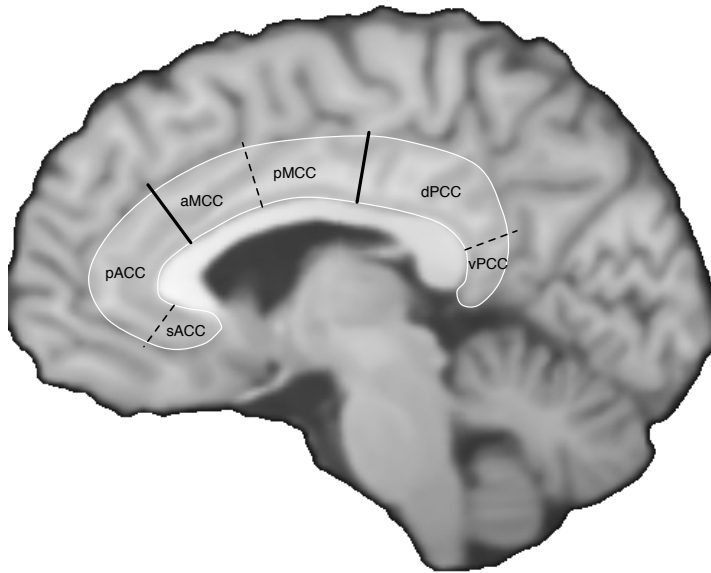
### *Neuroanatomie*

Le cortex cingulaire est une aire médiane qui longe dorsalement le corps calleux. Il se divise en trois portions : antérieure (BA 25, 32 et 24 antérieures), moyenne (BA 32 et 24 postérieures) et postérieure (BA 23 et 31). Ces trois aires se subdivisent aussi en sous-sections

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<sup>4</sup> La partie médiane de l'opercule pariétale est constituée des aires OP3 (antérieure) et OP2 d'après l'étude cystologique de Eickhoff et al. (2006). À ne pas confondre avec le rétro-insula associé aux fonctions vestibulaires (zu Eulenburg, Caspers, Roski & Eickhoff, 2012). Elle est postérieure à l'insula et médiale à l'opercule pariétal, mais n'en fait pas partie. Selon Eickhoff et al. (2006), SII ne couvre ni les OP2 et OP3, ni le rétro-insula, mais seulement l'OP1, portion postérolatérale de l'opercule.

suivant un axe rostro-caudal comme suit (Vogt, 2009 et 2005; Figure 2) : le cortex cingulaire antérieur subgenuel et prégenual (sACC et pACC), le cortex cingulaire moyen antérieur et postérieur (aMCC et pMCC), et enfin, le cortex cingulaire postérieur dorsal et ventral (dPCC et vPCC). Ces trois régions du cortex cingulaire se distinguent sur le plan neurochimique par rapport aux neurotransmetteurs et leurs récepteurs spécifiques (Palomero-Gallagher, Vogt, Schleicher, Mayberg & Zilles, 2009), ainsi qu'en regard de leur connectivité anatomique (Beckmann, Johansen-Berg & Rushworth, 2009). Le MCC est une des principales cibles d'afférences nociceptives thalamocorticales de la voie spinothalamique (Dum et al., 2009). Elle contient des neurones répondant spécifiquement à la nociception comparativement à des stimulations non douloureuses (Hutchison, Davis, Lozano, Tasker & Dostrovsky, 1999). De plus, le pMCC dorsal envoie des projections corticospinales vers les motoneurons de la moelle épinière (Dum & Strick, 1991) et est directement impliqué dans le contrôle moteur associé au contrôle volontaire du comportement (Paus, 2001).



**Figure 2.** Morphologie du cortex cingulé d'après Vogt (2009).

### *Connectivité*

Sur le plan de la connectivité anatomique chez le singe, l'ACC rostroventral reçoit majoritairement des projections frontales dorsolatérales et orbitofrontales médianes (Vogt & Pandya, 1987). Cette région reçoit également des afférences du lobe temporal, notamment en provenance du gyrus supérieur, ainsi que de l'amygdale, de l'hippocampe et du gyrus parahippocampique. L'ACC dorsal et le MCC reçoivent également des afférences frontales dorsolatérales, avec des projections orbitofrontales médianes et insulaires. Le PCC quant à lui reçoit ses principales afférences du gyrus temporal supérieur, du gyrus parahippocampique, de la portion caudale du lobule pariétal inférieur et de l'aire péristriée occipitale (BA 19; Vogt & Pandya, 1987).

Chez l'humain, les méthodes corrélationnelles montrent que l'ACC est davantage connecté à des régions associées à la motivation et aux émotions (cortex orbitofrontal médian, amygdale, striatum ventral, hypothalamus), l'aMCC à des aires impliquées dans la cognition (cortex préfrontal dorsolatéral), le MCC dorsal à des zones motrices (striatum dorsal, cortex prémoteur), tandis que la portion postérieure du cortex cingulaire (pMCC et dPCC) connecte surtout avec le gyrus postcentral (SI) et le cortex pariétal latéral. Aussi, le MCC ventral et le vPCC sont surtout connectés à l'hippocampe (Beckmann et al., 2009). La région cingulaire est donc intrinsèquement hétérogène sur le plan anatomique. Elle l'est également sur le plan fonctionnel. En effet, la connectivité fonctionnelle<sup>5</sup> du cortex cingulaire telle que mesurée à l'état de repos concorde approximativement avec la progression rostrocaudale de sa connectivité anatomique (Margulies et al., 2007). La région cingulaire rostroventrale (sACC et pACC) est fonctionnellement connectée au cortex orbitofrontal médian et au pôle temporal, l'aMCC dorsal est associé au réseau fronto-pariétal attentionnel et exécutif, alors que le pMCC est surtout lié à des zones sensorimotrices (Margulies et al., 2007).

### *Rôles fonctionnels généraux*

Le cortex cingulaire est impliqué dans une vaste étendue de tâche faisant intervenir la cognition, la motivation, les émotions et la perception de stimuli aversifs, ainsi que dans de

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<sup>5</sup> L'analyse de connectivité fonctionnelle cherche les corrélations temporelles d'activations cérébrales (Friston, Frith, Liddle & Frackowiak, 1993). Plusieurs méthodes existent pour faire ce type d'analyse (Rubinov & Sporns, 2010), chacune menant à des inférences qui leur sont propres (Horwitz, 2003). La connectivité fonctionnelle au repos indique les patrons de fluctuations spontanées du signal hémodynamique (*c.f.* 1.4.1.) lorsque le sujet est simplement étendu dans l'appareil sans avoir aucune tâche à accomplir. Cette méthode devrait donc révéler des activations (ou désactivations) qui sont synchronisées temporellement et spatialement, entre des régions cérébrales qui sont anatomiquement et fonctionnellement associées (Greicius, Supekar, Menon & Dougherty, 2009).



nombreuses psychopathologies telles que la dépression, le trouble obsessionnel-compulsif et l'abus de substances (Gasquoin, 2013; Holroyd & Yeung, 2012; Shackman et al., 2011).

Le rôle du pACC est couramment associé à des processus affectifs. En effet, des études de métaanalyses quantitatives ont démontré que l'activation du pACC est spécifiquement associée aux tâches expérimentales à contenu émotionnel (Torta & Cauda, 2011), tout comme elle covarie avec l'activation d'un ensemble d'aires cérébrales connues pour leur implication dans le traitement des émotions, le contrôle cognitif et l'autoréflexion (Yu et al., 2011). Alors que la partie rostrale du ACC est surtout liée aux domaines affectifs, ces études ont également mis en évidence l'implication du MCC dans une pluralité de tâches et de processus, tel que l'attention, la mémoire, le langage, la douleur et l'exécution d'action, tandis que la portion caudale du cortex cingulaire (pMCC et dPCC) est liée aux fonctions sensorimotrices (Torta & Cauda, 2011; Yu et al., 2011).

Ainsi, l'activation du MCC est fréquemment rapportée dans la littérature, probablement en raison de sa multidimensionnalité fonctionnelle. Dans cette optique, cette région cérébrale est de plus en plus considérée comme un lieu de convergence et de régulation des afférences provenant de diverses structures et réseaux (Yeung, 2013; Yu et al., 2011; Torta & Cauda, 2011; Shackman et al., 2011; Holroyd & Yeung, 2012).

### *Rôle fonctionnel dans la douleur*

Dans le contexte de la douleur, pratiquement toutes les études rapportent une activation du cortex cingulaire en lien avec une stimulation douloureuse (Treede & Apkarian, 2008). Plus

précisément, le plus fort lieu de convergence des foyers d'activations tel que révélé par une métaanalyse se situe dans sa partie moyenne, le MCC (Duerden & Albanese, 2013).

Enfin, un grand nombre d'études supporte le lien entre le aMCC et l'aspect affectif-motivationnel de la douleur (Apkarian et al., 2013). À titre d'exemple, l'étude classique de Rainville et al. (1997) a démontré que l'activité dans cette région varie en fonction de l'aspect désagréable de la douleur par opposition à l'évaluation sensorielle de l'intensité de la stimulation (Rainville, Duncan, Price, Carrier & Bushnell, 1997).

### **Thalamus**

Le thalamus est une structure diencephalique qui, de manière générale, relaie les inputs visuels, auditifs et somatosensoriels, via des circuits formés de connexions réciproques avec le cortex, les noyaux gris centraux et le cervelet (Strominger, Demarest & Laemle, 2012). Par ces relais modulateurs, le thalamus joue un rôle critique dans l'activité somatomotrice, mais aussi dans la cognition, la conscience et l'éveil. Il est constitué de plusieurs noyaux ayant chacun leurs interconnexions avec des zones corticales et sous-corticales spécifiques.

Le thalamus fait partie des aires cérébrales où une activation en lien avec la douleur est le plus fréquemment rapportée (Bushnell & Apkarian, 2006). Les noyaux thalamiques ventropostérieurs latéral et médian (VPL et VPM) sont directement concernés par la douleur puisqu'ils relaient les afférences nociceptives spinothalamiques vers les aires corticales somatosensorielles SI et SII (Strominger et al., 2012). D'autre part, les interconnexions entre les noyaux thalamiques antérieurs, médians et intralaminaires, avec les zones préfrontales et limbiques pourraient être associés aux dimensions cognitives et affectives de la douleur.

### **1.1.3. Sommaire**

En résumé, la douleur est le fruit de l'ascension d'un influx nerveux émanant de cellules périphériques plus ou moins spécifiques à la nociception, dont le signal est transmis de la corne dorsale de la moelle épinière vers le tronc cérébral (notamment le PAG et le RVM) et le thalamus (noyaux VPL/VPM, postérieurs et médians), puis vers le cortex. Certaines aires cérébrales ont fréquemment été associées à la perception de la douleur par leur activation en lien avec l'application d'un stimulus douloureux, telle que mesurée en imagerie cérébrale fonctionnelle. Il s'agit notamment de SI, SII, l'insula, le cortex cingulaire antérieur et moyen (Apkarian et al., 2013; Duerden & Albanese, 2013). SI, SII et le pINS ont plus spécifiquement été associés à l'aspect sensoridiscriminatif de la douleur, tandis que l'ACC, le aMCC et l'aIN sont davantage liés à sa dimension affective-motivationnelle. D'autre part, la perception de la douleur ne découle pas uniquement d'afférences unidirectionnelles. Plusieurs mécanismes modulateurs se mettent en branle à divers niveaux du système nerveux central.

## **1.2. La modulation de la douleur**

Le vaste réseau cérébral engagé dans la perception de la douleur reflète toute la complexité de cette expérience. La relation entre l'intensité d'un stimulus douloureux et l'expérience subjective rapportée n'est pas toujours linéaire. L'expérience douloureuse est issue d'une constante interaction entre plusieurs facteurs d'ordre psychologique (p.ex. engagement attentionnel, état émotionnel, interprétation du contexte) et physiologique (p.ex. degré d'activation sympathique, stimulation douloureuse d'un site différent) qui sont intrinsèquement liés. En effet, le signal nociceptif entraîne une sensation, de laquelle découle une activation

autonomique associée à une évaluation cognitive de la menace ou de l'intrusion. Subséquemment, cette évaluation conduit à une réaction émotionnelle, qui, à son tour, teinte les cognitions et les sensations, et ainsi de suite (Price & Bushnell, 2004; Price, Hirsh & Robinson, 2009).

Ces influences modulatrices ne sont pas seulement "interprétatives". Elles se produisent par un système de contrôle descendant pro- et anti-nociceptif via des interactions mésencéphalo-spinales, cortico-mésencéphalo-spinales et cortico-corticales (Heinricher & Fields, 2013). Le rôle de la PAG et du RVM est majeur dans cette modulation (Figure 1).

### **1.2.1. Système descendant de modulation de la douleur**

La PAG est une structure allongée de matière grise qui entoure l'aqueduc de Sylvius dans le mésencéphale dorsomédial. Elle reçoit des afférences corticales (cortex préfrontal médian, ACC, aINS), limbiques (amygdale) et diencephaliques (hypothalamus; Heinricher & Fields, 2013). Plusieurs noyaux du tronc cérébral projettent également vers le PAG, dont le noyau cunéiforme adjacent, la formation réticulée pontique et bulbaire, le locus coeruleus et le RVM. La PAG reçoit aussi des afférences spinales directement des neurones nociceptifs de la corne dorsale. Enfin, ses projections vers le thalamus médian et le cortex orbitofrontal seraient impliquées dans la régulation de la douleur, tandis que ses projections vers le tegmentum pontique et le bulbe ventrolatéral seraient impliquées dans la régulation autonome associée (Heinricher & Fields, 2013).

La PAG est une plaque tournante des mécanismes analgésiques descendants, mais son action dépend de ses connexions avec le RVM. En effet, la suppression (p.ex. par lésions,

anesthésie locale) des afférences de la PAG vers le RVM bloque l'action antinociceptive de la PAG (Fields, Heinricher & Mason, 1991). Le RVM est une région du bulbe rachidien qui est composé du noyau raphé magnus et de la formation réticulée ventrale adjacente au noyau réticulaire gigantocellulaire. La majorité de ses afférences proviennent de la PAG et du noyau cunéiforme adjacent, mais il reçoit aussi des projections pontiques dorsolatérales (région parabrachiale et bulbe rostroventrolatéral). La majorité des projections du RVM vise directement les neurones nociceptifs de la corne dorsale de la moelle épinière, mais quelques efférences parviennent également à l'hypothalamus et l'amygdale (Fields et al., 1991; Heinricher & Fields, 2013). L'action antinociceptive du système descendant PAG-RVM est principalement médiée par le système opioïdérique, qui répond d'ailleurs aux opioïdes exogènes (narcotiques; Fields et al., 1991; Heinricher & Fields, 2013).

### **1.2.2. Substrats cérébraux de la modulation de la douleur**

Plusieurs méthodes psychologiques ont démontré leur efficacité pour réduire la douleur, notamment la modulation attentionnelle (Villemure & Bushnell, 2002; Valet et al., 2004), le placebo (Benedetti, Mayberg, Wager, Stohler & Zubieta, 2005), l'hypnose (Rainville & Price, 2013), la modulation émotionnelle (Seymour & Dolan, 2013; Roy, Lebus, Peretz & Rainville, 2011), la méditation (Grant, 2014) et la perception de contrôle du stimulus (Wiech et al., 2006; Mohr, Leyendecker, Petersen & Helmchen, 2012). L'hypoalgésie induite psychologiquement reposerait sur des mécanismes endogènes de régulation de la douleur faisant intervenir divers processus cérébraux selon l'intervention préconisée, le paradigme expérimental, et les effets psychophysiques de ces interventions. En effet, le système du contrôle descendant de la

douleur semble agir conjointement avec un ensemble de structures corticales et sous-corticales dans la modulation endogène de la douleur (Bingel & Tracey, 2008; Schweinhardt & Bushnell, 2010), ce qui est par ailleurs appuyé par l'observation d'interconnexions cortico-mésencéphaliques liant la région du PAG avec le PFC, l'amygdale, le thalamus et l'hypothalamus (Hadjipavlou, Dunckley, Behrens & Tracey, 2006). Il n'existe pas jusqu'à maintenant de patron clair d'activation cérébrale associé au déclenchement de l'hypoalgésie induite psychologiquement puisque ceux-ci varieraient en fonction des approches (Wiech, Ploner & Tracey, 2008). Toutefois, le PFC pourrait être à l'origine de cette modulation endogène de la douleur (Lorenz, Minoshima & Casey, 2003; Bingel & Tracey, 2008). En effet, l'importance de l'action du PFC dans la modulation de la douleur est suggérée notamment par l'association entre un dysfonctionnement frontal chez des patients présentant une démence de type Alzheimer et une réduction de l'efficacité analgésique d'un placebo (Benedetti et al., 2006). Cette action du PFC dans la modulation endogène de la douleur pourrait refléter des processus cognitifs d'anticipation ou d'interprétation émotionnelle (Wager, Atlas, Leotti & Rilling, 2011), ainsi que certains processus exécutifs et attentionnels (Buhle, Stevens & Wager, 2012).

### *Le placebo*

L'hypoalgésie placebo est produite lorsqu'un sujet présente une diminution de sa douleur suivant, de manière générale, l'administration d'un agent inerte présenté comme analgésique sous diverses formes : crème (p.ex. Bingel, Lorenz, Schoell, Weiller & Büchel, 2006; Wager et al., 2004), injection saline (p.ex. Petrovic, Kalso, Petersson & Ingvar, 2002), ingestion de

comprimés (p.ex. Nemoto, Nemoto, Toda, Mikuni & Fukuyama, 2007; Kong et al., 2006), "fausses" aiguilles d'acupuncture (Kong et al., 2006), ou toute autre forme d'intervention sans ingrédient pharmacologique actif. Au niveau psychologique, l'effet placebo dépendrait d'un conditionnement automatique non conscient et d'une modulation consciente des attentes en fonction des expériences passées (Kong & Benedetti, 2014).

De récentes métaanalyses indiquent que l'hypoalgésie placebo s'accompagne d'une baisse d'activation dans les aires cérébrales généralement associées à la perception de la douleur, dont le aMCC dorsal, le thalamus et l'insula, ainsi que dans l'amygdale et le striatum. De plus, les attentes de réduction de la douleur dans l'hypoalgésie placebo sont associées à une augmentation de l'activité dans plusieurs régions préfrontales dorsolatérales, ventromédianes et orbitofrontales, ainsi que dans le pACC (Atlas & Wager, 2014).

### *La distraction*

Plusieurs stratégies de modulation de l'attention visant l'hypoalgésie ont été employées dans le cadre d'études d'imagerie cérébrale fonctionnelle (Wiech et al., 2008), notamment des tâches d'interférence cognitive (Stroop; Bantick et al., 2002), d'identification de direction de mouvements de stimuli visuels (Brooks, Nurmikko, Bimson, Singh & Roberts, 2002), de génération de mots selon une catégorie donnée (Frankenstein, Richter, McIntyre & Rémy, 2001), de résolution de labyrinthes (Petrovic, Petersson, Ghatan, Stone-Elander & Ingvar, 2000), ou par l'instruction au sujet de porter attention ou non au stimulus appliqué (Tracey et al., 2002).

Les circuits cérébraux impliqués dans la modulation de la douleur par la distraction seraient différents de ceux associés à la modulation émotionnelle (Villemure & Bushnell, 2009), ce qui suggère une certaine spécificité cérébrofonctionnelle de cette approche psychologique. Par un brillant paradigme expérimental, Villemure et Bushnell (2009) ont pu séparer l'effet modulateur de l'attention et celui de l'état émotionnel induit par des odeurs. On présentait des paires de stimuli thermiques douloureux simultanément avec des paires d'odeurs. La tâche des participants était soit de discriminer l'intensité des deux stimulations douloureuses, soit de faire la distinction entre deux intensités d'odeurs. De cette façon, l'attention des participants était dirigée vers l'une ou l'autre des modalités de stimulation. De plus, dans la moitié des essais, la stimulation odorante était plaisante dans 50% du temps, et déplaisante aux autres essais. Avec un tel paradigme expérimental, l'influence des deux sources potentielles de modulation de la douleur pouvait être isolée: la direction de l'attention sur la douleur ou loin de la douleur, et l'état émotionnel ("*mood*") induit par une odeur agréable ou désagréable. L'insula antérieure montrait une certaine spécificité à la modulation de la douleur par la redirection de l'attention.

De manière générale, l'hypoalgésie induite par une tâche de distraction est associée, d'une part, à une réduction de l'activité dans le thalamus ainsi que dans plusieurs aires corticales impliquées dans la perception de la douleur, comme SI, le MCC et l'insula. D'autre part, elle est également associée à une activation de certaine partie du ACC/MCC, du PAG et du cortex orbitofrontal (Apkarian et al., 2013).



## *L'hypnose*

On induit un "état hypnotique" chez un sujet principalement par des suggestions afin que celui-ci utilise ses propres habiletés cognitives pour vivre une expérience subjective de relaxation et d'absorption mentale envers l'objet de la suggestion. Cet état de relaxation et d'absorption conduit à une suspension de la vigilance, du jugement et de l'orientation temporelle et spatiale, donnant lieu à une perception d'automatisme, c'est-à-dire une impression que ses actions sont involontaires et exécutées sans effort (Price & Barrell, 1990; Rainville & Price, 2013). L'hypoalgésie hypnotique peut être produite par diverses stratégies cognitives comme la relaxation profonde, l'imagerie dissociative (s'imaginer flotter hors de son corps), et l'hypoalgésie focale (se concentrer sur la sensation qui s'atténue) (De Pascalis, Magurano, Bellusci & Chen, 2001).

L'étude cérébrofonctionnelle de l'hypoalgésie hypnotique a démontré la spécificité de certaines aires cérébrales à différentes dimensions de la perception de la douleur. Ainsi, des suggestions visant la réduction ou l'augmentation du caractère déplaisant de la douleur sont associées au aMCC (Rainville et al., 1997), et la modulation de l'intensité de la douleur (aspect sensoridiscriminatif) est liée à SI (Hofbauer, Rainville, Duncan & Bushnell, 2001). Aussi, les suggestions hypnotiques de modulation de la douleur sont associées à une augmentation de l'activité dans des régions préfrontales et dans le tronc cérébral (Rainville et al., 1999; Faymonville et al., 2000).

## *Les émotions*

L'induction d'états émotionnels dans le but de modifier la perception d'un stimulus douloureux peut être produite de diverses façons, notamment par des images (Roy, Piché, Chen, Peretz & Rainville, 2009; Rudy et al., 2005), des odeurs (Villemure & Bushnell, 2009), des vidéos (Loggia, Mogil & Bushnell, 2008), des suggestions hypnotiques (Rainville, Bao & Chrétien, 2005), des épreuves d'arithmétique (induction de stress; Yilmaz et al., 2010), ou encore des états religieux (Wiech et al., 2009). On observe généralement une augmentation de la douleur avec les émotions négatives ou déplaisantes, et inversement, une diminution avec des émotions positives ou agréables (Villemure & Bushnell, 2002; Meagher, Arnau & Rhudy, 2001). L'étude des mécanismes cérébraux de l'augmentation de la douleur par les émotions négatives indique un engagement de structures limbiques telles que le ACC, l'insula, des aires frontales, l'hippocampe (Schweinhardt & Bushnell, 2010), le gyrus parahippocampal (Roy et al., 2009) et l'amygdale (Wiech & Tracey, 2009). À l'opposé, l'étude des corrélats cérébraux de la diminution de la douleur par des émotions positives est par ailleurs peu concluante (p.ex. Roy et al., 2009), malgré qu'un effet psychophysique ait clairement été démontré (Villemure & Bushnell, 2002), ce qui, par conséquent, fait appel à de nouvelles recherches en ce sens.

## *La méditation*

L'étude des mécanismes neuronaux de l'hypoalgésie produite par la méditation est en essor depuis quelques années. Les deux grandes catégories d'approches sont la focalisation de l'attention (*focused attention*) et la *open monitoring* qui comprend la méditation pleine conscience (*mindfulness*; Grant, 2014). Un des mécanismes physiologiques sous-tendant l'effet

analgésique de la méditation pleine conscience consisterait en une dominance de l'activation parasympathique (Grant, 2014). Les devis expérimentaux les plus souvent utilisés pour examiner l'activité cérébrale en lien avec une réduction de la douleur attribuable à la méditation consiste en une comparaison intersujet, c'est-à-dire entre des méditants expérimentés et des participants naïfs à la méditation. Ce type d'études nous indique qu'une douleur moins grande chez les méditants, comparativement aux sujets contrôles, est associée paradoxalement à une plus grande activation cérébrale dans les zones généralement associées à la douleur (Grant, Courtemanche & Rainville, 2011; Lutz, McFarlin, Perlman, Salomons & Davidson, 2013), mais aussi une moins grande activation dans des aires limbiques et frontales (Grant et al., 2011; Gard et al., 2012).

### **1.2.3. Sommaire**

En résumé, la perception de la douleur résulte d'une dynamique entre de multiples variables physiologiques, émotionnelles et cognitives. Le signal nociceptif peut être modulé dès son entrée dans le système nerveux central, via le système du contrôle descendant de la douleur. La PAG et le RVM du tronc cérébral sont deux structures clé de ce système, dont l'action serait en partie médiée par des efférentes indirectes corticales, notamment en provenance du PFC (Heinricher & Fields, 2013).

Plusieurs méthodes psychologiques ont démontré leur efficacité à réduire la douleur (Price & Bushnell, 2004), comme le placebo, la distraction, l'hypnose, l'induction d'émotions et la méditation, ce qui reflète le remarquable potentiel de régulation endogène de la douleur. De manière générale, le PFC pourrait jouer un rôle pivot dans le déclenchement de

l'hypoalgésie induite psychologiquement (Bingel & Tracey, 2008). Néanmoins, les patrons d'activations cérébrales associés au déclenchement de l'hypoalgésie induite psychologiquement varient entre ces diverses approches, mais aussi entre les études portant sur la même approche. Conséquemment, il est difficile de dresser un portrait clair des bases cérébrofonctionnelles qui les unissent ou les distinguent. Cette thèse vise une meilleure compréhension des mécanismes neuropsychologiques à la base de cette capacité de régulation endogène.

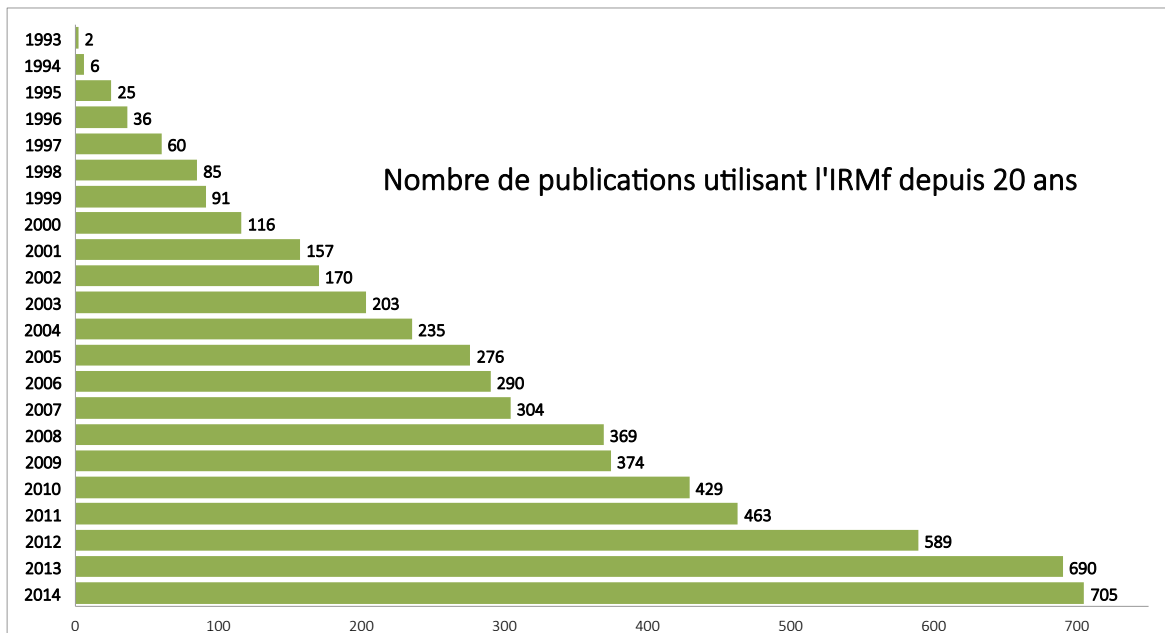
Dans la mesure où une certaine confusion et une méconnaissance de ces mécanismes persistent en dépit du nombre considérable d'études dans le domaine, une réévaluation et une synthèse de ces résultats s'imposaient. Le choix d'une méthode de métaanalyse était d'autant plus opportun que de récentes techniques d'analyse quantitative de résultats de neuroimagerie étaient en train d'émerger au début de ce travail. Dans les prochaines lignes, nous exposons les raisons pour lesquelles une méthodologie métaanalytique était le meilleur moyen de répondre aux questions de cette thèse, et pourquoi une telle méthodologie peut faire avancer les connaissances significativement. De plus, puisqu'il s'agit d'une méthodologie relativement nouvelle, la présentation de ces principes méthodologiques et statistiques est proposée dans la prochaine section.

### **1.3. Métaanalyse : méthodologies**

*"We are drowning in information and starving for knowledge."* — Rutherford D. Roger

Depuis l'accessibilité des techniques d'imagerie cérébrale fonctionnelle telles que l'fMRI et la PET, la quantité d'études utilisant ces méthodes s'est accrue de façon exponentielle.

L'fMRI, à elle seule, a donné lieu à plus de 2800 publications depuis 2010, comparativement à plus de 1600 lors des cinq années précédentes (Figure 3).



**Figure 3.** Nombre de publications utilisant l'fMRI depuis 1993.

Recherche effectuée dans la base de données Medline le 5 septembre 2014, avec les mots-clés "fMRI" et "human".

Lorsque les données empiriques sur un sujet s'accroissent, une vue d'ensemble est nécessaire pour en tirer des conclusions globales et pour orienter les recherches futures. La métaanalyse est alors toute indiquée. La dernière décennie a d'ailleurs connu un nombre grandissant de métaanalyses de données d'imagerie cérébrale fonctionnelle (Jennings & Van Horn, 2012). Plusieurs facteurs sont à l'origine de cette multiplication, dont l'accumulation d'études expérimentales (Stelzer, Lohmann, Mueller, Buschmann & Turner, 2014), la nécessité d'en synthétiser les résultats (Fox, Parsons & Lancaster, 1998; Derrfuss & Mar, 2009). Par conséquent, les métaanalyses basées sur les coordonnées d'activation ont

récemment gagné en popularité en raison notamment de l'influence scientifique considérable qu'elles présentent.

### **1.3.1. Influences des métaanalyses**

Le système scientifique est ainsi fait que la citation d'une étude reflète la reconnaissance de la communauté scientifique envers celle-ci. La mesure la plus commune de l'impact scientifique d'une étude est donc son nombre de citations (Uthman, Okwundu, Wiysonge, Young & Clarke, 2013). À ce sujet, les métaanalyses sont citées plus fréquemment que tout autre type d'études (Patsopoulos, Analatos & Ioannidis, 2005). Avec les revues systématiques, elles occupent le rang le plus élevé d'évidence scientifique<sup>6</sup>. Cette valorisation s'explique par une méthodologie systématique, exhaustive, quantitative et statistique. La perspective globalisante qu'elles fournissent permet de statuer sur l'état des connaissances dans un domaine à un moment donné (Ioannidis, 2001). C'est en effet l'examen systématique et statistique de centaines, et même de milliers de résultats qui permet de déterminer les effets les plus robustes et reproductibles, sur lesquels devraient reposer l'élaboration de nos recherches futures. En outre, les métaanalyses sont susceptibles de résoudre certaines divergences d'opinions (Lau, Ioannidis & Schmid, 1998), en plus d'identifier des faiblesses méthodologiques à reviser (Ioannidis, 2001). Ceci est particulièrement estimable sur le plan de l'avancement scientifique. Ce faisant, la métaanalyse aide à générer de nouvelles hypothèses (p.ex. Eickhoff et al., 2011; Poldrack, 2011), tout comme elle contribue à l'amélioration des protocoles expérimentaux (p.ex. Stroup et al., 2000; David et al., 2013).

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<sup>6</sup> <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>.

En neuroimagerie fonctionnelle plus particulièrement, les métaanalyses offrent un avantage supplémentaire: celui de renforcer la validité des inférences inversées<sup>7</sup> (*reverse inference*; Poldrack, 2011), surtout lorsque la sélection des contrastes implique de retirer l'activation cérébrale non spécifique à l'objet d'étude (Hutzler, 2014), ce qui est par ailleurs le cas, et la force, de cette thèse.

La métaanalyse offre de nombreux avantages et peut s'avérer une méthode de premier choix en fonction des hypothèses à évaluer et de l'état de la recherche. Dans le cas présent, le sujet de cette thèse comporte une approche globalisante pour mener à l'identification d'aires cérébrales impliquée dans l'autorégulation de la douleur. Qui plus est, l'état actuel de la recherche est propice à une telle vue d'ensemble en raison du nombre élevé d'études portant sur ces questions.

### **1.3.2. Démarche méthodologique générale**

La métaanalyse est une extension méthodologique et statistique des études expérimentales : elle permet d'amener encore plus loin les données empiriques, notamment en comblant les lacunes des études individuelles, afin de tendre vers des vérités scientifiques (Lieberman & Cunningham, 2009). Jusqu'à quel point? L'utilité de la métaanalyse, sa portée scientifique, dépend de sa méthodologie, au même titre que la qualité de l'étude expérimentale dépend de son devis, et il y a autant de bonne façon de réaliser une métaanalyse qu'il y a de question de recherche (Borenstein, Hedges, Higgins & Rothstein, 2009).

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<sup>7</sup> Identifier l'activité cérébrale en lien avec une manipulation expérimentale est une inférence directe (*forward inference*). Conclure à l'engagement d'un processus mental d'après un patron d'activations cérébrales est une inférence inversée.

## *Sélection des études*

Toute métaanalyse comporte une première étape de sélection des articles et des foyers d'activation à regrouper statistiquement. Cette sélection peut se faire de différentes façons, avec un niveau plus ou moins élevé de contrôle : par une sélection et une compilation automatisée ou manuelle. Par exemple, NeuroSynth ([neurosynth.org](http://neurosynth.org)) développé par Yarkoni et collaborateurs (2011) vise un regroupement à très large échelle de foyers d'activation à l'aide d'une sélection automatisée de coordonnées rapportées dans le texte d'articles publiés et répertoriés. D'un autre côté, des bases de données comme SumsDB ([sumsdb.wustl.edu/sums/dispatch.do?forward=index](http://sumsdb.wustl.edu/sums/dispatch.do?forward=index); Van Essen, 2002; Van Essen et al., 2001) et Sleuth ([brainmap.org/sleuth/](http://brainmap.org/sleuth/); Fox & Lancaster, 2002; Fox et al., 2005; Laird, Lancaster & Fox, 2005) contiennent des données codifiées manuellement, et sont issues d'un effort de collaborations entre divers laboratoires.

La procédure de sélection des études n'est donc pas uniforme à travers les métaanalyses et dépend de ses objectifs spécifiques. Il en est de même pour la codification des paramètres méthodologiques des études sélectionnées. Cependant, ces deux étapes sont cruciales puisque la validité des inférences subséquentes leur sera tributaire (Borenstein et al., 2009). En effet, les caractéristiques expérimentales des études guideront leur regroupement afin de favoriser l'homogénéité des effets représentés parmi les jeux de données. Dans cette thèse, l'approche manuelle réalisée spécifiquement pour ses questions de recherche a été privilégiée afin de fournir un maximum de contrôle sur les données (*c.-à-d.* minimiser les effets confondants) et sur les variables à considérer pour l'analyse.



## *Analyse*

Contrairement aux méthodes classiques de métaanalyse qui s'effectuent sur la base des tailles d'effet, les métaanalyses en neuroimagerie sont basées sur les effets de localisation (Fox, Parsons & Lancaster, 1998). Elles ont donc des méthodes statistiques qui ont spécifiquement été développées pour la combinaison quantitative de ce type de données (Turkeltaub, Eden, Jones & Zeffiro, 2002; Chein, Fissell, Jacobs & Fiez, 2002; Wager, Phan, Liberzon & Taylor, 2003; Yarkoni, Poldrack, Nichols, Van Essen & Wager, 2011). De manière générale, l'analyse se fait à partir des coordonnées d'activation cérébrales telles que rapportées dans les articles sélectionnés, c'est pourquoi on nomme ces méthodes "métaanalyse basée sur les coordonnées d'activation" (CBMA; *coordinate-based meta-analysis*). Les deux principaux algorithmes de CBMA actuellement utilisés sont la méthode ALE (*activation likelihood estimation*; Turkeltaub et al., 2002) et la *Multilevel Kernel Density Analysis* (MKDA; Wager et al., 2003; Wager, Lindquist & Kaplan, 2007). Leur algorithme et l'interprétation de leur statistique comportent certaines nuances : la ALE calcule la probabilité qu'une activation ait réellement eu lieu dans une coordonnées, alors que la MKDA calcule le nombre d'études rapportant une activation proche d'une coordonnée. Leurs résultats sont toutefois cohérents et relativement comparables (Salimi-Khorshidi, Smith, Keltner, Wager & Nichols, 2009). Dans cette thèse, la méthode ALE a été privilégiée en raison de l'abondance de la littérature supportant sa validité, de son accessibilité, et de l'optimisation continue de son

algorithme<sup>8</sup> (Laird et al., 2005; Eickhoff et al., 2009; Turkeltaub et al., 2012; Eickhoff, Bzdok, Laird, Kurth & Fox, 2012).

Les CMBA reposent essentiellement sur des résultats d'études d'imagerie cérébrale, c'est pourquoi il importe d'abord de clarifier certains aspects élémentaires de cette méthode. Voici donc une brève introduction aux méthodes d'imagerie cérébrale fonctionnelle qui permettra de comprendre le tout premier niveau d'acquisition des données dans une CMBA. Cette compréhension est en effet nécessaire à l'interprétation subséquente des résultats des méta-analyses de cette thèse. La présentation des étapes computationnelles de l'algorithme ALE suit subséquemment dans les prochaines sections.

### **1.3.3. Imagerie cérébrale fonctionnelle**

Qu'est-ce qu'une activation cérébrale? Le fonctionnement neuronal et la communication synaptique s'appuient sur des phénomènes électriques et neurochimique. Pour s'activer, le neurone a besoin de nutriments transportés dans le sang, comme l'oxygène et le glucose. En fMRI, l'activation cérébrale est l'interprétation que l'on fait des variations vasculaires locales, la réponse hémodynamique, en lien avec une manipulation expérimentale. Puisque cette réponse hémodynamique est fortement corrélée à l'activité neuronale (Logothetis, Pauls, Augath, Trinath & Oeltermann, 2001), cette mesure est considérée comme le reflet indirect d'une activation cérébrale. Il s'agit donc d'une méthode corrélationnelle indirecte plutôt que

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<sup>8</sup> Une collaboration est d'ailleurs en cours afin de produire un guide détaillé vulgarisant les étapes de l'algorithme d'analyse découlant des explications déjà élaborées dans le cadre de cette thèse.

causale, comme peut l'être l'enregistrement cellulaire directe (Logothetis, 2008). C'est sur ce principe hémodynamique que sont basées les études d'fMRI et de PET.

### *fMRI et PET*

L'fMRI est totalement non-invasive et emploie de puissants champs magnétiques (habituellement 1,5 ou 3 teslas) combinés à des radiofréquences pour produire des images tridimensionnelles plus ou moins contrastées. Les détails des images proviennent des propriétés magnétiques variables des molécules qui composent les tissus ou les fluides corporels examinés, comme la matière blanche et la matière grise du cerveau (p.ex. images T1 et T2), ainsi que l'hémoglobine. Les cartes d'activation cérébrale sont dérivées des variations locales de consommation d'oxygène sanguin (image T2\*): le taux d'hémoglobine *oxygénée* comparativement au taux d'hémoglobine *désoxygénée*. Ces variations forment le signal *BOLD* (*Blood Oxygenation Level Dependant*) que l'on interprète comme le résultat d'une activité neuronale locale *associée* à un événement expérimental.

La PET localise l'émission d'une certaine quantité de positons émis par un traceur radioactif préalablement injecté à l'individu. Le radiotraceur le plus couramment utilisé est l'oxygène fixé aux molécules d'eau (c.-à-d. mesure de volume/débit sanguin), mais un ligand au glucose est parfois choisi (c.-à-d. mesure métabolique). L'image est dérivée du positionnement des densités, ou des amas, de positons. Une augmentation de la concentration de positons dans une aire cérébrale indique généralement une augmentation locale du débit

sanguin, le signal *rCBF* (*Regional Cerebral Blood Flow*), résultant d'une plus grande activité neuronale<sup>9</sup>.

L'IRM et la PET sont couramment utilisées en imagerie médicale pour obtenir des images tridimensionnelles des organes internes. L'aspect *fonctionnel* de ces techniques d'imagerie provient de l'ajout de la dimension temporelle aux images tridimensionnelles, par l'acquisition séquentielle de plusieurs images, chacune associée à un événement dans le temps, par exemple l'application d'un stimulus douloureux. La résolution spatiale, de l'ordre du millimètre, est comparable entre les deux méthodes, quoique l'fMRI surpasse légèrement la PET. La résolution temporelle la PET est un peu moins grande que l'fMRI : elle peut aller en deçà de la seconde pour l'fMRI, tandis qu'elle est de l'ordre de la minute pour la PET (Meyer-Lindenberg, 2010).

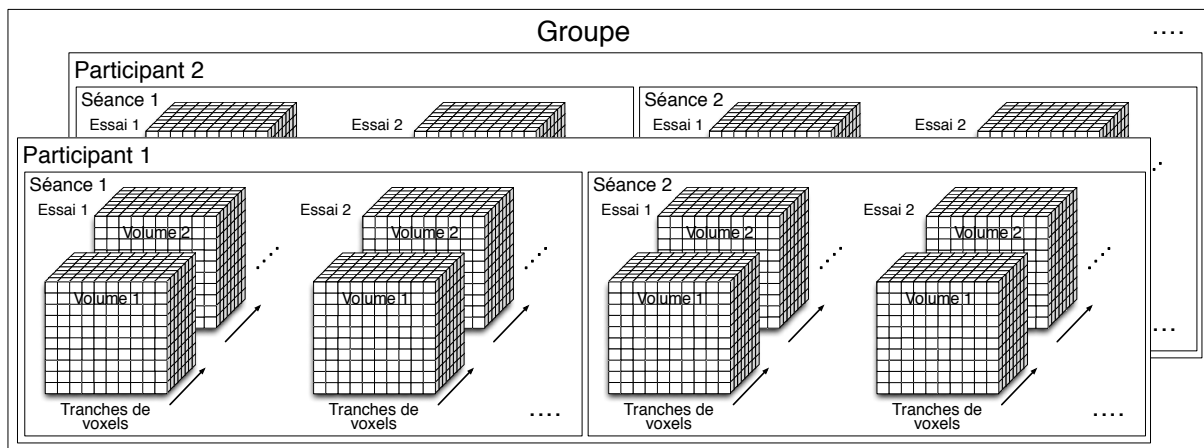
L'fMRI est maintenant la plus couramment utilisée puisqu'elle est totalement non-invasive et qu'elle offre une meilleure résolution temporelle, d'autant plus que cette technique a connu des avancées substantielles au courant des dernières décennies (Bandettini, 2009). Elle présente par contre quelques limitations, comme une très grande sensibilité aux mouvements subtils comme la respiration et les pulsations cardiaques. La non-uniformité du signal à travers le cerveau constitue une autre contingence méthodologique. En effet, la proximité des sinus faciaux et des aires orbito-frontales et temporales occasionne une baisse relative ou une distorsion spatiale du signal dans ces zones (Cabeza & Kingstone, 2006).

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<sup>9</sup> Depuis l'accessibilité de l'fMRI, la PET est à présent surtout utilisée en recherche dans l'étude de systèmes de neurotransmetteurs plutôt que pour l'observation d'activation cérébrale non spécifique à un type de cellule nerveuse.

## Acquisition des données

Un signal BOLD, ou rCBF, est enregistré pour chaque voxel de l'image. Le voxel est l'analogie tridimensionnelle du pixel. Son volume se situe généralement autour de 1 à 3 mm<sup>3</sup>. Pour couvrir tout le cerveau, l'acquisition des données se fait par multiples tranches (p.ex. imagerie écho-planaire ou EPI), typiquement de 64 x 64 voxels, à intervalles de plusieurs dizaines de millisecondes<sup>10</sup> (Figure 4). Un volume (une image complète tridimensionnelle du cerveau) comprend environ 40 tranches et prend généralement 2 à 3 secondes. La durée de l'essai (du *scan* ou du *run*) déterminera le nombre de volumes. Chaque participant peut être soumis à un ou plusieurs essais.



**Figure 4.** Acquisition des données fMRI ou PET.

Un seul volume contient près de 200 000 voxels. Par conséquent, une acquisition produit une immense quantité de données qui contiennent les effets d'intérêt (la variance attribuable à

<sup>10</sup> Les paramètres d'acquisition des données dans ce paragraphe sont donnés à titre indicatif seulement. Ces valeurs peuvent varier selon les protocoles d'expérimentation. L'explication des trajectoires d'acquisition (p.ex. *echo-planar*, *spiral*, *radial*) est omise ici, ainsi que l'étape du *slice timing* dans la préparation des données.

la manipulation expérimentale), mais aussi des effets non spécifiques (le "bruit"). Il est donc nécessaire de départager ces sources de variance en "nettoyant" les données.

### *Préparation des données*

La préparation (*pre-processing*) des données avant l'analyse statistique comporte généralement les étapes suivantes : le réalignement (*motion-correction*), la normalisation et le filtrage-lissage (*smoothing*) spatial. D'abord, les artefacts de mouvements sont corrigés avec une méthode rétrospective de réalignement. Ensuite, les images de chaque sujet sont normalisées afin de minimiser la variabilité anatomique interindividuelle, en fonction d'un espace stéréotaxique standard, soit Talairach (Talairach & Tournoux, 1988) ou MNI (Collins, Neelin, Peters & Evans, 1994; Mazziotta et al., 2001). Puis, les données sont filtrées-lissées spatialement (*smoothing*) afin d'harmoniser le signal entre voxels avoisinants, ce qui a comme effet d'augmenter le ratio signal/bruit (élimine les hautes fréquences et garde les basses fréquences spatiales).

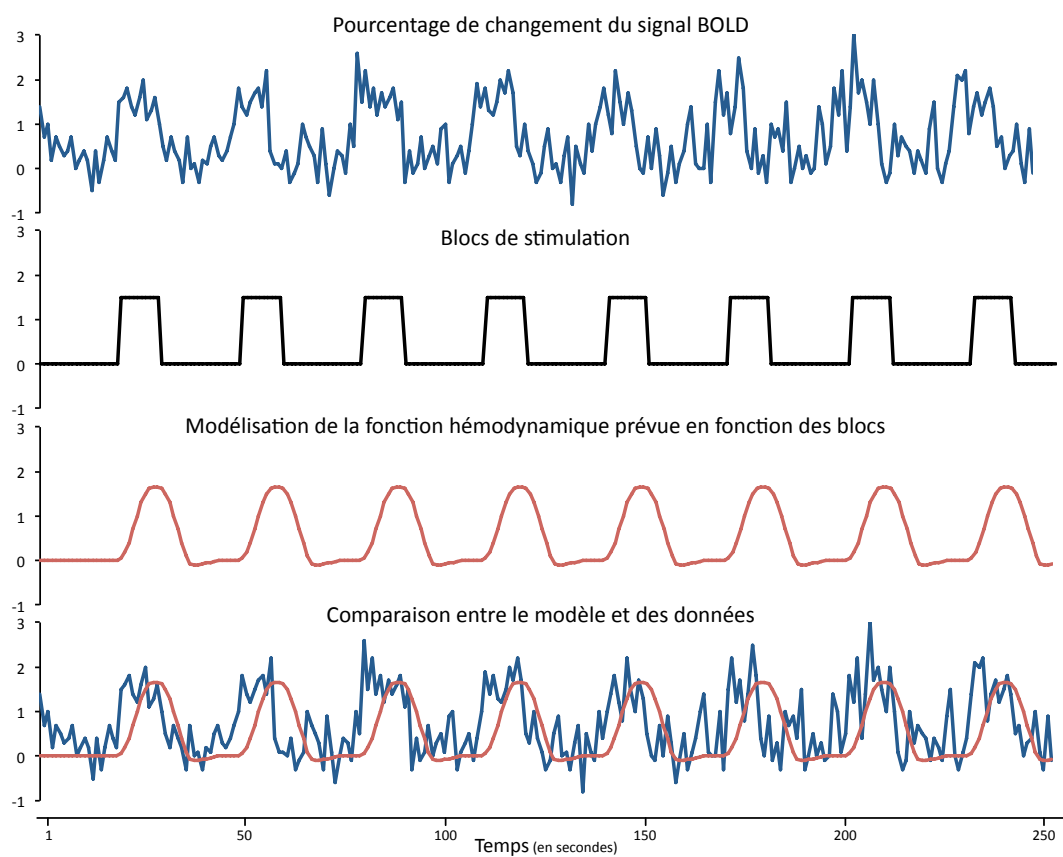
### *Analyses statistiques*

Les données ainsi préparées sont ensuite analysées en fonction d'un devis expérimental, typiquement à l'aide d'un modèle général linéaire (*General Linear Model*; Friston et al., 1994) en blocs (*block-design*; p.ex. stimulation d'une durée de 10 secondes) ou événementiel (*event-related*; p.ex. choc électrique de quelques millisecondes). On estime donc l'adéquation entre le modèle et les données par une convolution de la réponse hémodynamique prédite avec le modèle expérimental suivi d'une estimation de la correspondance (régression linéaire) entre cette réponse théorique et le signal réel observé, et ce pour chaque voxel (Figure 5). Cette

modélisation est le premier niveau de l'analyse statistique, et la variance qui en découle est l'effet intrasujet (*fixed-effect*). Cette étape produit une image *contraste* permettant de visualiser la distribution spatiale de l'activité cérébrale associée au paradigme expérimental (p.ex. les variations significatives de la réponse hémodynamique évoquée par le stimulus) pour chaque sujet. Un second niveau d'analyse intersujet est ensuite effectué. Il s'agit de l'analyse de groupe (*random-effect*) effectuée en comparant, voxel par voxel, les images contrastes de chaque sujet, le plus souvent à l'aide d'un test-t ou d'une analyse de variance. Cette étape est nécessaire pour permettre les inférences au-delà du groupe de sujets évalués, c'est-à-dire pour extrapoler les conclusions de l'étude à la population générale de laquelle est tiré l'échantillon de participants. Enfin, l'étape finale consiste à établir un seuil statistique. Il est important ici de tenir compte des multiples comparaisons (milliers de voxels par sujet) puisque la probabilité d'obtenir un résultat significatif par hasard augmente en fonction du nombre de tests effectués. En effet, l'analyse statistique des données d'imagerie cérébrale fonctionnelle comporte autant de comparaisons que de voxels, d'où la nécessité d'appliquer une correction dont l'objectif est de restreindre la probabilité de fausses découvertes (erreur de type I). Plusieurs méthodes de correction existent, dont la FDR (*False Discovery Rate*; Genovese, Lazar & Nichols, 2002) et la FWER (*Family Wise Error Rate*; Nichols & Hayasaka, 2003). Les détails de ces méthodes seront abordés dans la section dédiée à l'algorithme ALE (p. 43).

Au final, on obtient une carte d'activations cérébrales associées à la manipulation expérimentale à laquelle des sujets ont été soumis. Une même étude peut générer autant de cartes d'activation que d'effet d'intérêt; ce sont différents *contrastes*. Par exemple, pour une étude dans laquelle on veut identifier 1) les régions cérébrales associées plus spécifiquement à

une stimulation chaude douloureuse, ainsi que 2) les aires associées plus spécifiquement à une stimulation tiède non douloureuse, deux images contrastes (de groupe) peuvent être obtenues, c'est-à-dire un premier contraste *douleur* > *chaleur*, et un second contraste *chaleur* > *douleur*. Cette notion de contraste sera reprise dans les prochaines sections lors de l'exposition de la méthodologie de cette thèse.



**Figure 5.** Modélisation de la réponse hémodynamique aux données acquises en fMRI.



### 1.3.4. Métaanalyses basées sur les coordonnées d'activation

Les qualités méthodologiques des études fMRI et PET ainsi que la portée de leurs conclusions dépendent donc des paramètres d'acquisition des données, de l'analyse des images, mais surtout, elles découlent directement de la conception et de l'application du protocole expérimental. Les résultats de ces études sont rapportés sous forme de coordonnées des foyers d'activations cérébrales. C'est à partir de ces résultats publiés dans des articles que se font les CBMA.

L'idée générale de la méthode ALE de CBMA est d'assigner à chaque voxel d'une carte cérébrale une valeur indiquant la probabilité que l'activité cérébrale associée à l'effet d'intérêt soit réellement située à cet endroit. Le résultat final de cette analyse consiste en une carte 3D de probabilités de localisation de l'activité cérébrale en question. Les étapes préalables à cette matrice comprennent la sélection des articles selon des critères prédéfinis, la compilation de leurs caractéristiques méthodologiques et de leurs résultats, puis l'analyse de ces résultats à l'aide du logiciel GingerALE. Cette analyse comprend la création de la valeur ALE, la création d'une distribution nulle, puis le seuillage statistique. Une étape supplémentaire consistant à contraster des cartes ALE peut ensuite être réalisée.

#### *Terminologie*

Les termes relatifs aux procédures méthodologiques de CBMA qui sont utilisés dans cette thèse suivent la terminologie conventionnelle de la méthode ALE. Par contre, cette terminologie a été adaptée afin de favoriser la fluidité de la lecture en français. Les mots "étude" et "*study*" réfèrent à un article scientifique. Les termes "contrastes" et "*experiment*"

renvoient à un contraste d'analyse (p.ex. *douleur* > *chaleur*). Une même étude peut présenter plus d'un contraste. Pourquoi différencier les contrastes d'une même étude? Parce que ceux-ci contiennent des effets différents, ils renvoient donc à des phénomènes sous-jacents différents. De plus, un foyer (*foci*) d'activation signifie un pic d'activité tel que rapporté pour un contraste (*experiment*), dans un voxel positionné à une coordonnée x, y, z (Talairach ou MNI).

Rappelons enfin qu'un volume (une carte, une matrice) est une image tridimensionnelle du cerveau. Il est constitué de voxels, et chaque voxel "contient" une valeur (*c.f.* Figure 4).

### ***Algorithme général de GingerALE***

Les étapes de l'analyse telles qu'implémentées dans le logiciel GingerALE (version 2.3; [brainmap.org/ale/](http://brainmap.org/ale/); Eickhoff et al., 2009; Eickhoff et al., 2012; Turkeltaub et al., 2012) comprennent 1) le calcul à chaque voxel de la valeur ALE qui constitue la variable dépendante, 2) la création d'une distribution aléatoire de valeurs ALE en vue de réfuter l'hypothèse nulle selon laquelle les foyers d'activations sont répartis au hasard dans le cerveau, et 3) l'établissement d'un seuil statistique à partir duquel les résultats de la métaanalyse seront considérés significatifs. Cette analyse générale produit une carte ALE des probabilités de localisation d'activations cérébrales. Enfin, un second niveau d'analyse permet d'identifier les divergences et les convergences entre deux cartes ALE significatives : l'analyse de soustraction et de conjonction. Une description simplifiée de ces étapes computationnelles est maintenant présentée. Ces étapes sont également résumées et schématisées dans la Figure 6.

## Calcul de la valeur ALE

L'analyse se fait à partir d'un fichier texte contenant les foyers d'activations séparés par contrastes et présentés sous forme de coordonnées stéréotaxiques x, y, z standards (Talairach ou MNI). Ces coordonnées sont comparées à un masque de matière grise afin d'identifier les foyers qui en dépassent ses limites spatiales. Le calcul de la valeur ALE implique de combiner des foyers d'activations provenant d'études différentes. Les données sont donc inévitablement hétérogènes. Le degré d'hétérogénéité, ou ses effets, doivent être considérés en fonction de la question de recherche et de la méthodologie de chaque étude (Borenstein et al., 2009). Par conséquent, si la question est de connaître les aires cérébrales associées à l'hypoalgésie induite psychologiquement, les foyers provenant d'études où les effets psychophysiques indiquent une augmentation de la douleur ne seront pas combinés aux foyers associés à une diminution des évaluations de douleur. C'est donc pour favoriser l'homogénéité des données que les études et les contrastes à inclure dans la métaanalyse doivent être sélectionnés à l'aide de critères rigoureux, afin d'éliminer autant que possible l'hétérogénéité des données due aux variations dans les devis expérimentaux. Outre cette source de variance, il persiste une hétérogénéité attribuable aux divers paramètres d'acquisition initiale des données d'imagerie qui varient à travers les équipes de recherche ; p.ex. : la technique utilisée (fMRI, PET), la résolution des images, le logiciel d'analyse (SPM, Brainvoyager, FSL, etc.), les paramètres du lissage spatial (*smoothing*), le *template* de normalisation (Talairach, MNI), les variations anatomiques entre les sujets, etc. (Eickhoff et al., 2009). L'algorithme ALE modélise cette incertitude spatiale lors de la création de la valeur ALE, en dérivant de chaque foyer du jeu de données une distribution gaussienne 3D dont l'étendue est fonction du nombre de sujets de chaque

contraste. En effet, la précision des données tend à augmenter avec le nombre de sujets. Plus précisément, la variance intersujet est inversement proportionnelle à la taille de l'échantillon (Eickhoff et al., 2009). Les distributions gaussiennes des foyers pour chaque contraste seront donc plus ou moins larges selon le nombre de participants qui lui est associé.

Pour chaque contraste, une carte (*c.-à-d.* une matrice, un volume) est produite dans laquelle chaque voxel reçoit une valeur tirée des distributions gaussiennes à proximité. Ainsi, chaque voxel obtient une valeur égale à la "*probability of an activation being located at exactly that position based on the reported coordinates and the employed model of spatial uncertainty*" (p. 2911 de Eickhoff et al., 2009). Cette valeur est appelée *modeled activation (MA)*<sup>11</sup>. Il existe deux façons de dériver cette valeur : soit par une méthode additive qui consiste à prendre l'union probabiliste des points des distributions adjacentes (l'union probabiliste est une combinaison "pondérée", et non une somme; Eickhoff et al., 2009), soit par une méthode non additive qui consiste à prendre la valeur correspondante à la probabilité maximale la plus proche du voxel (Turkeltaub et al., 2012). Ces deux choix se différencient au niveau de l'influence relative d'un contraste par rapport à un autre. Avec la méthode additive, un contraste comportant un grand nombre de foyers influencera davantage les résultats qu'un contraste ayant peu de coordonnées. La méthode non additive permet de minimiser ce biais. Elle a été privilégiée dans cette thèse. Finalement, les cartes MA (une par contraste) sont combinées par union probabiliste afin de créer une carte ALE finale.

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<sup>11</sup> La valeur MA est équivalente à la valeur ALE: elles correspondent toutes les deux à la probabilité d'une localisation réelle de l'activité cérébrale. Leur différenciation est une conséquence de l'évolution de l'algorithme qui a nécessité une variable intermédiaire dans le calcul de la valeur ALE. L'utilisation du terme MA réfère au processus de calcul et d'analyse, alors que ALE réfère au résultat final de cette analyse.

## Test d'hypothèses

L'hypothèse nulle stipule que les foyers d'activation sont répartis de façon aléatoire à travers de cerveau (Eickhoff et al., 2012). Afin de tester cette hypothèse, une distribution nulle est générée par une méthode analytique de permutation à partir des cartes MA précédemment créées. Dans un premier temps, chacune des cartes MA est convertie en histogramme d'occurrences des valeurs MA afin de retirer toute information spatiale, où chaque barre représente la fréquence d'occurrence d'une certaine valeur MA. Ces histogrammes sont normalisés, de sorte de chaque barre représente maintenant la probabilité relative d'occurrence de la valeur. Ils sont ensuite cumulés par une approche multiplicative d'une série exhaustive de combinaisons bipartites des barres de chaque histogramme (p.ex.  $\text{histogramme}_1\text{barre}_1 * \text{histogramme}_2\text{barre}_6$ ,  $\text{histogramme}_1\text{barre}_2 * \text{histogramme}_2\text{barre}_7$ ,  $\text{histogramme}_{16}\text{barre}_{648} * \text{histogramme}_{20}\text{barre}_{789}$ , .... etc., jusqu'à ce qu'il n'y ait plus de barre à combiner). Ceci produit donc un histogramme "total", et aléatoire en raison de permutations de probabilités d'occurrences des valeurs ALE, de laquelle sont tirées les valeurs de  $P$  exprimant la probabilité qu'une valeur soit observée dans la distribution nulle, c'est-à-dire sous l'hypothèse nulle. Les valeurs de  $P$  sont ensuite assignées aux voxels correspondant dans la carte ALE (créée à l'étape précédente). Le nombre extrêmement élevé de valeurs de  $P$  générées entraîne un nombre proportionnel de risques d'obtenir un résultat statistiquement significatif qui n'est attribuable qu'au hasard, implique un haut risque de conclure erronément à une réelle localisation d'activation. La solution à ce problème est appliquée lors du seuillage statistique effectué avec une méthode de correction pour comparaisons multiples.

## Seuillage statistique

Deux des plus courantes techniques de correction pour comparaisons multiples ont été adaptées aux données ALE : la FWER (Eickhoff et al., 2012) et la FDR (Laird et al., 2005). Il est aussi possible de n'appliquer aucune correction et de fixer le seuil à une valeur  $P$  maximale arbitraire. Toutefois, il est plus valide statistiquement d'appliquer l'une ou l'autre des méthodes de corrections. Le seuillage statistique se fait en deux étapes : établir le seuil au niveau des valeurs des voxels, puis au niveau de la taille des regroupements de voxels significatifs ou *clusters*.

### *Seuillage des valeurs des voxels (voxel-level)*

La correction FWER, consiste ici à calculer le seuil à l'aide de permutations de type *Monte-Carlo*, par la simulation de données aléatoires (Eickhoff et al., 2012). Ces simulations servent à produire une distribution nulle à partir de laquelle la probabilité de commettre une erreur de type I (faux positif) est estimée. On choisit le seuil en fonction de parvenir à un maximum de  $\alpha$  probabilités d'obtenir le même résultat dans la distribution nulle, c'est-à-dire par hasard.

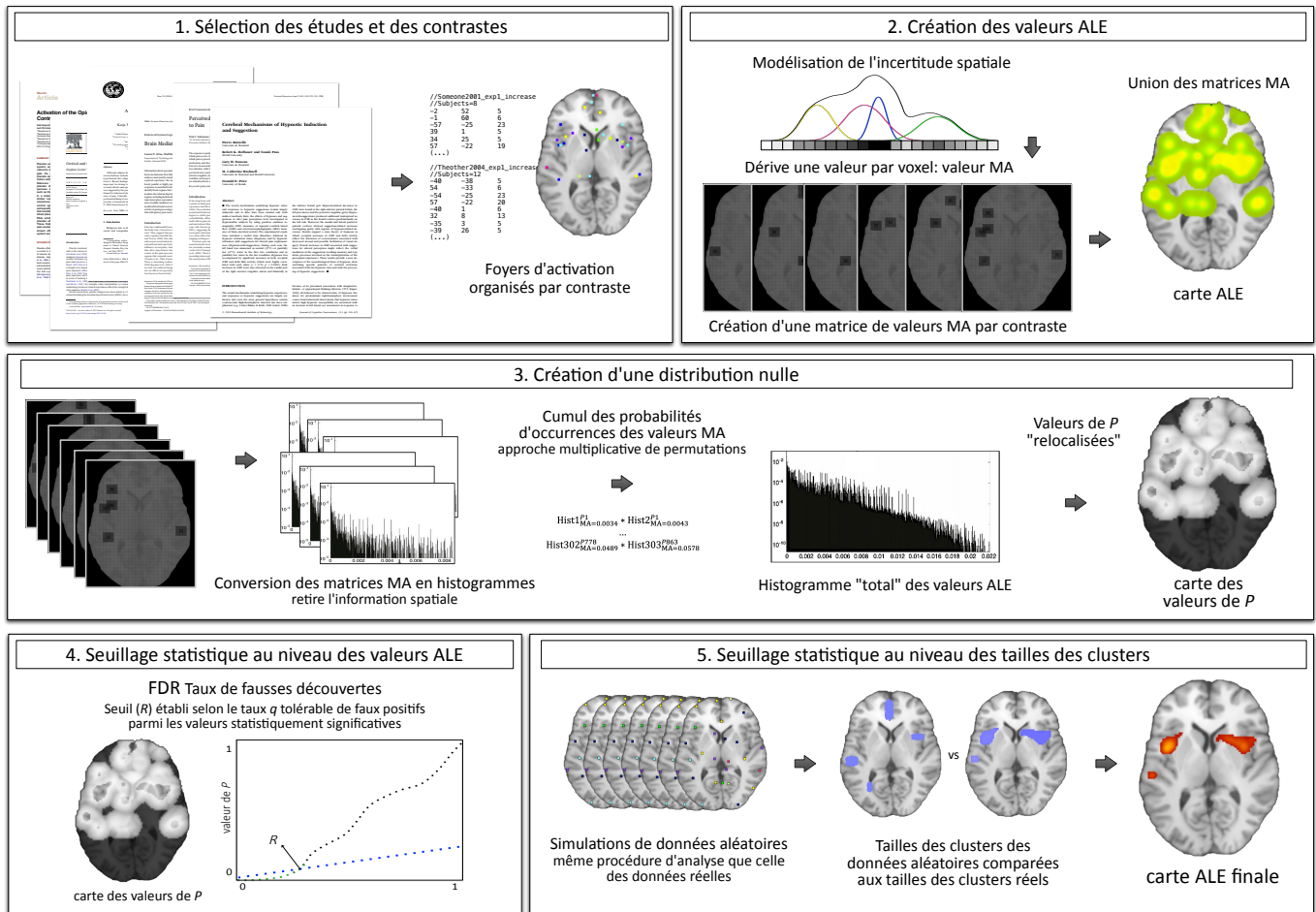
La correction FDR, utilisée pour les études de cette thèse, se fait directement à partir des valeurs  $P$  de la distribution nulle générée précédemment. Un seuil  $q$  est sélectionné de telle sorte que l'on peut s'attendre à un taux maximal de  $q\%$  de fausses découvertes. Alors que la FWER est plutôt conservatrice (p.ex.  $p = .05$ ; 5% de risque d'obtenir un faux positif), la FDR concède un nombre tolérable de faux positifs (p.ex.  $q = .05$ ; 5% des résultats sont

vraisemblablement des faux positifs) afin de minimiser l'erreur de type II (faux négatif) où l'hypothèse d'un effet réel est rejetée à tort.

#### *Seuillage des tailles des clusters (cluster-level)*

Cette analyse permet de déterminer les tailles statistiquement significatives des regroupements de voxels. Ce niveau bonifie le précédent, car il tient compte des interrelations spatiales entre les groupes de voxels activés (Eickhoff et al., 2012). En effet, cette analyse considère l'étendue des regroupements des plus forts voxels (déjà seuillés), ce qui ouvre la voie aux inférences relatives aux interrelations entre des voxels. La procédure implique encore une fois des simulations itératives de type *Monte-Carlo* de données aléatoires seuillées avec la méthode FWER. De ces multiples distributions aléatoires de valeurs sont extraites les tailles des clusters formés par les voxels dont les valeurs dépassent le seuil. Puis, ces tailles des clusters aléatoires sont comparées aux tailles des clusters provenant des données réelles. Finalement, un seuil statistique est établi en appliquant une correction (ou pas). La méthode FDR a encore une fois été privilégiée dans cette thèse. Il en résulte ainsi une valeur  $P$  pour chaque cluster des données réelles signifiant que  $q\%$  des clusters "aléatoires" ont un volume supérieur ou égal, et sont donc grands par hasard.

En définitive, on obtient ainsi une carte ALE seuillée au niveau des valeurs des voxels et sur le plan des tailles des clusters. Cette carte ALE, interprétable comme telle, peut être comparée à d'autres cartes ALE.



**Figure 6.** Étapes computationnelles de l'analyse ALE telles qu'utilisée dans le cadre de cette thèse.

### *Analyse de soustraction et conjonction*

GingerALE permet une étape supplémentaire d'analyse qui consiste à rechercher les différences significatives entre deux cartes ALE (Eickhoff et al., 2011). Cette comparaison quantitative s'obtient en soustrayant directement les valeurs de chaque voxel contenu dans une première carte aux valeurs de la seconde, et vice-versa ( $A > B$  et  $B < A$ ). Dans le cas où le



nombre de contrastes dans chaque groupe est différent ( $N_A=40$ ,  $N_B=100$ ), il est probable que le plus grand jeu de données influence davantage l'issue de cette comparaison. Ce problème est corrigé par une analyse de permutations visant à randomiser l'appartenance des données à leur groupe. Tous les contrastes contribuant à l'une ou l'autre des cartes ALE sont regroupés ( $N_{A+B}=140$ ), puis divisés aléatoirement de manière à former deux nouveaux groupes de données ayant les mêmes tailles que les groupes originaux ( $N_{A'}=40$ ,  $N_{B'}=100$ ). À l'instar des données réelles, une carte ALE est créée pour chacun des groupes constitués aléatoirement, pour ensuite soustraire leurs valeurs respectives ( $A'>B'$  et  $B'<A'$ ). Ce procédé est répété 10 000 fois afin de former une distribution nulle des différences entre les cartes. Les différences observées entre les données réelles sont comparées aux différences des données aléatoires, générant des valeurs de  $P$  pour chaque voxel basées sur la proportion de différences égales ou supérieures (Eickhoff et al., 2011). Ces cartes sont alors seuillées avec les méthodes *FWER* ou *FDR* (*FDR* choisie dans cette thèse), puis les valeurs de divergences significatives sont converties en scores  $Z$  pour faciliter l'interprétation des valeurs de divergences. Enfin, la comparaison des deux cartes ALE permet d'identifier les activations conjointes en faisant la saisie de leurs valeurs communes.

### 1.3.5. Sommaire

En conclusion, par leurs approches quantitative et systématique, les métaanalyses permettent de 1) fournir une vue d'ensemble lorsqu'il y a multiplication de données sur un sujet, 2) contourner certaines faiblesses des études expérimentales, comme la faible puissance statistique du fait des échantillons limités de participants en fMRI et en PET (Salimi-

Khorshidi, Smith, Keltner, Wager & Nichols, 2009), et 3) orienter les recherches futures, autant du point de vue méthodologique que sur le plan des questions et des hypothèses. La portée des inférences émanant d'une métaanalyse dépend des paramètres de sa réalisation établis en fonction des questions initiales de recherche, notamment en regard de la procédure de sélection des études et de sa méthodologie statistique. Les CBMA sont basées sur la localisation des effets plutôt que sur les tailles d'effet. La méthode ALE estime les probabilités d'une réelle activation cérébrale localisée dans un voxel donné (Eickhoff et al., 2009; Eickhoff et al., 2012; Turkeltaub et al., 2012).

## **1.4. Objectifs de cette thèse**

Cette thèse a pour but de préciser les mécanismes neuropsychologiques de la douleur, de la régulation endogène de la douleur et de l'hypoalgésie induite psychologiquement. Mieux comprendre ces mécanismes favorisera l'exploitation de ce potentiel endogène d'autorégulation de la douleur. Étant donné l'abondance des études sur le sujet et le manque d'intégration de leurs résultats, une méthodologie offrant une vue d'ensemble a été privilégiée dans cette thèse. En effet, aucune étude à ce jour n'a examiné les mécanismes de régulation endogènes de la douleur à travers la plupart des approches psychologiques connues visant à réduire la douleur perçue comme le placebo, l'hypnose, la méditation, etc. Inversement, les spécificités cérébrofonctionnelles entre ces approches n'ont pas non plus été étudiées. C'est pour pallier à ce manque que la technique de métaanalyse quantitative basée sur les coordonnées d'activation cérébrale fut mise à profit, telle qu'implémentée dans l'algorithme

ALE (*Activation Likelihood Estimate*). Cette thèse fournit donc une analyse intégrative quantitative et conceptuelle de près de 30 ans de recherche scientifique en imagerie cérébrale fonctionnelle portant sur la douleur en contexte expérimental, ainsi que sur l'utilisation d'interventions psychologiques visant à réduire cette douleur. Ses deux articles constitutifs seront présentés dans le second chapitre.

La première étude porte sur les mécanismes cérébraux de l'hypoalgésie induite psychologiquement en englobant une variété d'interventions, telles que le placebo, la distraction, l'hypnose, la perception de contrôle sur la douleur, l'induction d'émotions et la méditation.

La deuxième étude pousse plus loin les observations de la précédente en identifiant les spécificités cérébrales propres à la perception de la douleur, à sa régulation endogène, ainsi que ceux propres à l'hypoalgésie induite psychologiquement.

Dans le chapitre final, nous contextualiserons les résultats de ces deux études originales à la lumière des plus récentes données sur la question, pour ensuite explorer leurs significations en terme de processus neuropsychologiques et neuropsychologiques.

## **Chapitre 2 : ARTICLES DE LA THÈSE**

**Article 1. Brain activity associated with psychologically induced  
hypoalgesia: A coordinate-based meta-analysis**

Manuscrit soumis, en revision

**Brain activity associated with psychologically induced hypoalgesia:  
A coordinate-based meta-analysis**

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Running head: Meta-analysis of pain modulation

## **Abstract**

More than fifteen years of brain imaging studies on pain modulation have shown the remarkable ability of endogenous mechanisms to regulate and modify nociceptive information at various level of the CNS. These cerebral and cerebro-spinal regulatory processes are thought to subserve the now widely demonstrated hypoalgesic effects of psychological approaches to pain control (Price and Bushnell, 2004). However, the common key cerebral mechanisms that may underlie different forms of psychologically induced hypoalgesia, as well as their distinctiveness, are yet unknown. We conducted a quantitative meta-analysis of brain-imaging studies meeting strict inclusion criteria and reporting focal increases in BOLD signal or rCBF during psychological procedures producing statistically significant hypoalgesic effects (placebo, distraction, hypnosis, perceived control, emotion and meditation). Analysis across these various studies indicated that psychologically induced hypoalgesia involves a broad network of activation that includes the anterior cingulate cortex, along with anterior insulae, orbital and lateral prefrontal and frontal areas, as well as parietal, temporal and subcortical regions. This activation network may reflect the involvement of diverse neuropsychological mechanisms in the various affective, self-awareness, cognitive and motivational processes underlying the psychological interventions targeted by these studies. In addition, we explored some specific patterns of brain activity related to placebo and distraction, in comparison to the other approaches. Some hypotheses are proposed regarding the distinctive neuropsychological processes underlying these approaches.

## **Introduction**

Pain is a multi-factorial phenomenological state that involves sensory, cognitive and emotional dimensions, which can be influenced by mental processes (Price and Bushnell, 2004; Flor & Turk, 2006). This possibility of influencing, or modulating, pain perception through changes in one's mental state has fueled a longstanding interest in hypoalgesia induced by various psychological procedures like placebo, hypnosis, distraction, induction of emotions, and more recently, controllability and meditation. Placebo hypoalgesia can result from the belief that an inert agent is a powerful painkiller (e.g. Levine et al., 1978; Benedetti et al., 2005); distraction from pain can be produced by a concomitant attention-demanding task (e.g. Petrovic et al., 2000); and hypnotic hypoalgesia can be induced by suggesting to a hypnotized subject that he no longer feels the noxious stimulation as unpleasant or intense (e.g. Rainville et al., 1997). More recently, studies have shown that inducing pleasant or unpleasant emotions via emotional pictures produces pain modulation (Rhudy et al., 2005); likewise, controlling the perceived self-agency over the stimulation (Wiech et al., 2006) or practicing Zen meditation (Grant and Rainville, 2009) have also been shown to reduce pain perception.

The now widely demonstrated hypoalgesic effect of these psychological methods is thought to rely on various brain regulatory processes (Price and Bushnell, 2004; Tracey and Mantyh, 2007). More than fifteen years of functional brain imaging studies on pain modulation suggest a substantial influence of cognitive and emotional factors on pain perception that likely occur through cortico-cortical interactions and/or descending nociceptive control (Price et al., 2009; Bingel and Tracey, 2008) originating in higher-order cortical



structures (Petrovic and Ingvar, 2002; Price et al., 2009; Rainville, 2002). At the cortical level, the prefrontal cortex is thought to initiate a descending stream of anti-nociceptive activity (Bingel and Tracey, 2008) involving the anterior cingulate cortex, insula, amygdala and hypothalamus (Tracey and Mantyh, 2007) as well as cortico-thalamic and mesencephalic interactions (via PAG).

Several reviews have described the existing literature on brain imaging of pain modulation (e.g. Peyron et al., 2000; Apkarian et al., 2005; Tracey and Mantyh, 2007), but these were mostly based on qualitative methods and have not systematically integrated and compared results from various psychological interventions. Here we present a quantitative, systematic and exhaustive meta-analysis of brain-imaging studies of psychologically induced hypoalgesia using strict inclusion/exclusion criteria and state-of-the-art methods for the integration of neuroimaging findings using activation likelihood estimation (ALE; Eickhoff et al., 2012; Laird et al., 2005; Turkeltaub et al., 2002). Research articles were categorized according to the psychological procedure used to trigger hypoalgesia resulting in 6 groups of interventions: placebo (P), distraction/attention (D), hypnosis (H), controllability (C), emotion (E) and meditation (M).

Firstly, our study aimed to identify the general network of brain activation sites underlying endogenous hypoalgesia triggered by psychological interventions, i.e. all areas associated with psychological processes entailing pain-inhibitory mechanisms, regardless of the specific approach. A second goal to this study was to assess the contribution of each type of intervention to these activation sites. Lastly, we examined possible differences among the various patterns of brain activity associated with the psychological approaches by using a

subtraction analysis (one - all other) to reveal areas more specifically associated with each of the interventions.

## **Methods**

### *Literature selection*

An exhaustive literature search was conducted to identify studies of psychological hypoalgesia using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). A large search was executed on March 14<sup>th</sup> 2014 in the databases PsychInfo and Medline using concepts covering psychological approaches intended to modulate pain<sup>12</sup>. The results were then limited to journal articles written in English describing human studies. Next, the following inclusion criteria were applied (the literature search and selection process are shown in Figure 1).

- Imaging method: Brain-imaging methods for detecting changes in cerebral blood flow or glucose metabolism; i.e. BOLD fMRI or PET using water or glucose as a radiotracer;
- Subjects: Group studies involving normal, healthy human subjects (to avoid the potential disease-related plasticity in neural systems activated during the perception of pain or the endogenous regulation of nociceptive activity);
- Pain: Administration of controlled physical/somatic stimuli perceived as painful;

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<sup>12</sup> Exact syntax: (fMRI or functional magnetic resonance imaging or PET or positron emission tomography) and ((cognitive modulation) or (psychological and modulation) or (cognitive and hypoalgesia) or (psychological and hypoalgesia) or (psychological and intervention) or (cognitive and intervention) or attention or distraction or hypnosis or placebo or emotion or control or controllability or meditation) and (pain or nociception).

- Psychological intervention: Use of a psychological intervention aimed to reduce pain perception;
- Control condition: Within- and/or between-subject comparison with a painful control condition where no hypoalgesic intervention is involved, or two levels of an experimental condition that allows the isolation of an hypoalgesic effect when contrasted;
- Hypoalgesic effect: A significant psychophysical reduction of pain, as reported by subjective ratings by the participants, during the experimental condition (psychological intervention) compared with the control condition, as indicated by the result of a statistical test or a reported  $p$ -value;
- Contrasts content: The imaging data analysis and contrast results identified positive brain activation during the hypoalgesic response evoked by the psychological intervention;
- Results presentation: The imaging peak activation results are given in standard coordinate format (x, y, z) and reach at least a threshold  $p < 0.05$ .
- Review articles not including original results were excluded.

Please note that the conventional terminology of the ALE method is used in this paper, namely the word "experiment" refers to a single experimental contrast analysis (e.g. activation during pain with placebo > activation during pain alone) while the term "study" refers to the scientific article which reports one or more experiments (Laird et al., 2011).

### *Meta-analytical procedure*

We performed a coordinate-based meta-analysis using the revised ALE method as implemented in GingerALE 2.3 (<http://www.brainmap.org/ale/>). Coordinates originally reported in MNI space were converted to the Talairach space from the original normalization templates indicated in each paper (FSL, SPM or other) using the Lancaster (icbm2tal) transform (Lancaster et al., 2007) implemented in GingerALE. Coordinates were modeled using a three-dimensional Gaussian distribution that quantitatively adjusts for the spatial uncertainty resulting from between-subject and between-template variance of the neuroimaging foci. Thus, the width of these Gaussian functions was computed based on the number of subjects in each experiment (Eickhoff et al., 2009). For each experiment, a modeled activation (MA) map was created from the activation foci (peak coordinates reported for an experiment); the MA map contains, for each voxel, the probability that an activation occurred exactly at this  $x y z$  coordinate while preventing summation of effects across foci from the same experiment (Turkeltaub et al., 2012). These MA maps were then masked with an ICBM gray matter tissue probability map [International Consortium on Brain Mapping]. The 'true' convergence was distinguished from the random convergence on a between-experiment level (rather than a between-foci level) using an analytical solution to the null-distribution of random spatial association between experiments, allowing random-effect inference (Eickhoff et al., 2012). ALE maps were thresholded at a cluster-level to a  $q < 0.05$  (general and subtraction analyses) and  $q < 0.001$  (general analysis) using the False-Discovery-Rate (FDR) method (Laird et al., 2005), while cluster forming was thresholded to a  $q < 0.05$  FDR-corrected (Eickhoff et al., 2012).

To disentangle common and specific effects associated with the different kinds of psychologically induced hypoalgesia, three levels of analyses were conducted: a general analysis, a contribution analysis, and a subtraction analysis.

*General analysis.* An initial ALE map was generated from all the coordinates associated with an increase in BOLD signal or rCBF (activation) during all psychological hypoalgesic interventions. Contrasts described in individual studies were collected, including subtraction of the control condition (no hypoalgesia) from the hypoalgesic condition (see Figure 1) and negative regression with pain ratings during the hypoalgesic condition (i.e. activity increased inversely correlated with pain ratings). Each of these experiments reflected increased brain activity associated with the hypoalgesic effect. This ALE map thus contained data extracted from all 6 interventions: placebo (P), distraction/attention (D), hypnosis (H), controllability (C), emotion (E), and meditation (M) studies (see methodological details in Table 1). The ALE map was thresholded at  $q < 0.05$  and  $q < 0.001$ , FDR-corrected, and based on cluster formation thresholded at  $q < 0.05$ , FDR-corrected. A corollary analysis was also performed after removing the studies reporting only activation within regions of interest (ROI) to assess possible biases associated with this method (i.e. inflation of type I error within the ROIs and of type II error outside the ROIs).

*Contribution analysis.* The contribution of each experiment to each cluster was quantitatively assessed using in-house Matlab scripts. First, the non-linear contribution of each experiment to a given cluster in the general ALE map was computed from the average ratio of ALE-values at the location of the cluster without and with the experiment in question. Hence, a low number indicates that removing this experiment from the analysis has little impact on

the ALE scores, while a high number indicates that the scores are driven strongly by that experiment. Second, the values were summed over the experiments according to their category of approach in order to yield one contribution value per intervention. As the different number of experiments may influence the contribution values, the (summed) contribution value per intervention was divided by the number of experiments in each category of approach.

*Subtraction analysis.* In order to assess statistically the differences between psychological hypoalgesic approaches, a subtraction analysis was conducted (Eickhoff et al., 2011). Only placebo and distraction groups had an adequate number of experiments to insure the validity of the analysis (see Table 2). First, ALE maps were created according to the type of intervention (P and D) using a threshold of  $q < 0.05$  and based on clusters formation thresholded at  $q < 0.05$  (both FDR-corrected). Secondly, ALE maps of all the other approaches pooled together were generated for both groups (DHCEM and PHCEM). Then, a subtraction was computed for each voxel between the ALE-values of the two individual analyses (P-DHCEM and D-PHCEM). In the next step, all studies from both sides of the subtraction were pooled and randomly split into two sets of the same size as the original two analyses going into the contrast (label-exchange permutation). An ALE-map was computed for each of these two randomly assembled groups and these were contrasted with each other (as in the actual analysis). The voxel-wise differences between these randomly assembled groups were then stored. This process was performed 5,000 times, yielding a null-distribution for the voxel-wise differences in ALE-scores between the two individual analyses, under the assumption of label exchangeability. The observed difference in ALE-scores was then tested

against this null-distribution yielding a  $p$ -value for the difference at each voxel based on the proportion of equal or higher random differences. The resulting map was thresholded at  $q < 0.05$  (FDR-corrected), and ALE values were converted into z-scores for display (see Table 3 for the parameters of the ALE maps in the subtractions).

## **Results**

### *Sample description*

A total of 682 articles published between 1986 and 2014 were retrieved from the search in Medline and PsychInfo; 3 additional articles were identified from the lists of references. These new articles were inspected according to the same selection criteria (Figure 1), ending with a final sample of 26 papers (methods summarized in Table 1). These studies included 48 experiments of interest that were conceptually and methodologically comparable (i.e. showing an isolated effect of increased brain responses during hypoalgesic procedures), with a total of 268 foci. Table 2 describes this sample in terms of number of papers, experiments, foci and subjects included in the analysis, as well as information about the sex and age of the latter. Psychophysical results for each study are compiled in Table 4 to show the respect of our 6th inclusion criteria requiring a significant reduction of perceived pain during the intervention.

### *General analysis*

The general meta-analysis on psychological hypoalgesia, which included all 6 interventions – (placebo (P), distraction/attention (D), hypnosis (H), controllability (C), emotion (E) and meditation (M), yielded numerous significant convergences of increased activity in bilateral frontomedial areas including pregenual anterior cingulate cortex (pACC),

left anterior midcingulate cortex (aMCC) and the medial part of the left and right superior frontal gyri, as well as the left anterolateral middle frontal gyrus, posterolateral superior frontal sulcus and precentral gyrus. Orbital regions also appeared, as well as the anterior insulae (left ventral and right dorsal), bilateral posterior temporal areas, left parietal precuneus and angular gyrus. Subcortical regions, like the hypothalamus and the periaqueductal grey/locus coeruleus, were also associated with psychologically induced hypoalgesia (Table 5 and Figure 2). Thus, these results suggest that psychological hypoalgesia is mediated by a distributed network dominated by frontal activation and accompanied by some temporal, parietal and subcortical areas. A large proportion of experiments reported results using an ROI analysis (42%; partition by intervention type is presented in Table S1). To protect against potential biases that this approach might introduce, a corollary analysis was performed using only results of experiments not using ROIs (i.e. whole brain search). The ALE maps obtained without the ROI-based experiments was very similar with significant activation observed in most areas reported in the general analysis above (e.g. aMCC, insula, DLPFC). However, a few of the areas did not reach significance after excluding the ROI-based results (e.g. left DLPFC, MPFC).

### *Contribution analysis*

The influence of each psychological approach on the clusters resulting from the above reported ALE analysis was subsequently assessed by a contribution analysis (see Contribution values in Table 5). Colored bar graphs in Figure 3 show the magnitudes of these contributions according to the clusters revealed by the general analysis, as well as their respective maximal ALE values and volume size.



All six interventions contributed to the wide anterior cingulate cortex (ACC) activation (first colored bar in Figure 3), which extends rostrally to the pgACC and dorsally to the mid-cingulate region. However, dissection of this cluster (increased threshold at  $p < 0.001$ ) revealed that its rostral part is dominated by placebo on the left side, with distraction to a lesser degree and meditation to a minimal part. The right pgACC is dominated by studies on emotional modulation, and by hypnosis and placebo to a lesser degree. The aMCC is dominated by distraction, and also driven by studies on controllability to a lesser degree, and by meditation.

The right orbitofrontal cluster reflected the strong contribution of meditation, as well as placebo and hypnosis to a lesser degree. On the other hand, convergence of activity in the orbital part of the right inferior frontal gyrus was mostly driven by the emotion category of intervention and also placebo, as well as controllability and hypnosis to a lesser degree.

Lateral frontal activity on the left side was also mostly driven by placebo, with some convergence of controllability. The right precentral gyrus was mostly driven by controllability, as well as emotion, distraction, placebo and hypnosis.

Activity in the dorsal portion of the right anterior insula (aINS) was driven mostly by emotion, meditation and controllability, and also by placebo. The left ventral aINS activation was evoked strongly by meditation, with influences of hypnosis, as well as distraction and placebo to a lesser degree.

The left posterior temporal clusters were dominated by meditation and controllability in the middle temporal gyrus. The cluster located in the superior temporal gyrus was driven by

meditation and controllability, along with placebo and distraction to a lesser degree. The cluster located in the right anterior transverse temporal gyrus was mainly driven by distraction and meditation. In the left parietal areas, placebo was a dominant contributor, with little contribution of distraction in the precuneus.

Subcortical responses, lateralized on the left, were largely driven by placebo in the hypothalamus and in the area covering the locus coeruleus and the periaqueductal grey, with some influence of meditation.

Hence, medial prefrontal activity seems to subserve psychologically driven endogenous hypoalgesia common to all types of intervention, while other brain areas may be associated with different psychological approaches.

#### *Subtraction analysis*

In order to delineate the preferential response location of each psychological hypoalgesic intervention, a subtraction analysis was conducted, which contrasted the ALE map of one approach to the other five other interventions pooled together. Considering the small number of experiments within some category – hypnosis (6), controllability (2), emotion (4), and meditation (5), subtraction analyses were conducted only on the two intervention groups which contain the highest number of experiments: placebo (21) and distraction (10). Statistical and localization results are reported and illustrated in Table 6 and in Figure 4.

Peaks of activity specifically associated with placebo were located almost exclusively in the left hemisphere, in the pACC, the triangular and opercular parts of the inferior frontal gyrus, in the anterior middle frontal gyrus, and in the hypothalamus. Left and right

dorsoparietal regions, at the location of the angular gyrus/inferior parietal lobule, were also evoked in this analysis.

The distraction-specific contrast revealed peaks almost exclusively in the right hemisphere, that is, in the orbital part of the inferior frontal gyrus, in the superior and precentral gyrus, as well as in the transverse temporal gyrus. The left posterior cingulate cortex was also specific to distraction.

## **Discussion**

This study is the first to quantitatively assess neuroimaging results from all approaches of psychological hypoalgesia studied over a period of 28 years. We investigated the cerebral network underlying psychologically induced hypoalgesia via diverse interventions, namely placebo, distraction, hypnosis and meditation hypoalgesia, as well as pain reduction brought by the controllability of the stimulation and the induction of emotion. One major strength of the study lies in the strict selection of studies according to well-defined criteria, thus enabling a rigorous investigation of the brain network(s) associated with psychologically induced hypoalgesia. The quantitative meta-analysis based on foci of brain activity was performed on *increases* in activation during psychological hypoalgesic procedures. This selection aimed to reveal areas activated by these interventions during pain and possibly involved in the *production* of hypoalgesia, as opposed to areas showing reduced activity and possibly reflecting the *consequence* of the hypoalgesic process. Importantly, brain activity uncovered by this meta-analysis is hypoalgesia-specific: only experiments from which the main effect of pain was subtracted were included in the analyses (e.g.  $\text{Pain}_{\text{intervention}} > \text{Pain}_{\text{alone}}$ , see Figure 1).

Included articles were categorized according to the method used to produce hypoalgesia (placebo, distraction, hypnosis, controllability, emotion, meditation). Hence, in addition to the delineation of the overall brain network associated to psychological hypoalgesia (i.e. regardless of the exact approach), we examined the relative contribution of each type of intervention to the general activation sites. Moreover, we assessed the between-approach distinctiveness of brain patterns specific to placebo and distraction.

#### *General aspects of psychologically induced hypoalgesia*

Our results demonstrate a robust convergence of activations across the pACC and the aMCC during psychologically induced hypoalgesia, which, considering its co-occurrence with the other parts of the revealed network, may constitute a hub for adaptive processes underlying pain regulation across approaches. Many additional peaks were also found, including medial, lateral and orbital frontal regions, as well the aINS, the posterior temporal and parietal lobes, which may contribute differentially to the production of psychologically induced hypoalgesia.

The network of common activity revealed in the present study across interventions closely matches the cognitive control network where the dorsolateral prefrontal cortex (DLPFC), the dorsal aINS, the ACC, the dorsal premotor cortex, the inferior frontal junction and the posterior parietal cortex are involved in a large variety of cognitive tasks (Cole & Schneider, 2007).

*Dorsolateral prefrontal cortex.* Part of this cognitive control network (Cole & Schneider, 2007) revealed in this meta-analysis is the DLPFC, mostly lateralized on the right side. The common activation of this site may be due to executive processes and working

memory load inherent to the manipulation of interoceptive information (c.f. Braver et al., 2012; Cieslik et al., 2013; Rottschy et al., 2011; Seeley et al., 2007) and the expectancies and anticipation that come with pain sensation and its reduction. Indeed, Rottschy et al. (2011) recently identified in a quantitative meta-analysis a "core network" composed of the lateral frontal cortex along with insula and parietal regions specifically linked to working memory. A working-memory load is inherently involved during psychologically induced hypoalgesia because of the continuous updating of the detected changes in pain perception, together with the attentional focus on the task or context of the experimental condition.

This frontal area is also involved in top-down regulation. Lorenz et al. (2003) found an inverse relation between DLPFC and subjective pain evaluation in their subjects, a negative inter-regional correlation between DLPFC activity and that of the midbrain and the medial thalamus, as well as a weakened relation between aINS and pain ratings. Their results point to a top-down inhibition by the DLPFC of the neuronal coupling of cortico-cortical and cortico-subcortical modulatory pathways (Lorenz et al. 2003). Dosenbach et al. (2008) put forward a dual model of top-down control and sustained attention by contrasting the complementary actions of the fronto-parietal network's association with rapid adjustments of control in response to cues with the role of the cingulo-opercular network involved in a stable set control and maintenance. The complementarity of these dual levels of cognitive control is in line with our results considering the rapid updating of the perception changes, as well as the sustained and more global monitoring and maintenance of the task's or context's goal (e.g. the so called action of the placebo agent, the suggestions given by during hypnosis).

The major contributor to activity in the DLPFC in terms of intervention was studies that used the modulation of emotion to reduce the perceived pain (with reference to clusters # 8 and 9 in Figure 2), by inducing a religious state of mind during painful stimulations (Wiech et al., 2009) and by producing stress from a mental arithmetic task combined with white noise (Yilmaz et al., 2010). Given that these studies presumably involved opposite valence of emotional states (religious state = positive, stress = negative emotion), the hypothesis of a reappraisal process of the emotional state is less probable. We may speculate that the involvement of the DLPFC may reflect the maintenance of the new emotional context during the procedure.

*Insular cortex.* We found convergence of activity in right dorsal and left ventral aINS. The insular cortex is commonly associated with pain processing, and Jasmin et al. (2003) showed activation of this area at the onset of hypoalgesia. Tracing studies in rats show that the aINS is reciprocally connected to cortical areas including the orbital, the infralimbic (homolog of ventromedial prefrontal cortex in humans) and the anterior cingulate cortices, as well as limbic structures (mostly amygdala and nucleus accumbens) and contralateral aINS (Allen, Saper, Hurley & Cechetto, 1991; Jasmin, Burkley, Granato & Ohara, 2004).

In humans, the anterior portion of the insula is believed to integrate the interoceptive representation of bodily signals, which may provide a subjective feeling of the body (Craig, 2009). This area is thought to contribute to self-awareness and autonomic interoception with its close functional relationship with the ACC (Medford and Critchley, 2010). Further, the aINS is connected to limbic (Nieuwenhuys, 2012), prefrontal, and frontal (Jakab et al., 2012) areas. Its dorsal portion is associated to cognitive processes (Kurth et al., 2010) and decision

making (Deen et al., 2011), while its ventral aspect is linked to emotional processes (Kurth et al., 2010; Deen et al., 2011) and their associated autonomic changes (Mutschler et al., 2009). Activity in the anterodorsal portion of the right insula was predominantly driven by studies that used the induction of emotion as a way to reduce pain perception. Considering that these studies were also the strongest contributor to the DLPFC cluster, this result may again reflect co-occurring cognitive processes induced by the emotional task. Conversely, meditation and hypnosis (respectively; Zeidan et al., 2011, Faymonville et al., 2000) were the strongest contributors to activity in the anteroventral left insula. This may reflect an emotional control and detachment regarding the saliency of the painful stimuli, generally (but not exclusively) aimed by the studies within these categories of intervention (Zeidan et al., 2011; Grant, 2014).

*Orbitofrontal cortex.* Lateral orbital areas appeared to be linked to psychologically induced hypoalgesia in the present study. Orbitofrontal cortex (OFC) is known to play a role in outcome-guided behavior (Murray et al. 2007) by coding the abstract subjective value of a potential source of reward (Padoa-Schioppa, 2011; Rolls and Grabenhorst, 2008) and signal reward-relevant state signal (Schoenbaum et al., 2011). More precisely, the medial part of the OFC may be specifically involved in monitoring and learning aspects of the reward value, while the lateral part (activated here) would deal with the evaluation of the punishers, leading to changes in behavior (Kringelbach, 2005). The latter role is consistent with the aversiveness of the residual pain perceived during the psychological procedure, functioning as a motivator to engage in the process of producing hypoalgesia.

Kennerley et al. (2011) further dissociated the roles of OFC and ACC, with the former being responsible for a dynamic trial-by-trial value coding, and the later involved in encoding

the probability of error. Accordingly, the specific role of OFC is providing adaptability of the value coding, which is dynamically adjusted based on previous experience and contextual factors (Kennerley et al., 2011). This finding fits the view of a complementary role of OFC and aMCC in psychologically induced hypoalgesia, where the OFC would "code" for a dynamic adaptation of the aversive value of pain and/or the pleasant value of the expected outcome (i.e. pain reduction), while the aMCC would provide the management of the resources for descending control and the monitoring of the effective pain reduction.

*Cingulate cortex.* Our study revealed a massive participation of the cingulate region in psychologically induced hypoalgesia, as shown by the magnitude in size and intensity of the cluster covering the ACC, from the pregenual to its middle portion, with extensions into the medial frontal cortex. Most importantly, this convergence of cerebral activity in the ACC was driven by all approaches (see the upper part of Figure 2). These results convey to this region a key role in the recruitment of endogenous pain reduction mechanisms. We propose that the ACC could be viewed as a 'manager' that integrates inputs from other region of the network to provide control over the perceived pain.

First, the rostral portion of the ACC is linked to self-referential processes and affective-cognitive integration (Torta et al., 2011). In an extensive meta-analytic connectivity-modeling study, pgACC was specifically linked to studies with emotion as a behavioral domain, while other parts of the cingulate cortex were associated with a plurality of tasks (Torta et al., 2011). Plus, Yu et al. (2011) found that pgACC was connected to a set of regions known to play a role in the integration of emotional processing, cognitive control, and conscious self-reflection.



While the rostral part of the ACC is related to the affective domain, its middle portion was found to be involved in a variety of behavioral domains, including attention, sensation, language, and pain (Torta et al., 2011). This led Torta et al. (2011) to propose that aMCC may act as a 'hub' area interconnecting different networks. This region is moreover increasingly considered to be a locus of convergence and regulation of inputs from diverse brain structure and networks (Yeung, 2013; Yu et al.; 2011; Torta et al., 2011; Shackman et al., Holroyd & Yeung, 2012).

Shackman et al. (2011) conducted an integrative review and meta-analysis on the cognitive processes linked to the aMCC. They suggest that aMCC represents a pivotal region for the processing of aversive information and the preparation of adaptive actions. Their 'adaptive control hypothesis' states that this area receives and uses information about punishment in order to generate an adaptive response to the aversive situation by choosing and regulating action (Shackman et al., 2011).

Similarly, Holyold and Yeung (2012) proposed a 'hierarchical reinforcement-learning' model in which the aMCC is crucial to the generation and maintenance of potential actions deriving from an 'initiation state' (e.g. hunger). According to that model, this region would be responsible for the initiation of the action, as well as for its management relative to the goal, and in coordination with the input from other systems, such as the cognitive control network, the executive processing of the DLPFC, and the predictions of valence information and reward provided by OFC. Moreover, along with its integrative role, the aMCC would calibrate the level of efforts deployed for the execution of action as a function of motivation (Holyold & Yeung, 2012).

But more precisely, what would be the concept of an 'adaptive action' in the sense proposed by Shackman et al. (2011)? From our understanding of their model, as well as that of Holyoak & Yeung (2012), the notion of adaptation refers to a better internal and affective state; in other words, a more appropriate homeostatic balance. Put another way, it implies a rise of pleasure (reward) and the reduction of aversiveness (punishment). That is exactly the principle of psychologically-induced hypoalgesia – the reward inherent to pain reduction. The recently proposed relation between pain, pleasure, motivation and reward (e.g. Seymour et al., 2005; Fields, 2007; Leknes & Tracey, 2008), is especially interesting concerning the respective roles of opioids and dopamine in pain relief and reward-seeking behavior (e.g. Potvin et al., 2009; Wanigasekera et al., 2012). Leknes & Tracey (2008) describe interacting dual neurotransmitter systems where dopamine provides the motivation to experience pleasure ('wanting'), whereas opioids are necessary for the hedonic experience. Furthermore, "the overlap in regions that are involved in pain and pleasure processing might explain the modulatory effects of one over the other" (Leknes & Tracey, 2008), as well as regions shown in our study to be involved in endogenous hypoalgesia, especially in pgACC, anterior insula, lateral prefrontal cortex, medial prefrontal cortex, OFC and hypothalamus (Leknes & Tracey, 2008). Although our meta-analysis does not allow us to extend conclusions on the neurotransmitter systems, the dopamine-opioid synergy is a promising avenue to better understand the engagement of endogenous pain inhibitory mechanisms.

#### *Between-approach specificity*

We isolated the effects of the placebo and distraction, compared to the other interventions, and showed some preferential patterns of activation underlying these two

psychological approaches used to induce hypoalgesia. Note here that these analyses were made on a limited number of studies, which might have an impact on their statistical validity. We thus consider these results as exploratory.

From a psychological perspective, these two interventions are functionally distinct on different dimensions including volition and agency: voluntary active self-regulation in distraction; and involuntary passive expectation in placebo.

First, the set of regions that showed the strongest convergence of increased activation during distraction-related hypoalgesia, when compared to the other five approaches, includes the posterior cingulate cortex (PCC), the inferior frontal gyrus, dorsal motor and premotor areas, as well as the transverse temporal gyrus. The PCC is traditionally associated with self-referential processing (e.g. Northoff et al., 2006). In a recent perspective, Brewer et al. (2013) discussed the possibility that the PCC encodes a sub-aspect of the self-reflection process: personal engagement in the task or in the mental activity. They suggested that this process involves "being caught up in" the experience, as opposed to "letting go" of the experience. In the context of distraction as a procedure to reduce pain perception, the convergence of activation in the PCC could represent an attentional disengagement from the painful stimulation (and/or a reversal of the pain-related decrease in PCC activation observed in the absence of distraction). A similar effect was demonstrated by Kucyi et al. (2013) in an fMRI study where increased activity in the PCC was related to the spontaneous mind wandering away from the painful stimuli. However, the distraction produced by the engagement in a competing task further involves active voluntary processes which may reflect fronto-parietal interactions. The co-occurrence of premotor area activation may underlie this cognitive shift

onto another attentional focus, consistent with the role of this region in non-motor cognitive processes (Hanakawa, 2011). Of course, these distraction-related responses must be interpreted in the context of the strong prefrontal activity found across interventions and specificity may be further uncovered in the distinctive functional interactions between nodes of partly shared networks. Studies are needed that directly compare distraction with other types of psychological hypoalgesic interventions.

Second, our study showed a specific convergence of activity for placebo hypoalgesia in the pACC, hypothalamus, posterior parietal cortex, and dorsolateral prefrontal areas. The rostral portion of the cingulate cortex contains high levels of opioid receptors (Jones et al., 1991; Vogt et al. 1995), which is consistent with the known action of the endogenous opioid system in placebo hypoalgesia (Amanzio and Benedetti, 1999; Zubieta et al., 2005; Wager et al., 2007). This result is consistent with the results of Amanzio and colleagues (2013) who conducted an ALE meta-analysis of placebo analgesia and found convergence of increased activity in the rostral ACC during placebo. We also both observed convergence in the posterior parietal cortex, but on opposite sides of the brain. Also, the meta-analysis by Amanzio et al. (2013) show many more areas of activity that we did not observed, including the PAG, the aIns and the postcentral gyrus. We interpret this by methodological differences, notably in regard to the chosen contrast analysis to be included in the meta-analysis. Amanzio et al. (2013) included foci of activity for which the placebo analgesia condition was contrasted with the resting condition (placebo pain > baseline), while we choose contrasts where activity during the placebo hypoalgesic procedure was isolated from pain perception (placebo pain > pain alone). Thus, the additional peaks reported in this previous study may reflect pain

processes not specific to the placebo effect. On the other hand, the joined activation of the DLPFC and the posterior parietal cortex fits within the framework of the fronto-parietal network that could support the cognitive components of the placebo response, which includes the anticipation and the prediction of the reduction in pain.

### *Limitations*

This meta-analysis of brain imaging studies is the first to use within- and between-approach comparisons of many psychological interventions directed towards pain reduction. However, since we only considered brain activity during the painful stimulation, our analyses may have missed some pain reduction mechanisms that take action before the stimulation (e.g. Wager et al., 2004; Watson et al., 2009). Furthermore, the low number of studies that survived the selection criteria may have reduced the statistical power, especially that of the subtraction analysis. The sample may seem surprising small considering the abundance of brain imaging studies on psychological hypoalgesia. However, a thorough application of strict selection criteria (e.g. statistically significant pain reduction) is vital to the validity of the inferences that may be drawn relating to the mechanisms of psychologically induced hypoalgesia.

Finally, a large proportion of experiments included relied on ROI analysis and removing these experiments from the analysis did modify the general results in some areas (see Supplementary material Figure S1). Within the targeted ROIs, this procedure may reduce type II error by reducing the local activation threshold considered significant in areas for which a priori hypotheses are formulated. However, this approach might also inflate type II error

outside the ROIs. Ideally, whole brain analyses should always be reported as supplementary results in studies relying primarily on ROI analysis in order to reduce this potential bias.

## **Conclusions**

Our results demonstrate the activation of the pACC and the aMCC, along with the aINS, orbital, and lateral frontal regions, elicited by various psychological hypoalgesic interventions. This network may reflect the crucial involvement of dynamic neuropsychological actions (i.e. self-awareness, as well as affective, motivational, adaptive, and cognitive processes), which could trigger a cascade of endogenous descending pain-inhibitory mechanisms resulting in hypoalgesia. A specific activity in PCC was linked to distraction and may reflect the redirection of attention from the painful sensation. Placebo hypoalgesia was characterized more specifically by activity in pACC, with DLPFC and posterior parietal regions. These activations may reflect the action of the endogenous opioid system, as well as the cognitive aspects of placebo responding. Our results strongly emphasize the need for more experimental research to disentangle the multiple neurophysiological processes underlying the diverse psychological approaches contributing to pain control.

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## Figures

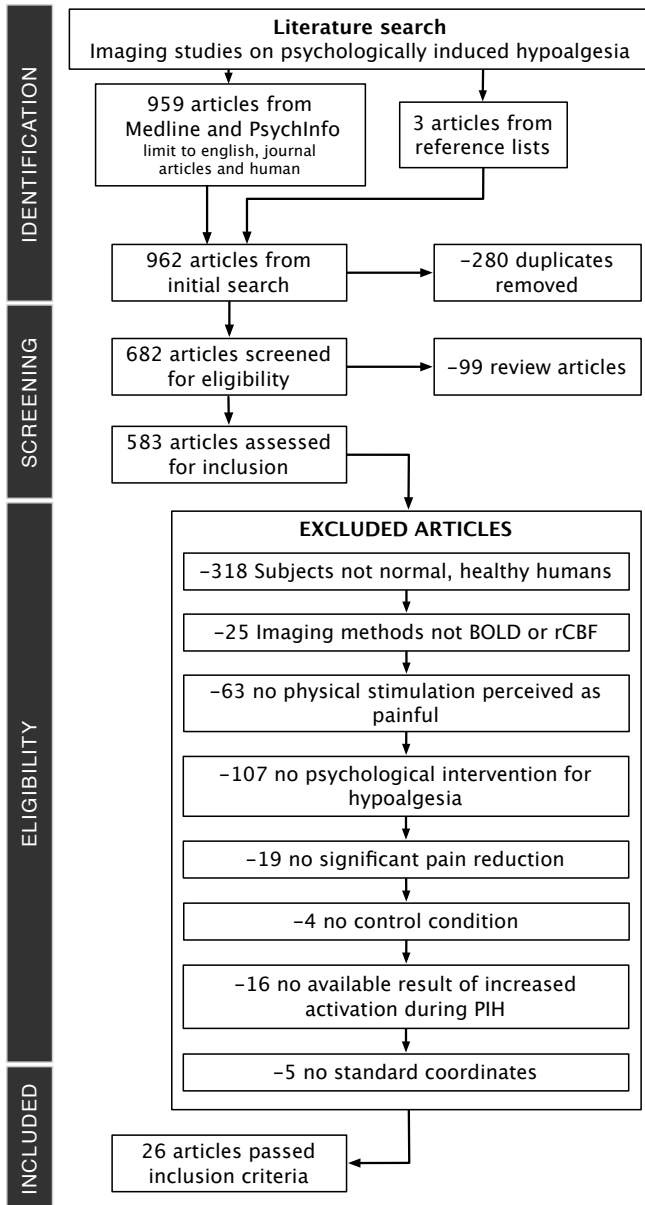


Figure 1. Flow chart of the selection procedure according to PRISMA guidelines (Liberati et al., 2009).

Inclusion criteria applied to search results with the number of studies that were rejected according to each criteria during the selection process (see text for details).

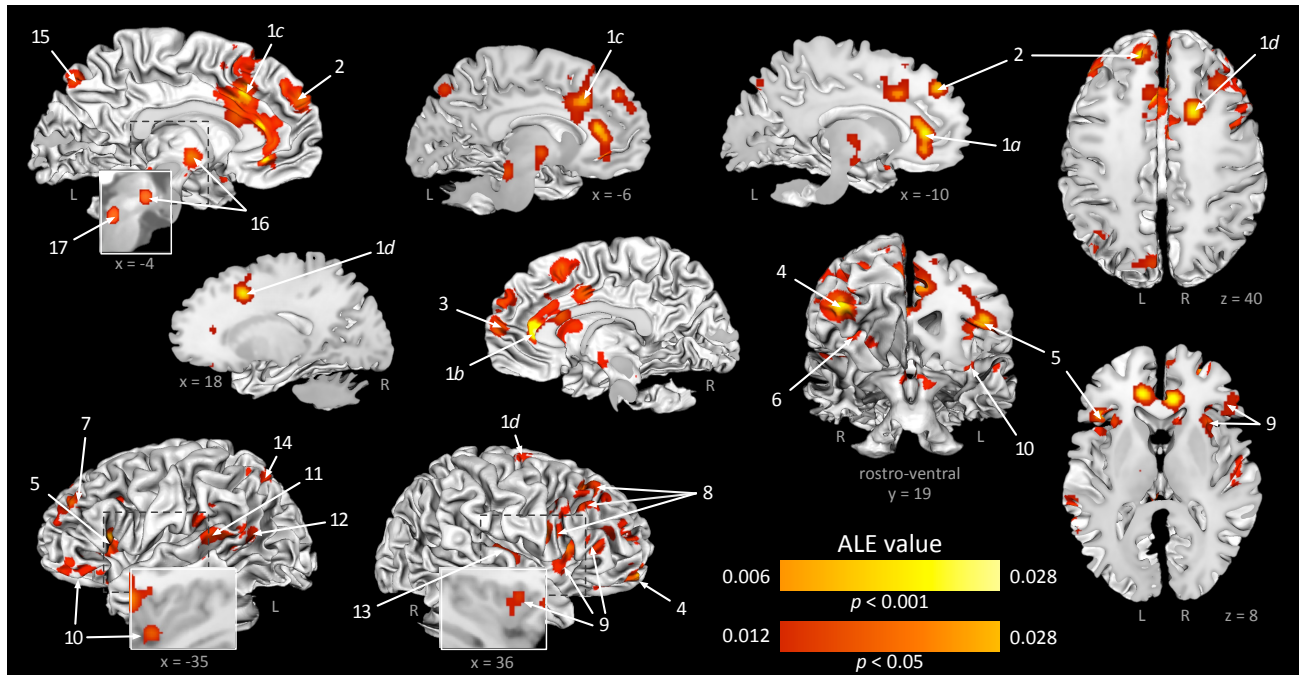


Figure 2. Convergence of brain activity increases during psychologically induced hypoalgesia, all intervention combined: placebo, distraction, hypnosis, controllability, emotion and meditation.

The alphanumeric code refers to the cluster identification in Table 5. ALE maps are overlaid on the Colin27 anatomical model template (<http://www.brainmap.org/ale/>; Kochunov et al., 2002) using Mango software (<http://rii.uthscsa.edu/mango/>). Abbreviations: R: right, L: left.

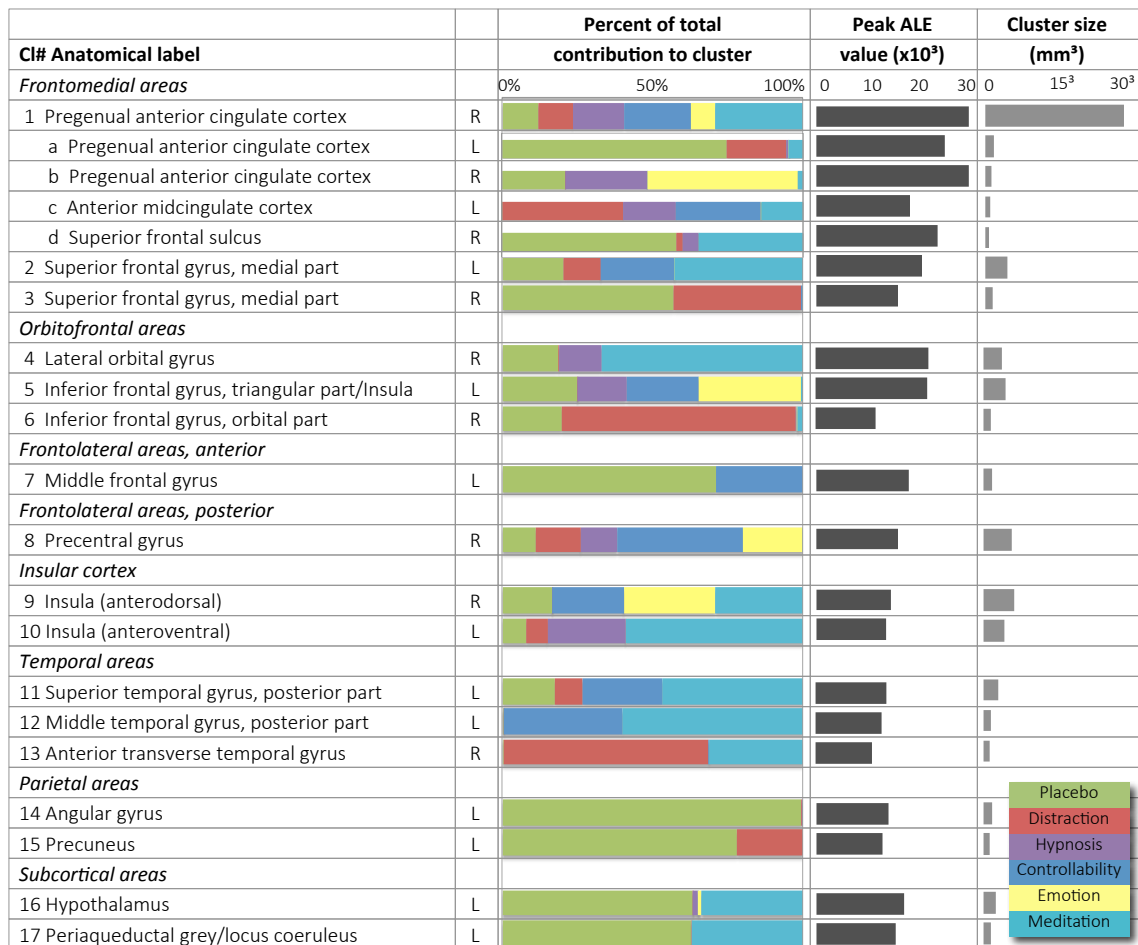


Figure 3. Contribution analysis results by clusters.

Colored bar graphs show how much a psychological hypoalgesic intervention contributes to a given cluster revealed in the general ALE maps (the alphanumeric code refers to the cluster identification in Table 5 and Figure 2). Along with the contribution graph, two bar charts are shown to illustrate the magnitude of the contributions in terms of maximum peak ALE values and cluster size. The contribution values are corrected for the number of experiments in each category of intervention. Abbreviations: R: right, L: left, Cl#: cluster's number.

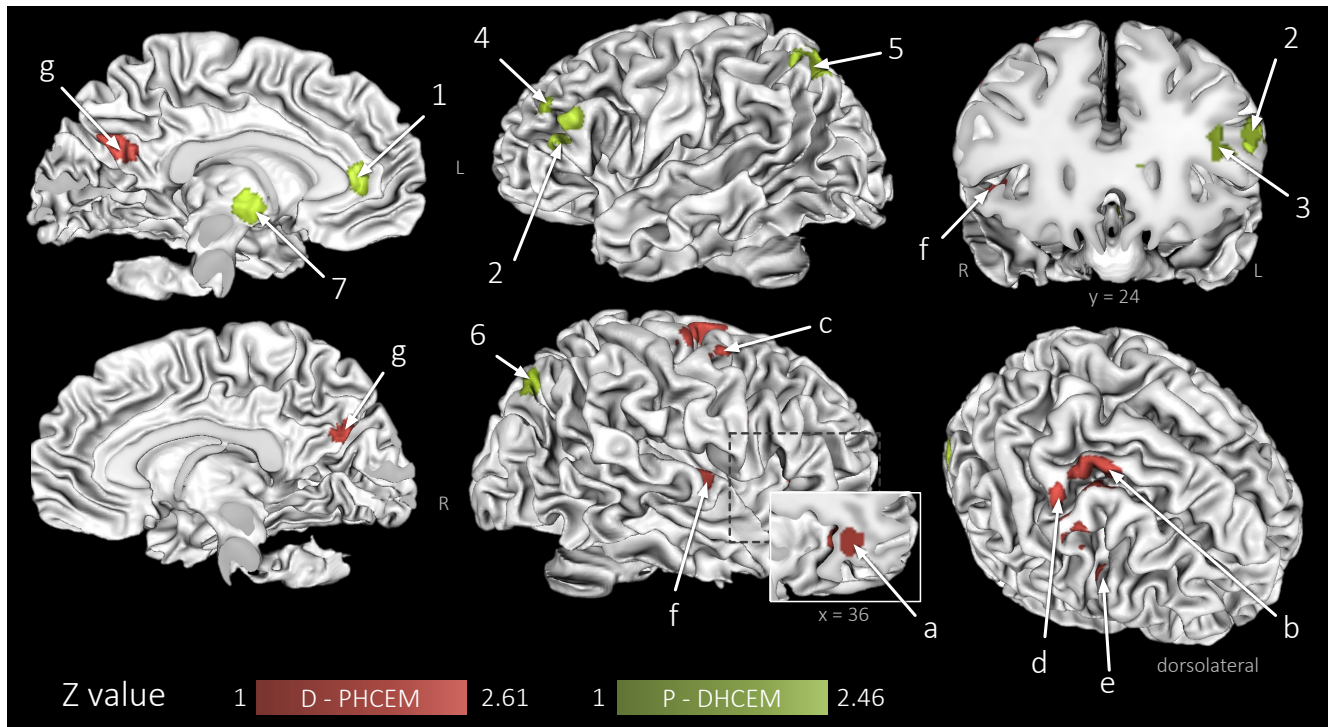


Figure 4. Results of the specificity analysis, i.e. the subtraction (z-maps) of the intervention ALE maps.

The alphanumeric code refers to the cluster identification in Table 6 (numbers → placebo - all other; letters → distraction - all other). Activation maps are overlaid on the Colin27 anatomical model template (<http://www.brainmap.org/ale/>; Kochunov et al., 2002) using Mango software (<http://rii.uthscsa.edu/mango/>).

## Tables

Paper	Ss	Imaging	Stimuli				Psychological intervention for analgesia induction
			Body part	Side	Modality	Intensity	
<i>Placebo</i>							
Bingel et al., 2006	19	fMRI	Hand	L	Thermal	Fx	Cream ('a new analgesic') and conditioning
Eippert et al., 2009	40	fMRI	Arm	L	Thermal	Sd	Cream ('lidocaine') and conditioning
Ellingsen et al., 2013	28	fMRI	Hand	L	Thermal	Sd	Intra-nasal saline spray ('may contain oxytocin')
Geuter et al., 2013	40	fMRI	Arm	L	Thermal	Sd	Acrylate gel ('expensive' and 'low priced' analgesic) and conditioning
Huber et al., 2013	28	fMRI	Foot	L&R	Thermal	Sd	conditionning, cue with fake "subthreshold electric shock" to ankle
Kong et al., 2006	16	fMRI	Arm	R	Thermal	Sd	Conditionning, sham acupuncture pre-treatment
Kong et al., 2013	46	fMRI	Arm	R	Thermal	Sd	Anticipation cues of low pain stimulation
Lui et al., 2010	31	fMRI	Foot	L&R	Thermal	Sd	conditionning, cue with fake "subthreshold electric shock" to ankle
Nemoto et al., 2007	5	PET	Arm	R	Thermal	Fx	Tablets taken for 7 days prior to testing
Petrovic et al., 2002	9	PET	Hand	L	Thermal	Fx	Saline injection told to be a 'potent powerful analgesic'
Petrovic et al., 2010	9	PET	Hand	L	Thermal	Fx	
<i>Distraction / attention</i>							
Bantick et al., 2002	8	fMRI	Hand	L	Thermal	Sd	Counting Stroop task with 2 level of difficulty
Dunckley et al., 2007	12	fMRI	Rectum&Abdomen	M	Electrical	Fx	Counting auditory tones of different frequencies
Frankenstein et al., 2001	12	fMRI	Foot	R	Thermal	Sd	Silent categorical word generation
Petrovic et al., 2000	7	PET	Hand	L	Thermal	Fx	Computerized perceptual maze solving task
Remy et al., 2003	12	fMRI	Hand	L	Thermal	Sd	Semantic word generation vs word repetition.
Valet et al., 2004	7	fMRI	Arm	R	Thermal	Sd	Classic Stroop task
Wiech et al., 2005	15	fMRI	Arm	L	Chemical +thermal	Fx Sd	Rapid serial visual detection task with high or low cognitive demand
<i>Hypnosis</i>							
Faymonville et al., 2000	11	PET	Hand	R	Thermal	Sd	Hypnotic state (muscle relaxation, pleasant autobiographical memory)
Rainville et al., 1999	8	PET	Hand	L	Thermal	Sd	Hypnotic state with suggestions of reduced pain unpleasantness
<i>Controllability</i>							
Wiech et al., 2006	12	fMRI	Hand	L	Electrical	Sd	Self-, other- and computer-controlled painful stimulations
<i>Emotion</i>							
Wiech et al., 2009	12	fMRI	Hand	L	Electrical	Sd	Religious state of mind induced by image of the Virgin Mary
Yilmaz et al., 2010	21	fMRI	Hand	L	Mechanical	Sd	Stress induced by mental arithmetic task and increasing white noise
<i>Meditation</i>							
Gard et al., 2012	31	fMRI	Arm	L	Electrical	Sd	Mindfulness meditation during pain, meditator experts vs control subjects
Naglatzki et al., 2012	13	fMRI	Arm	NR	Electrical	Sd	Pain during autogenic relaxation state in practitioners
Zeidan et al., 2011	15	fMRI	Leg	R	Thermal	Fx	Mindfulness meditation training, meditating during painful stimulations

Table 1. Outline of experimental characteristics of selected studies.

Overview of the experimental elements of included studies grouped by category of psychological intervention. Abbreviations: Ss: final number of subjects (after exclusions and drop-out); L: left, R: right, Sd: subject dependent and Fx: fixed intensity (classification method of stimuli intensity derivation; from Farrel et al. 2005).



Intervention	Studies	Experiments	Foci	Participants			
				N	% male	% female	Mean age
Placebo	11	21	85	566	68	29	25.3*
Distraction	7	10	52	108	67	33	27.2*
Hypnosis	2	6	25	63	63	26	31.7*
Controllability	1	2	44	24	0	100	24.0
Emotion	2	4	10	87	38	62	30.8
Meditation	3	5	52	89	65	31	33.8
Total	26	48	268	937	63	34	28.2

Table 2. Description of sample.

Number of selected studies (papers), their enclosed experiments (analysis contrasts), their foci of increased activity, total subjects and the proportion of male and female participants and the mean age in selected studies. \*Information unavailable in 6 papers: 3 in placebo, 2 in distraction and 1 in hypnosis.

Subtraction analysis	ALE map in the subtraction	Foci	Experiments	Subjects
P - DHCEM	P	85	21	566
	DHCEM	183	27	371
D - PHCEM	D	52	10	108
	PHCEM	216	38	829

Table 3. Parameters of the ALE map's subtraction analyses.

Name of subtraction analyses and the ALE maps used in the computation, with their respective number of foci, experiments and subjects.

Papers	Scale range and wording (pain threshold)	Exp.c	Cont.c	Test and <i>p</i> -values
<i>Placebo</i>				
Bingel et al., 2006	0=no sensation 4=max pain used (2)	1.5±NR	2.5±NR	F(1,17)=13.1; <i>p</i> < 0.05
Eippert et al., 2009	0=no pain 100=unbearable pain* (1*)	37±6†	60±5†	F(1,38)=30.76; <i>p</i> < 0.001
Ellingsen et al., 2013	-5=unpleasant +5=pleasant (NR)	-1.9±0.2	-2.4±0.2	F(1,24)=7.2; <i>p</i> = 0.01
Geuter et al., 2013	0=no pain 100=unbearable pain (≥60*)	NR	NR	F(1,39)=23.43; <i>p</i> < 0.001
Huber et al., 2013	0=no pain 10=worst pain imaginable (1*)	NR	NR	t(NR)
Kong et al., 2006	0 to 20 Gracely Sensory Scale of pain intensity (≈5)	12.9±2.7	13.5±2.1	NR
Kong et al., 2013	0 to 20 Gracely Sensory Scale of pain intensity (≈5)	11±2.9	14±2.0	F(NR); <i>p</i> < 0.0001
Lui et al., 2010	0=no pain 10=worst pain imaginable (1*)	17±19.5	27±12	t(NR)
Nemoto et al., 2007	0=no sensation 10=intolerable pain (4)	5.5±1.4	7.5±1.1	NR; <i>p</i> < 0.05
Petrovic et al., 2002	0=no pain intensity 100=highest imaginable pain (1*)	16/18 block less painful		χ <sup>2</sup> (1)=10.89; <i>p</i> < 0.001
Petrovic et al., 2010				
<i>Distraction / attention</i>				
Bantick et al., 2002	0=no pain 10=max imaginable pain* (1*)	6.6 ±0.2	7.3±0.3	NR; <i>p</i> = 0.006
Dunckley et al., 2007	0=no pain 100=excruciating pain (1*)	30.2±3.5†	33.4±3.4†	F(1,10)=17.1; <i>p</i> = 0.002
Frankenstein et al., 2001	0=no pain 10=worst pain imaginable (1*)	4.5±2.0	5.8±1.8	NR; <i>p</i> < 0.013
Petrovic et al., 2000	0=no pain 100=highest imaginable pain (1*)	21.4±17.2	27.7±17.3	NR; <i>p</i> < 0.002
Remy et al., 2003	0=no pain 10=worst pain imaginable (1*)	6.1±1.4	6.5±1.5	NR; <i>p</i> < 0.026
Valet et al., 2004	0=no pain 100=most imaginable pain* (1*)	52±8	57±6	NR; <i>p</i> = 0.04
Wiech et al., 2005	0=no pain 10=worst imaginable pain (4)	6.4±0.4†	7.6±0.3†	t(10)=4.04; <i>p</i> < 0.01
<i>Hypnosis</i>				
Faymonville et al., 2000	0=no pain sensation 10=most intense imaginable (1*)	3.6±1.6†	6.3±0.9†	F(2,126)=9.66; <i>p</i> < 0.001
Rainville et al., 1999	0=not at all unpleasant 100=extremely unpleasant (1*)	Decreased by 29%±35%		t=-3.75; <i>p</i> = 0.04
<i>Controllability</i>				
Wiech et al., 2006	0=not painful at all 100=strongest imaginable pain (1*)	63.74±9.97	68.90±11.03	t(11)=-3.06; <i>p</i> = 0.01
<i>Emotion</i>				
Wiech et al., 2009	0=not painful at all 100=very painful (1*)	65.4±4.5†	73.2±2.5†	t(11)=2.81; <i>p</i> = 0.02
Yilmaz et al., 2010	0=no pain 10=most intense pain (1*)	5.2±0.5†	6.8±0.3†	t(20)=2.70; <i>p</i> < 0.05
<i>Meditation</i>				
Gard et al., 2012	0 =not unpleasant 10=very unpleasant (5=moderate)	3.4±0.25†	4.35±0.45†	t(16)=2.97; <i>p</i> = 0.009
Naglatzki et al., 2012	0=no pain and no sensation 10=pain, not acceptable (5=moderate)	5±0‡	1,1±1.2‡	t(12)=11.91; <i>p</i> < 0.001‡
Zeidan et al., 2011	0=no pain sensation 7=most intense imaginable (1*)	3±0.4†	4.7±0.5†	F(1,14)=23.43; <i>p</i> < 0.001

Table 4. Reported significant hypoalgesic effect of selected studies.

Studies were selected in part according to the presence of a significant behavioral decreased in pain perception. Details on the pain rating procedure and results are shown. \*Not reported explicitly but understood from the context. †Estimated from figure (not available in results section). ‡Calculated from raw results provided in the article. Abbreviations: Ss : number of subjects, Exp.C : experimental condition, Cont.C : control condition, NR : not reported in the paper, M: mean, SD: standard deviation.

Cl#	Anatomical label	Talairach					Vol. size (mm <sup>3</sup> )	peak ALE value (x10 <sup>3</sup> )	Threshold	P	Contribution values				
		BA	Side	x	y	z					D	H	C	E	M
<i>Frontomedial areas</i>															
1	Pregenual anterior cingulate cortex	24/32	R	8	30	10	24304	28.3	$p < 0.05$	2.06	1.97	2.97	3.81	1.39	5.04
	<i>a</i> Pregenual anterior cingulate cortex	32/24	L	-10	34	6	1384	23.8	$p < 0.001$	8.08	2.15	0.09	0.00	0.01	0.52
	<i>b</i> Pregenual anterior cingulate cortex	24/32	R	8	30	10	992	28.3	$p < 0.001$	5.19	0.00	6.81	0.00	12.48	0.41
	<i>c</i> Anterior midcingulate cortex	24	L	-6	18	32	704	17.3	$p < 0.001$	0.00	11.38	5.00	8.03	0.02	3.96
	<i>d</i> Superior frontal sulcus	8	R	18	10	40	600	22.5	$p < 0.001$	13.43	0.51	1.19	0.04	0.01	8.04
2	Superior frontal gyrus, medial part	9/8	L	-10	42	36	3760	19.6	$p < 0.05$	6.92	4.17	0.00	8.36	0.00	14.48
3	Superior frontal gyrus, medial part	10	R	6	54	12	1232	15.3	$p < 0.05$	15.98	11.83	NC	0.18	NC	0.01
<i>Orbitofrontal areas</i>															
4	Lateral orbital gyrus	11	R	32	54	-6	3184	20.8	$p < 0.05$	5.06	0.11	3.87	NC	NC	18.34
5	Inferior frontal gyrus, triangular part/Insula	45/13	L	-38	20	10	3864	20.6	$p < 0.05$	6.94	0.00	4.57	6.71	9.55	0.15
6	Inferior frontal gyrus, orbital part	47	R	32	32	2	1152	11.1	$p < 0.05$	5.77	23.01	0.16	0.00	0.07	0.49
<i>Frontolateral areas, anterior</i>															
7	Middle frontal gyrus	46	L	-40	38	30	1432	17.1	$p < 0.05$	14.64	NC	NC	5.98	NC	NC
<i>Frontolateral areas, posterior</i>															
8	Precentral gyrus	44	R	48	4	18	4784	15.2	$p < 0.05$	3.38	4.66	3.75	12.96	6.10	0.03
<i>Insular cortex</i>															
9	Insula (anterodorsal)	13	R	32	16	8	5328	13.8	$p < 0.05$	5.27	0.04	0.00	7.63	9.75	9.31
10	Insula (anteroventral)	13	L	-36	8	-10	3576	13.0	$p < 0.05$	2.37	2.17	7.87	NC	0.00	17.86
<i>Temporal areas</i>															
11	Superior temporal gyrus, posterior part	22	L	-58	-42	8	2616	13.3	$p < 0.05$	11.27	6.15	NC	17.26	NC	30.47
12	Middle temporal gyrus, posterior part	37	L	-52	-54	12	1240	12.3	$p < 0.05$	0.29	0.00	NC	39.41	NC	59.85
13	Anterior transverse temporal gyrus	41	R	46	-20	12	1112	10.5	$p < 0.05$	0.11	34.15	NC	0.07	NC	15.67
<i>Parietal areas</i>															
14	Angular gyrus	39	L	-36	-62	44	1344	13.3	$p < 0.05$	19.91	0.08	0.03	NC	NC	NC
15	Precuneus	7	L	-4	-76	40	992	12.4	$p < 0.05$	26.00	7.28	NC	NC	NC	NC
<i>Subcortical areas</i>															
16	Hypothalamus	-	L	-4	-10	-2	1984	16.1	$p < 0.05$	17.88	0.02	0.51	0.00	0.34	9.52
17	Periaqueductal grey/locus coeruleus	-	L	-4	-34	-16	1176	14.7	$p < 0.05$	38.46	0.08	NC	0.00	0.04	22.68

Table 5. Results of the general analysis (all approaches) with the contribution analysis values.

Results of the general analysis categorized by broad cerebral areas. The first column indicates the alphanumeric code for the identification of clusters in Figure 1. Letters indicates sub-clusters of the large pregenual anterior cingulate cortex as revealed by a raised threshold of  $p < 0.001$ . Contribution values are the sum of the contribution values (corrected for the number of experiments within a category of intervention) of individual studies in each of the following categories: P: placebo, D: distraction, H: hypnosis, C: controllability, E: emotion, M: meditation (See “Methods – Meta-analytic procedure – Contribution analysis” for details on the calculation on the contribution value for each study). Abbreviations: Cl#: cluster number, BA: Brodmann area, Vol.: volume, L: left, R: right, NC: not contributing.

Cl#	Anatomical label	BA	Side	Talairach			Vol. size (mm <sup>3</sup> )	Z-score
				x	y	z		
P-DHCEM								
<i>Frontomedial areas</i>								
1	Pregenua anterior cingulate cortex	24/32	L	-8	38	10	1848	2.60
<i>Frontolateral areas</i>								
2	Inferior frontal gyrus, opercular part	45	L	-48	31	15	928	2.52
3	Inferior frontal sulcus	45/46	L	-36	24	20	344	2.18
4	Middle frontal gyrus	46	L	-45	33	28	72	2.04
<i>Parietal areas</i>								
5	Angular gyrus	39	L	-39	-61	45	1928	2.13
6	Angular gyrus/Inferior par. lobule	39/19	R	46	-76	34	704	2.30
<i>Subcortical areas</i>								
7	Hypothalamus	–	L	-8	-10	-1	1280	2.33
D-PHCEM								
<i>Orbitofrontal areas</i>								
a	Inferior frontal gyrus, orbital part	47	R	26	32	2	960	2.20
<i>Frontolateral areas</i>								
b	Superior frontal gyrus	6	R	33	-8	59	1016	1.77
c	Precentral gyrus (around fingers areas)	6	R	53	-2	47	512	1.77
d	Precentral gyrus (around hand region)	4	R	47	-13	54	392	1.77
e	Precentral sulcus	9	R	50	2	24	104	1.88
<i>Temporal areas</i>								
f	Transverse temporal gyrus (posterior)	41	R	50	-6	6	1000	1.84
<i>Parietal areas</i>								
g	Posterior cingulate cortex	31	L	-6	-61	20	1096	2.46

Table 6. Results of the subtraction analyses.

Results of the subtraction analysis categorized by broad cerebral areas. Z-scores of the maximal peak per cluster are provided. Abbreviations: Cl#: cluster number, BA: Brodmann area, Vol.: volume, P: placebo, D: distraction, H: hypnosis, C: controllability, E: emotion, M: meditation, L: left, R: right.

**Brain activity associated with psychologically induced hypoalgesia:  
A coordinate-based meta-analysis**

**Supplementary material**

	ROI-r/total	% experiments
Total PIH	20/48	42%
Placebo	14/21	67%
Distraction	2/10	20%
Hypnosis	0/6	0%
Controllability	0/2	0%
Emotion	3/4	75%
Meditation	1/5	20%

Table S1. Number and proportion of experiments included in the meta-analysis whose activation maps were masked with a priori region of interest.

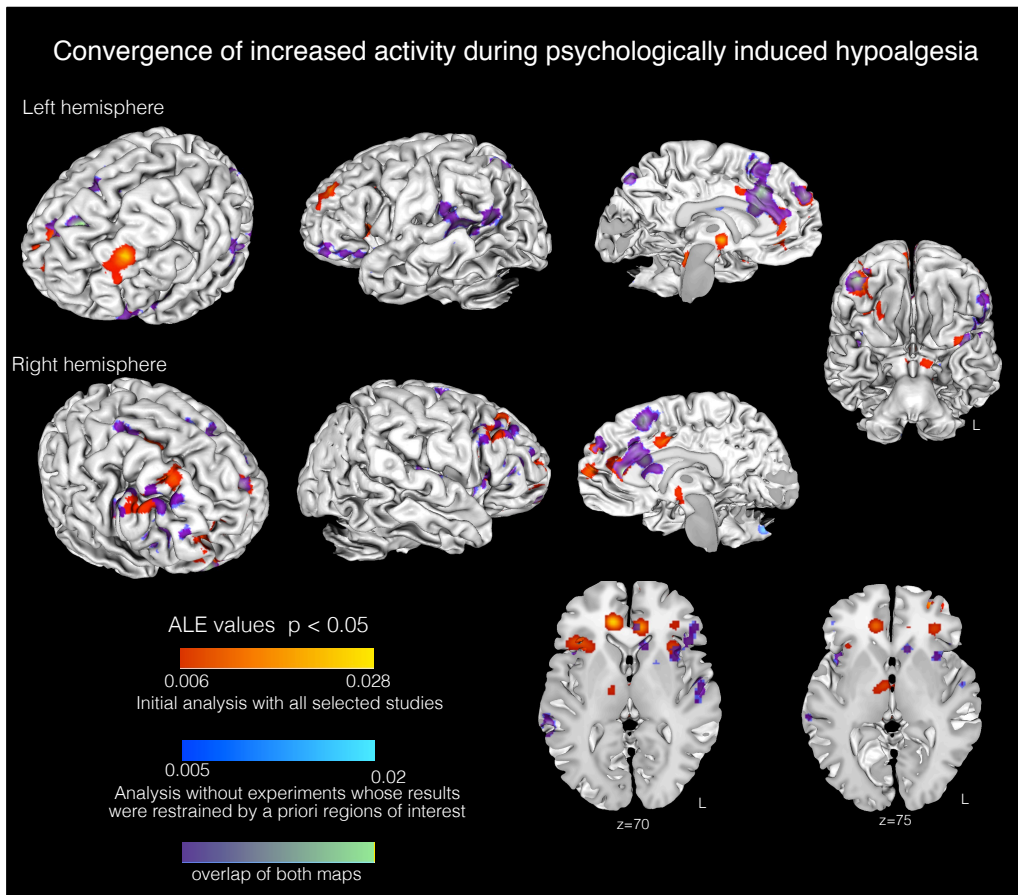


Figure S1. ALE maps with and without the masked experiment's results.

**Article 2. Cerebral correlates of pain perception and regulation: a quantitative ALE meta-analysis**

Manuscrit en préparation

**Cerebral correlates of pain perception and regulation: a quantitative ALE meta-analysis**

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Running head: Cerebral correlates of pain perception and regulation

*Keywords:* pain, brain imaging, coordinate-based meta-analysis, pain regulation, psychologically induced hypoalgesia, cognitive analgesia, hypoalgesia



## ABSTRACT

Experimental pain is typically associated with activity in a set of brain regions including the somatosensory cortices, the insula, the midcingulate cortex, the thalamus, the amygdala, the prefrontal cortex and the primary motor cortex. Given the complexity of the pain experience which involves various physical, psychological and behavioral processes, many characteristics of the pattern of activation associated with pain still need to be investigated. Among these processes are endogenous pain regulation mechanisms engaged either spontaneously during the stimulation, or deliberately through psychological interventions. This study aimed to investigate brain patterns of activity preferentially associated with pain perception or with psychologically induced hypoalgesia (PIH). Firstly, we conducted ALE meta-analyses to assess patterns of increased and decreased activity during experimental pain in healthy volunteers. Secondly, we determined the brain regions preferentially activated during pain perception or during PIH with subtraction analyses. Using a conjunction analysis, we also determined a set of brain regions possibly involved in regulatory processes activated spontaneously during acute pain. Results show that 1) somatosensory and motor areas are preferentially related to pain perception, which may reflect the preparation of a motor response, 2) dorsolateral prefrontal areas, anterior insula and the anterior mid cingulate cortex were associated with both pain and PIH and may reflect spontaneous activation of top-down regulation mechanisms during pain, and 3) antero-medial and orbital prefrontal regions were preferentially associated with PIH, which may indicate motivational and emotional processes associated with the engagement of an externally driven hypoalgesic procedure.

## 1. INTRODUCTION

Since the initial description of the pain matrix proposed by Melzack (Melzack, 1989), brain regions consistently activated during pain determined using meta-analyses include the primary and secondary somatosensory cortex (SI and SII), the insula (INS), the mid cingulate cortex (MCC), the thalamus, the amygdala, the prefrontal cortex, and the primary motor cortex (Apkarian, Bushnell & Schweinhardt, 2013; Duerden & Albanese, 2013). Pain is a complex experience that comprises multiple dimensions (sensory, affective and cognitive) that are associated with physiological and behavioural responses. Brain activity evoked by a painful event may therefore reflect various processes associated with pain perception, including nociceptive, motor and autonomic regulation, cognitive-evaluative processes, as well as attentional processes.

In spite of the consistent brain activation during pain, pain perception and pain-related brain activity can be greatly influenced by descending modulatory pathways (Heinricher & Fields, 2013), regulated by contextual and psychological factors such as beliefs, attention and emotions (Price, Hirsh & Robinson, 2009). Psychological interventions (e.g. distraction, hypnosis, placebo) have been proven effective at reducing pain perception and pain-related brain activity and are thought to rely on these mechanisms (Price & Bushnell, 2004).

Pain modulation may be generated either spontaneously (e.g. triggered the painful stimulus itself) or intentionally (e.g. through active self-regulation). However, spontaneous and intentional pain regulation may involve different and complementary mechanisms engaging to various degrees the classical top-down mechanisms affecting low-level nociceptive processes (e.g. Tracey & Mantyh, 2007) as well as higher-order mechanisms

subserving affective and/or cognitive-evaluative processes (e.g. Woo, Roy, Buhle & Wager, 2015). It was proposed that prefrontal and anterior cingulate projections to brainstem structures might be "responsible for the generation, maintenance, and integration of expected pain relief " (Bingel & Tracey, 2008). Besides, the dorsolateral prefrontal cortex (DLPFC) is engaged during cognitive pain modulation (e.g. Lorenz, Minoshima & Casey, 2003) and emotional reappraisal (Buhle et al., 2014), and its activity may reflect executive and attentional processes (Buhle, Stevens & Wager, 2012). In addition, the orbitofrontal cortex (OFC) is also involved during cognitive pain modulation (Wager, Atlas, Leotti & Rilling, 2011; Rainville et al., 1999; Petrovic, Carlsson, Petersson, Hansson & Ingvar, 2004). We have recently reported the activation in many of these areas in a meta-analysis investigating brain activity associated with various forms of psychologically induced hypoalgesia (PIH) (Dubé et al., submitted). Importantly, many of these areas may also be activated during acute pain without the involvement of pain modulatory interventions (see Duerden and Albanese, 2013) suggesting the spontaneous activation of pain regulatory processes.

To extend previous findings on the different brain regions activated during acute pain perception and pain modulation, the goal of the present study was to determine brain activity patterns preferentially or commonly associated with either pain perception and/or pain modulation induced by PIH. To examine consistent and reproducible activation across studies, a validated method of coordinate-based meta-analysis was used: the Activation Likelihood Estimate (ALE). Firstly, we investigated patterns of increased and decreased activity during experimental pain in healthy volunteers. Secondly, we compared brain regions preferentially activated during pain perception or during PIH using the results of our recent meta-analysis on

PIA (Dubé et al., submitted). In addition to pain-related activation of regions receiving nociceptive inputs from spinothalamo-cortical pathways as demonstrated previously (Apkarian et al., 2005, 2013; Duerden and Albanese, 2013), we predicted that pain-related brain activation includes some areas solicited by PIA. These responses are suggested to reflect the *spontaneous* activation of self-regulatory mechanisms associated with pain modulation during acute pain.

## 2. METHODS

### 2.1. Literature search

#### 2.1.1. Pain study

An exhaustive literature search was performed to identify studies on experimental pain perception conducted on healthy volunteers using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). This search was executed on June 25<sup>th</sup> 2014 in the Medline database using this syntax: ((fMRI or functional magnetic resonance imaging or PET or positron emission tomography) and pain). The results were limited to original journal articles (no review) written in English language and involving adult participants. The following selection criteria were systematically applied to the retrieved studies (see Figure 1).

- Population: group studies involving healthy adult participants; clinical population data were not included to avoid potential disease-related changes in neural systems activated during pain perception.

- Pain: administration of controlled experimental somatic and visceral stimuli intended to be painful and perceived as such by participants, without any intervention to alter pain perception. Studies using models of hyperalgesia or allodynia were excluded.
- Imaging: Whole-brain functional imaging methods based on hemodynamic changes related to neuronal activity (BOLD fMRI) or on changes in cerebral blood flow, oxygen or glucose metabolism (PET) with radioactive water or glucose as tracer).
- Contrast content: Imaging data analyses and contrast results documenting increases or decreases in activity during pain perception compared with baseline or a non painful stimulation. Regression maps of the BOLD or rCBF signal change on pain ratings were also included.
- Result presentation: Results of activated foci are given in a standard coordinate format (x, y, z; either MNI or Tailarach), and reach a statistical threshold of at least  $p < 0.05$  uncorrected.

Note that the conventional terminology of the ALE method is used in this paper: the word "experiment" refers to a single experimental contrast analysis (e.g. activation during heat pain > activation during warmth) while the term "study" refers to the scientific article which reports one or more experiments (Laird et al., 2011).

#### 2.1.2. Psychologically induced hypoalgesia (PIH) study

The search and selection procedures for the PIH study is fully described elsewhere (Dubé et al., submitted), but an outline of the method is provided in supplementary material for a matter of clarity. Briefly, these procedures were similar to those described above, with the keywords covering pain and psychological approaches intended to modulate pain. The

results were also limited to journal articles written in English (no review) describing healthy adult participants. Similar criteria were applied to the retrieved articles: healthy adult participants, BOLD or rCBF, somatic or visceral pain, standard coordinates. Moreover, selected studies had to use a psychological method aiming at reducing pain and for which significant pain reduction was observed: placebo, distraction, hypnosis, control over the stimulation, emotion, and meditation. In order to limit confounding factors in the effect attributable to the PIH, a control condition where pain stimulation was not accompanied by the intervention was necessary for the study to be included. Papers also had to provide analysis results where this control condition was subtracted from the experimental PIH condition.

## 2.2. Compilation of data

Several experimental characteristics of the selected studies were coded. These characteristics include the number of participants, the modality of stimulation, the stimulation site and side, the type of contrast analysis, the direction of rCBF or BOLD effect (increase or decrease) and the perceptual effect, ensuring that the experimental stimulation was reported as painful. This codification was intended to support the selection process, as well as to facilitate the grouping and the interpretation of data. Figure 2 summarizes these classification procedures as described below.

The compiled foci were grouped according to their contrast analysis ("experiments" in the ALE nomenclature). First, we grouped these experiments in order to perform two meta-analyses:

Meta-analysis 1: A) *increased* and B) *decreased activity related to the main effect of pain*. These groups each included the contrasts "Pain>Nopain" (non-painful stimulus used as control), "Pain>Baseline", regression on the subjective evaluation of pain, and a the non-specified pain effect for experiments with no clear indication about the specific contrast analysis used to reveal pain-related responses.

Meta-analysis 2: To differentiate the preferential brain activity patterns associated with pain perception from those linked to PIH, a subtraction analysis was conducted. To do so, a third pain-related map was created from the group *Main effect of pain, increased activation*, by only keeping the experiments for which the effect of pain perception was contrasted with the non-specific sensory component of the stimulation, i.e. *Pain-Nopain*. This *Pain-Nopain* ALE map was used as the first term of the subtraction, the second item the ALE map of *PIH*, which was created earlier from an additional set of data (Dubé et al., submitted).

Meta-analysis 3: A conjunction between the *Pain-Nopain* and the *PIH* ALE maps allowed the identification of the brain activity patterns commonly related to both pain perception and PIH.

### 2.3. Meta-analytical procedure

The coordinate-based meta-analyses used the revised ALE method as implemented in GingerALE 2.3 (<http://www.brainmap.org/ale/>). Coordinates originally reported in MNI space were converted to the Talairach space using the Lancaster (icbm2tal) transform (Lancaster et al., 2007). Coordinates were modeled using a three-dimensional Gaussian distribution that quantitatively adjusts for the spatial uncertainty resulting from between-participant and

between-template variance of the neuroimaging foci. The widths of these Gaussian functions were computed based on the number of participants in each experiment (Eickhoff et al., 2009). For each experiment, a modeled activation (MA) map was created from the activation foci (peak coordinates reported for an experiment); the MA map contains, for each voxel, the probability that an activation occurred exactly at this  $x y z$  coordinate while preventing summation of effects across foci from the same experiment (Turkeltaub et al., 2012). The 'true' convergence was distinguished from the random convergence on a between-experiment level (rather than a between-foci level) using an analytical solution to the null-distribution of random spatial association between experiments, allowing random-effect inference (Eickhoff, Bzdok, Laird, Kurth & Fox, 2012). ALE maps were created using this method for every group of experiments described in the previous section and in Figure 2.

### 2.3.1. Meta-analysis 1: Main effects of pain

Two ALE maps were generated from all coordinates associated with 1) an increase (activation) and 2) a decrease (deactivation) in BOLD signal or rCBF during pain perception, across all types of pain contrast analysis. We refer to these maps as *Main effect of pain, increased activation* and *Main effect of pain, decreased activation*. These ALE maps were thresholded at cluster- and voxel-levels to a  $q < 0.001$  using the False-Discovery-Rate (FDR) method (Eickhoff et al., 2012; Laird et al., 2005). This conservative threshold was applied to maximize specificity across experiments, and to provide a more interpretable amount of results in view of the very large data set available leading to high statistical power. Note that increasing this threshold mainly decreased the number of significant peaks within the major clusters shown in Figure 3.



### 2.3.2. Meta-analysis 2: Subtraction analysis

Subtraction analyses were conducted in order to reveal statistically significant differences in increased activity during pain perception compared to activity observed during PIH.

*Pain study [Pain-Nopain].* An ALE map was created with the group of foci *Pain-Nopain*. This map only comprised experiments where pain was contrasted from the non-specific somatic sensations produced by a non-painful stimulation (e.g.  $\text{Pain}^{48^\circ\text{C}} - \text{Warmth}^{32^\circ\text{C}}$ ), thus presumably reflecting areas activated during pain that may be particularly involved in nociception. This *Pain-Nopain* map relied on a smaller data set than the *Main effect of pain* and was thresholded at a cluster- and voxel-levels to a  $q < 0.05$  using the FDR method.

*Psychologically induced hypoalgesia study.* An ALE map was generated from all coordinates associated with an increase in BOLD signal or rCBF across all psychological hypoalgesic interventions. This map only comprised experiments in which the main effect of pain was subtracted (e.g.  $\text{Pain}_{\text{PIH}} - \text{Pain}_{\text{alone}}$ ). Thus, the included experiments documented the preferential effect of hypoalgesia over pain perception (Dubé et al., submitted). This ALE map was thresholded at a cluster- and voxel-levels to a  $q < 0.05$  using the FDR method to allow for a balanced comparison with the *Pain-Nopain* map. We refer to this map as *PIH*.

*Subtraction analysis procedure.* The *Pain-Nopain* map and the *PIH* map were used for the subtraction analysis following the procedure described in Eickhoff et al. (2011). First, bidirectional subtractions were computed for each voxel between the ALE-values of the two

individual maps ( $[Pain-Nopain] - PIH$ , and vice-versa). Next, all experiments from both sides of the subtraction were pooled and randomly split into two sets of the same size as the original two analyses going into each comparison (label-exchange permutation). An ALE-map was computed for each of these two randomly assembled groups and these were contrasted with each other (as in the actual analysis). The voxel-wise differences between these randomly assembled groups were then stored. This process was performed 5,000 times, yielding a null-distribution for the voxel-wise differences in ALE-scores between the two individual analyses, under the assumption of label exchangeability. The observed difference in ALE-scores was then tested against this null-distribution yielding a  $p$ -value for the difference at each voxel based on the proportion of equal or higher random differences. The resulting map was thresholded at  $q < 0.05$  (FDR-corr.) and ALE values were converted into z-scores to ease interpretations. The  $[Pain-Nopain] > PIH$  map shows brain activity preferentially related to pain perception, reflecting cerebral processing of the ascending nociceptive inputs. The  $PIH > [Pain-Nopain]$  map shows brain activity involved in pain regulation, independently of nociceptive and/or sensory afferences.

### 2.3.3. Meta-analysis 3: conjunction analysis

The conjunction ALE map contains the voxel-wise minimum between the two thresholded individual ALE maps and shows the probabilistic activation common to both maps. Considering the experiments that constitute the *Pain-Nopain* and the *PIH* maps, this conjunction map comprises a set of brain regions that are both activated by ascending nociceptive inputs and involved in top-down regulation of pain. This could involve, for

example, regions that receive nociceptive input and are involved in local pain regulation or that project to other regions involved in pain perception or pain regulation.

### 3. RESULTS

#### 3.1. Selected studies

##### 3.1.1. Pain study

A total of 1604 articles published between 1974 and 2014 were retrieved from the initial search in Medline. These papers were screened according to information presented in their title and abstract (1227 removed; Figure 1). The full text of the remaining 377 articles was assessed for eligibility to the present study, and 201 articles were discarded because they did not fulfill inclusion criteria. The final selection consisted in 176 articles from which we collected details about the experimental paradigm, the analysis parameters as well as the results of increased and decreased activity in coordinate format. From these 176 selected studies, 303 experiments (contrast analyses) were retained, from which a total of 3814 foci were compiled. These 303 experiments were grouped for the ALE maps (see Methods for details). Table 1 shows the quantitative description of each group of experiments. All articles included are listed in Table S1, and all excluded ones are listed in Table S2 with the associated unfulfilled criteria.

##### 3.1.2. Psychologically induced hypoalgesia study

The PIH study (Dubé et al., submitted) comprised a final sample of 26 articles, which included 48 experiments of interest that were conceptually and methodologically comparable

(i.e. showing increased brain responses during analgesic procedures), or a total of 268 foci (Table 1).

## 3.2. Probabilistic brain activation

### 3.2.1. Main effect of pain

*Increased activity.* The meta-analysis of the main effect of pain yielded convergence of increased activity in several regions bilaterally, with the highest ALE values in the right MCC (BA 32/24; Talairach coordinates 4, 8, 38; Figure 3 and Table 2). Most of the bilateral INS showed high and extensive probabilistic activity (highest values in anterior portions) extending posteriorly to the ventral part of the pre- and postcentral gyri, as well as to the inferior parietal lobule (IPL). In the left hemisphere, the insular cluster extended even more laterally to the opercular portion of the inferior frontal gyrus, and in the pre- and postcentral gyri. Other clusters were observed in several areas of the DLPFC, predominantly in the right hemisphere. Several peaks were also observed in bilateral subcortical areas, including the thalamus, the amygdala, the putamen, the globus pallidus, as well as the anterior lobe of the left cerebellum (Table 2 and Figure 3).

*Decreased activity.* Convergence of decreased activity in different areas were observed solely on the medial wall of both hemispheres, in the pre- and subgenual anterior cingulate cortex (ACC), the posterior cingulate cortex and the posterior region of the paracentral lobule (Table 3 and Figure 3).

### 3.2.2. Subtraction analysis

With the subtraction analyses, activity preferentially related to pain perception or to PIH was localized, as indicated in Tables 4-5 and Figure 4. The *Pain-Nopain* map produced results generally comparable to the *Main effect of pain* as shown in the left panel of Figure 4A (see also Table S3). The PIH map is shown in the right panel of Figure 4A. The contrasts between these maps are shown in Figure 4B.

*[Pain-Nopain] – PIH*. This analysis revealed peaks of activity preferentially associated with pain perception in the bilateral posterior MCC (pMCC), with activation extending to the dorsal medial frontal gyrus (Table 4; see yellow clusters in Figure 4B). Activity was also observed in most of the INS bilaterally, excluding the most anterodorsal and anteroventral zones on the left, as well as a subregion of the right anterior INS (aINS). On both sides, these large insular clusters extended laterally to the frontal operculum, the inferior frontal gyrus (IFG) and to the most inferior part of the pre- and postcentral gyrus. In addition, it extended posteriorly to the parietal operculum and the IPL. Peaks were also observed at the junction between the right precentral gyrus and the middle frontal gyrus. Additionally, subcortical activation sites were observed in the posteromedial and anterolateral parts of left and right thalami, from which activation extended to the globus pallidus in both hemispheres, and to the right putamen. Finally, activation was observed in the anterior lobe of the cerebellum.

*PIH – [Pain-Nopain]*. This analysis revealed peaks of activity preferentially associated with PIH (Table 5; see red clusters in Figure 4B). Smaller and fewer clusters were observed compared with the *[Pain-Nopain] – PIH*. Medially, PIH was associated with activity in the bilateral rostral ACC and medial prefrontal gyrus. Peaks were also observed in the right lateral and medial OFC, as well as in the DLPFC, in the right middle and left superior frontal gyri.

Activation was also observed in the left posterior part of the superior and middle temporal gyri, along with the left superior parietal lobule. No insular or subcortical activation was detected.

### 3.2.2. Conjunction analysis

*[Pain-Nopain] and PIH.* We further investigated the common activation produced by pain perception and PIH by looking at the conjunction between the *Pain-Nopain* and the *PIH* maps (Table 6; blue clusters in Figure 4B). This revealed a large frontomedial cluster covering the left anterior MCC (aMCC) and the right MCC, extending to bilateral dorsal pregenual ACC, ventral pMCC and dorsal medial frontal gyrus. Regarding the INS, activation was observed in the most anterior zone of its dorsal and ventral aspects on the left side, as well as in the right aINS. Activation was also observed in the anterior portion of the right middle frontal gyrus, along with the right posterior part of the IFG, at the junction with the precentral gyrus. Moreover, clusters were revealed in the right transverse temporal gyrus, and the left IPL. Finally, subcortical areas included the left anterior thalamus, as well as the right caudate body.

## 4. DISCUSSION

This is the first quantitative meta-analysis that provides a direct comparison of brain activity related to pain perception and PIH, showing that pain perception is preferentially associated with activation in the insula and midcingulate as well as in sensorimotor and several subcortical areas, while PIH is preferentially associated with activation in the anterior

cingulate and prefrontal areas. Also, activation common to both pain perception and PIH was observed predominantly in subregions of the anterior MCC and anterior insula.

#### 4.1. Pain perception

Brain regions in which activity was preferentially related to pain perception included the posterior insula (pINS), the parietal operculum and the posterior MCC, which receive direct nociceptive inputs from the spinothalamic system (Dum, Levinthal & Strick, 2009). The large cluster extending from the pINS to the parietal operculum is consistent with the idea that this region has an essential role in nociception and pain perception (Brooks, Zambreau, Godinez, Craig & Tracey, 2005; Craig, 2009; Garcia-Larrea, 2012; Mazzola, Failletot, Barral, Mauguière & Peyron, 2012).

In the last decade, some have proposed that pain can leave a specific and distributed neural signature detectable with more advanced brain imaging methods (Brown et al. 2011; Wager et al., 2013). In these studies, pain could be discriminated from non-painful heat or pain-related tasks by applying machine learning approaches to fMRI data. This provided convincing arguments in favor of the existence of such a pain signature (Apkarian, 2013; Iannetti, Salomons, Moayedi, Mouraux, & Davis, 2013); although these results have generated a legitimate debate on the use of “objective measures” of pain, see Robinson et al, (2013) and Sullivan et al. (2013). It is interesting to note that within the "neural signature" of pain put forward by Wager and colleagues (2013), the operculo-insular region was most closely attributable to physical pain when compared to social pain.

In spite of some discrepancies, the present results are generally consistent with these findings, showing activity preferentially related to pain perception in regions identified by machine-learning approaches as specific to pain as opposed to non-painful stimulation or pain-related processes such as pain anticipation or pain memory (see Wager et al., 2013). Moreover, the present results support the proposition by Garcia-Larrea (2012) based on multiple sources of data that the posterior insula and its adjoining medial operculum, named PIMO, may constitute a primary pain cortex.

However, we must emphasize that meta-analysis results can only be interpreted as reflecting brain activity preferentially related to pain perception or as a correlate of pain but not as specific to pain. We also argue that it reflects not only perception per se but also processes related to various pain-related responses. For instance, activation of the supplementary motor area (SMA), the ventral premotor area, the pMCC as well as basal ganglia may rather reflect motor responses or motor regulation in the context of experimental pain. Accordingly, some of these regions send direct projections to spinal motoneurons (Dum & Strick, 1991) and are directly involved in voluntary motor control (Paus, 2001).

#### 4.2. Psychologically induced hypoalgesia

Activity in rostral ACC, in the medial prefrontal cortex (MPFC) and in the lateral OFC was preferentially associated with PIH. The rostral ACC is involved in self-referential and affective processes (Torta & Cauda, 2011), and MPFC is related to emotional processing (Phan, Wager, Taylor & Liberzon, 2002). More precisely, the dorsal MPFC is thought to be involved in the evaluation processes of emotions (e.g. appraisal, expression), whereas the ventral MPFC (including the rostral ACC) would play a role in emotional regulation (e.g.



suppression/enhancement; Etkin, Egner & Kalisch, 2011). Moreover, Woo et al. (2015) have recently shown that the ventral MPFC was a mediator of pain reduction brought by directed self-regulation by cognitive strategies. They also showed that brain activation related to self-regulation could be dissociated from areas composing the “neurologic pain signature”. Besides, the OFC could allow the valuation of pain as a punisher. Accordingly, while medial OFC is preferentially involved in monitoring and learning aspects of a reward value, its lateral part is preferentially involved in the evaluation of a punisher, in order to produce an adapted behavioral response (Kringelbach, 2005). We propose that psychological interventions reduce pain through parallel emotional and/or motivational processes that engage and potentiate endogenous pain regulation mechanisms.

#### 4.3. Pain monitoring and regulation

The conjunction analysis was designed to reveal areas activated by pain and could reflect the spontaneous engagement of pain regulatory mechanisms. A set of brain areas was commonly involved in both pain perception and PIH, including the aINS, the aMCC, the DLPFC. This pattern is consistent with the alternative interpretation of the pain matrix of a brain network non specific to pain perception, rather reflecting the salience-detection system of multi-modal stimulation (Mouraux et al., 2011).

The aINS is a key node of the salience network (Uddin, 2015), which is thought to integrate sensory information from external stimuli with internal bodily and emotional state (Medford & Critchley, 2010). It is also related to emotional processing (Klein, Ullsperger & Danielmeier, 2013; Christopher, Koshimori, Lang, Criaud & Strafella, 2014). According to Craig (2002, 2009), the aINS encodes self-awareness of bodily signals, and the "significance"

of the detected saliency (Craig, 2009). We propose that, in the context of pain regulation, the aINS would translate pain signal into interoceptive salience that leads to top-down control. This is supported by the joint involvement of the DLPFC and the aMCC. The DLPFC is involved in cognitive control and executive functions (Dosenbach, Fair, Cohen, Schlaggar & Petersen, 2008; Cieslik et al., 2013) and may reflect the processing of interoceptive information according to its saliency to determine its priority. This is coherent with the established role of DLPFC in cognitive modulation of pain and attention control.

In addition, the large cluster covering the aMCC suggests a pivotal role of this area in spontaneous endogenous pain regulation. The aMCC has been considered as being central for the generation of an adaptive response following a goal. A coordinate-based meta-analysis showed that the aMCC was the site of convergence of brain activity related to pain, negative affect and cognitive control (Shackman et al., 2011), leading the authors to suggest a role of this area in action selection and control for instrumental defensive behavior in response to aversiveness (e.g. finding a way to reduce the suffering from pain). Similarly, Holroyd & Yeung (2012) argued that the aMCC is responsible for the selection and the management of "options" (context-specific sequences of behavior) according to a goal, and the coordination of inputs from multiple systems (e.g. executive function from DLPFC, sensory afferents, etc.). Taken together, our results confirm that many regions found to be activated by painful stimuli may reflect the spontaneous activation of pain regulatory processes. PIH relies partly on the activation of those same systems but may further recruit additional brain areas depending on the specific type of intervention used (see Dubé et al., submitted).

#### 4.4. Limitations

Firstly, it should be noted that convergent activation revealed by a meta-analysis may be influenced by the focus on a priori search areas (e.g. region of interest) in each study, according to the specific hypothesis tested. This allows reducing the probability of type II error (false negative). However, it increases the probability of obtaining circular auto-confirmatory results, and inducing bias in meta-analyses. Ideally, brain imaging results should be reported from the global search, in addition to the initial directed search. Secondly, these activation results may be attributable to an underlying neuronal mechanism, but may also be affected by methodological and statistical considerations (e.g. thresholding). The proposed interpretations should be considered accordingly (Poldrack, 2011). There are promising emerging analysis methods that could be applied to meta-analysis data in order to provide stronger inferences about the neuronal mechanisms underlying brain activation (e.g. Woo et al., 2014).

#### 4.5. Summary and conclusion

In the present study, coordinate-based meta-analyses were used to examine the brain response to pain perception in comparison to psychologically induced analgesia. First, results show a pattern of brain activity preferentially related to pain perception, which may reflect various processes inherent to pain perception and pain-related responses such as the preparation of a motor response. Second, brain activity commonly related to pain and PIA likely reflect a set of regions that could be involved in spontaneous pain regulation triggered by nociceptive inputs. Third, areas preferentially associated with PIA may indicate cognitive,

emotional and motivational processes responsible for the modulation of endogenous pain regulation and engaged specifically in response to externally driven interventions.

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#### CONFLICT OF INTEREST

The authors have no conflict of interest in relation to this work.

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## TABLES

**Table 1.** Number of experiments, foci and subjects in each group for meta-analyses.

Group of experiments	N of experiments	N of foci	N	Participants		
				% female	% male	Mean age*
Main effect of pain						
increased activity	261	3494	3857	37	63	29
decreased activity	42	320	646	na	na	na
Pain-Nopain	48	579	695	32	68	29
PIH	48	268	937	63	34	28

Table 1. Number of experiments, foci and subjects with descriptive statistics of the sample of participants in each group for meta-analyses. \*Calculated from the means reported in articles.

**Table 2.** Main effect of pain: increased activity related to painful stimuli (all experiments).

Anatomical label	BA	ALE Value	Side	x	y	z
<b>Frontal lobe</b>						
Anterior cingulate cortex	—	—	—	—	—	—
Midcingulate cortex						
Midcingulate cortex	32/24	0.236	R	4	8	38
Medial prefrontal cortex						
Medial frontal gyrus	6	0.059	L	-4	-10	58
Orbitofrontal cortex	—	—	—	—	—	—
Ventrolateral prefrontal cortex						
Inferior frontal gyrus, opercular part	44	0.088	L	-52	4	6
Dorsolateral prefrontal cortex						
Middle frontal gyrus	10	0.083	R	34	42	24
Middle frontal gyrus	10	0.078	R	40	40	10
Middle frontal gyrus	9	0.054	L	-32	38	30
Middle frontal gyrus	9	0.047	R	46	10	36
Middle frontal gyrus	10	0.047	L	-34	44	16
Precentral gyrus (M1)						
Precentral gyrus/Inferior frontal gyrus	6/44	0.125	R	50	2	8
Precentral gyrus/Inferior frontal gyrus	6/44	0.091	L	-52	-2	8
Precentral gyrus/Middle frontal gyrus	6	0.055	R	44	-2	46
Precentral gyrus/Inferior frontal gyrus	9/6	0.043	R	46	6	28
Anterior insula						
Anterodorsal insula	—	0.227	L	-36	6	8
Anterodorsal insula	—	0.201	R	36	12	6
Posterior insula						
Posterior insula	—	0.148	L	-36	-20	14
Posterior insula	—	0.132	R	38	-18	16
Posterior insula	—	0.067	R	36	-10	0
<b>Parietal lobe</b>						
Postcentral gyrus (SI)						
Postcentral gyrus	5/2	0.039 <sup>a</sup>	R	24	-38	58
Post/precentral gyrus	3/4	0.039 <sup>a</sup>	R	34	-30	58
Post/precentral gyrus	3/4	0.039 <sup>a</sup>	L	-52	-14	42
Postcentral gyrus	5	0.035 <sup>a</sup>	R	12	-50	62
Operculum (SII)						
Postcentral gyrus	40	0.190	L	-56	-26	20
Inferior parietal lobule	40	0.211	R	52	-26	24
Posterior cingulate cortex						
Dorsal posterior cingulate cortex	23	0.078	L	0	-28	28
Inferior parietal lobule						
Inferior parietal lobule	40	0.070	R	48	-38	42
Inferior parietal lobule	40	0.039 <sup>a</sup>	R	44	-52	42
Superior parietal lobule						
Superior parietal lobule	7	0.036 <sup>a</sup>	R	34	-46	40
<b>Temporal lobe</b>						
—	—	—	—	—	—	—
<b>Sub-cortical areas</b>						
Thalamus (lateral)	—	0.219	L	-12	-16	6
Thalamus	—	0.199	R	10	-18	8
Globus pallidus	—	0.089	R	14	4	4
Globus pallidus	—	0.060	L	-14	0	4
Amygdala	—	0.072	R	22	0	-14
Parahippocampal gyrus/Amygdala	34/—	0.061	L	-20	0	-10
<b>Cerebellum</b>						
Cerebellum, culmen	—	0.071	L	-28	-60	-26
Cerebellum, culmen	—	0.045	L	-16	-56	-18

Significance level: p&lt;0.001 (\*); p&lt;0.05) FDR-corrected for multiple comparisons.

x, y, z: Talairach coordinates. BA: Brodmann areas; R: right; L: left

**Table 2.** Main effect of pain: increased activity related to painful stimuli (all experiments).

**Table 3.** Main effect of pain: decreased activity related to painful stimuli (all experiments).

Anatomical label	BA	ALE Value	Side	x	y	z
<b>Frontal lobe</b>						
Anterior cingulate cortex						
Pregenual/Subgenual anterior cingulate cortex	32	0.038	L	-6	34	-6
Midcingulate cortex	---	---	---	---	---	---
Medial prefrontal cortex	---	---	---	---	---	---
Orbitofrontal cortex	---	---	---	---	---	---
Ventrolateral prefrontal cortex	---	---	---	---	---	---
Dorsolateral prefrontal cortex	---	---	---	---	---	---
Precentral gyrus (M1)						
Paracentral lobule	5	0.019	L	-2	-38	52
Anterior insula	---	---	---	---	---	---
Posterior insula	---	---	---	---	---	---
<b>Parietal lobe</b>						
Postcentral gyrus (SI)						
Paracentral lobule (posterior)	5	0.019	R	2	-40	52
Operculum (SII)	---	---	---	---	---	---
Posterior cingulate cortex						
Dorsal/ventral posterior cingulate cortex	23	0.034	L	-2	-50	24
Dorsal posterior cingulate cortex	31	0.015	L	-6	-42	34
Inferior parietal lobule	---	---	---	---	---	---
Superior parietal lobule	---	---	---	---	---	---
<b>Temporal lobe</b>						
	---	---	---	---	---	---
<b>Sub-cortical areas</b>						
	---	---	---	---	---	---
<b>Cerebellum</b>						
	---	---	---	---	---	---

Significance level:  $p < 0.001$  FDR-corrected for multiple comparisons.

x, y, z: Talairach coordinates. BA: Brodmann areas; R: right; L: left

Table 3. Main effect of pain: decreased activity related to painful stimuli (all experiments).

**Table 4.** Results of the subtraction analysis [*Pain-Nopain*] - *PIH*.

Anatomical label	BA	Z Value	Side	x	y	z
<b>Frontal lobe</b>						
Anterior cingulate cortex	---	---	---	---	---	---
Midcingulate cortex						
Midcingulate gyrus	24	3.54	R	6	13	34
Anterior mid cingulate cortex	32	2.54	R	4	32	28
Medial prefrontal cortex						
Medial frontal gyrus/Anterior	9/32	2.56	L	0	32	30
Medial frontal gyrus	6	2.24	R	4	0	58
Medial frontal gyrus	6	2.22	R	4	2	62
Medial frontal gyrus	6	2.20	R	8	0	64
Medial frontal gyrus	8	2.12	L	0	30	38
Orbitofrontal cortex	---	---	---	---	---	---
Ventrolateral prefrontal cortex						
Inferior frontal gyrus/Middle	46	2.29	R	38	32	24
Dorsolateral prefrontal cortex	---	---	---	---	---	---
Precentral gyrus (M1)						
Precentral gyrus	6	2.95	R	42	0	40
Precentral gyrus	6	2.67	R	44	-8	42
Precentral gyrus	6	2.46	R	40	-4	48
Precentral gyrus	6	2.43	R	45	-4	45
Anterior insula						
Anteroventral insula	---	2.32	L	-26	18	-4
Anterodorsal insula	---	2.19	L	-22	22	-2
Posterior insula	---	---	---	---	---	---
<b>Parietal lobe</b>						
Postcentral gyrus (SI)						
Postcentral gyrus	2	2.91	L	-44	-20	32
Operculum (SII)	---	---	---	---	---	---
Posterior cingulate cortex						
Posterior midcingulate cortex	24/31	3.72	L	-1	-7	41
Inferior parietal lobule						
Inferior parietal lobule	40	2.35	R	52	-10	16
Inferior parietal lobule	40	2.12	L	-64	-34	26
Superior parietal lobule	---	---	---	---	---	---



**Table 4.** Results of the subtraction analysis [*Pain-Nopain*] - PIH.

Anatomical label	BA	Z Value	Side	x	y	z
<b>Temporal lobe</b>	--	--	--	--	--	--
<b>Sub-cortical areas</b>						
Thalamus (anterior)	--	3.72	R	9	-8	9
Thalamus (posteromedial)	--	3.04	L	-4	-32	4
Thalamus (anterior)	--	2.24	L	-4	-2	4
Caudate nucleus	--	2.49	L	-18	4	22
Putamen	--	3.54	R	25	3	3
Globus pallidus	--	3.24	R	-20	-10	8
Globus pallidus	--	3.09	R	12	0	4
Globus pallidus	--	2.85	L	-14	2	0
<b>Cerebellum</b>						
Cerebellum, culmen	--	3.72	L	-13	-58	-18
Cerebellum, cerebellar tonsil	--	3.72	L	-26	-62	-27
Cerebellum, nodule	--	3.54	L	0	-58	-24
Cerebellum, cerebellar tonsil	--	3.54	L	-32	-60	-25
Cerebellum, cerebellar tonsil	--	3.35	L	-30	-62	-36
Cerebellum, anterior lobe	--	2.99	R	16	-66	-24
Cerebellum, declive	--	2.65	R	2	-64	-18
Cerebellum, pyramis	--	2.49	R	22	-63	-27
Cerebellum, pyramis	--	2.42	R	28	-64	-28
Cerebellum, culmen	--	2.18	R	32	-60	-26

Significance level:  $p < 0.05$  FDR-corrected for multiple comparisons.

x, y, z: Talairach coordinates. BA: Brodmann areas; R: right; L: left

Table 4. Results of the subtraction analysis [*Pain-Nopain*] - PIH.

**Table 5.** Results of the subtraction analysis *PIH - [Pain-Nopain]*.

Anatomical label	BA	Z Value	Side	x	y	z
<b>Frontal lobe</b>						
Anterior cingulate cortex						
Pregenua/Subgenual anterior cingulate cortex	32	2.59	R	16	36	-4
Pregenua anterior cingulate cortex	24/33	2.40	R	14	32	6
Pregenua anterior cingulate cortex	24/33	2.20	R	4	26	10
Pregenua anterior cingulate cortex	24/33	2.20	R	4	26	10
Pregenua anterior cingulate cortex	32	2.01	L	-13	38	2
Pregenua/Subgenual anterior cingulate cortex	24/33	2.00	L	-12	32	4
Pregenua anterior cingulate cortex	32	1.97	L	-16	36	6
Midcingulate cortex						
Medial prefrontal cortex						
Medial frontal gyrus	9/8	2.25	L	0	48	36
Medial frontal gyrus	42/255	2.25	L	0	48	36
Medial frontal gyrus	9	2.23	L	-6	46	33
Medial frontal gyrus	9/8	2.22	L	-8	42	36
Orbitofrontal cortex						
Orbitofrontal gyrus (medial)	11	2.71	R	20	44	-14
Orbitofrontal gyrus (medial)	11	2.35	R	20	40	-14
Orbitofrontal gyrus (lateral)	11	1.99	R	27	54	-8
Orbitofrontal gyrus (lateral)	11	1.95	R	32	50	-9
Orbitofrontal gyrus (lateral)	11	1.94	R	35	47	-11
Ventrolateral prefrontal cortex						
Dorsolateral prefrontal cortex						
Middle/Superior frontal gyrus	8	2.79	R	26	24	42
Superior frontal gyrus	8/9	2.24	L	-8	44	42
Superior frontal gyrus	8/9	2.21	L	-14	46	38
Superior frontal gyrus	8	2.19	R	20	16	46
Superior frontal gyrus	6	1.96	R	18	10	48
Superior frontal gyrus	9	1.90	R	10	50	34
Superior frontal gyrus/Midcingulate gyrus	32/9	1.88	R	20	14	34
Precentral gyrus (M1)						
Anterior insula						
Posterior insula						
<b>Parietal lobe</b>						
Postcentral gyrus (SI)						
Operculum (SII)						
Posterior cingulate cortex						
Inferior parietal lobule						
Superior parietal lobule						
Superior parietal lobule	7	1.95	L	-30	-66	43
Superior parietal lobule	7/19	1.76	L	-32	-72	42
<b>Temporal lobe</b>						
Middle temporal gyrus (posterior)	22/37	2.00	L	-56	-46	6
Middle temporal gyrus (posterior)	22/37	2.00	L	-60	-46	6
Superior temporal gyrus (posterior)	22	1.85	L	-59	-33	9
Superior temporal gyrus (posterior)	22	1.81	L	-52	-42	8
Middle temporal gyrus (posterior)	22	1.80	L	-60	-39	4
Superior temporal gyrus (posterior)	22/42	1.80	L	-60	-32	4
<b>Sub-cortical areas</b>						
<b>Cerebellum</b>						

Significance level:  $p < 0.05$  FDR-corrected for multiple comparisons.  
x, y, z: Talairach coordinates. BA: Brodmann areas; R: right; L: left

Table 5. Results of the subtraction analysis *PIH - [Pain-Nopain]*.

**Table 6.** Results of the conjunction analysis [*Pain-Nopain*] ∩ *PIH*.

Anatomical label	BA	ALE Value	Side	x	y	z
<b>Frontal lobe</b>						
Anterior cingulate cortex						
Pregenua anterior cingulate cortex	24/32	0.011	L	-6	30	18
Pregenua anterior cingulate cortex	32	0.010	R	2	34	18
Midcingulate cortex						
Anterior midcingulate cortex	32	0.015	L	-2	20	32
Midcingulate gyrus	24	0.014	R	6	0	34
Anterior midcingulate cortex	24/33	0.013	L	-2	14	24
Midcingulate gyrus	24/32	0.009	R	14	10	38
Midcingulate cortex	24	0.007	L	-10	6	42
Anterior midcingulate cortex	24	0.007	R	14	10	28
Medial prefrontal cortex						
Medial frontal gyrus	6/8	0.012	R	4	14	52
Medial frontal gyrus	8/6	0.011	R	4	14	44
Medial frontal gyrus	8/6	0.010	L	0	20	48
Medial frontal gyrus	8	0.007	L	-4	8	48
Orbitofrontal cortex						
---	---	---	---	---	---	---
Ventrolateral prefrontal cortex						
Inferior frontal gyrus, opercular part	44	0.012	R	46	6	14
Inferior frontal gyrus, triangular part	45	0.009	R	44	20	6
Dorsolateral prefrontal cortex						
Middle frontal gyrus	10	0.008	R	42	44	20
Middle frontal gyrus	10	0.008	R	32	42	22
Middle frontal gyrus	10	0.007	R	32	44	16
Middle frontal gyrus	10	0.006	R	42	42	16
Precentral gyrus (M1)						
---	---	---	---	---	---	---
Anterior insula						
Anterodorsal insula	---	0.014	R	32	16	8
Anterodorsal insula	---	0.013	L	-38	16	10
Anterodorsal insula	---	0.013	L	-34	18	8
Anterovernal insula	---	0.012	L	-36	8	-8
Anterodorsal insula	---	0.009	L	-32	8	14
Anterior insula	---	0.008	R	34	10	-2
Posterior insula						
---	---	---	---	---	---	---
<b>Parietal lobe</b>						
Postcentral gyrus (S1)						
---	---	---	---	---	---	---
Operculum (SII)						
---	---	---	---	---	---	---
Posterior cingulate cortex						
---	---	---	---	---	---	---
Inferior parietal lobule						
Inferior parietal lobule	40	0.009	L	-58	-32	18
Inferior parietal lobule	40	0.007	L	-52	-36	28
Inferior parietal lobule	40	0.006	L	-54	-36	26
Superior parietal lobule						
---	---	---	---	---	---	---
<b>Temporal lobe</b>						
Transverse temporal gyrus	41	0.010	R	46	-20	12
<b>Sub-cortical areas</b>						
Thalamus (anterovernal)	---	0.012	L	-6	-12	0
Thalamus (ventroanterolateral)	---	0.010	L	-12	-14	4
Thalamus (anterior)	---	0.008	L	-4	-6	0
Caudate nucleus	---	0.009	R	10	6	12
<b>Cerebellum</b>						
---	---	---	---	---	---	---

Table 6. Results of the conjunction analysis [*Pain-Nopain*] ∪ *PIH*.

Significance level:  $p < 0.05$  FDR-corrected for multiple comparisons.  
x, y, z: Talairach coordinates. BA: Brodmann areas; R: right; L: left

## FIGURE LEGENDS

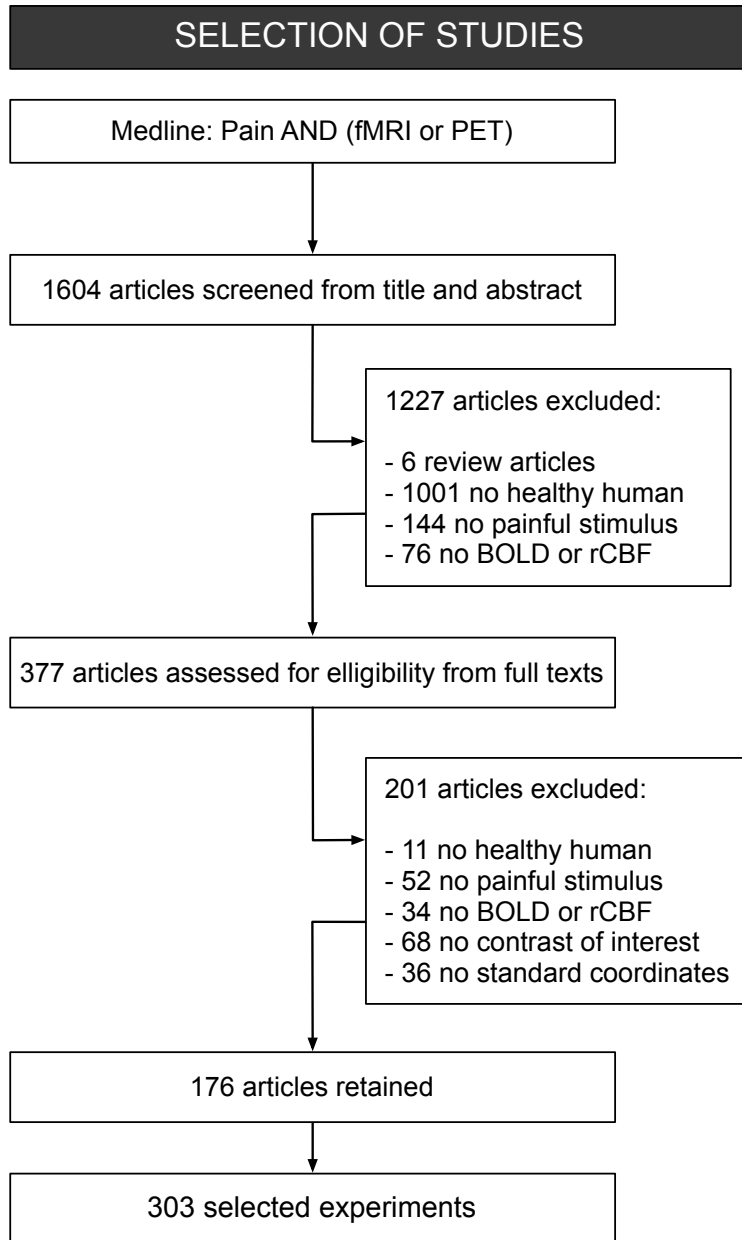


Figure 1. Flow chart based on PRISMA guidelines for the search and the selection procedures when conducting a meta-analysis. (Liberati et al., 2009)

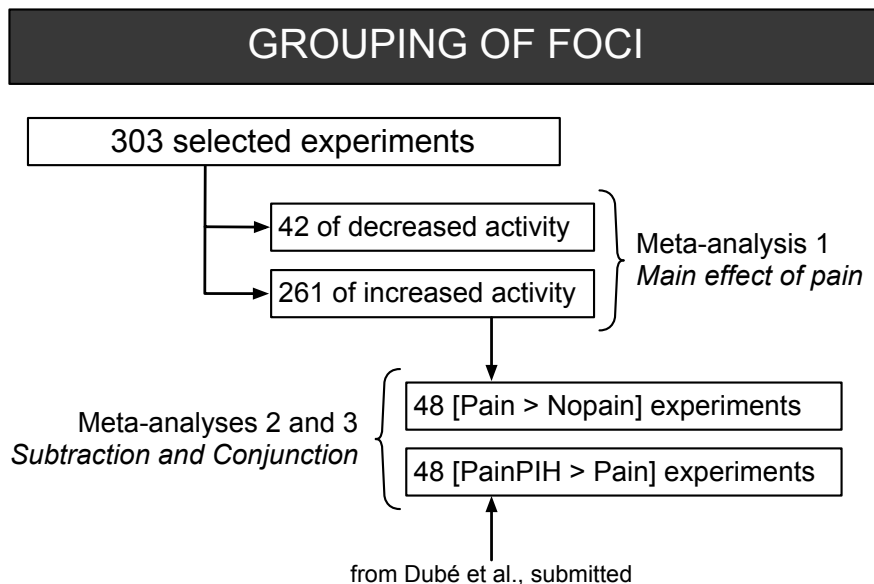


Figure 2. Grouping of foci according to the intended meta-analysis.

From the 303 selected experiments, there was 42 experiments of decreased activation and 261 experiments of increased activation. The meta-analysis on the *Main effect of pain* was generated from these two groups of foci. From the 261 experiments of increased activation, 48 were selected to create the ALE map used in the subtraction and conjunction analyses (see Methods, section 2.2). The ALE map of psychologically induced hypoalgesia (PIH) was created from 48 experiments from unpublished results.

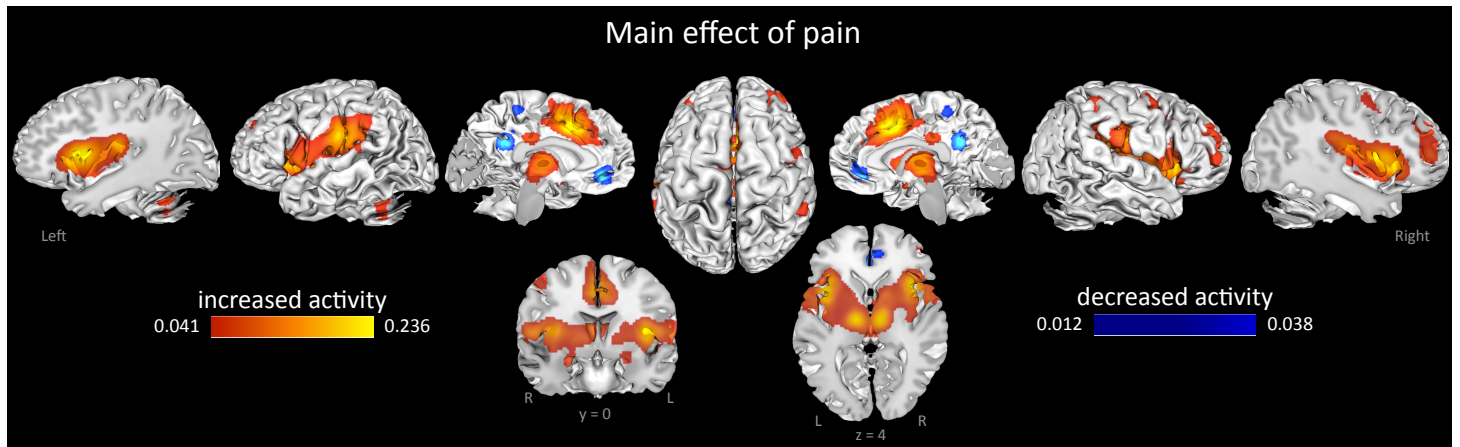


Figure 3. Brain convergence of increased and decreased activity related to the *Main effect of pain* meta-analysis.

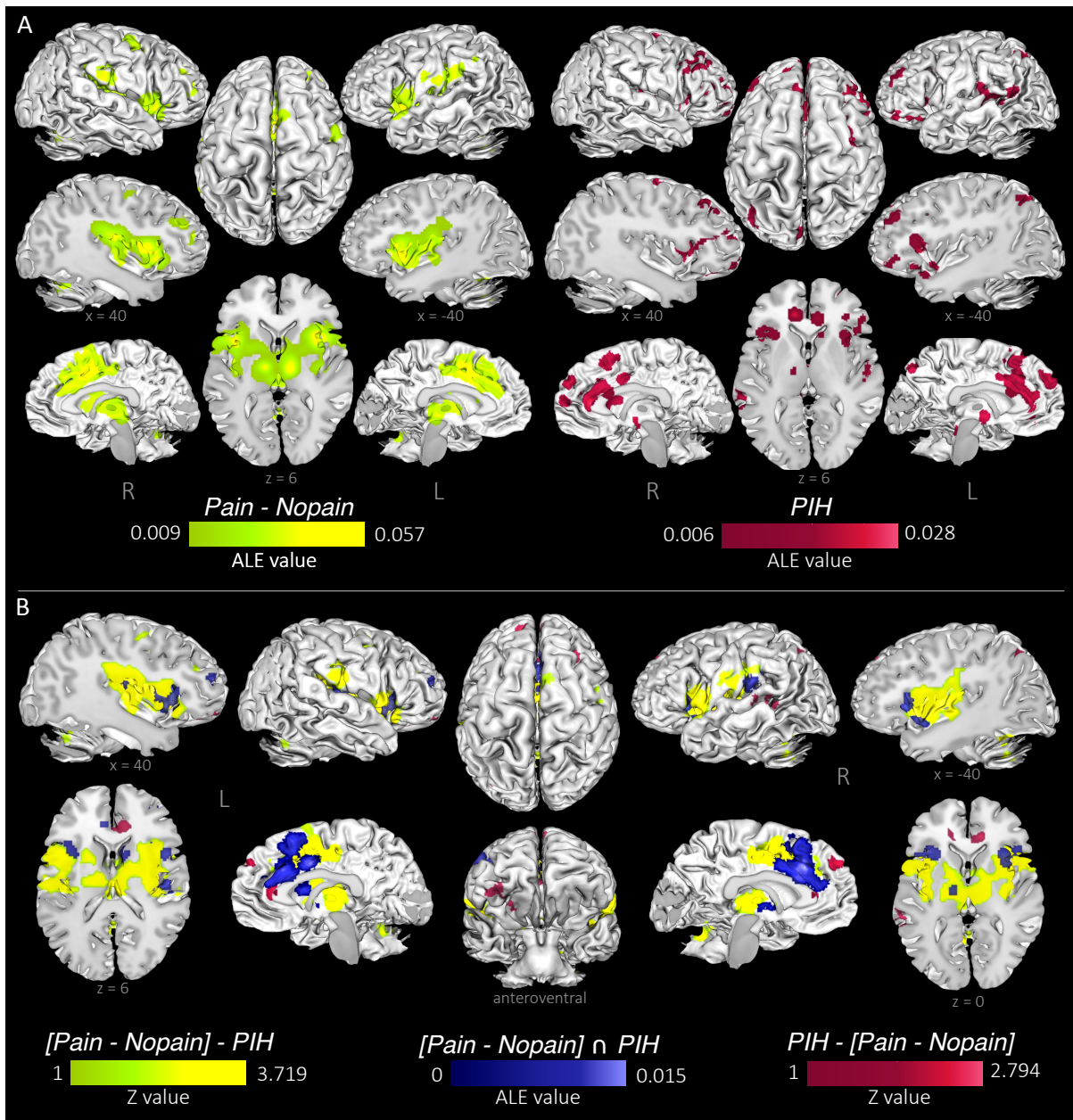


Figure 4. Results of the subtraction and conjunction analyses.

Top: *Pain-Nopain* and *PIH* ALE maps. Bottom: Brain increases of activity specific to the *Pain - Nopain* ALE map pain (yellow), or specific to the *PIH* ALE map (red), and common to both (blue). ALE maps are overlaid on the Colin27 anatomical model template (<http://www.brainmap.org/ale/>; (Kochunov et al., 2002)) using Mango software (<http://rii.uthscsa.edu/mango/>).

## Cerebral correlates of pain perception and regulation: a quantitative ALE meta-analysis

### Supplementary material

Methodological details for the PIH study  
adapted from Dubé et al., submitted.

#### *Literature selection*

An exhaustive literature search was conducted to identify studies of psychological hypoalgesia using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). A large search was executed on March 14<sup>th</sup> 2014 in the databases PsychInfo and Medline using concepts covering psychological approaches intended to modulate pain<sup>13</sup>. The results were then limited to journal articles written in English describing human studies. Next, the following inclusion criteria were applied.

- Imaging method: Brain-imaging methods for detecting changes in cerebral blood flow or glucose metabolism; i.e. BOLD fMRI or PET using water or glucose as a radiotracer;
- Subjects: Group studies involving normal, healthy human subjects (to avoid the potential disease-related plasticity in neural systems activated during the perception of pain or the endogenous regulation of nociceptive activity);
- Pain: Administration of controlled physical/somatic stimuli perceived as painful;

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<sup>13</sup> Exact syntax: (fMRI or functional magnetic resonance imaging or PET or positron emission tomography) and ((cognitive modulation) or (psychological and modulation) or (cognitive and hypoalgesia) or (psychological and hypoalgesia) or (psychological and intervention) or (cognitive and intervention) or attention or distraction or hypnosis or placebo or emotion or control or controllability or meditation) and (pain or nociception).



- Psychological intervention: Use of a psychological intervention aimed to reduce pain perception;
- Control condition: Within- and/or between-subject comparison with a painful control condition where no hypoalgesic intervention is involved, or two levels of an experimental condition that allows the isolation of an analgesic effect when contrasted;
- Hypoalgesic effect: A significant psychophysical reduction of pain, as reported by subjective ratings by the participants, during the experimental condition (psychological intervention) compared with the control condition, as indicated by the result of a statistical test or a reported  $p$ -value;
- Contrasts content: The imaging data analysis and contrast results identified positive brain activation during the hypoalgesic response evoked by the psychological intervention;
- Results presentation: The imaging peak activation results are given in standard coordinate format (x, y, z) and reach at least a threshold  $p$  of 0.05.
- Review articles not including original results were excluded.

### *Meta-analytical procedure*

We performed a coordinate-based meta-analysis using the revised ALE method as implemented in GingerALE 2.3 (<http://www.brainmap.org/ale/>). Coordinates originally reported in MNI space were converted to the Talairach space from the original normalization templates indicated in each paper (FSL, SPM or other) using the Lancaster (icbm2tal) transform (Lancaster et al., 2007) implemented in GingerALE. Coordinates were modeled using a three-dimensional Gaussian distribution that quantitatively adjusts for the spatial

uncertainty resulting from between-subject and between-template variance of the neuroimaging foci (Eickhoff et al., 2009). For each experiment, a modeled activation (MA) map was created from the activation foci (peak coordinates reported for an experiment); the MA map contains, for each voxel, the probability that an activation occurred exactly at this  $x y z$  coordinate while preventing summation of effects across foci from the same experiment (Turkeltaub et al., 2012). The 'true' convergence was distinguished from the random convergence on a between-experiment level (rather than a between-foci level) using an analytical solution to the null-distribution of random spatial association between experiments, allowing random-effect inference (Eickhoff et al., 2012). ALE maps were thresholded at a cluster-level to a  $q < 0.05$  using the False-Discovery-Rate (FDR) method (Laird et al., 2005), while cluster forming was thresholded to a  $q < 0.05$  FDR-corrected (Eickhoff et al., 2012).

This ALE map was generated from all the coordinates associated with an increase in BOLD signal or rCBF (activation) during all psychological hypoalgesic interventions. Contrasts described in individual studies were collected, including subtraction of the control condition (no hypoalgesia) from the hypoalgesic condition and negative regression with pain ratings during the hypoalgesic condition. Each of these experiments reflected increased brain activity associated with the hypoalgesic effect.

Table S1. Included references. (see appendix)

Table S2. Excluded references with unfulfilled criteria. (see appendix)

Table S3. Results of the increased activity in the [*Pain-Nopain*] ALE map. (see appendix)

## **Chapitre 3 : DISCUSSION GÉNÉRALE**

### **3.1. Rappel des objectifs**

Cette thèse avait comme objectif de clarifier les mécanismes cérébraux de la douleur, de la régulation de la douleur et de l'hypoalgésie induite psychologiquement en synthétisant, quantitativement et conceptuellement, près de trente ans de recherche. Le premier article a identifié un groupe d'aires cérébrales associées à l'hypoalgésie induite psychologiquement (HIP), en englobant une variété d'interventions, telles que le placebo, la distraction, l'hypnose, la perception de contrôle sur la douleur, l'induction d'émotions et la méditation. Le deuxième article a démontré des patrons d'activation cérébrale préférentiellement associés à la perception de la douleur et à l'HIP, ainsi que des régions conjointement associées à la douleur et à l'HIP. Dans les prochaines sections, un résumé de ces résultats sera présenté, puis ils seront discutés à la lumière des plus récentes données et perspectives sur le sujet.

### **3.2. Résumé des résultats**

Par une série de métaanalyses basées sur des coordonnées d'activation cérébrale, cette thèse a démontré un ensemble de régions associées et potentiellement impliquées dans la production de l'HIP, dont le aMCC, l'aINS, le DLPFC et l'OFC. De plus, l'implication des régions associées à la matrice de la douleur a été confirmée, c'est-à-dire le MCC, l'INS, le SII, le PFC, les aires motrices supplémentaire et pré-supplémentaire (SMA et pre-SMA), le thalamus ainsi que l'amygdale, lors de la perception d'une douleur expérimentale chez des participants en santé (Duerden & Albanese, 2013; Apkarian et al., 2005). Il a aussi été

démontré que la perception de la douleur et l'HIP semblent partager certains territoires cérébraux, mais impliqueraient également des régions et des processus distincts.

Notre confiance dans les résultats et les interprétations proposées dans cette thèse découle en grande partie de la rigueur, toutefois simple, de la procédure de sélection des études et de l'organisation des données d'activation. Cette procédure a été élaborée dans l'objectif de circonscrire le mieux possible les effets présumément mesurés. Ainsi, la métaanalyse sur l'HIP a été réalisée uniquement à partir des études dans lesquelles un effet psychophysique statistiquement significatif de réduction de la douleur en lien avec l'intervention était rapporté. De plus, seulement les foyers d'activation issus des contrastes pour lesquels cet effet avait été isolé de l'effet non spécifique de la douleur ont été considérés (p.ex. Douleur<sub>crème placebo</sub>-Douleur<sub>crème contrôle</sub>). Ceci a permis de mettre précisément en évidence les mécanismes liés à la production de l'HIP, par opposition aux processus liés à la perception de la douleur. Le même principe de sélection a été suivi pour produire la carte d'activation préférentiellement associée à la douleur (*[Pain-Nopain]*), pour laquelle ont été gardés uniquement les contrastes pour lesquels l'effet sensoriel non spécifique d'une stimulation non douloureuse avait été soustrait à l'activation évoquée par la stimulation nociceptive (p.ex. stimulation chaude douloureuse – stimulation tiède non douloureuse). Par conséquent, l'analyse de soustraction a été réalisée à partir de deux cartes présentant un maximum de précision, d'une part, sur l'activation associée à l'HIP, et d'autre part, sur l'activation associée à la douleur.

De cette façon, nous avons pu mettre en évidence la participation d'aires sensorimotrices dans la perception de la douleur expérimentale, telles que SII, l'insula postérieure et la SMA.

Le patron d'activation préférentiellement lié à la douleur était également composé de l'insula antérieure, du pMCC, des IFG gauche et droit, des lobules pariétaux inférieurs, et de certaines régions sous-corticales comme le thalamus, les noyaux gris centraux, l'amygdale et le cervelet antérieur. L'HIP quant à elle était plus particulièrement associée à l'ACC rostral, le gyrus préfrontal médian, le cortex orbitofrontal, le lobule pariétal supérieur et la jonction temporopariétale. Enfin, des localisations d'activation communes à la douleur et à l'HIP ont été identifiées au niveau de l'insula antérieure, du aMCC, de la pre-SMA, du DLPFC droit, du IPL et du thalamus antérieur.

En raison de la vision élargie conférée par l'approche métaanalytique de cette thèse, les résultats permettent de proposer, avec davantage de précision, des mécanismes neuropsychologiques et neurophysiologiques distinctifs et complémentaires sous-jacents à la perception de la douleur et à sa régulation endogène, notamment suscitée par l'entremise d'interventions psychologiques.

### **3.3. Mécanismes cérébraux de la douleur**

#### **3.3.1. Afférences nociceptives et somatosensorielles**

Le patron d'activations cérébrales préférentiellement associé au traitement de la douleur tel qu'identifié par notre analyse de soustraction révèle des cibles thalamiques et corticales d'afférences spinales nociceptives et somatosensorielles, telles que SII, l'insula postérieure et le pMCC (qui correspond à l'aire cingulée motrice chez le primate non humain; Dum, Levinthal & Strick, 2009). L'implication du thalamus dans le relai des afférences spinales vers

les aires corticales est amplement démontrée (Strominger, Demarest & Laemle, 2012). Dans le contexte de la douleur, le thalamus redirige les afférences spinales nociceptives en grande partie vers les cortex somatosensoriels et vers la zone postérodorsale de l'insula (Strominger et al., 2012; Dum et al., 2009). L'insula postérieure serait d'ailleurs la seule région avec l'opercule pariétal médial à produire une perception de douleur lorsque stimulée électriquement (Mazzola, Isnard, Peyron & Maugière, 2011) ou par une décharge d'origine épileptique (Isnard, Magnin, Jung, Maugière & Garcia-Larrea, 2011).

### *La région operculo-insulaire*

Nos résultats démontrent qu'une large zone d'activité cérébrale couvrant l'insula postérieure et les opercules frontal et pariétal semble particulièrement associée aux stimuli nociceptifs. Ceci appuie l'idée selon laquelle cette région pourrait être considérée comme une seule entité fonctionnelle, la région operculo-insulaire. Il a été suggéré que cette région soit centrale à la perception de la douleur (p.ex. Garcia-Larrea, 2012; Craig, 2011; Baumgärtner et al., 2010; Peyron et al., 2002). Plus précisément, en se basant sur de multiples sources de données, Garcia-Larrea (2012) propose que le cortex PIMO (pour "*posterior insula and its adjoining medial operculum*") constitue le cortex sensoriel primaire de la douleur. En effet, le cortex PIMO posséderait suffisamment de propriétés anatomo-fonctionnelles, de connections thalamiques et limbiques pour être considérée comme une troisième aire somatosensorielle dédiée au traitement des afférences de la voie spinothalamique (Garcia-Larrea, 2012).

Est-ce que ce cortex PIMO inclue SII? La réponse n'est pas encore claire à ce jour puisqu'une confusion persiste dans la littérature autour de la localisation anatomique précise de SII. À l'examen histologique post-mortem de cerveaux humains, Eickhoff et son équipe

(2006a) ont identifié quatre régions distinctes de l'opercule pariétal<sup>14</sup> et ont étudié les corrélats leurs corrélats fonctionnels rapportés dans la littérature. Seulement une de ces quatre aires correspondrait à SII (OP1; section postérolatérale). Dans notre étude, la zone d'activation operculo-insulaire préférentiellement associée à la douleur couvrait effectivement OP1, ce qui fournit un appui supplémentaire en faveur de l'implication de SII dans la perception de la douleur.

L'idée d'une signature cérébrale spécifique à la douleur alimente encore la recherche, d'autant plus que de nouvelles technologies d'apprentissage machine<sup>15</sup> (*machine learning*) permettent maintenant une remarquable amélioration de la précision de l'analyse des données d'imagerie (Marquand et al., 2010; Brown, Chatterjee, Younger & Mackey, 2011; Wager et al., 2013; Liang, Mouraux, Hu & Iannetti, 2013; Woo et al., 2014). Wager et son équipe (2013) ont utilisé cette technique dans une série de quatre études en vue d'identifier une "signature neuronale de la douleur physique" (Wager et al., 2013), notamment en départageant l'activité cérébrale associée à l'anticipation de la douleur, à la stimulation douloureuse et à la mémoire de la douleur. Des participants en santé recevaient quatre intensités de stimulations thermiques (une stimulation chaude non-douloureuse et trois niveaux de douleur) dans un paradigme constitué d'une période d'anticipation du stimulus, d'une stimulation puis d'une période d'évaluation pendant laquelle ils devaient se remémorer la douleur ressentie (première étude). Leur modèle de la signature neuronale de la douleur a été en mesure de discriminer très

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<sup>14</sup> OP3 adjacente à l'insula postérieure, OP2 adjacente à l'aire rétroinsulaire (ventrale) et postérieure à OP3, OP4 adjacente à SI, puis OP1 adjacente au lobule pariétal inférieur. OP1 et OP4 sont latérales à OP2 et OP3.

<sup>15</sup> Par exemple, l'analyse multivariée en patrons (*Multivariate Pattern Analysis [MVPA]*) que nous présentons avec plus de détails dans la conclusion de cette thèse.



clairement (100% de prédiction avec un test de choix forcé) avec sensibilité et spécificité l'activité cérébrale évoquée par la douleur de celle liée à l'anticipation de la douleur ou du rappel de la sensation douloureuse. Ce résultat confère donc un poids considérable à l'idée d'une signature cérébrale spécifique à la douleur. D'autre part, cette série d'études de Wager et collègues (2013) visait également à clarifier la thèse selon laquelle la détresse suscitée dans un contexte social (tel que le rejet) partagerait des substrats neuronaux communs avec la douleur nociceptive (initialement proposée par Eisenberger, Lieberman & Williams, 2003). En comparant l'activité cérébrale évoquée par la douleur issue de stimulations thermiques avec celle évoquée par la douleur "sociale" (rejet d'un partenaire amoureux, troisième étude), Wager et al. (2013) ont démontré que la signature neuronale spécifique à la douleur se distinguait de l'activité évoquée par la douleur sociale, et ce indépendamment de la détection de la saillance<sup>16</sup>. Il est intéressant de noter que la région operculo-insulaire était le plus étroitement attribuable à la douleur physique (Figure 3B dans Wager et al., 2013).

Pourtant, la spécificité de la région operculo-insulaire dans le traitement de la douleur ne peut pas pour autant être affirmée puisque cette région répond à d'autres stimuli non douloureux (Eickhoff, Amunts, Mohlberg & Zilles, 2006b). De plus, les résultats sont contradictoires lorsqu'il est question de déterminer la zone operculaire (antérieure, postérieure, médiane, latérale) préférentiellement associée au traitement de l'information nociceptive (Mazzola, Faillenot, Barral, Mauguière & Peyron, 2012; Coghill et al., 1994; Ferretti et al., 2003; Eickhoff et al., 2006a; Eickhoff, Schleicher, Zilles & Amunts, 2006b). Enfin, d'autres

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<sup>16</sup> La saillance subjective des stimuli n'a pas été mesurée auprès des participants, mais ce facteur aurait été isolé par des analyses complémentaires.

données récentes vont plutôt dans le sens d'un rôle associatif de cette région operculo-insulaire, dans l'intégration multimodale de stimuli saillants (Lötsch et al., 2012; zu Eulenburg, Baumgärtner, Treede & Dieterich, 2013). En ce sens, l'implication dans nos études de plusieurs aires cérébrales associées à la perception de la saillance nous amène à examiner l'hypothèse selon laquelle la matrice de la douleur reflète le traitement de cette saillance.

### **3.3.2. Détection de la saillance**

Dans cette thèse, l'insula antérieure, le MCC, l'amygdale et le lobule pariétal inférieur ont également été identifiés comme préférentiellement évoqués par la douleur comparativement à l'HIP. Ensemble, ces activations pourraient refléter un engagement attentionnel en réponse à la présentation d'un stimulus (le système attentionnel ventral; Fox, Corbetta, Snyder, Vincent & Raichle, 2006; Yeo et al., 2011), ou secondaire à la détection de la saillance de ce stimulus douloureux (Uddin, 2015; Seeley et al., 2007; Wiech et al., 2010).

Un stimulus est saillant lorsqu'il se distingue des stimuli environnants par ses qualités physiques, mais également par sa signification subjective influencée, par exemple, par des expériences passées ou le contexte dans lequel il se présente (Uddin, 2015; Legrain, Iannetti, Plaghki & Mouraux, 2010). En soi, un stimulus douloureux est saillant. Plusieurs études récentes ont démontré que plusieurs régions constituant la matrice de la douleur répondent aussi à la saillance d'un stimulus, peu importe la modalité sensorielle (Mouraux, Diukova, Lee, Wise & Iannetti, 2011; Legrain et al., 2010; Wiech et al., 2010; Iannetti & Mouraux, 2010; Lötsch et al., 2012).

La douleur, via sa saillance, a comme fonction d'alerter l'organisme d'un dommage potentiel aux tissus si aucune action n'est mise en oeuvre pour l'éviter. Il pourrait donc s'agir d'une saillance aversive, propre à la douleur et à la préparation à une action adaptative. Cette proposition est à tout le moins supportée par l'observation d'aires motrices dans les régions préférentiellement associées à la douleur parmi nos résultats.

### **3.3.3. Réponse motrice**

Nos résultats montrent que la SMA, l'aire prémotrice (ventrale), le pMCC, le putamen et le globus pallidus sont activés pendant la douleur. Le pMCC dorsal envoie des projections corticospinales directement vers les motoneurones spinaux (Dum & Strick, 1991). Il est aussi directement impliqué dans le contrôle moteur volontaire du comportement (Paus, 2001). Puisque la douleur signale une menace potentielle à l'intégrité corporelle, il est naturel qu'elle entraîne une réponse motrice adaptée, ou un réflexe de retrait visant à soustraire le membre de la source de douleur. Ainsi, l'initiation d'une réponse motrice de retrait causée par la douleur pourrait expliquer l'activation hautement probable (*activation likelihood*) des zones motrices observée dans nos résultats.

### **3.3.4. La douleur: saillance, aversion et alerte**

En somme, nos résultats quant à l'activité cérébrale la plus vraisemblablement liée à la douleur semblent refléter le traitement d'afférences somatosensorielles nociceptives, ainsi qu'une préparation à l'action. D'autre part, ceux-ci corroborent également l'idée selon laquelle l'ensemble des régions constituant la matrice de la douleur reflète la détection de la saillance du stimulus douloureux que la douleur spécifiquement, ou la nociception en soi (Legrain et al.,

2010; Mouraux et al., 2011). Pourtant, la saillance a beau être partagée par d'autres modalités, il demeure qu'un stimulus douloureux est aisément discernable de tout autre stimulus saillant aversif. Alors quels sont les éléments distinctifs de la douleur? L'input somatosensoriel nociceptif dans un premier temps, qui est directement acheminé vers la région operculo-insulaire (en grande partie; Dum et al., 2009), qui semble effectivement jouer un rôle majeur dans la perception de la douleur (Garcia-Larrea, 2012; Wager et al., 2013). Ensuite, la douleur n'étant pas uniquement la nociception, ce sont également ses différentes dimensions qui la définissent. Rappelons en effet que la douleur est une expérience issue d'une constante interaction entre plusieurs facteurs d'ordre psychologique, et physiologique, dont la nociception. Surtout, la douleur se distingue des autres sensations saillantes par sa fonction d'*alerte* d'un dommage potentiel aux tissus, ainsi que la motivation sous-jacente à exercer un contrôle sur cette douleur, que ce soit par le retrait puis l'évitement du stimulus physique (p.ex. la source de chaleur), ou par la réduction de l'expérience subjectivement désagréable. Ainsi, les patrons d'activité cérébrale préférentiellement évoquée par la douleur reflèteraient bien plus que la détection de la saillance du stimulus nocif, mais aussi ce qui différencie *ce* stimulus de ceux d'autres modalités, notamment l'alerte au danger, la menace. Une étude s'est penchée sur les mécanismes cérébraux liés à cette interprétation de menace d'un stimulus nocif. Wiech et al. (2010) ont manipulé la perception de danger chez des participants sains par des signaux précédant des stimulations thermiques (laser) d'intensité constante, indiquant que celles-ci seraient soit "*entirely safe*" ou "*potentially harmful*" (Wiech et al., 2010; p.16324). D'abord, leurs données comportementales indiquent que les stimulations étaient plus susceptibles d'être évaluées comme douloureuses si elles étaient considérées comme

potentiellement dommageables. De plus, la connectivité fonctionnelle pré-stimulus entre l'aINS et le aMCC était associée à ce biais d'interprétation, suggérant qu'ensemble, ces deux régions encodent *"the perceived threat value or salience of the upcoming laser stimulation before stimulus encounter"* (Wiech et al., 2010; p.16330). Pendant la stimulation perçue comme dangereuse et douloureuse toutefois, seule l'association avec le aMCC persistait parmi ces deux régions. Il aurait été intéressant d'analyser cette relation en considérant la dynamique<sup>17</sup> en considérant également d'autres régions qui composent la matrice de la douleur, comme la région operculo-insulaire et les aires motrices identifiées dans la présente thèse.

### **3.4. Mécanismes cérébraux de la régulation de la douleur**

La relation entre l'input nociceptif et la douleur perçue n'est pas toujours linéaire. Dès l'activation des fibres nociceptives périphériques, l'organisme produit des réponses protectrices et adaptatives via des signaux neuronaux, autonomiques, immunitaires et endocriniens (Jänig & Levine, 2013). Au niveau du système nerveux central, un contrôle de la transmission de l'input nociceptif est réalisé au niveau de la moelle épinière, puis au niveau du tronc cérébral, principalement via la PAG et le RVM. Le traitement de l'information relative à la douleur, incluant l'input nociceptif spinal, subit également des influences corticales en provenance des régions frontales et limbiques. Ainsi, l'input nociceptif est sujet à être modulé, à la fois par des mécanismes autonomes et spontanés de régulations du système nerveux central, ainsi que par

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<sup>17</sup> Cette hypothèse pourrait être testée notamment par des techniques d'analyse causale telles que le *Dynamic causal modelling* ou la Causalité de Granger (Friston, Moran & Seth, 2013).

des influences physiologiques de contrôle descendant médiées par des processus psychologiques tels que l'engagement attentionnel, l'état émotionnel, l'interprétation du contexte, le désir de soulagement, etc. (Bushnell, Ceko & Low, 2013). De là toute la complexité de l'expérience subjective découlant d'une stimulation douloureuse, où la douleur relève d'une constante dynamique entre la nociception, les réponses physiologiques, les réactions émotionnelles et les cognitions, comme le désir de soulagement (Price, Hirsh & Robinson, 2009).

Pourquoi ces mécanismes de régulation endogène se mettent-ils spontanément en oeuvre? Entre autres pour répondre au message d'alerte, de menace à l'intégrité du corps, émis par la douleur, et pour retourner à un équilibre homéostatique et diminuer le désagrément (Seymour et al., 2005; Fields, 2007). Cette régulation endogène s'enclenche de façon spontanée et réactionnelle à la perturbation. Certaines actions dirigées peuvent favoriser cette autorégulation, comme une intervention psychologique (p.ex. un placebo). Dans les prochaines lignes, nous étudierons les possibles mécanismes cérébraux impliqués dans cette régulation à la lumière des résultats de nos études.

### **3.4.1. Régulation endogène**

La douleur et l'hypoalgésie induite psychologiquement ont en commun d'engager des mécanismes de contrôle descendant. Nos travaux ont permis de préciser le patron d'activation qui leur est commun. D'abord, la présence de l'aINS dans ce patron pourrait relever d'une transposition de l'input sensoriel en perception intéroceptive aversive et en signal d'alerte, source de motivation pour qu'une action mentale (p.ex. autorégulation psychologique) ou

comportementale soit entreprise. Cette hypothèse suit la proposition de Craig (2002, 2009) qui confère à cette région un rôle d'intégration des signaux corporels engendrés par des sensations et des émotions pour la génération d'une expérience subjective et d'une conscience intéroceptive.

En fait, l'activation de l'insula est observée dans un très grand nombre d'études portant sur une étonnante variété de sujets (p.ex. perception sensorielle, langage, émotions sociales, tâches cognitives, musique, perception du temps, etc.; Craig, 2009; Nieuwenhuys, 2012), et plusieurs métaanalyses indiquent que l'aINS est impliquées dans des processus cognitifs et émotionnels (Klein, Ullsperger & Danielmeier, 2013; Christopher, Koshimori, Lang, Criaud & Strafella, 2014). Selon Craig, la variable commune à toutes ses études serait une conscience (*awareness*) perceptive suscitée par une variété de tâches (Craig, 2009). La perception de la saillance d'un stimulus pourrait être vue comme une conscience perceptive dans la mesure où ce stimulus, la source de la saillance, est interne et menaçant. De ce fait, l'insula antérieure est considérée par plusieurs comme le siège de la détection de la saillance (Uddin, 2015) provenant de stimuli externes (p.ex. un bruit, une lumière), mais également de perceptions internes (p.ex. augmentation du rythme cardiaque, réaction émotionnelle). Donc, cette région intégrerait l'importance de l'input, la valeur menaçante de sa saillance, pour le processus allostatique<sup>18</sup>.

Dans le cadre de nos études, il est possible que l'activité de l'insula antérieure associée à la douleur et celle liée à la régulation endogène (conjonction douleur et HIP) reflète des

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<sup>18</sup> Recherche de la stabilité et de l'homéostasie par une réponse physiologique et/ou comportementale à un stressor (McEwen & Wingfield, 2003).

niveaux différents et complémentaires de traitement des signaux de saillance, l'un extéroceptif (douleur, afférences sensorielles), et l'autre intéroceptif (régulation, interprétation). Ce serait cette intéroception qui activerait une régulation descendante (*top-down control*), ainsi que la production de réponses adaptatives, possiblement coordonnées par le aMCC, avec l'influence du DLPFC et du lobule pariétal inférieur dont l'activation a également été révélée par la conjonction des cartes de douleur et d'HIP.

Le DLPFC, avec le lobe pariétal inférieur, est impliqué dans le contrôle cognitif, c'est-à-dire dans la régulation de l'attention, dans la planification et dans la mémoire de travail (Rottschy et al., 2011; Arnsten & Rubia, 2012; Cieslik et al., 2013). L'implication de cette région avec le IPL dans la régulation de la douleur pourrait être attribuable à la manipulation des informations intéroceptives saillantes et au contrôle des pensées qui leur sont associées. D'autant plus que le rôle du DLPFC dans la régulation descendante de la douleur a été suggéré par une relation inverse entre son activation et les évaluations de douleur, possiblement attribuable à une inhibition descendante ou une interférence des interactions modulateurs cortico-corticales et cortico-souscorticales (Lorenz, Minoshima & Casey, 2003).

Nos résultats suggèrent de plus que le aMCC jouerait un rôle pivot dans la régulation endogène de la douleur (articles 1 et 2). Nous croyons que cette région agirait comme un coordonnateur qui intégrerait les afférences d'autres systèmes cérébraux, incluant les inputs intéroceptifs en provenance de l'insula antérieure, afin de fournir un contrôle sur la douleur perçue. Le MCC est impliqué dans le contrôle cognitif et dans l'identification d'erreurs (*conflict monitoring*; Orr & Weissman, 2009; Kerns et al., 2004; Venkatraman, Rosati, Taren & Huettel, 2009). Shackman et al. (2011) ont démontré par une CBMA que le aMCC était le



point de convergence d'activations associées au contrôle cognitif, mais aussi à la douleur et au traitement d'émotions négatives. Cette convergence reflète selon eux le rôle de cette région dans l'intégration d'informations aversives dans le but d'orienter une réponse défensive, une action adaptée (Shackman et al., 2011). Holroyd et Yeung (2012) proposent une idée similaire. Ils ne limitent pas toutefois le rôle du aMCC à l'adaptation face aux stimuli négatifs, mais le généralisent à toute forme de but nécessitant une action. Le rôle du aMCC serait celui d'initier l'action et de l'ajuster en fonction du but initial, et en fonction des divers inputs en provenance des autres systèmes, comme ceux codant pour la valeur renforçatrice d'un stimulus en provenance de l'OFC (Holroyd & Yeung, 2012).

En somme, l'activation cérébrale attribuable à la fois à la douleur et à l'hypoalgésie induite psychologiquement refléterait des mécanismes endogènes de régulation de la douleur. Ceux-ci seraient engagés spontanément via la perception intéroceptive de la saillance de la douleur possiblement encodée dans l'insula antérieure. Ces informations intéroceptives seraient traitées par le réseau fronto-pariétal (DLPFC et lobule pariétal inférieur) à partir duquel un contrôle descendant serait exercé, sous la coordination du aMCC. Le rôle pivot coordonnateur du aMCC tiendrait dans l'intégration d'afférences de divers systèmes (p.ex. sensoriel, cognitif, émotionnel) pour initier et coordonner une action adaptée visant à échapper à la menace, à réduire l'intensité ou le désagrément perçu, ou à favoriser la réinterprétation.

### **3.4.2. L'hypoalgésie induite psychologiquement**

Dans le premier article de cette thèse, un ensemble de régions cérébrales a été identifié comme participant à la production de l'hypoalgésie induite psychologiquement, et ce,

indépendamment du type d'approche. Jusqu'à maintenant, chacune de celles-ci avait été étudiée individuellement, ou en parallèle (p.ex. Buhle, Stevens & Wager, 2012). L'analyse complémentaire de contribution a révélé que, parmi cet ensemble de régions, le aMCC semblait jouer un rôle central dans l'HIP puisque toutes les approches concourraient à son activation (placebo, distraction, hypnose, contrôlabilité du stimulus, induction d'émotions et méditation). Toutefois, en approfondissant les analyses (deuxième article), nous avons constaté qu'une grande partie de cette activation était partagée avec la perception de la douleur, reflétant possiblement davantage des mécanismes *généraux* de régulation endogène activés spontanément pendant la douleur (explorés précédemment) plutôt que des mécanismes particuliers à l'HIP. D'un autre côté, un patron d'activation préférentielle à l'HIP a aussi été circonscrit. Ce patron tend vers des mécanismes indépendants et complémentaires à ceux de la régulation spontanée de la douleur. Ces activations associées plus précisément à l'HIP concernaient le cortex orbitofrontal latéral, le gyrus préfrontal médian, l'ACC rostral, ainsi que le lobule pariétal supérieur.

D'abord, l'OFC est une région où la valeur subjective d'une source potentielle de motivation serait encodée (Padoa-Schioppa & Cai, 2011; Rolls & Grabenhorst, 2008). Sa partie médiane est impliquée dans la détection de ces sources de valeurs positives influençant les apprentissages, alors que sa partie latérale (observée comme préférentielle à l'HIP) est plus particulièrement impliquée dans l'évaluation d'un stimulus aversif en vue de la préparation d'une réponse comportementale (Kringelbach, 2005). En regard de nos études, la réévaluation de l'efficacité de la procédure d'HIP et de la douleur résiduelle encore à réduire correspondrait à un motivateur, canalisateur des mécanismes de réduction de la douleur. ce qui serait cohérent

avec l'implication du cortex orbitofrontal latéral dans l'attribution d'une valeur relativement au contexte (Winston, Vlaev, Seymour, Chater & Dolan, 2014).

Ensuite, l'ACC rostrale a largement été associée à des processus émotionnel et autoréférentiel (*self-referential*; Yu et al., 2011; Torta & Cauda, 2011), alors que le MPFC est quant à lui impliqué dans le traitement de plusieurs émotions (Phan, Wager, Taylor & Liberzon, 2002). Plus précisément, différents processus émotionnels seraient représentés dans ces régions préfrontales médianes (ici observées), de sorte que la région préfrontale dorsale participerait à l'évaluation et à l'expression des émotions, alors que la partie ventrale (incluant l'ACC rostrale) jouerait un rôle dans la régulation émotionnelle (suppression, augmentation; Etkin, Egner & Kalisch, 2011). L'implication de ces structures préfrontales médianes pourrait refléter une régulation émotionnelle, soit liée à la dimension affective de la douleur, ou encore en lien avec une réponse émotionnelle secondaire à la douleur résiduelle.

En somme, l'hypoalgésie induite psychologiquement est associée à l'activation de structures préfrontales médianes connues pour leur implication dans la régulation émotionnelle, ainsi que l'activation du cortex orbitofrontal latéral associé à l'évaluation de la valeur aversive des stimuli. Il pourrait s'agir de mécanismes cérébraux médiateurs de la régulation endogène de la douleur dont le rôle serait de soutenir et de favoriser les processus *généraux* de contrôle descendant sous-jacents (abordés précédemment). Ces mécanismes pourraient relever d'une régulation émotionnelle continue qui ciblerait la réduction de l'aspect aversif de la douleur et l'optimisation du soulagement qu'entraîne la réduction de la douleur. Il s'agirait donc de mécanismes indépendants et complémentaires de la régulation endogène de la douleur. Cette conceptualisation serait par ailleurs cohérente avec une très récente étude fMRI

qui a permis de dissocier, dans une certaine mesure, deux systèmes cérébraux médiateurs des variations de perception de douleur dont l'activation est attribuable, d'une part, aux variations d'intensité des stimuli douloureux (input sensoriel), et d'autre part, à l'autorégulation produite à l'aide d'une stratégie de réinterprétation s'apparentant à des suggestions et de l'imagerie mentale (Woo, Roy, Buhle & Wager, 2015). Cette médiation associée à l'autorégulation de la douleur était justement associée à des activations préfrontales médianes, quoique situées ventralement comparativement à nos résultats.

### **3.5. Limites**

Les résultats et interprétations de cette thèse doivent être considérés à la lumière de leurs limites méthodologiques, et ce à la fois en regard de la méthodologie des articles de cette thèse, mais aussi au niveau de celles des études qui ont été incluses dans les métaanalyses. Aussi, l'absence de certaines observations dans les articles de cette thèse mérite d'être considérée. Dans un premier temps, nous aborderons ces résultats négatifs plus particulièrement à l'égard de la PAG et du RVM. Ensuite, nous énumérerons quelques enjeux méthodologiques soulevés par l'examen systématique de certaines d'articles scientifiques, puis de leurs impacts possibles sur les résultats de nos métaanalyses. Enfin, certaines limites de nos métaanalyses et de l'interprétation de leurs résultats seront abordées.

### 3.5.1. Résultats négatifs

La PAG et le RVM sont des structures clés du système descendant du contrôle de la douleur. Il est ainsi étonnant qu'aucune observation n'ait été faite en ce sens, du moins en regard de nos analyses de soustraction et de conjonction (article 2).

Il existe en effet tout un historique de données chez l'animal et l'humain indiquant que la stimulation électrique profonde directe de la PAG produit une analgésie (p.ex. Reynolds 1969; Mayer, Wolfle, Akil, Carder & Liebeskind, 1971; Richardson & Akil, 1977). Dans une revue exhaustive de la littérature sur la neuroimagerie de la PAG, Linnman et al. (2012) ont identifié 54 études chez l'humain dans lesquelles une activation de cette structure était induite par une stimulation douloureuse (Linnman, Moulton, Barmettler, Becerra & Borsook, 2012). L'activation de la PAG est aussi observée pendant la modulation de la douleur. Par exemple, Tracey et al. (2002) ont montré, en IRMf à haute résolution, une implication de cette structure lors de la réduction de la douleur produite par une procédure de distraction. Derbyshire et Osborn (2009) ont observé une implication de la PAG et du RVM dans le *offset analgesia*, phénomène perceptuel occasionnant une réduction disproportionnée de l'intensité perçue de la douleur en réponse à une légère diminution de l'intensité du stimulus, lorsqu'un stimulus de basse intensité suit immédiatement un stimulus de haute intensité. Plusieurs autres études ont aussi démontré un lien entre la PAG et la modulation de la douleur dans divers paradigmes expérimentaux (voir Linnman et al. 2012), ce qui porte à croire que cette région joue effectivement un rôle dans le contrôle endogène de la douleur.

Or, nos résultats ne supportent pas cette interprétation. Ceci pourrait relever de divers facteurs d'ordre méthodologique. La PAG et le RVM sont de très petites structures pour lesquelles le signal d'activation est difficilement détectable de manière robuste et reproductible. D'autre part, ce résultat négatif pourrait s'expliquer par un manque de puissance statistique du fait de la procédure conservatrice inhérente à la comparaison des cartes ALE (l'analyse de soustraction, *c.f.* section 1.4.2), puisque quelques activations ont effectivement été observées au niveau du tronc cérébral dans la carte ALE non contrastée de l'hypoalgésie induite psychologiquement (article 1). Il est de plus possible que la PAG et le RVM n'apparaissent pas dans les régions cérébrales d'intérêt initialement examinées dans certaines des études incluses dans nos métaanalyses (cette contrainte sera d'ailleurs plus amplement discutée dans la section suivante).

D'un point de vue cérébrofonctionnel, une explication alternative est que la régulation endogène et l'HIP reposeraient en majeure partie sur des processus supraspinaux, sans nécessairement engager les voies descendantes du contrôle de la douleur. Cette proposition rejoint par ailleurs l'idée présentée précédemment à propos de mécanismes cognitifs d'autorégulation émotionnelle médiateurs engagés en parallèle et en complémentarité avec le système spinal du contrôle descendant (*c.f.* Section 3.5.2).

En outre, un lien spécifique a été démontré entre la PAG et l'erreur de prédiction aversive dans un protocole de stimulations douloureuses (Roy et al., 2014). L'erreur de prédiction est la différence entre la valeur prédite d'un stimulus et sa valeur perçue. Dans le contexte de la douleur, l'erreur de prédiction aversive se produit lorsque la douleur est pire qu'anticipée. Dans le contexte de nos études, la réduction effective de la douleur pendant l'HIP

rencontrerait les attentes d'hypoalgésie et ne solliciterait pas la PAG spécifiquement pendant le stimulus (ce qui n'exclut pas une activation préalable; voir Wager et al., 2004 dans l'effet placebo). Par conséquent, l'implication de la PAG dans la douleur pourrait avoir une fonction motivationnelle et évaluative.

Assurément, le rôle précis de cette région dans la régulation endogène de la douleur demeure à être précisée, notamment en regard de l'autorégulation émotionnelle et des processus motivationnels associés.

### **3.5.3. Enjeux méthodologiques soulevés par cette thèse**

L'étude approfondie de la littérature dans le cadre de cette thèse a permis de mettre en lumière quelques faiblesses et enjeux méthodologiques de certains articles.

#### *Systemes de coordonnées*

Premièrement, le système de coordonnées (MNI ou Talairach) dans lequel les résultats sont rapportés n'est étonnamment pas toujours spécifié. Cette précision n'est pas anodine puisque les résultats des métaanalyses peuvent en être grandement influencés (Laird et al., 2010; Lancaster et al., 2007). Dans cette thèse, ce problème a été résolu en déduisant le système d'après le logiciel d'analyse utilisé pour le traitement des données, puisque le choix du système de coordonnées est souvent implémenté automatiquement dans les logiciels (p.ex. BrainVoyager→Talairach; SPM→MNI). Cette solution n'est cependant pas infaillible puisque certains logiciels donnent le choix du système à l'utilisateur. De plus, il est possible de convertir d'un système à l'autre les coordonnées lors de la présentation de ses résultats.

### *Analyse par régions d'intérêt*

Deuxièmement, les résultats de nos métaanalyses ont pu être influencés par la sélection de régions d'intérêt (*ROI*) propre à chaque étude. Cette sélection, par ailleurs orientée par leurs hypothèses, a pour but de réduire la quantité de tests statistiques effectués en confinant ceux-ci aux régions étudiées plutôt à l'ensemble des voxels du cerveau. De cette façon, il est possible d'appliquer une correction moins sévère pour les multiples comparaisons, et ainsi de réduire le risque de faux négatifs (erreur de type II). Hormis la pertinence de cette procédure (Kriegeskorte, Lindquist, Nichols, Poldrack & Vul, 2010; Bennett, Wolford & Miller, 2009), cela augmente la probabilité d'obtenir des résultats auto-confirmés, et par le fait même, les chances de découvertes au-delà des régions *a priori* sont grandement diminuées. Aucune solution satisfaisante n'est probablement disponible encore, mais nous pouvons tout de même suggérer que les auteurs fournissent les résultats sur tout le cerveau des analyses non dirigées.

### *Effet comportemental statistiquement significatif*

Troisièmement, il a été surprenant de constater qu'un grand nombre d'études prétendant faire la démonstration d'activation cérébrale sous-tendant une modulation de la douleur omettaient de présenter un effet comportemental (c.-à-d. évaluations subjectives des sujets) statistiquement significatif de réduction de la douleur. Cette faiblesse méthodologique est probablement imputable, entre autre, au nombre restreint de participants en raison de contraintes monétaires du fait des coûts élevés d'une étude utilisant l'IRMf. La sélection préalable des participants sur la base de leur réponse psychophysique de réduction de la douleur pendant la condition expérimentale placebo est une façon de s'assurer d'un effet comportemental suffisamment robuste pour l'étude d'imagerie subséquente. Or, on constate que



cette sélection se fait souvent sur la base de critères arbitraires peu spécifiques. Ainsi, les variations dans les évaluations de douleur de certains de ces participants identifiés comme présentant un effet placebo pourraient en fait simplement refléter des fluctuations spontanées de perception de douleur ne résultant pas du traitement placebo en tant que tel (Rainville & Duncan, 2006). Il est donc possible que, dans notre première métaanalyse, certaines études se soient glissées qui rapportent une modulation significative de la douleur, sans toutefois que cette modulation ne soit pas complètement due à l'intervention donnée. Dans plusieurs de ces cas toutefois, l'activation dans la condition hypoalgésique reflète au moins en partie l'engagement de mécanismes placebo, et peut-être plus probablement des mécanismes d'autorégulation engagés psychologiquement. L'impact de ce biais est par ailleurs probablement très faible puisque la méthodologie relative à l'inclusion des articles et des *experiments* dans l'analyse était quoi qu'il en soit très stricte.

Nous recommandons ainsi d'augmenter la rigueur sur ce point, soit de la part des équipes de recherche, soit de la part du processus de révisions des articles, puisque cette faiblesse induit un risque évident d'inférences abusives (Rainville & Duncan, 2006) et d'influences scientifiques indues (McCabe & Castel, 2008; Nieminen, Carpenter, Rucker & Schumacher, 2006).

### ***Méta-données***

Finalement, les métaanalyses fournissent plusieurs avantages sur les méthodes expérimentales, mais le meilleur moyen de faire la synthèse des données de la littérature sur un sujet demeure la mise en commun des données brutes originales et la réalisation de métaanalyses directement sur celles-ci (Salimi-Khorshidi et al., 2009). Ceci permettrait

notamment d'éviter plusieurs biais, dont ceux énumérés ci-dessus. En dépit de sa pertinence, plusieurs efforts passés menés en ce sens ont malheureusement connu de nombreuses embuches (Van Horn & Gazzaniga, 2013). Néanmoins, le projet *OpenfMRI* ([openfmri.org](http://openfmri.org)) débuté en 2010 semble être en bonne voie de remplir cette mission.

### **3.7. Conclusion**

Par des métaanalyses basées sur les coordonnées d'activité cérébrale, la présente thèse a fait la synthèse et l'intégration conceptuelle de plusieurs années d'études d'imagerie portant sur la douleur et l'hypoalgésie induite psychologiquement. Elle fait le point sur les mécanismes cérébraux impliqués différemment dans la perception de la douleur, dans sa régulation endogène et dans l'hypoalgésie induite psychologiquement. Il serait maintenant intéressant de poursuivre l'investigation des processus sous-jacents à chacune des diverses approches psychologiques. D'un point de vue méthodologique, de récents développements technologiques, comme l'analyse multivariée en patrons (*Multivariate Pattern Analysis* [*MVPA*]) et l'apprentissage machine (*machine learning*; p.ex. Wager et al., 2013), permettent à présent une analyse remarquablement plus fine des données d'imagerie. Voyons comment il pourrait être possible d'appliquer ces nouvelles avancées aux approches métaanalytiques, ou encore mieux, aux métadonnées.

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## **ANNEXES**

**Tableaux supplémentaires de l'article 2.**



**Table S1.** Included references

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Yuan, W, Ming, Z, Rana, N et al.(2010) A functional magnetic resonance imaging study of human brain in pain-related areas induced by electrical stimulation with different intensities. <i>Neurology India</i> . 58(6):922-7	Results
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Zubieta, JK, Smith, YR, Bueller, JA et al.(2005) Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. Journal of Neuroscience. 25(34):7754-62	Imaging
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**Table S3.** Results of the increased activity in the *[Pain-Nopain]* ALE map

Anatomical label	BA	ALE Value	Side	x	y	z
Anterodorsal insula	---	0.057	R	32	8	10
Midcingulate gyrus	24	0.050	R	2	4	42
Anterodorsal insula	---	0.049	L	-34	6	10
Thalamus (lateral)	---	0.047	L	-12	-16	10
Inferior parietal lobule	40	0.047	R	52	-28	26
Thalamus	---	0.046	R	12	-18	6
Anterior insula	---	0.043	L	-40	6	0
Posterior insula	---	0.036	R	38	-20	16
Inferior frontal gyrus/Precentral gyrus	44/6	0.034	L	-46	8	10
Posteroventral insula	---	0.032	R	42	16	-2
Brainstem	---	0.025	R	6	-24	-6
Thalamus (posteromedial)	---	0.025	L	-4	-26	4
Postcentral gyrus	40	0.025	L	-54	-22	16
Posterior insula	---	0.024	L	-34	-20	12
Globus pallidus	---	0.022	R	22	-4	-6
Precentral gyrus	6	0.021	R	56	6	4
Cerebellum, declive	---	0.021	R	26	-62	-22
Putamen	---	0.021	L	-20	2	8
Medial frontal gyrus	8	0.021	L	0	22	42
Medial frontal gyrus	8	0.020	R	2	28	36
Pregenua anterior cingulate cortex	32	0.020	L	-2	32	22
Putamen	---	0.018	L	-20	0	16
Medial frontal gyrus	6	0.018	R	10	4	58
Posterior insula/Superior temporal gyrus	---/41	0.018	L	-38	-20	-4
Middle frontal gyrus	9	0.017	R	36	36	28
Cerebellum, culmen	---	0.017	R	2	-60	-20
Precentral gyrus	6	0.017	R	46	-4	52
Anterior insula	---	0.016	L	-26	18	2
Postcentral gyrus	2	0.016	L	-44	-24	28
Cerebellum, declive	---	0.015	L	-32	-60	-22
Middle frontal gyrus	10	0.014	R	44	42	10
Cerebellum, cerebellar tonsil	---	0.013	L	-28	-62	-34
Cerebellum, culmen	---	0.013	L	-14	-56	-18
Postcentral gyrus	3	0.013	L	-56	-10	24
Precentral gyrus	6	0.012	R	46	-4	42
Precentral gyrus	6	0.012	R	46	0	42
Medial frontal gyrus	6/8	0.012	R	4	14	52
Caudate nucleus	---	0.011	R	14	6	24
Inferior parietal lobule	40	0.011	L	-56	-48	36
Caudate nucleus	---	0.011	L	-12	14	12
Posterior midcingulate cortex	31/23	0.010	R	10	-24	40
Cerebellum, culmen	---	0.010	R	34	-52	-26

Results are ordered by ALE values.

Significance level:  $p < 0.001$  (<sup>†</sup>:  $p < 0.05$ ) corrected for multiple comparisons.

x, y, z: Talairach coordinates. BA: Brodmann areas; R: right; L: left