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Mécanismes cérébraux et cérébraux-spinaux impliqués dans la modulation de la douleur par la musique et les émotions

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Cette thèse intitulée :
Mécanismes cérébraux et cérébraux-spinaux impliqués dans la modulation de la douleur par la musique et les émotions

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Résumé

En raison de sa forte composante affective la douleur s'avère facilement modulée par les émotions. Bien que diverses interventions thérapeutiques, telle que la musicothérapie, semblent s'appuyer sur ce principe pour réduire la douleur, l'implication des émotions dans leur effet analgésique n'a jamais été démontrée empiriquement. De plus, les mécanismes expliquant les effets des émotions sur la douleur restent peu connus. Les objectifs de cette thèse sont donc de démontrer l'implication des émotions dans l'analgésie induite par la musique et de préciser les mécanismes cérébraux et cérébraux--spinaux impliqués dans la modulation émotionnelle de la douleur.

Afin de distinguer le rôle des émotions de celui de l'attention dans l'analgésie induite par la musique, le premier article expérimental de la thèse a comparé l'influence de musiques agréables et désagréables sur la perception de douleur thermique auprès de 18 participants. Bien que la musique désagréable ait également constitué une distraction par rapport à la douleur, seules les musiques agréables parvinrent à réduire la douleur, démontrant le rôle des émotions dans l'analgésie induite par la musique. Dans le deuxième article expérimental, nous avons testé la capacité de la musique à induire des émotions en étudiant les effets des mêmes extraits musicaux sur le réflexe de sursaut chez 16 participants. Le réflexe se trouva augmenté par les musiques désagréables et réduit par les musiques agréables, confirmant la capacité de la musique à induire des émotions. Finalement, dans le troisième article expérimental, nous avons exploré les mécanismes neurophysiologiques impliqués dans les effets de la musique sur la douleur en mesurant l'effet de la musique sur un réflexe nociceptif spinal (réflexe RIII) chez 26 participants. Le fait que le réflexe RIII fut modulé par la musique suggéra l'implication de mécanismes modulateurs descendants dans l'analgésie induite par la musique.

Dans le quatrième article expérimental, nous avons contrasté les effets de l'attention et des émotions induites par des images émotionnelles sur la nociception spinale chez 33 participants. Les émotions influencèrent de façon parallèle le réflexe RIII et

les évaluations de douleur, alors que la distraction augmenta le réflexe, mais diminua la perception de douleur, suggérant que l'implication de mécanismes neurophysiologiques distincts dans la modulation émotionnelle et attentionnelle de la douleur. Finalement, dans le cinquième article expérimental et dernier article de la thèse, nous explorons les mécanismes cérébraux impliqués dans la modulation émotionnelle dans une étude d'imagerie par résonance magnétique fonctionnelle (IRMf) chez 13 participants. L'activation du lobule paracentral, de l'insula droite et du gyrus parahippocampal en réponse à la douleur fut augmentée par les images négatives comparativement aux images positives. La modulation du lobule paracentral sembla liée à l'action de mécanismes modulateurs descendants, alors que la modulation de l'insula droite fut plutôt liée à l'action de mécanismes cortico-corticaux. Finalement, la modulation du gyrus parahippocampal sembla résulter d'une convergence des effets de la douleur et des émotions.

Dans l'ensemble, ces résultats apportent un appui théorique solide à l'utilisation de techniques d'induction émotionnelle, telle que la musicothérapie, comme agents thérapeutiques dans le traitement de la douleur en milieu clinique.

Mots clés : Douleur, émotion, musique, cerveau, IRMf, moelle épinière, réflexe RIII

Abstract

Pain is a complex experience comprising both a sensory and an affective dimension. As a consequence of this affective dimension, emotions have been shown to easily influence our perception of pain. Although many therapeutic interventions, such as music therapy, seem to depend on this phenomenon to reduce pain, the implication of emotions in their analgesic effect has never been empirically assessed. Moreocer, the cerebral mechanisms explaining the effects of emotions on pain remain relatively unknown. The objectives of this thesis are thus to highlight the involvement of emotions in music-induced analgesia and to examine the cerebral and cerebro-spinal mechanisms involved in the emotional modulation of pain.

In order to distinguish the role of emotions and attention in music-induced analgesia, the first experimental study of the thesis compared the effects of pleasant and unpleasant musical excerpts on pain perception in 18 participants. Although the unpleasant excerpts were also distracting, only the pleasant excerpts managed to reduce pain, supporting the involvement of emotional processes in music-induced analgesia. In the second experimental article, we tested the capacity of music to induce emotions by assessing the effects of the same musical excerpts on the startle reflex in 16 participants. The reflex, which is a sign of activation of the defensive emotional system, was enhanced by unpleasant music and diminished by pleasant music, confirming the capacity of music to induce emotions. Finally, in the third experimental article, we explored the neurophysiological mechanisms involved in the effects of music on pain by measuring the influence of musically-induced emotions on a spinal nociceptive reflex (RIII reflex) in 26 participants. The results showed that the RIII was modulated by the emotions induced by music, suggesting the involvement of descending modulatory mechanisms in music-induced analgesia.

In the fourth experimental article, we contrasted the effects of attention and emotion on spinal nociception (RIII reflex) in 33 participants. While emotions influenced

the RIII reflex and pain ratings in parallel, distraction increased the reflex, but reduced pain perception, suggesting that different neurophysiological mechanisms might be involved in the emotional and attentional modulation of pain. Finally, in the fifth and last article of the thesis, we explored the cerebral mechanisms involved in the emotional modulation of pain using the same experimental paradigm in a functional magnetic resonance imaging (fMRI) study in 13 participants. The activation of the paracentral lobule, the right insula and the parahippocampal gyrus in response to pain was increased by unpleasant compared to pleasant pictures. The modulation of the paracentral lobule appeared to be the result of descending modulatory mechanisms, whereas the modulation of the right insula was linked to cortico-cortical mechanisms. Finally, the modulation of the parahippocampal gyrus seemed to be caused by a convergence of the effects of pain and emotions.

Altogether, these results bring a strong theoretical support for the use of emotional induction techniques, such as music therapy, as therapeutic agents for pain management in clinical settings.

Key words : Pain, emotion, music, brain, fMRI, spinal cord, RIII reflex

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Liste des abréviations

ACC.....Anterior cingulate cortex - cortex cingulaire antérieur

Amy.....Amygdala - amygdale

ANOVA.....Analysis of variance - analyse de variance

DLPFC.....Dorsolateral prefrontal cortex – cortex prefrontal dorsolateral

DLPT.....Dorsolateral pontine tegmentum - tegmentum dorsolateral du pons

fMRI/IRMf....Functionnal magnetic resonance imaging / Imagerie par résonance magnétque fonctionnelle

HT.....Hypothalamus

Ins.....Insula

M1.....Primary motor cortex - cortex moteur primaire

MPFC.....Medial prefrontal cortex - cortex préfrontal médian

Nacc.....Nucleus accumbens - noyau accumbens

NCF.....Nucleus cuneiformis - noyau cunéiforme

ns.....Not significant - non significatif

OFC.....Orbitofrontal cortex - cortex orbitofrontal

PAG.....Periaqueductal gray - Substance grise periaqueductale

PCC.....Posterior cingulate cortex - cortex cingulaire postérieur

PCL.....Paracentral lobule - lobule paracentral

PF.....Prefrontal cortex - cortex préfrontal

PHG.....Parahippocampal gyrus - gyrus parahippocampal

S1.....Primary somatosensory motor cortex - cortex somatosensoriel primaire

SMA.....Supplementary motor area - aire motrice supplémentaire

Thal.....Thalamus

VTA.....Ventral tegmental area – aire tegmetale ventrale

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INTRODUCTION

La douleur apparaît pour la personne qui la subit comme une expérience désagréable et envahissante, signe de dommage corporel réel ou potentiel. Généralement associée aux blessures et à la maladie, son contrôle est un défi majeur des soins apportés aux patients. Or, l'expérience de la douleur est un phénomène complexe composé non seulement d'une dimension sensorielle, mais également d'une dimension émotionnelle désagréable (Price et al., 1999). Ainsi, en raison de cette dimension affective, la douleur s'avère facilement affectée par nos états émotionels.

Bien que diverses interventions thérapeutiques, telle que la musicothérapie, semblent s'appuyer sur ce principe pour réduire la douleur, l'implication des émotions dans leurs effets analgésique n'a jamais été démontrée empiriquement. De plus, les mécanismes cérébraux expliquant les effets des émotions sur la douleur restent peu connus. Au cours des sections expérimentales de cette thèse, nous examinerons le rôle des émotions dans l'analgésie induite par la musique ainsi que les mécanismes cérébraux et cérébraux--spinaux impliqués dans la modulation émotionnelle de la douleur. Cependant, au cours de l'introduction, nous aborderons tout d'abord les principaux thèmes reliant les différentes études de cette thèse, à savoir la modulation émotionnelle de la douleur, l'analgésie induite par la musique, ainsi que les mécanismes cérébraux impliqués dans la modulation de la douleur.

La modulation émotionnelle de la douleur

Les effets des émotions sur la douleur sont bien connus des cliniciens oeuvrant auprès de patients souffrant de divers type de douleur. En effet, les patients manifestant davantage d'émotions négatives (stress, anxiété, dépression) semblent aussi être ceux présentant les douleurs les plus intenses (Keefe et al., 2001). Cette corrélation témoignerait, du moins en partie, de l'impact modulateur des émotions sur la douleur (Keefe et al., 2001). Ainsi, il a été démontré que les patientes présentant de hauts niveaux d'anxiété préopératoire étaient celles développant le plus de douleurs postopératoires suite à une hystérectomie (Kain, Sevarino, Alexander, Pincus, & Mayes, 2000). Le stress et

l'anxiété sembleraient même prédire les fluctuations quotidiennes de douleur chez des patients souffrant de douleur chronique. En effet, Affleck et al. (1997) ont constaté que la survenue d'événements stressants augmentait les douleurs articulaires de patients arthritiques pendant près d'une semaine suivant l'événement stressant. Il n'est donc pas surprenant de constater que l'un des principaux objectifs de la prise en charge psychologique de la douleur consiste à maximiser les capacités de régulation émotionnelle des patients, que ce soit à travers la thérapie cognitivo-comportementale, ou par l'apprentissage de techniques de régulation émotionnelle, telle que la relaxation (Molton, Graham, Stoelb, & Jensen, 2007). À cet effet, il est intéressant de noter que certains anxiolytiques, bien qu'ils n'aient pas d'effets directs sur la nociception, parviennent à diminuer la douleur via leurs effets sur l'anxiété (Dellemijn & Fields, 1994).

Sur le plan expérimental, plusieurs études ont cherché à moduler la douleur par l'induction d'émotions produites par des images (Meagher, Arnau, & Rhudy, 2001b), des films (Weisenberg, Raz, & Hener, 1998), des phrases émotionelles (Zelman, Howland, Nichols, & Cleeland, 1991), des odeurs (Villemure, Slotnick, & Bushnell, 2003) ou par l'hypnose (P. Rainville, Q. V. H. Bao, & P. Chretien, 2005). En général, ces études montrent que les émotions positives diminuent la perception de douleur alors que les émotions négatives l'augmentent. Une exception à cette règle touche cependant les émotions négatives très intenses, qui ont plutôt tendance à réduire la douleur. Ce phénomène, connu sous le nom « d'analgésie induite par la peur » a été extensivement étudié chez l'animal, où il a été démontré dépendre en partie de l'action d'opioïdes endogènes (Meagher, Grau, & King, 1989). La fonction de cette inhibition subite de la douleur lors d'émotions négatives très intenses serait de préparer l'organisme à réagir à une menace imminente. Bien que le phénomène ait été peu étudié chez l'humain, Rhudy et Meagher (2000) ont pu démontrer que la peur induite par l'administration de chocs électriques douloureux augmentait la tolérance à la douleur (i.e. réduction de la douleur), alors que l'anxiété suscitée par la crainte de ces chocs, sans leur administration, réduisait la tolérance à la douleur (i.e. augmentation de la douleur).

Mis à part le cas spécifique de l'analgésie induite par la peur, les résultats de ces études expérimentales supportent massivement la théorie de l'amorçage motivationnel de Lang (1995). Selon cette théorie, les émotions seraient gouvernées par deux systèmes motivationnels antagonistes : le système appétitif, responsable des comportements d'approche, et le système aversif, lié aux comportements de retrait. Ainsi, l'activation de l'un des systèmes potentialiserait les réponses de ce système tout en inhibant les réponses du système antagoniste. Cette théorie fut principalement supportée par des études portant sur la modulation émotionnelle du réflexe de sursaut. Ce réflexe, qui a une fonction défensive, est généralement mesuré par l'amplitude du clignement de l'œil en réponse à la présentation de bruits blancs forts et soudains. En accord avec le principe de l'amorçage motivationnel, l'amplitude de ce réflexe se trouve généralement augmentée par la présentation d'images négatives (Lang, 1995) de sons désagréables (Bradley & Lang, 2000), ou même en raison d'une anxiété pathologique (Grillon & Baas, 2003). À l'inverse, la présentation d'images ou des sons agréables diminue l'amplitude du réflexe (Bradley & Lang, 2000; Lang, 1995). Ces effets sont en parfaite correspondance avec ceux observés sur la douleur, suggérant que la modulation émotionnelle de la douleur suit globalement les mêmes principes que ceux proposés par la théorie de l'amorçage motivationnel.

Afin de déterminer à quels niveaux des voies de transmission nociceptive agissent les émotions, Rhudy et al. (2005) ont mesuré les effets d'émotions induites par des images affectives sur l'amplitude d'un réflexe spinal nociceptif (réflexe RIII ou réflexe nociceptif de flexion). Ce réflexe, qui dépend largement de la stimulation des fibres nociceptives A-δ afférentes, est déclenché par la stimulation du nerf sural dans sa voie rétro-malléolaire (i.e. : cheville), produisant une flexion du biceps femoris (Sandrini et al., 2005). Une des fonctions de ce réflexe serait d'assurer le retrait automatique du membre menacé par une stimulation potentiellement dangereuse. Étant donné que le seuil du réflexe coïncide avec le seuil de douleur et que son amplitude reflète l'intensité de la douleur, ce réflexe est considéré comme un bon indice du niveau de nociception spinale. Or, lors de l'étude de

Rhudy et al. (2005), le réflexe s'est avéré modulable par les émotions induites par les images de la même façon que les évaluations de douleur: les images positives ont réduit l'amplitude du réflexe, alors que les images négatives l'ont augmenté. Cette modulation du réflexe RIII par les émotions suggère l'implication de mécanismes cérébro-spinaux descendants qui viendraient moduler la transmission de l'influx nociceptif au niveau de la moelle épinière.

Malgré ces résultats probants, il reste difficile de départager le rôle des émotions de celui de l'attention dans la modulation émotionnelle de la douleur. En effet, il est bien connu que les émotions influencent de façon importante la direction de l'attention (Armony & Dolan, 2002; Ohman, Flykt, & Esteves, 2001). Dans le cas de la douleur, il a été démontré que les émotions négatives augmentaient de façon générale l'attention portée vers soi (Salovey, 1992), favorisant ainsi l'accessibilité et le rapport de symptômes somatiques (Gendolla, Abele, Andrei, Spurk, & Richter, 2005) et que la peur de la douleur augmentait l'attention portée à la douleur (Keogh, Ellery, Hunt, & Hannent, 2001). Ceci suggère que les émotions pourraient donc agir sur la douleur par le biais d'une redirection de l'attention (Villemure & Bushnell, 2002). Afin de départager le rôle respectif de l'attention et des émotions sur la douleur, Villemure et al. (2003) ont élaboré une expérience dans laquelle ils ont fait varier la direction de l'attention indépendamment de la valence émotionnelle. Pendant que des odeurs agréables ou désagréables étaient présentées en même temps que des stimulations thermiques douloureuses, leurs participants devaient effectuer une tâche de discrimination portant soit sur les odeurs, soit sur les stimulations thermiques. Bien que les deux types de manipulation aient agi sur la douleur, l'attention influença davantage la composante sensorielle de la douleur, alors que les émotions influencèrent plutôt sa composante affective, suggérant l'action de deux mécanismes modulateurs distincts. Cependant, la nature de ces mécanismes reste à déterminer sur le plan neurophysiologique. Ainsi, l'article 5 de cette thèse tentera de différencier les mécanismes cérébraux-spinaux impliqués dans la modulation émotionnelle de la douleur de ceux impliqués dans sa modulation attentionnelle.

L'analgésie induite par la musique

Les études portant sur la modulation émotionnelle de la douleur apportent un appui théorique solide à l'utilisation de divers types d'inducteurs émotionnels dans le traitement de la douleur clinique. Bien que ces appuis théoriques soient relativement récents, les hommes appliquent intuitivement ce principe depuis des temps immémoriaux en utilisant la musique comme agent thérapeutique (K. Gfeller et al., 2002). En effet, la pratique de la musique a pendant longtemps été intimement reliée aux pratiques médicales. On lui attribuait alors la capacité de conjurer les mauvais esprits à l'origine de la maladie et de la souffrance. Bien entendu, avec le développement de la médecine scientifique, les explications surnaturelles de l'origine des maladies furent abandonnées et l'usage de la musique en médecine disparu pendant quelques siècles. Ce n'est qu'à la fin de la deuxième guerre mondiale que des musiciens bénévoles firent revivre le potentiel thérapeutique de la musique en jouant auprès des vétérans hospitalisés dans les hôpitaux militaires. L'expérience fut si positive que la pratique perdura et conduisit quelques années plus tard à l'émergence de la musicothérapie en tant que discipline empirique visant à réintroduire la musique dans le milieu médical.

Au sein de cette nouvelle discipline, de nombreuses études ont tenté de démontrer empiriquement l'efficacité de la musique à réduire la douleur. Dans ce qui constitue la première étude d'envergure sur l'effet analgésique de la musique, Gardner, Licklider et Weisz (1960) ont constaté que la douleur associée à divers types de traitements dentaires se trouvait réduite par la présentation d'une stimulation auditive (musique et/ou bruit blanc) chez près de 90% des 5000 patients testés. Les auteurs attribuèrent alors l'effet analgésique à un ensemble de facteurs agissant simultanément: le masquage du bruit des instruments dentaires et la réduction de l'anxiété leur étant associées, l'effet relaxant de la musique et/ou du bruit blanc, la distraction causée par la musique, ainsi que plusieurs autres variables psychologiques. Ce résultat initial fut par la suite répliqué par plusieurs études menées auprès d'une multitude de populations cliniques, toutes constatant une

diminution de la douleur chez les patients recevant une intervention musicale en plus des soins médicaux standards, comparativement à ceux recevant uniquement les soins standards (Cepeda, Carr, Lau, & Alvarez, 2006b; Good, Anderson, Ahn, Cong, & Stanton-Hicks, 2005; McCaffrey & Freeman, 2003; Nilsson, Unosson, & Rawal, 2005; Phumdoung & Good, 2003; Tse, Chan, & Benzie, 2005b; Voss et al., 2004). Bien que ces résultats supportent l'utilisation de la musique en milieu clinique, ils ne permettent pas d'identifier les mécanismes d'action impliqués dans l'analgésie induite par la musique. En effet, en l'absence de condition expérimentale contrôlant les effets de l'attention, il s'avère impossible de dire si l'effet de la musique est uniquement dû à la distraction qu'elle procure, où si ce sont plutôt les émotions induites par la musique qui déterminent ses effets sur la douleur. Cette question sera d'abord abordée d'un point de vue psychophysique dans l'article 2 de cette thèse, puis du point de vue des mécanismes neurophysiologiques dans l'article 4 de cette thèse.

Un autre problème concernant l'hypothèse de l'implication des processus émotionnels dans l'analgésie induite par la musique concerne la capacité même de la musique à induire des émotions (Juslin, in press). En effet, puisque la musique n'a pas de fonction adaptative évidente (Pinker, 1997) et qu'elle ne semble pas avoir d'implications directes sur les buts et motivations de l'auditeur, certains auteurs ont proposé que la musique ne pouvait pas réellement induire d'émotions (Kivy, 1990; Konečni, 2003; Scherer, 2003). Selon Juslin (in press) cette impasse résulterait du fait que les chercheurs en psychologie de la musique ont trop longtemps négligé les mécanismes psychologiques sous-tendant les émotions musicales, ou sinon assumé qu'elles résultaient d'un mécanisme général d'évaluation cognitive. Or, les théories d'évaluation cognitive (i.e. *appraisal theories)* postulent que les émotions sont déclenchées lorsqu'un événement est évalué comme ayant la capacité d'affecter d'une façon ou d'une autre les buts de l'individu, ce qui manque cruellement à la musique.

Afin de résoudre l'impasse, Juslin recommande d'aller au-delà des théories d'évaluation cognitive des émotions et propose six mécanismes par lesquels la musique pourrait induire des émotions: 1 – les réflexes du tronc cérébral, 2- le conditionnement évaluatif, 3 – la contagion émotionelle, 4 – l'magerie visuelle, 5 – la mémoire épisodique et 6 – les attentes musicales. La combinaison de ces divers mécanismes expliquerait la diversité et la complexité des réactions émotionnelles à la musique. Cependant, l'implication de ces mécanismes dans l'induction d'émotions par la musique reste en grande partie à être confirmée par des études empiriques. Ainsi, dans l'article 3 de cette thèse, nous aborderont les effets modulateur des émotions induites par la musique sur le réflexe de sursaut afin d'évaluer la capacité de la musique à réellement induire des émotions.

Mécanismes cérébraux impliqués dans la modulation de la douleur

Le fait que la douleur puisse être si facilement influencée par les émotions souligne l'importante malléabilité de l'expérience douloureuse. En effet, les conceptions modernes de la douleur soutiennent fortement l'idée selon laquelle la douleur résulterait d'interactions constantes entre la transmission de l'information nociceptive vers le cerveau et sa modulation par des mécanismes pro et anti-nociceptifs (Melzack & Wall, 1965). Outres les émotions, de nombreux autres facteurs psychologiques, tels que l'attention, les attentes, l'anticipation, l'hypnose ou le placebo, peuvent influencer de façon importante la perception de la douleur. Au cours de cette section, nous aborderons dans un premier temps les mécanismes cérébraux impliqués dans ces divers types de modulation de la douleur, avant de se concentrer sur les mécanismes pouvant expliquer la modulation émotionnelle de la douleur dans l'article 1 de cette thèse. Finalement, dans l'article 6 de la thèse, nous tenterons de mettre à jour les mécanismes cérébraux impliqués dans l'effet des émotions sur la douleur grâce à l'imagerie par résonance magnétique fonctionnelle (IRMf).

La Figure 1 résume les principales voies nerveuses de transmission et de modulation descendante de la douleur. La corne dorsale de la moelle épinière constitue le premier endroit où l'influx nociceptif, provenant des fibres sensitives afférentes (A-δ et C), fait relais sur les neurones de projection spinaux. C'est à cette étape qu'agissent plusieurs analgésiques classiques, tels que la morphine, qui bloquent la transmission de l'influx nociceptif au cerveau par les neurones de projections spinaux. C'est aussi à cette étape que viennent agir de nombreux mécanismes modulateurs descendants endogènes. Les mieux connus sont les mécanismes inhibiteurs descendants dépendant de la substance grise péri-aqueductale (PAG). Ceux-ci seraient, entre autres, impliqués dans l'importante analgésie engendrée par des états de stress intense (i.e. analgésie induite par la peur). Outre la PAG, de nombreuses autres structures cérébrales participeraient à ces mécanismes inhibiteurs descendants (Millan, Mull, Freise, Richter, & Triclabendazole Study, 2000; I. Tracey, 2007). Au sein de ce réseau, la PAG occuperait un rôle de pivot en recevant d'une part des afférences de diverses structures cérébrales (lobes frontaux, cortex cingulaire antérieur, insula, amygdale, hypothalamus, noyeau cunéiforme), et en inhibant d'autre part la propagation de l'influx nocicepif dans la corne dorsale de la moelle épinière, soit par le biais d'efférences inhibitrices directes, soit via le tegmentum dorsolatéral du tronc cérébral ou la moelle épinière ventromédiale rostrale (RVM) (Figure 1). Curieusement, la PAG et la RVM seraient également impliquées dans des voies facilitatrices descendantes (Lovick, 2008; Porreca, Ossipov, & Gebhart, 2002), bien que celles-ci restent mal connues en comparaison avec les voies inhibitrices descendantes décrites plus haut.

Des études récentes en IRMf tendent à suggérer que des mécanismes inhibiteurs descendants liés à la PAG seraient impliqués dans les effets de l'attention sur la douleur. Ainsi, Tracey et al. (2002) ont mis en évidence des activations de la PAG prédisant le degré d'analgésie ressentie lorsque les participants détournaient leur attention de la douleur. Une étude subséquente utilisant une tâche de Stroop comme distracteur permit d'identifier le cortex cingulaire perigenual et les cortex orbitofrontaux comme des zones

supplémentaires d'inhibition de la douleur. Une troisième étude utilisant également une tâche de Stroop comme distracteur parvint à démontrer par le biais d'analyses de connectivité que le cortex cingulofrontal exerçait une influence 'top-down' sur la PAG et le thalamus postérieur afin de réduire la douleur lors de la distraction (Valet et al., 2004). Dans l'ensemble, ces études suggèrent que l'analgésie induite par la distaction dépendrait de l'activation des cortex cingulofrontaux qui stimuleraient la PAG afin qu'elle déclenche ses mécanismes inhibiteurs descendants. En appui à cette hypothèse, la connectivité fonctionnelle entre les cortex cingulofrontaux et la PAG se trouverait largement corroborée sur la plan anatomique par les résultats d'une étude récente de tractographie de diffusion confirmant la présence de connections anatomiques entre les deux régions (Hadjipavlou, Dunckley, Behrens, & Tracey, 2006).

Après ce premier relais dans la moelle épinière, l'influx nociceptif, propagé par les neurones de projection spinaux, se dirige principalement vers le thalamus, bien que quelques projections spinales se rendent également vers des zones impliquées dans la modulation descendante de la douleur, telles que la PAG, la moelle épinière ventromédiale, le noyaux parabrachial, et la formation réticulée. Une fois rendu au thalamus, l'influx nociceptif est rédirigé vers une multitude de structures corticales afin de produire notre expérience de douleur (Brooks & Tracey, 2005). Les projections partant des structures latérales du thalamus se dirigeront vers les cortex somatosensoriels primaires et secondaires (S1 et S2), servant à l'aspect senori-discriminitif de la douleur (Bushnell et al., 1999; Kanda et al., 2000), alors que les projections partant des structures médiales du thalamus vont quant à elles se diriger vers le cortex cingulaire antérieur (CCA) et l'insula et serviraient plutôt à la composante affective de la douleur (Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Cependant, l'insula aurait également un rôle sensori-discriminatif (Craig, Chen, Bandy, & Reiman, 2000), surtout dans sa partie postérieure, alors que la partie antérieure serait plutôt impliquée dans la composante émotionnelle de la douleur (Craig, 2008).

Plusieurs des régions cérébrales impliquées dans le traitement de la douleur s'avèrent également recrutées pendant l'anticipation de la douleur. Ainsi, le cortex cingulaire antérieur rostral (rACC) et l'insula s'activent lors de la simple présentation d'un signal prédisant l'administration d'une stimulation douloureuse (Chua, Reddy, Lee, & Patt, 1999). Ces activations, bien que proches de celles recrutées par la douleur, se révèlent en fait être situées rostralement aux aires activées par les stimulations douloureuses. Ainsi, Ploghaus et al. (1999) démontrèrent que l'anticipation de la douleur activait le rACC, l'insula antérieure et le cervelet postérieur alors que la stimulation douloureuse activait le cortex cingulaire moyen, l'insula moyenne et le vermis du cervelet. Étant donné que les régions liées à l'anticipation de la douleur étaient distinctes de celles impliquées par la stimulation douloureuse elle-même, Ploghaus et al. (2003) suggéra que ces régions étaient impliquées dans l'influence des attentes sur la douleur, notamment dans la diminution de douleur engendrée par la peur (i.e. analgésie induite par le stress) de recevoir une stimulation douloureuse (J. L. Rhudy & Meagher, 2000).

Les études portant sur l'hypnose et le placebo semblent confirmer cette hypothèse. Ainsi, lors de suggestions hypnotiques visant à réduire ou augmenter le désagrément de la douleur, Rainville et al. (1997) observèrent des activations du rACC, et ce peu importe la direction des suggestions hypnotiques. Dans une autre étude, Petrovic et al. (2002) employèrent des suggestions placebo afin d'induire des attentes de diminution de douleur. Lors de l'analgésie placebo, un patron d'activation semblable à celui observé lors de l'anticipation de la douleur émerga: le placebo activa le rACC et le cervelet postérieur, alors que la douleur activa le cortex cingulaire moyen et le vermis du cervelet. Combinant les résultats de ces deux études, Ploghaus et al. (2003) proposèrent que le rACC et le cervelet postérieur seraient activés par les attentes, et ce, tout au long de l'événement aversif et peu importe la direction des attentes. L'activation de ces régions semble donc refléter le biais perceptuel favorisant les attentes en dépit d'*inputs* nociceptifs potentiellement conflictuels.

Dans une étude récente, Bingel et al. (2006) utilisèrent des analyses de connectivité afin de démontrer que l'activité du rACC est liée à celle de la PAG pendant l'analgésie placebo. Étant donné l'implication de la PAG dans le mécanismes d'inhibition descendante, les auteurs suggérèrent que ces derniers soient impliqués dans l'analgésie placebo. La PAG et le rACC furent également liées à l'analgésie placebo dans une étude d'envergure sur les bases cérébrales du placebo menée par Wager et al. (2004). Dans cette étude, le placebo entraîna une activation de la PAG pendant l'anticipation de la stimulation nociceptive. De plus, l'amplitude de cette activation prédisait l'effet du placebo sur l'activité du thalamus et du rACC ainsi que sur les évaluations de douleur, suggérant encore l'action de mécanismes inhibiteurs descendants. Outre la PAG, les activations des cortex préfrontaux dorsolatéraux (DLPFC), orbitofrontaux (OFC) et du rACC pendant la période d'anticipation prédirent également la dimunition d'activation des aires de douleur pendant le placebo. De façon surprenante, l'effet du placebo sembla surtout affecter l'activition des aires de douleur vers la fin de la stimulation douloureuse, suggérant une ré-interprétation tardive de la signification de la douleur en fonction des attentes. Il semble donc que des mécanismes plus centraux soient également impliqués dans l'analgésie placebo, conformément à l'idée selon laquelle la douleur serait un construit psychlogique incluant autant l'affect douloureux et l'estimation des dommages potentiels liées à la douleur, que la dimension sensorielle de la douleur (Craig et al., 2000; Price, 2000).

La manipulation des attentes peut aussi conduire à une augmentation de la perception de la douleur lorsque l'incertude concernant l'intensité de la stimulation douloureuse produit de l'anxiété. Suivant ce principe, Ploghaus et al. (2001) associèrent la présentation d'un signal visuel à des stimulations douloureuses incertaines, soit légères ou élevées, alors qu'un autre signal prédisait de façon fiable la survenue de stimulations douloureuses légères. Tel qu'attendu, le signal visuel incertain suscita davantage d'anxiété et augmenta la perception de douleur. Cette hyperalgésie induite par l'anxiété s'avéra liée à l'activité du cortex entorhinal et de la formation hippocampale. Les auteurs interprétèrent ces résultats à la lumière de la théorie de l'anxiété de Gray-McNaughton

(Gray & McNaughton, 2000), qui propose que la formation hippocampale amplifierait la représention neuronale des événements aversifs en situation d'anxiété afin de préparer l'organisme à réagir aux pires conséquences possibles. Dans une étude récente, Fairhurst et al. (2007) ont constaté que la PAG était activée pendant l'anticipation de la douleur et que l'activité du cortex entorhinal et de l'aire tegmentale ventrale (VTA) corrélait avec l'intensité de la douleur anticipée. De plus, l'activité du cortex enthorinal et de la VTA pendant l'anticipation prédit l'activation des aires thermoceptives de l'insula postérieure pendant la stimulation thermique douloureuse. Il semble donc que le cortex entorhinal puisse agir de concert avec certaines structures du tronc cérébral, telles que la PAG ou la VTA, afin d'amplifier la douleur, possiblement par le biais de mécanismes facilitateurs descendants.

Présentation des études de cette thèse

Dans le premier article de cette thèse, nous aborderons d'un point de vue théorique les corrélats neuronaux de la dimension émotionnelle de la douleur, ainsi que les mécanismes cérébraux possiblement impliqués dans la modulation émotionnelle de la douleur. Dans le deuxième article de la thèse, nous tenterons de départager le rôle de l'attention et des émotions dans l'analgésie induite par la musique en comparant l'effet d'extraits musicaux agréables ou désagréables. Dans le troisième article, nous évaluerons les effets des mêmes extraits musicaux sur l'amplitude du réflexe de sursaut afin de démontrer la capacité de la musique à induire des émotions. Dans le quatrième article de la thèse nous explorerons les mécanismes cérébro-spinaux impliqués dans l'analgésie induite par la musique en mesurant l'effet de la musique sur un réflexe nociceptif spinal (réflexe RIII). Dans le cinqième article de la thèse, nous comparerons les mécanismes cérébro-spinaux impliqués la modulation émotionnelle et attentionnelle de la douleur en mesurant l'amplitude du réflexe RIII pendant la présentation d'images émotionnelles. Finalement, dans le sixième et dernier article de la thèse nous explorerons les mécanismes cérébraux impliqués dans la modulation émotionnelle de la douleur en utilisant le même paradigme en IRMf.

ARTICLES THÉORIQUES ET EMPIRIQUES

Article 1 : Mécanismes cérébraux impliqués dans l'interaction entre la douleur et les émotions

Duquette, M., Roy, M., Lepore, F., Peretz, I., Rainville, P. (2006). Mécanismes cérébraux impliqués dans l'interaction entre la douleur et les émotions. Revue Neurologique,162 :8, 1-11

Mécanismes cérébraux impliqués dans l'interaction entre la douleur et les émotions

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Résumé

Introduction. La douleur est une expérience déplaisante et intrusive associée à un dommage réel ou potentiel des tissus du corps. Les résultats d'une quinzaine d'années de recherche en imagerie cérébrale fonctionnelle ont permis de mettre en lumière le rôle de plusieurs régions cérébrales dans l'expérience de la douleur. **État des connaissances.** Intimement liée à la notion de souffrance, la dimension affective de l'expérience douloureuse repose sur l'activité de systèmes neurophysiologiques au moins partiellement distincts sur le plan anatomique de ceux impliqués plus spécifiquement dans sa dimension sensorielle. Certaines voies transportent les messages nociceptifs vers les cortex somatosensoriels et l'insula qui participent aux aspects sensoriels de la douleur (p. ex. : intensité sensorielle) et contribuent secondairement à sa dimension affective. D'autres voies projettent directement vers le cortex cingulaire antérieur, l'insula, l'amygdale, et les cortex préfrontaux, des structures cérébrales impliquées dans la dimension affective de la douleur (désagrément et régulation des réponses autonomiques et comportementales). Or, ces régions cibles de la douleur font partie intégrante des circuits émotionnels cérébraux. **Perpectives et conclusion.** Cette relation anatomique étroite entre les circuits de la douleur et des émotions pourrait expliquer l'impact émotionnel puissant de la douleur sur les émotions et l'effet modulateur réciproque des émotions sur la douleur. Cet effet modulateur pourrait dépendre plus spécifiquement des interactions entre les cortex préfrontaux et cingulaire, le striatum ventral, l'amygdale, et les régions

hippocampiques. Ces observations témoignent de la nature émotionnelle de la douleur.

Mots-clés : douleur, émotions, modulation de la douleur, neuroimagerie fonctionnelle, cerveau

Summary – Cerebral mechanisms involved in the interaction between pain and emotions

Introduction. Pain is an unpleasant and intrusive sensation, warning of actual or potential tissue damage. Over the last fifteen years, functional cerebral imaging research has demonstrated the involvement of many cerebral structures in the experience of pain. **Background.** Intimately linked to the notion of suffering, the affective dimension of pain relies on neurophysiological systems partly distinct anatomically from those involved more specifically in its sensory dimension. Some pathways convey nociceptive information to the somatosensory cortex and the insula, contributing to the sensory aspects of pain (e.g.: sensory intensity), and secondarily, to its affective dimension. Other pathways projects directly to the anterior cingulate cortex, the insula, the amygdala and to the prefrontal cortices, which are structures involved in the affective dimension of pain (unpleasantness of pain and regulation of autonomic and behavioural responses). Interestingly, these latter regions are an integral part of the cerebral emotional networks. **Perspectives and conclusion.** This close anatomical relationship between pain and emotions circuits could explain the

powerful emotional impact of pain as well as the reciprocal modulatory effect of emotions on pain observed in clinical and experimental studies. More specifically, this modulatory effect might reflect interactions between emotional and nociceptive systems in the prefrontal and cingulate cortices, ventral striatum, amygdala and hippocampal regions. Taken together, these observations further attest of the emotional nature of pain experience.

Keywords: pain, emotions, pain modulation, functional neuroimaging, brain

Introduction

La douleur est une expérience multidimensionnelle difficile à circonscrire. Elle est à la fois la perception d'un stimulus nociceptif et une sensation désagréable, indicatrice d'une atteinte réelle ou potentielle à l'intégrité de l'organisme. En ce sens, la douleur partage de nombreuses caractéristiques avec les émotions : les deux remplissent une fonction adaptative, sont accompagnées d'un affect subjectif, d'une motivation à agir ainsi que d'un patron de réponses autonomiques. Outre l'affect primaire inhérent à l'expérience de la douleur, l'évaluation cognitive de l'implication à long terme de la douleur peut conduire secondairement à l'expérience d'émotions négatives, telles que la dépression, l'anxiété, la frustration, la colère ou la peur. Ces deux dimensions affectives de la douleur, primaire et secondaire, se trouvent intégrées dans certaines théories contemporaines de la douleur (Price, 1988; Wade *et al.*, 1996).

L'importance de la composante émotionnelle de l'expérience douloureuse se reflète également dans l'anatomie fonctionnelle du système nerveux central. Ainsi, bon nombre de structures cérébrales liées à l'expérience d'émotions se trouvent également impliquées dans les réponses émotionnelles à la douleur. Cette caractéristique revêt une importance particulière pour le traitement de la douleur puisqu'elle suggère un substrat neuronal permettant d'expliquer l'influence des émotions sur l'expérience de douleur. L'objectif de cette revue de littérature est donc de mettre en évidence les mécanismes cérébraux impliqués d'une part, dans l'affect primaire et secondaire de la douleur et d'autre part, dans la modulation de la douleur par les émotions. Les aspects sensori-discriminatifs de la douleur seront décrits uniquement dans la mesure où ils contribuent de façon indirecte aux aspects affectifs de l'expérience douloureuse.

Les régions cérébrales participant aux dimensions émotionnelles de la douleur

La participation du cortex cérébral dans l'expérience subjective de la douleur a été démontrée à maintes reprises. Dans les études en imagerie cérébrale, il a été observé que chez l'humain neurologiquement sain, l'application d'une stimulation douloureuse produit une activation multifocale au niveau du cortex (Apkarian *et al.*, 2005; Peyron *et al.*, 2000; Laurent *et al.*, 2000) (figure 1a). Des activations ont été détectées au niveau des aires somesthésiques primaire (S1) et secondaire (S2) (dans l'opercule pariétal), du cortex cingulaire antérieur (CCA) et de l'insula de Reil (INS) (e.g., Talbot *et al.*, 1991; Derbyshire *et al.*, 1994; Paulson *et al.*, 1998). Diverses études électrophysiologiques présentant des données d'enregistrement ou de modélisation en

potentiels évoqués (e.g., Frot *et al.*, 2001; Frot et Mauguière, 2003) et/ou en champs magnétiques (e.g., Kakigi *et al.*, 1995; Kanda et al, 2000) ont confirmé la participation de S1, S2 et de l'INS dans l'expérience de la douleur. Des activations inconstantes ont été notées dans le cortex préfrontal (e.g., Casey *et al.*, 1996; Hsieh *et al.*, 1995), le cortex moteur, le cortex prémoteur, l'aire motrice supplémentaire (Coghill *et al.*, 1994) et le cortex pariétal postérieur (e.g., Svensson *et al.*, 1997; Aziz *et al.*, 1997). Plusieurs régions sous-corticales sont activées pendant la douleur et c'est au niveau du thalamus qu'une augmentation du débit sanguin cérébral régional est le plus fréquemment observée. L'imagerie cérébrale a aussi révélé plus rarement des activations pendant la douleur au niveau de l'amygdale (AMY) (e.g., Schneider *et al.*, 2001), du cervelet (e.g., Casey *et al.*, 1996; Xu *et al.*, 1997), des noyaux gris centraux (Jones *et al.*, 1991) ainsi que dans certaines parties de l'hypothalamus et du tronc cérébral (e.g., Derbyshire *et al.*, 1994; Hsieh *et al.*, 1995). Ces activations reflèteraient la contribution de ces structures cérébrales à divers aspects de la perception et des réponses à la douleur.

Le système neuroanatomique impliqué dans la perception de la douleur est constitué d'une multitude de voies neuronales (figure 1b). Une de ces voies se dirige vers les noyaux somatosensoriels du thalamus tel que le noyau ventro-postéro-latéral (VPL). Ces derniers acheminent ensuite l'information nociceptive aux régions somesthésiques S1 et S2 (Kenshalo *et al.*, 1980; Friedman et Murray, 1986). Les régions corticales S1 et S2 sont reliés anatomiquement par une voie qui permet l'intégration de l'information somatosensorielle avec celle de différentes modalités comme la vision et l'audition ainsi qu'avec l'apprentissage et la mémoire (Friedman *et*

al., 1986). À partir de S1 et S2, le signal nerveux peut se diriger vers diverses aires pariétales postérieures pour enfin converger vers l'INS, le CCA et l'AMY (Friedman *et al.*, 1986). Notons aussi qu'une voie directe achemine également l'information nociceptive de S2 à l'INS (Friedman *et al.*, 1986). Des données électrophysiologiques intracérébrales ont d'ailleurs montré récemment une activation séquentielle de S2 et de l'INS (Frot et Mauguière, 2003). D'autre part, certaines voies partent de la corne dorsale de la moelle épinière et projettent directement vers le tronc cérébral et des régions du système émotionnel cérébral. Parmi celles-ci, nous retrouvons notamment la voie spino-ponto-amygdalienne (Bernard et Besson, 1990) et une composante de la voie spinothalamique qui achemine l'information douloureuse vers la partie postérieure du noyau ventromédian du thalamus (VMpo) (Craig, 1995) ainsi que vers la partie ventrocaudale du noyau médiodorsal du thalamus (MDvc) (Sikes et Vogt, 1992). Les projections se dirigent alors vers des régions corticales comme l'INS (Craig, 1995), le CCA (Sikes et Vogt, 1992) et le cortex préfrontal (Monconduit *et al.*, 1999). Ces différentes structures cérébrales pourraient contribuer à l'aspect affectif de la douleur (tableau 1).

Le thalamus VPL et les cortex somesthésiques primaire (S1) et secondaire (S2)

Des patients présentant des lésions du thalamus VPL ou des cortex somesthésiques primaire et secondaire ont pu être étudiés. Ainsi, Ploner *et al.* (1999) ont évalué un patient souffrant d'une lésion postcentrale affectant S1 et S2 alors que Head et Holmes (1911) et Greenspan *et al.* (1997) ont étudié des patients atteints de

lésions incluant le noyau VPL du thalamus. Dans ces trois études, des perturbations dans les dimensions sensorielle et affective de la douleur ont été observées pour des stimulations douloureuses faiblement ou modérément intenses. Toutefois, chez certains de ces patients, un vague sentiment de déplaisir subsistait en dépit des perturbations sensorielles lorsque l'intensité du stimulus atteignait un niveau bien au-dessus du seuil de douleur normal (Ploner *et al.*, 1999; Head et Holmes, 1911). Interprétant toutes ces données, Price et Verne (2002) suggèrent que l'interruption de la voie allant vers la thalamus VPL ou de celle se dirigeant vers les cortex S1/S2 produit une perturbation dans l'évaluation de la dimension sensorielle de la douleur avec pour conséquence une diminution de son aspect désagréable. Cette interprétation témoignerait de l'influence robuste de la sensation de douleur sur la réponse affective immédiate à la douleur (Price, 2000). Par contre, lorsque l'intensité de la stimulation douloureuse atteint un niveau suffisamment élevé, d'autres voies contriburaient de façon parallèle au caractère déplaisant du stimulus.

Des données supplémentaires permettent de mettre en relief le lien étroit entre la dimension sensorielle de l'expérience douloureuse et sa dimension affective. Des études ont démontré que des suggestions hypnotiques peuvent efficacement augmenter ou diminuer la perception de l'intensité de la douleur (Rainville *et al.*, 1999) et modifier proportionnellement l'activité évoquée par la douleur dans S1 (Hofbauer *et al.*, 2001). Ces altérations dans l'activité de S1 et dans les aspects sensoriels de la douleur s'accompagnent également d'une modulation proportionnelle indirecte du désagrément de la douleur.

Le cortex insulaire (INS)

Plusieurs études ont démontré que le cortex insulaire a la capacité de coder l'intensité de la douleur perçue et présente ainsi des propriétés sensori-discriminatives (Coghill *et al.*, 1999 ; Frot et Mauguière, 2003). Par ailleurs, une atteinte de cette structure peut occasionner des perturbations dans la dimension affective de la douleur alors que la dimension sensorielle serait épargnée. Ce syndrome, connu sous le nom d'asymbolie à la douleur, est intéressant pour étudier l'interaction entre la douleur et les émotions. Typiquement, les patients qui en souffrent reconnaîtrait la douleur sans présenter de réponses émotionnelles correspondantes ou de réponse d'évitement (e.g., Berthier *et al.*, 1988). Cette dernière observation est compatible avec l'implication de l'INS dans l'anticipation (appréhension) de la douleur en imagerie cérébrale fonctionnelle (Ploghaus *et al.*, 1999). Par ailleurs, Greenspan *et al.* (1999) ont observé, chez des patients dont une grande partie de l'INS est endommagée, une plus grande tolérance à la stimulation douloureuse présentée controlatéralement à leurs lésions (comparativement à la présentation ipsilatérale).

Un argument supplémentaire en faveur de la participation du cortex insulaire dans la dimension affective de la douleur concerne les études impliquant cette région dans le contrôle et la régulation du système nerveux autonome. En effet, dans une étude effectuant des enregistrements unitaires des cellules du cortex insulaire chez le singe, Zhang *et al.* (1999) ont examiné la réponse neuronale à des changements de

pression sanguine provoqués par l'injection de drogues affectant l'activité sympathique périphérique. Les résultats ont montré que parmi les cellules insulaires répondant aux changements de pression sanguine, la majorité répondait également à des stimulations douloureuses. Cela suggère que chez le primate, le cortex insulaire peut être impliqué dans l'intégration des fonctions cardiovasculaires avec les entrées nerveuses somatosensorielles (principalement nociceptives). L'implication de l'INS dans la régulation du système cardiovasculaire a également été démontré chez l'homme (Oppenheimer *et al.*, 1992; Crithley *et al.*, 2000; Kimmerly *et al.*, 2005).

Le rôle de l'insula ne se limite vraisemblablement pas à l'affect douloureux. En effet, l'insula se trouve impliquée dans l'expérience de la faim et de la soif, des démangeaisons, des caresses et de la température (Craig, 2002). Des études en imagerie cérébrale ont aussi mis en évidence le rôle de l'insula dans la conscience émotionnelle et la perception de son propre rythme cardiaque (Critchley *et al.*, 2004). Dans cette perspective, la douleur est conçue comme une émotion homéostasique reflétant la condition interne du corps (Craig, 2002). Cette représentation de l'état interne du corps servirait également de base à l'empathie à la douleur. Des études en IRMf ont démontré une activation de cette structure lors de la perception et de l'évaluation de la douleur d'autrui (Singer *et al.*, 2004; Jackson *et al.*, 2005; Morrison *et al.*, 2004). Ces données appuient l'hypothèse suggérant que l'activité de l'insula reflète l'expérience émotionnelle évoquée par notre réaction à la douleur et constitue les bases neuronales de la compréhension de nos propres sentiments et de ceux d'autrui (Singer *et al*, 2004)

Le cortex cingulaire antérieur (CCA)

Les recherches ont démontré que le CCA participe à plusieurs facettes de l'expérience émotionnelle de la douleur. Tout d'abord, certaines études de cas ont suggéré que des lésions affectant cette région cérébrale résultent parfois en une altération de la perception de la douleur et, plus particulièrement, en une diminution de la réponse émotionnelle à la douleur. Ainsi, il a été démontré qu'une cingulotomie et/ou une capsulotomie antérieures bilatérales réduisent les évaluations subjectives (intensité et désagrément) des patients pour les stimulations faibles ou modérées (Davis *et al.*, 1994; Talbot *et al.*, 1995). Toutefois, une diminution de la latence du retrait de la main d'un bassin d'eau glacée (tolérance) a été observée à la suite de ces traitements chirurgicaux. Ces résultats, qui semblent contradictoires (réduction des évaluations subjectives et diminution de la tolérance), peuvent s'expliquer par une perte des mécanismes descendants du contrôle de la douleur permettant normalement de bloquer les réponses de retrait (désinhibition) (Talbot et al., 1995). Cette interprétation est d'ailleurs appuyée par une étude sur le contrôle oculomoteur manuel ou verbal démontrant un rôle du CCA caudal dans l'inhibition des réponses automatiques (Paus *et al.*, 1993).

Les travaux de Rainville *et al.* (1997) ont contribué à préciser le rôle fonctionnel du CCA. Dans une étude de TEP, ils ont utilisé la suggestion hypnotique pour altérer sélectivement le caractère déplaisant d'une stimulation thermique douloureuse sans changer l'intensité subjective de la douleur. Dans ces conditions, la réponse du CCA

était plus grande lorsque la suggestion augmentait le désagrément de la douleur que lorsqu'elle l'atténuait. De plus, une corrélation positive a été notée entre le débit sanguin cérébral régional dans le CCA et les évaluations subjectives du désagrément. Ces données fournissent des preuves expérimentales directes du lien entre l'activité du système émotionnel cérébral et la composante affective de la douleur. Le CCA jouerait donc un rôle dans l'encodage et la modulation du caractère déplaisant d'une stimulation douloureuse (voir aussi Zubieta *et al.*, 2001). Dans un même ordre d'idées, Tölle *et al.* (1999) ont utilisé la TEP pour comparer l'activation cérébrale suscitée par une stimulation douloureuse prolongée présentée à quatre reprises. Les résultats de cette recherche ont démontré une augmentation significative du caractère déplaisant de la stimulation douloureuse au cours de la troisième et la quatrième présentation. La seule structure cérébrale démontrant une association positive significative avec cet accroissement spécifique du désagrément est la partie postérieure du CCA.

Ploghaus *et al.* (1999) ont également observé une activation significative d'une région frontale incluant le CCA lors de l'anticipation d'une douleur thermique cutanée. Ces données présentent des similarités avec l'étude de Hsieh *et al.* (1999) qui ont démontré une activation du CCA pendant l'anticipation d'une douleur produite par l'injection intracutanée d'éthanol. Toutefois, les chercheurs ont noté une réduction de l'activité cérébrale dans cette région à mesure que la douleur pouvait être de mieux en mieux prédite par les sujets durant la phase d'anticipation. Ainsi, l'activité cérébrale observée dans le CCA pourrait refléter la dimension affective de la douleur et l'anxiété associée à l'anticipation d'un événement aversif imprévisible. Tout comme l'insula, le

CCA jouerait également un rôle dans l'empathie à la douleur. Effectuant des enregistrements unitaires sur des cellules de patients devant subir une cingulotomie, Hutchison *et al.* (1999) ont identifié des neurones dans le CCA qui répondent non seulement à un stimulus douloureux, mais également à l'anticipation ou à l'observation de la même stimulation appliquée sur une autre personne. Des études en imagerie cérébrale ont corroboré ces résultats (Singer *et al.*, 2004; Jackson *et al.*, 2005; Morrison *et al.*, 2004). Dans le modèle théorique de Craig (2002) précédemment exposé, le CCA engendre la motivation affective et l'activité autonomique y étant associée. Critchley *et al.*, (2003) ont aussi démontré le rôle du CCA rostral dans la régulation des réponses autonomique. L'activité du CCA est ainsi fortement reliée à la dimension affective de la douleur, est en mesure d'influencer les réponses motrices et autonomiques associées à la douleur et contribue à la représentation de la douleur d'autrui.

L'amygdale (AMY)

La participation de l'AMY à la douleur pourrait dépendre des liens anatomiques qu'elle entretient avec l'INS et le CCA (Friedman *et al.*, 1986; Augustine, 1996), mais aussi d'une voie directe spino-ponto-amygdalienne (Bernard et Besson, 1990). Bien que l'AMY entretienne une relation avec le système nociceptif cérébral, il existe à ce jour très peu d'études en imagerie démontrant une activation de cette structure pendant la douleur.

Dans une étude en imagerie par résonance magnétique fonctionnelle (IRMf), Schneider *et al.* (2001) ont induit une douleur vasculaire chez leurs sujets normaux.

Durant la stimulation douloureuse, des activations cérébrales ont été observées dans les régions généralement rapportées dans les études sur la douleur en imagerie (Apkarian *et al.*, 2005; Peyron *et al.*, 2000; Laurent *et al.*, 2000), mais également au niveau de l'AMY. En se référant à l'analyse de covariance basée sur les évaluations subjectives de la douleur, les chercheurs proposent que l'activité cérébrale dans les régions émotionnelles sous-corticales, et particulièrement dans l'AMY, représente la composante affective/intrusive particulièrement importante de la douleur vasculaire. D'autres études ont montré un rôle de l'AMY dans le conditionnement aversif (Ledoux, 1992). Toutefois, l'AMY serait activée seulement lors des premiers stades de l'acquisition (e.g., Büchel *et al.*, 1999) ou de l'extinction (LaBar *et al.*, 1998) d'une réponse aversive conditionnée, au moment où une incertitude considérable est présente par rapport à l'appariement du stimulus neutre avec le stimulus aversif. Ainsi, l'AMY pourrait jouer un rôle clé dans l'apprentissage associatif et l'appréhension de la douleur.

Le cortex préfrontal

Freeman et Watts (1948) furent parmi les premiers à observer qu'à la suite d'une lobotomie préfrontale, leurs patients arrêtaient de se plaindre de leur douleur et cela, même s'ils affirmaient que la sensation douloureuse restait présente. Toutefois, ces descriptions cliniques demeurent imprécises. En revanche, tel que décrit précédemment, une diminution de la réponse émotionnelle à la douleur a été bien documentée chez les patients ayant subi une cingulotomie ou une capsulotomie

antérieure bilatérale, des traitements qui affectent les fonctions préfrontales (Davis *et al.,* 1994; Talbot *et al.,* 1995). D'autre part, une étude récente en imagerie cérébrale a suggéré une participation du cortex préfrontal dans l'expérience émotionnelle associée à la douleur. Verne *et al.* (2003) ont utilisé l'IRMf pour étudier les régions cérébrales activées par des stimulations douloureuses viscérales (distension rectale) et cutanées (stimuli thermiques) chez des patients atteints du syndrome du colon irritable et des sujets normaux. Les résultats ont montré que pour les deux types de stimulation, les évaluations subjectives de l'intensité, du désagrément et de l'état émotionnel (peur et anxiété) ainsi que l'activation de certaines régions cérébrales (incluant le cortex préfrontal médian) étaient plus élevées chez le groupe de patients que chez le groupe de sujets normaux. Les chercheurs ont également comparé les données obtenues pour les stimulations viscérale et cutanée les plus intenses chez les patients souffrant du syndrome du colon irritable. Les résultats ont révélé que l'intensité perçue des stimulations viscérales et cutanées était comparable, mais que le désagrément et les réponses émotionnelles négatives (peur, anxiété), ainsi que l'activation dans le cortex préfrontral médian, étaient plus grands pour le stimulus viscéral que pour le stimulus cutané. Ces résultats suggèrent que la peur et l'anxiété ressenties sont associées à l'activation du cortex préfrontal médian et sont davantage reliées à la douleur clinique qu'à la douleur induite expérimentalement. Cette interprétation se comprend d'ailleurs facilement si l'on considère que dans une expérimentation bien contrôlée, les participants savent que les stimulations douloureuses auxquelles ils seront exposées sont temporaires et ne leur causeront aucun dommage corporel, réduisant ainsi les

émotions secondaires comme la peur et l'anxiété. En revanche, des émotions secondaires résultant de l'évaluation de l'implication de la douleur sur la santé et le bien-être sont plus susceptibles d'accompagner la douleur clinique.

Contributions respectives aux dimensions émotionnelles de la douleur

En résumé, plusieurs structures contribuent aux dimensions émotionnelles de la douleur. Certaines régions (thalamus VPL, S1, S2, INS) traitent l'information sensorielle détaillée et transmettent ces informations vers les circuits émotionnelles cérébraux pour participer indirectement aux aspects affectifs de la douleur. Par ailleurs, des régions sous-corticales (AMY) et corticales (INS, CCA) reçoivent directement les signaux nociceptifs ascendants et sont impliquées dans la régulation des réponses motrices et autonomiques et dans les aspects affectifs de la douleur. Ces structures sont en étroite relation avec des régions préfrontales en mesure de contribuer aux dimensions émotionnelles secondaires de la douleur. Réciproquement, les émotions secondaires pourraient influencer l'activité nociceptive des régions cérébrales impliquées dans la douleur.

Les mécanismes cérébraux impliqués dans la modulation émotionnelle de la douleur

Il a été maintes fois observé que l'état émotionnel des patients avait une influence non négligeable sur leur perception de douleur (Haythornthwaite et Bernud-Larson, 2000; Geisser *et al.*, 2000; Keefe *et al.*, 2001; Greenwood *et al.*, 2003). Généralement, ces études démontrent que les états émotionnels négatifs tels que la

dépression, l'anxiété, la frustration, la peur et la colère amplifient l'intensité de la douleur alors que les émotions positives comme la joie la réduisent. (Weisenberg *et al.*, 1998; DeWied et Verbaten, 2001; Meagher *et al.*, 2001; Roy *et al.*, 2003). À ce jour, l'effet modulateur des émotions sur la douleur nous apparaît suffisamment bien documenté sur le plan comportemental (Rhudy et Meagher, 2001, Keefe *et al.*, 2001) pour tenter une intégration de ce phénomène avec les connaissances actuelles de la physiologie des émotions et du système nociceptif.

Les travaux menés par Lang *et al.* (1997) sur l'amorçage motivationnel offrent une base conceptuelle propice à l'élaboration d'un modèle plus détaillé de la modulation émotionnelle de la douleur. Selon cette théorie, les émotions seraient gouvernées par deux systèmes motivationnels antagonistes : le système appétitif, responsable des comportements d'approche, et le système aversif, lié aux comportements de retrait. Bien que la presque totalité des travaux portant sur l'amorçage motivationnel aient utilisé le réflexe de sursaut comme mesure de l'engagement du système défensif, la réponse nociceptive apparaît comme la réponse type de ce système. Ainsi, l'administration de stimulations douloureuses chez l'animal (Davis, 1989) et chez l'humain (Greenwald *et al.*, 1998, Crombez *et al.*, 1997) activent le système défensif et potentialisent le réflexe de sursaut. De plus, des images agréables ou désagréables parviennent à réduire ou à augmenter la douleur ainsi que le réflexe de sursaut, soulignant l'appartenance de ces deux réponses à un système défensif commun (Wunsch *et al.*, 2003). À cet effet, il est intéressant de noter que plusieurs structures sous-corticales responsables du réflexe de sursaut, telles que

l'AMY ou la substance grise périacqueductale (SGPA), font également partie du système nociceptif. Ainsi ces structures semblent cruciales au système défensif et pourrait intervenir dans la modulation de la douleur par les émotions. Il est cependant important de noter que pour Lang *et al.* (1998), le principe de l'amorçage motivationnel s'étend bien au-delà des réflexes et englobe aussi des processus de nature plus cognitive et évaluative, qui dépendraient davantage de mécanismes corticaux. Ainsi, plusieurs structures corticales et sous-corticales pourraient être impliquées dans la modulation émotionnelle de la douleur (tableau 2).

Une des découvertes les plus remarquables des études d'imagerie de la douleur est que toute manipulation qui produit une réduction de la douleur perçue entraîne une diminution de l'activation des aires cérébrales liées à la douleur. De plus, comme il a été souligné précédemment, des manipulations visant à réduire l'affect subjectif de la douleur entraînent des diminutions de l'activité des régions spécifiquement liées à la dimension affective de la douleur (CCA), épargnant les régions liées à sa dimension sensorielle (S1, S2) (Rainville *et al.*, 1997). Ainsi, il est probable que des changements de la dimension affective de la douleur observés lors de la modulation émotionnelle de la douleur (Villemure *et al.*, 2003; Roy *et al.*, 2003) se reflètent par des changements correspondants au niveau du CCA. De plus, les nombreuses connexions qu'entretient le CCA avec l'ensemble du système émotionnel cérébral (Devinsky *et al.*, 1995; Vogt, 2005) suggèrent un rôle prépondérant du CCA dans la modulation émotionnelle de la douleur.

Cortex préfrontal

Le rôle privilégié du cortex frontal dans les réponses émotionnelles a été maintes fois démontré (Gainotti, 1998; Davidson,1992; Heilman, 2000). En effet, le cortex frontal se trouve activé par des stimuli aussi bien positifs que négatifs, et ce, indépendamment de la modalité sensorielle (Royet *et al.*, 2000). Cependant, une méta-analyse récente des études d'imagerie cérébrale des états émotionnels révèle que certaines régions du cortex frontal, comme le cortex préfrontal médian se trouvent davantage activés par les émotions positives alors que d'autres régions, comme le CCA rostral réagissent principalement aux émotions négatives. Bien qu'elles soient fortement interconnectées, ces deux régions présentent des structures cytoarchitecturales bien distinctes, soulignant leurs importantes différences sur le plan fonctionnel (Vogt *et al.*, 1996). Ainsi, le cortex préfrontal médian est associé de façon générale aux mécanismes de récompense (Pochon *et al.*, 2002) et aux comportements d'approche (Robbins et Everitt, 1996). De plus, la stimulation du cortex préfrontal médian inhibe les neurones du noyau basolatéral de l'AMY (Rosenkratz et Grace, 2001; 2002) et son activation se trouve inversement corrélé à celle de l'AMY lors de stimulations aversives (Liberzon *et al.*, 2002). Ainsi, une des fonctions du cortex préfrontal médian pourrait être le contrôle de l'anxiété lors de situations menaçantes (Bishop *et al.*, 2004).

Ce rôle du cortex préfrontal médian dans le contrôle des émotions négatives correspond étonnamment bien aux observations d'une implication de cette structure dans les mécanismes inhibiteurs de la douleur. En effet, l'analgésie placebo ainsi que

l'administration de fentanyl (analgésique opioïdergique) entraînent tous deux une augmentation de l'activité du cortex préfrontal médian associé à une diminution de la douleur (Petrovic *et al.*, 2002). De plus, le niveau d'activation du cortex préfrontal prédit la diminution subséquente de l'activité du CCA associée à l'analgésie placebo (Wager *et al.*, 2004). À ce titre, il est intéressant de noter qu'une des explicitations de l'analgésie placebo attribue la diminution de douleur à l'action des émotions positives induites par l'espoir d'un soulagement (Bootzin et Caspi, 2002). Quoiqu'il en soit, il semble que le cortex préfrontal exerce une influence inhibitrice sur le CCA, réduisant ainsi l'intensité de la douleur perçue. En appui à cette idée, Lorenz *et al.* (2003) ont constaté que l'activité du cortex préfrontal dorsolatéral était inversement corrélée à celle des aires cérébrales de la douleur lors de l'application de stimuli thermiques sur une peau sensibilisée par la capsaïcine. Les auteurs expliquent l'effet antinociceptif du cortex préfrontal dorsolatéral par une inhibition des projections nociceptives thalamo-cingulaire. Ainsi, l'activation du cortex préfrontal par des stimuli agréables, comme la musique consonante (Blood *et al.*, 1999) ou l'odeur d'agrumes (Anderson *et al.*, 2003), pourrait diminuer l'activité des aires cérébrales de la douleur par le biais de ces projections modulatrices.

Par ailleurs, il est important de souligner les importantes connexions qu'entretient le cortex préfrontal avec la SGPA (Cavada *et al.*, 2000). En effet, ces régions se trouvent fréquemment coactivées, autant lors de l'expérience de fortes émotions positives (Blood et Zatorre, 2001) que lors de manipulations visant à réduire la douleur (Petrovic *et al.*, 2002; Wager *et al.*, 2004; Valet *et al.*, 2004). Or, la SGPA, qui

présente une riche innervation opioïdergique, est une des structures centrales des mécanismes d'inhibition descendante de la douleur (Mitchell, Basbaum, & Fields, 2000).

Cortex cingulaire

Le CCA contribue non seulement à la dimension affective de la douleur, mais il est aussi fréquemment activé lors des comportements de retrait en général (Wager *et al.*, 2003). Ainsi, lors de la modulation émotionnelle de la douleur, l'activation du CCA induite par un stimulus aversif et celle suscitée par la stimulation nociceptive pourraient simplement s'additionner et mener à une augmentation du désagrément de la douleur perçue. Un tel mécanisme suggère que le désagrément causé par la douleur et celui causé par un stimulus aversif se trouveraient en quelque sorte confondus au sein du CCA. Par ailleurs, d'autres régions du cortex cingulaire présentant de fortes connexions avec le CCA, comme le cortex cingulaire postérieur (CCP) et le cortex cingulaire subcalleux (CCS), sont également fréquemment sollicitées par les émotions négatives. Ainsi, l'activation du CCP lors de l'écoute de musiques dissonantes (Blood *et al.*, 1999) pourrait exacerber l'activité du CCA lors de l'expérience douloureuse, expliquant l'augmentation du désagrément de la douleur perçue lors de l'écoute de musiques désagréables (Roy *et al.*, 2003). La partie subcalleuse du cortex cingulaire est, quant à elle, systématiquement activée lors de l'expérience de la tristesse (Phan *et al.*, 2002) ainsi que chez les patients dépressifs (Mayberg *et al.*, 2000). Cette proximité

anatomique pourrait en partie expliquer l'exacerbation de la douleur observée lors d'états émotionnels négatifs (Geisser *et al.*, 2000).

Striatum ventral

Étant donné leur riche innervation dopaminergique et leurs importantes connexions avec le cortex frontal, les ganglions de la base et le striatum ventral occupent une place importante dans l'affect positif suscité par la progression vers un but désiré (Davidson et Irwin, 1999, Robbins et Everitt, 1996). Ainsi, ces régions se trouvent activées par divers stimuli induisant des émotions positives (Phan *et al.*, 2002; Wager *et al.*, 2003). Parmi ces structures, le noyau accumbens (Jasmin, Rabkin, Granato, Boudah, & Ohara) est une zone de convergence majeure pour une myriade de structures émotionnelles cérébrales et s'avère essentiel à l'inhibition du réflexe de sursaut (Koch *et al.*, 1996). Ce noyau apparaît donc comme une structure clé de l'effet inhibiteur des émotions positives sur les réponses du système défensif dont la douleur fait partie. En effet, l'expérience de douleur entraîne la libération dans cette structure d'opioïdes endogènes qui réduisent en retour la perception de douleur (Zubieta *et al.*, 2001). En outre, une récente étude d'imagerie montre que l'activité de la partie postérieure du NAc décroît en réponse aux stimulations nociceptives (Becerra *et al.*, 2001) alors qu'elle augmente lors de l'administration de cocaïne ou à la perspective de gains monétaires (Breiter *et al.*, 1997; 2001). Ainsi, l'activité de cette région du NAc semble refléter de façon presque analogique la valence émotionnelle des stimuli, diminuant lors d'émotions négatives et augmentant pendant l'expérience d'émotions

positives. Cette particularité du NAc pourrait en faire un médiateur anatomique des effets des stimuli autant positifs que négatifs sur l'expérience douloureuse (Villemure et Bushnell, 2002).

Amygdale (AMY) et Hippocampe (HIPP)

Bien que les études effectuées chez l'humain montrent généralement une exacerbation de la douleur lors d'émotions désagréables, il arrive que des stimulations produisant une peur intense produisent l'effet inverse (Rhudy et Meagher, 2000). Ces effets contradictoires s'expliqueraient par le fait que les paradigmes expérimentaux utilisés suscitent deux états émotionnels négatifs qualitativement distincts : la peur et l'anxiété (McNaughton et Corr, 2004). Ainsi, la peur, une émotion mobilisant l'organisme afin de réagir à un stimulus menaçant, réduit l'intensité de la douleur. Inversement, l'anxiété, un état affectif servant à faciliter la détection d'un stimulus potentiellement menaçant, produit une augmentation de l'intensité de la douleur. Ces deux états émotionnels se distinguent également sur le plan anatomique: la peur active principalement l'AMY alors que l'anxiété est davantage associée à l'activation de l'hippocampe (HIPP) et du cortex parahippocampique (McNaughton et Corr, 2004). Les mécanismes par lesquels la peur parvient à réduire la douleur sont relativement bien connus. En effet, l'activation de l'AMY lors de l'expérience de la peur déclenche l'action descendante de mécanismes inhibiteurs opioïdergiques via la SGPA (Meagher *et al.*, 1989; Fanselow, 1994). Bien que ce phénomène procure une analgésie importante, son application clinique apparaît problématique pour des raisons

évidentes. En revanche, l'exacerbation de la douleur par l'anxiété est un problème auquel les intervenants de la santé sont confrontés sur une base quotidienne (Keefe *et al.*, 2001). Récemment, Ploghaus *et al.* (2001) ont constaté que l'anxiété suscitée par l'incapacité de prédire l'intensité d'une stimulation nociceptive augmentait la perception de la douleur et l'activation d'un réseau hippocampique. Par conséquent, les interventions visant à réduire l'anxiété, comme la présentation de musiques relaxantes (Khalfa *et al.*, 2002) ou l'utilisation de techniques de relaxation (Good, 1999), pourraient produire des effets analgésiques en réduisant l'activité du réseau hippocampique facilitateur de la douleur.

Conclusion

Nous pouvons constater, à la lumière de toutes ces études, que plusieurs régions cérébrales sont impliquées dans l'expérience émotionnelle reliée à la douleur (déplaisir immédiat et émotions secondaires). D'abord, le thalamus VPL, S1 et S2 semblent jouer un rôle dans la dimension sensorielle de l'expérience douloureuse. En effet, les structures de ce système contribuent surtout aux aspects sensoriels de la douleur (l'intensité par exemple), mais cette composante peut influencer le désagrément immédiat associé à l'expérience douloureuse grâce à certaines projections vers le système émotionnel cérébral. Ces régions cérébrales participent donc à la dimension affective de la douleur grâce à des mécanismes sériels par lesquels les aspects sensoriels de l'expérience douloureuse viennent contribuer au désagrément immédiat qui y est associé. D'autre part, des voies ascendantes

atteignent directement certaines structures corticales et sous-corticales impliquées dans la composante affective de la douleur. Premièrement, le cortex cingulaire antérieur constitue une région centrale qui reçoit plusieurs afférences nerveuses et qui est étroitement associée à l'encodage du désagrément immédiat de la douleur. Deuxièmement, le cortex insulaire peut contribuer à la dimension affective de l'expérience douloureuse, particulièrement dans la régulation du système nerveux autonome. Troisièmement, l'amygdale serait surtout impliquée dans l'incertitude associée à l'expérience douloureuse. Ces régions cérébrales reçoivent donc l'information nociceptive en parallèle et participent vraisemblablement à la dimension affective de la douleur. Ces différentes structures seraient davantage liées au caractère déplaisant immédiat de l'expérience douloureuse. Les données de la littérature suggèrent également que le cortex préfrontal serait impliqué lorsque la douleur est accompagnée de fortes émotions négatives. Par ailleurs, nous avons pu voir que les régions cérébrales impliquées dans l'expérience d'émotions peuvent influencer l'activité du système nociceptif cérébral. Bien que cette modulation émotionnelle de la douleur soit suffisamment documentée sur le plan comportemental, les mécanismes physiologiques responsables de ce phénomène restent à ce jour peu connus. Par ses nombreuses connexions avec le système émotionnel cérébral, le cortex cingulaire antérieur, associé à la dimension affective de la douleur, apparaît comme une structure clé dans l'influence des émotions sur l'expérience douloureuse. Ainsi, plusieurs structures des systèmes émotionnels appétitifs et défensifs, tels que le cortex préfrontal, le noyau accumbens, le cortex

cingulaire postérieur, le cortex cingulaire subcalleux et l'hippocampe, sont susceptibles de moduler l'activité du cortex cingulaire antérieur et le désagrément de la douleur lui étant associé. Cependant, ces hypothèses devront faire l'objet d'études supplémentaires afin de préciser l'influence respective de chacune de ces structures sur l'expérience de douleur. Nous espérons qu'une meilleure compréhension des mécanismes impliqués dans les effets des émotions sur l'expérience douloureuse facilitera leur intégration aux interventions cliniques de contrôle de la douleur.

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Figures et tableaux

(a) **(b)**

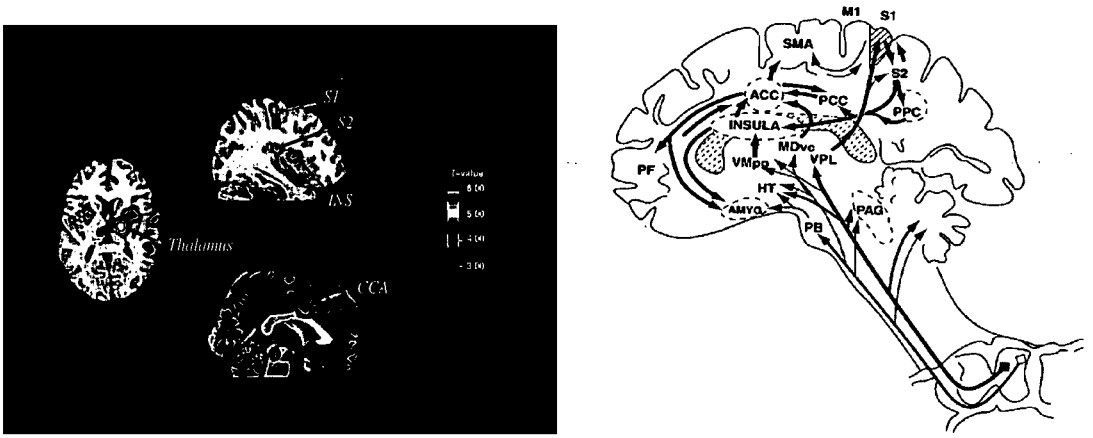

Figure 1. – *Structures cérébrales impliquées dans les processus de la douleur : (a) Principaux sites d'activation détectés dans les études en neuroimagerie (b) Schématisation des multiples voies ascendantes du système nociceptif et des interactions entre les régions corticales (tiré de Price, 2000).*
Cerebral structures involved in pain processings: (a) Principal activation sites detected in neuroimaging strudies (b) Schematic of ascending pathways of the nociceptive system and cortical interactions (from Price, 2000).

Abréviations : ACC = cortex cingulaire antérieur; AMYG = amygdale; HT = hypothalamus; M1 = cortex moteur primaire; MDvc = partie ventrocaudale du noyau médiodorsal du thalamus; PAG = substance grise périacqueductale; PB = noyau parabrachial; PCC = cortex cingulaire postérieur; PF = cortex préfrontal; PPC = cortex pariétal postérieur; S1 = cortex somesthésique primaire; S2 = cortex somesthésique secondaire; SMA = aire motrice supplémentaire; Insula = cortex insulaire; VMpo = partie postérieure du noyau ventromédian du thalamus; VPL = noyau ventro-postéro-latéral du thalamus

Tableaux 1 et 2

Tableau 1 – Contribution de différentes régions cérébrales aux dimensions fonctionnelles de la douleur

Contribution of different cerebral regions to the functional dimensions of pain

Structure	Fonction
S1/S2	Encodage sensoriel, contribution indirecte à l'affect primaire
INS	Encodage sensoriel, contribution indirecte à l'affect primaire, contribution directe à l'affect secondaire, régulation autonomique, intéroception, représentation de la douleur d'autrui (empathie)
CCA	Contribution directe à l'affect primaire, régulation motrice (CCA caudal) et autonomique (CCA rostral), anticipation, représentation de la douleur d'autrui (empathie), attention
AMY	Contribution à l'affect primaire, conditionnement aversif, appréhension de la douleur
CPF	Affect secondaire, cognition, attention

Abréviations : S1 = cortex somesthésique primaire; S2 = cortex somesthésique secondaire; INS = cortex insulaire; CCA = cortex cingulaire antérieur; AMY = amygdale; CPF = cortex préfrontal

Tableau 2 - Régions cérébrales impliquées dans les émotions et la modulation de la douleur

Brain regions involved in emotions and pain modulation

Structure	Fonction émotionnelle	Influence sur la douleur
CPFM	Émotions positives, mécanismes de récompense, contrôle de l'anxiété	Diminution de douleur
CCA/CCP/CCS	Émotions négatives	Augmentation de douleur
SGPA	Émotions positives et négatives intenses	Diminution de douleur
Striatum	Émotions positives, anticipation récompense	Diminution de douleur
Gyrus parahippocampique	Anxiété, émotions négatives	Augmentation de douleur
AMY	Peur, émotions négatives	Diminution de douleur

Abréviations : CPFM = cortex préfrontal médian; CCA = cortex cingulaire antérieur; CCP = cortex cingulaire postérieur; CCS = cortex cingulaire subcalleux; SGPA = substance grise périacqueductale; AMY = amygdale;

Article 2: Emotional valence contributes to music-induced analgesia

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Emotional valence contributes to music induced analgesia

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Running head: Emotional valence contributes to music induced analgesia

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Abstract

The capacity of music to soothe pain has been used in many traditional forms of medicine. Yet, the mechanisms underlying these effects have not been demonstrated. Here, we examine the possibility that the modulatory effect of music on pain is mediated by the valence (pleasant-unpleasant dimension) of the emotions induced. We report the effects of listening to pleasant and unpleasant music on thermal pain in healthy human volunteers. Eighteen participants evaluated the pain or warmth induced by 40,0°C, 45,5°C, 47,0°C or 48,5°C thermal stimulations applied to the skin of their forearm while listening to pleasant and unpleasant musical excerpts matched for their high level of arousal (relaxing-stimulating dimension). Compared to a silent control condition, only the pleasant excerpts produced highly significant reductions in both pain intensity and unpleasantness, demonstrating the effect of positive emotions induced by music on pain (Pairwise contrasts with silence: $p's<0.001$). Correlation analyses in the pleasant music condition further indicated that pain decreased significantly ($p's<0.05$) with increases in self-reports of music pleasantness. In contrast, the unpleasant excerpts did not modulate pain significantly, and warmth perception was not affected by the presence of pleasant or unpleasant music. Those results support the hypothesis that positive emotional valence contributes to music-induced analgesia. These findings call for the integration of music to current methods of pain control.

1.Introduction

Since ancient times, humans have attributed to music the capacity to cast out the malignant spirits causing sickness and suffering (K. E. Gfeller, 2002). Music was an integral part of the healing process in many cultures and still is an important component of many primitive forms of medicine. Nowadays, music therapy is emerging as an evidence-based discipline with the explicit goal to re-introduce music into modern medical settings. Among the many alleged benefits of music, pain reduction is one that has spurred the most early and constant interest. In a seminal study, Gardner, Licklider and Weisz (Gardner et al., 1960) reported that music was effective in reducing the pain of 90 percents of 5,000 patients undergoing dental surgery. This original finding has since been replicated several times with a wide diversity of clinical populations (Cepeda, Carr, Lau, & Alvarez, 2006a; Good et al., 2005; McCaffrey & Freeman, 2003; Nilsson et al., 2005; Phumdoung & Good, 2003; Tse, Chan, & Benzie, 2005a; Voss et al., 2004). In these studies, pain is reduced in patients receiving a musical intervention in addition to standard care, as compared to those receiving only standard care. Although this evidence supports the use of music in clinical settings, it does not demonstrate any specificity of this intervention and does not inform about the mechanisms of action. Because these clinical studies only compared the effects of music with a control condition without music, distraction appears to be the most parsimonious explanation of the observed analgesic effects of music.

Another account of the analgesic properties of music lies in its ability to induce strong positive emotions. Indeed, a recent meta-analysis on musical mood inductions procedures has revealed that musically-induced emotions could influence a wide range of cognitive abilities (Vastfjall, Larsson, & Kleiner, 2002), placing music among the most effective inducers of emotion (Westermann, Spies, Stahl, & Hesse, 1996). Thus, emotional reactions to music might be a key component explaining music-induced analgesia. Indeed, pain has been previously shown to be modulated by emotions induced by pictures (Meagher, Arnau, & Rhudy, 2001a), films (Weisenberg et al., 1998),

emotional sentences (Zelman et al., 1991), odors (Villemure et al., 2003), or hypnosis (P. Rainville, Q. V. Bao, & P. Chretien, 2005). In these studies, pleasant emotions are generally found to reduce pain while unpleasant ones tend to increase it. These results can not be solely explained by an effect of distraction because unpleasant emotional stimuli, which are also distractive, do not reduce pain. We adopted the same logic here and studied the pain-modulating effects of positive and negative emotional reactions to music.

Here, the pain induced by thermal stimulations was assessed while participants listened to musical excerpts selected to differ on the valence dimension (pleasant vs. unpleasant) and carefully matched on arousal (relaxing vs. stimulating). Non-painful thermal stimuli were included to account for non-specific effects of distraction on thermal perception (see (Bushnell, Duncan, Dubner, Jones, & Maixner, 1985b)). Based on the hypothesis that the emotional valence of music contributes to changes in pain, we hypothesized that pleasant excerpts would reduce pain whereas unpleasant ones would increase it.

2. Methods

2.1 Participants

Eighteen participants (9 men, 9 women), aged between 19 and 39 years (mean = 27, SD = 6) took part in this study. Subjects were recruited using ads posted throughout the campus of the University of Montreal. None of them had followed advanced musical training or had previously participated to other pain studies. Participants were also screened for the absence of skin problems, psychiatric or neurological disorders and chronic pain. Moreover, they had not consumed any analgesic medication in the 24 hours preceding the experiment.

2.2 Musical excerpts

Three 5-min excerpts of pleasant music and three 5-min excerpts of unpleasant music were selected from a pool of 30 musical excerpts. Each of the 30 excerpts had been previously evaluated by 20 independent participants on the dimension of valence (on a scale ranging from 0 to 9 with 0 – 'pleasant' and 9 – 'unpleasant') and arousal (with 0 – 'relaxing' and 9 – 'stimulating'). Three highly pleasant and three highly unpleasant excerpts were selected that matched on their level of arousal. Since unpleasant excerpts were always judged to be arousing, all excerpts were selected on the high range of arousal. Pleasant excerpts were judged to be more pleasant than unpleasant excerpts (mean valence for pleasant excerpts = 2.40, mean valence for unpleasant excerpts = 6.68; $t(19) = 5.58$, $p<0.05$) and did not differ in arousal (mean arousal for pleasant excerpts = 5.00, mean arousal for unpleasant excerpts = 5.18; t (19) = 1.535, $p>0.05$, n.s.). All selected excerpts were normalized to equate loudness range across musical excerpts.

2.3 Thermal stimuli

The thermal stimulations were produced by a 3cm x 3cm contact thermode (TSA Neuro-sensory analyser, Medoc Ltd. Advanced Medical system, Israel). Four temperatures were selected: one non-painful (40°C) and three painful (45.5°C, 47°C, 48.5°C). Subjects were not informed of the number of levels. Each stimulation consisted in a plateau of 6 seconds with a rise/fall time of 2 seconds from/to a baseline temperature of 32°C, leading to a total stimulus duration of 10 seconds. Stimuli were applied alternatively on three spots on each forearm.

2.4 Measures

Thermal stimuli were evaluated using numerical rating scales (Rainville et al., 1992). After each stimulus, participants indicated whether the stimulation received was

painful or not. Subjects then rated the stimuli on a scale ranging from 0 – 'no heat' to 100 – 'extremely warm' (not painful). Painful stimuli were rated on separate scales of pain intensity and unpleasantness ranging from 0 –'no pain' to 100 – 'extremely intense' or 'extremely unpleasant'. Subjects were allowed to give ratings higher than 100 on both pain scales if necessary (see Rainville et al., 1992).

In order to verify that the selected excerpts induced the intended emotions in the experimental sample, participants were explicitly asked *to rate the emotional state experienced* on the dimensions of valence (0 – 'pleasant', 9 – 'unpleasant') and arousal (0 – 'relaxing', 9 – 'stimulating'). The moods induced in each experimental condition were also assessed using the Profile Of Mood States (POMS; McNair et al., 1992). The POMS is a questionnaire comprising 30 items, each consisting of an emotional adjective for which subjects have to rate to what extent it describes their current mood (0 – 'not at all', 4- 'extremely'). Six emotional sub-scales can be derived from the 30 items: Tension, Depression, Anger, Vigor, Fatigue and Confusion. Subjects also rated the *perceived emotional intention* conveyed by each musical excerpt separately, at the end of the experiment, on scales of sadness, happiness, fear, anger, peacefulness and surprise (0 – 'not at all' to 9 – 'extremely'). While the valence, arousal and POMS scales were specifically used to measure the emotional states induced in the participants, ratings of perceived emotional intention were used to confirm that subjects could recognize consistently the emotions conveyed by each excerpt.

2.5 Procedure

At their entrance in the laboratory, participants were briefly told that the study investigated the effects of music on pain and that they would be asked to evaluate the sensations induced by heat stimulations, while listening to music. Then, they were familiarised with the thermal stimuli and evaluation scales by rating 8 thermal stimuli (twice each temperature) on the warmth or pain scales. After this practice block, the musical excerpts were presented using headphones (SONY MDR-CD370) at a

comfortable, individually-adjusted, intensity level that remained constant across pleasant/unpleasant music conditions. Each silence, pleasant music, and unpleasant music conditions lasted 15 minutes. In order to create audio-clips of 15-min of pleasant music and 15-min of unpleasant music, the three 5-min excerpts of the same type were presented successively. The order of presentation of the 15-min blocks of pleasant music, unpleasant music or silence was counterbalanced between subjects so that each condition occurred in the first, second or third position for an equal number of subjects.

The stimulation paradigm is described in Figure 1. During each 5–min musical excerpt or each 5-min period of silence, the subjects first listened passively to the music or sat in silence for 140 sec. During the next 160 sec, they received a series of 8 thermal stimulations. The presentation orders of the thermal stimuli were counterbalanced so that, in each experimental condition, each spot of skin received all four temperatures and no spot was stimulated in successive trials. Participants rated the warmth or pain intensity and unpleasantness in the 10-sec window after each thermal stimulus. After each musical excerpt and each 5-min silent period, participants also rated the valence and arousal of the emotions felt in the condition. After each 15-min experimental condition, participants rated their mood using the POMS. At the end of the experiment, participants listened again to each of the 5-min musical excerpts to rate the emotional intention expressed in the music.

3. Results

We first verified that the musical excerpts had the expected effects on arousal and valence and we further describe their effects on moods and the perceived emotional intention. Then, we report the effect of the pleasant and unpleasant excerpts on pain. Finally, we explore the potential mediator of the observed effect using correlation analyses. Partial eta-squared (η^2) was used as the effect size for ANOVAs and Cohen's *d* was used for pairwise contrasts (adjusted for r and using Hedges' bias correction).

Cohen (1988) provides guidelines for interpreting η^2 (small = .01, medium = .06, large = .14) and *d* (small = .2, medium = .5, large = .8).

3.1. Mood induction

The mean valence and arousal ratings of the pleasant music, unpleasant music and silence conditions were first compared to assess the efficacy of the induction of emotion by music. The analysis confirmed that the chosen excerpts induced the expected emotions. The pleasant and unpleasant excerpts differed significantly on the dimension of valence (pairwise contrast: F(1,17) = 86.24, p< 0.001, d=3.02, confidence interval: 2.06 to 3.97) (Table 1). Pleasant and unpleasant excerpts were also respectively more (pairwise contrast: F(1,17) = 8.67 p< 0.01, d=1.22, confidence interval: 0.51 to 1.93) and less (pairwise contrast: F(1,17) = 26.01, p< 0.001, d=2.58, confidence interval: 1.69 to 3.46) pleasant than the silence condition. In contrast, pleasant and unpleasant musical excerpts did not differ from each other on the dimension of arousal (pairwise contrast: F(1,17) = 2.41, p=0.14, ns, d=0.41, confidence interval: -0.25 to 1.07) but both conditions were felt as significantly more stimulating than the silence condition (pairwise contrast for pleasant music: F(1,17) = 17.37, p< 0.001, d=1.33, confidence interval: 0.61 to 2.05; pairwise contrast for unpleasant music: F(1,17) = 32.62, p< 0.001, d=1.58, confidence interval: 0.83 to 2.33).

Music also had some effects on reported moods as measured by the Profile of mood states questionnaire (POMS; Table 1) completed at the end of each 15-min condition. The effects of each experimental condition on participants' mood were assessed by conducting separate analysis of variance on each of the 6 sub-scales (Anger, Depression, Fatigue, Anxiety, Vigor, Confusion). Only the anger and anxiety scales were found to vary across experimental conditions (Anger: $F(2, 34) = 5.96$, $p<0.001$, $\eta^2=0.445$; Anxiety: $F(2, 34) = 3.35$, $p<0.05$, $\eta^2=0.165$). Anger was lower after the pleasant music condition than after the unpleasant music (pairwise contrast: $F(1, 17) = 13.62$, $p<0.01$, d=1.37, confidence interval: 1.10 to 2.67). Anxiety was lower after the pleasant music

condition compared to the silence condition (pairwise contrast: $F(1, 17) = 4.32$, $p<0.05$, d=1.03, 0.33 to 1.72).

Ratings of the emotional intention conveyed by the music were consistent with the valence of the excerpt (Table 1). Positive emotional intention, like happiness and peacefulness, were rated higher for pleasant excerpts than for unpleasant ones (Happiness: $t(17) = 5.33$, $p<0.001$, d=2.53, confidence interval: 1.65 to 3.40; Peacefulness: $t(17) = 4.62$, $p<0.001$, d=1.75, confidence interval: 0.99 to 2.52). Conversely, negative emotions, comprising sadness, fear and anger, were higher for the unpleasant excerpts (Sadness: $t(17) = -5.07$, $p<0.001$, d=1.89, confidence interval: 1.10 to 2.67; Fear: $t(17) = -5.24$, $p<0.001$, d=1.81, confidence interval: 1.03 to 2.59; Anger: $t(17) = -5.11$, $p<0.001$, d=1.67, confidence interval: 0.92 to 2.43). Finally, surprise, which can be either positive or negative, was found to be equally present in pleasant and unpleasant excerpts (Surprise: $t(17) = 0.21$, $p>0.05$, n.s., d=0.43, confidence interval: -0.22 to 1.09).

3.2. Pain and warmth ratings

The warmth, pain intensity and pain unpleasantness ratings were averaged separately for each of the four temperatures and in each condition. When a stimulus in the noxious range of temperature (≥45.5°C) was not felt as painful (i.e. rated on the warmth scale), a pain rating of 0 was attributed to that stimulation. This happened in 47% of the 45.5°C stimulations, 27% of the 47.0°C stimulations and 9% of the 48.5°C stimulations. The mean ratings of pain intensity and unpleasantness were then compared across experimental conditions and painful temperatures (Table 2). As expected, pain ratings increased with temperature (Intensity: $F(2, 34) = 62.50$, $p<0.001$, $\eta^2=0.786$; unpleasantness: $F(2, 34) = 41.39$, $p<0.001$, $\eta^2=0.709$), indicating that the participants could discriminate the thermal stimuli. More importantly, pain ratings differed significantly across the music conditions (intensity: $F(2, 34) = 6.15$, $p<0.001$, $\eta^2=0.266$; unpleasantness: $F(2, 34) = 6.11$, $p<0.01$, $\eta^2=0.264$). Both intensity and

unpleasantness ratings were lower during pleasant music compared to unpleasant music (pairwise contrasts: intensity: F (1,17) = 6.01, p< 0.05, d=0.89, confidence interval: 0.21 to 1.58; unpleasantness: F(1,17) = 6.63, p< 0.05, d=0.69, confidence interval: 0.02 to 1.37) and compared to silence (pairwise contrast: intensity: F(1, 17) = 18.69, p<0.001, d=1.66, confidence interval: 0.90 to 2.42; unpleasantness: F(1, 17) = 19.29, p<0.001, d=2.02, confidence interval: 1.21 to 2.82). In contrast, pain ratings did not differ significantly between the unpleasant music and the silence condition (pairwise contrasts: intensity: F(1,17) = 0.39, *p*>0.05, n.s., d=0.12, confidence interval: -0.53 to 0.77; unpleasantness: F(1,17) = 0.12, *p*>0.05, n.s., d=0.21, confidence interval: -0.45 to 0.86). Examination of Table 2 indicates very small reductions in pain compared to silence, infirming the hypothesized pain-enhancing effect of unpleasant music. Taken together, these results provide very strong evidence in favor of the main hypothesis of an effect of the valence of music on pain; however, only the analgesic effect of pleasant music was confirmed.

For all temperatures and conditions, pain unpleasantness was always lower than pain intensity (*F*(1, 17) = 16.90, p<0.001, η^2=0.498). However, no interaction was found with the pain dimension (intensity or unpleasantness), suggesting comparable effects of music and temperature on pain intensity and pain unpleasantness (interaction with temperature: *F*(2, 34) = 2.65, *p*>0.05, n.s., η^2=0.135; interaction with condition: *F*(2, 34) = 1.05, *p*>0.05, n.s., η^2=0.029).

Finally, warmth ratings obtained for the innocuous temperature (40°C) were also averaged for each experimental condition. In 12% of the 40°C stimuli, the innocuous heat was rated as painful and a warmth rating of 100 was attributed to those trials. The warmth ratings were then compared across the three experimental conditions. No effect of experimental condition was found on warm sensation intensity (*F*(2, 34) = 0,51, *p*>0.05, n.s., η^2=0.029).

3.3. Correlation analyses

In order to examine the influence of inter-individual differences in the emotions induced by the pleasant music on pain modulation, each subject's changes in pain ratings for the most painful temperature (48.5°C) were correlated with changes in their valence ratings. These correlations were not performed on the 45.5°C and 47°C stimulations because of the high percentage of stimuli not rated as painful within those temperature conditions (see section 3.2 Pain and warmth ratings). The change scores were calculated by subtracting the ratings obtained during the silence condition from the ratings of the pleasant music conditions. Inter-individual differences in valence ratings significantly predicted pain ratings, independently from differences in arousal ratings (partial correlations on valence controlling for arousal ratings: intensity: $r = 0.58$, $p<0.05$; unpleasantness, $r = 0.63$, $p<0.05$). Thus, the analgesic effects of pleasant music were most effective in participants that reported feeling highly pleasant emotions in response to music. In addition, inter-individual differences in arousal ratings also predicted pain rating, independently from differences in valence ratings (partial correlations controlling for valence ratings: intensity: $r = 0.59$, $p<0.05$; unpleasantness, $r = 0.49$, $p<0.05$). This means that the participants that felt the least stimulated while listening to the arousing pleasant music showed the largest reductions in pain. Similar analyses performed on the effects of unpleasant excerpts did not reveal any significant effect of valence or arousal (all p's > 0.05). Taken together, those effects are consistent with the reduction of pain observed specifically in the positive valence condition.

4. Discussion

The results show that music induces emotions and modulates the experience of pain. The pleasant and unpleasant excerpts induced the corresponding emotional valence and similar levels of arousal. Participants also felt less anxiety and anger after listening to pleasant music. Finally, the perceived emotional intention conveyed in the excerpts was consistent with their emotional valence. These results confirmed that the selected pleasant and unpleasant musical excerpts conveyed positive and negative emotions and induced the corresponding emotional states in the participants, while adequately controlling for the arousal dimension.

Pleasant music was found to reduce pain compared to both unpleasant music and silence. Moreover, subjects reporting larger increases in valence also reported the largest decreases in pain. In contrast, unpleasant music did not affect pain and there was no correlation between variations in pain and valence in this condition. Those results therefore confirmed that the analgesic effect of pleasant music is associated with positive valence but did not confirm the hypothesised effect of unpleasant music on pain perception.

Secondary analyses also suggested an involvement of arousal in the modulation produced by music. In addition to the analgesic effect of positive valence, partial correlation analyses performed between-subjects in the pleasant music condition indicated that participants reporting being less stimulated on the arousal scale also reported less pain. This was again not true for unpleasant excerpts. However, because our pleasant musical stimuli were all in the stimulating range, to match with highly arousing unpleasant excerpts, we cannot draw conclusion about a broader range of music-induced arousal. Future studies should include a comparison between pleasant-relaxing and pleasant-stimulating music to test the full extent of this effect.

The alternative explanation of music-induced analgesia in terms of attentional mechanisms appears insufficient to explain the present finding. First, the participants were instructed to direct their attention to the thermal stimuli in order to evaluate them. This procedure differs considerably from those used in studies examining the effects of distraction on pain and in which subjects are typically asked to ignore pain in order to process competing stimuli and perform a difficult task (Miron, Duncan, & Bushnell, 1989; Valet et al., 2004). Furthermore, in divided attention conditions where subjects are required to process both pain and a competing stimulus, the distraction effect on pain perception has been found to disappear (Miron et al., 1989). This is consistent with the primacy of pain processing in the absence of explicit demand to direct attention away from pain. In our experiment, music excerpts are likely to have acted more as a background inducer of emotion than as an active distractive task. A second argument is the absence of effect on warmth perception. Comparable effects of attention have been previously reported on the perception of painful and non-painful thermal sensations (Bushnell et al., 1985b). Here, the absence of changes in warmth perception is unlikely to be due to a lack of power as the effect size was modest compared to the very large effects of pleasant music on pain. The emotional valence of the music, rather than its distractor value, appears to be the most likely mediator of the analgesic effect of the pleasant music.

Additional factors that may contribute to the analgesic effect observed include expectations (e.g. : (Charron, Rainville, & Marchand, 2006; Goffaux P, 2007; Price et al., 1999) Here, multiple temperatures were administered to minimize the predictability of the pain sensation, thereby reducing (although not eliminating) this potential confounding effect. The robust stimulus-response function demonstrates that subjects did rely on their sensation to rate pain. Furthermore, contrary to the hypotheses there was a slight (non-significant) *decrease* in pain during unpleasant music; a finding inconsistent with a widespread effect of expectations induced in favour of the hypotheses. Nevertheless, it is possible that expectations contributed specifically to the

analgesic effect in the pleasant music condition. Interestingly, a structural equation modeling approach recently suggested that expected pain partly depends upon the emotional state of the patient before a painful dental procedure (Gedney JJ, 2007). The relative contribution of emotion and expectation and their interaction should be addressed in future experimental studies.

In comparing the effects of pleasant and unpleasant music at similar levels of arousal, our study is the first to highlight the role of emotional valence in music-induced analgesia. The only two studies that have used a similar experimental design have not controlled for arousal. In one prior study (Hekmat & Hertel, 1993), an advantage of preferred music over non-preferred music was obtained in music-induced analgesia. However, the analgesic effect could be due to inter-individual differences in arousal. Moreover, the possibility to choose the music in the preferred music condition leads to a heightened sense of control. In the other study where the possibility to choose the music was controlled for (Perlini & Viita, 1996), the superiority of the pleasant music could be ascribed to differences in arousal and distraction. By controlling the arousal of the musical excerpts and by adding a non-painful control condition, our study provides a more direct demonstration of the involvement of emotional valence in music-induced analgesia. Of course, the present results should not be interpreted as an absence of potential effects of arousal or attention but rather as a demonstration of a specific contribution of emotional valence to music-induced analgesia. Future studies should further examine the potential interaction between arousal and valence and the potential contribution of expectation in music-induced analgesia.

Overall, our results are consistent with previous studies on the effect of pain-unrelated emotional stimuli, including the fact that the unpleasant music condition did not increase pain significantly (see Rainville, 2004). This is a common finding. Negative emotional stimuli produce inconsistent pain-modulating effects (Villemure & Bushnell, 2002). Several studies have observed little or no augmentation of pain during the

presentation of unpleasant emotional stimuli (de Wied & Verbaten, 2001; Weisenberg et al., 1998). The reasons for these unstable pain-modulating effects of unpleasant stimuli remain speculative. One possibility is that unpleasant music was insufficient to induce negative moods. Although the participants reported feeling more unpleasant emotions after the unpleasant excerpts, most POMS sub-scales were not affected by this musical condition. Another possibility is that unpleasant stimuli might trigger both inhibitory and facilitatory pain processes (J. L. Rhudy & Meagher, 2000). In that perspective, stimuli that induce moderate levels of stress or negative emotions might produce a moderate activation of inhibitory mechanisms which may counteract pain enhancing effects of negative emotions.

Contrary to prior studies (P. Rainville et al., 2005; Villemure et al., 2003), unpleasantness ratings were not more affected than intensity ratings by the emotions conveyed by music. This may be due to the short time our participants had to evaluate each thermal stimulation (approximately 10 seconds). In order to speed up their ratings, participants might have judged intensity and unpleasantness in parallel. In the other two studies, participants had unlimited time. However, previous studies did not compare the effects of emotion on pain intensity and unpleasantness statistically. We thus provide a stricter test of the differences between pain intensity and unpleasantness. Another possibility is that the slower and more global retrospective ratings used in previous studies have introduced an additional memory dimension to the rating process which may differentially affect the sensory and affective evaluation of pain.

At a broader level, our results fit partly with the model of motivational priming (Lang, Bradley, & Cuthbert, 1998). According to this theory, responses of the defensive emotional system, will be inhibited by pleasant stimuli and enhanced by unpleasant ones. For example, the amygdala and the periacqueductal gray matter (PAG) appear to be key structures mediating the affective modulation of the startle reflex, a defensive

reaction to a strong and sudden stimulus (usually a loud white noise; (Vrana, Spence, & Lang, 1988; Walker, Cassella, Lee, De Lima, & Davis, 1997). Activation of this system by emotional stimuli may further activate descending pathways as suggested by the modulation of the spinally-mediated nociceptive (RIII) reflex reported in a recent study (J. L. Rhudy, A. E. Williams, K. M. McCabe, M. A. Nguyen, & P. Rambo, 2005). Interestingly, emotional reactions to music may also activate the PAG and other brain structures related to pain modulation such as the amygdala, the prefrontal cortex or the cingulate cortex (Blood & Zatorre, 2001b; Blood, Zatorre, Bermudez, & Evans, 1999; S. Koelsch, Fritz, DY, Muller, & Friederici, 2005). Moreover, there is evidence that emotional reactions induced by music involves endogenous opioids (Goldstein, 1980) and that music listening can increase the expression of mu opiate receptors (Stefano, 2004) and the secretion of serotonin (Evers, 2000). These mechanisms may contribute to the analgesic effect of pleasant music.

By its ability to induce strong positive emotions, music is more than just a distraction. In our study, pleasant music relieved pain by up to 18% for the most painful temperature, which is comparable to some effects of classic analgesic drugs such as NSAIDs (e.g. (Tanabe, Ferket, Thomas, Paice, & Marcantonio, 2002). Considering the availability, simplicity, and low cost, of musical interventions combined with the absence of any side effect, music appears to be of particular interest for pain management.

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Table 1

Table 1
Within-subject comparison of the mean (SD) ratings of the emotional states experienced in the three experimental conditions and of the emotional intention conveyed by pleasant and unpleasant music

Dependant variable	Result of statistical test	Pleasant music	Unpleasant music	Silence
Emotional dimension				
Valence	$F_{(2,34)} = 32.40$, p<0.001	2.25^{ab} (±1.87)	7.04^{bc} (±1.76)	3.97^{ac} (±1.32)
Arousal	$F_{(2,34)} = 17,30$, p<0.001	5.36^{b} (±2.33)	6.31^{b} (±1.92)	2.85^{ac} (±1.37)
POMS subscales				
Anger	$F_{(2,34)} = 5.32$, p<0.01	3.10^{a} (± 2.29)	4.09^{c} (± 3.86)	3.72 (± 3.05)
Depression	$F_{(2,34)} = 0.80$, p=n.s.	3.18 (± 1.64)	3.03 (± 1.58)	1.71 (± 3.21)
Fatigue	$F_{(2,34)} = 0.50$, p=n.s.	2.54 (± 3.87)	2.50 (± 3.61)	3.16 (± 3.88)
Anxiety	$F_{(2,34)} = 3.36$, p<0.05	2.35^{b} (± 1.71)	2.87 (± 2.81)	2.80^{c} (± 3.06)
Vigor	$F_{(2,34)} = 0.77$, p=n.s.	4.38 (± 4.59)	3.91 (± 4.82)	4.75 (± 4.93)
Confusion	$F_{(2,34)} = 0.79$, p=n.s.	2.18 (± 3.93)	2.46 (± 4.22)	4.34 (± 2.45)
Emotional Intention				
Sadness	$t(17) = 5.07$, $p<0.001$	0.61 (± 0.60)	3.29 (± 2.39)	----------
Happiness	$t(17) = 5.33$, $p<0.001$	6.53 (± 1.84)	2.51 (± 2.01)	----------
Fear	$t(17) = 5.24$, $p<0.001$	0.47 (± 0.61)	4.45 (± 3.11)	----------
Anger	$t(17) = 5.11$, $p<0.001$	0.75 (± 1.21)	3.49 (± 2.02)	----------
Peacefulness	$t(17) = 4.62$, $p<0.001$	3.63 (± 2.19)	0.78 (± 1.13)	----------
Surprise	$t(17) = 0.21$, n.s.	3.65 (± 2.00)	4.37 (± 2.34)	----------

a-c: Follow-up pairwise contrasts. a: significantly different from unpleasant music, b: significantly different from silence, c: significantly different from pleasant music .

Table 2

Table 2
Mean (±SD*) ratings of warmth or pain for each temperature and experimental condition

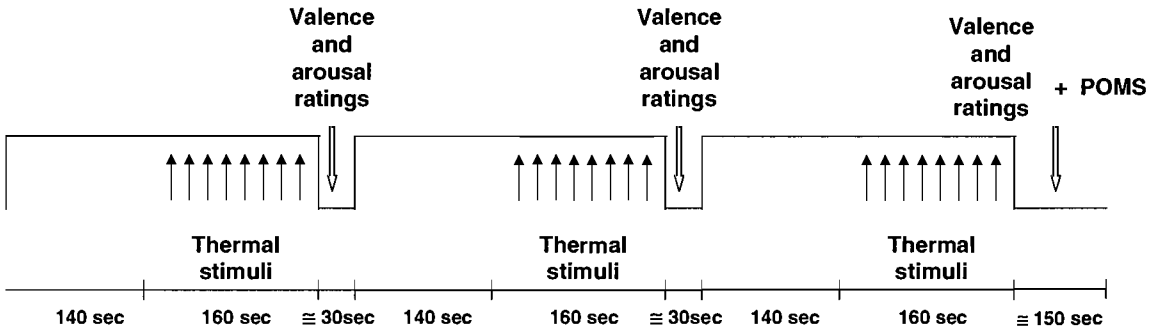
Experimental condition	Warmth ratings	Pain intensity ratings			Pain unpleasantness ratings		
	40°C	45,5°C	47°C	48,5°C	45,5°C	47°C	48,5°C
Pleasant music	34.26 (±25.65)	16.86^{b} (±16.35)	34.03^{b} (±22.16)	57.68^{ab}(±27.71)	12.82^{b} (±14.59)	27.06^{b} (±18.64)	47.84^{ab}(±27.59)
Unpleasant music	38.07 (±25.24)	22.29 (±23.89)	39.13 (±23.39)	68.62^{c} (±23.05)	17.93 (±21.56)	32.26 (±21.84)	60.10^{c} (±26.26)
Silence	36.70 (±27.10)	25.05^{c} (±23.37)	39.13^{c} (±25.99)	69.66^{c} (±30.43)	20.74^{c} (±22.42)	32.65^{c} (±24.42)	59.96^{c} (±31.93)

a-c: Follow-up pairwise contrasts. a: significantly different from unpleasant music, b: significantly different from silence, c: significantly different from pleasant music.
*Note that SD reflect the between-subjects variance within each condition whereas the results of the statistical test reflect the within-subject contrast across experimental conditions

Figure captions

Fig. 1. Time course of audio and thermal stimuli in one experimental condition. Participants listened passively to either music or silence for 300 sec. In the last 160 sec of each period, they rated the pain or warmth induced by each of 8 thermal stimulations (arrows). Emotions induced by music or silence were evaluated at the end of the 300 sec period. Emotional state was evaluated at the end of the whole experimental condition with the profile of mood states (POMS).

Figure 1


Valence and arousal ratings
Valence and arousal ratings
Valence and arousal ratings
+ POMS
Thermal stimuli
Thermal stimuli
Thermal stimuli
140 sec
160 sec
≅ 30sec
140 sec
160 sec
≅ 30sec
140 sec
160 sec
≅ 150 sec

Article 3: Modulation of the startle reflex by pleasant and unpleasant music

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Modulation of the startle reflex by pleasant and unpleasant music

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Abstract

The issue of emotional feelings to music is the object of a classic debate in music psychology. Emotivists argue that emotions are really felt in response to music, whereas cognitivists believe that music is only representative of emotions. Psychophysiological recordings of emotional feelings to music might help to resolve the debate, but past studies have failed to show clear and consistent differences between musical excerpts of different emotional valence. Here, we compared the effects of pleasant and unpleasant musical excerpts on the startle eye blink reflex and associated body markers (such as the corrugator and zygomatic activity, skin conductance level and heart rate) in 16 participants. The startle eye blink amplitude was larger and its latency was shorter during unpleasant compared with pleasant music, suggesting that the defensive emotional system was indeed modulated by music. Corrugator activity was also enhanced during unpleasant music, whereas skin conductance level was higher for pleasant excerpts. The startle reflex was the response that contributed the most in distinguishing pleasant and unpleasant music. Taken together, these results provide strong evidence that emotions were felt in response to music, supporting the emotivist stance.

Key Words: Music, emotion, startle reflex, zygomatic, corrugator, skin conductance, heart rate.

1. Introduction

The emotional power of music remains a mystery. Unlike most emotional inducers, music is not a sentient being nor does it seem to have any obvious adaptive value (Pinker, 1997). Yet, most people affirm that they feel strong emotions when they listen to music (Sloboda and O'Neill, 2001). This paradox led many music scholars to believe that music is only iconic or representative of emotion, a position coined as 'cognitivist' by Kivy (1990). Opponents to this view, known as 'emotivists', feel that the cognitivist position does not render justice to the direct and unmediated fashion in which emotions are experienced by listeners (Davies, 2001). Although the debate is stated at a very theoretical level, its resolution can have important implications for the practical use of music, such as music therapy. Indeed, if music is only representative of emotion, its therapeutic value could be seriously questioned. Although recent empirical studies measuring physiological, endocrine and brain responses to music as indices of emotional reactivity have brought some support to the emotivist stance, the nature of these emotional responses and their resemblance with emotions induced by other stimuli remain uncertain.

1.1. Autonomous nervous system responses

In order to show that people not only recognize but feel emotions in response to music, emotional reactions should be measured by techniques that fall out of the voluntary control of the subject. These measures typically pertain to the domain of psychophysiology. Following this line of research, Krumhansl was among the first to compare the autonomic responses elicited by different musical emotions (Krumhansl, 1997). She found that sad, happy and fearful music could be differentiated by their patterns of autonomic activation. In her study, sad music was most strongly associated with changes in heart rate, blood pressure, skin conductance and skin temperature. Fearful music was mostly associated with changes in the rate and amplitude of blood flow, whereas happy music principally produced changes in respiratory activity. However, subsequent studies have failed to replicate many of these findings. For

example, contrary to Krumhansl (1997) who observed that skin conductance level (SCL) was highest during the happy music condition, Khalfa et al. (2002) found that skin conductance responses (SCR) were highest during the listening of fearful music, Baumgartner et al. (2006) observed increased SCL during sad and fearful music compared to happy music, and Nater et al. (2006) found higher SCL during the listening of unpleasant compared to pleasant music. Moreover, Nater et al. (2006), Sammler et al. (2007) and Witvliet and Vrana (2007) found higher heart rates during unpleasant compared to pleasant music, whereas Krumhansl (1997) found the opposite for fearful and happy music. Therefore, there are inconsistent findings of the intensity and direction of these autonomic responses between studies.

Such inconsistencies across studies are relatively common in the field of the psychophysiology of emotion (Cacioppo et al., 2000). They might be related to some context-bound patterns of actions that allow the same emotion to be associated with a wide range of behavior and varying patterns of somatovisceral activation (Lang et al., 1990). Until those context-bound patterns are fully understood and controlled, more specific measures of emotional reactions to music are still needed to convince the sceptical cognitivist that music effectively induces emotions in the listener.

Some psychophysiological measures seem to be more reliable than others. For example, respiration rate appears to be consistently higher during happy and fearful music than during sad music (Baumgartner et al., 2006; Etzel et al., 2006; Krumhansl, 1997; Nyklicek et al., 1997). However, this may reflect differences in arousal, which differentiate happiness and fear from sadness, (Nyklicek et al., 1997) and not musical emotions *per se*. Indeed, cognitive theories of emotion have criticised the use of autonomic measures as indexes of felt emotions due to the non-specific nature of arousal (Schacter and Singer, 1962). For example, high arousal characterizes both fear and happiness. Moreover, in music, arousal is known to be mainly driven by its tempo (Gomez and Danuser, 2007). The fact that respiration rate was recently linked to

tempo through what appears to be a general entrainment mechanism (Etzel et al., 2006) further contributes to discredit respiration rate as a clear index of musical emotions. Indeed, although tempo is one of the main determinants of musical emotions, musical emotions depend on many other factors than simple tempo perception (e.g., Peretz et al., 1998).

1.2. *Hormonal responses*

Neuroendocrine and hormonal responses constitute yet another type of involuntary response that can be linked to emotional feelings. Contrary to physiological responses, some hormones can be more readily associated with positive or negative emotion (Barak, 2006), such as cortisol with stress and negative emotions, or immunoglobin A (S-IgA) with relaxation and positive emotions (Watanuki and Kim, 2005). A few studies have found that listening to relaxing and pleasant music was associated with lower levels of cortisol (Khalfa et al., 2003; Miluk-Kolasa et al., 1994), lower plasmatic levels of β-endorphins (McKinney et al., 1997) and higher mu-opiate receptor expression (Stefano et al., 2004). However, those studies only compared music with a silent control condition. Therefore, the observed effect may be attributed to non-emotional aspects of the musical condition, such as distraction. Indeed, when two musical conditions are compared, no differences are found between music inducing positive or negative moods on levels of cortisol (Clark et al., 2001), nor between up- or down-lifting musical excerpts on levels of S-Iga, dopamine, norepinephrenine, epinephrine or number of lymphocites (Hirokawa and Ohira, 2003), suggesting that the differences previously observed were mainly related to non-specific aspects of the task. One exception is the study by Gerra et al. (1998), who observed higher levels of β-endorphins, adrenocorticotropic hormone (ACTH), cortisol, norepinephrine and growth hormone in youngsters listening to techno-music compared to classical music. However, these changes in neuroendocrine responses appeared to be mainly linked to the high arousal induced by the techno-music, combined with the novelty-seeking

temperament of the participants. Neuroendocrine responses, although promising, appear to have the same limitations as autonomic responses.

1.3. Brain imaging

Brain imaging techniques provide yet another way to measure emotional reactions objectively. Studies using such techniques have shown that pleasant emotional reactions to music activate regions previously known to be involved in approach-related behaviors, such as the prefrontal cortex (Blood and Zatorre, 2001; Blood et al., 1999; Koelsch et al., 2006; Menon and Levitin, 2005), the periacqueductal gray matter (Blood and Zatorre, 2001) and the nucleus accumbens (Blood and Zatorre, 2001; Menon and Levitin, 2005), while negative emotions activate regions involved in withdrawal-related behavior, such as the parahippocampal gyrus (Blood and Zatorre, 1999) and the amygdala (Koelsch et al., 2006). Although these observations are fairly consistent with activations observed with other emotional inducers, brain activations alone do not allow for the distinction between processes involved in emotional perception and emotional feeling. Physiological changes that affect the body and its responses are necessary to demonstrate the induction of emotional feelings.

1.4. The present study

Although the studies reviewed so far tend to show that some emotions are felt in response to music, close examination of the results does not definitely refute the cognitivist stance. Indeed, most psychophysiological responses appear to be quite inconsistent from one study to the other, and the responses that appear to induce the most stable responses, such as respiration rate or hormonal responses, may be influenced by other confounding factors, such as arousal or distraction. Finally, brain imaging techniques cannot solely discriminate emotional feelings from other aspects of emotional processing.

Thus, in order to demonstrate the induction of emotional feelings, involuntary changes that affect the body and can be readily interpreted in terms of emotional processing have to be observed in response to musical excerpts conveying different emotions. The startle reflex is a good candidate in this regard. Indeed, it has been extensively and successfully used to probe emotional reactions. The startle reflex is an automatic defensive reaction to surprising stimuli. In experimental settings, it is usually measured by the magnitude of the eye blink triggered by a loud white noise. As a response of the defensive emotional system, it is frequently used to test the efficacy of anxiolytic drugs (Winslow et al., 2007) or to explore emotional reactivity in affective disorders (Grillon and Baas, 2003). In normal individuals, it is typically enhanced by negative emotions and diminished by positive ones, using pictures (Lang et al., 1998), films (Kaviani et al., 2004) or sounds (Bradley and Lang, 2000) to induce emotions. Here, we applied this affective startle modulation paradigm to musical stimuli and compared the effects of pleasant and unpleasant musical excerpts on the acoustic startle blink reflex. If emotions are really induced during music listening, then the startle reflex should be larger and of shorter latency during unpleasant music compared to pleasant music.

Moreover, in order to measure the effect of music on emotional reactions, we also monitored other classical psychophysiological measures, such as heart rate and skin conductance responses. Facial expressions were also assessed by recording the electromyographic (EMG) activity of the *zygomaticus major* (smiling) and the *corrugator supercilii* (frowning). Although these muscles can be controlled voluntarily, previous studies have shown that their activity discriminated well between pleasant and unpleasant emotions elicited by pictures (Lang et al., 1998). In line with previous research, we expect zygomatic activity to be higher during pleasant music and corrugator activity to be more noticeable during unpleasant music (Witvliet and Vrana, 2007).

2. Methods

2.1. Participants

Sixteen participants (7 men and 9 women), aged between 20 and 40 years (mean age = 25.1 ± 9.3) took part in this study. None of them were musicians, with less than five years of musical training and without any regular practice of a musical instrument.

2.2. Musical excerpts

The musical excerpts used in this study were adapted from those used in a prior study on pain modulation (Roy et al., in press). Three 100-sec excerpts of pleasant music and three 100-sec excerpts of unpleasant music were selected from a pool of 30 musical excerpts. Each of the 30 excerpts had been previously evaluated by 20 independent participants on the dimension of valence (on a scale ranging from 0 to 9 with 0 = 'pleasant' and 9 = 'unpleasant') and arousal (with 0 = 'relaxing' and 9 = 'stimulating'). Three highly pleasant and three highly unpleasant excerpts were selected. Since unpleasant excerpts were always judged to be arousing, all excerpts were selected in the high range of arousal. Pleasant excerpts were judged to be more pleasant than unpleasant excerpts (mean valence for pleasant excerpts = 2.40, mean valence for unpleasant excerpts = 6.68; $t(19) = 5.58$, $p < 0.05$) and did not differ in arousal (mean arousal for pleasant excerpts = 5.00, mean arousal for unpleasant excerpts = 5.18; $t(19) = 1.535$, n.s.). The selected pleasant excerpts were taken from the classical or jazz/pop repertoire and could be described as uplifting, with a rather fast tempo, such as the "Opening of William Tell" by Rossini. Unpleasant excerpts were mainly taken from the contemporary music repertoire. Examples of excerpts for each emotion category can be heard on our web site at www.brams.umontreal.ca/peretz. All selected excerpts were normalized to equate loudness across musical excerpts by setting the peaks of the excerpts at 8% of the maximum volume allowed, using the normalisation option of the *Cool Edit 2* sound editing software.

Apart from valence and arousal, the primary emotions (sadness, happiness, fear, anger, peacefulness and surprise) and moods (anger, depression, fatigue, anxiety, vigor and confusion, as measured with the "profile of mood states", POMS; McNair et al., 1992), induced by those excerpts were also assessed in a prior study (Roy et al., in press). Results showed that the primary emotions conveyed by the excerpts were consistent with their emotional valence. Pleasant excerpts were associated with happiness whereas unpleasant ones were associated with fear and anger. Results on the mood questionnaire confirmed these observations: the subscales for highly arousing negative moods, such as anger and anxiety, were higher after listening to the unpleasant excerpts, whereas the subscales for less arousing moods, such as depression, remained unaffected. Therefore, the selected excerpts convey primary emotions and induce moods consistent with their positive or negative valence and their high level of arousal.

2.3. *Data Collection and reduction*

Startle responses were elicited by a 100 dB SPL, 50 ms burst of white noise, with instantaneous rise time. The acoustic startle probe was presented over Sony MDR-v200 headphones. The eye-blink component of the startle reflex was recorded electromyographically from the orbicularis oculi muscle beneath the left eye, using two miniature 4mm Ag/AgCl shielded electrodes placed 1.5 cm apart and a signal ground electrode placed on the forehead, following the guidelines of Blumenthal et al. (2005). The signal was amplified by 1000 and band-pass filtered at 90 Hz–500 Hz using a Biopac MP150 System (Biopac Systems, Inc., Santa Barbara, CA). The sampling rate was set at 1000 Hz. The amplified signal was then transformed using the root mean square.

The maximum amplitude and latency of each startle response were extracted from the data. Following the guidelines of Balaban et al. (1986), only responses for which the onset occurred between 21 ms – 120 ms from noise onset were considered as startle responses and included in the analysis. The raw blink measurements were then standardised within each subject to decrease variability due to differences in the

absolute size of the startle blink across subjects, and expressed as T scores (i.e., (z x 10) +50). This produced a mean of 50 and a standard deviation of 10 for each subject. The blink amplitudes and latencies T scores were then averaged for the pleasant and unpleasant music condition.

In order to assess the sound intensity of the musical excerpts prior to each startle probe, the total root mean square amplitude (RMS) power was extracted for 1-sec windows preceding each burst of white noise and averaged for each subject and musical condition.

Facial EMG activities were recorded over the left corrugator and zygomatic sites as recommended by Frilund and Cacioppo (1986), using 8mm Ag/AgCl shielded electrodes. Signals were bandpass filtered from 90 Hz to 1000 Hz and transformed using the root mean square. Sampling rate was set at 1000 Hz. Area under the curve of the rectified EMG signal were then extracted for the corrugator and zygomatic muscle.

Electrocardiogram (ECG) was recorded using a standard 3 leads montage (Einthoven lead 2 configuration) (Biopac EL503). Instantaneous intervals between each R wave of the ECG (RRI) were calculated from the ECG using a peak detection algorithm to detect successive R-waves and obtain a continuous R-R tachogram. Careful examination of the ECG and the tachogram ensured that the automatic R-wave detection procedure had been performed correctly.

Skin conductance level (SCL) was recorded on the palmar surface of the left hand, at the thenar and hypothenar eminences according to the recommendations of Fowles et al. (1981). The signal was then smoothed and the mean SCL was calculated for the whole duration of each musical excerpt and averaged for the pleasant and unpleasant music condition.

2.4. Procedure

The physiological sensors were placed while the participants sat comfortably in a quiet room. The pleasant and unpleasant excerpts were then presented to the participants in an alternate order. There were two orders, one starting with a pleasant excerpt and the other starting with an unpleasant excerpt. The two orders were randomized across and within participants. The procedure is displayed for one musical excerpt in Figure 1. Each musical excerpt started with an emotional induction period of 21.3 seconds, in which there were no startle probes. The remaining 78.7 seconds were divided in six 11 seconds time window in which a startle probe occurred randomly. Each time window was separated by a period of 2.3 seconds in which no startle probe occurred. After each musical excerpt, the subject rated his/her emotional reaction to the music on the dimensions of valence (0 = unpleasant, 9 = pleasant) and arousal (0 = relaxing, 9 = stimulating).

2.5. Data analysis

First we assessed whether the musical excerpts had the expected emotional effects by comparing the mean ratings of valence and arousal, using students t-tests. In order to ensure that the sound intensity before each startle probe was equivalent in both musical conditions, a student t-test was performed on the means of the total RMS power preceding each startle probe for the pleasant and unpleasant music conditions. After these control analyses, a multivariate analysis of variance (MANOVA) was conducted to test for the effects of emotional condition (pleasant or unpleasant) on the means of all the physiological measures used (startle blink reflex amplitude and latency, corrugator and zygomatic activity, RRI and SCL). The MANOVA was followed by separate t-tests for each physiological measure. Finally, a discriminant function analysis was conducted to test if some patterns of physiological activation could reliably discriminate between the pleasant and unpleasant musical conditions.

3. Results

3.1. Self-reported emotions

The mean valence and arousal ratings were calculated for the pleasant and unpleasant excerpts. The t-tests performed on these average ratings confirmed that the intended emotions of the musical excerpts were well recognized. The pleasant and unpleasant excerpts differed significantly on the dimension of valence (with a mean rating of 8.49 and 1.91, respectively; t (15) = 13.04, $p<0.001$). In contrast, pleasant and unpleasant musical excerpts did not differ on the dimension of arousal (with a mean rating of 6.41 and 7.50, respectively; t (15) = 1.788, *n.s.* by bilateral test).

3.2. Sound amplitude

The RMS power of the 1-sec windows preceding each startle probe was equivalent for the pleasant (23.03 ± 0.68) and unpleasant (23.21 ±0.49) musical excerpts (t (15) = 0.31, *n.s.*).

3.3. Physiological Measures

Figure 2 illustrates the mean values of each physiological measure for the pleasant and unpleasant music condition. The results of the MANOVA showed that the physiological responses were significantly affected by the musical condition (F (6, 10) = 6.86, $p<0.01$, $\eta^2=0.81$). Subsequent t-tests were performed on each physiological measure showed that the startle blink reflex was larger (t (15) = 3.35, $p<0.01$, $\eta^2=0.43$) and faster (t (15) = 2.81, $p<0.05$, $\eta^2 = 0.35$) during the unpleasant music as compared to the pleasant music. Activity of the corrugator muscle was also found to be higher during the unpleasant condition (t (15) = 2.79, $p<0.05$, $\eta^2=0.34$), but no significant difference in the activity of the zygomatic muscle was observed between the two musical conditions (t (15) = 1.35, *n.s.*, $\eta^2=0.11$). RRI was also not affected by the valence of the musical excerpts (t (15) = 0.72, *n.s.*, $\eta^2=0.03$). In contrast, the SCL was found to be larger during the pleasant than the unpleasant music condition (t (15) = 2.43, $p<0.05$, $\eta^2 = 0.28$). The physiological responses were not limited to the 20 initial seconds without startle

probes but were considered for the whole excerpt instead because only nonsignificant trends in the same direction were obtained on the initial part of the musical excerpts.

3.4. Discriminant Analysis

The results of the discriminant analysis showed that the pleasant and unpleasant excerpts could easily be differentiated by a single function (Wilk's lambda (6) = 0.51, $p<0.01$). This function correctly classified pleasant excerpts in 75% of cases and unpleasant excerpts in 87.5% of cases. Table 1 shows the canonical variate correlation coefficients of each physiological variable for the discriminant function. These canonical variate correlation coefficients were much more important for startle amplitude and latency compared to the other physiological measures, indicating that the startle reflex was the measure that contributed the most to the separation of the musical conditions. Although there is a lack of consensus regarding how high correlations in a loading matrix should be interpreted, typically only variables with loadings of .32 and above are considered interpretable. Comrey and Lee (1992) suggest that loadings over 0.71 are considered excellent, 0.63, very good, 0.55, good, 0.45, fair and 0.32, poor. In light of those guidelines, the canonical variates coefficients appear excellent for the startle reflex, but difficult to interpret for the other physiological measures.

4. Discussion

4.1. Induction of emotional feelings by music

We found that the startle reflex was of higher amplitude and shorter latency during the listening of unpleasant in comparison with pleasant excerpts, suggesting that different emotional states were effectively induced by music. As the musical excerpts were manipulated to vary on the dimension of valence independently of arousal or loudness, the observed effects are likely to reflect induction of positive and negative emotional states in response to music, thus supporting the emotivist's stance. Indeed, the startle reflex paradigm appears to rebut all the critics made by cognitivists. Firstly, it is an

involuntary response that does not depend on the doubtful capacity of the subjects to adequately describe their own experience. Secondly, the affective startle modulation effect is a reliable measure that avoids the important variability characterising autonomous nervous system measures. Moreover, startle modulation can be ascribed to the emotional valence rather than arousal or attention, thereby contrasting with prior studies. Finally, because the modulation of the startle reflex indicates facilitation or inhibition of a motivational propensity to withdraw, it convincingly distinguishes the induction of emotional states from the cold perception of emotional features. Therefore, music appears to be as powerful as pictures (Lang et al., 1998), films (Kaviani et al., 2004) or sounds from natural objects (Bradley and Lang, 2000) to induce positive and negative emotions.

The absence of a neutral control condition in our study complicates the comparisons with studies using different inducers of emotion. Indeed, in the absence of a neutral point of comparison, it is difficult to tell if the startle modulation was due to an increase of the reflex during unpleasant music, a decrease of the reflex during pleasant music, or a combination of both. The absence of a neutral control condition was however not incidental. In fact, it is difficult to find music that is considered neutral by a majority of listeners. Moreover, other possible control conditions would also have drawbacks. For example, the use of a silent control condition would not have been helpful here since the sound level by itself has been shown to influence the acoustic startle (Franklin et al., 2007). Similarly, white noise matched with the musical excerpts for sound amplitude would not have been a better control condition because white noise is generally experienced as unpleasant. Nonetheless, a recent study using a similar design, in which three startle probes were delivered within 2-min long video clips, showed that pleasant videos reduced the magnitude of the startle reflex compared to neutral videos, whereas unpleasant ones increased it (Kaviani et al, 2004). Based on these findings, it is reasonable to assume that the results of our study depend on the effect of a combination of both facilitation and inhibition of the defensive

system. Nevertheless, the fact that the startle reflex was modulated by the emotional valence of the excerpts is sufficient to attest that emotional states were induced by music.

4.2. Startle reflex and physiological recordings as indices of felt emotion

In support to the idea that the startle reflex is one of the most reliable indices of emotional valence (Lang et al., 1998), we found that the startle reflex was the best response to discriminate between pleasant and unpleasant musical excerpts. Corrugator activity was the second most discriminative measure but was far behind the startle reflex. Although its contribution to the discriminant function was minimal, the analysis of variance showed that corrugator activity was significantly higher during the unpleasant excerpts compared to the pleasant excerpts, confirming that positive and negative emotions were felt during the listening of those excerpts. Zygomatic activity, however, was not shown to be significantly modulated by the excerpts' valence. Although unexpected, this lack of sensitivity for zygomatic compared to corrugator activity is a common finding (Larsen et al., 2003). This might be due to several reasons, such as the fact that the zygomatic is involved in some negatively valenced emotions, like disgust, or that it has a greater involvement in display rules and other fine voluntary motor behaviors.

Skin conductance, while having little contribution to the discriminant function, proved to be higher during the pleasant compared to the unpleasant excerpts. This finding adds to the controversy surrounding the interpretation of skin conductance changes in response to musical emotion. Our results are consistent with those of Krumhansl (1997) but are inconsistent with those of Baumgartner et al. (2006) and Nater et al. (2006). Moreover, our findings are opposite to that generally observed with other emotional induction techniques such as mental imagery or the presentation of emotional movie clips, for which SCL is higher during negatively valenced emotion (Cacioppo et al., 2000). This suggests that skin conductance levels might be related to

some aspects of the emotional response that are not directly linked to the perceived valence and arousal and may vary from one study to another. In the case of our study, this might be due to the fact that the pleasant and arousing excerpts might have prompted motoric activity such as dancing or tapping of the foot. Finally, no differences in heart rate were found between pleasant and unpleasant excerpts. Taken together with the negative findings of Baumgartner et al. (2006) and Etzel et al. (2006), this lack of difference strongly suggests that heart rate alone is not sufficient to differentiate pleasant from unpleasant musical conditions.

4.3. Implications of the study

The evidence that this study has brought in favor of the emotivist stance not only contributes to(Stefan Koelsch, 2005) the resolution of an important debate in music psychology, but also provides some theoretical justifications for the use of music as a therapy. Indeed, if music is able to induce emotions that can reduce the activity of the emotional defensive system, it can be used to alleviate some unpleasant emotional states, such as anxiety (Rudin et al., 2007), depression (Siedliecki and Good, 2006) (Siedliecki & Good, 2006)or pain (Roy et al., in press). Besides its implication for music therapy, the demonstration that emotions are indeed felt in response to music also opens up questions about how and why it does so. The combination of psychophysiological recordings with brain imaging techniques, in addition to self-reported measures of emotion and careful manipulation of the musical stimuli, will no doubt help to understand how the brain and the body interact to create emotional feelings to music (Koelsch, 2005)(Stefan Koelsch, 2005). However, the question of why music induces emotion appears more difficult to resolve empirically and is likely to continue to puzzle music scholars for many years to come. (Nyklicek, Thayer, & Van Doornen, 1997; Siedliecki & Good, 2006)

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Table 1

Table 1. Canonical variate correlation coefficients for the discriminant function

startle amplitude	0.875
startle latency	-0.728
corrugator activity	0.080
zygomatic activity	-0.074
skin conductance level	-0.030
R-R interval	-0.009

Figure Captions

Fig. 1. Distribution of startle probes during one musical excerpt. Participants listened passively to music for 21.3 s. In the last 78.7 s of the excerpts, six startle probes were randomly delivered within 11 tie windows separated by periods of 2.3 s during which no probe could occur.

Fig. 2. Mean physiological responses for the pleasant and unpleasant musical conditions. Error bar represents one standard error above the mean. Significant differences ($p<0.05$) are indicated by asterisks. Note that error bars reflect the between-subjects variance in each condition whereas the results of the statistical tests reflect the within-subject ?echerché?cross experimental conditions.

Figure 1

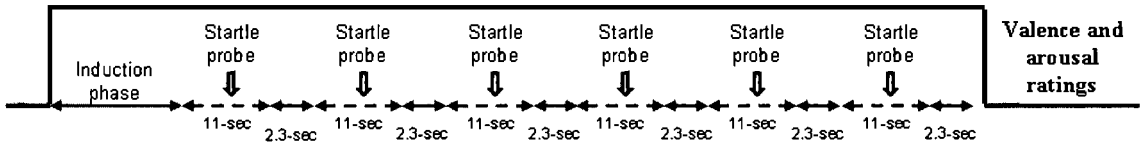
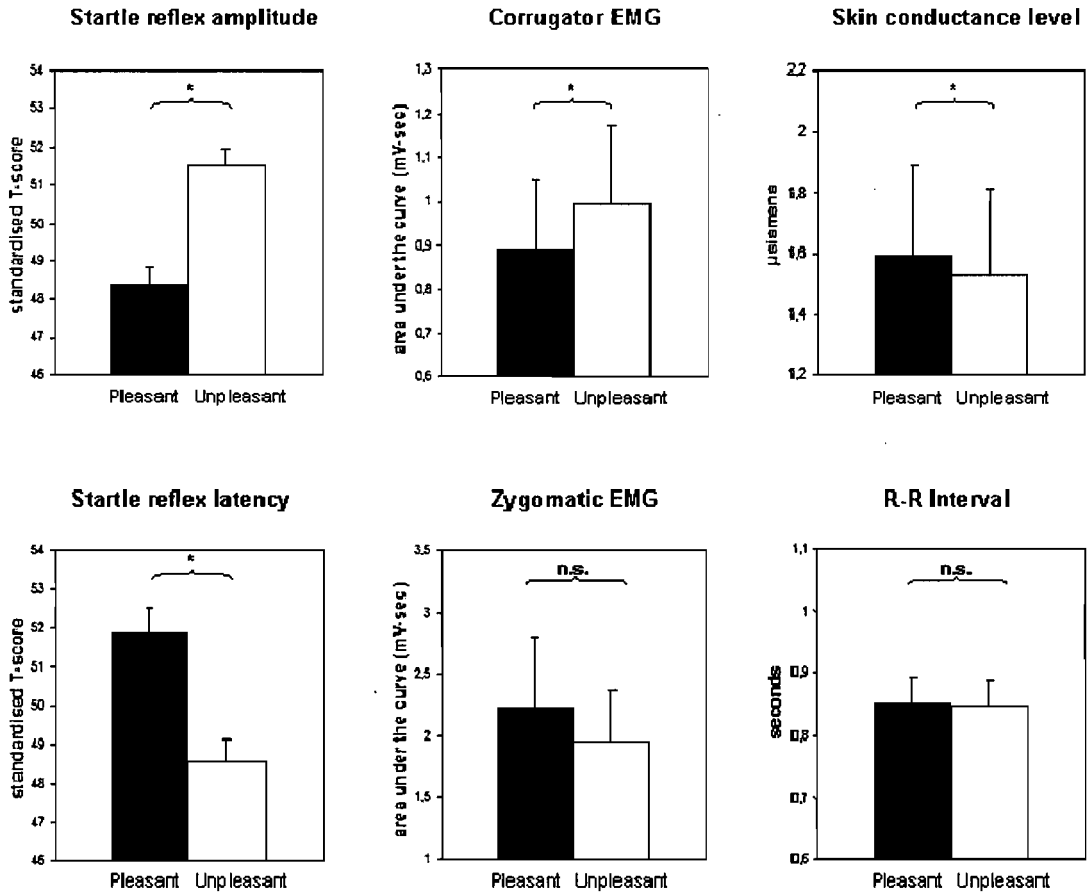


Figure 2



Article 4: Spinal modulation of nociception by music

Spinal modulation of nociception by music

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Running head: Spinal modulation of nociception by music

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Abstract

Numerous studies have demonstrated the capacity of music to reduce pain (Cepeda et al., 2006b). However, the neurophysiological mechanisms responsible for this phenomenon remain unexplained. In order to explore the neurophysiological mechanisms underlying music-induced analgesia, we evaluated the effects of musical excerpts conveying different emotions (pleasant-stimulating, pleasant-relaxing, unpleasant-stimulating) on the nociceptive flexion reflex (NFR or RIII), an index of nociception at the spinal level, as well as on pain ratings. Our results showed that the RIII reflex and pain ratings were lower during the listening of pleasant music compared to unpleasant music, suggesting the involvement of descending pain-modulatory mechanisms in music-induced analgesia. There were no significant differences between the pleasant-stimulating and pleasant-relaxing musical condition, indicating that arousal had little influence on pain.

Keywords: music, pain, emotion, RIII reflex, nociceptive flexion reflex, spine

4. INTRODUCTION

Music can make us smile or cry, dance or sleep (Sloboda & O'Neill, 2001), or even sometimes make us shiver with excitement (Blood & Zatorre, 2001a). In fact, this is what makes music such an exquisite art form. However, the ability of music to induce emotions can also be put at good use in clinical settings to alleviate the unpleasant emotional states that usually accompany illness, such as pain (Good et al., 2005). Yet, although many studies have demonstrated the efficacy of music to reduce pain (Cepeda et al., 2006b), the acceptation of music as a standard therapeutic intervention is still lagging behind. This state of affairs seems to be largely due to the lack of knowledge of the neuro-physiological mechanisms underlying music-induced analgesia.

Recently, we have shown that the analgesic effects of music depended on the emotions induced by music (Roy, Peretz, & Rainville, 2008). Pleasant musical excerpts reduced pain, whereas unpleasant ones had no effects and even tended to increase pain. These results were in perfect accordance with what has been observed with other emotional inducers, such as pictures (Meagher et al., 2001b), films (Weisenberg et al., 1998), emotional sentences (Zelman et al., 1991), odors (Villemure et al., 2003), or hypnosis (Pierre Rainville et al., 2005), for which pleasant emotions are generally found to reduce pain while unpleasant ones increase it. In a recent study, Rhudy and colleagues (2005) demonstrated that this effect was mediated in part by descending pain-modulatory pathways. They showed that emotional pictures modulated the amplitude of a spinally-mediated nociceptive reflex (nociceptive flexion reflex or RIII reflex; Sandrini et al., 2005), suggesting that emotions interfered with nociceptive processing at the level of the spinal chord. Given that music has been shown to act as other emotional inducers in reducing pain, it is likely that the same descending modulatory mechanisms are involved in music-induced analgesia.

In order to assess the influence of music on spinal nociception, we recorded RIII reflexes evoked by moderately painful electric stimulations during the presentation of

pleasant and unpleasant musical excerpts. In addition to the highly arousing pleasant and unpleasant musical excerpt used in our previous study (Mathieu Roy et al., 2008), we also included pleasant excerpts with low arousal. Indeed, musical therapists usually use relaxing music for pain relief, as their anxiolytic properties are supposed to be ideal to soothe pain (Good et al., 2005). At the opposite, Lang's motivational priming theory (1995) proposes that arousal amplifies the effects of valence, and would therefore predict that pleasant-stimulating excerpts would have greater analgesic effects than pleasant-relaxing ones, as has been recently shown with high and low arousal emotional pictures (Jamie L. Rhudy, Williams, McCabe, Russell, & Maynard, 2008). The comparison between the effects of pleasant-stimulating and pleasant-relaxing music will therefore allow to test if pleasant-relaxing music is effectively more suited than pleasant-stimulating music to reduce pain.

2. METHODS

2.1. Participants

A total of 26 healthy volunteers participated in the study (12 male, 15 female; mean age=23.21 y.o., SD=5.20, range=18-43 y.o.). The Research Ethics Board of the "Centre de Recherché de l'Institut de gériatrie de Montréal" approved the study. All participants gave written informed consent and received a compensation of 20$ for their participation. Five participants were excluded of the study because the threshold of 120% could not be attained within the limits of pain tolerance or because the reflex habituated quickly after the onset of the experiment.

2.2. Electrical Stimulation

Transcutaneous electrical stimulation was delivered with a Grass-S48 stimulator (Astro-Med Inc., West Warwick, RI, USA) isolated with a custom-made constant-current

stimulus-isolation unit. The stimulator was equipped with a custom-made RF filter preventing artefacts in fMRI data. The stimulation consisted in a 30 ms train of 10 X 1 ms pulse, delivered on degreased skin over the retro-maleolar path of the right sural nerve by means of a pair of custom made $1cm^2$ fMRI-compatible surface electrodes. The intensity of the electrical stimulation was recorded (Biopac systems Inc., Goleta, CA, USA) and the intensity of the stimulation was adjusted individually at 120% of the reflex threshold using the staircase method (Willer, 1977). This intensity minimizes ceiling and floor effects, and induces a stable and moderately painful pin-prick sensation.

2.3. Musical excerpts

Three 1-min excerpts of pleasant-stimulating (Phillips et al., 2003) pleasant-relaxing (PR) and unpleasant-stimulating (UNP) music were selected from a pool of 30 musical excerpts. Each of the 30 excerpts had been previously evaluated by 20 independent participants on the dimension of valence (on a scale ranging from 0 to 9 with 0 – 'pleasant' and 9 – 'unpleasant') and arousal (with 0 – 'relaxing' and 9 – 'stimulating') (Mathieu Roy et al., 2008). The pleasant-stimulating (valence: *M* = 2.40; arousal: *M* =5.00) and pleasant-relaxing excerpts (valence: *M* = 2.68; arousal: *M* =2.82) were matched on the valence dimension, whereas the pleasant-stimulating and unpleasant-stimulating excerpts (valence: *M* = 6.68; arousal: *M* =5.18) were matched on the arousal dimension. A fourth condition consisting of 1-min long period of silence was included as a control condition.

2.4. Procedure

Before the experiment, all participants were provided with an overview of the experiment and informed consent was obtained. Then the participants were installed in a comfortable chair and the electrical stimulation was adjusted at 120% of each participant's RIII threshold, following the staircase method (Willer, 1977). The

experiment comprised 26 experimental trials. The time course of a trial is depicted in Figure 1. Each trial consisted of the presentation of a 1-min long musical excerpts or silence control condition within which three electrical stimulation were delivered at either 20, 30 and 40 seconds, or 30, 40 and 50 seconds. The musical excerpts were presented using headphones (SONY MDRCD370) at a comfortable, individually adjusted, intensity level that remained constant across pleasant/unpleasant music conditions.

At the end of each block of music, participants had 8 seconds to rate the pain elicited by the electrical stimulation on a visual analogue scale (Vastfjall et al.). Participants were asked to provide an overall rating of the pain induced by the three stimulations in the preceding block. They were also instructed that their pain ratings should reflect the perceived intensity (sensory dimension), as well as the discomfort (affective dimension) elicited by the electrical stimulations. The VAS was presented horizontally and included the verbal anchors "0 – no pain" and "100 – extremely painful" at the left and right extremities, respectively. After the participants had given their pain ratings, they were asked to rate the valence and arousal of the musical excerpts or silence condition using a computerized version of the Self-Assessment Manikin (Lang, 1980; valence: 1 = unpleasant, 9 = pleasant; arousal: 1 = low arousal, 9 = high arousal).

Each scan started with two control trials in silence. These trials controlled for potential habituation effects, allowing for the RIII reflex to stabilize. Following these two trials, the remaining 24 trials were presented in a pseudo-random order consisting of six consecutive cycles, comprising each of the four experimental conditions. These cycles were ordered so that no experimental condition was presented twice consecutively. Two orders of presentation were created (order 2 inverse of order 1) and their administration was counterbalanced across participants.

2.6. RIII reflex recording

Electromyographic (EMG) activity of the biceps femoris was recorded with Ag-AgCl surface electrodes (Type EL-508, Biopac systems Inc., Goleta, CA, USA) with an inter-electrode distance of 2 cm. Electromyographic (EMG) activity was amplified, band pass filtered (100-500 Hz), digitized and sampled at 1000 Hz (MP150, Biopac systems Inc., Goleta, CA, USA). EMG data was analysed using Acknowledge 3.8 (Biopac systems Inc., Goleta, CA, USA). The raw EMG data were filtered off-line (120-130 Hz) and transformed using the root mean square. The resulting signal was integrated between 90-180 ms post-stimulus onset to quantify the RIII-reflex to single shocks for the covariance analysis.

3. RESULTS

3.1. Manipulation checks

To confirm that the expected emotions were correctly induced by the emotional pictures, mean ratings of valence and arousal were averaged for each experimental condition and compared pair by pair by means of t-tests. A Bonferonni correction was applied to the p values to control for the repetition of tests. Mean valence and arousal (Jasmin et al.) ratings for each experimental condition are reported in Table 1. The ratings confirmed that the different musical excerpts effectively induced the intended emotions. Pleasant-stimulating and pleasant-relaxing excerpts were judged as more pleasant than unpleasant ones, or the silence condition (pleasant-stimulating vs unpleasant: $t(20) = 12.28$, $p < 0.05$; pleasant-relaxing vs unpleasant: $t(20) = 10.53$, $p < 0.05$; pleasant-stimulating vs silence: $t(20) = 7.23$, $p < 0.05$; pleasant-relaxing vs silence: $t(20) = 6.428$, $p < 0.05$) and unpleasant excerpts were rated as more unpleasant than the silence condition (unpleasant vs silence: $t(20) = 8.58$, $p < 0.05$).

Pleasant-stimulating and pleasant-relaxing excerpts were judged as equally pleasant (pleasant-stimulating vs pleasant-relaxing: $t(20) = 1.42$, $p = ns.$). On the arousal scale, both pleasant-stimulating and unpleasant excerpts were judged as more arousing than pleasant-relaxing excerpts or the silence condition (pleasant-stimulating vs pleasant-relaxing : $t(20) = 6.21$, $p < 0.05$; unpleasant vs pleasant-relaxing: $t(20) = 4.80$, $p < 0.05$; pleasant-stimulating vs silence: $t(20) = 5.40$, $p < 0.05$; unpleasant vs silence: $t(20) = 5.84$, $p < 0.05$). However, pleasant-stimulating and unpleasant excerpts did not differ on the level of arousal (pleasant-stimulating vs unpleasant: $t(20) = 0.15$, $p = ns.$), nor did pleasant-relaxing excerpts and the silence condition (pleasant-stimulating vs silence: $t(20) = 1.77$, $p = ns.$).

3.1. Pain ratings and RIII reflex

Pain ratings and RIII reflex amplitudes were first standardised within participants by converting them into z-scores in order to reduce inter-subject variability and normalise the distribution of the data. The resulting scores were then averaged for each condition and compared through analyses of variance (ANOVA) with the experimental condition as a within-subject factor. Pairwise differences between conditions were then considered with the appropriate follow-up contrasts.

Mean pain ratings and RIII reflex amplitudes, converted into z-scores, are reported for each experimental condition in figure 2. There was a significant effect of emotions induced by music on pain ratings ($F(3, 60) = 13.79$, $p < 0.05$). Planned follow-up contrasts showed that pain ratings were higher during unpleasant excerpts than during pleasant-stimulating excerpts, pleasant-relaxing excerpts, or the silence condition (unpleasant vs pleasant-stimulating: $t(20) = 5.79$, $p < 0.05$; unpleasant vs pleasant-stimulating: $t(20) = 5.71$, $p < 0.05$; unpleasant vs silence: $t(20) = 4.20$, $p < 0.05$).

The RIII was also shown to be influenced by the experimental condition ($F(3, 60) = 7.21$, $p < 0.05$). Planned follow-up contrasts showed that the RIII reflex was increased during the listening of unpleasant excerpts compared to both types of pleasant excerpts ($t(20) = 4.39$, $p < 0.05$) and decreased during the silence condition compared with the presentation of music ($t(20) = 4.78$, $p < 0.05$). However, there were no differences in RIII amplitude between pleasant-stimulating and pleasant-relaxing excerpts ($t(20) = 1.28$, $p =$ *ns.*).

4. DISCUSSION

In this study, pain perception was reduced during the presentation of pleasant musical excerpts compared to unpleasant ones, replicating the valence effect observed in a prior study (Mathieu Roy et al., 2008). Moreover, this effect was paralleled by corresponding changes in RIII reflex amplitudes: RIII reflexes were higher during unpleasant than pleasant excerpts. This suggests that, as observed for emotional pictures (Jamie L. Rhudy et al., 2005), music-induced analgesia operates in part through descending pain-modulatory pathways.

However, pain ratings did not differ between the pleasant music conditions and the silence condition. Moreover, RIII reflex amplitudes were even shown to be lower during the silence condition compared to all other musical conditions. This can be due to dissociation between pain ratings and spinal reflexes during distraction. This effect has been reported in recent studies on the effects of distraction on pain (Edwards, Ring, France, al'Absi, McIntyre, Carroll et al., 2007; McIntyre, Edwards, Ring, Parvin, & Carroll, 2006; Petersen, Heesacker, & Schwartz, 2001) and will be discussed with more details in the next section. These studies typically show that pain is reduced while performing an engaging distractive task, whereas RIII reflexes are enhanced. These findings suggest that distraction might facilitate the motor output of the RIII reflex responses in order to promote automatic withdrawal of the affected limb while sensory processing is inhibited to help the brain stay focused on the distractive task.

This paradoxical effect of distraction on pain perception and RIII reflexes makes silence a poor neutral control condition, as it does not control for distraction. This emphasizes the difficulty of finding a good emotional control for music, as music is almost always emotional, and because white noise is generally considered as unpleasant (Meagher et al., 2001b). Although the effects of distraction were particularly salient on the RIII reflex, these could also have had some repercussions on pain ratings. Because we asked for retrospective ratings of average pain, it is quite

possible that participants might have used in part their own reflex amplitudes to infer their levels of perceived pain, which could explain the lack of differences in pain ratings between pleasant excerpts and the silence condition. Indeed, when immediate ratings are given in response to thermal stimulations that do not produce RIII reflexes, pleasant music was shown to reduce pain compared to silence (Mathieu Roy et al., 2008).

There were no significant differences between the effects of pleasant-stimulating and pleasant-relaxing music, suggesting that valence is the main emotional dimension influencing pain processing. However, visual inspection of the mean differences in pain ratings and RIII reflexes indicate a non-significant trend for pleasant-relaxing music to produce larger analgesic effects than pleasant-stimulating music. Although the effect is too weak to draw any strong conclusion about a possible superiority of relaxing music, these results seem to be in contradiction with Lang's motivational priming. Indeed, whereas the low arousal pictures (International Affective Picture System; Lang, 1980) really seem to be deprived of emotional content compared with highly arousing ones, relaxation rather appears as one category of emotional states that constitute music's emotional repertoire. This particularity of music could be linked to its fundamental role in calming young infants through their mother's singing, which appears to be universal (Trehub & Trehub, 2003). If proven right, the capacity of music to effectively induce relaxing emotions could constitute one the main advantage of music over other emotional inducers.

In summary, our results demonstrated that the valence of music modulated pain processing at the level of the spinal cord, suggesting the involvement of descending pain-modulatory mechanisms. This is particularly interesting for the use of music therapy in clinical settings since the dorsal horn of the spinal is one of the main targets of action of traditional analgesics drugs, such as opioids. Considering the

simplicity, low cost and absence of side effects of musical interventions, music could be an interesting complement to traditional methods of pain management.

Table 1

Table 1. Mean (±sd) valence and arousal ratings

	experimental condition			
	unpleasant	pleasant-stimulating	pleasant-relaxing	silence
valence	2.38^{bcd}(±0.90)	6.84^{ad}(±1.04)	6.48^{ad}(±1.29)	4.50^{abc}(±1.00)
arousal	5.81^{cd}(±2.07)	5.89^{cd}(±1.72)	3.34^{ab}(±1.21)	2.58^{ab}(±1.53)

^{a} = different from unpleasant ; ^{b} = different from pleasant-stimulating; c = different from unpleasant-relaxing; ^{d} = different from silence; $p < 0.05$, Bonferroni-corrected

Figure captions

Figure 1. Time course of an experimental trial. Three electric stimulations are delivered at the 20th, 30th and 40th or 30th, 40th and 50th seconds within 60 seconds long musical excerpts or periods of silence. At the end of each musical excerpt, the participants rated the pain elicited by the electrical stimulations, and the emotions induced by the musical excerpt.

Figure 2. Mean pain ratings and RIII reflex amplitudes (z-scores) for the four experimental conditions. Significant differences ($p < 0.05$) are marked by an asterisk.

Figure 1

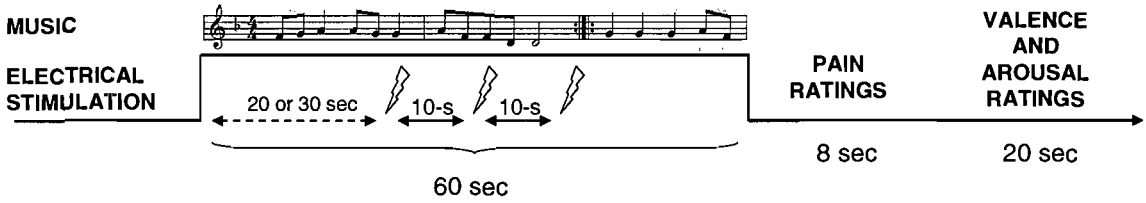
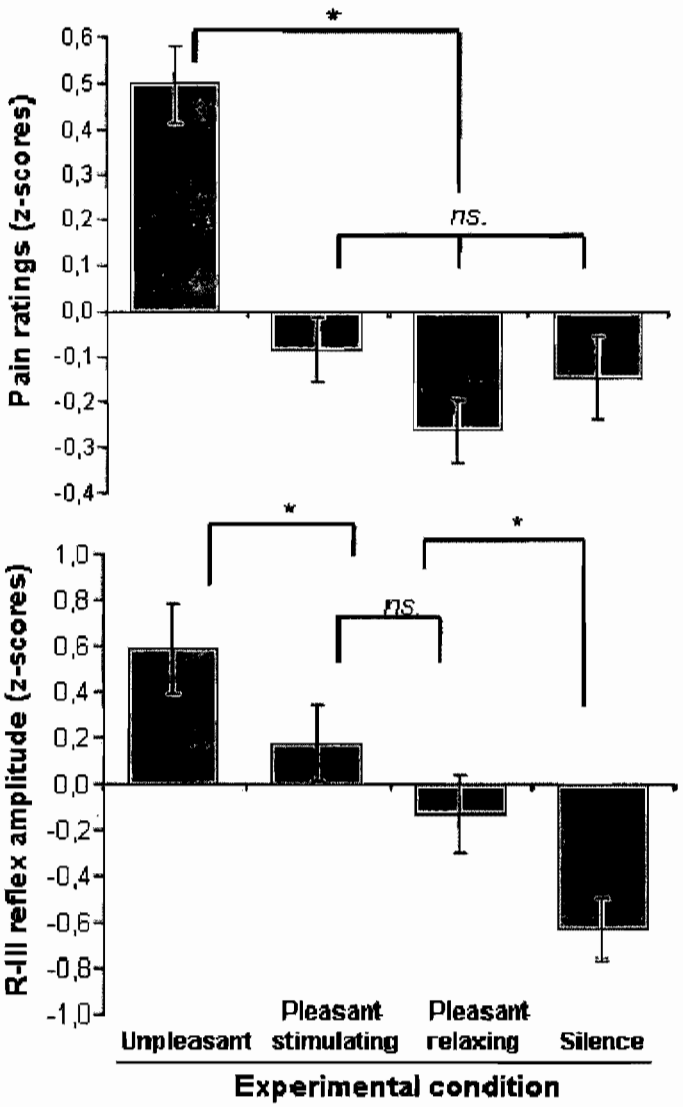

MUSIC
ELECTRICAL STIMULATION
20 or 30 sec
10-s
10-s
PAIN RATINGS
VALENCE AND AROUSAL RATINGS
8 sec
20 sec
60 sec

Figure 2


Pain ratings (z-scores)
0,6
0,5
0,4
0,3
0,2
0,1
0,0
-0,1
-0,2
-0,3
-0,4
*
ns.
R-III reflex amplitude (z-scores)
1,0
0,8
0,6
0,4
0,2
0,0
-0,2
-0,4
-0,6
-0,8
-1,0
*
ns.
*
Unpleasant
Pleasant stimulating
Pleasant relaxing
Silence
Experimental condition

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Article 5: Spinal and supra-spinal nociception during attentional and emotional modulation of pain

Spinal and supra-spinal nociception during attentional and emotional modulation of pain

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Running head: Attention and emotion

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ABSTRACT

Emotions have been shown to alter the transmission of pain through descending modulatory mechanisms. However, the specificity of these mechanisms to emotional modulation of pain remains questionable, as many studies have also shown that attention might engage descending inhibitory pathways. In order to differentiate the spinal and supra-spinal mechanisms involved in emotional and attentional modulation of pain, we measured pain rating and RIII reflexes during the presentation of pleasant, unpleasant and neutral pictures, as well as during a baseline condition without any distractor (experiment 1). In a second experiment, we manipulated emotional arousal along with emotional valence in order to compare the effects of distraction to those of arousal (experiment 2). Whereas emotional valence influenced both pain ratings and RIII reflexes in the same direction, distraction reduced pain ratings but increased RIII reflexes. This dissociation between RIII reflexes and pain ratings during distraction did not seem to be fully explainable by differences in arousal. Overall, these data provide strong evidence that attention and emotion modulate pain through different and dissociable neuro-physiological mechanisms.

1. INTRODUCTION

Pain is generally described as the unpleasant experience associated with potential or actual tissue damage. In line with its fundamentally subjective and affective nature, pain can vary quite widely according to the emotional state of the individual (Price et al., 1999). Indeed, pain has been previously shown to be modulated by emotions induced by pictures (Meagher et al., 2001b), films (Weisenberg et al., 1998), emotional sentences (Zelman et al., 1991), odors (Villemure et al., 2003), hypnosis (Pierre Rainville et al., 2005) or music (Mathieu Roy et al., 2008). In these studies, pleasant emotions are generally found to reduce pain while unpleasant ones tend to increase it. In a recent study, Rhudy and colleagues (2005) demonstrated that this effect was mediated in part by descending pain-modulatory pathways. Using emotional pictures from the International Affective Picture System (Lang, 1980), they showed that emotions modulated the amplitude of a spinally-mediated nociceptive reflex (nociceptive flexion reflex or RIII reflex; Sandrini et al., 2005). As for pain ratings, pleasant pictures decreased the amplitude of the reflex compared to neutral pictures, whereas unpleasant ones increased it.

However, the interpretation of these studies is difficult, because they did not control for associated changes in attention. Indeed, emotions are well known to influence the direction of attention (Ohman et al., 2001), including attention to pain (Keogh et al., 2001) or other somatic symptoms (Gendolla et al., 2005). It is therefore possible that the effects of emotion on pain mainly operate through a redirection of attention towards or away from pain (Villemure & Bushnell, 2002). Nonetheless, Villemure et al. (2003) succeeded in disentangling attentional and emotional effects on pain using an original factorial design in which these two factors were varied orthogonally. Emotions turned out to specifically alter pain unpleasantness, whereas attention preferentially altered pain intensity. Based on these findings and on prior knowledge (Bushnell, Duncan, Dubner, Jones, & Maixner, 1985a), the authors suggested that attentional modulation of pain might preferentially engage descending

pain modulatory pathways, probably originating in the periaqueductal gray matter (PAG) (Irene Tracey et al., 2002).

The involvement of descending mechanisms in attentional modulation of pain is well supported by neuroimaging studies showing activation of the PAG during distraction (Bantick et al., 2002; Irene Tracey et al., 2002; Valet et al., 2004). However, evidences of diminution in spinal nociception during distraction, as measured by the RIII reflex, appear contradictory. Although early studies suggested that directing attention away from the noxious stimulus attenuates the RIII (Bathien, 1971; Bathien & Hugelin, 1969; Bathien & Morin, 1972; Willer, Boureau, & Berny, 1979) more recent studies have shown that performing a distractive mental arithmetic task reduces RIII thresholds (Edwards, Ring, France, al'Absi, McIntyre, Carroll et al., 2007; Petersen, Heesacker, & Schwartz, 2001) and increased RIII amplitudes (McIntyre, Edwards, Ring, Parvin, & Carroll, 2006). These increases in RIII reflex during distraction appeared paradoxical because they were paralleled by decreases in pain ratings, suggesting a dissociation between spinal and supra-spinal nociception under these conditions. The reasons for these discrepancies across studies remain speculative, but some authors have pointed out that they might be explained by the use of experienced participants in the earlier studies, as well as by the possibly higher arousal induced by the distractive task in newer studies (McIntyre et al., 2006).

In order to decipher the role of attention and emotion on spinal and supra-spinal nociceptive processing, we measured RIII reflexes and pain ratings in response to painful electrical stimulations delivered during the viewing of pleasant, unpleasant and neutral pictures, as well as during a control condition with only a fixation point. Whereas we expected to replicate the findings of Rhudy et al. (2005) on pain responses during the presentation of emotional pictures, we hypothesised that the differences in pain responses during the presentation of neutral pictures compared with the fixation point would reveal the effects of distraction induced by simple picture viewing. In a

second experiment, we further manipulated the arousal of emotional pictures along with their valence in order to compare the effects related to emotional arousal to those related to distraction.

2. METHODS

2.1. Participants

A total of 33 healthy volunteers participated in the study (seventeen males and sixteen females; mean age: 24.2 years; SD: 4.1). All of these participants performed the two parts of the study. The Research Ethics Board of the "Centre de recherche de l'Institut de gériatrie de Montréal" approved the study. All participants gave written informed consent and received a compensation of 30$ for their participation. Four participants were excluded because the threshold of 120% couldn't be attained within the limits of pain tolerance.

2.2. Electrical Stimulation

Transcutaneous electrical stimulation was delivered with a Grass-S48 stimulator (Astro-Med Inc., West Warwick, RI, USA) isolated with a custom-made constant-current stimulus-isolation unit. The stimulation consisted in a 30 ms train of 10 X 1 ms pulse, delivered on degreased skin over the retro-maleolar path of the right sural nerve by means of a pair of custom made $1cm^2$ surface electrodes. The intensity of the electrical stimulation was recorded (Biopac systems Inc., Goleta, CA, USA) and the intensity of the stimulation was adjusted individually at 120% of the reflex threshold using the staircase method (Willer, 1977). This intensity minimizes ceiling and floor effects, and induces a stable and moderately painful pin-prick sensation.

2.3. Affect Induction

2.3.1. Experiment 1

Ninety pictures that evoked pleasant (POS), unpleasant (NEG) or neutral (Neugebauer et al.) temotions were selected from the International Affective Picture System (Center for the Study of Emotion and Attention, 1999)[1]. Based on their normative ratings, 30 pictures were chosen within each category in order to maximize valence differences between pleasant and unpleasant pictures, while equating their arousal levels. Neutral pictures were of intermediate valence and of lower arousal than pleasant and unpleasant pictures. The lower arousal of the neutral pictures was due to the fact that, within the IAPS, the most pleasant and unpleasant pictures are also of high arousal, whereas the neutral pictures are never of high arousal. As a result, it is impossible to match neutral pictures on arousal when selecting the most pleasant and unpleasant pictures (Lang, 1995; Jamie L. Rhudy et al., 2005).

For each category, pictures were grouped in six blocks of five pictures. The presentation length of each picture was of six seconds for a total of 30 seconds per block. The pictures were presented on a computer screen situated approximately at 60 cm from the participants. A fourth condition consisting of a white fixation cross (FIX) displayed in the middle of a black screen for 30 seconds served as an additional control with no picture.

2.3.1. Experiment 2

In this second part of the study, two categories of pictures were added in order to vary orthogonally the dimensions of valence and arousal. Therefore, 150 pictures that evoked pleasant-stimulating (POS_s), pleasant-relaxing (POS_r), unpleasant-stimulating (NEG_s), unpleasant-relaxing (NEG_r) or neutral (Neugebauer et al., 2004) emotions were selected from the International Affective Picture System (Center for the Study of Emotion and Attention, 1999)[2]. All the pictures were different from the ones used in experiment 1. Based on the normative ratings, the pictures were selected so that the sets of pictures within the same valence category had equivalent valence ratings, and that the sets of pictures within the same arousal category had equivalent

arousal ratings. As a consequence of this matching process, pleasant-stimulating and pleasant-relaxing pictures were a bit less pleasant or unpleasant than those used in experiment one. They were also slightly less arousing. Neutral pictures were of intermediate valence, but were of the same arousal level as the relaxing pictures. As in experiment one, pictures were grouped in six blocks of five pictures of the same category. The presentation length of each picture was of six seconds for a total of 30 seconds per block. Finally, a sixth condition consisting of a white fixation cross (FIX) displayed in the middle of a black screen for 30 seconds served as an additional control with no picture.

2.4. Procedure

2.4.1. Experiment 1

All participants started with the Experiment 1. Before the experiment began, the participants were installed in a comfortable chair and the electrical stimulation was adjusted at 120% of each participant's RIII threshold following the staircase method (Willer, 1977). The first experiment consisted of 26 experimental trials. The time course of a trial is depicted in Figure 1. Each trial consisted in a 30 seconds block of emotional pictures or fixation point. Blocks with emotional or neutral pictures included five images successively presented for six seconds each. Two electrical stimuli were delivered during each block of visual stimulation, always 300 ms before the end of a picture. The stimulations occurred pseudo-randomly according to 6 possible combinations of pictures: first and second, first and third, first and fourth, second and third, second and fourth or third and fourth pictures. The onsets of stimulations were balanced across the experimental conditions.

At the end of each block of images, participants had 8 seconds to rate the pain elicited by the electrical stimulation on a visual analogue scale (Vastfjall et al.). Participants were asked to provide an overall rating of the pain induced by the two

stimulations in the preceding block. They were also instructed that their pain ratings should reflect the perceived intensity (sensory dimension), as well as the discomfort (affective dimension) elicited by the electrical stimulations. The VAS was presented horizontally and included the verbal anchors "0 - no pain" and "100 – extremely painful" at the left and right extremities, respectively. After the participants had given their pain ratings, they were asked to rate the valence and arousal of the pictures (or fixation) blocks using a computerized version of the Self-Assessment Manikin (Lang, 1980; valence: 1 = unpleasant, 9 = pleasant; arousal: 1 = low arousal, 9 = high arousal).

Each scan started with two control trials with only the fixation point. These trials controlled for potential habituation effects, allowing for the RIII reflex to stabilize. Following these two trials, the remaining 24 trials were presented in a pseudo-random order consisting of six consecutive cycles, comprising each of the four experimental conditions (NEG, POS, NEU or FIX). These cycles were ordered so that no experimental condition would be presented twice consecutively. Two orders of presentation were created (order 2 inverse of order 1) and their administration was counterbalanced across participants.

2.4.1. Experiment 2

After the first experiment, participants took a 5-min break before starting the second experiment. The procedure of the two experiments was exactly the same, except for the pleasant-relaxing and unpleasant-relaxing conditions added in experiment 2. Therefore, experiment 2 comprised 36 experimental trials. As in experiment 1, these trials were arranged in six pseudo-random cycles, comprising each of the six experimental conditions (NEG_r, NEG_s, POS_r, POS_s, NEU or FIX). Two orders of presentation were created (order 2 inverse of order 1) and their administration was counterbalanced across participants.

2.6. RIII reflex recording

Electromyographic (EMG) activity of the biceps femoris was recorded with Ag-AgCl surface electrodes (Type EL-508, Biopac systems Inc., Goleta, CA, USA) with an inter-electrode distance of 2 cm. Electromyographic (EMG) activity was amplified, band pass filtered (100-500 Hz), digitized and sampled at 1000 Hz (MP150, Biopac systems Inc., Goleta, CA, USA). EMG data was analysed using Acknowledge 3.8 (Biopac systems Inc., Goleta, CA, USA). The raw EMG data were filtered off-line (120-130 Hz) and transformed using the root mean square. The resulting signal was integrated between 90-180 ms post-stimulus onset to quantify the RIII-reflex to single shocks for the covariance analysis.

3. RESULTS

3.1. Experiment 1

3.1.1.Manipulation checks

To confirm that the expected emotions were correctly induced by the emotional pictures, mean ratings of valence and arousal were averaged for each experimental condition and compared pair by pair by means of t-tests. A Bonferonni correction was applied to the p values to control for the repetition of tests. Mean valence and arousal (Jasmin et al.) ratings for each experimental condition are reported in Table 1, along with the results of the statistical tests. The ratings confirmed that the different blocks of emotional pictures effectively induced the intended emotions. Pleasant pictures were the most pleasant, neutral pictures and the fixation point were of intermediate valence and unpleasant pictures were the most unpleasant. There were no differences between the valence of the neutral pictures and the valence of the fixation point. On the arousal scale, pleasant and unpleasant pictures were found to be equally stimulating, and both were judged as more arousing than neutral pictures. Finally, the neutral pictures were rated as more arousing than the fixation point.

3.1.2. Pain ratings and R-III reflex

Pain ratings and RIII reflex amplitudes were first standardised within participants by converting them into z-scores in order to reduce inter-subject variability and normalise the distribution of the data. The resulting scores were then averaged for each condition and compared through analyses of variance (ANOVA) with the experimental condition as a within-subject factor. Pairwise differences between conditions were then considered with the appropriate follow-up contrasts.

Mean pain ratings and R-III reflex amplitudes, converted into z-scores, are reported for each experimental condition in figure 2. There was a significant effect of the experimental condition on pain ratings ($F(3, 84) = 28.87$, $p < 0.001$). Planned follow-up contrasts showed that pain ratings were lower during pleasant than neutral pictures ($t(28) = 2.84$, $p < 0.01$) and higher during unpleasant than neutral pictures ($t(28) = 5.95$, $p < 0.001$). Moreover, pain ratings also decreased during the presentation of neutral pictures compared with the fixation point ($t(28) = 3.09$, $p < 0.01$).

The R-III was shown to be influenced by the experimental condition ($F(3, 84) = 19.27$ $p < 0.001$). Planned follow-up contrasts showed that the R-III reflex was increased during the viewing of unpleasant pictures compared to the pleasant and neutral pictures ($t(28) = 5.90$ $p < 0.001$). However, there were no differences whatsoever between pleasant and neutral pictures ($t(28) = 0.95$ p = ns.). Surprisingly, the reflex was found to be higher during the presentation of neutral pictures than the fixation point ($t(28) = 2.01$ $p < 0.05$).

3.2. Experiment 2

3.2.1.Manipulation checks

To confirm that the expected emotions were correctly induced by the emotional pictures, mean ratings of valence and arousal were averaged for each

experimental condition and compared pair by pair by means of t-tests. A Bonferonni correction was applied to the p values to control for the repetition of tests. Mean valence and arousal (Jasmin et al.) ratings for each experimental condition are reported in Table 1, along with the results of the statistical tests. The ratings confirmed that the different blocks of emotional pictures effectively induced the intended emotions. Pleasant-stimulating and pleasant-relaxing pictures were judged as the most pleasant pictures, neutral pictures and the fixation point were of intermediate valence, and unpleasant-relaxing and unpleasant-stimulating pictures were judged as the most unpleasant pictures. Most crucially, there were no differences between the valence of stimulating and relaxing pictures within each valence category. Neutral pictures and the fixation point were also judged as equally pleasant.

On the arousal scale, the high-arousal pictures were judged as more arousing than the relaxing pictures, within their valence category. Moreover, there were no differences in arousal between the pleasant-stimulating and unpleasant-stimulating pictures. Pleasant-relaxing and neutral pictures were found to be equally arousing. However, they were judged as slightly less arousing than the unpleasant-relaxing pictures, although the differences were minimal. Finally, neutral pictures were judged as more arousing than the fixation point.

3.1.2. Pain ratings and R-III reflex

Pain ratings and RIII reflex amplitudes were first standardised within participants by converting them into z-scores in order to reduce inter-subject variability and normalise the distribution of the data. The resulting scores were then averaged for each condition. In order to test for the effects of valence and arousal on pain, the mean pain ratings and RIII amplitudes for the four emotional pictures conditions (NEG_r, NEG_s, POS_r and POS_s) were compared through means of an ANOVA with valence (positive or negative) and arousal (relaxing or stimulating) as a within-subject factor. Finally, the

neutral and fixation conditions were compared by means of t-tests to assess the effects of distraction.

Mean pain ratings and R-III reflex amplitudes, converted into z-scores, are reported for each experimental condition in figure 3. Pain ratings were lower during the pleasant compared to the unpleasant pictures (Main effect of valence: $F(1, 28) = 64.13$, $p < 0.001$). Moreover, this effect was modulated by arousal (valence x arousal interaction: $F(1, 28) = 19.22$, $p < 0.001$). Indeed, within each valence category, stimulating pictures had more effects than relaxing ones. As a result, the decrease in pain ratings was more important for pleasant-stimulating than pleasant-relaxing pictures ($t(28) = 2.50$, $p < 0.05$) and the increase in pain ratings was more pronounced for unpleasant-stimulating than pleasant-stimulating pictures ($t(28) = 1.98$, $p = 0.05$). There were no main effects or arousal (Main effect of arousal: $F(1, 28) = 0.23$, p = ns.). Finally, there were no significant differences between the pain ratings obtained during the neutral pictures condition and the fixation point ($t(28) = 0.45$, p = ns.).

The R-III was reduced during the viewing of pleasant compared to unpleasant pictures (Main effect of valence: $F(1, 28) = 64.13$, $p < 0.001$). However, arousal had no effects on the RIII reflex (Main effect of arousal: $F(1, 28) = 0.93$, p = ns. ; valence x arousal interaction: $F(1, 28) = 0.09$, p = ns.). Nonetheless, visual inspection of the mean R-III amplitude suggests that, within each valence category, stimulating pictures increased the reflex compared to relaxing ones. As a result, pleasant-relaxing and unpleasant-stimulating pictures were the only picture conditions to show differences in R-III reflex amplitude ($t(28) = 2.48$, $p < 0.05$). Finally, the reflex was found to be higher during the presentation of neutral pictures than the fixation point ($t(28) = 2.71$, $p < 0.01$).

DISCUSSION

The results of the first experiment largely replicated those obtained using a similar paradigm (Jamie L. Rhudy et al., 2005). Pain rating showed a typical effect of picture valence, with pain ratings being higher during the presentation of unpleasant pictures, intermediate during the presentation of neutral pictures, and lower during the presentation of pleasant pictures. These ratings were paralleled by higher RIII reflexes during the viewing of unpleasant pictures compared with pleasant and neutral pictures. However, we did not replicate the reduction in RIII reflex amplitude during the presentation of pleasant compared with neutral pictures. This lack of effect could be attributed to differences in the selection of pleasant pictures. Whereas Rhudy et al. (2005) only selected erotic pictures, we selected our pleasant pictures based solely on valence ratings, which led to the inclusion of extreme outdoor sports pictures (ex.: rafting, skydiving), along with erotic pictures. Since these pictures have previously been shown to produce effects generally associated with threat, such as enhanced startle reflex amplitude (Bernat, Patrick, Benning, & Tellegen, 2006), it is quite possible that they counteracted the effects of erotic pictures on RIII amplitude.

Turning to the effects of attention, pain ratings were shown to be reduced during the presentation of neutral pictures compared with the fixation point condition. However, RIII reflex amplitudes did not parallel this effect and were rather shown to be increased during the distraction caused by the neutral pictures. Thus, our results replicate the dissociation between pain ratings and spinal nociception during distraction observed in recent studies (Edwards et al., 2007; McIntyre et al., 2006; Petersen et al., 2001). In accordance with previous propositions, it is possible that the slight differences in arousal induced by the neutral pictures compared to the fixation point could explain these results, either directly by enhancing motor responses, or indirectly through systolic inhibition of the RIII driven by a faster heart rate (McIntyre et al., 2006).

Experiment 2 allowed us to examine more closely the influence of arousal on pain. First, the results replicated the main effect of emotional valence on pain ratings observed in experiment 1. In addition, high arousal amplified the effect of valence. Pain ratings were higher during unpleasant-stimulating than unpleasant-relaxing pictures, and lower during pleasant-stimulating than pleasant-relaxing pictures. These findings corroborate the results of a recent study also assessing the effects of arousal and valence of emotional pictures on pain (Jamie L. Rhudy et al., 2008). Moreover, this enhancement of valence effects by arousal fits with the motivational priming theory of Lang (1995) in which arousal is thought to determine the degree of activation of appetitive and defensive systems.

However, the effect of arousal on pain ratings was not paralleled by corresponding effects on RIII reflex amplitudes. Indeed, there were no significant differences in RIII reflex amplitude between pictures of different arousal. Nonetheless, visual inspection of the mean reflex amplitudes suggests that there was a trend towards increases in RIII reflex amplitude for highly arousing pictures, regardless of their valence. This is particularly evident on the pleasant pictures, for which RIII reflex amplitudes were qualitatively stronger during the pleasant-stimulating than pleasant-relaxing pictures, although the opposite was observed on pain ratings. Indeed, the only significant contrast between particular emotional picture conditions (i.e. unpleasant-stimulating vs pleasant-relaxing) combined the enhancing effects of negative valence and high arousal. These results contrast with those of Rhudy et al. (2008), who observed that pleasant-stimulating pictures significantly reduced RIII reflex amplitudes compared with pleasant-relaxing pictures. Again, these differences might be related to the particular content of the pictures. Whereas Rhudy et al. (2008) used only erotic and food pictures as pleasant-stimulating and pleasant-relaxing stimuli, we selected our pictures based solely on arousal normative ratings. Thus, in our study, outdoor sports pictures might have counteracted the effects of erotic pictures in our pleasant-stimulating condition, whereas the presence of low-arousal erotic pictures could have

amplified the effects of our pleasant-relaxing condition. Although the question of which approach provides the better index of arousal remains debatable, picture content and arousal were confounded in both studies. Thus, the specific contribution of emotional arousal to RIII reflex modulation remains to be assessed by strictly controlling the content of pictures.

The attentional modulation of pain ratings and RIII reflexes replicated those observed in Experiment 1, although the difference in pain ratings between neutral pictures and the fixation condition was weaker, whereas the difference in RIII reflex appeared larger. The disappearance of the effects of attention on pain ratings can be explained by the fact that the distraction provided by the neutral pictures was minimal, as the participants had no task to perform on them. This relative weakness made this effect vulnerable to slight changes in the experimental paradigm, such as the addition of new conditions. In that perspective, the inclusion of low-arousal conditions could have restricted the degree to which pain ratings could vary between the neutral and fixation conditions by adding supplementary intermediate levels of pain. Another difference between the two experiments was that arousal ratings for the fixation condition were lower in experiment 2, whereas they were almost equal to the neutral pictures condition in experiment 1. Again, this seems to be due to the inclusion of additional intermediate levels arousal in experiment 2, forcing a greater differentiation of pictures and fixation conditions along the arousal dimension.

The involvement of arousal in distraction-induced increases in RIII thus appears questionable. Indeed, the arousal of emotional pictures only produced very weak effects on the RIII reflex, which contradicted those obtained in prior study (Jamie L. Rhudy et al., 2008). Moreover, the difference in arousal between the neutral and fixation condition, although significant, appeared much lower than the observed effects of distraction on RIII amplitude. Indeed, it is unlikely that the passive viewing of neutral pictures induced much arousal. Nonetheless, this condition induced large

increases in RIII amplitude, similar to those observed when performing difficult attentional tasks (Edwards et al., 2007; McIntyre et al., 2006; Petersen et al., 2001).

It appears that distraction is the main factor involved in these increases of RIII reflex amplitude. This attentional effect can be due to a relief from supra-spinal tonic inhibition of the RIII reflex during distraction, as can be observed during hypnotically-induced analgesia (Danziger et al., 1998), or, more drastically, during cervical spinal cordotomy (Garcia-Larrea, Charles, Sindou, & Mauguiere, 1993). Indeed, the facilitation of spinal reflexes, such as the stretch reflex (McIntyre, Ring, & Carroll, 2004) during distraction is a common finding. The function of this facilitation would be to promote automatic adaptative responses, such as withdrawal from pain, while the brain's attention is occupied with the performance of the distractive task. Within that perspective, this facilitation of automatic responses would be accompanied with a reduced sensitivity in order to not interfere with the execution of the distractive task.

This is consistent with the findings of a recent study (Jamie L. Rhudy, Williams, McCabe, Rambo, & Russell, 2006), showing that the predictability of shocks reduces RIII amplitudes. Thus, the tonic inhibition of the RIII reflex during the fixation point could reflect baseline levels of anticipation and orientation toward incoming shocks, which were disrupted by competing visual processing during the presentation of the pictures. The fact that these mechanisms may vary across individuals (Danziger et al., 1998) can explain the discrepancies observed with prior studies conducted on experimented participants, or using slightly different paradigms (Bathien, 1971; Bathien & Hugelin, 1969; Bathien & Morin, 1972; Willer et al., 1979). Indeed, it is quite possible that experienced participants learned to actively dissociate themselves from the shocks during the baseline recordings, which would have lead to enhanced RIII amplitudes during the baseline period. In that perspective, the performance of the distractive task could have competed with this active dissociation process and reduced the RIII. However this explanation remains highly speculative and further research is

still needed to precise the conditions under which distraction causes RIII inhibition or facilitation.

Overall, our results indicate that emotion and attention influence pain through different spinal and supra-spinal modulatory mechanisms. Whereas emotional valence modulates pain ratings and RIII reflexes in parallel, distraction has opposite effects on pain ratings and R-III reflexes, reducing pain and enhancing the reflex. This further confirms that the distinct psychophysical effects of emotion and attention on pain (Villemure et al., 2003) are governed by distinct physiological mechanisms. However, further research is still needed to better understand how the dissociation between pain ratings and spinal nociception during attentional modulation of pain can be explained in terms of neuro-physiological mechanisms.

Footnotes

[1] Images numbers were : pleasant (4607, 4608, 4652, 4658, 4659, 4660, 4664, 4666, 4670, 4681, 4687, 4689, 4800, 4810, 5260, 5450, 5621, 5629, 8030, 8034, 8080, 8180, 8185, 8186 ,8190, 8200, 8370, 8400, 8490, 8501), unpleasant (2352_2, 3005_1, 3030, 3053, 3060, 3063, 3064, 3068, 3069, 3071, 3100, 3102, 3110, 3120, 3130, 3140, 3150, 3266, 3500, 3530, 6313, 6360, 6540, 6560, 6570, 9252, 9410, 9635_1, 9910, 9921) and neutral (2190, 2393, 2480, 2570, 2840, 2880, 2890, 5510, 5740, 7000, 7004, 7006, 7010, 7020, 7035, 7041, 7050, 7080, 7090, 7100, 7161, 7175, 7179, 7185, 7187, 7217, 7233, 7235, 7491, 7950). Mean valence and arousal ratings across pictures set were: pleasant (valence: *M* = 6.81, arousal: *M* = 6.58), unpleasant (valence: *M* = 1.64, arousal: *M* = 6.75) and neutral valence: *M* = 4.99, arousal: *M* = 2.54).

[1] Images numbers were : pleasant-relaxing (2250, 5300, 8330, 2341, 7095, 8032, 4100, 2372, 2222, 8600, 5661, 2650, 2092, 8497, 7475, 2600, 2331, 1740, 7351, 5594, 2310, 1510, 8320, 7281, 2575, 1500, 8050, 7238, 4532, 2375_2), pleasant-stimulating (4669, 8178, 4677, 5626, 8192, 8470, 8161, 5920, 4656, 4683, 8191, 8160, 4651, 4800, 8341, 8116, 5470, 4611, 8300, 8179, 4690, 2208, 4676, 8251, 8090, 1650, 4672, 8193, 8170, 5950), unpleasant-relaxing (9110, 9000, 2399, 9561, 9290, 6010, 2722, 2375_1, 9280, 9090, 2590, 2276, 9342, 9265, 3300, 2205, 9331, 9220, 9041, 2900_1, 2490, 9045, 9415, 2750, 9190, 9330, 9001, 2753, 2455, 9830), unpleasant-stimulating (2683, 6370, 9620, 3550, 6570, 8485, 6242, 4664_2, 1525, 9630, 6550, 6211, 1300, 9622, 6840, 6210, 2981, 1201, 6834, 6530, 2688, 1090, 9400, 6831, 6200, 1052, 9250, 6830, 6250_1, 5971) and neutral (1945, 4230, 7920, 2410, 5532, 7590, 2780, 2487, 1935, 9635_2, 4613, 2749, 1240, 9401, 7211, 2702, 2230, 1230, 7182, 4233, 2220, 1121, 7830, 6570_2, 2690, 1112, 7595, 5535, 4000, 2635). Mean valence and arousal ratings across pictures set were: pleasant-relaxing (valence: *M* = 6.13, arousal: *M* = 4.02) pleasant-stimulating (valence: *M* = 6.21, arousal: *M* = 6.03), unpleasant-relaxing (valence: *M* = 1.83, arousal: *M* = 4.09) unpleasant-stimulating (valence: *M* = 1.76, arousal: *M* = 6.11) and neutral (valence: *M* = 4.12, arousal: *M* = 3.98).

Table 1

Table 1. Mean (±sd) valence and arousal ratings and results of statistical tests for experiment 1

			results of statisticel tests			
		SAM ratings	pleasant	unpleasant	neutral	no picture
Valence						
	pleasant	7.34(±1.16)	-----	t(28)=15.73***	t(28)=11.16***	t(28)=11.16***
	unpleasant	1.91(±0.89)	-----	-----	t(28)=13.87***	t(28)=9.68***
	neutral	4.86(±0.77)	-----	-----	-----	t(28)=0.71
	no picture	4.71(±1.14)	-----	-----	-----	-----
Arousal						
	pleasant	5.99(±1.40)	-----	t(28)=3.72**	t(28)=9.12***	t(28)=9.87***
	unpleasant	6.80(±1.30)	-----	-----	t(28)=12.44***	t(28)=12.84***
	neutral	2.75(±1.28)	-----	-----	-----	t(28)=3.66**
	no picture	2.04(±1.45)	-----	-----	-----	-----

* = p <0.05, ** = p < 0.01, *** = p < 0.001, Bonferonni-corrected for multiple comparions

Table 2

Table 2. Mean (±SD) valence and aroual ratings and resuts of statistical tests for experiment 2

		Results of statistical tests					
	SAM rating	pleasant-stimulating	pleasant-relaxing	unpleasant-stimulating	unpleasant-relaxing	neutral	fixation
Valence							
pleasant-stimı	6.76 (±1.12)	-----	t(28)=2.61	t(28)=11.84***	t(28)=12.55***	t(28)=9.34***	t(28)=10.01***
pleasant-relax	6.30 (±0.69)	-----	-----	t(28)=12.39***	t(28)=13.49***	t(28)=8.84***	t(28)=8.11***
unpleasant-sti	2.93 (±1.01)	-----	-----	-----	t(28)=2.827	t(28)=9.14***	t(28)=5.11***
unpleasant-re	3.23 (±0.77)	-----	-----	-----	-----	t(28)=9.29***	t(28)=4.43***
neutral	4.70 (±0.80)	-----	-----	-----	-----	-----	t(28)=0.83
fixation	4.49 (±1.12)	-----	-----	-----	-----	-----	-----
Arousal							
pleasant-stimı	5.45 (±1.58)	-----	t(28)=5.91***	t(28)=2.03	t(28)=1.77	t(28)=6.74***	t(28)=9.55***
pleasant-relax	3.88 (±1.20)	-----	-----	t(28)=7.21***	t(28)=5.10***	t(28)=0.37	t(28)=6.57***
unpleasant-sti	5.95 (±1.36)	-----	-----	-----	t(28)=5.65***	t(28)=11.26***	t(28)=11.46***
unpleasant-re	4.97 (±1.28)	-----	-----	-----	-----	t(28)=6.55***	t(28)=9.36***
neutral	3.95 (±1.21)	-----	-----	-----	-----	-----	t(28)=7.63***
fixation	2.04 (±1.34)	-----	-----	-----	-----	-----	-----

* = p <0.05, ** = p < 0.01, *** = p < 0.001, Bonferonni-corrected for multiple comparions

Figure captions

Figure 1. *Time course of a typical experimental trial.* Each trial starts with the presentation of a 30-s long block of five 6-s long pictures (or fixation point in the control condition). Then, two electrical stimulations were delivered, either during the first, second or third picture for the first stimulation and the second, third or fourth stimulation for the second stimulation. After the block of pictures, participants rated the pain of the electrical stimulations and the emotions induced by the pictures.

Figure 2. Mean pain ratings and RIII reflex amplitudes (z-scores) for the four experimental conditions of Experiment 1. Significant differences are marked by asterisks (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$).

Figure 3. Mean pain ratings and RIII reflex amplitudes (z-scores) for the six experimental conditions of Experiment 2. The effects of emotions on pain ratings (A) and RIII reflex amplitudes (B) are assessed by the valence and arousal effects of emotional pictures (pleasant-stimulating (POS_s), pleasant-relaxing (POS_r), unpleasant-stimulating (NEG_s) and unpleasant-relaxing (NEG_r)). The effects of distraction on pain ratings (C) and RIII reflex amplitudes (D) are assessed by the difference between the neutral (Neugebauer et al.) picture condition and the fixation (FIX) condition. Significant differences are marked by asterisks (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$).

Figure 1

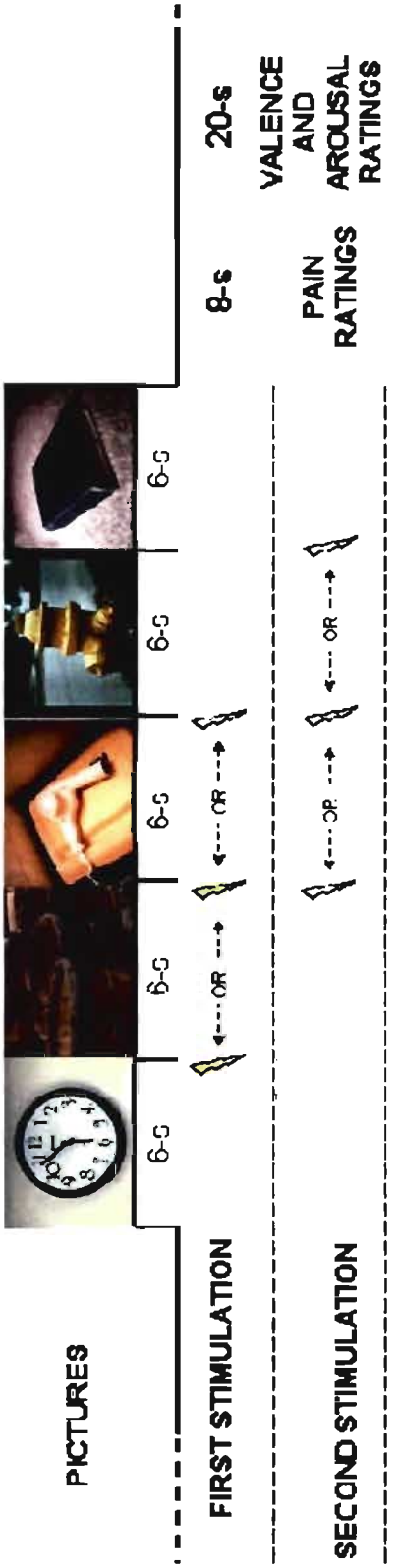

PICTURES
6-s
6-s
6-s
6-s
8-s
20-s
FIRST STIMULATION
OR
OR
PAIN RATINGS
VALENCE AND AROUSAL RATINGS
SECOND STIMULATION
OR
OR

Figure 2

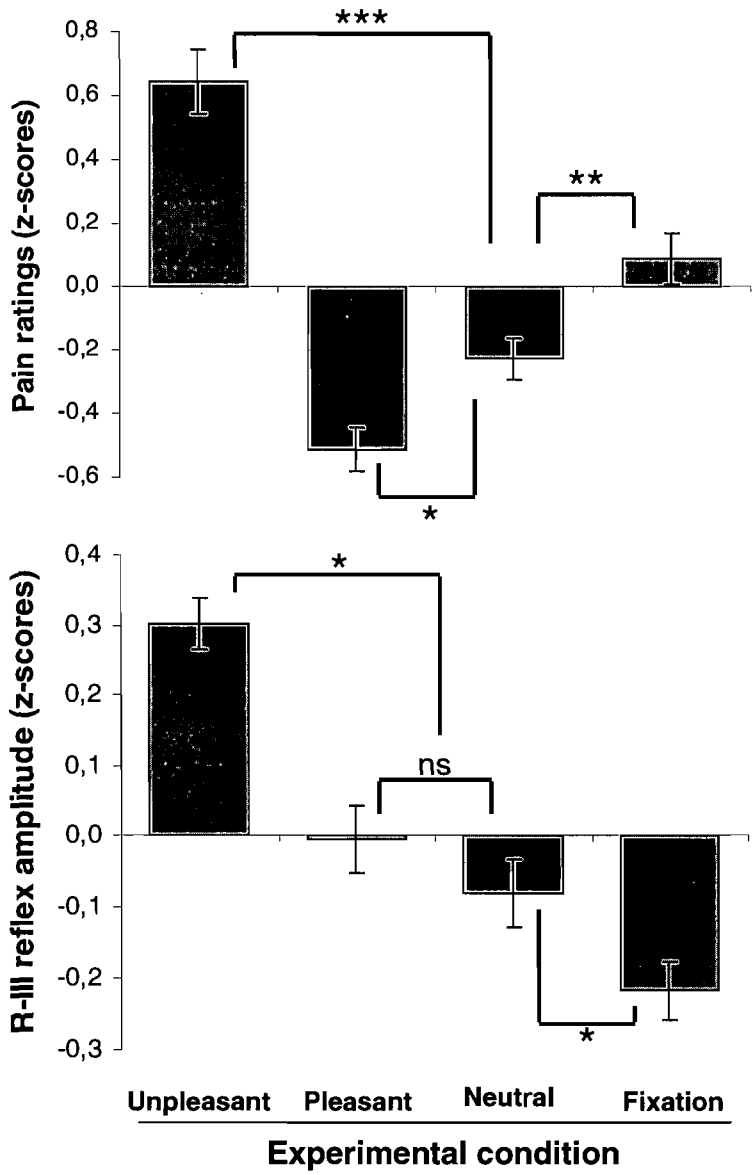
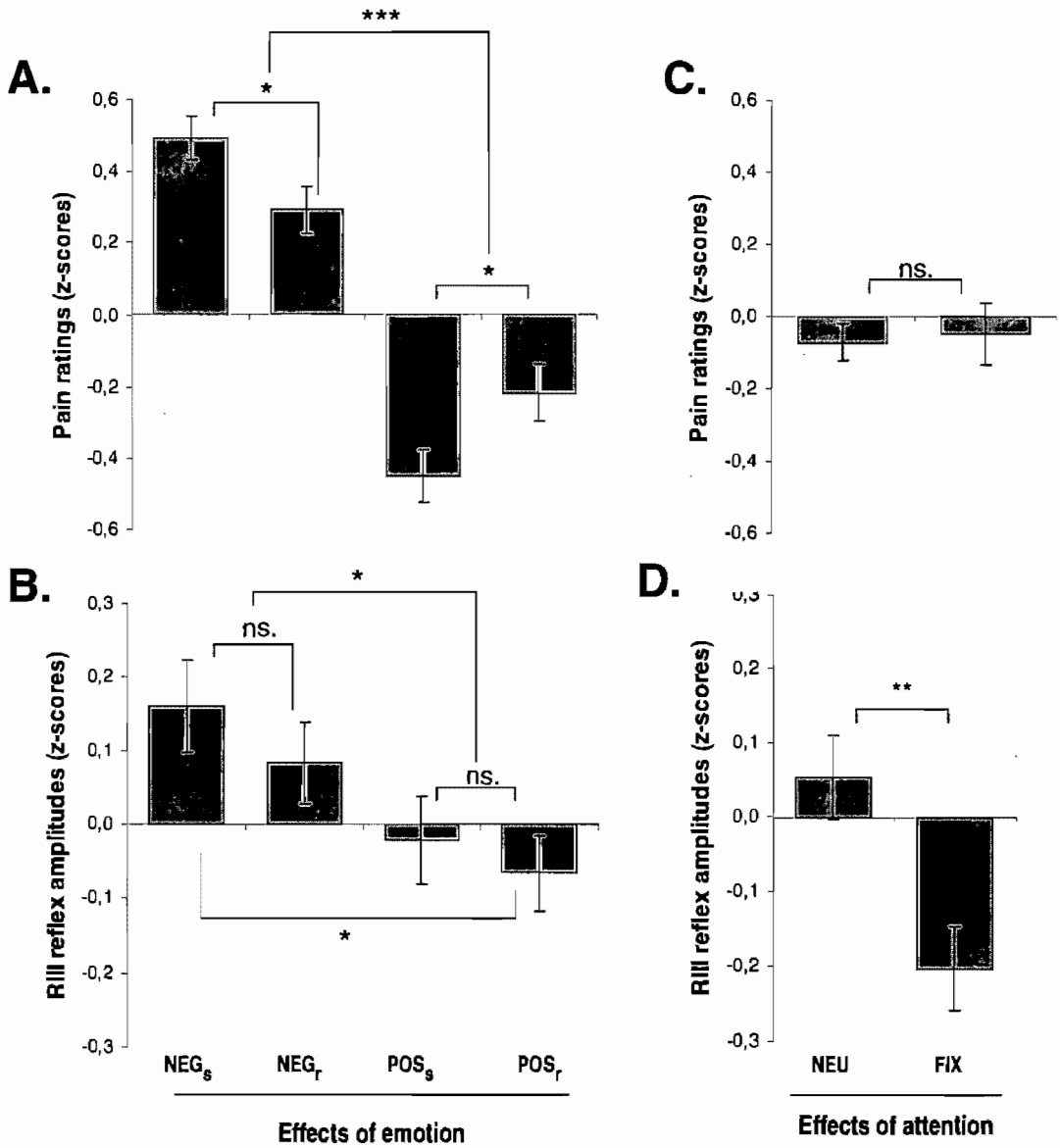

Pain ratings (z-scores)
0,8
0,6
0,4
0,2
0,0
-0,2
-0,4
-0,6
***
**
*
R-III reflex amplitude (z-scores)
0,4
0,3
0,2
0,1
0,0
-0,1
-0,2
-0,3
*
ns
*
Unpleasant
Pleasant
Neutral
Fixation
Experimental condition

Figure 3


A.
B.
C.
D.
Pain ratings (z-scores)
RIII reflex amplitudes (z-scores)
***
*
*
*
ns.
ns.
*
*
**
NEG$_s$
NEG$_r$
POS$_s$
POS$_r$
NEU
FIX
Effects of emotion
Effects of attention

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Article 6: Cerebral mechanisms involved in the emotional modulation of pain

CEREBRAL MECHANSISMS INVOLVED IN THE EMOTIONAL MODULATION OF PAIN

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Running head: Cerebral mechanisms of emotional pain modulation

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Abstract

In this study, we investigated the patterns of brain activation related to the emotional modulation of pain using fMRI in 13 healthy participants. Subjective pain ratings and nociceptive flexion reflexes (RIII reflex) elicited by painful electrical stimulations were recorded while participants observed 30-sec blocks of pleasant, unpleasant and neutral images from the IAPS. Consistent with previous work, pain ratings and the amplitude of RIII reflexes were lower during pleasant pictures, intermediate during neutral pictures and higher during unpleasant pictures. Shock-evoked BOLD-responses in the paracentral lobule, right ipsilateral insula, and bilateral parahippocampal gyrus were higher during unpleasant pictures compared to pleasant pictures. Activity within the paracentral lobule most likely reflects the modulation of the sensory-motor dimension of shock-evoked pain, which could result from a top-down modulation of nociceptive transmission at the level of the spinal chord, as evidenced by the modulation of the nociceptive reflex. In accordance with recent theories of emotions and interoception, modulation of pain-related activity in the right insula would reflect the integration of pain with the ongoing emotional states into a "global pain moment" that exceeds the simple intensity perception of the shocks (Craig, 2008). Altogether, our findings suggest that emotions modulate pain-related brain responses through various mechanisms, including cerebro-spinal modulation (paracentral lobule) and higher-order integration of pain with the ongoing emotional states (right insula, parahippocampal gyrii).

Keywords: images, IAPS, pain, emotions, brain, fMRI, nociceptive flexion reflex, RIII reflex, spine.

1. INTRODUCTION

Pain and emotions are closely related phenomena, both characterised by subjective interoceptive feelings and associated motivational dispositions, designed to maintain the homeostatic state of the individual and to promote his survival. Therefore, even though pain perception is generally a robust function of stimulus intensity, it can vary quite widely according to the emotional state of the individual (Price, 2000). For instance, anxious individuals often display exacerbated pain sensitivity (Kain et al., 2000; van den Hout, Vlaeyen, Houben, Soeters, & Peters, 2001) whereas extreme fear inhibits pain in order to facilitate appropriate responding to the incoming danger (Melzack, Wall, & Ty, 1982). Our pain experience thus appears to be the result of complex processes whereby the noxious stimulation is interpreted within the context of ongoing emotional states (Craig, 2005; Fields, 2007; Melzack & Casey, 1968).

Many experimental studies have brought empirical support to this phenomenon by showing that the induction of positive emotions can reduce pain, whereas negative ones increase it (Meagher et al., 2001b; Pierre Rainville et al., 2005; M. Roy et al., 2008; Villemure et al., 2003; Weisenberg et al., 1998; Zelman et al., 1991). In a recent study, Rhudy and colleagues (2005) demonstrated that this effect was mediated in part by descending pain-modulatory pathways. Using emotional pictures from the International Affective Picture System (Lang, 1980), they showed that emotions modulated the amplitude of a spinally-mediated nociceptive reflex (nociceptive flexion reflex or R-III reflex; Sandrini et al., 2005). Based on prior knowledge of the descending pain-modulatory pathways (Fields & Basbaum, 1999; LeDoux, 2000), they hypothesized that the amygdala and the periacqueductal gray could be the brain generators of these effects.

However, given the important interconnectivity between emotional brain regions and areas involved in the affective dimension of pain, such as the anterior

cingulate cortex and the insula (Craig, 2005), it is likely that cortical mechanisms are also involved in the emotional modulation of pain. Indeed, exacerbations of pain by anticipatory anxiety have been associated with increased activations of the parahippocampal gyrii, the perigenual cortex and bilateral insula (Ploghaus et al., 2001). Also, non-painful unpleasant oesophageal stimulation have been shown to evoke more ACC and insula activity during the presentation of fearful compared with neutral faces (Phillips et al., 2003). However, these studies only focused on the modulation of pain-related brain activity without examining the potential brain mechanisms underlying this modulation.

In order to explore the cerebral and cerebro-spinal mechanism involved in the emotional modulation of pain, we used functional magnetic to record the brain responses related to emotional states, as well as their effects on pain processing. Painful electrical stimulations were administered while participants viewed blocks of pleasant, unpleasant and neutral pictures. In addition to pain ratings, RIII reflexes were recorded as an index of spinal nociception. We hypothesised that emotions would have an effect on pain through both cerebro-spinal mechanisms, impacting on the RIII reflex and pain transmission in the spinothalamic tract, and additional cortico-cortical mechanisms involving regions related to the affective dimension of pain, such as the insula or the ACC.

2. METHODS

2.1. Participants

A total of 13 healthy volunteers participated in the study (six males and seven females; mean age: 23.4 years; SD: 5.1). Data from one male participant was excluded because of equipment failure during scanning. Participants were selected on the basis of their ability to tolerate the electrical stimulations during a pre-scanning session. The Research Ethics Board of the "Centre de recherche de l'Institut de gériatrie de

Montréal" approved the study. All participants gave written informed consent and received a compensation of 70$ for the brain imaging session.

2.2. Electrical Stimulation

Transcutaneous electrical stimulation was delivered with a Grass-S48 stimulator (Astro-Med Inc., West Warwick, RI, USA) isolated with a custom-made constant-current stimulus-isolation unit. The stimulator was equipped with a custom-made RF filter preventing artefacts in fMRI data. The stimulation consisted in a 30 ms train of 10 X 1 ms pulse, delivered on degreased skin over the retro-maleolar path of the right sural nerve by means of a pair of custom made $1cm^2$ fMRI-compatible surface electrodes. The intensity of the electrical stimulation was recorded (Biopac systems Inc., Goleta, CA, USA) and the intensity of the stimulation was adjusted individually at 120% of the reflex threshold using the staircase method (Willer, 1977). This intensity minimizes ceiling and floor effects, and induces a stable and moderately painful pin-prick sensation.

2.3. Affect Induction

Ninety pictures that evoked pleasant (POS), unpleasant (NEG) or neutral (Neugebauer et al., 2004) emotions were selected from the International Affective Picture System (Center for the Study of Emotion and Attention, 1999)[1]. Based on their normative ratings, 30 pictures were chosen within each category in order to maximize valence differences between pleasant and unpleasant pictures, while equating their arousal levels. Neutral pictures were of intermediate valence and of lower arousal than pleasant and unpleasant pictures. Pleasant pictures mainly consisted of erotic couples and outdoor sports, whereas unpleasant pictures represented images of threats or mutilations, and neutral pictures consisted of household objects and outdoor scenes. For each category, pictures were grouped in six blocks of five pictures. The presentation length of each picture was of six seconds for a total of 30 seconds per

block. A fourth condition consisting of a white fixation cross (FIX) displayed in the middle of a black screen for 30 seconds served as an additional control with no picture.

2.4. Procedure

Pre-scanning session

Before the scanning session, participants performed the experiment once outside the scanner in order to familiarize them with the procedure. The same pictures were used in the two sessions. Valence and arousal ratings were recorded only in the pre-scan session, following each block of emotional pictures or fixation point, using a computerized version of the Self-Assessment Manikin (Jasmin et al.) (Lang et al., 1980; valence: 1 = unpleasant, 9 = pleasant; arousal: 1 = low arousal, 9 = high arousal). All other measurements were done similarly in the pre-scan and scanning sessions as described below.

Scanning session

Subjects were positioned in the scanner and the electrical stimulation was adjusted at 120% of each participant's RIII threshold. The scanning session was then divided into two functional scans separated by an anatomical scan. Each functional scan consisted of 26 experimental trials. The time course of a trial is depicted in Figure 1. Each trial consisted in a 30 seconds block of emotional pictures or fixation point. Blocks with emotional or neutral pictures included five images successively presented for six seconds each. Subjects were asked to attend to each visual stimulus in order to be able to answer questions about the images after the end of scanning. Two electrical stimuli were delivered during each block of visual stimulation, 300 ms before the end of the second and fourth picture (or equivalent timing for the FIX condition). The timing of the electrical stimuli was also synchronized with the 500ms temporal delay inserted between successive fMRI volumes (see section 2.5).

At the end of each block of images, participants had 18 seconds to rate the pain elicited by the electrical stimulation on a visual analogue scale (Vastfjall et al.). Participants were asked to provide an overall rating of the pain induced by the two stimulations in the preceding block. They were also instructed that their pain ratings should reflect the perceived intensity (sensory dimension), as well as the discomfort (affective dimension) elicited by the electrical stimulations. The VAS was presented horizontally and included the verbal anchors "0 - no pain" and "100 – extremely painful" at the left and right extremities, respectively. In order to give their ratings, participants used a MRI-compatible response key to move a cursor on the VAS with their left index and middle fingers, contralateral to the side of stimulation. In order to control for possible differences in motor preparation between conditions, the cursor appeared at random positions on the VAS scale on each trial.

Each scan started with two control trials with only the fixation point. These trials controlled for potential habituation effects, allowing for the RIII reflex to stabilize. Following these two trials, the remaining 24 trials were presented in a pseudo-random order consisting of six consecutive cycles, comprising each of the four experimental conditions (NEG, POS, NEU or FIX). These cycles were ordered so that no experimental condition was presented twice consecutively. Two orders of presentation were created (order 2 reverse of order 1). The presentation of these two orders within a scanning session was counterbalanced across individuals.

After the scanning session, a picture recognition test was administered to each participant to insure that subjects attended to the images. The 90 pictures used in the experiment were randomly presented on a computer screen intermixed sequentially with 90 new pictures matched for emotional category. The participants simply had to indicate whether they had seen each picture in the experiment. The purpose of this memory test was to make sure that participants paid attention to all the pictures presented in the test. The performances for the three picture categories were

calculated as mean 'hits – false alarms' rates and compared pair by pair by means of t-tests. Recognition scores, displayed in Table 1, were equally high for the three emotional conditions, suggesting that the participants carefully paid attention to the pictures that were presented.

2.5. fMRI acquisition

Imaging data was acquired at the "Unité de Neuroimagerie Fonctionnelle" of the "Centre de recherche de l'Institut de gériatrie de Montréal" on a 3T Siemens Trio scanner (Munich, Germany) using a CP head coil. The head of the participant was stabilized in a comfortable position using a vacuum bag. Participants were instructed to refrain from moving as much as possible throughout the imaging session and were given earplugs to reduce the noise from the scanner. The anatomical scans were T1-weighted high-resolution scans [repetition time (TR): 13 ms; echo time (TE): 4.92 ms; flip angle: 25°; field of view: 256 mm; voxel size: 1 x 1 x 1.1 mm]. The functional scans were collected using a blood oxygen level-dependent (BOLD) protocol with a T2*-weighted gradient echo-planar imaging sequence (TR: 3.0 s with an inter-volume delay of 500 ms; TE: 30 ms; flip angle: 90°; 64 x 64 matrix; 433 volume acquisitions). Electrical stimuli were always administered during the inter-volume delay (see Figure 1A), thereby avoiding the potential contamination of fMRI images by shock-induced artefacts and of EMG recordings by RF-pulse artefacts. The scanning planes were oriented parallel to the anterior-posterior commissure line and covered the entire brain from the vertex of the cortex to the first segments of the spinal cord (41 contiguous 5-mm-thick slices; voxel size, 3.44 x 3.44 x 5 mm).

2.6. RIII reflex recording

Electromyographic (EMG) activity of the biceps femoris was recorded with MRI-compatible Ag-AgCl surface electrodes (Type EL-508, Biopac systems Inc., Goleta, CA,

USA) with an inter-electrode distance of 2 cm. Electromyographic (EMG) activity was amplified, band pass filtered (100-500 Hz), digitized and sampled at 1000 Hz (MP150, Biopac systems Inc., Goleta, CA, USA). A custom made RF filter was used for the recording of physiological measures to prevent introducing artefact in the fMRI data. EMG data was analysed using Acknowledge 3.8 (Biopac systems Inc., Goleta, CA, USA). The raw EMG data were filtered off-line (120-130 Hz) and transformed using the root mean square in order to rectify the signal. The resulting signal was integrated between 90-180 ms post-stimulus onset to quantify the RIII-reflex to single shocks for the covariance analysis.

2.7. fMRI data analyses

Pre-processing

Brain imaging data was analyzed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/) for the pre-processing and SPM5 for the functional analyses. Pre-processing included slice-time correction and realignment. Anatomical and functional images were then spatially normalized to a standard stereotaxic space using the MNI template. Subsequently, functional images were spatially smoothed using a Gaussian kernel of twice the voxel size (FWHM: 7 x 7 x 10 mm). For each participant, activation related to the pictures and the electrical stimulation were identified with a mixed block/event-related design where electrical stimulations were modeled as instantaneous events and experimental conditions as 30s blocks of images. The vectors created for the electrical stimulations and experimental conditions were then convolved with a canonical hemodynamic response function (hrf). At the second level, group analyses were conducted using random-effect models with contrast images of individual-subject effects.

Tresholding

The significance of the t-values obtained for the different neuroimaging analyses described above were thresholded at $p < 0.05$ Bonferonni-corrected for multiple comparisons (one-tail), based on Random Field Theory (Worsley, Evans, Marrett, & Neelin, 1992). Depending if the analysis was related to pain or picture processing, two directed search volumes were applied. The directed search volume for pain analyses comprised structures previously shown to be involved in pain (SI and SII, the cingulate cortex, INS, OFC, the PGH/amygdala, hypothalamus, thalamus and brainstem), whereas the directed search volume for picture analyses was composed of structures previously shown to be involved in emotional picture processing (occipital lobe, medial temporal lobe, thalamus, brainstem and prefrontal cortices excluding motor cortex). The pain directed search volume was estimated at 109.58 resels (using the effective FWHM) and led to a t-threshold of 4.1 ($p < 0.0013$, unc.) for pain activation falling within this volume. The picture directed search volume was estimated at 153.12 resels (using the effective FWHM) and led to a t-threshold of 4.2 ($p < 0.0011$, unc.). Activation falling out of these directed search areas were thresholded at a t-value of 5.1, according to a global search volume of 626.38 resels for the whole brain grey matter. Occasionally, a threshold of $p < 0.005$, uncorrected was applied for descriptive purposes only.

3. RESULTS

3.1. Manipulation checks

To confirm that the expected emotions were correctly induced by the emotional pictures, mean ratings of valence and arousal were averaged for each experimental condition and compared by means of t-tests. A Bonferonni correction was applied to the p values to control for the repetition of tests. Valence and arousal ratings (Jasmin et al.) acquired during the pre-scan session are reported in Table 1. The ratings confirmed that the different blocks of emotional pictures effectively induced the intended emotions. Pleasant pictures were the most pleasant, neutral pictures were of intermediate valence and unpleasant pictures were the most unpleasant. On

the arousal scale, pleasant and unpleasant pictures were found to be equally stimulating, but both were judged as more arousing than neutral pictures.

3.2. Pain ratings and RIII reflex

RIII reflex amplitudes were first standardised within participants by converting them into z-scores in order to reduce inter-subject variability and normalise the distribution of the data. Normalized RIII reflex amplitudes and raw pain ratings were then averaged for each condition and compared through analyses of variance (ANOVA) with the experimental condition as a within-subject factor. Pairwise differences between conditions were then considered with the appropriate follow-up contrasts.

Mean pain ratings and RIII reflex amplitudes are reported for each experimental condition in Figure 2. There was a significant effect of picture content on pain ratings ($F(3, 33) = 13.88$, $p < 0.001$, $\eta^2 = .59$). Planned follow-up contrasts showed that pain ratings were higher during unpleasant than neutral pictures (NEG vs NEU: $t(1,11) = 5.11$, $p < 0.001$, $d = 2.57$) and lower during pleasant than neutral pictures (POS vs NEU: $t(1,11) = 2.30$, $p < 0.05$, $d = 0.91$). Two participants were excluded from the RIII-reflex analysis. In one participant, the stimulation intensity required to reach 120% of the RIII-reflex threshold could not be attained at the maximal level of stimulation allowed by the isolation unit. In the other participant, the reflex habituated quickly after the onset of the experiment and was undetected in the last 90% of trials. These participants were also excluded from all analysis implicating the RIII reflex. In the remaining participants, the RIII was shown to be influenced significantly by the experimental condition ($F(3, 27) = 8.74$, $p < 0.01$, $\eta^2 = .67$). Planned follow-up contrasts showed that the RIII reflex was increased during the viewing of unpleasant pictures compared to pleasant and neutral pictures (NEG vs POS: $t(1,9) = 2.64$, $p < 0.05$, $d = 1.16$; NEG vs NEU: $t(1,9) = 4.18$, $p < 0.05$, $d = 1.82$)

3.2. BOLD activation

Main effects of electrical stimulation and picture presentation

In order to check if the paradigm succeeded in disentangling pain from image-related activation, a preliminary analysis was conducted to assess the patterns of activation elicited by the electric shock events and the pictures blocks, irrespective of image category. Activation related to the acute painful stimulation and to blocks of pictures are displayed in Figure 3 and significant peaks are reported in Table 2. The electrical stimulation induced the typical pattern of pain-related activation involving bilateral SI, SII, mid to anterior insula extending into the inferior frontal gyrus, in the right, mid and anterior cingulate cortex and thalamus Other activations were also found in the hypothamus, parahippocampal gyrii, pons, cerebellum, and bilateral middle and medial frontal gyrii. Significant activation to all picture blocks (POS, NEG and NEU) was found in the cuneus and bilateral middle occipital, fusiform and parahippocampal gyrii (Table 2). This first preliminary analysis confirmed that the paradigm produced coherent and distinctive patterns of activation for the painful events and pictures blocks.

Pain regions modulated by emotion

The modulation of pain-evoked brain activity by the emotional conditions were first identified by contrasting the shock-related responses in the different experimental conditions. Here, the number of contrasts tested was restricted to the conditions showing significant differences on either pain ratings or RIII reflex amplitude (i.e.: NEG > POS, NEG > NEU, NEU > POS) (Table 3). The neutral and the fixation conditions did not differ significantly on those measures (at p-threshold = 0.05) and the FIX condition is not considered further in this report. The neutral pictures were preferred over the fixation point as the intermediate valence condition because it provides a better control for the effects of visual presentation.

The NEG > POS contrast showed activation in the right ipsilateral insula, paracentral lobule, bilateral parahippocampal gyrii and lingual gyrii (Figure 4a). Notably, the right and left insula was also detected (p- uncorrected < 0.005) in the NEG > NEU and NEU > POS contrast, respectively. In addition, the NEG > NEU contrast revealed activation in the frontopolar cortex. These regions were thus more activated in response to painful electrical stimulation during the viewing of unpleasant compared to pleasant or neutral pictures. Finally, the NEU > POS contrast showed activation in bilateral parahippocampal gyrii and left cuneus, indicating lower pain-evoked activation in these structures during the viewing of pleasant compared to neutral pictures.

In a second analysis, the functional significance of the observed modulations was explored by covarying the NEG > POS, NEG > NEU and NEU > POS contrasts with the corresponding inter-individual effects (NEG – POS, NEG – NEU, NEU - POS) on pain ratings and RIII reflex. This analysis allowed to identify the shock-related regions where activity covaried with the amplitude of the emotional modulation of pain perception or RIII reflex. The results showed that different brain areas were specifically associated with either pain ratings or RIII-reflex modulation. The pain ratings covariate revealed activation in the right insula, left medial prefrontal cortex, bilateral lingual gyrus and cerebellar nodule (Table 4, Figure 4c). In contrast. the RIII reflex covariate was associated with activation in the medial thalamus, bilateral amygdala, left brainstem, right uncus, left perigenual cingulate, left medial and dorsolateral prefrontal cortex, left contralateral SI (outside of the putative foot area), cerebellar nodule and bilateral superior occipital gyrii (Table 4, Figure 4b).

Main effects of emotional pictures

As a first step in the process of identifying the sources of the modulatory effects of emotional pictures on pain-related responses, brain regions related to the unpleasant and pleasant pictures blocks were identified (i.e. NEG > NEU, POS > NEU,

NEG > POS, POS > NEG) (Table 5, Figure 5). The NEG > NEU contrast revealed activation in many areas related to emotional processing, such as the left amygdala, bilateral parahippocampal gyrii, ventromedial prefrontal cortex, left orbitofrontal cortex and right midbrain. In addition, visual activation was also seen in bilateral cuneus, middle occipital and fusiform gyrii, and bilateral superior parietal lobules. Finally, other peaks of activation were found in the right premotor cortex and cerebellum. For the NEG > POS contrast, additional activation in the medial prefrontal cortex, right retrosplenial cortex and right middle temporal gyrus were observed. The NEG > POS also showed activation in the cerebellum and visual cortices, such as the cuneus and right middle temporal and bilateral fusiform gyrii. The pleasant pictures produced much fewer activation peaks. The POS > NEU contrast only showed activation in visual areas including the right cuneus, right middle occipital gyrus and bilateral lingual gyrii. Finally, the POS > NEG contrast revealed no significant activation.

Picture-related activation were then linked to their effects on pain processing by covarying the brain activity during the pictures blocks (NEG, POS and NEU) with the pain ratings and averaged RIII reflex amplitudes. The average of the two reflexes within each block was used as the index of global RIII reflex amplitude for that block. These analyses allowed the identification of picture-related regions where activity predicted pain responses. While the averaged RIII amplitude did not show any correlations with picture-related activation, the pain ratings appeared to be predicted by activity in the left amygdala, right premotor cortex, left fusiform gyrus and cerebellum (Table 6, Figure 5d). These regions were thus shown to be more activated for pictures blocks that led to higher pain ratings.

Psycho-physiological interactions.

Finally, psycho-physiological interactions (PPI) analyses were conducted to identify the brain structures showing emotion-dependent interactions with pain-

related regions analyses (Friston et al., 1997). A psycho-physiological interaction represents the effect of an experimental or psychological context on the contribution of one area to another. For these analyses, the effect of NEG > POS pictures on the event-related responses to the electrical stimulations was chosen as the psychological variable of interest because it maximises the effects valence while controlling for arousal. Activation in the right insula and the paracentral lobule (sensori-motor cortex) were selected as seed regions for the PPI because of their established role in pain processing and their strong modulation in the NEG > POS contrast (Table 3). Time series were extracted from a sphere (6 mm radius) centered on the selected seed regions maximum of the NEG > POS contrast for each participants using the first eigen time series (principal component) of this area. The PPI regressor was then computed as the element-by-element product of the mean-corrected seed region activity and a vector coding for the differential effect of unpleasant compared to pleasant pictures (1 for unpleasant and -1 for pleasant). The results of these PPIs thus revealed the brain regions where activity covaried positively more strongly with the seed regions during the presentation of unpleasant compared to pleasant pictures.

The results of the PPI are displayed in Table 6 and Figure 6. The regions showing enhanced connectivity with the right insula for the stimulations delivered during unpleasant vs pleasant pictures included areas related to emotional processing, such as the bilateral orbitofrontal cortices and left inferior frontal gyrus. The regions showing enhanced connectivity with the paracentral lobule also included a combination of areas related to emotional processing, such as the medial prefrontal cortex, inferior frontal gyrus, middle temporal gyrus and parahippocampal gyrus. A peak of activation in the left supplementary motor area was also observed near the paracentral seed region. Both analyses also revealed increased functional connectivity with visual areas of the occipital cortex consistent with interactions between visual and pain networks.

4. DISCUSSION

In this study, we explored the brain mechanisms involved in the emotional modulation of pain. The experimental design of the study was particularly fit for this objective, as it enabled us to examine separately the brain activations related to emotions from the ones related to pain modulation, as well as their interactions within the brain. Moreover, the recording of a spinally-mediated nociceptive reflex, along with ratings of perceived pain, allowed us to explore the relative involvement of descending cerebrospinal and cortical mechanisms at play during the emotional modulation of pain. In this section, we first examine the effects of our emotional manipulations on pain ratings and spinal nociception, before proposing potential underlying cerebral mechanisms in light of the neuroimaging data.

4.1. Emotional modulation of pain perception and R-III reflexes

Pain perception was shown to be substantially influenced by the valence of the experimental conditions. In accordance with previous findings (Jamie L. Rhudy et al., 2005), pain ratings were lowest during pleasant pictures, intermediate during neutral pictures, and highest during unpleasant pictures. These effects were independent of arousal, since the equally arousing pleasant and unpleasant pictures produced opposite effects on pain ratings. In addition, the performance on the recognition test was equally good for all emotional categories, suggesting comparable allocation of attention across conditions.

The effects of emotion on the R-III reflex replicated only partially previous findings (Jamie L. Rhudy et al., 2005). Although the reflex was enhanced during unpleasant compared to pleasant and neutral pictures, we found no differences in reflex amplitude between the pleasant and neutral conditions. This lack of effect might stem from the heterogeneity of the pictures constituting the blocks of pleasant pictures. Indeed, the outdoors sports pictures depicting scenes where danger is impending (parachuting, kayaking, etc.) have been shown to sometimes produce the opposite effects than those expected by their valence, such as enhanced startle reflex

amplitude (Bernat et al., 2006). Moreover, the remaining pictures, which mainly represented erotic couples, have been shown to produce much larger pain reductions in men than females (Meagher et al., 2001b). Most importantly for the present study though, the valence effect, as evidenced by the enhanced RIII amplitude during unpleasant compared with pleasant pictures, paralleled the one observed on pain ratings and indicate the presence of a valence effect on spinal nociception.

4.2. Insula and interoceptive integration of emotion

This valence effect was associated with the modulation of many pain-related regions activated by the electrical stimulations. The largest modulation occurred in the right mid-insula, which showed enhanced shock-related activity during the viewing of unpleasant compared to pleasant and, to a lesser extent, neutral pictures. This finding fits well with current theories of pain and interoception attributing to the right insula a pivotal role in the integration of emotions stemming from different modalities (Craig, 2008). The first step of this integration is believed to occur precisely through the right mid-insula's connections with sensory cortices and subcortical homeostatic control regions, such as the hypothalamus and the amygdala (Chikama, McFarland, Amaral, & Haber, 1997). Strikingly, in our experiment, activation of the left amygdala in response to unpleasant pictures also predicted subsequent pain ratings. Moreover, the amplitude of pain ratings modulation was in turn positively correlated with activity within the right mid-insula. These findings suggest that the increased right mid-insula pain responses during the viewing of unpleasant pictures indeed reflected the integration of emotions and pain into a subjective "global pain moment".

Results of the PPI analyses also showed that the modulation of the right mid-insula responses to pain was correlated with bilateral orbitofrontal activity during the presentation of unpleasant compared with pleasant pictures. Again, these results fit particularly well with the proposed posterior-to-anterior sequential integration of interoception within the insular cortex, which culminates in the anterior insula, and

extends into the orbitofrontal cortices (Craig, 2008). Within this perspective however, the orbitofrontal cortex does not have a direct role in interoception *per se*, but rather provides motivational inputs to the interoceptive processes of the insula. In accordance with this theory, the anticipation of pain has been shown to produce activations in the anterior insula/orbitofrontal cortices, rostrally to the regions actually activated by the painful stimuli (Keltner et al., 2006; Koyama, McHaffie, Laurienti, & Coghill, 2005; Ploghaus et al., 1999). Similarly, risk assessment and harm avoidance also produce activations in the anterior insular/orbitofrontal cortices, rostrally to those involved in the processing of the punisher itself (Paulus et al., 2003). These findings are consistent with the established role of the orbitofrontal cortex in emotional valuation (Kringelbach, 2005; Murphy, Nimmo-Smith, & Lawrence, 2003). Accordingly, the unpleasant pictures presented in our experiment produced activations in the left orbitofrontal cortex, in a region associated with the evaluation of punishers (Murphy et al., 2003). Taken together, these findings suggest that the presentation of unpleasant pictures, representing threats or body mutilations, could have influenced pain processing in the right insula in part through orbitofrontal activations related to threat perception or pain anticipation.

4.3. Anxiety-induced hyperalgesia

A second locus of modulation was found in the paracentral lobule, in a region involved in the primary sensorimotor representation of the foot (Dobkin, Firestine, West, Saremi, & Woods, 2004). Increased activation of this region during the viewing of unpleasant compared with pleasant pictures could result from a downstream modulation of nociception in the spinothalamic tract, whose efferents densily project onto primary sensory cortices. In support of this interpretation, the amplitude in R-III reflex modulation was positively correlated with activity in the contralateral thalamus, suggesting enhanced transmission of nociceptive inputs from the spinal chord to the thalamus during the viewing of unpleasant pictures. In addition, activity in bilateral amygdala strongly correlated with the amount of R-III reflex modulation. Since the

amygdala is the endpoint of the spinoparabrachial tract, this result could again be a sign of increased transmission of nociception in the spinal chord. Indeed, descending facilitatory mechanisms are now becoming the object of increased attention, especially in relation with anxiety-induced hyperalgesic states, which have been shown to involve cholecystokinins activity within the periacqueductal grey (PAG) (Lovick, 2008). In accordance with these findings, a recent neuroimaging study found activations during the anticipation of pain within the entorhinal cortex, the PAG and the ventral tegmental area (VTA), that predicted subsequent responses to heat pain in the posterior thermoceptive insula, possibly through ways of a descending facilitatory system (Fairhurst et al., 2007).

Interestingly, some of these structures, such as the entorhinal cortices and the PAG, were activated in our study during the presentation of unpleasant pictures. Moreover, the PPI analyses showed that the emotional modulation of the paracentral lobule activity was strongly related to bilateral parahippocampal gyrii activity. This is consistent with previous studies suggesting that anxiety-induced hyperalgesia first involves the activation of an anxiety-related hippocampal network, which in turn increases pain by sending amplifying signals to the neural representation of the pain stimulus (Gray & McNaughton, 2000; Ploghaus et al., 2001). This theory fits perfectly well with our results, although we propose, together with recent theories of anxiety-induced hyperalgesia (Lovick, 2008) and concordant neuroimaging evidence (Fairhurst et al., 2007), that this happens in part through a descending facilitatory system. However, other mechanisms might also have influenced the paracentral lobule activity. Indeed, the PPI analyses highlighted the covariation of various structures with the paracentral lobule during the viewing of unpleasant compared with pleasant pictures. Among these stuctures, the medial prefrontal cortex (MPFC) and supplementary area (Kong et al.), which have previously been implicated in the anticipation of pain (Hsieh, Meyerson, & Ingvar, 1999; Koyama et al., 2005; Ploghaus et al., 1999), could well have

influenced the activity of the paracentral lobule through their connections with it (Koyama et al., 2005).

Finally, the parahippocampal gyrii represented a third locus of modulation of pain by emotions. Its enhanced shock-related activations during unpleasant compared to pleasant pictures appears to be mainly due to a reduction of its activity during the pleasant pictures, as evidence by the higher activations during neutral compared with pleasant images. In addition to its role in anxiety (Gray & McNaughton, 2000), many studies have found parahippocampal activations in response to pain (Apkarian, Bushnell, Treede, & Zubieta, 2005), where it is believed to mediate the aversive drive and affect characteristic of pain (Melzack & Casey, 1968). Interestingly, parahippocampal responses to pain were shown to be increased by anxiety (Ploghaus et al., 2001), as well as in pain disorders related to anxiety (Geuze et al., 2007; Gündel et al., 2008; Lackner et al., 2006). It thus appears as if the pre-stimulation level of activity within the parahippocampal gyrii, which is influenced by anxiety, influences the region's subsequent responses to pain. Hence, the activation of the parahippocampal gyrus during unpleasant pictures might have contributed to its enhanced responsivity to the electrical stimulations. The increases in amygdala activity, observed in covariation with the R-III reflex modulation, might be explained by a similar mechanism. Indeed, in addition to its well-known involvement in emotional perception (Adolphs, 2002), the role of the amygdala in pain perception has also been documented (Neugebauer et al., 2004). As for the parahippocampal gyrus, the amygdala is shown to respond more strongly to pain in individuals prone to pain disorders related to anxiety (Giesecke et al., 2005; Gündel et al., 2008). Thus, the activations in the left amygdala in response to unpleasant pictures might well have increased its reactivity to the painful electrical stimulations.

4.4. Limitations and future directions

Although the present study revealed many of the brain mechanisms involved in the effects of unpleasant pictures on pain, the mechanisms involved in the pain reduction associated with the pleasant pictures largely remains to be identified. Indeed, pleasant pictures only produced scarce activations in visual areas of the brain. One reason for the lack of emotion-related activations to pleasant pictures, intrinsic to the paradigm, could be related to the fact that pain reduces the pleasantness of pleasant pictures and associated patterns of brain activity (Godinho, Frot, Perchet, Magnin, & Garcia-Larrea, 2008). Another reason for this lack of activations might stem from the heterogeneity of the pictures constituting the blocks of pleasant pictures. Indeed, the outdoors sports pictures depicting scenes where danger is impending (parachuting, kayaking, etc.) have been shown to sometimes produce the opposite effects than those expected by their valence, such as enhanced startle reflex amplitude (Bernat et al., 2006). Moreover, the remaining pictures, which mainly represented erotic couples, have been shown to produce much larger pain reductions in men than females (Meagher et al., 2001b). The use of a more homogeneous set of pleasant pictures showing strong pain reductions effects, such as erotic pictures in men, could have helped to identify more accurately the mechanisms involved in pain reduction to pleasant pictures.

Another surprising result was that the anterior cingulate cortex (ACC), which plays an important role in the affective dimension of pain (Rainville et al., 1997), was not found to be involved in the emotional modulation of pain in our study. This might results from the use of electrical stimulations as the pain inducer, as these produce instantaneous pin-prick sensations that contrast with the long-lasting burning sensation of thermal pain. Indeed, long-lasting thermal stimulations add a tolerance dimension to the experience of pain, which might be more closely linked to the ACC role in the affective dimension of pain. Therefore, it is possible that longer thermal stimulations would have been associated with stronger emotional modulation of the ACC.

4.5. Conclusion

Our results show that a variety of brain mechanisms are responsible for the effects of emotion on pain. One of these mechanisms appears to involve the integration of interoceptive feelings related to pain and background emotions in the right mid-insula. Another mechanism rather seem to recruit anxiety-related facilitatory descending mechanisms originating in the parahippocampal gyrii and brainstem nuclei that facilitate the transmission of nociceptive inputs to the thalamus and primary sensorimotor cortex. However these mechanisms do not appear completely segregated, as many other areas related to emotion or expectations were shown to be connected with the modulated pain areas, reflecting the deep intermingling of pain and emotions.

Footnotes

[1] Images numbers were : pleasant (4607, 4608, 4652, 4658, 4659, 4660, 4664, 4666, 4670, 4681, 4687, 4689, 4800, 4810, 5260, 5450, 5621, 5629, 8030, 8034, 8080, 8180, 8185, 8186 ,8190, 8200, 8370, 8400, 8490, 8501), unpleasant (2352_2, 3005_1, 3030, 3053, 3060, 3063, 3064, 3068, 3069, 3071, 3100, 3102, 3110, 3120, 3130, 3140, 3150, 3266, 3500, 3530, 6313, 6360, 6540, 6560, 6570, 9252, 9410, 9635_1, 9910, 9921) and neutral (2190, 2393, 2480, 2570, 2840, 2880, 2890, 5510, 5740, 7000, 7004, 7006, 7010, 7020, 7035, 7041, 7050, 7080, 7090, 7100, 7161, 7175, 7179, 7185, 7187, 7217, 7233, 7235, 7491, 7950). Mean valence and arousal ratings across pictures set were: pleasant (valence: $M = 6.81$, arousal: $M = 6.58$), unpleasant (valence: $M = 1.64$, arousal: $M = 6.75$) and neutral valence: $M = 4.99$, arousal: $M = 2.54$).

Table 1

Table 1. Mean (±sd) valence and arousal ratings and recognition scores

	experimental condition		
	pleasant	neutral	unpleasant
SAM ratings			
valence	7.38[bcd](±0.96)	4.86[ac](±0.86)	2.07[acd](±0.68)
arousal	5.56b[d](±0.94)	2.83[ac](±1.30)	6.29[bd](±1.37)
Recognition (% hits- false alarms)	0.88(±0.11)	0.91(±0.07)	0.93(±0.06)

[a] = different from pleasant pictures; [b] = different from neutral pictures; c = different from unpleasant pictures; $p < 0.05$, Bonferonni corrected for multiple comparisons.

Table 2

Table 2. Brain activations peaks* to the painful stimulations and the pictures blocks

Region of activation	BA	Side**	*t*	*x, y, z***
All painful stimulations				
Postcentral gyrus/Paracentral lobule	1-3,5	L	9.20	-7, -41, 75
Precuneus/Postcentral gyrus	1-3,5,7	R	9.91	7, -55, 70
Precentral gyrus/SMA	4/6	L	7.07	-7, -10, 80
Cingulate cortex				
Anterior	24	L	6.90	-7, 14, 40
Mid	24	L	6.69	-10, -3, 45
Dorsal	32	L	7.30	-3, 10, 50
Insula	13	L	8.67	-34, 17, 10
	13	R	7.02	38, 14, 0
Parietal operculum	40	L	9.46	-59, -24, 20
	40	R	9.83	69, -24, 20
Parahippocapal gyrus	28/35	L	5.10	-21, -21, -15
	28/35	R	5.32	21, -21, -15
Inferior frontal gyrus	45	R	8.66	41, 38, 5
Middle frontal gyrus	10/46	L	7.49	-45, 45, 20
	10/46	R	6.66	34, 38, 25
Medial frontal gyrus	25	L	5.43	-21, 17,-15
	25	R	6.11	14, 14, -15
Thalamus	----	L	6.14	-7, -28, 10
	----	R	6.28	7, -28, 5
Hypothalamus	----	----	5.40	0, 0, -15
Pons	----	R	7.13	3, -38, -30
Cerebellum				
culmen	----	L	6.18	3, -58, -5
uvula of vermis	----	----	7.32	0, -86, -30
tonsils	----	L	6.30	-31, -55, -45
	----	R	6.24	28, -41, -50
All pictures				
Midlle occipital gyrus	18	L	17.71	-31, -86, -5
	18	R	17.87	38, -86, 0
Fusiform gyrus	37	L	8.23	-31, -65, -15
	37	R	14.95	34, -65, -15
Cuneus	17	----	7.47	0 -96, 0
Parahippocampal gyrus	28/35	L	7.10	-24, -31, 0
	28/35	R	7.46	21, -28, 0

Note: Peaks of activity thresholded at $p<0.05$ corrected for multiple comparisons for the global search volume (626.38 resels), using RFT.
* only one peak (max. T-value) per region of interest is reported
** R: right ipsilateral side; L: left contralateral side
*** Coordinates are reported in MNI space

Table 3

Table 3. Shock-related activations
modulated by pleasant and unpleasant pictures

Region of activation	BA	Side*	*t*	*x, y, z***
Pain during unpleasant > pleasant pictures				
Insula	13	R	7.81	38, 7, 10
Paracentral lobule	5/6	- - - -	4.96	0, -24, 60
Dorsal posterior cingulate	31	R	3.89***	7, -28, 45
Parahippocampal gyrus	28/35	L	4.27	-31, -34, -20
	28/35	R	5.00	28, -34, -20
Lingual gyrus	17	L	4.27	-17, -103, -10
	17	R	4.79	14, -89, 0
Pain during unpleasant > neutral				
Insula	13	R	3.42***	31, 3, 10
Frontopolar cortex	10	R	5.46	-17, 58, 25
Pain during neutral > pleasant				
Insula	13	L	3.25***	-34, -28, 15
Parahippocampal gyrus	28/35	L	8.77	-28, -45, -10
	28/35	R	4.78	28, -34, -20
Cuneus	18	L	5.13	-17, -103, 15

Note: *A priori* regions are thresholded at p<0.05, corrected for multiple comparisons using RFT (pain directed search volume = 109.58 resels).
Other regions are thresholded at p<0.05, corrected for multiple comparisons using RFT (global search volume = 626.38 resels).
* R: right ipsilateral side; L: left contralateral side
** Coordinates are reported in MNI space
*** p < 0.005, uncorrected

Table 4

Table 4. Brain regions correlating with pain ratings and R-III reflex modulation during unpleasant vs pleasant pictures

Region of activation	BA	Side*	*t*	*x, y, z***
Correlation with pain ratings modulation				
Insula	13	R	4.52	41, 17, -5
Medial prefrontal cortex	10	L	5.41	-14, 48, 5
Lingual gyrus	17	L	7.54	-10, -86, -5
	17	R	457	14, -96, -5
Cerebellar nodule	----	L	5.18	-14, -58, -35
*Correlation with R-III reflex modulation****				
Medial thalamus	----	L	5.50	-7, -17, 10
Amygdala	----	L	6.25	-17, -7, -20
		R	6.29	20, -10, -30
Brainstem	----	L	4.19	-10, -21, -25
Uncus	38	R	4.62	27, 10, -30
Perigenual cingulate	25	L	6.83	-7, 31, -15
Medial prefrontal cortex	10	L	4.87	-17, 52, 10
Dorsolateral prefrontal cortex	9	L	5.20	-55, 14, 35
Postcentral gyrus	2	L	5.17	-58, -27, 50
Cerebellar nodule	----	L	6.07	-7, -62, -30
Superior occipital gyrus	19	L	7.34	-34, -89, 25
	19	R	5.86	31, -83, 45

Note: *A priori* regions are thresholded at $p<0.05$, corrected for multiple comparisons using RFT (pain directed search volume = 109.58 resels).
Other regions are thresholded at $p<0.05$, corrected for multiple comparisons using RFT (global search volume = 626.38 resels).
* R: right ipsilateral side; L: left contralateral side
** Coordinates are reported in MNI space
*** Two participants excluded due to insufficient R-III reflex (n = 10)

Table 5. Brain activations to pleasant and unpleasant pictures

	a. Unpleasant vs neutral pictures				b. Pleasant vs neutral pictures				c. Unpleasant vs pleasant pictures*			
Region of activation	BA	Side	*t*	*x, y, z***	BA	Side	*t*	*x, y, z***	BA	Side	*t*	*x, y, z***
Cuneus	18	L	8.04	-14. -100, 15	----	----	----	----	----	----	----	----
	18/19	R	9.50	14, -100, 20	18	R	5.48	17,-100, 25	18	R	4.68	3, -100, 10
Lingual gyrus	----	----	----	----	17/18	R	5.16	3,-93, 5				
Middle Occipital gyrus	19	L	8.27	-48, -82, 0	19	L	5.25	-52, -67, 5	19	L	7.25	-48, -82, -5
	19	R	9.09	41, -80, 5	19	R	4.94	52, -72, 0	19	R	5.03	48, -72, -5
Fusiform gyrus	37	L	7.10	-38, -55, -15	----	----	----	----	37	L	4.92	-34, -58, -15
	37	R	9.16	48, -62, -25	----	----	----	----	37	R	5.72	38, -52, -15
Superior parietal lobule	7	L	4.78	-24, -58, 70	----	----	----	----	7	L	4.23	-31, -65, 60
	7	R	5.09	31, -55, 55	----	----	----	----	----	----	----	----
Retrosplenial cortex	----	----	----	----	----	----	----	----	26/29-30	R	4.49	3, -38, 0
Thalamus	----	----	4.41	0, -14, 5	----	----	----	----	----	----	----	----
Thalamus\Pulvinar	----	R	4.92	3, -31, -5	----	----	----	----	----	----	----	----
Amygdala	----	L	5.68	-28, -10, -20	----	----	----	----	----	----	----	----
Parahippocampal gyrus	28/35	L	4.43	-17, -17, -20	----	----	----	----	----	----	----	----
	28/35	R	4.10	28, -28, -5	----	----	----	----	----	----	----	----
Orbitofrontal cortex	38	L	4.84	-38, 24, -25	----	----	----	----				
Middle temporal gyrus	----	----	----	----	----	----	----	----	21	R	4.53	58, -38, -10
Ventromedial prefrontal cortex	10/14	----	4.00	0, 52, -15	----	----	----	----	----	----	----	----
Medial prefrontal cortex	----	----	----	----	----	----	----	----	8	----	4.69	0, 38, 55
Premotor cortex	6/8	R	5.33	53, 3, 50	----	----	----	----	----	----	----	----
Midbrain	----	R	4.92	3, -31, -5	----	----	----	----	----	----	----	----
Cerebellum												
Culmen	----	L	5.73	-34, -48, -30	----	----	----	----	----	----	----	----
	----	R	8.07	34, -45, -30	----	----	----	----	----	----	----	----
Nodule	----	----	----	----	----	----	----	----	----	----	4.14	0, -48, -30
Tuber of vermis	----	R	6.40	7, -72, -30	----	----	----	----	----	----	4.79	0, -83, -25
Declive	----	----	----	----	----	----	----	----	----	L	5.31	-45, -72, -25
Pyramis	----	----	----	----	----	----	----	----	----	L	4.63	-14, -83, -45
	----	----	----	----	----	----	----	----	----	R	5.39	10, -79, -45

Note: Peaks of activity thresholded at p<0.05 corrected for multiple comparisons for the pictures directed search volume (153.12 resels) using the Random Field Theory. Peaks of activity falling out of a priori defined regions are tresholded at p<0.05 corrected for multiple comparisons for the global search volume (626.38 resels)

*There were no significant peaks for the pleasant vs unpleasant pictures contrast

** Coordinates are reported in MNI space

Table 6

Table 6. Brain activity related to emotional pain modulation

Region of activation	BA	Side*	*t*	*x, y, z***
*Picture-related activations predicting pain ratings****				
Premotor cortex	6/8	R	4.22	45, 10, 20
Amygdala	----	L	4.39	-17, -3, -10
Fusiform gyrus	18	L	4.12	-34, -58, -20
Cerebellum				
Declive of vermis	----	----	3.96	0, -75, -15
Uvula	----	L	5.79	-10, -93, -25
Higher connectivity with right insula for pain during unpleasant vs pleasant pictures (PPI)				
Orbitofrontal cortex	14	L	3.78	-21, 38, -15
	14	R	5.58	17, 41, -15
Inferior frontal gyrus	47	L	3.94	-55, 28, 0
Cuneus	18	----	4.10	0, -79, 5
Middle occipital gyrus	19	R	4.76	28, -96, 20
Higher connectivity with right paracentral lobule for pain during unpleasant vs pleasant pictures (PPI)				
Medial prefrontal cortex	9	----	4.65	0, 58, 30
	10	L	4.10	10, 55, 5
Inferior frontal gyrus	45	L	5.15	-55, 28, 15
Supplemetary motor area	6	L	4.62	-7, -17, 80
Middle temporal gyrus	21	R	4.85	55, 3, -20
Parahippocampal gyrus	28/35	L	5.12	-24, -27, 0
Fusiform gyrus	18	L	3.72	-34, -58, -10
	18	R	5.28	38, -62, -20
Inferior occipital gyrus	18	L	5.20	-34, -90, -20
Cuneus	18	L	7.20	-21, -103, 10
	18	R	5.81	7, -103, 10

Note: *A priori* regions are thresholded at p<0.05, corrected for multiple comparisons using RFT (pictures directed search volume = 153.12 resels). Other regions are thresholded at p<0.05, corrected for multiple comparisons using RFT (global search volume = 626.38 resel

* R: right ipsilateral side; L: left contralateral side

** Coordinates are reported in MNI space

*** There were no significant activations for correlations with R-III reflex

Figure captions

Figure 1. *Time course of a typical experimental trial.* Each trial starts with the presentaiton of a 30-s long block of five 6-s long pictures (or fixation point in the control condition). Then, two electrical stimulations are delivered 300 ms before the end of the second and fourth pictures. At the end of the block participants evaluated the pain elicited by the stimulations on a VAS.

Figure 2. *Pain ratings and R-III reflex amplitudes.* The top panel illustrates the effects of the experimental condition on pain ratings. The bottom panel illustrates the effects of the experimental condition on sandardised R-III reflex amplitudes. * = $p < 0.05$.

Figure 3. *Main effects of electrical stimulation (left) and picture presentation (right).* Painful electical stimulation elicited activations in the primary somatosensory cortices (SI), left precentral gyrus (PCG) and supplementary motor area (Kong et al.), anterior cingulate cortex (ACC), cerebellum (CB), bilateral insula (Ins), left inferior frontal gyrus (IFG), bilateral secondary somatosensory cortices (SII), Thalamus (Thal), Pons, bilateral middle frontal gyrii (MFG) (A-E), and other regions (see table 2). Images were thresholded at $p < 0.05$, bonferroni corrected for multiple comparisons for a global search volume of 626.38 resels.

Figure 4. *Pain regions modulated by emotions.* (A) Regions where pain-related activity was higher during the viewing of unpleasant compared to pleasant pictures included the paracentral lobule (PCL), posterior dorsal cingulate cortex (PCC), right insula (Ins), bilateral parahippocampal gyrii and others (see table 3). (B) Regions where the amplitude of the modulation between unpleasant and pleasant pictures correlated with the amplitude of R-III modulation were the perigenual cingulate cortex (pgACC), bilateral amygalae (Amy), cerebellum (Cb), Thalamus (Thal), medial prefrontal cortex (MPFC) and others (see table 4). (C) Regions where the amplitude of the modulation between unpleasant and pleasant pictures correlated with the amplitude of pain ratings modulations were the bilateral lingual gyrii (LG), right insua (Ins), medial prefrontal cortex (MPFC) and others (see table 4). Activations were thresholded at $p < 0.005$ for display purposes.

Figure 5. *Main effects of emotional pictures.* (A) Unpleasant pictures elicited stronger activations than neutral pictures in the bilateral fusiform gyrii (FFG), bilateral parahippocampal gyrii (PHG) and amygdala (Amy), the left lateral orbitofrontal cortex (OFC), the ventromedial prefrontal cortex (VMPFC), the cuneus (Cun), the cerebellum (Cb), the midbrain (Mb), the thalamus (Thal) and hyothalamus (Hyp), the right premotor cortex and bilateral middle occipital gyrii. (B) Pleasant pictures elicited stringer activations than neutral pictures the right lingual gyrus (LG) and middle occipital gyrus (MOG), and others (see table 5). (C) Unpleasant pictures elicited stronger activations than pleasant pictures in the Cuneus (Cun), cerebellum (Cb), retrosplenial cortex (RSplC) and medial prefrontal cortex (MPFC). (D) Activations to the

picture blocks that correlated with subsequent pain ratings were found in the left fusiform gyrus (FFG), right premotor cortex (PMC), left amygdala (Amy) and others (see table 6). Activations were thresholded at $p < 0.005$ for display purposes.

Figure 6. *Results of the psycho-physiological interaction (PPI) analyses.* (A) The psychological variable for the interaction is the contrast between the electrical stimulations presented during unpleasant and plesant pictures. (B) On the left, the bilateral orbitofrontal cortices (OFC) and cuneus (Cun) exhibited higher connectivity with the right insula for the electrical stimulations presented during the viewing of unpleasant compared with pleasant pictures. On the right, the cuneus (Cun), supplementary motor area (Kong et al.), medial prefrontal cortex (MPFC), bilateral fusiform gyrii (FFG) and left parahippocampal gyrus (PHG) exhibited higher connectivity with the paracentral lobule for the electrical stimulations presented during the viewing of unpleasant compared with pleasant pictures. (C) The right insula (Ins) and the paracentral lobule (PCL), where activations to electrical stimulations were shown to be higher during unpleasant than pleasant pictures, served as the physiological variables ('seeds') for the psycho-physiological interactions. Activations were thresholded at $p < 0.005$ for display purposes.

Figure 1

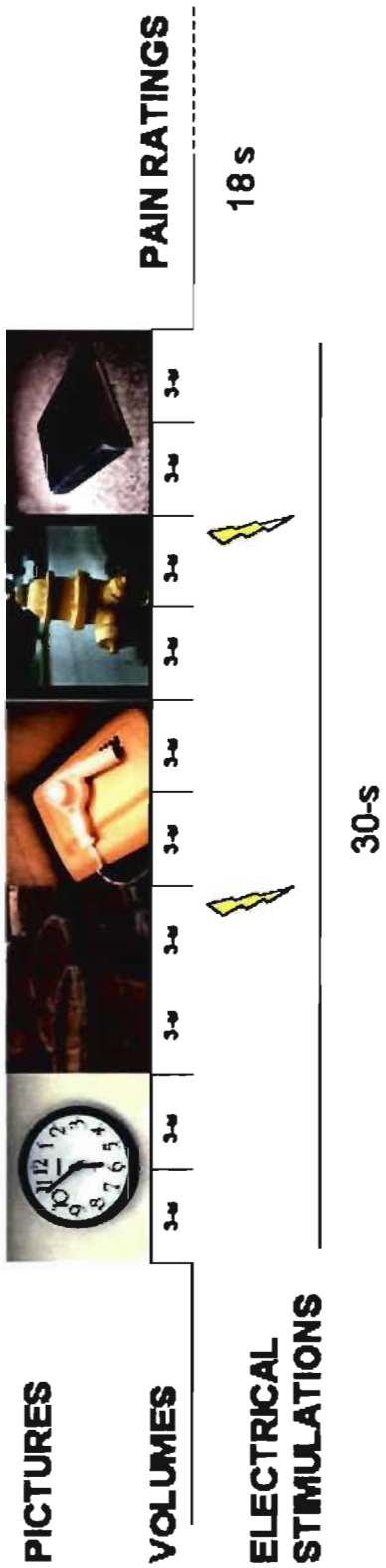

PICTURES
VOLUMES
ELECTRICAL STIMULATIONS
PAIN RATINGS
18 s
30-s

Figure 2

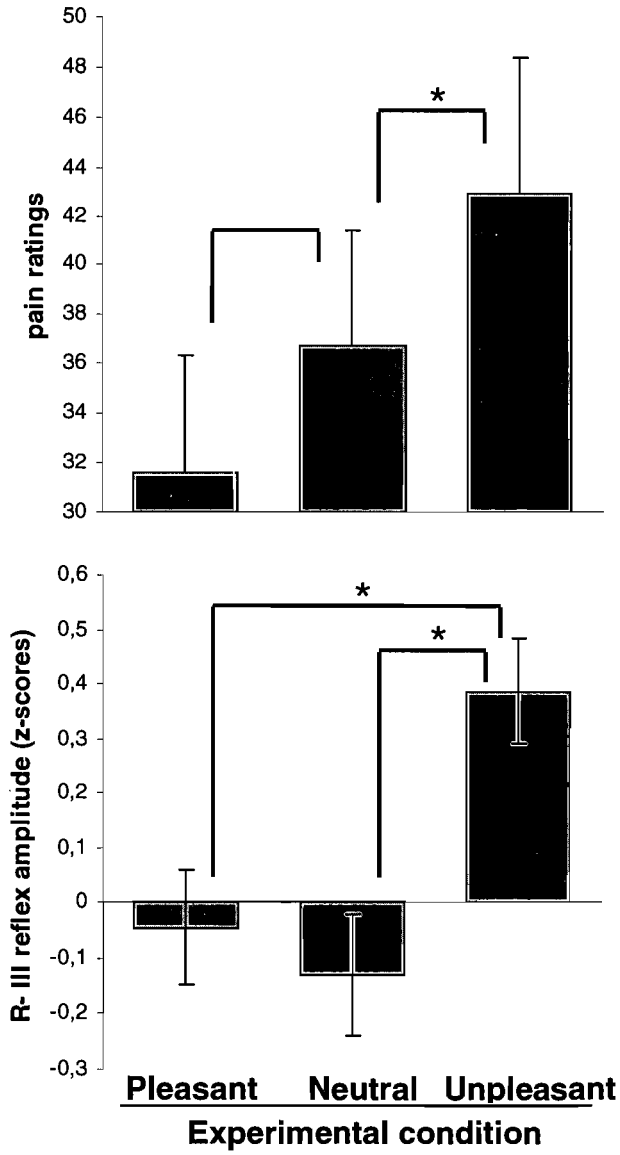

50
48
46
44
42
40
38
36
34
32
30
pain ratings
*
0,6
0,5
0,4
0,3
0,2
0,1
0
-0,1
-0,2
-0,3
R- III reflex amplitude (z-scores)
*
*
Pleasant
Neutral
Unpleasant
Experimental condition

Figure 3

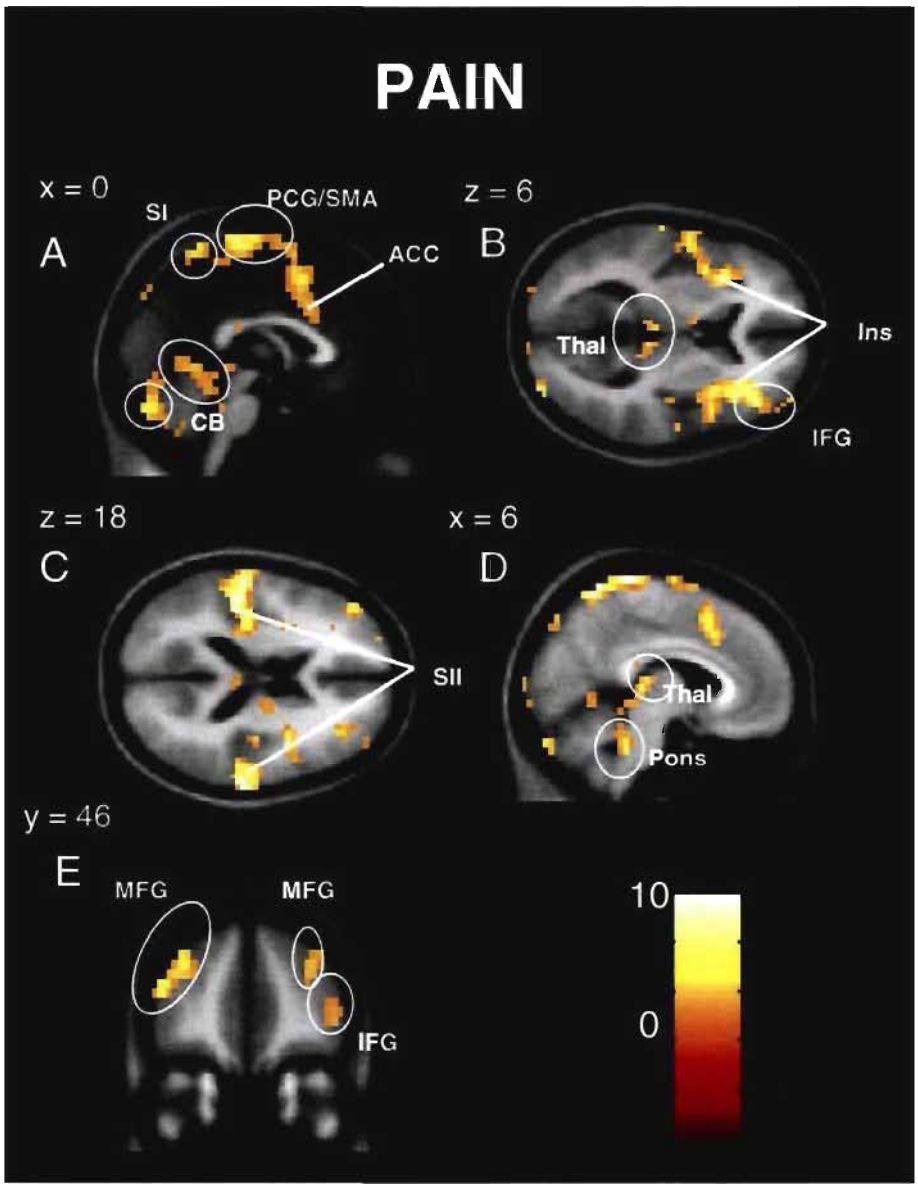

PAIN
x = 0
A
SI
PCG/SMA
ACC
CB
z = 6
B
Thal
Ins
IFG
z = 18
C
SII
x = 6
D
Thal
Pons
y = 46
E
MFG
MFG
IFG
10
0

Figure 4

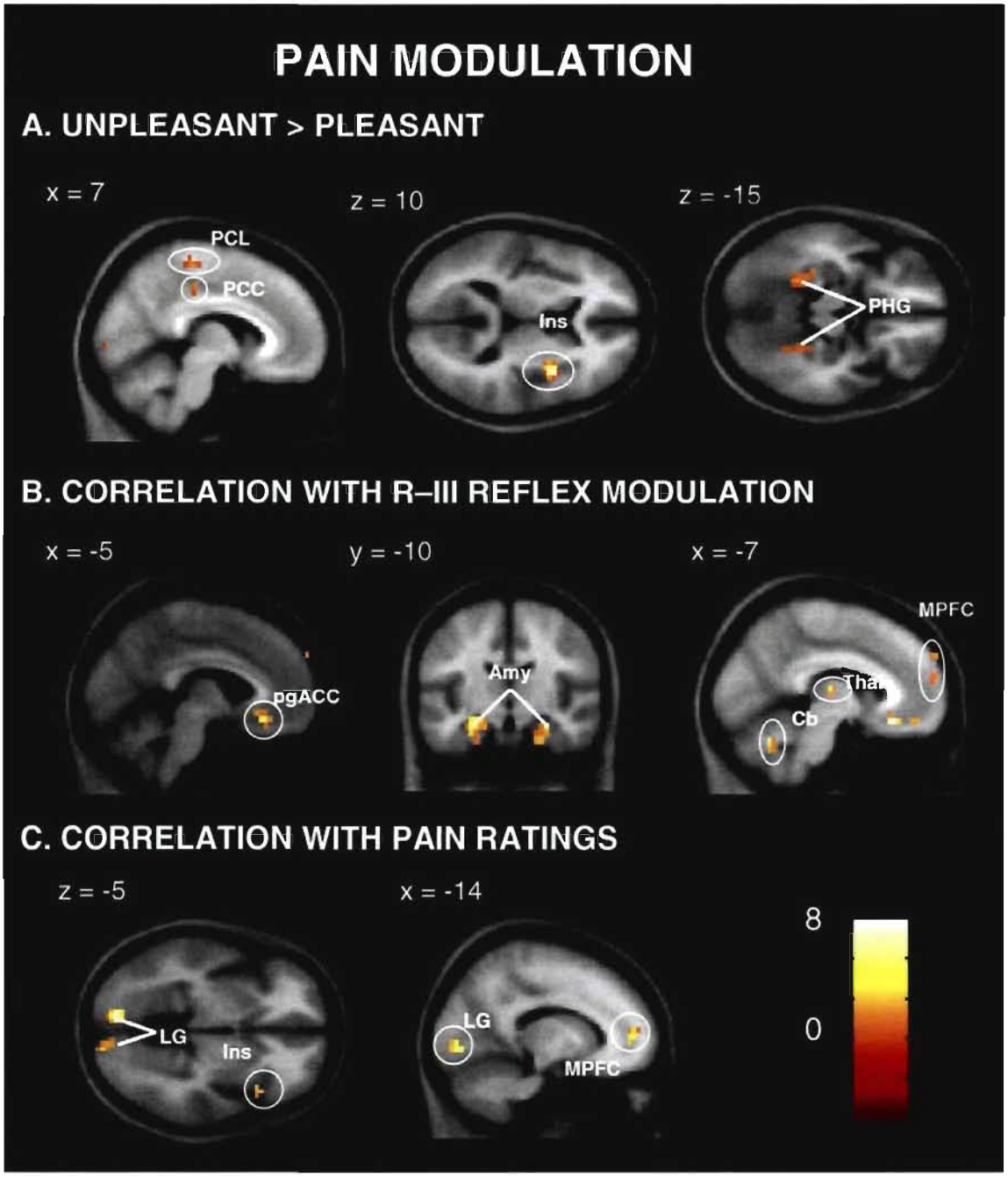

PAIN MODULATION
A. UNPLEASANT > PLEASANT
x = 7
z = 10
z = -15
PCL
PCC
Ins
PHG
B. CORRELATION WITH R–III REFLEX MODULATION
x = -5
y = -10
x = -7
pgACC
Amy
MPFC
Cb
C. CORRELATION WITH PAIN RATINGS
z = -5
x = -14
LG
Ins
LG
MPFC
8
0

Figure 5

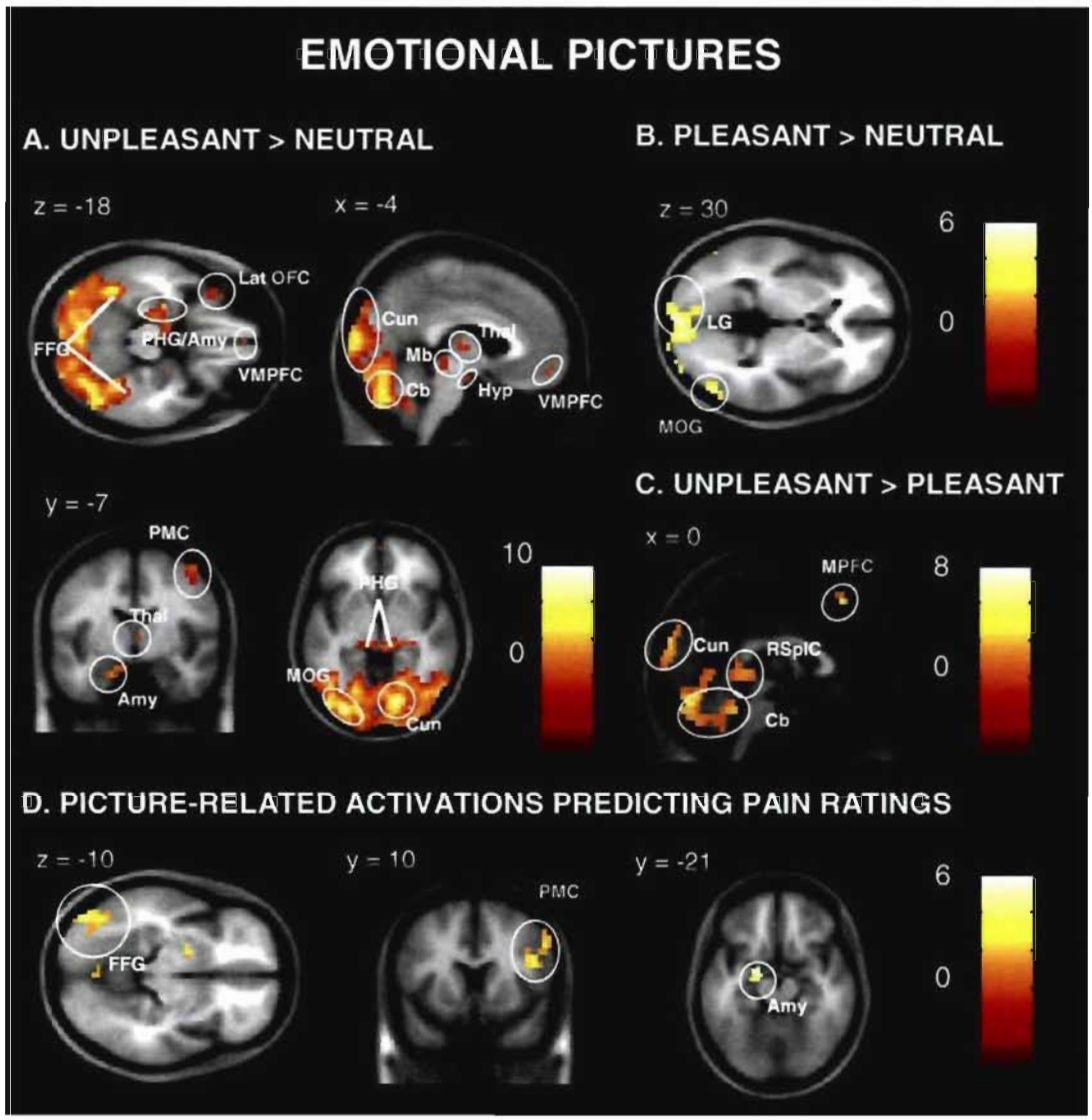
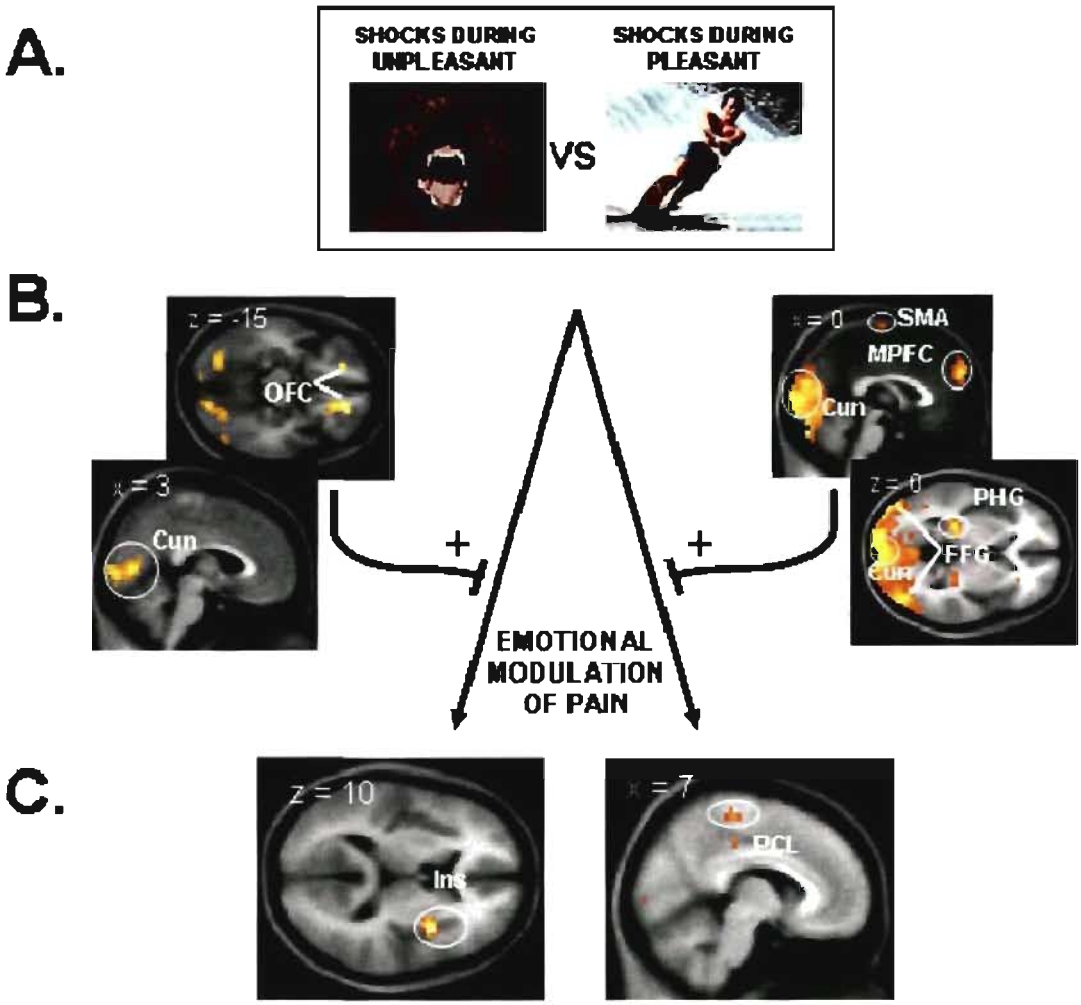

EMOTIONAL PICTURES
A. UNPLEASANT > NEUTRAL
z = -18
Lat OFC
FFG
PHG/Amy
VMPFC
x = -4
Cun
Thal
Mb
Cb
Hyp
VMPFC
B. PLEASANT > NEUTRAL
z = 30
LG
MOG
6
0
C. UNPLEASANT > PLEASANT
y = -7
PMC
Thal
Amy
PHG
MOG
Cun
10
0
x = 0
MPFC
Cun
RSplC
Cb
8
0
D. PICTURE-RELATED ACTIVATIONS PREDICTING PAIN RATINGS
z = -10
FFG
y = 10
PMC
y = -21
Amy
6
0

Figure 6


A.
SHOCKS DURING UNPLEASANT
VS
SHOCKS DURING PLEASANT
B.
z = -15
OFC
x = 3
Cun
+
+
z = 0
SMA
MPFC
Cun
z = 0
PHG
FFG
EMOTIONAL MODULATION OF PAIN
C.
z = 10
Ins
x = 7
PCL

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DISCUSSION GÉNÉRALE

Au cours de cette dernière section, nous tenterons d'intégrer les principaux résultats obtenus dans les sections expérimentales de la thèse au sein d'une perspective plus globale des mécanismes impliquées dans la modulation émotionnelle de la douleur. Suivant l'ordre des études de la thèse, nous aborderons tout d'abord les effets de la musique sur la douleur (articles 2 et 4), puis le rôle de la musique en tant qu'inducteur émotionnel (article 3). Nous démontrerons ensuite le statut particulier des émotions comme modulateurs de la douleur en distinguant leurs effets des ceux de l'attention (article 5). Finalement, nous examinerons les mécanismes cérébraux impliqués dans la modulation émotionnelle de la douleur (article 6).

Analgésie induite par la musique

Bien que l'efficacité de la musique à réduire la douleur ait été démontrée par de nombreuses études (Cepeda et al., 2006), les facteurs expliquant les effets de la musique avaient été peu étudiés. En comparant les effets de musiques agréables et désagréables sur la perception de douleurs thermiques, nous avons tout d'abord pu démontrer que les effets analgésiques de la musique dépendaient en grande partie des émotions qu'elle induisait (article 2). En effet, bien que les musiques désagréables aient également constitué une distraction par rapport à la douleur, seules les musiques agréables parvinrent à réduire la douleur. De plus, ni les musiques agréables, ni les musiques désagréables n'eurent d'effets sur les évaluations de chaleur non-douloureuse, tel que l'aurait laissé présager un effet de l'attention (Bushnell et al., 1985a).

Afin d'explorer les mécanismes cérébraux-spinaux responsables de cet effet, nous avons dans un deuxième temps mesuré l'amplitude du réflexe RIII pendant l'écoute d'extraits agréables et désagréables (article 4). Le réflexe, qui est un indice établi de la nociception au niveau spinal (Sandrini et al., 2005), se révéla être facilité par l'écoute de musiques désagréables et inhibé par l'écoute de musiques agréables. Ces résultats démontrent donc que la musique parvient à moduler la transmission de la

douleur au niveau de la moelle épinière, suggérant l'action de mécanismes modulateurs descendants. Ces mécanismes tirent leur source de plusieurs structures cérébrales, dont certaines ont pu être liées aux émotions musicales (voir figure 3). Ainsi, Blood et Zatorre (2001a) ont révélé des activations de la PAG, une zone inhibitrice de la douleur pendant l'expérience d'émotions extrêmement agréables (i.e. : 'frissons') à l'écoute de la musique. À l'inverse, l'écoute de musiques désagréables a été associé à l'activation du gyrus parahippocampal (Blood & Zatorre, 2001a), et de l'amygdale (Stefan Koelsch, Fritz, V Cramon, Muller, & Friederici, 2006). Or, ces deux structures semblent également avoir un rôle à jouer dans la modulation descendante de la douleur. D'une part, l'amygdale a été associée aux mécanismes descendants facilitateurs (Crown, King, Meagher, & Grau, 2000) et inhibiteurs de la douleur (Helmstetter, 1993), et d'autre part, le gyrus parahippocampal a été impliqué dans l'hyperalgésie induite par l'anxiété (Ploghaus et al., 2001). Bien que le gyrus parahippocampal ne soit pas directement impliqué dans les mécanismes descendants de la douleur, une étude récente d'imagerie cérébrale a démontré qu'il agissait de pair avec des régions du tronc cérébral (PAG, aire tegmentale ventrale) engagées dans la facilitation descendante de la douleur lors de l'hyperalgésie liée à l'anticipation (Fairhurst et al., 2007; Lovick, 2008).

Les résultats de notre étude permettent donc enfin de proposer des mécanismes neurophysiologiques pouvant expliquer la modulation de la douleur par la musique. Ces mécanismes tireraient fort probablement leur origine des aires cérébrales activées par les émotions musicales (PAG, gyrus parahippocampal, amygdale) et influenceraient la transmission de la douleur au niveau de la moelle épinière par le biais de mécanismes modulateurs descendants. L'utilisation de techniques d'imagerie cérébrale, couplées avec la mesure du réflexe RIII (tel que dans l'article 6), permettra sûrement de confirmer l'implication de ces mécanismes, et peut-être même de mettre en évidence des mécanismes supplémentaires plus centraux.

Dans l'ensemble, nos résultats apportent donc une contribution importante à l'utilisation de la musique comme agent thérapeutique.

Ainsi, la modulation de la douleur par la musique semble dépendre en partie de mécanismes descendants tirant leur source des régions cérébrales activées par les émotions musicales. Ce rôle causal des émotions induites par la musique sur la modulation de la douleur se trouve de surcroît supporté par les résultats de notre étude subséquente (article 5), utilisant des images affectives comme inducteur émotionnel dans un paradigme expérimental similaire. Comme pour la musique, les images agréables réduisirent la perception de douleur et l'amplitude du réflexe RIII par rapport à des images désagréables d'*arousal* équivalent. Ces résultats répliquèrent largement les résultats de Rhudy et al. (2005), qui avaient toutefois utilisé un paradigme expérimental légèrement différent. Cette convergence des résultats suggère fortement que les mêmes mécanismes soient impliqués dans les effets de la musique et des images émotionnelles sur la douleur. Ainsi, Rhudy et al. (2005) postulèrent également que la PAG et l'amygdale puissent être les générateurs cérébraux des effets modulateurs descendants qu'ils avaient observés en utilisant des images comme inducteurs émotionnel. Il semble donc que le recrutement de structures émotionnelles multimodales, telles que la PAG et l'amygdale, puisse être le point commun reliant les effets des multiples inducteurs émotionnels sur la douleur.

Induction d'émotions par la musique

Ces résultats démontrent aussi que la musique peut être un inducteur émotionnel aussi efficace que les images affectives de l'IAPS (*International Affective Pictures System*). Cependant, la capacité de la musique à induire des émotions au même titre que les autres inducteurs émotionnels 'classiques' demeure l'objet de débats au sein de la psychologie de la musique (Kivy, 1990; Konečni, 2003; Scherer, 2003). Afin de démontrer la capacité de la musique à induire des émotions, nous avons testé les effets des musiques agréables et désagréable sur le réflexe de sursaut (article 3).

En effet, la modulation émotionnelle de ce réflexe, abondemment étudiée avec les images de l'IAPS, est l'une des pierres angulaires de la recherche en psychophysiologie des émotions (Lang, 1995). À ce titre, il est fréquemment utilisé afin de tester l'efficacité de médicaments anxiolytiques (Winslow, Noble, & Davis, 2007), ou pour étudier la réactivité émotionnelle dans les troubles affectifs (Grillon & Baas, 2003). Le fait que, au cours de notre étude, le réflexe ait été diminué pendant l'écoute de musiques agréables par rapport aux musiques désagréables supporte donc fortement l'idée selon laquelle la musique est capable d'induire des émotions au même titre que les inducteurs émotionnels plus classiques, telless que les images de l'IAPS.

Cependant, ceci n'enlève en rien la possibilité que d'autres mécanismes plus spécifiques à la musique, telles que les attentes musicales, puissent être impliqués dans certaines formes d'émotions musicales plus élaborées. En effet, dans son article de revue, Juslin (in press) propose six différents mécanismes d'induction émotionnelle en musique. Le premier mécanisme, qui correspond aux réflexes du tronc cérébral, s'applique bien aux effets que nous avons pu observés sur le réflexe RIII et sur le réflexe de sursaut. Juslin (in press) propose en effet que des sons forts, dissonants ou soudains pourraient suffire à induire des émotions négatives chez l'auditeur. Ces sons activeraient directement des structures du tronc cérébral, telles que la formation réticulée, afin de mettre l'organisme sur un pied d'alerte. De plus, ces structures du tronc cérébral pourraient également être modulées par d'autres structures corticales telles que l'amygdale, les cortex orbitofrontaux et l'hypothalamus. Or, l'amygdale, par ses efférences sur le noyaux réticulé du pons caudal (*nucleus reticularis pontis caudalis*), a été démontrée être l'un des principaux modulateurs cérébraux du réflexe de sursaut (Davis, Walker, & Lee, 1997). À l'inverse, le noyau accumbens apparaît nécessaire à l'inhibition du réflexe de sursaut par des stimuli appétitifs (Koch, Schmid, & Schnitzler, 1996). La Figure 3 illustre les mécanismes par lesquels la musique pourrait moduler le réflexe de sursaut. L'amygdale et le noyau accumbens feraient partie de systèmes motivationnels aversifs et appétitifs mutuellement

antagonistes (Konorski, 1967), suggérant que les effets de l'un ou l'autre des systèmes agisse partiellement par l'inhibition du système opposé (Lang, 1995).

Plusieurs structures des ces systèmes aversifs et appétitifs ont été également liées aux émotions musicales et pourraient servir de générateurs cérébraux à la modulation du réflexe de sursaut observée. Ainsi, l'activation de l'amygdale pendant l'écoute de musiques désagréables (Stefan Koelsch et al., 2006), pourrait être liée à l'augmentation du réflexe de sursaut observée à l'écoute des musiques désagréables de notre étude. De plus, des activations du nucleus accumbens ont été observées pendant l'écoute d'extraits musicaux agréables (Menon & Levitin, 2005), ainsi que lors d'émotions positives intenses suscitées par la musique (Blood & Zatorre, 2001a). Il apparaît donc que, dans certains cas, la musique puisse avoir valeur de récompense et activer le nucleus accumbens, expliquant la diminution du réflexe de sursaut observée en réponse aux musiques agréables.

Il est intéressant de noter que, tout comme dans notre étude, les musiques désagréables utilisées dans les études de Menon et Levitin (2005) et de Koelsch et al. (2006) semblent avoir des caractéristiques acoustiques et structurelles très différentes des musiques agréables utilisées. Ainsi, dans l'étude de Koelsch et al. (2006), les musiques désagréables sont créées par l'ajout d'une masse spectrale supplémentaire créant un fort niveau de dissonance, alors que la condition contrôle de Menon et Levitin (2005) est le résultat d'une fragmentation aléatoire du morceau musical créant de rapides changements de tonalité ou d'intensité au sein du morceau (Menon & Levitin, 2005). De plus, les 'frissons' étudiés dans l'étude de Blood et Zatorre (2001a) étaient évoqués uniquement par de brefs passages à l'intérieur des extraits musicaux. Ceci correspond bien à la proposition de Juslin (in press) selon laquelle ce seraient les paramètres musicaux de relativement bas niveau, tels que la dissonance ou la présence de changements soudains, qui détermineraient les réponses du tronc cérébral (et régions associées) à la musique.

Modulation attentionnelle et émotionnelle de la douleur

Le fait que la musique puisse induire des émotions au même titre que les autres inducteurs émotionnels soutient donc notre interprétation de l'analgésie induite par la musique en terme de mécanismes émotionnels. Cependant, étant donné l'influence des émotions sur l'attention (Armony & Dolan, 2002; Ohman et al., 2001), il est difficile de dire si les émotions agissent directement sur la perception douleur, ou si elles agissent par le biais d'une redirection de l'attention. Le fait que l'attention et les émotions influencent de façon différente les composantes sensorielles et affectives de la douleur (Villemure et al., 2003), ainsi que l'absence d'effet de la musique sur la perception de chaleur non-douloureuse (article 2) suggèrent cependant que l'effet des émotions puisse être indépendant de celui de l'attention.

Au cours de l'article 5 de la thèse, nous avons tenté de dissocier les effets de l'attention de ceux des émotions sur la nociception spinale, telle que mesurée par l'amplitude du réflexe RIII. Alors que la valence émotionnelle des images de l'IAPS modula de façon parallèle l'amplitude du RIII et les évaluations de douleur, la distraction causa une importante dissociation entre le RIII et les évaluations de douleur. En effet, pendant que les participants portaient attention à des images non chargées émotionnellement, l'amplitude de leur réflexe fut dramatiquement amplifiée comparativement à une condition contrôle sans images. À l'inverse, leurs évaluations de douleur diminuèrent ou demeurèrent inchangées. Cet effet semble relativement robuste puisqu'on le retrouve également dans les résultats de l'étude 4 de la thèse. En effet, le réflexe s'avéra largement diminué pendant la condition sans musique comparativement aux conditions musicales. Cette dissociation entre la perception de douleur et l'amplitude du réflexe pourrait s'expliquer par une facilitation de l'*output* moteur du réflexe en situation de distraction, combinée à une inhibition de la transmission nociceptive.

L'exacerbation des réflexes par la distraction est un phénomène bien établi (McIntyre et al., 2004) et sert notamment à faciliter le déclenchement de réponses automatiques ayant une fonction adaptative, tel le retrait à la douleur, pendant que le

cerveau est occupé par la tâche distrayante. Dans le cas du RIII, cette facilitation des réponses automatiques serait accompagnée d'une diminution de la sensibilité à la douleur afin de ne pas interférer avec la tâche à accomplir. Bien que plusieurs études aient démontré la dissociation entre la perception de douleur et la réactivité du RIII lors de la distraction (Edwards et al., 2007; Edwards, Smith, Kudel, & Haythornthwaite, 2006; McIntyre et al., 2006; Petersen, Heesacker, & Schwartz, 2001), cet effet n'avait jusqu'à présent jamais été considéré comme un phénomène robuste nécessitant une interprétation théorique indépendante du contexte particulier de l'expérience dans laquelle il avait été observé. Cet état de fait semble principalement découler des résultats contradictoires obtenus dans les premières études sur l'effet de la distraction sur le RIII qui démontraient que distraction diminuaient plutôt l'amplitude du RIII (Willer, 1977). Bien que nous proposions quelques explications pour ces résultats contradictoires dans la discussion de l'article 5 de la thèse, ces divergences de résultats restent à être expliquées empiriquement afin que l'interprétation que nous faisons de la dissociation entre douleur et RIII pendant la distraction soit pleinement admise.

Quoiqu'il en soit, l'observation d'effets diamétralement opposés pour les émotions et l'attention apporte un dernier argument en faveur d'une dissociation entre les effets des émotions et de l'attention sur la douleur. En effet, si les émotions avaient agi sur la douleur par une redirection de l'attention, la diminution de douleur observée pendant la présentation d'images agréables aurait été accompagnée d'une augmentation du RIII, et l'inverse aurait été observé pour les images désagréables. Le même effet semble également s'appliquer aux effets de la musique sur le RIII. Ainsi, les évaluations de douleur et l'amplitude du RIII furent modulées de façon parallèle par la valence des musiques, alors que RIII s'avéra largement diminué pendant la condition sans musique, bien que les évaluations de douleurs demeurèrent inchangées. Cette similitude entre les effets de la musique et des images souligne encore davantage le rôle central qu'occupent les émotions dans leurs effets sur la douleur.

Mécanismes cérébraux impliqués dans la modulation émotionnelle de la douleur

Les premiers articles de la thèse ont principalement porté sur les mécanismes spinaux impliqués dans la modulation émotionnelle de la douleur. Cependant, très peu d'indices permettaient d'identifier les générateurs cérébraux de ces effets. Ainsi, afin d'explorer les corrélats cérébraux de la modulation émotionnelle de la douleur, nous avons enregistré l'activité cérébrale grâce à l'IRMf pendant la modulation émotionnelle de la douleur. La seule étude à avoir précédemment abordée cette question était celle Ploghaus et al. (2001), dans laquelle les aires cérébrales liées à l'hyperalgésie induite par la crainte de recevoir un choc douloureux avaient été étudiées. Cependant, la technique d'induction émotionnelle utilisée, liée à la manipulation des attentes, ne permettait pas de départager pleinement l'effet du contexte émotionnel de celui de mécanismes cognitifs plus élaborés, tels que l'anticipation ou la ré-interprétation de la douleur en fonction des attentes. De plus, leur exploration des corrélats neuronaux de l'hyperalgésie induite par l'anxiété se limita uniquement aux aires cérébrales de douleur modulées par leur manipulation expérimentale, sans que les mécanismes responsables de cet effet ne soient abordés.

Afin d'explorer les mécanismes responsables des effets des émotions sur la douleur, nous avons utilisé un paradigme expérimental permettant de séparer les aires de douleur modulées par les émotions de celles liées à l'induction d'émotion en soi. Puis, nous avons exploré les mécanismes sous-tendant la modulation des aires de douleur observée par le biais d'analyses de connectivité. Finalement, la mesure du réflexe RIII en tant qu'indice de nociception spinale nous permit de distinguer les régions davantage liées à une modulation descendante de la douleur de celles impliquées dans des mécanismes plus centraux de modulation de la douleur. Les principaux mécanismes mis en évidence par notre étude sont résumés dans la figure 4 de cette section.

Tout d'abord, trois principales zones de douleur furent modulées par les émotions : l'insula droite, le lobule paracentral et les gyrus parahippocampaux. Ces régions démontrèrent toutes des activations plus importantes en réponse à la stimulation douloureuse pendant la présentation d'images négatives comparativement aux images positives. De plus, l'activation de l'amygdale et du thalamus controlatéral en réponse au choc s'avéra liée à l'amplitude de la modulation du RIII par les émotions, alors que l'activation de l'insula droite fut liée à l'amplitude de la modulation des évaluations de douleur. Finalement, les analyses de connectivité révélèrent que les effets des émotions sur l'insula droite corrélaient avec l'activation du cortex orbitofrontal, alors que la modulation du lobule paracentral est liée à l'activation du gyrus parahippocampal, du cortex préfrontal médian et de l'aire motrice supplémentaire.

Étant donné que le lobule paracentral sert à la représentation sensorimotrice du pied et qu'il est impliqué dans la dimension sensorielle de la douleur, nous avons postulé que sa modulation résultait d'une modulation descendante de la transmission nociceptive dans la voie spinothalimique. La corrélation entre la modulation du RIII et l'activité du thalamus controlatéral, sur lequel se projettent les neurones nociceptifs de la voie spinothalamique, semble bien supporter cette interprétation. Aussi, la corrélation entre la modulation du RIII et de l'amygdale pourrait également découler de la modulation spinale de la transmission nociceptive, puisque l'amygdale est l'une des structures-cibles sur laquelle se projettent les neurones nociceptifs de la voie spinoparabrachiale. Finalement, les analyses de connectivité ont montré que la modulation émotionnelle du lobule paracentral était prédite par l'activité du gyrus parahippocampal et du cortex préfrontal médian. Étant donné que le gyrus parahippocampal s'est montré activé par les images négatives au cours de notre étude, et qu'une étude récente a démontré qu'il agissait de pair avec la PAG pour augmenter la douleur (Fairhurst et al., 1997), il est fort probable que cette structure soit l'un des générateurs cérébraux de la facilitation descendante observée en réponse aux images

négatives. Le cortex préfrontal médian, quant à lui, aurait pu influencer directement l'activité du lobule paracentral, tel que proposé dans une étude sur les effets des attentes sur la douleur (Koyama et al., 2005).

La modulation de l'insula droite par les émotions semble plutôt refléter un processus différent de modulation de la douleur. En effet, l'insula droite, se trouvant du côté ipsilatéral à la stimulation, ne semblait pas jouer dans cette étude un rôle primaire dans la perception de douleur. En fait, selon Craig (2008), l'insula droite serait plutôt impliquée dans l'intégration de la douleur avec le contexte motivationnel et affectif, afin de créer une représentation interoceptive intégrée qu'on pourrait qualifier de « moment de douleur global ». En appui à cette interprétation, l'activité de l'insula droite s'avéra corrélée avec l'effet des émotions sur les évaluations de douleur, confirmant le rôle intéroceptif global de cette structure. De plus, Craig postule que l'intégration émotionnelle au sein de l'insula se ferait selon un axe postérieur-antérieur dans lequel l'information sensorielle intéroceptive, issue de l'insula postérieure, se trouverait graduellement intégrée avec les dispositions affectives et motivationnelles de l'individu plus l'on progresse vers l'insula antérieure. Ce processus se ferait sous l'influence de plusieurs aires émotionnelles, dont les cortex orbitofrontaux, qui sont situés dans l'extension rostrale de l'insula antérieure. Les résultats de nos analyses de connectivité, qui montrent que la modulation émotionnelle de l'insula droite est liée à l'activation des cortex orbitofrontaux, soutiennent donc fortement cette théorie en démontrant que la modulation émotionnelle de l'insula droite dépendrait des effets des émotions sur les cortex orbitofrontaux.

Finalement, la modulation du gyrus parahippocampal semble également dépendre d'un processus de modulation différent. En effet, le gyrus parahippocampal se montra également activé par les images négatives, ainsi que par les stimulations douloureuses. Ceci cadre bien avec le rôle proposé de la formation hippocampale dans l'anxiété (Gray & McNaughton, 2000). Ainsi, il semble que le gyrus parahippocampal

réponde de façon indistincte aux stimuli aversifs, quelle que soit leur nature, et que ces réponses s'additionneraient au sein de cette structure. Le gyrus parahippocampal agirait donc comme un « thermomètre » de l'anxiété totale et servirait ici à la composante affective de l'expérience douloureuse. Il n'aurait cependant pas le rôle intéroceptif propre à l'insula droite et serait donc plus éloigné de la perception de la stimulation douloureuse en soi. Il est également intéressant de constater que le gyrus parahippocampal a été la seule structure à montrer une diminution de la douleur pendant les images positives par rapport à la condition neutre, suggérant un effet anxiolytique des images agréables sur la douleur. Enfin, la modulation émotionnelle de l'amygdale (en corrélation avec le RIII) pourrait également s'expliquer par le même type de mécanisme puisque l'amygdale s'est également avérée répondre aux images négatives.

En reliant l'activité cérébrale liée à la douleur à celle liée au contexte émotionnel, cette dernière étude apporte une contribution significative à l'exploration des corrélats neuronaux de la modulation émotionnelle de la douleur. De plus, la mesure du RIII nous a permit de distinguer les mécanismes impliquant une modulation descendante de l'influx nociceptif dans la moelle épinière de ceux davantage liés à des interactions cortico-corticales. Malgré tout, plusieurs questions restent toujours en suspens, notamment en ce qui a trait à l'influence inhibitrice des émotions positives, ainsi qu'en ce qui concerne l'implication du cortex cingulaire antérieur dans les effets des émotions sur la douleur. Les résultats de cette première étude contribueront néanmoins à ouvrir la voie à d'autres études qui permettront sûrement de répondre à ces questions et de raffiner notre compréhension des processus en jeu dans la modulation émotionnelle de la douleur.

Conclusion

Les apports scientifiques de cette thèse sont multiples. Tout d'abord, nous avons pu montrer que les effets de la musique sur la douleur dépendaient en grande

partie des émotions qu'elle induisait et que ceux-ci agissait sur la douleur par le biais de mécanismes modulateurs descendants. Nous avons également pu démontrer que les émotions et l'attention influençait la douleur par des mécanismes physiologiques distincts, soutenant l'idée que les émotions avaient un rôle particulier à jouer dans la modulation de la douleur. Finalement, nous avons pu mettre en évidence les mécanismes cérébraux impliqués dans la modulation émotionnelle de la douleur. Dans l'ensemble, ces résultats apportent donc un appui théorique solide à l'utilisation de techniques d'induction émotionnelle, telle que la musicothérapie, comme agents thérapeutiques dans le traitement de la douleur en milieu clinique.

FIGURES

Légendes des Figures

Figure 1. Voies nociceptives ascendantes et voies modulatrices descendantes de la douleur. Le cortex somatosensoriel secondaire (S2), sur la face latérale du cerveau, n'est pas représenté. Adapté de Price (2000), Tracey (2007) et Millan (2000). PF = cortex préfrontal, Amy = amygdale, HT = hypothalamus, SMA = aire motrice supplémentaire, ACC = cortex cingulaire antérieur, PCC = cortex cingulaire postérieur, Thal = thalamus, M1 = aire motrice primaire, S1 = cortex somatosensoriel primaire, NCF = noyau cunéiforme, PAG = substance grise périaqueductale, DLPT = tegmentum du pons dorsolatéral.

Figure 2. Modulation descendante de la douleur par la musique. L'activation de l' Amy et du PHG par des musiques désagréables faciliterait la transmission nociceptive par le biais de la PAG. L'activation de la PAG par les musiques agréables inhiberait la transmission nociceptive dans la corne dorsale de la moelle épinière.

Figure 3. Modulation du réflexe de sursaut par la musique. L'activation de l'amygdale (Amy) et du noyaux accumbens (Nacc) par la musique inhiberait ou faciliterait le réflexe de sursaut par leurs connections avec le noyau réticulé du pons caudal. De plus, les deux régions, faisant partie de systèmes antagonistes, peuvent également moduler le réflexe à travers une modulation du système opposé.

Figure 4. Mécanismes de modulation émotionnelle de la douleur mis en évidence par l'étude d'imagerie (article 6). Les émotions influenceraient la douleur par le biais (1) de projections de l'OFC vers l'Ins droite, (2) de mécanismes modulateurs descendants tirant leur source de l'Amy, du PHG et de la PAG et influençant la transmission nociceptive vers le Thal, le PCL et l'Amy, et (3) par une influence directe sur l'Amy et le PHG. Notre étude a révélé un effet inhibiteur des émotions uniquement sur le PHG. À noter que la figure ne comprends que le réseaux ayant pu être mis en évidence par notre étude et que d'autres mécanismes peuvent également être impliqués. Ins = insula, OFC = cortex orbitofrontal, MPFC = cortex préfrontal médian, PCL = lobule paracentral, Thal = thalamus, Amy = amygdale, PHG = gyrus parahippocampal, PAG = subtance grise périaqueductale.

Figure 1

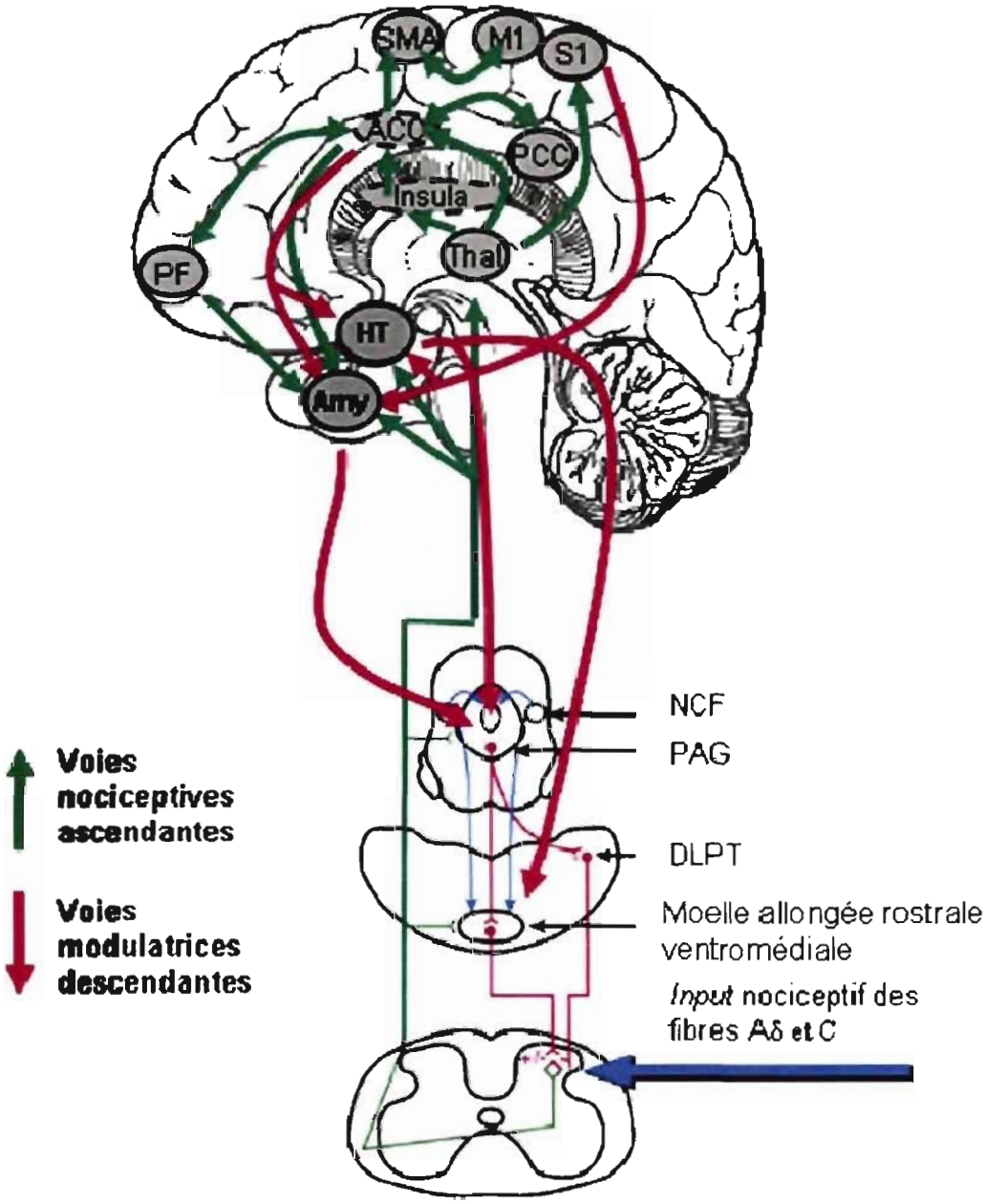

SMA
M1
S1
ACC
PCC
Insula
Thal
PF
HT
Amy
NCF
PAG
DLPT
Moelle allongée rostrale ventromédiale
Input nociceptif des fibres Aδ et C
Voies nociceptives ascendantes
Voies modulatrices descendantes

Figure 2

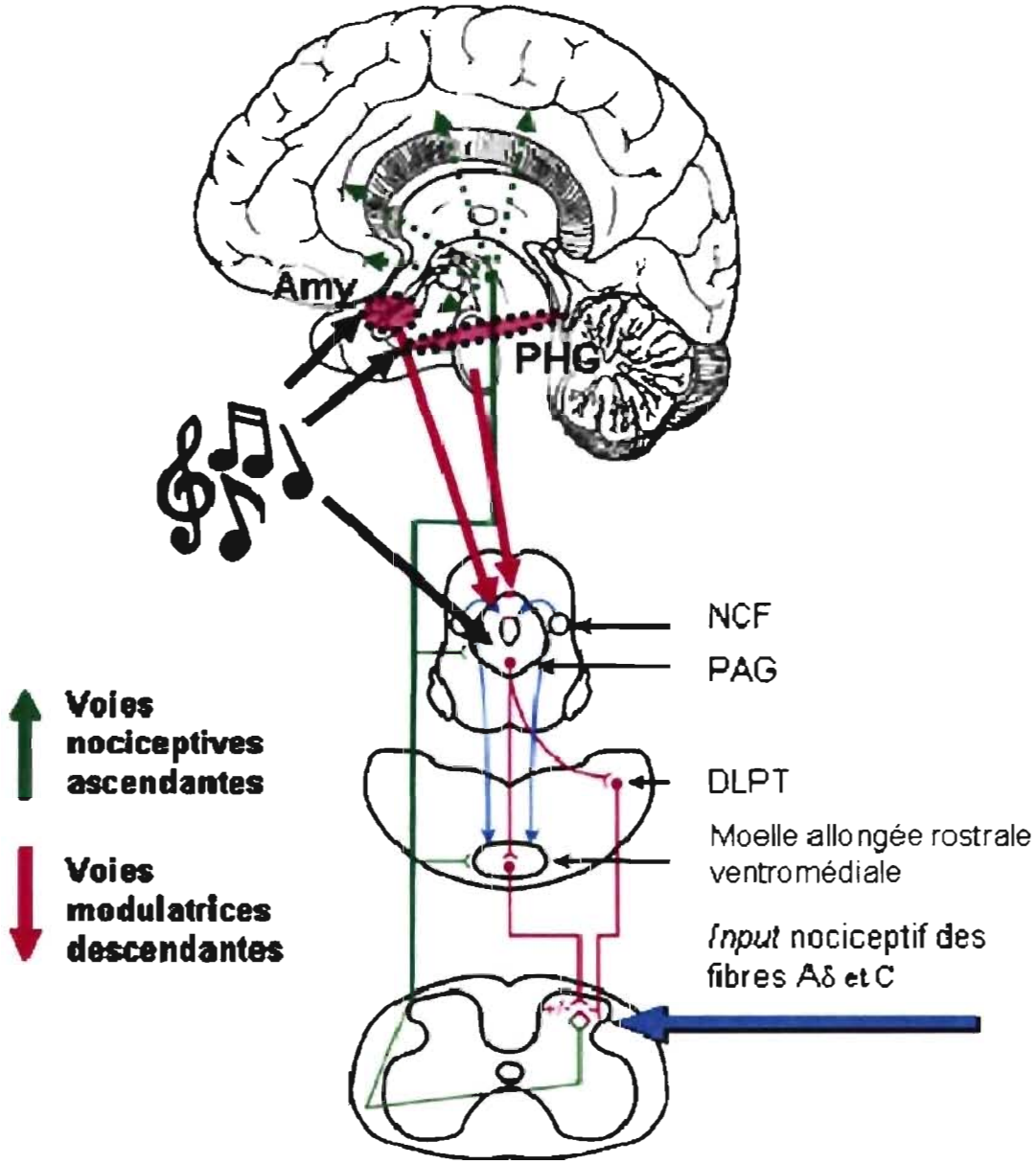

Amy
PHG
NCF
PAG
DLPT
Moelle allongée rostrale ventromédiale
Input nociceptif des fibres Aδ et C
Voies nociceptives ascendantes
Voies modulatrices descendantes

Figure 3

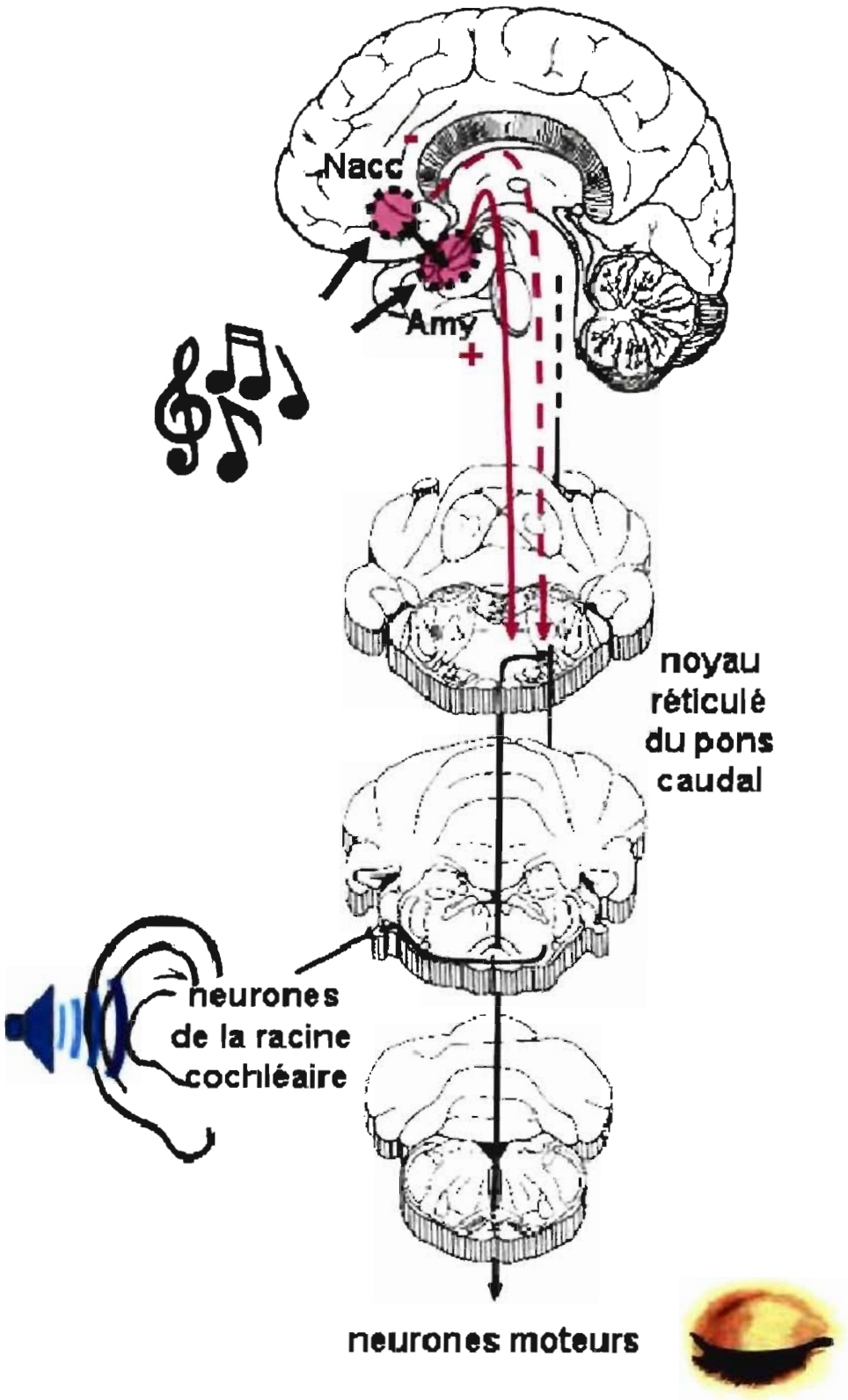
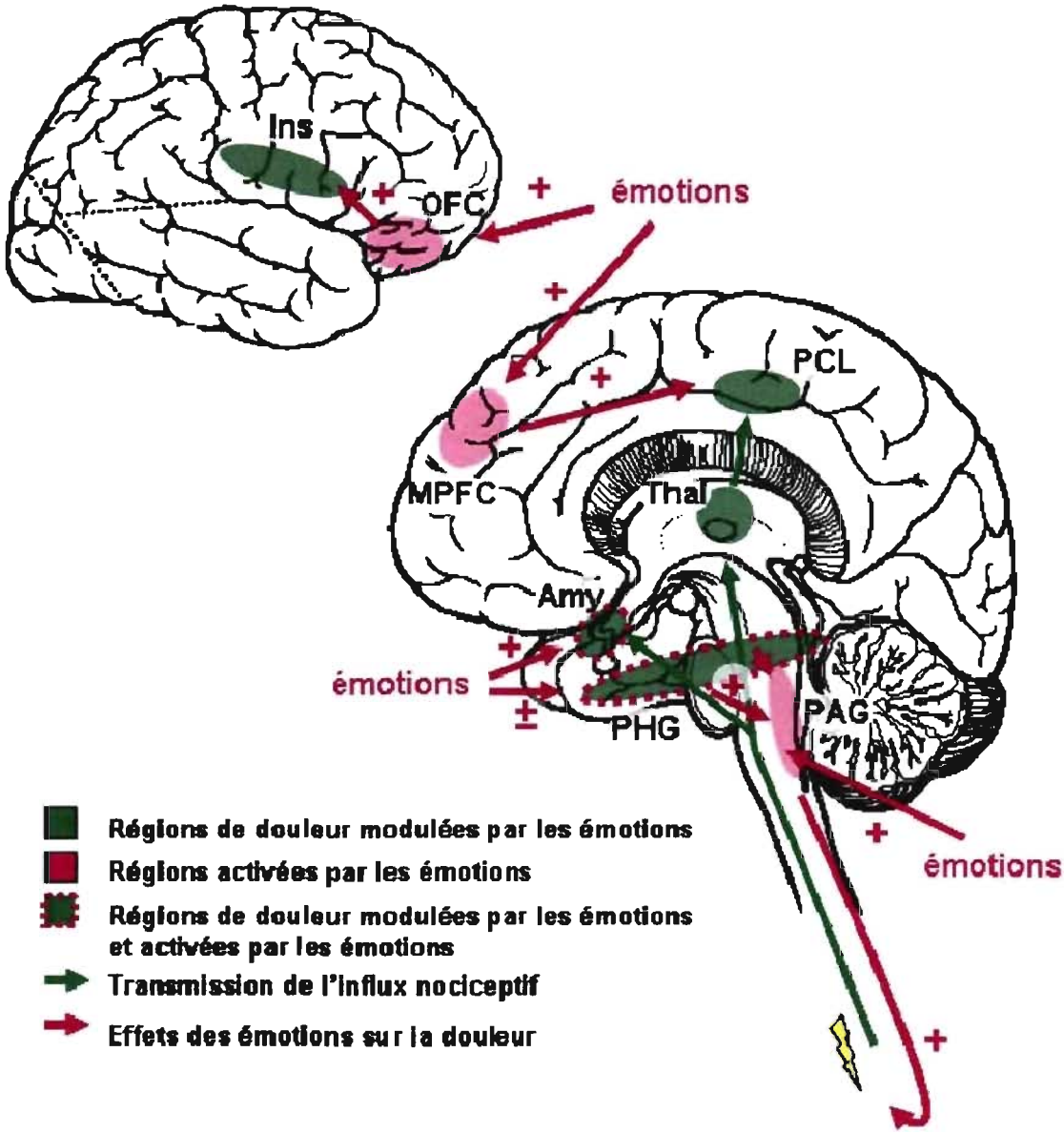

Nacc
Amy
+
noyau réticulé du pons caudal
neurones de la racine cochléaire
neurones moteurs

Figure 4


Ins
OFC
émotions
PCL
MPFC
Thal
Amy
émotions
PHG
PAG
émotions
Régions de douleur modulées par les émotions
Régions activées par les émotions
Régions de douleur modulées par les émotions et activées par les émotions
Transmission de l'influx nociceptif
Effets des émotions sur la douleur

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ANNEXES