Université de Montréal

La contribution des attentes et de l'expérience passée sur l'analgésie par placebo.

par
Julie Charron

Département de psychologie
Faculté des arts et des sciences

Thèse présentée à la Faculté des études supérieures
en vue de l'obtention du grade de Ph.D.
en psychologie recherche et intervention
option psychologie clinique béhaviorale

Octobre 2003

Université de Montréal
Faculté des études supérieures

Cette thèse intitulée:
La contribution des attentes et de l'expérience passée
sur l'analgésie par placebo.

présentée par
Julie Charron

A été évaluée par un jury composé des personnes suivantes:

Michael Sullivan
président-rapporteur

Jean-Pierre Blondin
Directeur de recherche

Serge Marchand & Pierre Rainville
Codirecteurs

Gilles Lavigne
membre du jury

Gary Rollman
examinateur externe

Yves Joanette
représentant du doyen de la FES

Résumé en français

Divers mécanismes ont été proposés pour expliquer la modulation de la douleur par un traitement placebo. Nous nous sommes penchés plus spécifiquement sur deux théories psychologiques, soit le conditionnement et les attentes. L'objectif général de la thèse était de clarifier dans quelle mesure les cognitions (les attentes) et l'expérience passée (modifiée par conditionnement) sont impliquées dans une analgésie placebo. Nous avons examiné de concert ces deux théories en créant des modèles intégratifs qui pourraient évaluer leur contribution relative. Un premier article résume les recherches récentes sur le placebo qui ont recours à des modèles expérimentaux de douleur. Il se penche sur les théories du conditionnement, des attentes, de même que sur celle démontrant le rôle des endorphines dans l'analgésie placebo. Chacun de ces modèles a reçu un appui scientifique. Le chapitre propose également un regroupement des différentes facettes de ce phénomène.

Puis, une étude compare l'effet analgésique placebo sur la douleur clinique et expérimentale dans un échantillon de sujets souffrant de douleur lombaire chronique. La douleur au dos et la douleur provoquée par l'immersion de la main dans l'eau froide ont été mesurées avant et après une injection d'eau saline. Les sujets étaient soumis à deux jours d'expérimentation, l'un où l'injection était présentée comme un analgésique puissant (condition placebo) et l'autre où elle était présentée comme une substance inactive (condition contrôle). Les résultats indiquent que les maux de dos sont plus sensibles au traitement placebo que les douleurs expérimentales, un effet qui ne s'explique pas par une différence dans les attentes. De plus, les sujets ayant reçu le placebo après le traitement contrôle ont présenté une moins grande analgésie que ceux recevant le placebo en premier. L'expérience anti-analgésique (condition contrôle) semble ainsi bloquer l'effet pro-analgésique des attentes.

Une deuxième étude s'intéresse au soulagement d'une douleur thermique expérimentale chez des sujets sans douleur chronique soumis à une stimulation électrique transcutanée (TENS) placebo. Les situations contrôles sans traitement étaient comparées aux situations avec des électrodes posées sur un des bras. À l'insu

des sujets, un conditionnement analgésique était effectué en diminuant la température des stimulations sur le bras traité. L'effet placebo était mesuré lorsque l'intensité des stimulations était rétablie, c'est-à-dire identique sur les deux bras. Les résultats suggèrent que le changement de douleur produit par le traitement placebo est la conséquence du conditionnement, mais que cet effet est expliqué en partie par l'impact de l'expérience analgésique sur les attentes. L'utilisation de plusieurs mesures du changement de douleur suite au placebo a aussi confirmé la sensibilité accrue des évaluations rétrospectives de soulagement à l'analgésie placebo. Les modèles intégratifs proposés soulignent la similitude de la réponse placebo entre les deux études, menées pourtant avec une méthodologie sensiblement différente. Le phénomène de l'analgésie suite à un traitement placebo semble donc s'expliquer de manière interreliée par les processus cognitifs et par l'expérience passée.

Mots clé français:

Douleur, placebo, attentes, conditionnement, cognitions, mémoire

Résumé en anglais

Various mechanisms have been proposed to explain the modulation of pain in response to a placebo treatment. We focused on two psychological theories: conditioning and expectations. The thesis main goal was to clarify the relative influence of cognitions (expectations) and past experience (modified by conditioning) in placebo analgesia. We have examined both theories, creating integrative models that could underline their relative contribution. A first article reviews the recent placebo research using experimental pain models. It describes conditioning and expectation theories of placebo, and the mediating role of endorphin in placebo analgesia. Supporting evidences are available for each of these models. The chapter also suggest an integration of the different aspects of this phenomenon.

Then, a study compares the placebo response on clinical and experimental pain in a sample of chronic back pain patients. Back pain and cold pressor pain were measured both before and after a saline injection. Subjects were tested in two experimental days, one in which the injection was presented as a potent pain-killer (placebo condition), and the other in which the injection was presented as an inactive substance (control condition). Results indicated that back pain is more sensitive than cold pain to placebo treatment, an effect that could not be explained by differences in expectations. Moreover, subjects who received the placebo after the control treatment reported less analgesia then those submitted to the placebo treatment first. The anti-analgesic experience (control condition) seems to have blocked the pro-analgesic effect of relief expectations.

A second study looks at the relief of experimental thermal pain in healthy subjects (without chronic pain) submitted to placebo transcutaneous electrical nerve stimulation (TENS). Control situations without treatment were compared to situations with electrodes on one arm. Subjects were not informed that an analgesic conditioning was induced by decreasing the temperature of the stimulation on the

treated arm. Placebo effect was then measured when the stimulus intensities were returned to the same level on both arms. Results suggest that changes in pain induced by the placebo were a consequence of conditioning, but the effect was partly explained by the impact of the analgesic experience on expectations. The use of many measures of pain change after the placebo further underlined the higher sensitivity of evaluations to placebo effects. The integrative models proposed similarities of placebo response in the two studies, using different methodologies. The phenomenon of analgesia after a placebo treatment seems to be explained both by cognitive processes and by past experience.

Mots clé anglais:

Pain, placebo, expectations, conditioning, cognitions, memory

Table des matières

Liste des tableaux

Liste des figures

Liste des abbréviations

ANCOVA: analysis of covariance (analyse de covariance)

ANOVA: analysis of variance (analyse de variance)

CCK: cholecystokinin

ES: effect size (taille de l'effet)

IV: intraveineux

SD: standard deviation

SEM: standard error mean

TENS: transcutaneous electrical nerve stimulation (stimulation électrique transcutanée)

UQAT: Université du Québec en Abitibi-Témiscamingue

VAS: visual analogue scale (échelle visuelle analogue ou EVA)

Remerciements

L'appui de directeurs de recherche stimulants est essentiel pour une thèse. Merci à Serge Marchand, Pierre Rainville et Jean-Pierre Blondin pour leur support et leur enthousiasme.

Mon travail fut facilité par l'appui financier du Fonds de la Recherche en Santé du Québec (FRSQ) et de la Fondation Canadienne pour l'Innovation (CFI) à qui j'adresse mes remerciements.

Merci à Dominique Saheb pour ses judicieux conseils et son support soutenu.

Merci aussi à ma mère Monique et mon père Roger qui m'ont transmis la curiosité intellectuelle et l'importance de la persévérance.

Je tiens finalement à souligner le soutien moral et technique de mon conjoint Martin qui m'a encouragé sans faillir durant le long processus du doctorat. La réalisation de ce projet aurait été beaucoup plus ardue sans son appui.

1. Introduction

1. *Effet placebo: historique*

Depuis des millénaires, les guérisseurs ont proposé des traitements dont les propriétés pharmacologiques laissent encore de nos jours sceptique. Dents de crocodile, invocation des esprits, saignées et panacées arrivaient pourtant à soulager les maux des patients. La confiance et la croyance d'un soulagement ainsi que l'aspect symbolique du soin contribuaient à une amélioration de l'état du patient probablement plus que la technique spécifique utilisée. Le traitement acquérait ainsi une signification soulageante pour le patient (Moerman, 2002). Le mot *placebo* vient d'ailleurs du latin *je plairai*.

Dans l'histoire de la santé, le phénomène a longtemps eu mauvaise réputation. Il faut dire que les premières publications sur l'effet placebo, dans les années 1950, présentaient des récits anecdotiques plutôt que des études contrôlées (Hròbjartsson, 2002). L'analyse scientifique de l'effet placebo à l'aide d'une méthodologie en double aveugle est plus récente. L'évolution de la technologie permet maintenant de distinguer la part du placebo et celle qui appartient aux propriétés pharmacologiques d'un médicament. Dans les dernières années, nous avons vu émerger la légitimité de l'étude des mécanismes de l'effet placebo et son utilité clinique. On considère que cet effet est présent à divers degrés dans tout traitement d'ordre pharmacologique (Quitkin, 1999), chirurgical (Gracely et al., 1983), psychologique (Horvath, 1988) de même que dans l'utilisation de procédures médicales diverses (Long et al., 1989) et de l'acupuncture (Streitberger et al., 1998).

Il existe pourtant un écart entre la compréhension du concept dans le monde scientifique et dans la population en général. Le dictionnaire Larousse (2003) définit le placebo comme suit: " Substance et, par extension, traitement pouvant améliorer des symptômes chez certains malades, mais sans activité thérapeutique reconnue scientifiquement autre que psychologique." Soulignons au passage le sens péjoratif attribué au même mot: "Traitement que l'on juge inefficace" (Larousse, 2003). La plupart des patients et des infirmières ont encore une perception négative de la

thérapie par placebo (Berthelot et al., 2001). Pour certains, avoir une réponse positive à un simulacre de traitement est un peu honteux, voire malhonnête. Ils peuvent avoir l'impression qu'ils ont imaginé leur mal ou leur soulagement. L'utilisation de traitements placebos dans l'optique de détecter les cas de simulation ou de somatisation a contribué à cette image peu reluisante. Pourtant, dans des conditions loin d'être imaginaires comme celles des chirurgies cardiaques ou des extractions dentaires, on a observé l'importance du phénomène.

On sait maintenant que la séparation entre l'effet physique et psychologique est erronée et que le placebo déclenche des changements physiologiques réels. Bandura et ses collègues (1987) ont en effet suggéré que l'utilisation de "*coping*" cognitif pour le contrôle de la douleur amenait un relâchement d'endorphines. De plus, une étude d'imagerie a démontré l'effet positif ou au contraire inhibiteur de l'hypnose sur l'activité de certaines régions cérébrales durant une stimulation douloureuse, selon les suggestions proposées (Rainville et al., 1997). Il est donc possible que des composantes cognitives (comme les attentes) déclenchent dans certaines conditions un mécanisme physiologique endogène de contrôle de la douleur.

Plusieurs voix s'unissent d'ailleurs pour augmenter la partie du soulagement dépendant de l'effet non spécifique des traitements, qui s'apparente au placebo dans son sens large (Crow et al., 1999; Brown, 1998; Evans, 1974). Ces derniers considèrent qu'il s'agit là d'un effet puissant et utile s'ajoutant à l'action pharmacologique intrinsèque des médicaments. Cette position contraste avec celle de certains milieux de la recherche clinique qui tente de contrôler l'effet placebo tel un "contaminant" de l'effet thérapeutique spécifique du traitement étudié.

Dernièrement, des compte-rendus dérivés de conférences sur ce phénomène ont été publiés (Guess et al., 2002; Harrington, 1997). On a aussi assisté en 1996 à la création d'un groupe de chercheurs intéressés spécifiquement au placebo au sein de l'*International Association for the Study of Pain*. En 2001, le prestigieux organisme américain *National Institute of Health* offrait un fonds de recherche dédié aux études

sur les mécanismes expliquant l'effet placebo. Quoique toujours controversée l'étude du placebo semble donc maintenant considérée comme pertinente et suscite un intérêt grandissant dans le monde de la science, de la médecine et de la psychologie (Hròbjartsson et al., 2001; Kienle et al., 1997).

2. *Définitions*

La définition scientifique de placebo n'est pas simple (Hròbjartsson, 2002). Dans le cadre de cette thèse de doctorat, nous utiliserons le mot **placebo** comme une intervention conçue pour simuler un traitement efficace, mais pour laquelle on ne connaît pas d'efficacité intrinsèque (Turner et al., 1994). Il existe sous diverses formes: procédure d'imitation d'acupuncture, dosage non thérapeutique d'un médicament, traitement jadis utilisé mais dont l'efficacité est maintenant contestée, sans parler de l'exemple classique de la pilule de sucre. L'utilisation de placebos est associée à des effets secondaires qu'on appelle parfois effet nocebo (Barsky et al., 2002) et peut imiter des effets pharmacologiques (Lasagna et al., 1958).

Quant à l'impact thérapeutique de l'utilisation de ce traitement, nous en parlerons de façon interchangeable comme une réponse placebo ou un effet placebo. On peut définir l'**effet placebo** comme une réponse positive d'un sujet à une substance ou à toute procédure connue pour n'avoir aucun effet thérapeutique pour la condition spécifique traitée (Benedetti et al., 1997). Ceci contraste avec la version plus large de la définition, soit tous les processus psychologiques impliqués dans une interaction patient-soignant (Hròbjartsson, 2002). Dans ce sens, l'impact de l'attitude chaleureuse d'un médecin peut être considéré comme un effet placebo et la présence même d'un traitement placebo n'est pas nécessaire. Nous n'utiliserons ici que la définition plus restrictive et considérerons que l'effet placebo est la conséquence du traitement placebo.

Nous mentionnerons à plusieurs reprises dans cette thèse le terme **cognitions**. Les facteurs cognitifs ou pensées correspondent aux significations, aux attributions, aux

croyances qu'un individu associe aux événements. Différents processus cognitifs ont été proposés dans le domaine de l'effet placebo (Price et al., 1997), notamment le désir de soulagement (à quel point je *souhaite* voir une amélioration de ma condition) et les attentes de soulagement (à quel point je *prédis* une amélioration de ma condition). Nous nous attarderons principalement sur les attentes de soulagement, un type de cognitions qui semble particulièrement important dans l'effet placebo.

Nous souhaitons proposer des **modèles intégratifs** de l'effet placebo suite à nos recherches. Nous regarderons de concert différentes variables pouvant influencer la réponse des sujets au traitement placebo. L'impact relatif des attentes et de l'expérience passée sur les différentes mesures de soulagement de la douleur sera schématisé dans un modèle regroupant ces variables.

3. *Théories expliquant l'effet placebo analgésique*

Plusieurs champs d'études se sont intéressés aux mécanismes de l'effet placebo. L'anthropologie s'est surtout penchée sur les différences culturelles et sur le symbolisme des traitements alors que la physiologie s'est intéressée aux substances endogènes stimulées par l'administration d'un placebo. On a ainsi démontré l'implication des endorphines, les opiacés endogènes, dans les études sur l'effet placebo et la douleur (ter Riet et al., 1998). Toutes les études publiées à l'exception d'une indiquent la modulation de l'analgésie par le naloxone (un antagoniste des endorphines) ou la proglumide (un médicament qui potentialiserait les endorphines). Les endorphines inhibent la transmission nociceptive au niveau du cerveau et de la moelle épinière et diminuent ainsi l'intensité de la douleur (Price et al., 2002). Une étude d'imagerie cérébrale (Petrovic et al., 2002) a également souligné la similitude entre les zones du cerveau activées lors d'une analgésie par placebo et celles activées par la morphine. D'autre auteurs ont suggéré un rôle pour la dopamine impliquant un mécanisme relié aux attentes de récompense dont le soulagement peut faire partie (De La Fuente-Fernandez et al., 2002).

De son côté, la psychologie a étudié notamment le rôle de la personnalité, de l'anxiété, du support social, de l'apprentissage et des cognitions sur la réponse placebo. Les théories du conditionnement et celle des attentes de soulagement ont servies de cadre conceptuel pour les études menées dans la thèse. Bien que chaque approche aborde l'analgésie placebo sous un angle différent, ces théories ne sont probablement pas mutuellement exclusives et représentent des aspects différents de la réponse placebo (Peck et al., 1991). Le premier article de la thèse se penchera plus en détails sur les modèles conceptuels de l'effet placebo en douleur. Les deux autres articles tenteront de combiner l'étude de ces modèles.

A) Conditionnement - modulation par l'expérience passée

Le modèle de conditionnement considère que la réponse placebo est la conséquence directe d'un conditionnement classique, peu importe les stimuli (Wickramasekera, 1985). Un traitement efficace est habituellement accompagné d'endroits, d'objets, de rituels et de procédures ou de personnes spécifiques à ce contexte. Les patients peuvent ressentir un soulagement de leur douleur parce qu'ils ont appris qu'un traitement ou un environnement similaire est accompagné par une analgésie. On parle également d'effet non spécifique relié à l'attention et à l'intérêt du médecin, de la réputation du traitement et de son apparence (Turner et al., 1994). On a d'ailleurs montré que l'expérience antérieure d'un traitement analgésique efficace augmente l'effet analgésique d'un traitement placebo semblable présenté subséquemment (Laska et al., 1973).

Selon ce modèle, l'analgésie par placebo (la réponse conditionnée) est une conséquence de l'association d'éléments neutres (les stimuli conditionnés) et d'expérience directe d'analgésie avec des traitements dont l'efficacité pharmacologique est reconnue (la réponse inconditionnelle). Il y a apprentissage et les stimuli préalablement neutres, comme la forme d'une pilule, une salle d'examen ou un uniforme d'infirmière, deviennent des stimuli conditionnés. Ces éléments sont considérés neutres au départ puisqu'ils ne devraient pas en soi provoquer de changement au plan du soulagment de la douleur. On reconnaît toutefois que la

réponse à tout médicament (stimulus inconditionnel) comporte à la fois un élément de réaction physiologique due à ce médicament (réponse inconditionnelle) qui s'ajoute à une réponse apprise (réponse conditionnée) due aux éléments accompagnant le traitement.

Wickramasekera propose que la réponse placebo serait d'autant plus importante lorsque la personne est privée de santé, comme dans un contexte clinique. Comme le chien privé de nourriture détecte et répond plus fortement et plus rapidement aux stimuli conditionnés associés à la nourriture, ce patient deviendrait plus sensible à tous les stimuli qui peuvent être associés à la santé (Wickramasekera, 1985). Notons toutefois que les gens souffrant de douleur chronique ont souvent essayé, sans grand succès, plusieurs médicaments, ce qui devrait mener à l'extinction de la réponse conditionnelle et diminuer l'effet placebo puisque le stimulus inconditionnel n'est plus suivi de la réponse inconditionnelle. Ce n'est cependant pas toujours le cas et il s'agit là d'une critique formulée au sujet de cette théorie qui tient peu compte de l'aspect symbolique des traitements (Kirsch, 1997). Selon Spiro (1986), le modèle de conditionnement n'offrirait d'ailleurs qu'une explication partielle à la réponse placebo.

Souvent pratiquées sur l'animal (Ader, 1997), les études de conditionnement et de placebo chez l'humain sont assez récentes (Voudouris et al., 1990; Voudouris et al., 1989; Voudouris et al., 1985). Même en l'absence de suggestions d'analgésie visant à créer des attentes, on a démontré que le conditionnement peut amener une réponse placebo (Amanzio et al., 1999). Il semble donc que l'expérience passée modulée par le conditionnement ait un impact en soi qui ne serait pas dépendant des attentes, notamment dans certains contextes comme un conditionnement des réactions hormonales (Benedetti et al., 2003). Quant au lien entre le conditionnement et les changements physiologiques, une étude propose que le conditionnement dans un contexte d'analgésie implique un mécanisme endorphinergique seulement lorsque le médicament utilisé lors du conditionnement est un opiacé (Amanzio et al., 1999).

B) Attentes - modèle cognitif

Selon le modèle des attentes (Kirsch, 1985), l'expérience d'une personne est déterminée par ses attentes spécifiques de ce qui arrivera dans une situation donnée. Les croyances face aux conséquences d'un traitement peuvent être acquises par une expérience directe, comme lors d'un conditionnement, ou par d'autres méthodes d'apprentissage (par exemple par l'observation, par des informations reçues verbalement ou par la lecture). De plus, la façon d'acquérir les attentes est moins importante que l'intensité subjective de ces dernières. Ce modèle se situe d'ailleurs clairement dans un paradigme cognitif ou dans une vision plus contemporaine du conditionnement classique (Rescorla, 1988) et n'exclut pas l'importance de l'expérience passée dans l'élaboration des attentes. La parenté entre les théories du conditionnement et celle des attentes est ainsi évidente, avec les cognitions servant de médiateur entre le conditionnement et ses conséquences.

Une étude a d'ailleurs démontré que ce n'est pas tant la présence simultanée de traitement et de soulagement qui détermine la réponse au traitement, mais bien la signification de ce pairage (Montgomery et al., 1997). En effet, dire aux sujets qu'il s'agit d'un placebo diminue l'effet du conditionnement et donc le soulagement via une baisse des attentes de soulagement. D'un autre côté, l'effet positif à long terme des placebos, pour lequel le modèle de conditionnement n'a pas d'explication claire, peut s'expliquer par un modèle cognitif. L'extinction n'arrivera pas tant que la personne maintient ses attentes, et ce malgré l'absence de réponse inconditionnelle. On a d'ailleurs montré une augmentation de l'effet placebo avec le temps plutôt qu'une diminution (Montgomery et al., 1997).

Les interactions entre le conditionnement et les attentes sont nombreuses et leurs effets semblent s'additionner. La manipulation de l'expérience passée par conditionnement aurait plus d'impact sur les attentes de soulagement que le simple fait de suggérer verbalement une diminution de douleur (Montgomery et al., 1997; Voudouris et al., 1990). À l'inverse, manipuler les cognitions en suggérant un soulagement ou une augmentation de douleur (hyperalgésie) a un impact, même

après un conditionnement (Benedetti et al., 2003). Une méta-analyse des études sur les mécanismes de l'effet placebo analgésique a démontré que la taille de l'effet pour les études sur les attentes ou sur le conditionnement seul sont similaires, alors que celle pour la combinaison des deux phénomènes est supérieure (Vase et al., 2002).

Par ailleurs, les attentes de soulagement peuvent avoir un impact très spécifique sur la réponse placebo. Les caractéristiques physiques du traitement placebo peuvent influencer son efficacité, comme la couleur, le mode d'administration et la quantité (Moerman, 2002; Buchaleq, 1982). D'autres études ont démontré une analgésie localisée à une petite partie du corps (Benedetti et al., 1999; Montgomery et al., 1996). Cette particularité de l'effet placebo a remis en question la conception des endorphines comme mécanisme global agissant de façon non spécifique sur tout le corps.

Certains auteurs ont suggéré un rôle causal des attentes sur l'analgésie placebo après avoir observé la relation proportionnelle avec les évaluations de douleur (Price et al., 1999b). Il semble également que les attentes peuvent déclencher les systèmes endogènes d'opiacés (Amanzio et al., 1999), ce qui donnerait un rôle de médiateurs d'effets physiologiques aux attentes. Par ailleurs, ces dernières ont un impact sur tout traitement pharmacologique et non seulement sur les traitements placebo, comme l'a montrée une étude au cours de laquelle des sujets avec des attentes élevées avaient besoin d'une plus faible dose d'analgésique pour atteindre le même soulagement que ceux dont les attentes étaient plus faibles (Pollo et al., 2001).

4. Aspects méthodologiques

A) Contexte

Les études présentées dans cette thèse ont été menées dans un contexte d'analgésie, c'est-à-dire que les traitements placebos proposés aux sujets étaient présentés comme pouvant soulager leur douleur. La mesure de l'effet placebo était donc le changement dans la perception de la douleur avant et après l'administration du placebo, comparativement à la condition contrôle.

B) Études ayant recours à la douleur expérimentale

L'effet du placebo sur la douleur clinique a été plus largement étudié, mais on sait que la douleur expérimentale est aussi modifiée par un placebo. Une des études de la présente thèse compare la réponse des mêmes sujets sur les deux types de douleur. Pour l'autre étude, seule de la douleur expérimentale a été utilisée.

Par opposition à la douleur clinique, la douleur expérimentale est provoquée par des stimuli externes au sujet. L'utilisation de douleur expérimentale pour étudier un traitement analgésique, dont le placebo, a plusieurs avantages méthodologiques. Le contrôle des paramètres de stimulation permet en effet la répétition des stimulations nociceptives. La source de la douleur peut être contrôlée précisément, ce qui diminue sa variabilité et augmente, en principe, la puissance statistique pour examiner les effets du traitement placebo. De même, la durée plus courte de la douleur expérimentale par rapport à la douleur clinique minimise les fluctuations naturelles qui peuvent rendre difficile l'interprétation d'un changement suite à un traitement. La confusion entre un effet thérapeutique et une variation due au passage du temps est donc moins probable dans ce contexte.

C) Utilisation d'un contrôle

Étant donné que certaines variables peuvent aussi expliquer le changement mesuré suite à l'administration du placebo (histoire naturelle, régression vers la moyenne, réactivité de la mesure), l'utilisation d'une situation contrôle est essentielle pour s'assurer que les résultats obtenus dépendent bien du placebo (Bootzin et al., 2002; Hròbjartsson, 2002). Pour nos études où les sujets étaient soumis à la fois au traitement placebo et au traitement contrôle, il s'agissait d'une condition où l'administration du traitement, présenté comme un contrôle, était associée à des suggestions verbales d'absence d'effet analgésique.

D) Choix de la mesure d'analgésie

La diminution de douleur peut être mesurée de différentes manières. Nous avons choisi de demander aux sujets d'évaluer deux dimensions des stimuli douloureux, soit

leur intensité et l'aspect désagréable de la sensation. Ces mesures ponctuelles étaient prises immédiatement après chacune des stimulations. De plus, les sujets devaient donner une évaluation globale du changement de douleur à la fin de blocs de stimulation. On a observé que l'effet placebo est plus grand lorsque l'évaluation de la mesure dépendante est faite de manière rétrospective que si elle est faite immédiatement après la stimulation nociceptive (Price et al., 1999b). Nous avons choisi de comparer les deux moments d'évaluation, soit les mesures ponctuelles et les mesures globales, pour voir si nous pouvions observer une réponse placebo plus importante dans le dernier cas.

5. *Considérations déontologiques*

Les projets de recherche ont été approuvés par le comité d'éthique de l'Université du Québec en Abitibi-Témiscamingue (UQAT), où a eu lieu l'expérimentation pour l'étude avec les lombalgiques, et par le Comité d'éthique de recherche des Sciences de la santé de l'Université de Montréal pour le projet de stimulation électrique transcutanée (TENS). Compte tenu du type d'études, certains questionnements éthiques ont été soulevés en cours de processus.

Infliger de la douleur pour les besoins d'une expérimentation est toujours délicat et nous avons eu le souci de rendre l'étude la moins désagréable possible pour nos sujets. Nous avons donc choisi une douleur expérimentale de courte durée et sur une petite surface corporelle. Les sujets connaissaient bien les risques (douleur, rougissement temporaire de la peau, picotements). Ils étaient libres de participer ou de cesser l'expérimentation à tout moment, et ce, sans préjudice. Quelques-uns se sont d'ailleurs prévalus de ce droit. Par ailleurs, nos sujets étaient indemnisés pour leur participation.

Un autre aspect délicat de notre recherche concernait le consentement éclairé. La nature de nos études nous a obligés à n'informer les sujets que partiellement sur la nature exacte de notre recherche, les sujets devant croire qu'ils avaient reçu une

substance active. Le but décrit aux participants était de tester une hypothèse sur les mécanismes de fonctionnement d'un traitement dont l'efficacité est déjà reconnue au plan scientifique, et non pour vérifier son efficacité. Cet énoncé est véridique puisque la réponse analgésique aux placebos a été démontrée dans plusieurs recherches. Nous avons considéré qu'il n'était pas justifié de les informer de façon systématique de l'utilisation d'un traitement placebo dans toutes les conditions lors d'un *debriefing* immédiatement après la fin de l'expérimentation. Cette information pouvait à notre avis causer davantage de tort que d'utilité chez les participants à cause du préjugé généralement défavorable face au placebo en dehors du monde scientifique. De plus, l'utilisation d'un traitement placebo ne soumettait pas les gens à un risque. Les sujets étaient toutefois invités à communiquer avec nous à la fin de l'étude s'ils désiraient connaître l'identité du traitement utilisé. Les comités d'éthique consultés ont accepté cette position.

Notre modification des exigences du consentement est conforme aux cinq critères de l'Énoncé de politique des trois conseils (1998), notamment parce que, sur un plan pratique, la recherche ne pouvait pas être menée sans modifier ces exigences du consentement. La nature même des études, portant sur l'effet placebo, nécessitait une certaine manipulation des attentes et des perceptions des sujets. La communication explicite de tous les renseignements risquait de fausser les réponses des sujets et donc d'invalider la recherche. Néanmoins, les sujets étaient au courant de l'utilisation de conditions contrôles et avaient donné leur consentement éclairé à cet égard.

6. *Objectifs et hypothèses*

On sait maintenant que l'effet placebo dans un contexte d'analgésie est un phénomène réel. Plusieurs études ont également démontré le rôle des attentes et du conditionnement sur la réponse placebo. Nous avons voulu intégrer ces deux théories dans un modèle unique. L'objectif général de la thèse est donc de clarifier dans quelle mesure les cognitions et l'expérience passée sont impliquées dans une analgésie placebo.

Les objectifs plus spécifiques sont de

1. Comparer la réponse placebo pour la douleur clinique et pour la douleur expérimentale chez un groupe de sujets lombalgiques.
2. Vérifier si les attentes expliquent la différence attendue entre l'analgésie placebo sur la douleur clinique et sur la douleur expérimentale.
3. Comparer l'impact de l'expérience passée (modifiée par conditionnement) et des attentes induites verbalement sur l'analgésie par TENS placebo sur un échantillon de sujets sans douleur clinique.
4. Vérifier si le modèle explicatif de l'effet placebo chez les lombalgiques peut s'appliquer également aux sujets sains.
5. Comparer la réponse placebo sur les mesures prises ponctuellement en cours d'expérimentation avec celles données de façon globale et rétrospective.

Sur la base des études recensées dans la littérature, les hypothèse de recherche suivantes ont été avancées:

1. Les attentes de soulagement seront plus grandes pour les maux de dos que pour la douleur expérimentale. L'analgésie placebo sur la douleur clinique sera par conséquent plus importante que celle sur la douleur expérimentale.
2. Il y aura une corrélation entre les attentes et la diminution de douleur suite au traitement placebo.
3. Il y aura une corrélation entre la diminution de douleur suite au conditionnement et l'analgésie suite au TENS placebo.
4. Le modèle explicatif chez l'échantillon de gens souffrant de douleur chronique et chez celui de gens sans douleur clinique sera sensiblement le même.
5. Les mesures globales de soulagement montreront un plus grand effet placebo que celles ponctuelles.

7. *Organisation de la thèse*

Cet ouvrage expose notre recherche sous la forme de trois articles. Le premier (chapitre 2, p. 27) dresse un portrait des connaissances actuelles sur les mécanismes de l'effet placebo dans un contexte d'analgésie et propose un modèle intégratif du phénomène de l'analgésie placebo sous l'angle du conditionnement, des attentes et des endorphines.

Le deuxième article (chapitre 3, p. 50) compare la réponse placebo à une douleur clinique (des lombalgies chroniques) à une douleur expérimentale chez le même groupe de sujets. Cette méthodologie nous apparaissait plus utile que des études comparatives de différents échantillons. Les attentes de soulagement ont été induites à la fois par des suggestions verbales et par un protocole rigoureux d'application du traitement, soit une injection intraveineuse d'eau saline faite par des infirmières. L'étude se penche notamment sur le rôle des attentes et suggère un modèle explicatif de l'effet placebo chez cette population. La comparaison de l'ordre de présentation des conditions placebo et contrôle permet aussi d'observer l'impact de l'expérience passée sur la réponse à un nouveau traitement. Le rôle de la mémoire sur la réponse placebo a également été étudié.

Finalement, le troisième article (chapitre 4, p. 87) étudie à la fois l'impact de l'expérience passée suite à un conditionnement et celui des attentes chez un groupe de volontaires sains soumis à une douleur expérimentale et un traitement de TENS utilisé sans courant électrique. Le conditionnement consistait à une baisse des stimuli douloureux à l'insu des sujets en présence du traitement placebo. Quant aux attentes, elles ont été induites avant le conditionnement par des suggestions verbales d'analgésie et par l'utilisation d'un protocole d'application du traitement. L'impact du conditionnement sur les attentes subséquentes a aussi pu être étudié. À nouveau, un modèle explicatif de l'effet placebo chez cette population a été proposé.

2. *Article 1.* Understanding placebo analgesia: the contribution of experimental pain studies

Cet article a été soumis au *Journal of Pain.* Les auteurs sont Julie Charron et Serge Marchand.

Abstract

The role of placebo in analgesic response has been extensively studied, particularly in pharmacological studies, where the main goal is to demonstrate how active treatment is superior to placebo. However, relevant information is now available on the psychological and physiological mechanisms of placebo analgesia that could lead to better pain management with all types of treatment. Experimental pain studies have identified placebo analgesia mechanisms in a laboratory setting where the nociceptive stimuli are well-controlled. Thus, using three models (conditioning, expectations and endogenous opioids), the following discussion will evaluate studies in which placebo analgesia was examined in an experimental pain setting. Of interest, supporting evidence is available for all three models, and each is useful in explaining placebo analgesia mechanisms at a different level. We propose a model that integrates these findings, and identify areas of future research.

1. Introduction

Any type of treatment, (e.g., pharmacology, (Quitkin, 1999) surgery, (Gracely et al., 1983) acupuncture, (Streitberger et al., 1998) psychotherapy (Horvath, 1988) or exposure to medical devices (Long et al., 1989)) can induce a placebo reaction. Placebo analgesia is defined as a decrease in pain after a placebo treatment designed to simulate medical therapy, or as an analgesic response to a treatment known to have no therapeutic effect for the relief of pain (Benedetti et al., 1997; Brody, 1985). Thus, in the case of placebo analgesia, the patient usually believes he has received a potent painkiller while being administered an inactive substance.

Three models are generally used to explain placebo analgesia: conditioning, expectations and endogenous opioids. Although each approach examines placebo analgesia from a different perspective, these theories may not be mutually exclusive and could represent three different aspects of the placebo response (Peck et al., 1991). The goal of this review is to use these three models to examine the effect of placebo analgesia in experimental pain conditions and to integrate this knowledge into a conceptual paradigm.

Most of the studies conducted on placebo analgesia examine this phenomenon within the context of clinical pain (for a review, see Turner et al., 1994), but some have done so under experimental conditions. Experimental pain is caused by an external nociceptive stimulus, i.e., heat, cold, electrical, pressure, chemical or ischemic stimulation (Gracely, 1994), that is generally applied to healthy, volunteer subjects. The advantage of using experimental pain is the ability to control the stimulation's parameters, i.e., intensity, onset, offset, duration and repetition over time.

There are many reasons that favor experimental pain over clinical pain in the study of any analgesic procedure, including placebo. First, the ability to produce repeated nociceptive stimulations is an important advantage of experimental pain studies

(Price, 2000). Secondly, the problems associated with a natural history of pain are less important with experimental pain than with clinical pain, reducing the need for a control group. An untreated group or a control session for the same subject is interesting if the painful stimulation has been repeated several times. In this situation, the changes in pain sensation may not be a consequence of the placebo treatment but rather of the sensitization or the habituation to the stimuli. Lastly, the impact of desire for relief may be less important for subjects experiencing experimental pain than those with clinical pain, resulting in a more homogenous sample.

For these reasons, two early studies (Jospe, 1978; Beecher, 1955) argue that the magnitude of placebo analgesic effects are larger in clinical pain studies. A meta-analysis (Harkness et al., 2000) found a larger placebo response with acute pain compared to chronic, experimental or post-operative pain. However, the size of the placebo effect was similar to that seen with chronic and experimental pain. In fact, as Price states (2000), few studies looking at clinical analgesia really measure the placebo effect. Instead they use the difference between the placebo and the active conditions.

Jospe (1978) states that stressful forms of experimental pain are associated with a greater placebo effect. In fact, one often-cited study where brief pain was induced by a 5-sec heat stimuli applied to the skin, showed very little placebo effect (Price et al., 1985). In another study (Roelofs et al., 2000), the strong suggestion of analgesia did not create a significant decrease in pain ratings. The reasons for this lack of effect have been outlined by the authors: the experimental pain was mildly painful, of short duration, without any conditioning manipulation, and the experimenter was not blind to the placebo condition. Thus, the creation of a placebo response in the laboratory is not always easy. However, to our knowledge, no study directly compares the susceptibility of different types of experimental pain for their effects on placebo analgesia, or compares clinical and experimental pain response to placebo in the same subjects.

2. Studies on conditioned placebo analgesia (Table I, p. 47)

The conditioning model states that the placebo response is a consequence of classical conditioning (Wickramasekera, 1985). A repeated association of neutral places, persons or objects typically accompanies an effective treatment. Subjects may feel a decrease in pain because they have learned that a similar treatment and/or environment is followed by an analgesic effect. From this point of view, learning is a consequence of direct experience.

Although some research has been done with animals (for a review, see McMillan, 1999), a group of investigators in the mid '80s published the first studies on placebo response to experimental pain in humans, whose behavior was modified by conditioning. (Voudouris et al., 1990; Voudouris et al., 1989; Voudouris et al., 1985) Due to large individual differences in pain responsiveness to the same stimulus, the authors decided that the use of equivalent pain-rating levels (and not equivalent intensity of the stimulus) would be more useful. Each subject received a subjectively similar level of pain stimulation, determined through calibration procedures.

In one of these studies, Voudouris and his colleagues (1985) examined "positive placebo effect" (reduced pain or therapeutic effect) and "negative placebo effect" (increased pain or anti-therapeutic effect), also referred to as "nocebo" effect (Benedetti et al., 1997). They used a 1-sec iontopheric pain generator that produces a noxious stimulation causing prickling or cramping sensations. They placed a placebo cream on the forearm skin, near the apparatus delivering painful stimuli, where subjects reported experiencing pain. All subjects attended three sessions and were told that the level of stimulation would remain constant throughout the study. They were further instructed to give a pain rating after each nociceptive stimulation with or without the placebo cream, which was presented as a local analgesic. During the second session (conditioning), the stimulation varied between placebo and no-placebo trials. For half of the subjects, the stimulation was increased during the placebo trials, and for the other half it was decreased. During the first and the third

session, the noxious stimulation remained constant. The assumption was that the subjects would associate the cream with the pain change of session 2 and that they would respond in the same way during the third session, even if the stimulation was returned to the same intensity as the first. They would have learned that relief (placebo group) or increase in pain (nocebo group) followed the treatment. The results for the placebo response in the third trial followed the expected direction. They concluded that it was possible to increase or decrease pain ratings using conditioning principles. It is worth mentioning that they had a difference in placebo and no-placebo ratings (although it is not known whether this was statistically significant) even *before* the conditioning session.

Voudouris et al. published a second study (1989), comparing iontopheric and ischemic pain. Again, the results show a conditioning effect in the expected direction. Moreover, the group with increased stimulation (nocebo conditioning) during iontopheric pain did generalize the effect of the placebo cream to ischemic pain. However, the decreased stimulation group did not show this effect. The authors suggest that this may be because the conditioned learning that was in the opposite direction of the subject's expectations had a larger impact than the change that was predictable. Some methodological aspects of this experiment are reviewed in Table I (p.47).

3. Studies on expectations (Table II, p. 48)

Another experiment by the same research group (Voudouris et al., 1990) compared the conditioning and expectation models to better understand their role in the placebo effect. The expectation model (Kirsch, 1985) states that a person's specific expectations of what will happen in a given situation are determinants of what they will experience. Expectations can be acquired via direct experience, like conditioning, but there are also various other learning methods outlined in this model.

Furthermore, the way expectations are learned is not as important as the cognitive strength of the expectation. This model could be placed in a cognitive framework where the subject is more active than in the traditional classical conditioning vision (Rescorla, 1988). There is obviously considerable overlap between the two models and many authors have tried to distinguish them.

In the study by Voudouris (1990), noxious stimulation consisted of 1-sec iontopheric pain, the intensity of which was calibrated for each subject. The placebo was a cream applied at the site of the noxious stimulation. They used four different groups with a 2x2 design (types of expectation manipulation x types of conditioning manipulation). Half of the subjects (expectation groups) were told that the cream was a local analgesic while the other half were informed that the cream was neutral (no expectation groups). A conditioning session, where half of the subjects had reduced nociceptive stimuli during cream trials, was included. For the other half of the subjects, the stimulation remained constant. During each session, subjects had to rate their pain for the cream trials and the no-cream trials using a visual analogue scale (VAS). Their data showed: 1) a larger placebo effect for the subjects who had a conditioning session compared to those who did not, and 2) the conditioning effect was greater than that of the verbal expectation manipulation used here. The authors mention that this does not suggest that expectations have no effect on placebo response, since conditioning potentially creates response expectations. Their results can be interpreted as an indication that the conditioning effects were more effective than the type of expectation manipulation (Montgomery et al., 1997). Although well designed, the study fails to mention whether there was control for randomization of the groups or if the investigators were blinded.

Another study attempted to separate expectations from conditioning using iontopheric experimental pain (Montgomery et al., 1997). The study replicated the conditioning procedure of Voudouris et al. (1990) with the addition of more control groups and inclusion of measures of expectations. They compared a conditioned group with one that was informed about the stimulation decrease during the placebo

trials. They argue that if the conditioning effect is mediated by expectations, then informed pairing should fail to produce conditioning. They also used a no treatment and an extinction group. These groups participated in all of the trials (without any manipulation) to see if repeated stimulation would produce extinction of the placebo response as predicted by the conditioning model (Wickramasekera, 1985). The subjects were randomly assigned to one of the groups. They rated their pain intensity and expectations on an 11-point scale. Compared to the trials without the cream, the results showed that the use of the cream produced a small, yet significant effect before the conditioning manipulation in all groups. The uninformed pairing group (conditioned without awareness) showed the largest placebo response and the larger expectations of relief. Based on these results, the conditioning procedure was mediated by the expectations since conditioning had much less effect when the expectations were controlled in the informed pairing group. The correlation between the post-test placebo response and expectation rating was highly significant. The authors concluded that the interpretation of conditioning trials is more important than the trials themselves for placebo responding. Also, for the extinction group, an unexpected increase of the placebo effect was present. These data are inconsistent with the conditioning model of placebo response, but can be understood with the expectation model. The conditioned response model states that the repetition of the placebo treatment (the conditioned stimulus) without the active treatment (the unconditioned stimulus) will create a weaker placebo response over time (Wickramasekera, 1985). Since this was not the case in the study reviewed here, Kirsch (1991) suggests that the conditioning model is not as strong as expected. However, by producing an effect similar to that of a drug, the placebo confirms expectations of the drug response. The extinction procedure will need to be tested in future studies to see if this result can be replicated.

More recently, Price and colleagues published an extension and replication of the above study by examining the impact of two different psychological concepts of placebo response: desire for relief (motivation) and expectations of relief (Price et al., 1999b). Their subjects were submitted to thermal pain for 5 seconds with a 3-cm^2

probe. They used a conditioning paradigm, decreasing the temperature of the probe after the placebo application at the stimulation site. The subjects were unaware of the variability of the stimulus intensity. To alter desire for relief, they gave different instructions to the participants. Subjects rated the pain intensity and unpleasantness immediately after each trial as well as after the end of the manipulations (remembered pain) on two well validated visual analogue scales that have ratio properties (Price et al., 1994). The desire for relief was measured with a similar VAS. The analysis of variance showed a significant decrease of both intensity and unpleasantness ratings after the conditioned placebo manipulation. There was also an effect of expectation on the ratings. The authors argue that these results further establish expectation as a causal factor in placebo analgesia. However, the study did not show that desire for pain relief was related to the placebo response. This finding challenges the idea that clinical pain is more sensitive to placebo treatment than experimental discomfort because the motivation to escape the sensation is stronger. If clinical pain is more sensitive (yet to be proven), it may be for other reasons. Finally, the study found a three-times greater placebo response with the memory ratings than for the evaluation immediately after the stimulation.

4. Studies on endogenous opioids (Table III, p. 49)

A third model explaining placebo analgesia is based on the action of endogenous opioids. A review of placebo analgesia and endorphin studies shows that endogenous opioids may be implicated (ter Riet et al., 1998). Of these studies, all but one (Posner et al., 1985) indicate that naloxone (a μ-opioid antagonist) or proglumide (an endorphin synergistic drug) may play a role in placebo-induced analgesia.

One study (Benedetti et al., 1999) compared 173 subjects assigned to one of six different groups. The authors injected capsaicin subcutaneously into both of their hands and feet. This induces an intense, burning pain sensation that lasts a few minutes. They applied a neutral cream around some of the subcutaneous needles as the placebo treatment. The subjects reported less pain where the placebo was applied,

compared to the sites where there was no treatment. For two groups however, a hidden injection of naloxone completely blocked the placebo response, i.e., the pain ratings and duration were similar for the body parts treated with the placebo and for those not treated with the placebo. These results indicate that the opioid system can be activated by a placebo applied locally. Before this study, endogenous opioids were thought to act throughout the entire nervous system and to produce only a diffuse, non-specific analgesic effect. This explanation however, cannot explain the finding of a localized placebo effect blocked by naloxone and may have important implications for the understanding of the endogenous opioid systems (Mason, 1999).

This same group (Amanzio et al., 1999) was able to demonstrate that placebo analgesia has opioid and non-opioid components, depending on the procedure used to induce the placebo response. The authors measured the pain tolerance at 60-sec intervals, using the tourniquet technique to create ischemic pain. The placebo was a saline injection.

This experiment used a complex methodology with 12 different groups. Some subjects had conditioning trials with opioid (morphine) or non-opioid (ketorolac) analgesic drugs. Some had analgesic expectations concerning the placebo, while others did not. (They were told the solution was an antibiotic). Naloxone was used to determine in what conditions the analgesia was mediated by endorphins. The data indicated that expectations seem to trigger endogenous opioid responses. However, the conditioned placebo responses did not seem to be mediated by endogenous opioids in all conditions, but rather by specific subsystems, depending on the drug used for conditioning. Thus, when saline injection followed the repeated injection of ketorolac, a non-opioid analgesic, the subjects had a longer tolerance to noxious stimulation than without any treatment. However, naloxone did not block this conditioned placebo analgesia, even though it did block the morphine-conditioned placebo response. This study also indicates that even without verbal cues to create expectations, conditioning can induce a placebo response. The lack of such "expectation cues" reduced but did not completely block the placebo effect. This

further demonstrates that cognition and conditioning can be present in different ways during a placebo procedure and that a physiological response of the body can be a consequence of learning.

A prior examination of the placebo response (Benedetti, 1996) showed that placebo analgesia can be modulated in two opposite directions by using different drugs. In this study, the opioid antagonist naloxone diminished the placebo response while the cholecystokinin (CCK) antagonist proglumide enhanced it. The action of exogenous and endogenous opiates is potentiated by proglumide. These drugs did not have an effect on the experimental ischemic pain itself, but affected the placebo-induced decrease in pain. Of interest, when compared to a group where the injection of saline was hidden, the analgesic effect was present up to 45 minutes after the open placebo injection. This finding is contrary to the many beliefs about placebo response, namely that the placebo effect is necessarily brief (Turner et al., 1994). However, the naloxone only partially reversed the placebo response, and the authors mention that this may be explained by the involvement of a non-opiate component.

A study conducted by Posner and Burke (Posner et al., 1985) however, failed to support the involvement of endogenous opioids in placebo analgesia. Their subjects showed a decrease in pain after placebo administration but this placebo analgesia was not affected by naloxone. However, their sample of 12 volunteers was quite small and they prepared the naloxone injection in full view of the subjects. This procedure could have lead to a placebo response in itself (ter Riet et al., 1998). Usually, naloxone or proglumide are administrated without the subjects' awareness in order to prevent this undesired effect. The investigators also suggest that their study was done in a low anxiety condition because of an extensive familiarization procedure. The effect of anxiety on placebo analgesia was studied in the past, but no consensus has been reached because it is not clear if anxiety reduction is a cause or consequence of the placebo response (Benedetti et al., 1997).

However, a study based on the same induction of ischemic pain demonstrates an effect of naloxone on placebo analgesia and suggests that endorphins mediate the decrease of pain (Grevert et al., 1983). In this study, naloxone or saline was administered behind a screen, without the subject's awareness, forty minutes after the open injection of placebo. The naloxone alone did not have an effect on pain ratings. However, after placebo analgesia, the subjects receiving the saline injection reported less pain than the subjects receiving naloxone, showing that this opiate antagonist diminished the effectiveness of the placebo-induced analgesia. The placebo response was not completely blocked since pain ratings were lower than during a control session without any placebo. Because of the discrepancy between these last two studies (Posner et al., 1985; Grevert et al., 1983), more research is needed to see if small procedural differences can actually change the effect of naloxone on placebo analgesia.

A study on the effect of naloxone on placebo-induced analgesia during a cold pressor pain procedure (Bandura et al., 1987) shows that a placebo response using this kind of experimental pain (produced by the immersion of the hand in 0°C circulating water) may also be mediated by endorphins. This experiment compared cognitive coping and the placebo response. It is interesting to note from this study that cognitive coping increased pain tolerance. This effect was blocked by naloxone injections, suggesting that cognitive strategies may also have an effect on endorphins. This may be paralleled with results seen by Amanzio and colleagues (1999) that showed how differences in expectations alone can induce a placebo response and that this response can be blocked by naloxone.

In Bandura's study (1987), a placebo pill (described as a common analgesic drug) was given. A naloxone or saline injection was administered after 30 minutes in full view of the subjects, using a double-blind procedure. As mentioned earlier, this may prove to be a methodological error since an open injection can create a placebo effect. In addition, subjects were not blind to the fact that the injection could affect the physiological mechanisms of pain. The results showed an increase in pain

tolerance after the placebo administration. Compared to saline, the naloxone injection decreased the pain tolerance, indicating that the placebo analgesia is partially blocked by naloxone. Despite these methodological constraints, the findings of this study again provide some evidence for both an opioid-mediated component and a non-opioid component in placebo analgesia.

5. Introducing an integrative model (Figure 1, p. 45)

In order to have a more complete view of the mechanisms involved, we propose an integrative model. Figure 1 (p. 45) illustrates our conceptualization of placebo analgesia in a simple four-level fashion: 1) psychological changes; 2) physiological changes and 3 & 4) two levels of mediators acting on these mechanisms.

When a placebo is introduced, the context (1) is of great importance for the subject or the patient since past experience with similar treatments will be retrieved from memory and information will be processed within the framework of the individual's background. Context include the treatment, the environment and the caregiver. Learning processes, such as conditioning, will be activated at this level. The conditioning model analyzes the components of this level that mediate expectations. Then, if the actual context of treatment seems congruent with past experiences of analgesia, a psychological change (2) will occur and expectation can be measured. The subject will expect a decrease of pain. The expectation model was most interested in this level of placebo analgesia mechanisms. Different hypotheses about the mechanisms of pain reduction modulated by expectations and desire for pain relief include: effect on the pain affect component, response bias, and triggering of the descending control of the pain signal (Price et al., 1999a).

We propose that an intermediate step, the subjective change level (3), potentiates the action of expectations on the physiological (endogenous opioids) mechanism, since expectation of relief potentially modifies the way we perceive pain. Selective

attention is directed towards pain sensations, which could changes the way we respond by creating a response bias toward a larger pain decrease (Eccleston et al., 1999; Bushnell et al., 1985). We are not suggesting that subjects or patients *imagine* pain relief, but that they might be more *aware* of subtle changes because of their expectations.

For example, at this level, the pain ratings would decrease and subjects could perceive a change that enhances their expectations. In most instances, this subjective change will precede a deeper change mechanism, i.e., the physiological response of placebo analgesia, which is being mediated by endogenous opioids and non opioids mechanisms (4). During this review we found that there are increasingly more studies that link endorphins and placebo analgesia. However, there seems to be also a non-opioid component, since the analgesia is not completely blocked by naloxone and subtle methodological changes do not seem to produce opioid-mediated analgesia (Posner et al., 1985).

Of course, the effect of activating descending pain pathways will be added to the subjective changes and increased pain relief will be perceived. The contexts of expectation and subjective levels will further be enhanced, creating a self-fulfilling loop. However, based on our observations in the laboratory, in some instances the intensity of psychological change is not strong enough to promote subjective and physiological changes after a placebo intervention. Supporting this, it was demonstrated that the variability across subjects increases with the open injection of an analgesic compared to an hidden injection (Amanzio et al., 2001), suggesting individual differences in the placebo activation of endogenous opioids systems. A recent brain imaging study also reflected inter-individual variability in μ-opioid receptor binding at similar levels of pain intensity (Zubieta et al., 2001).

This model also has important implications for caregivers of "real" pain treatment. The studies on conditioning and placebo response outline the importance of the patient's history in determining their response to a new treatment or placebo

(Voudouris et al., 1985). Individual differences in the capacity to create expectation could explain the differential responses to treatment aside from the substance's physiological effects. The faster a certain level of expectation is obtained, the sooner subjective, followed by physiological, changes are possible. For exemple, Pollo and colleagues (Pollo et al., 2001) have clearly demonstrated that expectations have a significant impact on the efficacy of analgesic drugs. For the same amount of relief, subjects with higher expectations needed smaller doses of analgesic than subjects with lower expectations. The data regarding the impact of expectations on analgesic placebo response also indicate that expectations can mediate drug effects (Montgomery et al., 1997), and we postulate that this is the case with any therapeutic treatment. In fact, compliance could be seen as a marker of expectations (Roehr, 2001), since a patient who believes in the treatment's efficacy would be more careful while following the doctor's recommendations. Therefore, targeting an increase of expectation to influence adherence could lead to better efficacy of any treatment.

Even if every patient is given the same treatment, some will be more positive about its effect than others. Based on our model, a certain amount of expectation is necessary to trigger subjective and physiological changes that in turn have an additive effect on top of the specific treatment effects (Figure 2, p. 46). It is important to reassure patients about the effectiveness of any prescribed treatment. The impact of the manner in which we present the treatment information is of great importance to the psychological as well as physiological changes. As Price pointed out (2001), the combined effect of placebo and pharmacological responses is an improvement that can be further enhanced by "adding one or two sentences to each pain treatment". This point of view emphasizes the interaction between the patient's psychological characteristics and the efficacy of their pain treatment. The more skeptical the patient, the less likely they will be to trigger endogenous pain reduction mechanisms, thereby decreasing their perception of pain relief.

6. Concluding remarks

Although a more comprehensive view of the factors influencing placebo response is coming into focus, further well-controlled studies are needed. While experimental pain studies are useful to understand the placebo analgesia response, we must examine carefully the methodology being used when interpreting the results. Kienle and Kienle (1996) bring an interesting discussion on the differences between verbal placebo effects (experimental subordination by the patients) and true placebo effects. We see a parallel here with our "subjective" and "physiological" change levels. Since we are looking for a response influenced by expectations, using a blind evaluator to record the subjects' pain ratings must be included to control for the investigator's effect. Without that control, pain ratings are open to suggestion and it is difficult to know if the subjects really feel a difference in their pain or just respond to please us based on social desirability. This should be kept in mind for clinical and experimental pain trials, as well as everyday practice.

Special attention should also be paid to the dimension of pain that is being measured. Using two different scales for intensity and unpleasantness ratings, it has been shown that different kinds of experimental pain result in different patterns of ratings on each dimension of pain (Rainville et al., 1992). Moreover, different pharmacological (Price et al., 1985; Gracely et al., 1978) and non-pharmacological (Marchand et al., 1993) procedures have differential effects on pain intensity and unpleasantness. It could be interesting to separate these two dimensions during the assessment of pain in future experimental pain studies to see if placebos have a differential effect on them. The study by Price and colleagues (1999b) also shows the importance of a rating being given immediately after the stimulation, since the remembered pain ratings may result in an artificial inflation of the placebo response.

As already mentioned, the importance of masked naloxone injection must also be acknowledged for future studies. Finally, studies using other kinds of experimental pain than ischemic pain are needed. Methodological problems are present in the only

study using cold pressor pain (Bandura et al., 1987) and there is only one study using capsaicin (Benedetti et al., 1999).

All three models used to explain placebo analgesia have supporting evidence. However, we should try to combine learning, psychological and physiological mechanisms in our conceptualization of placebo effect since learning and expectations are closely related concepts. (Price et al., 1999b; Montgomery et al., 1997; Voudouris et al., 1990) and because studies have linked cognitive state and endogenous opioids (Amanzio et al., 1999; Bandura et al., 1987). Our model needs further investigation, but we think it should stimulate research on placebo analgesia because it gives a positive view of placebo response by seeing it as a real phenomenon with endogenous psychological and physiological mechanism that helps humans cope with pain. We suggest expanding traditional research one level at a time (conditioning, expectations or endogenous opioids), making an effort to combine more than one mechanism in the same study. For example, trying to validate or invalidate the different hypotheses regarding the impact of psychological changes on physiological changes would be a challenging topic.

Patients as well as health professionals have frequently a negative perception of placebo treatment (Berthelot et al., 2001). We should stop seeing placebo effects solely as a methodological problem and use it instead to help patients reduce their pain. As seen in Figure 2 (p.46), defining pain relief only as a direct effect of the active treatment, as in pharmacological changes, is a reductive view that forgets important endogenous systems triggered by expectations based on the past experiences that are present in any treatment.

Acknowledgements

We wish to thank Nancy Julien, Anie Paiement-Lamothe and Clare Lord for their valuable comments of this manuscript.

Supported in part by the *Fonds pour la Formation de Chercheurs et l'Aide à la Recherche* and *Fonds de la recherche en santé du Québec*.

Figure 1. Four-levels integrative model of placebo analgesia.

Psychological (2) and physiological (4) changes are mechanisms involved in placebo analgesia, whereas the context (1) and the subjective change (3) levels are thought to mediate the mechanisms.

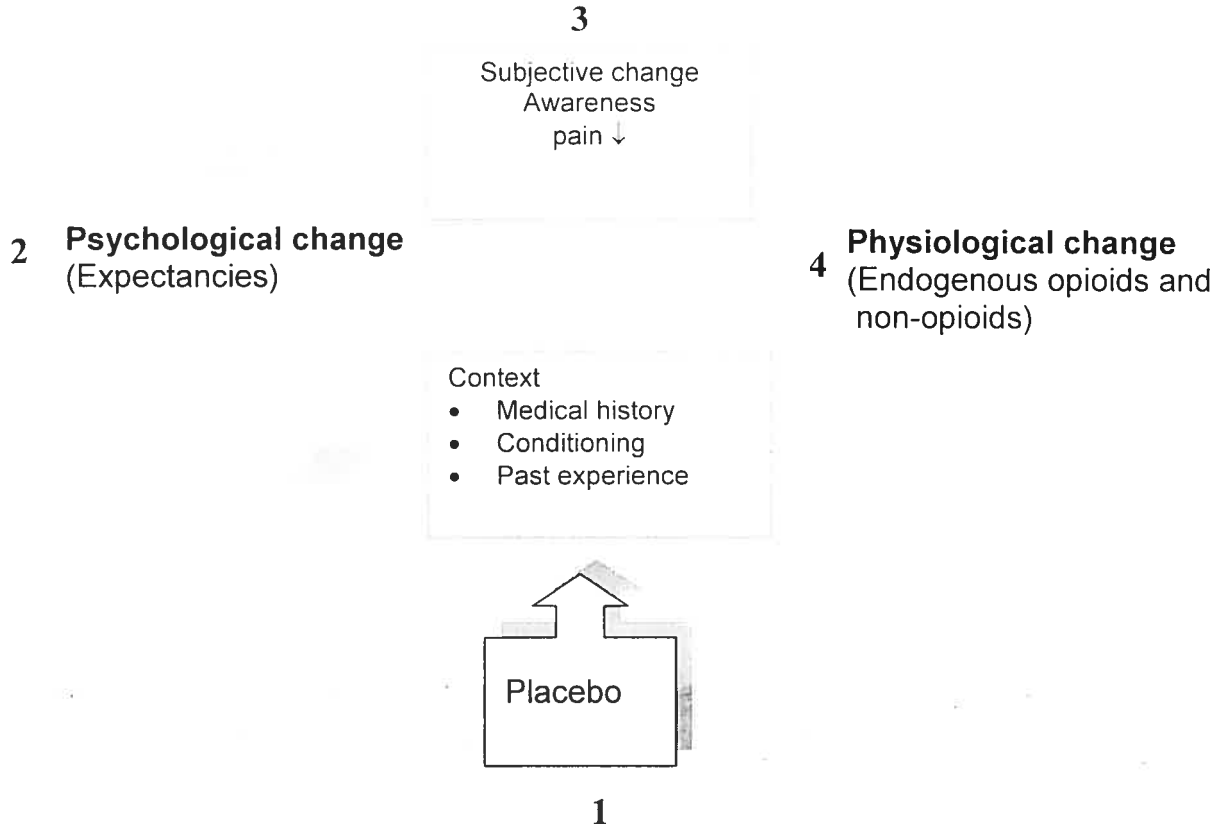


Figure 2. Additive effect of exogenous and endogenous pain modulation mechanisms.

Note that the subjective change is the first to occur, followed by the endogenous and the specific treatment effects.

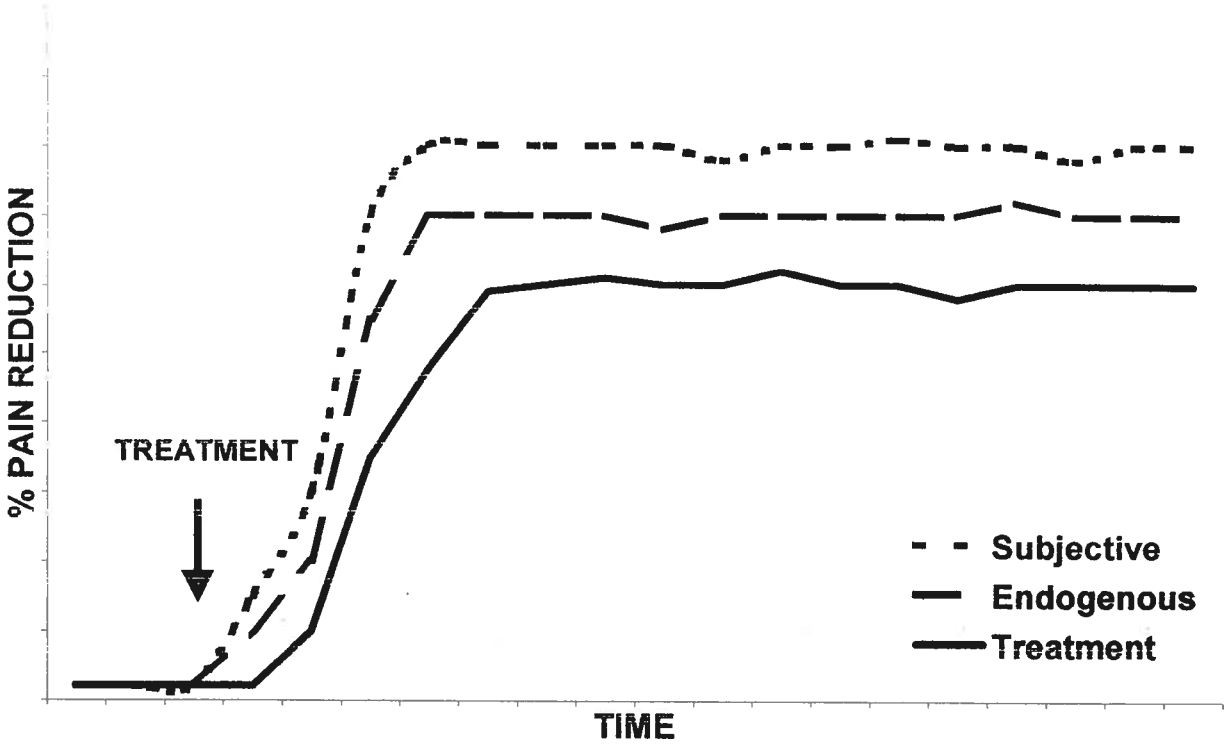


TABLE I. Studies on conditioned placebo analgesia

Authors	Noxious stimulation	n	Type of placebo	Dimension of pain measured	Methodological limits	Findings
Voudouris, Peck, Coleman, 1985	Iontopheric	32	Topical cream	Intensity (0=no pain to 10= intolerable pain)		Conditioning could induce placebo and nocebo effects in humans.
Voudouris, Peck, Coleman, 1989	Iontopheric, ischemic	20	Topical cream	Mainly affective (tolerance)	Measure. No control group. Display of results.	Conditioning could induce placebo and nocebo effects. Generalisation of nocebo but not placebo effects on ischemic pain.

TABLE II. Studies on expectations

Authors	Noxious stimulation	n	Type of placebo	Dimension of pain measured	Methodological limits	Findings
Voudouris, Peck and Coleman, 1990	Iontopheric	40	Topical cream	Mainly intensity (no pain to extreme pain)	Control	Conditioning effect was more effective than expectation manipulation to induce placebo responses.
Montgomery & Kirsch, 1997	Iontopheric	48	Topical cream	Mainly intensity (11 points from no pain to intolerable pain)		Conditioning procedure is mediated by expectations. Increase of the placebo effect with repeated stimulations.
Price, Milling, Kirsch, Duff, Montgomery, Nicholls, 1999	Thermal	40	Topical cream	Intensity (no pain sensation to the most intense pain sensation imaginable) and unpleasantness (not at all unpleasant to the most unpleasant imaginable)	Control	Conditioning could induce placebo effect, as shown on both intensity and unpleasantness ratings. Placebo analgesic effects are mediated by expectations. Desire of relief is not related to the placebo response. Memory ratings inflates placebo effect.

TABLE III. Studies on endogenous opioids

Authors	Noxious stimulation	n	Type of placebo	Dimension of pain measured	Methodological limits	Findings
Grevert, Albert, Goldstein, 1983	Ischemic	30	Saline injection IV*	Mainly intensity (0=no pain to 10=unbearable pain)		Injection of naloxone partially blocks the placebo response.
Posner & Burke, 1985	Ischemic	20	Saline injection IV, pill	Mainly intensity (no pain to max pain)	Open injection of naloxone.	Placebo analgesia was not affected by naloxone.
Bandura, O'Leary et al., 1987	Cold pressor	72	Pill	Mainly affective (tolerance)	Open injection of naloxone.	Injection of naloxone partially blocks the placebo response.
Benedetti, 1996	Ischemic	340	Saline injection IV	Mainly intensity (no pain at all to as much pain as you can imagine)		Injection of naloxone partially blocks the placebo response. Injection of proglumide potentiate it.
Benedetti, Arduino, Amanzio, 1999	Capsaicin injection	173	Topical cream	Mainly intensity (0=no pain to 10=unbearable pain)	No control cream.	Injection of naloxone completely blocks the local placebo response.
Amanzio, Benedetti, 1999	Ischemic	229	Saline injection IV	Mainly affective (tolerance)		Injection of naloxone blocks the expectancies-induced and the opioid-conditioned placebo response, but not the ketorolac-conditioned placebo response.
Amanzio, Pollo, Maggi, Benedetti, 2001	Ischemic	86	Open drug injection IV	Mainly affective (tolerance)		Individual differences in placebo activation of endogenous opioid systems are present. The difference between open and hidden injection may be taken as a measure of placebo effect.

*IV= intravenous

3. *Article 2.* Direct comparison of placebo effects on clinical and experimental pain

Cet article a été soumis au journal *Pain.* Les auteurs sont Julie Charron, Pierre Rainville et Serge Marchand.

Abstract

Placebo effects have been suggested to be more potent for clinical than experimental pain. However, this proposition is based on the comparison of the magnitude of placebo analgesia between studies using different methodologies or between different groups of subjects within the same study. We sought to provide a more direct test of this hypothesis using a within subject design and to investigate the potential mediating effect of expectancy. Sixteen low back pain patients rated the intensity and the unpleasantness of their clinical pain and underwent two cold pressor tests, both before and after a saline injection presented either as a potent painkiller (placebo treatment) in one session or as an inactive substance in a control session. The placebo treatment produced large and comparable increases in expected relief for clinical and experimental pain. However, ratings of pain intensity, pain unpleasantness and perceived relief confirmed the larger placebo effect in low back pain in comparison to cold pressor pain. Retrospective ratings of perceived relief in low back pain generally showed the largest placebo effect compared to pain intensity and unpleasantness ratings. Furthermore, when the placebo session was performed after the control session, the placebo effect on low back pain was substantially reduced and only observed in perceived relief. Perceived relief was robustly predicted by changes in pain unpleasantness and secondarily by expected relief but not by changes in pain intensity. These results suggest a memory-dependent magnification of placebo effects in retrospective ratings and a privilege relation between pain affect and pain memory. Expectations largely mediated the placebo effect on low back pain intensity and secondarily contributed to changes in perceived relief. However, variations in expectation could not account for the large difference in placebo analgesia between clinical and experimental pain. This implies that additional stimulus- and subject-related variables such as a stronger desire for relief in clinical than experimental pain may have interacted with pro-analgesic expectations to regulate the placebo effect. Similarly, the important reduction in placebo analgesia in low back pain after the single pre-exposure to the ineffective control treatment suggests the additional involvement of highly flexible mechanisms that may counteract the pro-analgesic effects of expectations.

1. Introduction

Placebo-induced change in pain is a fascinating phenomenon that underlines the impact of cognitive state on physical health. In recent years, the interest in this phenomenon has grown from a clinical concern to a methodological problem and a research subject that has important clinical implications (e.g. : Pollo et al., 2001; Price, 2001). Indeed, a better understanding of the mechanisms of placebo analgesia brings promises to applications in any analgesia settings, with both active and placebo treatments.

Experimental pain studies contribute to the understanding of basic processes implicated in pain and analgesia as they provide well-controlled stimulation conditions and allow the assessment of treatment-related effects in normal individuals. These studies have largely contributed to the assessment of the relative importance of conditioning, expectations, and the endogenous opioid system in placebo analgesia (reviewed in Price et al., 2002). However, one concern with experimental studies is the generalizability of findings to clinical settings. This problem can be addressed by a direct comparison of clinical and experimental studies to establish their similarities and differences and identify the factors that may contribute to those differences. In contrast, as Price emphasized (2000), few studies of clinical analgesia directly measure the placebo effect. They instead use the difference between the placebo condition and the active condition to assess the efficacy of the active treatment of interest. Recent studies on the mechanisms underlying placebo analgesia used either clinical (Amanzio et al., 2001; Pollo et al., 2001) or experimental pain paradigms (Petrovic et al., 2002; De Pascalis et al., 2002; Amanzio et al., 2001; Roelofs et al., 2000; Amanzio et al., 1999; Benedetti et al., 1999; Price et al., 1999), but no study directly compared the two types of pain within individuals.

It has been previously suggested that the magnitude of placebo analgesic effects are larger in clinical pain compared to experimental pain studies (Beecher, 1955). Forms

of experimental pain that are more stressful are associated with a greater placebo effect (Jospe, 1978) and this may explain the hypothesize stronger placebo effect in clinical than experimental pain. However, in a recent meta-analysis, Vase et al. (2002) reported that the effect sizes (ES) observed in clinical and experimental studies examining placebo mechanisms were comparable (mean ES: clinical = 0.87; experimental = 0.93). A meta-analysis of 187 studies (Harkness et al., 2000) did find a larger placebo response with acute pain in comparison to chronic, experimental and post-operative pain. However, the size of the placebo effect was similar for experimental and chronic pain. It is difficult to interpret the comparison between clinical and experimental studies considering that the analysis was based on a comparison of studies performed on different subjects and in different contexts. Furthermore, the large range in ES for both clinical (-0.64 to 2.29) and experimental studies (0.44 to 2.10) reported by Vase et al. (2002) attests of the great variability in the magnitude of placebo effects observed between studies.

One possible explanation for these large differences between studies relies on the expectations of relief experienced by patients and healthy volunteers submitted to a placebo procedure. Expectation of relief has been shown to mediate placebo analgesia, at least in part, in both clinical and experimental contexts (De Pascalis et al., 2002; Pollo et al., 2001; Price et al., 1999; Montgomery et al., 1997; Kirsch, 1985). This mediating variable may contribute to the hypothesized difference between placebo effects on clinical and experimental pain to the extent that the expectations associated with any analgesic treatment may be linked to specific outcomes (e.g. reduction of specific types of pain). Although this hypothesis may run against the old notion that placebo effects are non-specific and should equally affect clinical and experimental pain, there is unequivocal evidence that very specific expectations may be induced that lead to restricted placebo effects (e.g. analgesia restricted to a specific body area (Benedetti et al., 1999)). This implies that the mechanisms underlying expectation-mediated placebo effects are highly flexible and could differentially affect different types of pain.

To our knowledge, no study has directly compared clinical and experimental pain for the effect of placebo analgesia within the same subjects.

The present study had two main goals:

1) Compare the effect of placebo analgesia for clinical and experimental pain in the same subjects;
2) Investigate the effect of expectations of relief as a potential explanatory factor for the hypothesized difference between clinical and experimental pain in placebo analgesia.

To do so, the effect of placebo analgesia on clinical and experimental pain was measured in patients suffering from low back pain. We measured pain sensation intensity, pain unpleasantness, and perceived relief separately for clinical (low back pain) and experimental pain (cold pressor test) in the same subjects and during the same sessions. In order to verify the mediating effect of expectancy, we also measured the expected outcome of the placebo treatment separately for clinical and experimental pain. Preliminary report of this study has been presented in abstract form (Charron et al., 2002).

2. Methods

2.1. Participants

Following Ethics Committee approval and informed consent, 16 chronic low back pain patients (10 men and 6 women) completed the study. One additional subject dropped out of the study after the first session and is not included in the analyses. The participant's age was 18 to 60 years old (mean=39.8, SD=13.2) and the persistent pain duration was between 10 months and 25 years (average=8.4 years, SD=6.9). Patients volunteered to come to the laboratory for two three-hours sessions performed on two different days in which an analgesic treatment and an inactive control substance would be administered intravenously on separate days. Exclusion criteria

included pregnancy, the use of narcotic, analgesic, antidepressant or antiepileptic drugs, as well as the presence of cardiovascular or neurological disease.

2.2. Low back pain

In each of the two sessions, patients rated the intensity and unpleasantness of their current low back pain every two minutes for 20 minutes. Subjects were free to move during the session and to change from sitting to standing positions between tests. The evaluation was done with 0 to 100 numerical scales (Marchand et al., 1993; Rainville et al., 1992) and collected by an experimenter who was blind of the treatment condition (placebo vs. control instructions). We stressed the difference between intensity and unpleasantness using the instructions from Price et al. (1983).

2.3. Experimental pain

In each of the two sessions, circulating cold water was used to create cold pressor pain. At the beginning of the first session, subjects immersed their right hand in the water bath for a one-minute pre-test. Water temperature was adjusted individually to produce moderate pain (10-13°C). Then, two experimental tests of two minutes each were performed at the selected temperature, both before and after the treatment. Subjects rated the intensity and unpleasantness of cold pain every 15 seconds using the same scales than during the low back pain measures. The two successive tests were separated by a five-minutes pause.

2.4. Experimental design and procedure

A fully-factorial, within-subject design was applied to test for the effects of the placebo treatment condition (Placebo vs. Control) and the different types of pain (Clinical vs. Experimental). The control and placebo treatments were administered in the same subjects in separate sessions performed on separate days. This design was used to control for the natural history of pain during the testing session and to allow

for a more powerful within-subject comparison; each subject being his own control to evaluate the effect of the treatment for both clinical and experimental pain.

In each testing session, subjects first rated their low back pain and then underwent the first pair of cold pressor tests, as illustrated in Figure 1 (p. 73). The placebo or the control treatment was administered next. Both treatments consisted in one intravenous injections of 1ml of saline and differed only by the instructions given to the patients immediately following the injection. (see section 2.5.) One of two trained nurses pseudo-randomized the order of the control and placebo sessions, performed the injection, and gave the placebo or control instructions in both testing sessions. The experimenter that administered the cold pressor test and collected the subjects' ratings was out of the testing room during that time and was not informed of the treatment condition. Cold pressor tests were repeated after the treatment, followed by another series of low back pain ratings.

2.5. Placebo and control instructions

On one test day, subjects were told they received a potent analgesic (placebo condition), while in another day, they were told they received saline injection as a control (control condition). The nurses' instructions to the subjects were standardized and as similar as possible between conditions, except for the analgesic properties of the solution suggested only in the placebo condition.

During the placebo condition, the instructions were as follow (translated from French):

> "We will now administer the analgesic solution. It is a substance known to give a rapid and effective relief for many types of pain. We will wait 10 minutes before we take other measures. We ask you to stay sit during this time. We will inject 1 ml of solution in your arm's vein. You might feel some pricking or a temporary burning sensation at the injection site. The dose we used very rarely causes side effects like drowsiness or

cutaneous reactions, but we ask you to warn us of any discomfort you might feel."

During the control condition, the instructions were as follow (translated from French):

"We will now administer the control solution. It is a substance that should have little impact on your pain. We will wait 10 minutes before we take other measures. We ask you to stay sit during this time. We will inject 1 ml of salty water solution in your arm's vein. You might feel some pricking or a temporary burning sensation at the injection site. This substance very rarely causes side effects like drowsiness or cutaneous reactions, but we ask you to warn us of any discomfort you might feel."

2.6. Expected and perceived relief

Immediately after the injection, subjects were asked to rate their expectations of change for the post-treatment evaluation. They were specifically asked : "Do you think the treatment we administered will change your pain?" and they had to give a numerical rating for the expected level of change for both types of pain (low back pain and cold pressor test pain). The scale had a –100 anchor point (maximal increase of my pain) on the left side, a 0 (no change) in the middle, and a +100 (total relief) at the right extremity. Finally, after the end of the tests, subjects were asked to report their perceived changes in pain after the treatment. They were asked "Do you think the treatment we administered did change your pain during the last test?" and had to give a rating for the perceived change for both clinical and experimental pain. The same scale was used for ratings of expectation and perceived changes.

2.7. Statistics

Pain ratings were averaged within each condition for each subject and transformed into a difference pain-score by calculating the decrease in pain following the

treatment (mean pre-treatment rating minus the mean post-treatment rating). Differences between the placebo treatment condition and the control condition were further calculated for ratings of expectation, perceived relief and the difference pain-score to obtain global indices of expected and felt placebo analgesia. A 2x2 repeated-measures ANOVA (treatment [placebo vs. control] x type of pain [clinical vs. experimental]) was first performed using SPSS 8.0.0 for Windows. The session in which the placebo was administered [placebo in the first vs. second session] was further included as a third variable to examine the possible moderating effect of this factor. Then, additional 2x2 ANOVA's were performed separately for the two orders when the three-way interaction was significant. Data were further explored using bivariate correlations and multiple regression analyses performed between the dependent variables. Finally, standardised estimates of analgesic effects were calculated based on Cohen (1988) effect size analysis method.

3. Results

3.1. Expectation of relief

The placebo procedure was effective in inducing considerable expectation of relief as shown in Figure 2A (p. 74). Ratings of expected relief increased significantly in the placebo treatment compared to the control condition for both low back pain (mean 33.75%) and cold pressor pain (mean 30.94%; main effect of treatment: F=12.980, p=.003). However, when the session order entered the analysis, a three-way interaction was significant (treatment x pain x order; F=7.194, p=.018). When the placebo was given in the first session (Figure 2B, p. 74), only the main effect of treatment was marginally significant (F=4.528, p=.066; main effect of type of pain: F= .190, p=.674; interaction F=1.694, p=.229). In contrast, when the placebo was given in the second session (Figure 2C, p. 74), the main effect of the treatment was highly significant (F=12.633, p=.012), and this effect was larger with the low back pain than with the cold pressor pain (interaction F=6.729, p=.041; main effect of type of pain: F= 2.588, p=.159). This indicated that patients expected relief of both clinical

and experimental pain following the placebo procedure, and that patients who received the placebo instructions in the second session expected slightly more relief of low back pain than cold pain.

Further examination of the ratings of expectations indicated that all but four subjects expected more pain relief in the placebo than the control condition. These four subjects expected: no pain relief in any condition (n=2), equal pain relief in both the placebo and control conditions (n=1), or some *increase* in clinical pain in the placebo condition and no change in the other conditions (n=1). Exclusion of these subjects from the analyses of expectation logically led to more robust statistical results. The main effect of treatment reached significance when the placebo session was performed first (F=10.09, p=.025) or second (F=18.92, p=.007) and the interaction between treatment and type of pain was again significant only when the placebo session was performed second (F=8.05, p=.036). Since an increase in expectation was posited a priori as a mediating factor for the placebo effect, we excluded those four subjects from the analysis of pain intensity, unpleasantness, and perceived changes in pain. However, these subjects entered the correlation and regression analyses examining the relations between the dependent variables.

3.2. Pain intensity and unpleasantness

3.2.1. Baseline pain and effects of the control treatment

Mean ratings of the intensity and unpleasantness of cold pressor pain and low back pain are presented in Table I (p. 82). Pre-treatment ratings of cold pressor pain intensity and unpleasantness were higher than those of low back pain (intensity: F=15.222, p=.003; unpleasantness: F=11.423, p=.007), but no generalized difference was observed between the placebo and control condition for neither type of pain (main effects of treatment and interactions between pain and treatment: all p's>.20). The control treatment did not produce significant changes in pain intensity or unpleasantness of cold pressor pain or low back pain in any condition (pre- Vs post-

treatment; main effects and interactions: all *p*'s>.05). Further analyses were therefore conducted on treatment-related changes in pain intensity and unpleasantness.

3.2.2. Placebo effects on pain

The treatment-related effects on pain ratings are illustrated in Figure 3 (p. 76). Compared to the control condition, the placebo treatment produced significant decreases in pain unpleasantness (main effect of treatment: F=5.740, *p*=.038) and marginally significant decreases in pain intensity (F=3.707, *p*=.083). However, this effect interacted with the type of pain and the session order for both pain intensity (F=6.790, *p*=.026) and unpleasantness (F=11.586, p=.007). When the placebo was administered in the first session (Figure 3C and 3D, p. 76), there was a larger placebo effect for low back pain than experimental pain (interaction treatment x pain) for both pain intensity (F=9.38, *p*=.028) and unpleasantness (F=12.806, *p*=.016). The main effect of treatment (placebo > control) also reached significance on unpleasantness (F=6.946, *p*=.046) but not intensity (F=3.033, *p*=.142). In contrast, no main effect or interaction approached significance when the placebo instructions were given in the second session (all p's>.10; see Figure 3E and 3F, p. 76). These results confirmed that the placebo procedure produced a larger decrease in low back pain than experimental pain. However, this effect reached significance only when the placebo instructions were given in the first session.

3.3 Placebo effects on perceived relief

Post-treatment ratings of the perceived changes in pain (Figure 4, p. 78) were generally consistent with changes in concurrent ratings of pain intensity and unpleasantness. There was a highly significant main effect of treatment (placebo > control; F=20.661, p<.001), a main effect of pain (F=6.273, *p*=.031), and an interaction between treatment and pain (F=14.112, *p*=.004), confirming the superior placebo effect on low back pain (Figure 4A, p. 78). The treatment x pain x order interaction also approached significance (F=3.872, *p*=.077) so we examined data

again according to the order of the sessions. Pain relief increased with the placebo treatment, but more so when the placebo was given in the first session (Figure 4B, p.78; main effect of treatment: F=18.462, p=.008), than the second session (Figure 4C, p. 78; F=3.858, p=.107). Similarly, the superior placebo effect observed for low back pain (interaction treatment x pain) was confirmed only when the placebo was administered in the first session (placebo first: F=18.618, p=.008; placebo second: F=1.429, p=.286). Examination of the means indicated that the perceived relief in low back pain increased considerably in the placebo condition mainly when the placebo procedure was administered first (see Figure 4B, p. 78). In contrast, ratings of perceived relief in cold pressor pain indicated a modest but significantly stronger relief of 7.5 in the placebo condition compared to 4.2 in the control condition (F=5.50, one-tailed p=.019). These effects confirmed the stronger placebo effect in low back pain than cold pressor pain and the stronger placebo effect on low back pain when the placebo treatment was administered first.

3.4 Standardized estimates of the placebo effect

The magnitude of the placebo effects observed in low back pain and cold pressor pain are summarized in Table II (p. 83). The overall placebo effects were larger for low back pain than cold pressor pain both in absolute changes in ratings and in standardized mean difference. Retrospective evaluations of the perceived relief in low back pain showed larger effect sizes than ratings of pain intensity and unpleasantness. Very large placebo effects were confirmed in low back pain when the placebo condition was administered first (ES ranged from 2.23 to 3.28) but only ratings of perceived relief showed a placebo effect when the placebo was administered second (ES = 1.22). There were small to moderate placebo effects in cold pressor pain and the absolute magnitude of those effects were clearly much smaller than those observed in low back pain.

3.4 Relation between expectation, changes in pain, and perceived relief in low back pain

The placebo effect observed in low back pain was further examined using bivariate and partial correlation analyses to document the relation between the dependent variables and consider the possible mechanisms involved (Table III, p. 84). The expectation of relief predicted the changes in pain intensity induced by the placebo [(pre-placebo – post-placebo) – (pre-control – post-control)], most consistently when the placebo was administered in the first session (Table III, Placebo 1st), when the placebo effect was the strongest (Figures 3-4, p. 76-78). However, the expectation of relief did not significantly predict changes in pain unpleasantness induced by the placebo, although unpleasantness was equally or more sensitive than pain intensity to the placebo effect (see Table II and Figure 3, p. 83 and 76). The expectation of relief also predicted the perceived relief and this effect was largely mediated by changes in intensity as the correlation subsided after controlling for this variable (see Table III, p. 84). Nevertheless, controlling for changes in both intensity and unpleasantness led to a residual significant correlation suggesting that a small part of the variance in perceived relief may be explained by expectations, after pain-related variance is accounted for.

Not surprisingly, changes in pain unpleasantness were strongly correlated to changes in pain intensity in all conditions (Table III, p. 84). In the *absence* of a significant placebo effect (Placebo 2nd), almost all of the variance in unpleasantness was explained by intensity (R^2=.86). In contrast, in the presence of a robust placebo effect (Placebo 1st) a smaller amount of variance was shared between intensity and unpleasantness (R^2=.52), consistent with the differential magnitude of expectations and placebo effects on pain intensity and unpleasantness. This implies that in the effective placebo condition (Placebo 1st), unpleasantness was specifically influenced by additional factors not measured here.

The perceived relief was most strongly correlated to changes in pain unpleasantness (r=.78), and this relation was again stronger in the more effective placebo condition (Placebo 1st; Table III, p. 84). Furthermore, this effect persisted after the variance associated with expectation and pain intensity, or both variables, was controlled for. Perceived relief was moderately correlated to changes in pain intensity, mainly when the placebo effect was strongest (Placebo 1st: r=.60). However, this effect disappeared completely after controlling for expectations (r=.22) or unpleasantness (r=.07).

Taken together, results of the correlation analyses suggested that in the effective placebo condition, (1) expectations affected mainly pain intensity, (2) changes in pain unpleasantness reflected the changes in pain intensity and the influence of additional unidentified factor(s), and (3) perceived relief reflected mainly the changes in pain unpleasantness and, secondarily, the expected relief independent of the changes in pain.

3.5 Predictors of the placebo response in perceived relief

Linear regressions were performed on the increase in perceived relief of low back pain induced by the placebo as the dependant variable (perceived relief after the placebo minus perceived relief after the control). Based on the significant correlations, placebo-induced changes in expectation of relief and in pain intensity and unpleasantness, entered as independent variables (Table IV, p. 85). Using a stepwise approach, only the changes in unpleasantness contributed significantly to predict the perceived relief induced by the placebo (R^2=.576), while expectation was marginally significant, and changes in intensity did not contribute to the model. Forcing all variables into the model (Table IV, Enter, p. 85) slightly improved the fitness of the model (R^2=.658) and revealed a significant contribution of expectation. These models were confirmed when the placebo was administered in the first (Placebo 1st) but not the second session (Placebo 2nd; see Table IV, p. 85). No model

significantly predicted the differences in perceived changes in cold pressor pain between the placebo and control session (all *p*s > .2; not shown).

3.6 Summary of results

In summary, results showed that the expectation of relief of both low back pain and cold pressor pain increased after the placebo treatment. Placebo analgesia was evidenced in ratings of pain intensity, unpleasantness and perceived changes and was stronger for low back pain than cold pressor pain. Placebo effects on low back pain were found most consistently when the placebo session was performed *first*, before the control session. Placebo-induced changes in expectations of low back pain relief predicted primarily the changes in pain intensity and, secondarily, the changes in perceived relief. In turn, changes in pain unpleasantness were predicted by changes in pain intensity and by additional undetermined factors. Placebo-induced changes in perceived relief were mainly predicted by changes in pain unpleasantness and secondarily by changes in expectations.

4. Discussion

4.1. Efficacy of the placebo induction

Previous authors have clearly demonstrated the critical role of expectation in placebo analgesia (e.g. Price et al., 2002; Kirsch, 1997). Here, patients reported relatively high expectations of pain relief in the placebo condition, confirming that our experimental procedure was adequate to generate expectation-induced placebo analgesia. The placebo effect was largely confirmed by the significant decreases in pain intensity, unpleasantness and by the increase in perceived relief observed in the placebo condition compared to the control condition. Standardized estimates confirmed the moderate to large placebo effects consistent with those reported previously (Vase et al., 2002).

4.2 Clinical pain is more sensitive than experimental pain to placebo analgesia

As previously suggested (Jospe, 1978; Beecher, 1955), clinical pain was more sensitive to the placebo treatment than experimental pain. However, we did not confirm the hypothesis that differences in expectations account for this difference in placebo effects in low back pain and cold pain. The procedure employed here to produce placebo effects was very similar to those used in other experimental studies (e.g. Amanzio et al., 1999; Price et al., 1999; Montgomery et al., 1997), and the expectations of relief induced for clinical and experimental pain were robust and very similar. For these reasons, the smaller placebo effect observed in experimental pain is unlikely to be caused by specific aspects of the placebo instructions and procedure used here.

This difference in placebo effect between clinical and experimental pain may be explained by pain-related factors and/or subjects-related factors. First, the nature of clinical and experimental pain may contribute to the differential effect observed here. Persistent clinical pain is often felt as a meaningful threat that intrudes many aspects of one's life. Furthermore, the causal agent of persistent low back pain is internal and often undetermined. In contrast, experimental pain has a definite and known short duration, subjects are typically reassured about the safety of the procedure used to produce pain, and the causal agent (the nociceptive stimulus) is external and clearly identified. Each of these factors may contribute to render clinical pain more susceptible to the effects of expectation of analgesia. However, this explanation is incomplete in view of the numerous studies showing robust placebo analgesic effects on experimental pain in healthy individuals (reviewed in Vase et al., 2002).

The second group of factors that may contribute to explain this difference between the susceptibility of clinical and experimental pain to expectation-induced placebo analgesia relates to the characteristics of the subjects. As clinical pain studies are, by necessity, conducted in patients, while experimental studies are generally conducted in healthy volunteers, there is a constellation of non-specific individual differences

that may contribute to the differences between placebo analgesia observed in experimental and clinical studies (e.g. emotional state, personality variables). However, the present results do restrict the range of potential explanatory variables. The differential placebo effect observed here using a within-subject design permitted to control for the involvement of a non-specific factor, because such a factor would have affected both types of pain. The explanation may reside in the interaction between subject-related factors and the specific context of a study on pain and analgesia.

Patients may respond differently to comparable levels of expectation of analgesia for clinical and experimental pain. Price et al. (1980) have shown that individual differences in the specific goal adopted by participants in a pain study (e.g. avoid pain altogether or experience less pain) interact with expectations to modulate pain perception. This effect was shown most consistently on pain affect, the dimension most readily modulated by the placebo effect in the present study. Motivation or the desire of relief was also shown to contribute to placebo responses in a study investigating sedative or stimulant effects (Jensen et al., 1991). In a study of placebo analgesia in healthy volunteers, however, the desire of relief was not associated with changes in pain (Price et al., 1999). In that study, the magnitude of the changes induced in desire of relief was fairly small and the authors suggested that the desire of relief might be of importance mostly for clinical pain. We did not measure the desire for relief in the present study but it appears plausible that the patients experienced more significant goals related to their clinical condition and stronger desires for relief of their clinical pain than the experimental pain. Expectations would have affected most effectively the experience that was most significant for the patients. As suggested previously by Price (1997), the interaction between the expectations of relief and goal-directed desire for relief may be critical to produce robust placebo analgesia.

4.3. A model of placebo analgesia

The correlations between the dependent variables measured in this experiment are consistent with those reported between visual analogue scale ratings of pain and pain relief in surgery patients (Jensen et al., 2002). However, the partial correlation revealed unique interactions between the variables that were further confirmed in the multiple regression analyses. In an attempt to summarize the main findings of this study, we propose a model of placebo analgesia illustrated in Figure 5 (p.80).

4.3.1. Expectancy and placebo analgesia

The potential implication of motivational aspects (goal and desire for relief) to placebo effects does not compromise the importance of cognitive appraisal and expectancy for an outcome (Kirsch, 1990). Expectations for pain relief following placebo treatment are hypothesized to directly influence post-treatment change in pain and to be a causal factor in placebo analgesia (Price et al., 1999). Although expectation of relief did not explain the difference between clinical and experimental pain in the present study, changes in low back pain induced by the placebo procedure strongly supported the critical role of expectancy. Placebo effects on clinical pain were partly mediated by relief expectancy, as reflected by the correlation between expectations and changes in pain intensity, and between expectations and perceived relief in low back pain. Furthermore, partial correlation analyses suggested that the effects of expectation on perceived relief were only partly mediated by changes in pain intensity and unpleasantness and that a second mechanism may underlie the impact of expectation on perceived relief, independent of the actual pain felt. The linear regression predicting perceived relief also loaded partly on the expectancy factor. These effects are illustrated in Figure 5 (p. 80) by a direct influence of pro-analgesic expectation on pain sensation and on perceived relief, the latter effect being under the influence of memory processes (see section 4.3.2).

Another new finding not reported in previous studies is the differential relation of expectation with pain sensation intensity and unpleasantness. In the effective placebo condition the correlation analyses revealed a moderate effect of expectation on low back pain intensity that did not reached significance on pain unpleasantness ratings. This relatively strong effect is illustrated in the Figure 5 (p. 80) by the direct and specific effect of expectation on pain sensation. This finding was unexpected, especially in view of the larger placebo effects observed in pain unpleasantness than pain intensity ratings when the placebo effect was strongest (Figure 3C-3D, p. 76). Previous studies have shown clear evidence of a dissociation between pain intensity and unpleasantness in both clinical (Marchand et al., 1993; Price et al., 1987) and experimental settings (Rainville et al., 1999; Rainville et al., 1992). The present results suggest that expectations of pain relief may act primarily on pain sensation processes and that changes in pain unpleasantness are mediated by changes in pain sensation intensity.

However, as the placebo effect was not confirmed in the experimental pain condition, we speculate that additional stimulus and/or subject-related conditions are necessary to allow expectation to exert their effects on pain, as illustrated in Figure 5 (p. 80). The goal and desire for relief experienced by patients entering a pain study may contribute to create those critical conditions as discussed above (see section 4.2.). Those motivational factors may also contribute to produce larger placebo effects on pain unpleasantness and perceived relief than pain intensity (Figures 2-4, p. 74-78). These factors may be less relevant to experimental pain in chronic pain patients and this may explain the weaker placebo effects observed in experimental pain.

4.3.2. Placebo effects in retrospective ratings of relief

Changes in the retrospective evaluation of relief were more sensitive to placebo effects than changes in concurrent ratings of pain intensity and unpleasantness. This effect is consistent with previous studies investigating placebo analgesia (Price et al., 1999) and pain memory (Feine et al., 1998). Here, perceived relief was predicted by

expectations and by changes pain unpleasantness, even after the variance associated pain intensity and expectation of relief was accounted for (Table III-IV; Figure 5, p. 84-85, 80). This result strongly emphasizes the primary impact of affective processes on retrospective evaluation of relief based on pain memory. This pivotal role of affect on the retrospective evaluation of pain and pain relief likely goes beyond the immediate effect of the pain unpleasantness experienced during a treatment and may encompass the effects of the patient's global affective state prior and during a treatment (Gedney et al., 2003). This role of affect in pain memory further underscores the importance of assessing both pain sensation and pain affect.

The distorting effect of memory processes on pain-related information raises some concern about studies relying solely on retrospective ratings of pain to assess analgesic treatment or placebo effect as they may not reflect specifically changes in the experience of pain (as discussed in Price et al., 1999). On the other hand, the memory of pain and relief may better reflect how the patient generally feels about the treatment and this may affect subjective well-being, compliance to the treatment, and the development of beliefs and expectations about future treatment. These effects may contribute significantly to predict future outcomes. These effects may also explain the persistent differences found between actual pain reduction and estimated pain relief in some clinical conditions, even when the analgesic procedure have been used for years (Marchand et al., 2003).

4.4. Does pre-exposure to an ineffective treatment block placebo analgesia?

There is one last finding of this study that requires some attention. The robust placebo effects observed here in low back pain were much stronger or exclusively observed when the placebo session was performed before the control session. Taken from a different angle, placebo effects in low back pain were largely blocked when the placebo session followed the control session. This unexpected but large difference should be considered with caution as it is based on the comparison of two small subgroups of subjects. However, this effect may reflect another puzzling

dissociation between expectation and the placebo effect. Indeed, expectations of relief in low back pain were stronger when the placebo suggestions were given in the second session, yet, placebo analgesia was smaller and only observed in ratings of relief in that condition.

One possible explanation for this finding may be the carry-over effect of the first session on the second session. Patients that performed the control session first were exposed to the complete experimental procedure, including the injection of saline. They did not expect or experience analgesia on that session. On the second day they went through the same procedure again with the addition of suggestions for analgesia. The experience of no changes in pain in the context of the first session might have triggered some anti-analgesic mechanisms that partialy blocked the placebo effect on the second session.

Recent models have emphasized the relative role of expectation and conditioning in placebo analgesia. However, Montgomery and Kirsch (1997) have shown that in some conditions, pro-analgesic conditioning effects are mediated completely by expectations and that anti-analgesic expectations induced by verbal suggestions could block pro-analgesic conditioning effects. In another recent study, the pre-exposure to an effective treatment (pro-analgesic conditioning with ketorolac) on experimental ischemic pain contributed to the analgesia observed on a placebo test day but this effect was completely blocked by anti-analgesic suggestions (hyperalgesia) (Benedetti et al., 2003). These findings imply that anti-analgesic expectations can counteract conditioned analgesia. In contrast, results of the present study suggest that conditioned anti-analgesia, produced by the control session performed first, may have blocked the pro-analgesic effect normally associated with relief expectancy on the placebo test session performed subsequently.

The conceptualization of our control session as anti-analgesic conditioning is consistent with previous methodologies using pro-analgesic conditioning paradigms (e.g. Benedetti et al, 1999). However, we do not dispute the possible role of

expectation in this anti-analgesic process. Indeed, from a broader perspective, chronic low back pain patients entered the study with an unknown level of expectation regarding pain treatment and some level of pre-conditioning with effective or ineffective treatments. Many symbols associated with an effective treatment were present in the context of this experiment (e.g. nurse, syringe, ...) but their effect was possibly blocked in the control condition by the instructions and the expectations that there would be no pain relief. Therefore, anti-analgesic expectations may have played a crucial role in stripping off the symbols and the context associated with the treatment from their usual meanings and conditioned effects in the control condition. However, when the placebo session followed the control session, the placebo instructions may have been insufficient to overcome this earlier anti-analgesic effect. We must admit that this explanation should be regarded as provisional until there is additional data adressing that issue directly in a study adequately designed to test this possibility. However, if this hypothesis receives furhter confirmation, this implies that anti-analgesic conditioning may block, at least in part, the pro-analgesic effect of expectation.

4.5 Conclusion

The presents results confirmed that placebo effects are stronger for clinical than experimental pain. These results also demonstrate two cases of dissociation between high levels of expectations and placebo effects. First, the mediating role of expectancy was demonstrated in the effective placebo condition on low back pain, whereas high expectations did not lead to strong placebo effects on experimental pain. Second, high expectations of relief in low back pain produced no placebo effect on concurrent ratings and a reduced placebo effect on perceived relief when the placebo session was performed after the control session. We emphasize the need for a more comprehensive examination of motivational factors that may facilitate or obstruct expectation-induced placebo effects. Future studies should also systematically include measurements of pain sensation and pain affect as these dimensions of pain may be differentially affected by placebo procedures and may be

selectively related to different aspects of placebo mediators. Finally, we raise the unexpected possibility that the anti-analgesic effect of a single experience with an ineffective treatment may critically influence future responses to a treatment, in spite of pro-analgesic expectations associated with that treatment. This underscores the importance of previous experience on pain relief and attests of the remarkable flexibility of pro- and anti-analgesic processes affecting the magnitude of placebo effects.

Acknowledgements

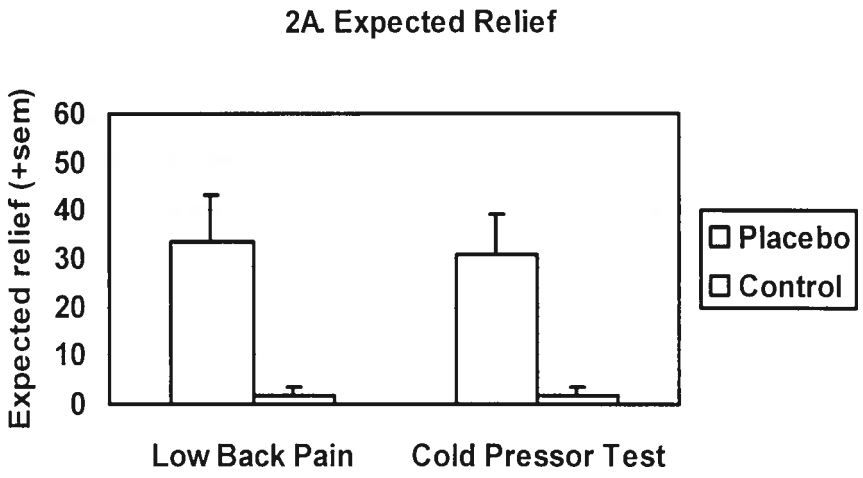
We thank Paule Julien, Serge Daigle, Line Fecteau, Guylaine Leblond and Anie Paiement-Lamothe for their precious technical support. This research was supported by the Fonds de la recherche en santé du Québec and the Canadian Foundation for Innovation.

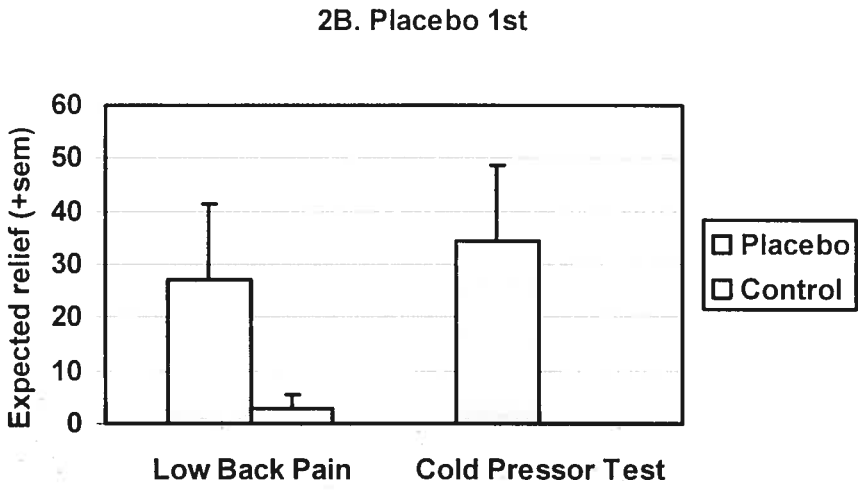
Figure 1. Time-course of the experimental procedure.

Baseline Pain		**Treatment**	**Expected relief for LBP and CPT**	**Post-treatment Pain**		**Perceived relief for LBP and CPT**
Low back Pain	Cold pressor test (2 tests)	Saline injection: suggestions for analgesia (placebo) or no analgesia (control)		Cold pressor test (2 tests)	Low back Pain	
20 min.	10 min.	10 min.	1 min.	10 min.	20 min.	1 min.

All patients evaluated their low back pain and the pain felt during two cold pressor tests, both before and after the I.V. administration of saline (Treatment) with suggestions for analgesia (placebo session) or no-analgesia (control session). Ratings of expectation were obtained immediately after the injection and ratings of perceived relief were obtained after the last low back pain measurements.

Figure 2. Expectations of relief





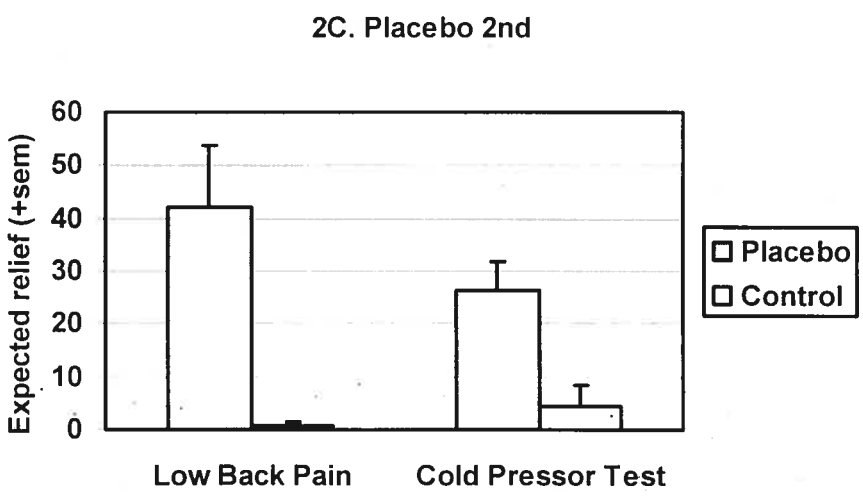


Figure 2. Expectation of relief in low back pain and cold pressor pain immediately following the injection of saline presented either as a potent analgesic (Placebo) or as a control inert substance (Control). Results are shown for the whole sample (A) and for subjects who received the analgesic suggestions before the first (B) or second session (C).

Figure 3. Treatment-induced decreases in pain sensation intensity and unpleasantness ratings

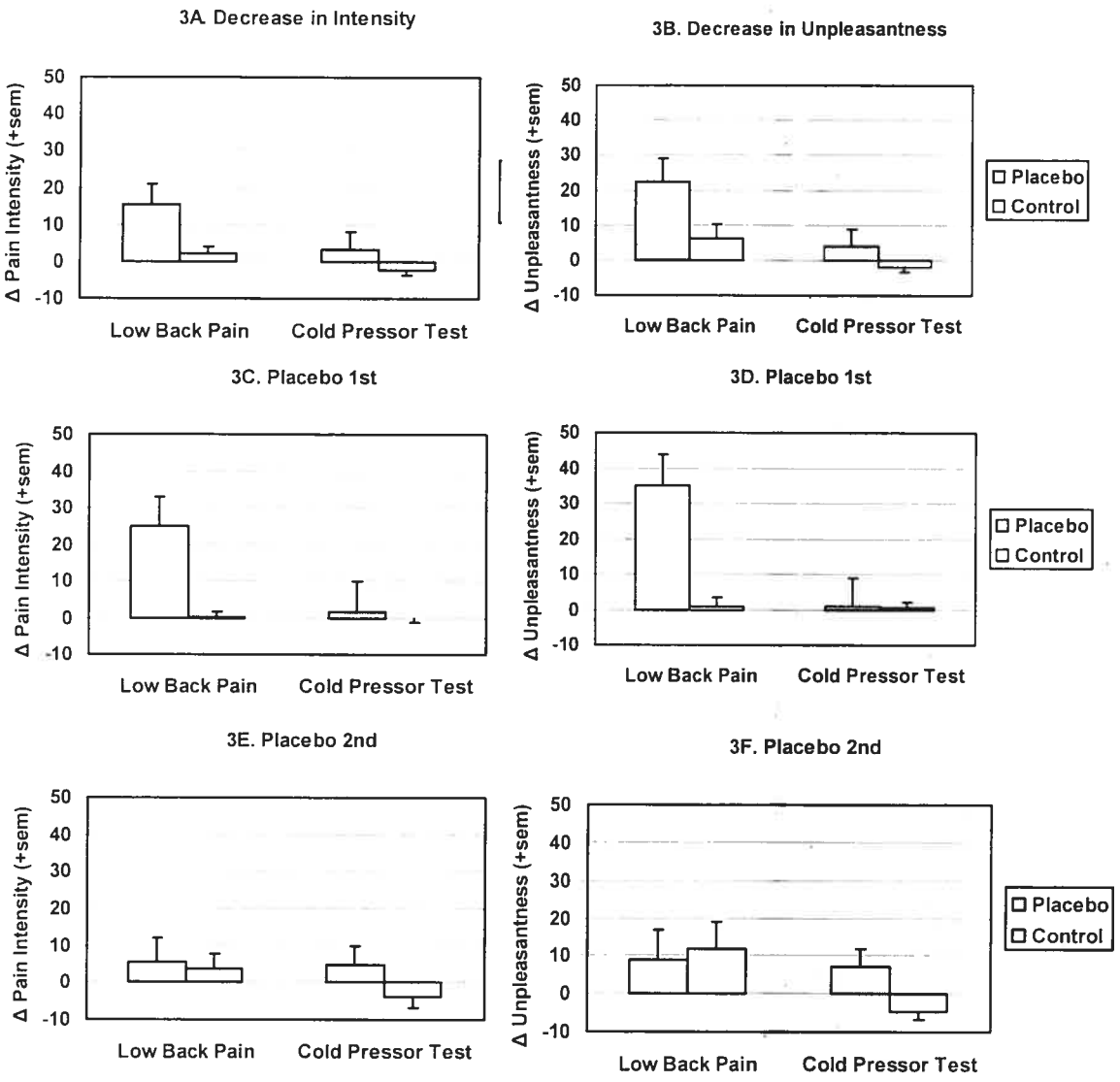
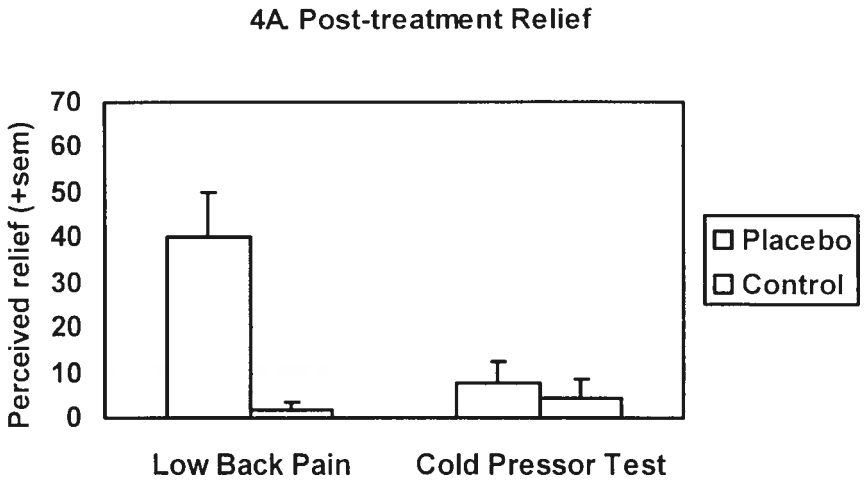
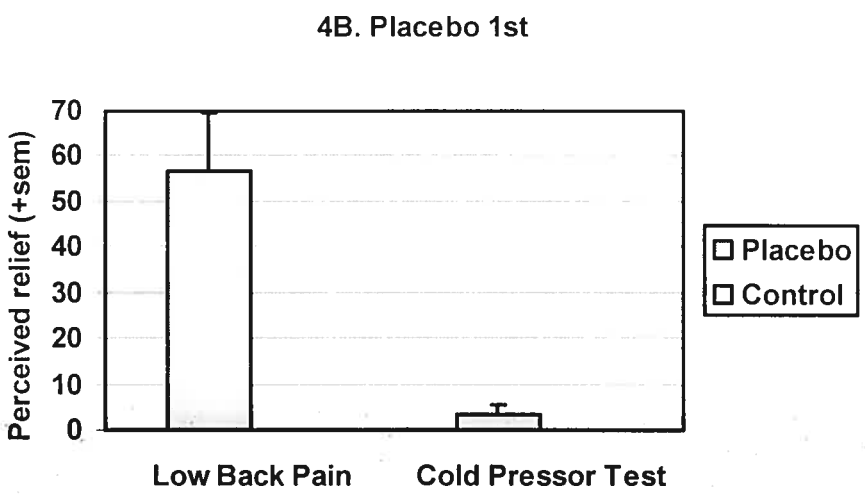


Figure 3. Treatment-induced decreases in pain sensation intensity and unpleasantness ratings of low back pain and cold pressor pain as a results of the injection of saline presented either as a potent analgesic (Placebo) or as a control inert substance (Control). Results are shown for the whole sample (A and B) and for subjects who received the analgesic suggestions before the first (C and D) or second session (E and F).

Figure 4. Post-treatment relief





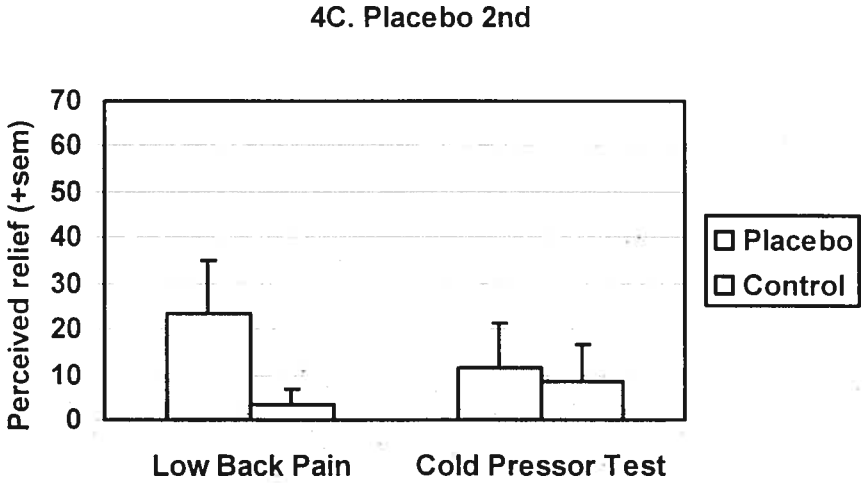


Figure 4. Perceived relief in low back pain and cold pressor pain reported at the end of each session in which the injection of saline was presented either as a potent analgesic (Placebo) or as a control inert substance (Control). Results are shown for the whole sample (A) and for subjects who received the analgesic suggestions before the first (B) or second session (C).

Figure 5. Tentative model of the placebo modulation of pain

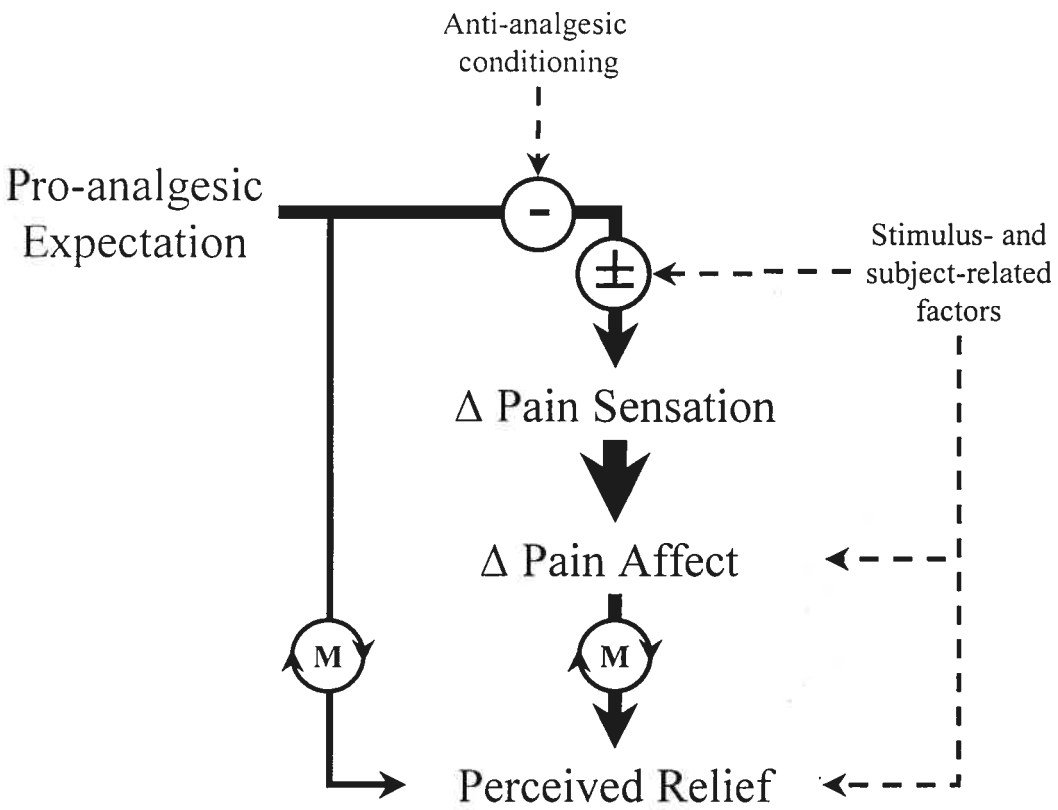


Figure 5. Tentative model of the placebo modulation of pain summarising the results and the hypothesised processes involved in the present study. Full lines represent relations specifically tested in this experiment and dotted lines indicate potential influences that may explain some of our results. Expectation of relief affects primarily the changes in pain sensation intensity, which in turn determines largely (but not completely) the changes in pain unpleasantness. Pain unpleasantness is the primary predictor of perceived relief with the additional magnifying influence of memory processes (M). Perceived relief may also be influenced secondarily by expectations through a secondary route dependent on memory processes (M), but independent of changes in pain. The difference in placebo analgesia between clinical and experimental pain may reflect the critical influence of stimulus and subjects-related factors (e.g. desire for relief) that gated (±) the effect of expectations on pain and critically reduced the analgesic effect of expectation on experimental pain. These factors may also exert a positive influence on placebo analgesia, particularly on low back pain affect and perceived relief, as those two aspects of pain showed stronger placebo effects compared to pain sensation intensity. The absence of placebo analgesia observed when the placebo session was performed after the control session may reflect anti-analgesic processes that blocked expectation-induced placebo analgesia (-).

Table I. Mean (SEM) intensity and unpleasantness ratings

		Pain Intensity		Unpleasantness	
Sample	Condition	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
All Subjects	Placebo session				
	Cold pressor test	58.35 (5.85)	52.52 (8.78)	60.93 (6.44)	56.84 (7.99)
	Low back pain	35.00 (5.66)	19.77 (5.97)	41.53 (6.47)	20.42 (7.15)
	Control session				
	Cold pressor test	55.43 (6.74)	57.50 (6.89)	56.24 (7.09)	58.27 (6.88)
	Low back pain	29.23 (4.57)	27.26 (5.07)	33.73 (6.54)	27.43 (6.67)

Table II. Magnitude of the placebo effect (95% confidence interval)

	Measure	Placebo effect[a]	Effect size[b]
Low Back Pain	Change in Pain Intensity	13.2 (4.2 – 22.2)	1.20 (0.33 – 2.07)
	Changes in Pain Unpleasantness	15.9 (4.4 – 27.5)	1.13 (0.27 – 1.99)
	Perceived Relief	38.3 (23.8 – 52.9)	2.15 (1.15 – 3.16)
Cold Pressor Pain	Change in Pain Intensity	5.5 (-1.8 – 12.7)	0.62 (-0.20 – 1.44)
	Changes in Pain Unpleasantness	6.1 (-0.9 – 13.2)	0.71 (-0.12 – 1.53)
	Perceived Relief	3.3 (-6.1 – 12.8)	0.29 (-0.52 – 1.09)

[a] The placebo effect is the arithmetic difference between the placebo and the control condition in treatment-related changes in pain intensity and unpleasantness and in perceived relief.

[b] Standardized difference (Hedges bias-corrected) and confidence intervals are calculated for paired-samples of unequal variance using the pooled SD (pooled SD = SQRT(SDa^2+SDb^2)/2) according to Cohen (1988). Note that this method tends to gives a slightly lower estimate of the pooled SD and higher estimates of the effect size.

Table III. Bivariate and partial correlation coefficients between expectations, changes in pain intensity and unpleasantness, and perceived relief of low back pain.

Pearson-r		Expectation				Intensity				Unpleasantness			
	Sample[a]	Bivariate	(Int)[b]	(Unp)[c]	(Int, Unp)[d]	Bivariate	(Exp)[e]	(Unp)[c]	(Exp, Unp)[f]	Bivariate	(Exp)[e]	(Int)[b]	(Exp, Int)[g]
Intensity	All subjects	**.45***											
	Placebo 1st	**.70***											
	Placebo 2nd	.36											
Unpleasantness	All subjects	.27	-.20			**.82‡**	**.81‡**						
	Placebo 1st	.46	-.10			**.72***	**.63***						
	Placebo 2nd	.61	**.81***			**.93‡**	**.96‡**						
Perceived Relief	All subjects	**.51***	.33	**.49***	**.56***	**.63†**	**.52***	-.03	-.29	**.78‡**	**.77‡**	**.59†**	**.70†**
	Placebo 1st	**.69***	.47	.60	**.70***	**.60***	.22	.07	-.46	**.79†**	**.73***	**.64***	**.79***
	Placebo 2nd	**.68***	.63	.49	.45	.50	.38	-.27	.15	.62	.35	.49	-.05

[a] All subjects: n = 16; Placebo 1st: n = 9; Placebo 2nd : n = 7
[b] Controlling for changes in pain intensity
[c] Controlling for changes in pain unpleasantness
[d] Controlling for changes in pain intensity and unpleasantness
[e] Controlling for changes in expectation
[f] Controlling for changes in expectation and in pain unpleasantness
[g] Controlling for changes in expectation and in pain intensity
*: $p < .05$; †: $p < .01$; ‡: $p < .001$; significant effects are indicated in bold.

Table IV. Linear Regression Models predicting the Changes in Perceived Relief

Sample	Method	Variable	Standardized β	t (*p*)	Model – Adj. R^2	Model – F (*p*)
All subjects	Stepwise [a]	Expectation [a]	.323	2.045 (.062)	**.576**	**21.354 (.0004)***
		Changes in Intensity [a]	-.028	-0.093 (.927)		
		Changes in Unpleasantness	**.777**	**4.621 (.0004)***		
	Enter	**Expectation**	**.399**	**2.311(.039)***	**.658**	**10.608 (.001)***
		Changes in Intensity	-.309	-1.063 (.309)		
		Changes in Unpleasantness	**.922**	**3.423 (.005)***		
Placebo 1st	Stepwise [a]	Expectation [a]	.415	1.834 (.116)	**.567**	**11.487 (.012)***
		Changes in Intensity [a]	.060	0.167(.873)		
		Changes in Unpleasantness	**.788**	**3.389 (.012)***		
	Enter	Expectation	.608	2.203 (.079)	**.694**	**7.049 (.030)***
		Changes in Intensity	-.410	-1,.160 (.299)		
		Changes in Unpleasantness	**.805**	**2.844 (.036)***		
Placebo 2nd	Stepwise [a]	Expectation	.684	2.099 (.090)	.362	4.408 (.090)
		Changes in Intensity [b]	.293	0.811 (.463)		
		Changes in Unpleasantness [b]	.323	0.748 (.496)		
	Enter	Expectation	.625	.875 (.446)	.089	1.195 (.443)
		Changes in Intensity	.410	.265 (.808)		
		Changes in Unpleasantness	-.142	-.078 (.943)		

[a] Variable excluded based on the criterion p=.05
[b] Variable excluded based on the criterion p=.10
* Significant at p<.05 (in bold)

4. *Article 3.* Multiple factors contribute to the perceived relief induced by placebo TENS

Cet article était en préparation au moment du dépôt de la thèse. Les auteurs sont Julie Charron, Pierre Rainville et Serge Marchand.

Abstract

Expectations of relief has been suggested to be an important component in placebo analgesia. Conditioning could also induce expectations and modulate placebo effects. We conducted a study in twenty volunteers submitted to experimental thermal pain treated with a placebo TENS. The relative impact on pain relief of placebo-induced paresthesias, conditioning and expectations was examined. Conditioning was produced by a 2°C decrease of stimulation on the sham TENS-treated arm compared to the control arm without electrodes. Results showed a correlation between expectations and pain relief following placebo. Modulation of experience via conditioning had an impact of subsequent expectations of relief. Paresthesias were related to expectations, but not to pain change. An integrative model illustrating the relative importance of the variables in predicting placebo analgesia in this study was similar to another model with chronic low back pain sufferers.

1. Introduction

Several recent studies have clarify the neurophysiological and psychological mechanisms of placebo analgesia (see Guess et al., 2002, for a review). Placebo-induced change in pain is an interesting phenomenon that underlines the impact of cognitive state on physical health. In recent years, the interest in this phenomenon has grown from a methodological problem to a legitimate research subject that has clinical applications (Pollo et al., 2001; Price, 2001). Indeed, a better understanding of the mechanisms of placebo analgesia brings promises to applications in any analgesia settings, with a "real" pharmacological treatment or with placebo treatment (Crow et al., 1999).

The use of clinical and experimental pain helps to understand the processes implicated in placebo analgesia. In a previous study where we measured the effect of placebo TENS and active TENS on low back pain, we found that active TENS was as effective as placebo TENS in reducing pain unpleasantness but was superior to placebo TENS for pain intensity (Marchand et al., 1993). Moreover, in a recent study we found that the analgesic effect of placebo thalamic stimulations was positively correlated to the perceived paresthesia during the placebo treatment, suggesting that the perceived secondary effect of the manipulation influenced the placebo outcomes (Marchand et al., 2003).

The role of conditioning, expectations, and endogenous opioids in placebo analgesia were underlined (Charron et al., 2003a). Expectations of relief has been presented as a cognitive factor that could have an impact on placebo analgesia in a clinical or experimental context (De Pascalis et al., 2002; Pollo et al., 2001; Price et al., 1999; Montgomery et al., 1997; Kirsch, 1985). A conditioning protocol may also influence outcomes via the expectations modulation caused by an analgesic perception. Investigating the factors influencing expectations, like paresthesias and past experience, will permit a better understanding of its role in placebo analgesia. We conducted a study (Charron et al., 2003b) where low back pain patients received a

saline injection presented as a potent painkiller. The subjective decrease of clinical pain after the treatment was related to their expectancies of relief and to the pain unpleasantness ratings.

The main goal of this study was to identify factors that contribute to placebo analgesia responses during sham TENS. Healthy volunteers were submitted to a placebo TENS treatment. We looked at expectations of relief, pain ratings and sensations related to the placebo TENS. We also added a conditioning manipulation during which the nociceptive thermal stimulations were reduced during placebo TENS to create an experience of analgesic effect, as previously described (Price et al., 1999). Preliminary report of this study was presented in abstract form (Charron et al., 2003c).

The specific goals of the study were to: 1) compare the relative impact of conditioning and verbally-induced expectations of relief on placebo TENS analgesia and 2) investigate the relationships between the placebo paresthesias, expectations of relief, and analgesic response.

2. Methods

2.1. Participants

Following Ethics Committee approval and informed consent, 20 healthy volunteers (10 women) were enrolled to study their response on experimental pain after a placebo-TENS treatment. The participant's age was 20 to 34 years old (average=23.45, SD=3.95). The paid volunteers came for a three hours session. Exclusion criteria included chronic or current pain, pregnancy, skin problems, the use of analgesic drugs, as well as the presence of psychiatric or neurological disease.

2.2. Experimental pain

Computer-controlled thermal stimuli were applied on both arms, using a 1-cm^2 contact thermode (Peltier device). Stimulations were given alternatively on two sites of the volar surface of each forearm. A calibration test was carried out to control for individual difference in pain threshold and tolerance. Four temperatures were used for each participants: a "warm" temperature, rated clearly warm but not painful (40-42°C, average 41.3°C) and three "painful" temperatures, rated as clearly painful but tolerable for the duration of 10 seconds (46-49°C, average 46.2°, 47.2° and 48.6°C). Baseline temperature was set at 33°C. The various temperatures of the thermode were applied pseudo-randomly on both arms so that each arm received the 4 stimuli levels 4 times for a total of 32 stimulations per block.

2.3. Placebo TENS

A TENS apparatus was modified so that no current ran in the electrodes while the device looked normal. Participants were unaware of this modification and a whole protocol was designed to make them believe in the efficacy of the treatment. After the first block of thermal stimulation, electrodes were cleaned with alcohol pads, contact gel was applied on the two T-shaped electrodes, which were attached to one arm. The arm used for the TENS was counter-balanced. Care was taken to place the electrodes, and the experimenter verbalised that she needed to make sure the current was going through the two electrodes effectively.

The experimenter asked the participants if they had ever been exposed to TENS before. Those who had an experience with it (n=6) were told there were many types of TENS protocol and that it might not feel the same way as they remembered it. Participants were told TENS was a recognised procedure to produce local analgesia, widely used for different types of pain, and that the goal of the study was to explore the spatial effect of this treatment and the extent to which current on one arm has an effect on the other. General explanations were given on the physiological effects of

TENS. Moreover, participants were asked to be very precise on the sensations they might feel during TENS stimulations (especially pricking, numbing, warmth or coolness), these sensations indicating the adequate current for them.

The electrodes were fixed to the control module in full view of the participants after these explanations had been given. The experimenter then turned on the power switch. Green moving light circles on the machine were put to the participants' attention, indicating that everything was doing well and that the electrodes contact with the skin was adequate. Different switches were pressed for a few seconds, asking the participants if they felt anything. Then, the current dial was slowly turned up and the participants asked for any sensations. When a sensation was reported, the participant was asked to describe and localise it. A "touch test" was done on both arms by the searcher finger, and participants had to evaluate if there was a difference between the two. This information was written on a standardised record sheet with a drawing of the body. Areas of sensations range from the electrode zone to the whole treated arm, from the finger tips to the elbow. Only 2 participants did not report any sensations and were told they would receive the average amount of current.

2.4. Protocol

The 2 (arms) x 4 (temperatures) x 4 (conditions: control A, conditioning, placebo, control B) design was completed by every participant in a repeated measure fashion (figure 1, p. 102). The four-block design consisted of (1) control session with the 4 calibrated temperatures, without the TENS electrodes (2) conditioning session with TENS electrodes on one arm and a decrease of 2°C for the temperatures on this treated arm compared to the other arm, (3) placebo session with TENS electrodes on one arm and the 4 calibrated temperatures, and (4) another control session without the electrodes.

2.5. Pain measures

After each 10-seconds stimulation, participants were prompted to give warm or pain ratings. The evaluation was done with a 0 to 100 numerical scale and collected by the experimenter. If the stimulation was not painful, participants had to give a rating of the warmth intensity, with anchor points set at 0 *no sensation* to 100 *extremely warm*. If the stimulation was painful, participants had to give an intensity and an unpleasantness ratings. Anchor points were *no pain* and *extremely intense* for the intensity scale and *not at all unpleasant* and *extremely unpleasant* for the unpleasantness (Rainville et al., 1992). We stressed the difference between intensity and unpleasantness, using the example from Price et al. (1983).

2.6. Other measures

Sensations (pricking, numbness, warmth, coolness or other) were rated in percent by the participants before block 2 and block 3 test. These paresthesias were added together, giving a global sensation rating for each block.

Before each block, participants were asked to rate their **expectation of change** for the block to come. They had to estimate in percent the amount of pain in the treated arm compared to the control arm within the same block.

Finally, after the end of the block tests, participants were asked to compare their **subjective level of pain** in both arms within the block. Again, they had to estimate in percent the amount of pain in the treated arm compared to the control arm.

2.7. Statistics

For every block, the intensity and unpleasantness ratings were averaged for each temperature and each arm. The ratings were transformed in percent with the formula

$$\frac{\text{mean for TENS of treated arm} - \text{mean for control arm}}{\text{mean for control arm}} \times 100$$

A negative difference indicate a relief (a decrease of pain for the TENS treatment) whereas a negative difference indicate an increase of pain during the treatment. This transformation was done for every participant.

A repeated-measure ANOVA for the 4 conditions (or blocks) was first performed. Simple within-subjects contrasts were performed for the significant analysis using control B (block 4) as the reference category. All analyses used a significance threshold of $p = 0.05$. Standardised estimates of analgesic effects were calculated based on Cohen (1988) effect size analysis method.

Bivariate correlations (two-tailed) were performed between ratings (intensity, unpleasantness), paresthesias, expectations and subjective level of pain. This was done within the conditioning condition and the placebo condition (blocks 2 and 3). Finally, a linear regression was performed to further investigate the predictors of placebo analgesia.

2.8. Between subjects differences

A 2x(4) ANOVA with the 4 conditions was performed, with the between subject factor of sex. No significant interaction condition x sex was found for pain intensity (F=.984, p=.425), for pain unpleasantness (F=.819, p=.502), for expectation (F=.486, p=.697), nor for subjective difference between the arms (F=1.834, p=.182).

Another 2x(4) ANOVA with the 4 conditions was performed, with the between subject factor of TENS-treated arm (right or left). Again, no significant interaction condition x arm was found for intensity (F=.599, p=.625), for unpleasantness (F=1.201, p=.341), for expectation (F=.820, p=.501), nor for subjective difference between the arms (F=.670, p=.583).

Finally, the 6 participants who had an experience with TENS treatment were compared to those who did not. No significant interaction condition x experience was present on any measure (F=.503, p=.685 for expectations, F=.928, p=.450 for intensity, F=.616, p=.614 for unpleasantness and F=.251, p=.859 for perceived difference). Since the factors of sex, treated arm and experience did not interact with treatment effects, they were excluded from further analysis.

2. Results

3.1. Expectations of change

The expectations of change, rated before the blocks, were analysed using a repeated-measure ANOVA on the 4 conditions (Figure 2, p. 103). The main effect of conditions was significant (F=19.898, p=.000). The contrasts analysis indicate no difference between control A and control B (F=.201, p=.659). The conditioning condition (F=14.288, p=.001) and the placebo condition (F=62.338, p=.000) were significantly different than the control B condition. The presence of TENS electrode during the tests generate more expectations of relief than during control conditions.

3.2. Intensity and unpleasantness ratings

A (4x4) ANOVA with the 4 conditions and the 4 temperature levels indicate a non-significant main effect for temperature (F=2.616, p=.085 for intensity ratings). Since we were most interested in the pain ratings, painful stimuli (the 3 highest temperatures) were averaged together. Average group ratings for intensity and unpleasantness of pain are presented in table I (p. 106).

The **pain intensity** repeated-measure ANOVA on the 4 conditions was significant (F=9.961, p=.001). The contrasts revealed no difference between the control A and B (F=.469, p=.502), a difference between the conditioning condition and the control B

(F=22.759, p=.000), but no significant difference between the placebo condition and the control B condition (F=2.040, p=.169). The **pain unpleasantness** repeated measure ANOVA on the 4 conditions was also significant (F=11.701, p=.000). Again, the contrasts revealed no difference between the control A and B (F=.188, p=.670), a difference between the conditioning condition and the control B (F=23.303, p=.000), but no significant difference between the placebo condition and the control B condition (F=.857, p=.366). Therefore, pain ratings were decreased on the sham TENS-treated arm during the conditioning block, but not during the placebo block.

3.3. Perceived difference between arms

The perceived difference of pain between the two arms was analysed using a repeated-measure ANOVA on the 4 conditions (Figure 2, p. 103). There was a significant main effect (F=12.009, p=.000). The contrasts revealed no difference between the control A and B (F=1.090, p=.310), a difference between the conditioning condition and the control B (F=36.762, p=.000), and a significant difference between the placebo condition and the control B condition (F=8.155, p=.010). Subjects rated more relief for the placebo TENS-treated arm than for the control one, both for the conditioning and placebo block.

Moreover, the correlation between the perceived change and the repeated ratings was significant during the placebo condition (r=-.46, p=.04 for intensity and r=-.48, p=.03 for unpleasantness).

3.4. Standardised estimates of the placebo effect

The magnitude of the conditiong and placebo effects observed in blocks 2 and 3 are summarised in Table II (p. 107). The conditioning condition, where the temperatures were decreased by 2°C, gave a larger decreased in intensity, unpleasantness as well as perceived overall change (ES ranged from 1.64 to 2.56) than the placebo condition

with the usual stimuli levels. However, the effect size on perceived relief was the largest for the two conditions, and the effect size for the placebo block was 1.31 on this measure. Effect size for the intensity and unpleasantness during that condition was negative and minimal (there were slightly higher average ratings for the TENS-treated arm than for the control arm).

3.5. Relationship of sensations, expectations and pain ratings

The paresthetic sensations rated before the conditioning condition were correlated to the expectations of change of this same block (r=.45, p=.05). This correlation was not significant for the placebo condition (r=-.37, p=.11). Paresthesias were not correlated to intensity, unpleasantness, or perceived relief (see Table III, p. 108).

To further examine the relationship between the expectations of change and the different pain measures, bivariate correlations were carried on for the placebo condition. The correlation was significant for perceived change (r=.55, p=.01), but not for intensity (r=-.41, p=.08) nor unpleasantness (r=-.28, p=.23). The correlation between expectation of relief and perceived relief was partly mediated by changes in intensity as the correlation decreased after controlling for this variable. Nevertheless, controlling for changes in both intensity and unpleasantness led to a residual significant correlation suggesting that part of the variance in perceived relief may be explained by expectations, after pain-related variance is accounted for. Moreover, an ANCOVA analysis was done on the perceived difference ratings, with the 4 conditions as a variable and the expectations before the placebo block as a covariable. The condition main effect was no longer significant when the variance associated with expectations was removed (F=.277, p=.841) and the interaction conditions x expectations was significant (F=9.225, p=.001).

Changes in pain unpleasantness were strongly correlated to changes in intensity in both placebo and conditioning block. This correlation was not affected by expectations (Table III, p.108). The correlation between the perceived changes and the repeated ratings was significant only for the placebo condition (block 3), (r=-.46

for intensity and r=-.48 for unpleasantness). However, this effect disappeared after controlling for expectations and the other pain measure.

3.6. Predictors of the placebo response on perceived relief

Different models of linear regression were studied to predict the subjective difference in pain in the two arms during the placebo condition. The perceived difference after the conditioning block, expectations for placebo condition, as well as intensity and unpleasantness ratings during the placebo condition were entered as potential predictors. Table IV (p. 109) present a summary of the models. The best predictor was perceived relief during block 2 conditioning with placebo TENS. A look at Table III (p. 108) shows that this effect is partly mediated by expectations since the correlation is no longer significant when the variance of this measure is accounted for.

3.7. Summary of results

Expectations of change between arms were higher when the TENS was used, in the conditioning and placebo conditions, than within the control conditions. Conditioning effect (block 2 vs, block 4) was present for intensity, unpleasantness and the subjective difference in arms. The placebo effect (block 3 vs, block 4) was significant only for the subjective difference in arm pain. However, intensity and unpleasantness ratings were correlated to this measure. The ANCOVA and correlation analysis suggested that the expectations before the placebo condition contributed to the perceived difference in pain after this condition. Finally, expectations, pain ratings, as well as subjective difference in pain after the conditioning predicted the subjective difference in pain after the placebo condition.

4. Discussion

4.1. The correlation between the conditioning and the placebo conditions is partly explained by expectations of relief

Table III (p. 108) underlines the relationship between perceived relief in blocks 2 and 3. Partial correlation suggest that this is partly explained by expectations of relief. There was a strong correlation (r=.87, p <.001) between perceived relief after conditioning and expectations of the subsequent block (Figure 2, p. 103), and a moderate one (r=.55, p <.05) between these cognitions and perceived relief after the placebo condition.

The mediating role of expectations during a placebo conditioning was documented in other studies (Price et al., 1999; Montgomery et al., 1997). Montgomery and Kirsch (1997) showed that informing subjects of the use of a placebo blocked the conditioning analgesia effect by decreasing the expectations of relief compared to an uninformed subgroup of subjects. This suggests that the pairing of a treatment with a relief is not sufficient to create a placebo effect, and that cognitive factors are involved (Rescorla, 1988). The study by Price and colleagues (1999) also reported a mediating effect of expectations on thermal pain relief after a placebo cream treatment and a conditioning procedure. The expectancy hypothesis, suggesting that a person's specific expectations of what will happen in a given situation are determinants of what they will experience (Kirsch, 1985), is supported by the present results based on a different type of placebo treatment.

Moreover, the site-specific placebo effect observed in this study suggests that placebo-induced expectations can be somatotopically organised. This result replicates previous findings (Price et al., 1999; Montgomery et al., 1997; Montgomery et al., 1996) and could be related to endogenous opioids release (Benedetti et al., 1999).

4.2. Perceived difference in pain is more sensitive than concurrent pain ratings

The effect size of the conditioned and placebo effect was larger when looking at the global relief ratings, given at the end of the block, than at the pain changes in intensity and unpleasantness which were rated after each 10-seconds stimulation both in conditioning and placebo blocks. This effect is consistent with previous studies investigating placebo analgesia (Marchand et al., 2003; Price et al., 1999) and pain memory (Feine et al., 1998). The inter-arm differences in pain intensity and unpleasantness during the control block 4 were similar than during placebo block 3. This result contrasts with a study comparing sham TENS with TENS who did find a significant decrease on low back pain immediately after placebo TENS sessions (Marchand et al., 1993). The correlation between retrospective ratings and repeated pain ratings of the two dimensions of pain was however significant in the present study during placebo condition. Table IV (p. 109) also suggest that these measures add some precision to the regression models and have indeed a role to play in placebo analgesia.

4.3. Paresthetic sensations are correlated to expectations of relief

Before any conditioning manipulation, expectations of relief rated by the volunteers were correlated with their paresthesias. The sensations - pain changes relationship, however, was non significant, contrary to our results with placebo thalamic stimulation (Marchand et al., 2003). In this experiment block 2, however, the analgesia was provoked by a conditioned decrease of the stimuli temperature, a procedure most likely affecting the analgesia ratings. During block 3, the paresthesias associated with the TENS were decreased by almost a half and not related to expectations anymore. The role of paresthesias as predictors of pain relief via their effect on expectations needs further investigations.

4.4. Multiple factors predict the magnitude of the placebo effect

We combined the conditioning impact with the cognitions (expectations), showing their relative strength in Figure 3 (p. 104). The role of memory on the perceived relief measure is also underlined. Another integrative model of placebo predictors was

created in a study involving low back pain patients (Charron et al., 2003b). It seems that placebo response is more sensitive in patients with chronic pain than with volunteers with experimental pain (Charron et al., 2003b; Marchand et al., 1993), even thought a meta-analysis found a similar effect size with chronic and experimental pain (Vase et al., 2002). Table V (p. 111) indicate clear similarities between the two experiments using quite different methodologies (population studied, type of pain, type of placebo treatment). These results suggest a possible generalisation of this explanatory model in a variety of placebo contexts.

A closer look at the correlation between expectations and intensity ratings indicate that, even if it is significant in the patients, but not in the volunteers, the link between these two variables is quite similar. The r =.41, p = .08 correlation in the present study could be a statistical artefact of an outlier subject. Indeed, when this participant who showed a very large relief (more than twice the relief of the others) was excluded, the correlation remained low but was now significant (r = .48, p = .04). Since we have no explanation for this discrepancy in this subject's evaluation, we decided to kept him in the analysis.

This result suggest, however, that the relationship between intensity ratings and expectations seen in the previous study was replicated and we decided to add an arrow in our model. Expectations of relief may act primarily on pain intensity processes and mediate changes in pain affect. This privileged relationship between pain intensity and placebo response further indicate the importance of using multiple measures of pain. It has been shown that some dimension of pain are more sensitive to one type of treatments than others (Marchand et al., 2003; Rainville et al., 1999; Marchand et al., 1993; Rainville et al., 1992).

4.4. Conclusion

The placebo response seen on perceived relief ratings was correlated to expectations of relief. These cognitions had previously been influenced by the post-conditioning

perceived relief, suggesting a mediating effect of expectations between a conditioning-induced modulation of experience and analgesia evaluation. The relative impact of conditioning and expectations on placebo pain relief seem to be similar in different experimental settings. However, the global measures are more sensitive to placebo treatment than repeated pain ratings.

Acknowledgements

This research was supported by the *Fonds de la Recherche en Santé du Québec* and the *Canadian Foundation for Innovation*.

Figure 1. Protocol of the four block design

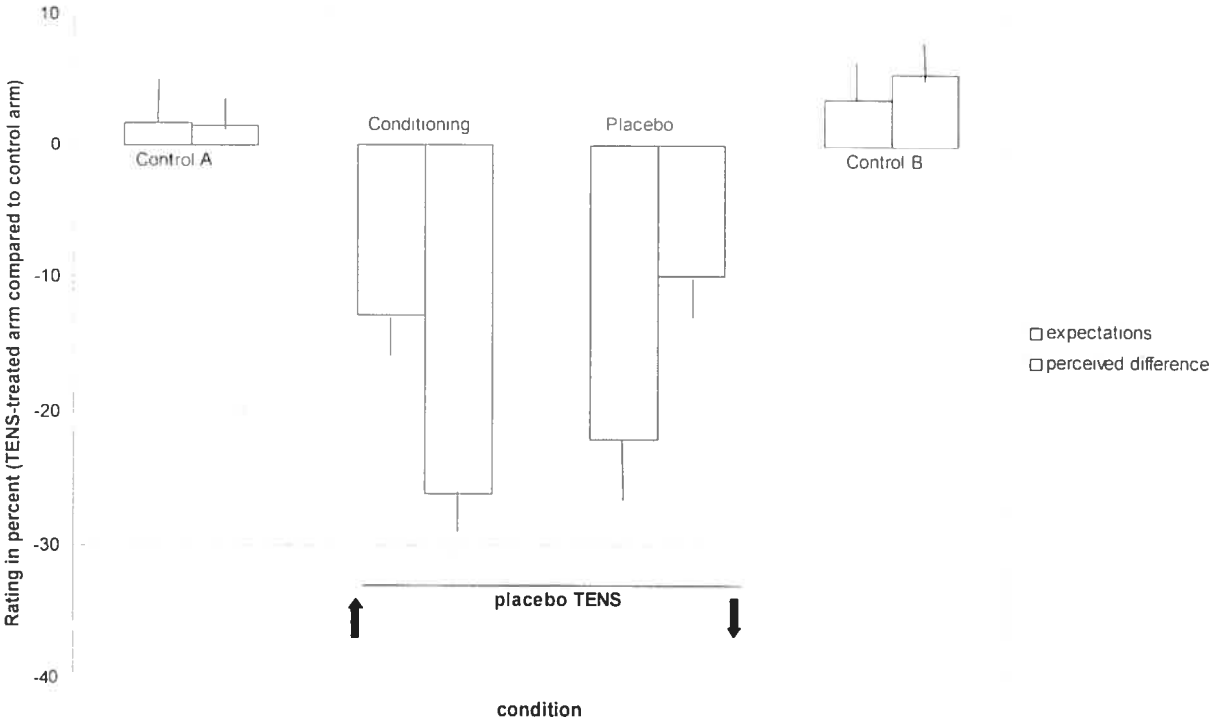
Block 1 : CONTROL A on arms 1 and 2

Block 2 : CONTROL on arm 1
PLACEBO TENS on arm 2 **PLACEBO CONDITIONING** on arm 2 (stimuli temperature lowered by 2°C)

Block 3: CONTROL on arm 1
PLACEBO TENS on arm 2 **PLACEBO TEST** on arm 2 (back to normal stimuli levels)

Block 4: CONTROL B on arms 1 and 2

Figure 2. Expectations and perceived difference in pain between the arms



Mean ratings of expectations of pain difference between the arms, rated before the actual stimulations, and of perceived difference between the arms, rated after each block.

Figure 3. Integrative model of the placebo modulation of pain

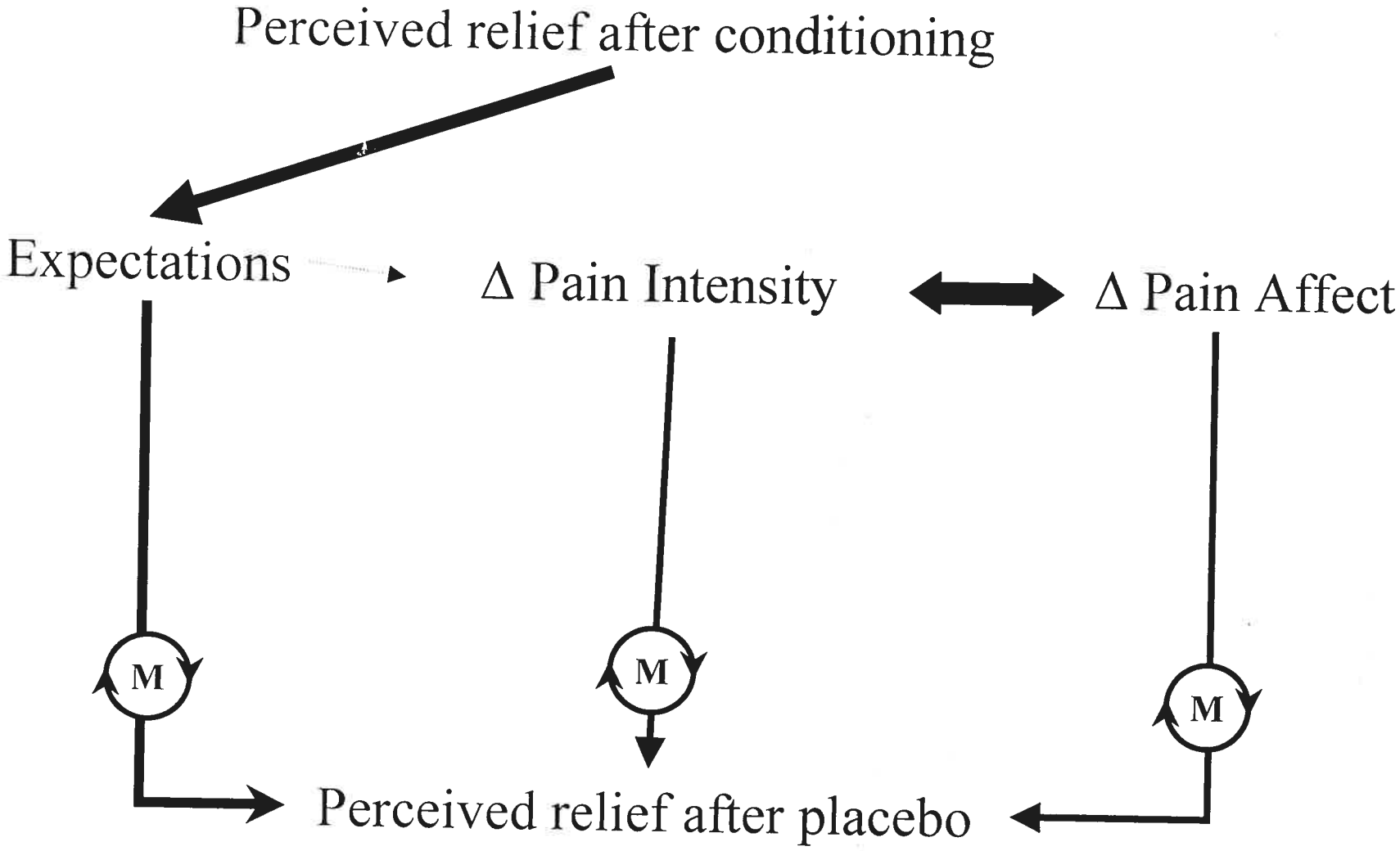


Figure 3. Integrative model summarising the results and the hypothesised processes involved in the present study during the placebo test. Full lines represent relations specifically tested in this experiment. The dotted line between expectations and pain intensity difference (Δ) indicate a non-significant relationship that may be explained by statistical power. Perceived relief after block 2 (conditioning) is related to subsequent expectations of relief before block 3 (placebo). Expectations of relief, changes in pain sensation intensity, and pain unpleasantness are predictors of perceived relief with the additional magnifying influence of memory processes (M).

Table I. Mean (SEM) intensity and unpleasantness ratings

	Pain Intensity		Unpleasantness	
Condition	TENS arm	Control arm	TENS arm	Control arm
Control A	36.18 (5.97)	38.95 (5.89)	26.91 (6.35)	32.51 (7.22)
Conditioning	6.00 (7.44)	45.16 (6.52)	0*	39.64 (7.13)
Placebo	40.47 (5.99)	38.13 (6.63)	31.11 (6.35)	29.24 (6.86)
Control B	36.53 (7.06)	39.34 (6.53)	26.25 (7.24)	29.15 (7.39)

* This sensation was rated as warm by many subjects. No unpleasantness ratings was asked for a warm sensation.

Table II. Magnitude of the placebo effect (95% confidence interval)

Measure	Analgesic effect[a]	Effect size[b]
Conditioning (block 2)		
Change in Pain Intensity	21.9 (13.6 – 30.3)	1.64 (0.93 – 2.36)
Changes in Pain Unpleasantness	36.6 (24.1 – 49.1)	1.84 (1.10 – 2.57)
Perceived Relief	31.7 (23.9 – 39.4)	2.56 (1.72 – 3.39)
Placebo (block 3)		
Change in Pain Intensity	-5.3 (-10.9 – 0.3)	-0.60 (-1.23 – 0.04)
Changes in Pain Unpleasantness	-7.4 (-17.7 – 3.0)	-0.45 (-1.08 – 0.18)
Perceived Relief	15.4 (8.0 – 22.8)	1.31 (0.62 – 1.99)

[a] The placebo effect is the arithmetic difference between the placebo and the control condition in treatment-related changes in pain intensity and unpleasantness and in perceived relief.

[b] Standardized difference (Hedges bias-corrected) and confidence intervals are calculated for paired-samples of unequal variance using the pooled SD (pooled SD = SQRT(SDa^2+SDb^2)/2) according to Cohen (1988). Note that this method tends to gives a slightly lower estimate of the pooled SD and higher estimates of the effect size.

Table III. Bivariate and partial correlation coefficients between expectations, changes in pain intensity and unpleasantness, and perceived relief during the conditioning and placebo condition.

Pearson-r		Expectation				Intensity				Unpleasantness			
	Condition[a]	Bivariate	(Int)[b]	(Unp)[c]	(Int, Unp)[d]	Bivariate	(Exp)[e]	(Unp)[c]	(Exp, Unp)[f]	Bivariate	(Exp)[e]	(Int)[b]	(Exp, Int)[g]
Intensity	Cond.	.21											
	Placebo	.41											
Unpleasant ness	Cond.	.15	-.18			**.96‡**	**.96‡**						
	Placebo	-.28	.24			**.91‡**	**.91‡**						
Perceived Relief	Cond.	.32	.42	.39	.44	-.31	-.40	-.15	-.27	-.28	-.35	.06	.15
	Placebo	**.55***	.44	**.49***	**.50***	**-.46***	-.31	-.07	.15	**-.48***	-.40	-.16	-.30

Pearson-r		Perceived relief after conditioning				
	Condition[a]	Bivariate	(Int)[b]	(Unp)[c]	(Int, Unp)[d]	(Exp)[e]
Perceived Relief	Placebo	**.59†**	**.50***	**.51***	**.51***	.29

[a] Cond.= conditioning (block 2), placebo (block 3)
[b] Controlling for changes in pain intensity
[c] Controlling for changes in pain unpleasantness
[d] Controlling for changes in pain intensity and unpleasantness
[e] Controlling for changes in expectation
[f] Controlling for changes in expectation and in pain unpleasantness
[g] Controlling for changes in expectation and in pain intensity *: $p < .05$; †: $p < .01$; ‡: $p < .001$; significant effects are indicated in bold.

Table IV. Linear Regression Models predicting the Changes in Perceived Relief after the placebo condition (block 3)

Method	Variable	*Standardized β*	t (*p*)	Model – Adj. R^2	Model – F (*p*)
Stepwise [a]	Expectation [a]	.129	.330 (.745)	**.315**	**9.734 (.006)***
	Changes in Intensity [a]	-.264	-1.299 (.211)		
	Changes in Unpleasantness [a]	-.302	-1.539 (.142)		
	Perceived relief after conditioning	**.592**	**3.120 (.006)***		
Enter	Expectation	.232	.539 (.598)	.293	2.968 (.054)
	Changes in Intensity	.840	.360 (.724)		
	Changes in Unpleasantness	-.481	-.915 (.375)		
	Perceived relief after conditioning	.296	.710 (.489)		
Enter	**Perceived relief after conditioning**	**.484**	**2.470 (.024)***	**.363**	**6.420 (.008)***
	Changes in Unpleasantness	-.302	-1.539 (.142)		

(...)

Method	Variable	*Standardized β*	t (*p*)	Model – Adj. R^2	Model – F (*p*)
Enter	**Expectation**	**.447**	**2.304 (.034)***	**.341**	**5.908 (.011)***
	Changes in Unpleasantness	-.349	-1.798 (.090)		
Enter	**Perceived relief after conditioning**	**.487**	**2.400 (.028)***	**.340**	**5.897 (.011)***
	Changes in Intensity	-.264	-1.299 (.211)		
Enter	Changes in Intensity	.068	.143 (.888)	**.324**	**4.040 (.026)***
	Changes in Unpleasantness	-.362	-.776 (.449)		
	Perceived relief after conditioning	**.490**	**2.383 (.030)***		

[a] Variable excluded based on the criterion p=.05

* Significant at p<.05 (in bold)

Table V. Comparison of models of placebo predictors

Population	Chronic pain patients [a]	Healthy volunteers
n	16	20
Pain	Low back pain	Thermal pain
Placebo	Saline injection	Sham TENS
Effect size		
On pain intensity change	1.20	-0.60
On pain unpleasantness changes	1.13	-0.45
On subjective relief	2.15	1.31
Correlation expectations		
And pain intensity changes	**.45***	.41
And pain unpleasantness changes	.27	-.28
And subjective relief	**.51***	**-.55***
Correlation subjective relief		
And pain intensity changes	**.63†**	**-.46***
And pain unpleasantness changes	**.78‡**	**-.48***

[a] Charron et al., 2003b

*: $p < .05$; †: $p < .01$; ‡: $p < .001$; significant effects are indicated in bold.

5. Conclusion

Les études menées ont permis de mettre en lumière les interactions complexes entre deux théories explicatives de la réponse placebo, soit le conditionnement et les attentes. Nous ne pouvons que constater leur complémentarité puisqu'aucun modèle unique ne peut expliquer les résultats obtenus dans les recherches. La principale contribution expérimentale de cette thèse est justement de présenter un modèle intégratif tentant de chiffrer l'importance relative des relations entre ses différents éléments.

1. Synthèse des résultats

Nous avions comme **première hypothèse** que l'analgésie placebo sur la douleur clinique serait plus importante que celle sur la douleur expérimentale à cause des attentes de soulagement plus grandes dans cette condition. Cette hypothèse a été confirmée en partie seulement. En effet, la réponse placebo a été plus grande pour les maux de dos que pour la douleur expérimentale. Par contre, les attentes de soulagement seules n'expliquent pas la différence entre les types de douleur puisqu'elles étaient semblables pour les deux conditions. D'autres facteurs liés à la fois au choix de la douleur mesurée et/ou aux caractéristiques des sujets ont été proposés comme médiateurs de l'écart observé.

Le rôle des attentes sur l'analgésie n'est toutefois pas à exclure totalement. Comme le prédisait notre **deuxième hypothèse**, les différences interindividuelles sur les attentes influençaient la diminution de douleur au dos ressentie chez les patients. On a démontré une corrélation entre les attentes et la diminution de douleur au dos suite au traitement placebo. De même, dans l'étude TENS, on a observé une corrélation entre les attentes de soulagement et le changement perçu après la condition placebo. La théorie des attentes est donc partiellement confirmée par nos études menées auprès de différents échantillons de sujets.

Notre **troisième hypothèse** proposait une corrélation entre le soulagement suite au conditionnement et celui suite au TENS placebo. Cette corrélation a été effectivement trouvée, bien qu'elle ne soit que partiellement expliquée par les attentes. Le rôle de l'expérience passée sur les attentes a été souligné. Ceci est cohérent avec la conception moderne du conditionnement qui propose que les cognitions sont des médiateurs de l'effet de l'expérience (Rescorla, 1988). L'impact du conditionnement sur la réponse placebo dépendrait en effet de la modification des attentes du sujet sur le traitement proposé.

Nous proposions, en **quatrième hypothèse,** que le modèle explicatif chez l'échantillon de gens souffrant de douleur chronique serait sensiblement le même que celui de gens sans douleur clinique. Le Tableau I (p. 124) résume les trois types d'effet placebo mesurés. Alors que nous avons pu produire un modèle pour les volontaires sains, la taille de l'effet était plus faible lorsque nous nous sommes penchés sur l'effet placebo de la douleur expérimentale chez les gens souffrant de douleur chronique. Aussi, aucune corrélation significative entre les attentes et les mesures d'analgésie n'a été trouvée dans cette condition, ce qui empêchait la description d'un modèle impliquant les cognitions. Nous notons toutefois des similitudes intéressantes entre le modèle placebo sur les lombalgies et celui sur les stimulations chaudes, et ce, pour toutes les corrélations étudiées. La corrélation entre les attentes et l'intensité, significative dans le 1er cas, mais non dans le 2^{e}, montre tout de même une tendance similaire (p=.08) qui pourrait avoir été minimisée par la présence d'un sujet avec des évaluations extrêmes (*outlier*). D'autres études seront nécessaires avant de pouvoir généraliser ces modèles à d'autres populations, mais le parallèle entre les deux contextes expérimentaux pourtant différents sur plusieurs dimensions (population, type de douleur, type de placebo) nous paraît prometteur.

Quant à la **cinquième hypothèse** proposant que les mesures globales de soulagement montreraient un plus grand effet placebo que les mesures ponctuelles, elle a été confirmée dans les deux études. Cette variable dépendante s'est montrée plus sensible que l'intensité ou l'aspect désagréable pour démontrer un changement entre la

situation contrôle et la condition placebo. La taille de l'effet était également plus importante sur cette mesure pour deux des trois types d'effet placebo mesurés, tel que résumé dans le Tableau I (p. 124). Des processus mnésiques pourraient expliquer en partie ces données puisque les évaluations globales étaient données quelques minutes après les stimulations douloureuses alors que les mesures ponctuelles étaient notées quelques secondes après celles-ci. De plus, les mesures rétrospectives nécessitaient de la part du sujet d'effectuer mentalement la moyenne des sensations reçues, une tâche demandant de la mémoire.

L'impact de l'expérience sur la réponse placebo a également été étudié dans l'étude avec les lombalgiques lorsque nous avons constaté la différence de résultats selon le moment où les sujets avaient reçu le traitement placebo (avant ou après la situation contrôle). L'**analyse post-hoc** a en effet démontré que la réponse analgésique était diminuée lorsqu'elle était précédée d'une situation contrôle. Ce blocage ne semble pas s'expliquer par les attentes qui étaient légèrement plus importantes dans cet ordre que lorsque les suggestions placebo étaient présentées en premier. Un conditionnement anti-analgésique supérieur à l'effet pro-analgésique des attentes a donc été proposé, mais d'autres études seront nécessaires pour confirmer cette explication.

2. Implications des résultats: études scientifiques et pratique clinique

A) *Le soulagement placebo est corrélé aux attentes*

L'étude chez les lombalgiques semble indiquer que les attentes sont particulièrement importantes pour prédire le soulagement de la douleur clinique, mais non pour celui de la douleur expérimentale. Quant à elle, l'étude TENS a montré l'impact des attentes sur la douleur expérimentale. Il semble donc que les attentes soient corrélées au soulagement placebo dans différents types de population, celles-ci étant soumises à diverses douleurs. Pour les études scientifiques voulant comparer l'efficacité d'un traitement analgésique et d'un placebo, ces données soulignent la sensibilité exacerbée des patients à générer des attentes pour les conditions cliniques. Elles n'excluent cependant pas l'impact des cognitions sur les douleurs expérimentales.

Cela réitère l'importance d'une méthodologie où les attentes de soulagement des sujets ne sont pas différentes pour la condition expérimentale et la condition contrôle, comme dans les situations à double insu (*double blind*). On sait cependant que les effets secondaires de certains médicaments sont parfois décelables par les participants et/ou les expérimentateurs. Une mesure des attentes des volontaires pour chacune des conditions pourrait être utilisée de façon systématique pour vérifier la similitude entre les traitements proposés au plan des attentes. Ce contrôle permettrait aussi d'évaluer l'impact des cognitions sur les résultats obtenus.

Dans le domaine clinique, on souhaite au contraire utiliser au maximum le levier cognitif qui s'ajoute à l'effet physiologique des traitements. Les résultats obtenus chez les patients sont cohérents avec le courant de pensée qui suggère aux soignants de ne pas lésiner sur l'enthousiasme et les informations susceptibles de générer des attentes de soulagement bénéfiques au patient. Cette pratique était utilisée bien avant l'apparition des études scientifiques d'efficacité du traitement. Soigner va bien au-delà de l'administration de substances dont les propriétés pharmacologiques sont reconnues au plan scientifique. Appliquer en clinique la neutralité des chercheurs ne pourrait que diminuer l'impact des traitements, qu'ils soient placebo ou non.

B) *L'ordre des séances peut influencer le soulagement*

L'analyse de l'ordre des séances sur l'analgésie chez les lombalgiques a souligné l'impact négatif d'une séance amenant peu de soulagement (la situation contrôle) sur une séance subséquente générant pourtant des attentes de soulagement. Laska et ses collaborateurs avaient démontré que l'expérience d'un analgésique efficace augmentait l'effet analgésique d'un placebo présenté après (Laska et al., 1973). Dans le même ordre d'idée, notre étude suggère que l'expérience d'un traitement non analgésique, quoique présenté comme tel aux sujets, peut diminuer le soulagement associé subséquemment à un placebo et probablement celui lié à tout médicament ou manipulation analgésique. Le contrôle de l'effet d'ordre, tel qu'utilisé dans notre étude, nous apparaît particulièrement important dans le cas d'études en chassé-croisé (*cross-over*) où la séquence de traitement est inversée pour une partie des sujets.

L'utilisation d'un ordre unique pourrait biaiser les recherches et amoindrir un effet thérapeutique à cause d'un artefact méthodologique. Les résultats obtenus permettent également de souligner l'importance de l'évaluation de l'historique médical d'un volontaire. Les critères d'exclusion concernent habituellement l'usage actuel d'un traitement, mais pas toujours son utilisation passée. Notons toutefois que nous n'avons observé aucune différence pour notre étude TENS entre les sujets qui avaient de l'expérience avec cette procédure et ceux qui n'en avaient pas. Cette vérification de routine devrait être effectuée dans toutes les études pour éviter une variable confondante.

Au plan clinique, ces résultats démontre bien l'impact possible, chez les patients, des expériences passées avec des analgésiques sur leur réponse à un nouveau médicament anti-douleur. Le conditionnement peut affecter négativement la réponse à un traitement même en présence d'attentes de soulagement. Cela pourrait expliquer en partie les cas identifiés comme "compliqués", soit ceux qui semblent résister à toute médication dont l'efficacité en clinique a pourtant été reconnue pour une population semblable. Ces patients sont parfois abordés avec suspicion par les soignants, qui attribuent souvent davantage d'importance à des facteurs de personnalité qu'à l'histoire médicale de traitements. Cette dernière dimension mériterait peut-être plus d'attention qu'elle n'en a actuellement pour expliquer ou prévenir la faible amélioration de certains patients suite aux traitements.

C) *Les mesures influencées par la mémoire sont plus sensibles à l'effet placebo*

Dans les deux études présentées, la mesure globale de soulagement, donnée par les sujets à la fin de l'expérience, a montré la réponse positive la plus robuste au placebo. Cette variable dépendante risque d'être influencée par la mémoire et l'état émotif global des participants plus que par les cotes répétées de l'intensité et de l'aspect désagréable. Dans le domaine de la recherche, cela commande un choix consciencieux des mesures et suggère que les études basées sur ce seul type d'évaluation ont à être interprétées avec précaution puisqu'elles peuvent montrer un effet positif artificiellement gonflé.

En clinique, ce type de mesure permet d'obtenir la perception globale du patient sur le traitement proposé. Il s'agit probablement pour le patient d'une évaluation importante de son expérience risquant d'influencer ses croyances face à cette intervention, son adhérence (*compliance*) et son bien-être. Dans la pratique, la mesure est plus facile à obtenir pour le soignant et donne des informations importantes à propos des cognitions du soigné, ces pensées pouvant avoir un impact sur la réponse future de ce dernier au traitement administré. Elles peuvent ainsi avoir leur utilité dans la pratique, bien qu'elles devraient être accompagnées à titre informatif par des mesures moins affectées par la mémoire et la désirabilité sociale.

D) *La réponse placebo analgésique est influencée par de multiples facteurs*

Les modèles intégratifs proposés pour expliquer l'effet placebo dans différents contextes ont un intérêt surtout au plan de la recherche fondamentale cherchant à mieux comprendre les mécanismes de ce phénomène. Nous verrons dans la prochaine section des types d'études permettant d'utiliser ces modèles comme cadre de référence pour tester des hypothèses.

3. Directions futures

Suite à l'étude avec les lombalgiques, nous avons proposé différents facteurs pouvant expliquer le plus grand effet placebo pour la douleur clinique que pour la douleur expérimentale. Malheureusement, le désir de soulagement, ou le souhait du patient d'observer une diminution de douleur, n'a pas été mesuré. Une étude reprenant la comparaison entre les deux types de stimulation chez un échantillon de gens souffrant de douleur chronique pourrait ajouter cette mesure de la motivation pour vérifier s'il est possible qu'elle s'intègre au modèle des attentes et de l'expérience passée. De même, l'effet possible de dimensions reliées au type de douleur utilisée pourrait être évalué, notamment en utilisant une douleur clinique aiguë au lieu d'une douleur chronique comme comparaison à une douleur expérimentale de courte durée.

Les découvertes concernant l'importance de l'effet d'ordre sur la réponse placebo mériteraient également d'être étudiées plus en détails et avec un échantillon plus important de sujets. On pourrait modifier volontairement l'expérience passée indépendamment des suggestions verbales, en créant par exemple des attentes neutres chez le sujet en lui parlant de situation contrôle, mais en amenant une expérience d'analgésie, d'hyperalgésie ou neutre. L'utilisation de médicaments dont l'efficacité est reconnue ou d'une solution saline pourrait produire ces réactions. L'utilisation subséquente d'un placebo présenté comme un analgésique efficace permettrait de voir l'impact du conditionnement sur les attentes et sur la réponse placebo. L'emploi d'un ordre inverse aiderait justement à distinguer les attentes créées par des suggestions verbales et celles amenées par l'expérience. On pourrait s'attendre à une réponse placebo amplifiée lorsque la condition placebo est précédée par une analgésie, à une réponse diminuée si elle suit une hyperalgésie et à un effet placebo d'intensité intermédiaire suite à la situation neutre. Il serait également intéressant de voir l'impact des expériences contraires aux attentes lors de la situation contrôle sur les attentes subséquentes lors de la condition placebo.

Toujours suite à l'émergence d'une différence liée à l'effet d'ordre, un autre type de recherche pourrait se pencher sur l'aspect temporel de ce phénomène. Pour notre étude, les deux séances d'expérimentation (contrôle et placebo) étaient séparées de quelques jours. On pourrait volontairement modifier ce délai à différents niveaux (par exemple: 2 jours, 10 jours, 30 jours) et observer combien de temps l'effet anti-analgésique se maintient. Cette information pourrait être utile, tant au plan méthodologique pour les études testant différents outils thérapeutiques où le contrôle de l'ordre peut avoir son importance, qu'au plan clinique lorsqu'on connaît l'historique de traitement d'un patient.

Une dernière avenue de recherche à considérer concerne la combinaison des trois modèles d'explication des mécanismes de l'effet placebo analgésique présentés dans le premier article, soit l'évaluation de l'impact des attentes et de l'expérience passée sur les substances neurochimiques. On a suggéré un rôle des endorphines, de la

dopamine et de la sérotonine dans la réponse placebo (Benedetti, 2002). L'ajout d'une condition expérimentale avec ou sans injection de naloxone, un antagoniste des opiacés, permettrait d'intégrer le rôle des substances endogènes dans nos modèles explicatifs. L'utilisation d'imagerie cérébrale lors d'analgésie placebo, comme la résonance magnétique fonctionnelle, serait également intéressante. À ce jour, une seule étude de tomographie par émission de positrons s'est penchée sur ce phénomène (Petrovic et al., 2002). L'observation d'activation de certaines zones du cerveau accentuerait sûrement l'intérêt de l'étude de l'impact physiologique des mécanismes cognitifs.

4. Limites des études

L'écart entre un idéal méthodologique et la réalité expérimentale est inévitable. Les études composant cette thèse n'ont pu échapper à certaines limites. Certaines facettes de la validité interne sont considérées, dont les attentes du chercheur et les attentes du sujet. Nous nous penchons également sur un des facteurs affectant la validité externe, soit la validité de l'échantillon. Finalement, les limites concernant les études corrélationnelles sont abordées.

A) Validité interne

Il a été difficile dans le cadre de ce type d'expérimentation de contrôler totalement les attentes du chercheur. Pour étudier l'effet placebo, nous voulions créer des attentes de soulagement chez les sujets par nos suggestions verbales et ainsi laisser transparaître nos propres souhaits. L'application du traitement placebo, que ce soit l'injection saline ou le TENS, n'était par ailleurs pas faite de manière aveugle par les expérimentateurs qui étaient au courant de l'utilisation d'une thérapie sans effet pharmacologique intrinsèque. Cette connaissance peut avoir modifié involontairement leur comportement, affectant ainsi les attentes du sujet.

Pour limiter l'impact de la désirabilité sociale, nous avons mis en place différents moyens de contrôle. D'abord, pour l'étude avec les lombalgiques, l'expérimentateur

qui notait les changements de douleur était aveugle à l'ordre des séances. Les suggestions lors des conditions contrôle ou placebo étaient verbalisées par une autre personne. Nous mentionnions que le traitement contrôle ne devait pas vraiment affecter la perception de la douleur et avons voulu ainsi diminuer la pression sur les sujets à répondre de manière positive. Nous espérions qu'ils oseraient davantage mentionner un changement qui n'allait pas dans le sens espéré en utilisant deux expérimentateurs distincts pour l'administration du traitement et la mesure de son effet. Quant à l'étude TENS, le contexte présenté dans le formulaire de consentement mentionnait la possibilité que le traitement affecte le côté sans électrodes puisque ce type d'intervention agit à un niveau central. Nous disions vouloir tester dans quelle mesure cette hypothèse se vérifiait, tout en restant vagues sur nos propres souhaits. Masquant ainsi nos véritables objectifs, soit mesurer l'impact d'un conditionnement sur les attentes et sur le soulagement, nous espérions limiter la tendance des sujets à répondre pour plaire à l'expérimentateur.

B) Validité externe

L'échantillonnage des participants devrait être fait au hasard parmi une population accessible. Pour créer un échantillon le plus homogène possible de patients souffrant de douleur chronique, nous avons appliqué des critères d'inclusion et d'exclusion assez précis pour l'étude avec les lombalgiques. Nous demandions notamment de ne pas utiliser une médication prescrite pouvant affecter la douleur (narcotiques, antidépresseurs, anti-convulsivants ou autres). Cette précaution était nécessaire pour ne pas confondre l'effet de ce traitement avec le placebo. Le recrutement de sujets a été plus difficile que prévu puisque nous avons réalisé que la majorité des volontaires prenaient une médication et ne pouvaient pas être acceptés pour l'étude. Dans les faits, choisir des lombalgiques acceptant d'être soumis à des stimulations douloureuses et n'ayant pas de traitement pharmacologique prescrit amène fort probablement une sélection particulière de sujets. Nous croyons toutefois que, loin de créer un biais positif envers le placebo présenté comme un analgésique, ce choix de participants a amené un échantillon de gens plus sceptiques envers un nouveau traitement que la population souffrant de douleur chronique utilisant une médication.

La généralisation des résultats obtenus à une population de patients ayant de la douleur chronique peut ainsi être amoindrie par les caractéristiques de nos sujets.

L'utilisation de la douleur expérimentale a également ses limites. Accepter volontairement de se soumettre à une douleur créée en laboratoire, pouvant être suspendue au besoin par l'expérimentateur, implique probablement un impact émotif moins négatif que souffrir sans l'avoir choisi. Nos stimulations, de plus, étaient d'une durée maximale de quelques minutes, d'une intensité tolérable choisie pour chacun des sujets et suivaient une série d'essais visant à amoindrir l'effet de surprise. Ces dimensions sont loin d'être un reflet fidèle des situations de douleur clinique, où le sentiment de manque de contrôle sur la souffrance contribue à la détresse des patients (Sullivan et al., 2001). La généralisation des résultats obtenus dans une population chez qui on a induit une douleur à une population souffrant de douleur clinique doit donc être extrêmement prudente. L'application des connaissances acquises lors des études sur les mécanismes de l'effet placebo semble pourtant plus intéressante pour les patients que pour les sujets sains.

C) Études corrélationnelles

Les études effectuées dans cette thèse ont permis de proposer des modèles explicatifs fondés sur des analyses corrélationnelles. Ce type de recherche ne permet pas de conclure sur l'existence d'une relation causale entre les variables à l'étude, quoiqu'elles amènent des informations intéressantes sur la force relative de leurs liens. La direction des liens entre les facteurs s'est donc principalement fondée sur des raisons temporelles, les mesures de soulagement étant prises, par exemple, après celles des attentes. L'interprétation des résultats obtenus doit donc mener avec prudence à une conclusion comme "les attentes élevées *amènent* un grand soulagement", quoique ce lien ait déjà été proposé par certains chercheurs (Price et al., 1999). L'utilisation de méthodes statistiques différentes, nécessitant de plus grands échantillons de sujets, sera nécessaire pour éclairer la direction des interrelations entre les facteurs impliqués dans l'analgésie par placebo.

5. Mot de la fin

Nous avons souligné dans l'introduction de cet ouvrage que la légitimité de l'étude des mécanismes de l'effet placebo semblait maintenant beaucoup mieux acceptée par les communautés scientifique et clinique. Nous espérons que nos études auront permis de lever une partie du voile de ce qu'il nous reste à découvrir sur ce fascinant phénomène démontrant l'impact physiologique de facteurs psychologiques sur le soulagement de la douleur par l'administration d'un traitement placebo. Actuellement, le contexte scientifique et social favorise l'étude combinée de l'esprit et du corps, comme en témoigne la multiplicité des études cognitives utilisant l'imagerie cérébrale. Tout porte à croire qu'il s'agit là d'une tendance à long terme et non d'une mode passagère. Il semble que le monde de la science, tout autant que les patients, bénéficieront de ce courant prônant la réconciliation entre deux écoles de pensée.

Tableau I. Comparaison des trois types d'effet placebo mesurés

Population	Gens souffrant de douleur chronique [a]	Gens souffrant de douleur chronique [a]	Volontaires sans douleur chronique [b]
n	16	16	20
Douleur	Lombalgies	Immersion de la main dans l'eau froide	Stimulations chaudes
Placebo	injection d'eau saline	injection d'eau saline	TENS sans courant électrique
Taille de l'effet sur changement dans l'intensité de la douleur	1.20	0.62	-0.60
sur changement dans l'aspect désagréable de la douleur	1.13	0.71	-0.45
sur soulagement subjectif	2.15	0.29	1.31
Corrélation attentes et changement dans l'intensité de la douleur	**.45***	.02	.41
et changement dans l'aspect désagréable de la douleur	.27	.02	-.28
et soulagement subjectif	**.51***	-.17	**-.55***
Corrélation soulagement subjectif et changement dans l'intensité de la douleur	**.63†**	-.18	**-.46***
et changement dans l'aspect désagréable de la douleur	**.78‡**	-.30	**-.48***

[a] Charron et al., 2003b
[b] Charron et al., 2003c
*: $p < .05$; †: $p < .01$; ‡: $p < .001$; les effets significatifs sont mis en caractères gras.

Références

Énoncé de politique des trois conseils (CRM, CRSNG, CRSH): Éthique de la recherche avec des êtres humains. (1998).

Anonymous. (2003). Le petit Larousse. Paris: Larousse.

Ader,R. (1997). The role of conditioning in pharmacotherapy. In A. Harrington (Ed.), The placebo effect: An interdisciplinary exploration. (pp. 138-165). Cambridge, MA: Harvard University Press.

Amanzio,M., & Benedetti,F. (1999). Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. Journal of Neuroscience, 19(1), 484-494.

Amanzio,M., Pollo,A., Maggi,G., & Benedetti,F. (2001). Response variability to analgesics: a role for non-specific activation of endogenous opioids. Pain, 90, 205-215.

Bandura,A., O'Leary,A., Taylor,C.B., Gauthier,J., & Gossard,D. (1987). Perceived self-efficacy and pain control: opioid and nonopioid mechanisms. Journal of Personality and Social Psychology, 53(3), 563-571.

Barsky,A.J., Saintfort,R., Rogers,M.P., & Borus,J.F. (2002). Nonspecific medication side effects and the nocebo phenomenon. Journal of the American Medical Association, 287(5), 622-627.

Beecher,H.K. (1955). The powerful placebo. Journal of the American Medical Association, 159(17), 1602-1608.

Benedetti,F. (1996). The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. Pain, 64(3), 535-543.

Benedetti,F. (2002). How the doctor's words affect the patient's brain. Evaluation and the Health Professions, 25(4), 369-386.

Benedetti,F., & Amanzio,M. (1997). The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. Progress in Neurobiology, 52(2), 109-125.

Benedetti,F., Arduino,C., & Amanzio,M. (1999). Somatotopic activation of opioid systems by target-directed expectations of analgesia. Journal of Neuroscience, 19(9), 3639-3648.

Benedetti,F., Pollo,A., Lopiano,L., Lanotte,M., Vighetti,S., & Rainero,I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. Journal of Neuroscience, 23(10), 4315-4323.

Berthelot,J.M., Maugars,Y., Abgrali,M., & Prost,A. (2001). Interindividual variations in beliefs about the placebo effect: a study in 300 rheumatology inpatients and 100 nurses. Joint Bone Spine, 68, 65-70.

Bootzin,R.R., & Caspi,O. (2002). Explanatory mechanisms for placebo effects: cognition, personality and social learning. In H. A. Guess, A. Kleinman, J. W. Kusek, & L. W. Engel (Eds.), The science of the placebo. Toward an interdisciplinary research agenda. (pp. 108-132). London: BMJ Books.

Brody,H. (1985). Placebo effect: an examination of Grünbaum's definition. In L. White, B. Tursky, & G. E. Schwatrz (Eds.), Placebo: Theory, research, and mechanisms. (pp. 37-58). New York: Guilford Press.

Brown,W.A. (1998). The placebo effect. Scientific American, 278(1), 90-95.

Buchaleq,L.W. (1982). Investigation of drug expectancy as a function of color, size and preparation. Journal of Clinical Pharmacology, 2, 245-248.

Bushnell,M.C., Duncan,G.H., Dubner,R., Jones,R.L., & Maixner,W. (1985). Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. Journal of Neuroscience, 5(5), 1103-1110.

Charron,J., & Marchand,S. (2003a). Understanding placebo analgesia: the contribution of experimental pain studies. Journal of Pain, submitted.

Charron,J., Rainville,P., & Marchand,S. (2002). Placebo analgesia: Clinical pain is more sensitive than experimental pain [Abstract]. International Association for the Study of Pain 10th World Congress on Pain, San Diego.

Charron,J., Rainville,P., & Marchand,S. (2003b). Direct comparison of placebo effects on clinical and experimental pain. Pain, submitted.

Charron,J., Rainville,P., & Marchand,S. (2003c). Multiple factors contribute to the perceived relief induced by placebo TENS [Abstract]. Canadian Pain Society Annual Conference, Toronto.

Cohen,J. (1988). Statistical power analysis for the behavioral sciences, second edition. Hillsdale, NJ: Lawrence Erlbaum Associates.

Crow,R., Gage,H., Hampson,S., Hart,J., Kimber,A., & Thomas,H. (1999). The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. Health Technology Assessment, 3(3), 1-106.

De La Fuente-Fernandez,R., & Stoessl,A.J. (2002). The biochemical bases for reward. Implications for the placebo effect. Evaluation and the Health Professions, 25(4), 387-398.

De Pascalis,V., Chiaradia,C., & Carotenuto,E. (2002). The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. Pain, 96(3), 393-402.

Eccleston,C., & Crombez,G. (1999). Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychological Bulletin, 125(3), 356-366.

Evans,F.J. (1974). The power of a sugar pill. Psychology Today, 7(11), 55-59.

Feine,J.S., Lavigne,G.J., Dao,T.T.T., Morin,C., & Lund,J. (1998). Memories of chronic pain and perceptions of relief. Pain, 77, 137-141.

Gedney,J.J., Loganm,H., & Baron,R.S. (2003). A psychophysical analysis of experimential factors that selectively influence the affective dimension of pain. Journal of Pain, 4(2), 47

Gracely,R.H. (1994). Studies of pain in normal man. In R. Melzack & P. D. Wall (Eds.), Textbook of pain. (pp. 315-336). London: Churchill Livingstone.

Gracely,R.H., Dubner,R., Wolskee,P.J., & Deeter,W.R. (1983). Placebo and naloxone can alter post-surgical pain by separate mechanisms. Nature, 306(5940), 264-265.

Gracely,R.H., McGrath,P., & Dubner,R. (1978). Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptors: manipulation of affect by diazepam. Pain, 5(1), 19-29.

Grevert,P., Albert,L.H., & Goldstein,A. (1983). Partial antagonism of placebo analgesia by naloxone. Pain, 16(2), 129-143.

Guess,H.A., Kleinman,A., Kusek,J.W., & Engel,L.W. (2002). The science of placebo: Toward an interdisciplinary research agenda. London: BMJ Books.

Harkness,E., & Ernst,E. (2000). The enigmatic placebo effect - A systematic review to define its determinants. Perfusion, 13, 164-170.

Harrington,A. (1997). The placebo effect : An interdisciplinary exploration. Cambridge, MA: Harvard University Press.

Horvath,P. (1988). Placebos and common factors in two decades of psychotherapy research. Psychological Bulletin, 104(2), 214-225.

Hróbjartsson,A. (2002). What are the main methodological problems in the estimation of placebo effects? Journal of Clinical Epidemiology, 55(5), 430-435.

Hróbjartsson,A., & Gotzsche,P.C. (2001). Is the placebo powerless? New England Journal of Medecine, 344(21), 1594-1602.

Jensen,M.P., Chen,C., & Brugger,A.M. (2002). Postsurgical pain outcome assessment. Pain, 99(1-2), 101-109.

Jensen,M.P., & Karoly,P. (1991). Motivation and expectancy factors in symptoms perception: a laboratory study of the placebo effect. Psychosomatic Medecine, 53, 144-152.

Jospe,M. (1978). The placebo effect in healing. Lexington, MA: Lexington Books.

Kienle,G.S., & Kiene,H. (1996). Placebo effect and placebo concept: A critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. Alternative Therapies in Health and Medicine, 2(6), 39-54.

Kienle,G.S., & Kiene,H. (1997). The powerful placebo effect: Fact or fiction? Journal of Clinical Epidemiology, 50(12), 1311-1318.

Kirsch,I. (1985). Response expectancy as a determinant of experience and behavior. American Psychologist, 40(11), 1189-1202.

Kirsch,I. (1990). Changing expectations: a key to effective psychotherapy. Pacific Grove, CA: Brooks/Cole.

Kirsch,I. (1991). The placebo effect as a conditioned response: Failures of the "litmus test". Behavioral and Brain Sciences, 14(1), 200-201.

Kirsch,I. (1997). Specifying nonspecifics: psychological mechanims of placebo effects. In A. Harrington (Ed.), The placebo effect: An interdisciplinary exploration. (pp. 166-186). Cambridge, MA: Harvard University Press.

Lasagna,L., Laties,V.G., & Dohan,J.L. (1958). Further investigation on the "pharmacology" of placebo administration. Journal of Clinical Investigation, 37(4), 533-537.

Laska,E., & Sunshine,A. (1973). Anticipation of analgesia a placebo effect. Headache, 1, 1-11.

Long,D.M., Uematsu,S., & Kouba,R.B. (1989). Placebo responses to medical device therapy for pain. Stereotactic and Functional Neurosurgery, 53(3), 149-156.

Marchand,S., Charest,J., Li,J., Chenard,J., Lavignolle,B., & Laurencelle,L. (1993). Is TENS purely a placebo effect? A controlled study on chronic low back pain. Pain, 54(1), 99-106.

Marchand,S., Kupers,R.C., Bushnell,M.C., & Duncan,G.H. (2003). Analgesic effects of normal and placebo thalamic stimulation. Pain, 105(3), 481-488.

Mason,P. (1999). Central mechanisms of pain modulation. Current Opinion in Neurobiology, 9(4), 436-441.

McMillan,F.D. (1999). The placebo effect in animals. Journal of the American Veterinary Medical Association, 215 (7), 992-999.

Moerman,D.E. (2002). Explanatory mechanisms for placebo effects: cultural influences and the meaning response. In H. A. Guess, A. Kleinman, J. W. Kusek, & L. W. Engel (Eds.), The science of the placebo. Toward an interdisciplinary research agenda. (pp. 77-107). London: BMJ Books.

Montgomery,G.H., & Kirsch,I. (1996). Mechanisms of placebo pain reduction: an empirical investigation. Psychological Science, 7(3), 174-176.

Montgomery,G.H., & Kirsch,I. (1997). Classical conditioning and the placebo effect. Pain, 72(1-2), 107-113.

Peck,C., & Coleman,G. (1991). Implications of placebo theory for clinical research and practice in pain management. Theoretical Medicine, 12(3), 247-270.

Petrovic,P., Kalso,E., Petersson,K.M., & Ingvar,M. (2002). Placebo and opioid analgesia - Imaging a shared neuronal network. Science, 295, 1737-1740.

Pollo,A., Amanzio,M., Arslanian,A., Casadio,C., Maggi,G., & Benedetti,F. (2001). Response expectancies in placebo analgesia and their clinical relevance. Pain, 93(1), 77-84.

Posner,J., & Burke,C.A. (1985). The effects of naloxone on opiate and placebo analgesia in healthy volunteers. Psychopharmacology, 87(4), 468-472.

Price,D.D. (2000). Factors that determine the magnitude and presence of placebo analgesia. In M. Devor, M. C. Rowbotham, & Z. Wiesenfeld-Hallin (Eds.), *Proceedings of the 9th World Congress on pain*, Progress in Pain Research and Management. (pp. 1085-1095). Seattle: IASP Press.

Price,D.D. (2001). Assessing placebo effects without placebo groups: an untapped possibility? Pain, 90, 201-203.

Price,D.D., & Barrell,J.J. (1999a). Expectation and desire in pain and pain reduction. In I. Kirsch (Ed.), How expectancies shape experience. (pp. 145-171). Washington, DC: American Psychological Association.

Price,D.D., Barrell,J.J & Gracely, R.H. (1980). A psychophysical analysis of experimental factors that selectively influence the affective dimension of pain. Pain, 8, 137-149.

Price,D.D., Bush,F.M., Long,S., & Harkins,S.W. (1994). A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain, 56(2), 217-226.

Price,D.D., & Fields,H.L. (1997). Where are the causes of placebo analgesia? A behavioral experiential analysis. Pain Forum, 6, 44-52.

Price,D.D., Harkins,S.W., & Baker,C. (1987). Sensory-affective relationships among different types of clinical and experimental pain. Pain, 28(3), 297-307.

Price,D.D., McGrath,P.A., Rafii,A., & Buckingham,B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain, 17(1), 45-56.

Price,D.D., Milling,L.S., Kirsch,I., Duff,A., Montgomery,G.H., & Nicholls,S.S. (1999b). An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. Pain, 83(2), 147-156.

Price,D.D., & Soerensen,L.V. (2002). Endogenous opioid and non-opioid pathways as mediators of placebo analgesia. In H. A. Guess, A. Kleinman, D. J. W. Kusek, & L. W. Engel (Eds.), The science of placebo: Toward an interdisciplinary research agenda. (pp. 183-206). London: BMJ Books.

Price,D.D., Von der Gruen,A., Miller,J., Rafii,A., & Price,C. (1985). A psychophysical analysis of morphine analgesia. Pain, 22(3), 261-269.

Quitkin,F.M. (1999). Placebos, drug effects, and study design: a clinician's guide. American Journal of Psychiatry, 156(6), 829-836.

Rainville,P., Carrier,B., Hofbauer,R.K., Bushnell,M.C., & Duncan,G.H. (1999). Dissociation of sensory and affective dimensions of pain using hypnotic modulation. Pain, 82(2), 159-171.

Rainville,P., Duncan,G.H., Price,D.D., & Bushnell,M.C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science, 227, 968-971.

Rainville,P., Feine,J.S., Bushnell,M.C., & Duncan,G.H. (1992). A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. Somatosensory and Motor Research, 9(4), 265-277.

Rescorla,R.A. (1988). Pavlovian conditioning:It's not what you think it is. American Psychologist, 43(3), 151-160.

Roehr, B. The problematic placebo effect. HMS Beagle (103). 2001. Electronic Citation

Roelofs,J., ter Riet,G., Peters,M.L., Kessels,A.G.H., Reulen,J.P.H., & Menheere,P.P.C.A. (2000). Expectations of analgesia do not affect spinal nociceptive R-III reflex activity: An experimental study into the mechanism of placebo-induced analgesia. Pain, 89(1), 75-80.

Spiro,H.M. (1986). How can the placebo work? In Anonymous, Doctors, patients and placebos. (pp. 209-226). New Haven: Yale University Press.

Streitberger,K., & Kleinhenz,J. (1998). Introducing a placebo needle into acupuncture research. The Lancet, 352(9125), 364-365.

Sullivan,M.J.L., Rodgers,W.M., & Kirsch,I. (2001). Catastrophizing, depression and expectancies for pain and emotional distress. Pain, 91(1-2), 147-154.

ter Riet,G., de Craen,A.J.M., de Boer,A., & Kessels,A.G.H. (1998). Is placebo analgesia mediated by endogenous opioids? A systematic review. Pain, 76(3), 273-275.

Turner,J.A., Deyo,R., Loeser,J.D., Von Korff,M., & Fordyce,W.E. (1994). The importance of placebo effects in pain treatment and research. Journal of the American Medical Association, 271(20), 1609-1614.

Vase,L., Riley,J.L., & Price,D.D. (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. Pain, 99, 443-452.

Voudouris,N.J., Peck,C.L., & Coleman,G. (1985). Conditioned placebo responses. Journal of Personality and Social Psychology, 48(1), 47-53.

Voudouris,N.J., Peck,C.L., & Coleman,G. (1989). Conditioned response model of placebo phenomena: further support. Pain, 38(1), 109-116.

Voudouris,N.J., Peck,C.L., & Coleman,G. (1990). The role of conditioning and verbal expectancy in the placebo response. Pain, 43(1), 121-128.

Wickramasekera,I. (1985). A conditioned response model of the placebo effect: predictions from the model. In L. White, B. Tursky, & G. E. Schwatrz (Eds.), Placebo: Theory, research, and mechanisms . (pp. 255-287). New York: Guilford Press.

Zubieta,J.-K., Smith,Y.R., Bueller,J.A., Xu,Y., Kilbourn,M.R., Jewett,D.M., Meyer,C.R., Koeppe,R.A., & Stohler,C.S. (2001). Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science, 293(5528), 311-315.