Pain 126 (2006) 115–122

PAIN

www.elsevier.com/locate/pain

Categories of placebo response in the absence of site-specific expectation of analgesia

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Received 16 November 2005; received in revised form 6 June 2006; accepted 16 June 2006

Abstract

Experimental placebo analgesia is induced by building an expectation of reduced pain in a specific body part, usually using an inert cream in the guise of a local anaesthetic in conjunction with conditioning. We investigated non-site-specific placebo analgesia by conditioning subjects to expect the anaesthetic cream on one arm, without specifying if they will definitely receive the cream, or to which arm it might be applied. Painful heat pulses (150 ms) from a CO_2 laser were delivered randomly to both arms. A treatment group ($n = 24$) underwent three experimental blocks (pre-cream, conditioning after cream, and post-conditioning). During the conditioning block, the intensity of the stimulus was reduced on one arm only. In the post-conditioning block it was returned to the painful level. We evaluated the change of intensity rating post-conditioning compared to the pre-cream block. In contrast to a control group ($n = 16$), the treatment group reported a significant reduction in intensity ratings ($F_{1,38} = 12.1$; $p = 0.001$). In the treatment group, we observed a range of placebo responses: unilateral responders (33.3%), subjects with a placebo response in the conditioned arm only; bilateral responders (33.3%), subjects reporting reduction in the intensity ratings in both arms, and non-responders, whose intensity ratings were not influenced by conditioning. We discuss these responses in terms of different levels of expected analgesia, facilitated by the absence of a site-specific focus for the treatment. We suggest this allowed the individuals suggestibility to influence their assessment of the pain experience by combining different levels of expectation with the information from the actual pain stimulus.

Keywords: Placebo; Expectation; Conditioning; Bayesian statistics; CO_2 laser

1. Introduction

There is an increasing interest in the psychophysiological mechanisms that mediate placebo analgesia. Placebo analgesia is a reduction in pain sensation following the administration of a pharmacologically inert substance in the guise of an analgesic drug. Experimental placebo analgesia has been demonstrated by several groups using expectation and conditioning cues (Voudouris et al., 1985, 1989, 1990;Montgomery and Kirsch, 1996; Montgomery and Kirsch, 1997; Amanzio and Benedetti, 1999; Benedetti et al., 1999; Price et al., 1999; Petrovic and Ingvar, 2002; Wager et al., 2004; Bingel et al., 2006; Zubieta et al., 2006).

The majority of studies used a placebo cream in the guise of a local anaesthetic and specified the area of the body to which the placebo would be applied. Amanzio and Benedetti (1999), Petrovic and Ingvar (2002) and Zubieta et al., 2006, however used a saline injection as a placebo. All of these studies explicitly informed the sub-

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0304-3959/$32.00
doi:10.1016/j.pain.2006.06.021

jects of the placebo's potency as an analgesic. Montgomery and Kirsch (1997), Benedetti et al. (1999) and Bingel et al. (2006) tested other sites on the body, distant from the area to which the placebo cream had been applied. They found a reduction in pain sensation only at the site to which the placebo had been applied, but not at the distant sites. The anatomical specificity of the placebo effect, in this context, may be due to the explicit instructions focusing the subjects' attention on the site of the placebo cream. Legrain et al. (2002), Bentley et al. (2004) and Kulkarni et al. (2005) showed that when attention is not directed to the location of an experimental pain stimulus, neural responses within the pain matrix are altered. If similar changes in neural processing occur during placebo experiments, the expectation of analgesia and therefore placebo responses may also change resulting in less site-specific response. Our current study investigates this possibility by providing ambiguity about the potential site of analgesia.

Using Bayesian inference as an analogy, Wager (2005) suggested that the judgment about pain might result from a balance between two components: (prior) expectation and actual experience (evidence). Placebo analgesia might therefore be regarded as influencing this balance by putting more weight onto the expectation of reduced pain than the evidence. De Pascalis et al. (2002) found that the magnitude of the placebo response was affected by personality traits like suggestibility. They proposed that the individual differences in placebo responses might be due to different levels of expectancy or degree of belief in the treatment, adding support to the expectation or "prior" component of Wager's model.

The aim of the current study was to investigate whether placebo analgesia shows site-specificity even when the instructions regarding the treatment are non-site-specific.

2. Methods

2.1. Subjects

The study was approved by the Local Research Ethics Committee and subjects gave written informed consent. Subjects were randomly assigned to two groups: a treatment group (15 females, 9 males, mean age 23.8 ± 0.77 years) and a control group (7 females, 9 males, mean age 23.8 ± 3.7 years). Subjects who had previously used local anaesthetic creams were excluded from the study.

2.2. Laser stimuli

The radiant heat stimuli were delivered by a continuous wave 50 W CO_2 laser with a computer-modulated pulsed output. Laser pulses of 150 ms duration and with a beam diameter of 15 mm at the skin were delivered at 15 s intervals to a 5×3 cm stimulation area marked on the dorsal surface of each forearm. Stimuli were randomly moved around each stimulation area, in order to minimise sensitisation and/or habituation and possible skin damage. For each stimulation block, 10 laser stimuli were delivered to each arm, alternating between each arm in a pseudo-randomised manner. All subjects wore laser-protective eyewear and earplugs to mask acoustic interference from the laser.

Subjects were trained to rate the intensity of each laser stimulus using a 0–100 scale, where 0 = not at all intense and 100 = extremely intense with verbal anchors for slightly and moderately intense. The scale used was similar to that used previously by Rainville et al. (1992). The laser energies corresponding to each subject's rating of slightly and moderately intense were determined at the start of the study using a series of stimuli of ascending intensities, and were checked for reproducibility. The mean (±standard deviation) laser energy that corresponded to the subjects rating of moderately intense for arm A was 17.2 ± 2.7 mj/mm^2, arm B 17.2 ± 2.4 mj/mm^2 and a rating of slightly intense for arm A 8.9 ± 2.9 mj/mm^2. After each stimulus subjects reported whether it was painful or not by answering with yes or no. Stimuli rated as slightly intense were consistently reported as non-painful heat, whereas those rated as moderately intense were consistently reported as painful heat. These intensities were used in the study (see Experimental design below).

3. Experimental design

3.1. Treatment group

The subjects' forearms were pseudo-randomly labelled A and B. The arm (left or right) that was labelled A or B was counterbalanced across subjects. Arm A was subsequently the side that was conditioned in the treatment group but not in the control group. Subjects in the Treatment group were explicitly told that they may receive a local anaesthetic on one arm, but they were not told which arm. They were also told that inactive cream would be applied to the other arm. In fact, subjects received an inactive cream on both arms. Fig. 1(i and ii) indicates the experimental paradigm and timing sequence of the laser pulses.

The experiment was divided into 3 blocks. The cream was applied in between blocks 1 and 2.

3.1.1. Block 1 (pre-conditioning)

Prior to the application of the cream, subjects received 10 laser stimuli of moderate pain intensity to each arm, randomly alternating between arms. They rated the intensity of each stimulus.

3.1.2. Cream application

Inactive aqueous cream was applied to the entire laser stimulation area on both arms. The cream was applied, covered with an occlusive dressing and left in place for 1 h. Subjects were told that the cream would take effect during this time. The appearance of the cream and the application procedure were the same as those for the

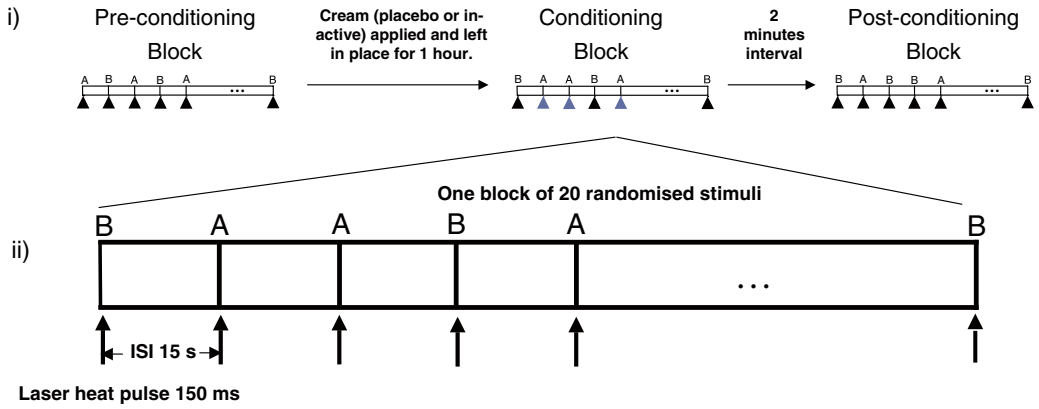

Fig. 1. Schematic of the experimental design. (i) Three experimental blocks for both the treatment and control groups. The pre-conditioning block was identical for both groups; laser heat stimuli were delivered at a moderately intense level. During the conditioning block the intensity of the laser stimulus was reduced on arm A only for the treatment group, the stimulus was not turned down on arm B. The laser heat stimulus remained at the moderately intense level on both arms during the conditioning block for the control group. The post-conditioning block (2 min later) was identical for both groups; laser heat stimuli were delivered at the moderately intense level used in the pre-conditioning block. (ii) In each of the three blocks 20 laser heat stimuli (150 ms) were randomly delivered between arms A and B (10 stimuli to each), with a 15 s inter-stimulus interval (ISI).

commonly used local anaesthetic cream EMLA. After this time, the dressing was removed and the cream wiped off.

3.1.3. Block 2 (placebo conditioning)

The intensity of the laser stimuli delivered to arm A was reduced to each subjects' slightly intense (non-painful) level, whilst those delivered to arm B remained at the moderately intense (painful) level. Subjects were not told that the intensity had been decreased for arm A. They received 10 laser stimuli to each arm, randomly alternating between arms, and rated the intensity of each stimulus.

3.1.4. Block 3 (post-conditioning)

This block was identical to the pre-conditioning block; in that ten moderately intense (painful) laser stimuli were delivered to each arm, randomly alternating between arms, and rated the intensity of each stimulus.

3.1.5. Post-experiment questionnaire

Following the study session, subjects in the treatment group were given a questionnaire adapted from Borkovec and Nau (1972), to determine the success of the conditioning block (i.e. how strongly subjects believed that a local anaesthetic cream had indeed been applied to the skin). Subjects were told that the purpose of the questionnaire was to evaluate the effectiveness of the cream. Each subject was asked the following questions and responded by selecting the appropriate answer:

(1) *"How confident would you be that this treatment would be successful in eliminating the pain associated with, for example a needle injection or having a cannula inserted into a vein in your arm?"*

(2) *"How confident would you be in recommending this treatment to a friend who was extremely anxious about the pain they may feel when they had an injection or a cannula inserted into a vein in their arm?"*Answers to both questions: (1) Not at all confident; (2) Slightly confident; (3) Moderately confident; (4) Very confident; or (5) Totally confident.

(3) *"If you were extremely anxious about the pain when having an injection or cannula inserted, would you be willing to undergo such a treatment?"*Answer: Yes or No.

We ensured that the subjects understood the questions and terminology used in the questions.

3.2. Control group

This group was included to control for the effects of conditioning, expectation (as in Voudouris, 1990), habituation and duration of the experiment on stimulus intensity ratings.

Subjects in the control group were treated in the same way as the treatment group except they were told that an inactive cream would be applied to both arms. In addition, the intensity of the laser stimuli was not turned down during the conditioning period and remained at the subjects' moderately intense (painful) level for all 3 blocks. In each block, 10 laser stimuli were applied to each arm, alternating randomly between arms. Subjects rated the intensity of each stimulus.

3.3. Data analysis

For each subject, the change in intensity rating between the pre and post conditioning blocks for both

arms A and B was calculated. A placebo response was defined as a reduction in a subject's perceived intensity rating during the post-conditioning block (block 3) compared to their rating during the pre-conditioning block (block 1), over and above any difference reported by the control group between the equivalent blocks of stimuli.

For both the control and treatment groups mean and standard deviation stimulus intensity ratings were calculated. Comparisons were made between the control and treatment groups using repeated measures ANOVA. Paired *t*-tests were used to evaluate the change in intensity rating between the three experimental blocks for both the control and treatment groups.

4. Results

ANOVA comparing the stimulus intensity ratings for the pre-conditioning and post-conditioning blocks between the control and treatment groups revealed a significant effect of experimental block ($F_{1,38} = 12.1$; $p = 0.001$) and a group × block interaction ($F_{1,38} = 20.4$; $p < 0.001$). This demonstrates that the change in intensity rating from the pre-conditioning to the post-conditioning block is different between the two groups.

Paired *t*-tests for the control group showed no significant changes in intensity ratings throughout the experiment (Fig. 2a). In the treatment group, stimulus intensity ratings were significantly reduced between the pre-conditioning, conditioning and post-conditioning blocks (Fig. 2b).

In the pre-conditioning block for the treatment group the mean intensity (±standard deviation) ratings for arms A and B were 57.1 ± 18.2 and 56.6 ± 17.2. When the stimulus intensity was turned down for arm A only during the conditioning block the subjects perceived stimulus intensity rating for arm A reduced significantly to 12.8 ± 12.9 ($t(23) = 12.4$, $p < 0.001$). Although the stimulus was not turned down on arm B during the conditioning block there was a significant reduction in intensity rating to 46.5 ± 17.5 ($t(23) = 4.4$, $p < 0.001$).

During the post-conditioning block, when the stimulus intensity was turned back up on arm A to the same level used in the pre-conditioning block, the subjects perceived mean intensity (±standard deviation) ratings for arms A and B were 46.5 ± 19.7 and 50.0 ± 19.0, respectively. Both arms A and B showed a significant reduction in stimulus intensity rating compared to the pre-conditioning block ($t(23) = 6.0$, $p < 0.001$), ($t(23) = 3.6$, $p = 0.001$), respectively. The treatment group shows a placebo response occurring on both arms A and B.

We plotted the difference in intensity ratings between the pre- and post-conditioning blocks for arm A against the change in arm B for all subjects in the control and treatment groups (Fig. 3). The vertical and horizontal lines on the figure define the boundaries of pre-conditioning minus post-conditioning changes reported by the control group. The maximum reduction for arms A and B in the control group was 8 and 7 (on the 0–100 intensity rating scale), respectively.

The resulting four quadrants partition the range of responses observed (Fig. 3). Quadrant 4 encompasses

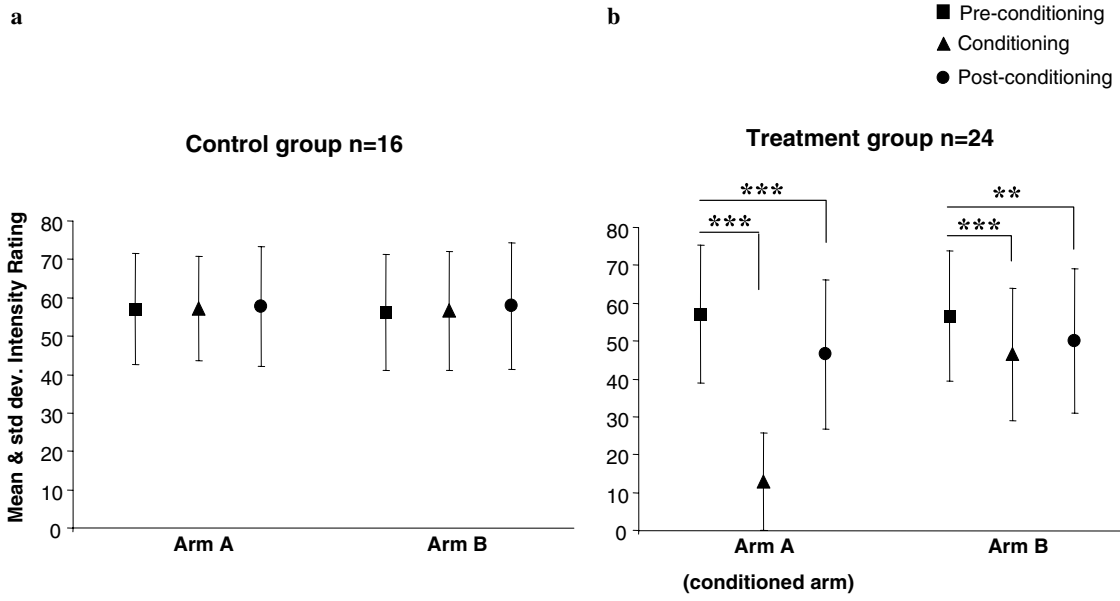

Fig. 2. Mean ± one standard deviation of subjects' stimulus intensity ratings (using a 0–100 numerical scale) during the three experimental blocks. The same laser energy was used in the pre- and post-conditioning blocks, set at each subject's moderately intense level (painful). During conditioning, the laser was turned down on arm A to the subject's slightly intense level (non-painful). $^{**}P < 0.01$, $^{***}P < 0.001$.

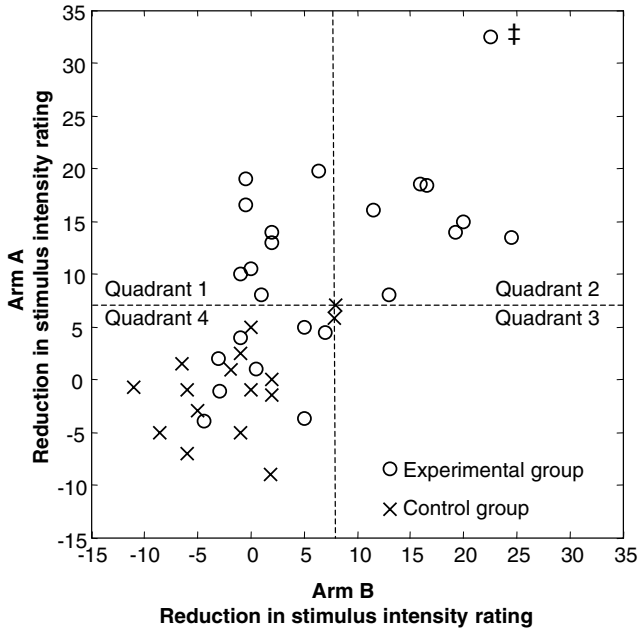

Fig. 3. Reduction in stimulus intensity rating (pre- and post-conditioning) in arm A against arm B. The horizontal and vertical dotted lines mark the extremities of the reduction in intensity reported by the control group. Subjects above the horizontal line reported greater reduction on arm A post conditioning than the control group. Subjects on the right of the vertical line reported greater reduction in arm B. Therefore, quadrant 1 marks a placebo response in arm A only, while quadrant 2 marks a placebo response in both arms. Quadrant 4 contains the controls and the non-responders. Even when subject ‡ was considered an outlier, the results of the statistical analysis were unchanged.

the sixteen subjects in the control group and a subset of eight subjects (33.3%) from the treatment group whose reductions in stimulus intensity did not exceed the reductions in the control group. We identified these subjects as non-placebo responders. Quadrants 1 and 2 show the placebo responders. Quadrant 1 encompasses eight (33.3%) subjects from the treatment group who reported a change in intensity on arm A (conditioned arm) we identified these subjects as unilateral responders. Quadrant two encompasses eight (33.3%) subjects who reported a reduction in both arms A and B. We identified these subjects as bilateral responders. There were no subjects who demonstrated a placebo response on the unconditioned arm B alone (quadrant 3).

The post experiment questionnaire aimed to determine the effectiveness of the conditioning session by establishing how strongly subjects believed that a local anaesthetic cream had been applied to the skin. Fig. 4 shows a breakdown of the answers to questions two and two by the three types of placebo responders (unilateral, bilateral and non-responders) we identified in the treatment group (Fig. 3).

In general, the majority of the bilateral responders were more confident that the 'treatment' would be successful in eliminating the pain, and in recommending the 'treatment' to an anxious friend prior to an injection. Unilateral responders varied between slightly to very confident, while the non-responders were generally less confident that the 'treatment' would be successful.

All twenty-four subjects in the treatment group answered "yes" to whether they would be willing to undergo 'treatment' prior to having an injection. Subjects in the non-responders category reported that the cream was effective in block 2 (during conditioning), but was too short-acting for the effect to persist through the 3rd block (post-conditioning). The bilateral and unilateral responders appear to be more convinced by the conditioning block than the non-responders, with the

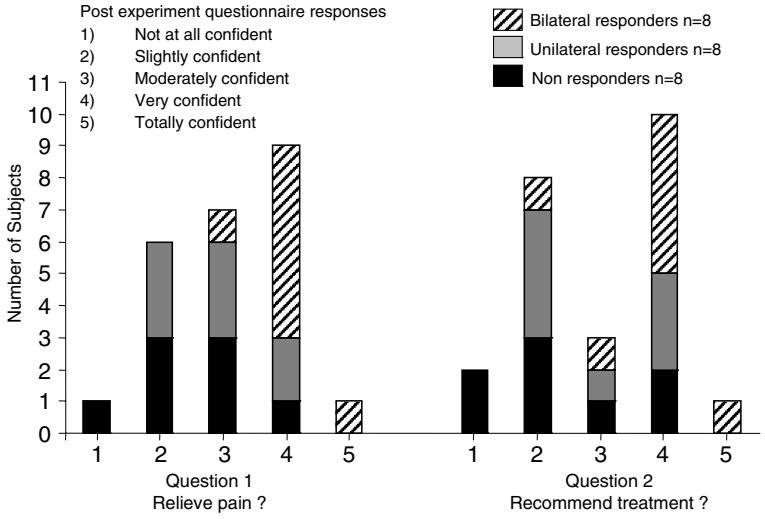

Fig. 4. Responses of the treatment group to the post experiment questions one and two. All twenty-four subjects in treatment group answered 'yes' to question 3. The questions checked the efficacy of the conditioning block. Subjects, including non-placebo responders, believed they received the local anaesthetic treatment.

bilateral responders being influenced most by the conditioning block.

5. Discussion

Previous studies have provided instructions to direct the subject's attention to the stimulus location that may be altered by the application of an inert cream. This results in expectation of analgesia on a specific body site (Voudouris, 1990; Montgomery and Kirsch, 1997; Price, 1999; Price et al., 1999; De Pascalis et al., 2002; Charron et al., 2006). When the instructions regarding the treatment are non-site-specific to the side of potential analgesic effect, as in the current study, a range of placebo responders were identified in the treatment group: non-placebo responders; those with a predominantly unilateral placebo response on the side where the stimulus intensity was turned down; and a group with a substantial bilateral response (Fig. 3).

The post experiment questionnaire was only intended to measure how effective the conditioning block was in generating the belief that subjects had received a local anaesthetic cream. In general, all subjects including all non-responders but one indicated some degree of confidence that a local anaesthetic cream had been applied and believed in the effectiveness of the cream (to varying degrees). However, the results of the questionnaire also suggest that the degree of confidence in the treatment is reflected in the range of placebo responses observed, whereby bilateral responders appear to be most convinced by the experiment, while non-responders are the least convinced.

The results of the unilateral group in the present study are in line with previous studies on experimental placebo response in that significant placebo responses were obtained on the site where the placebo cream was applied followed by conditioning (Voudouris et al., 1985, 1989, 1990; Montgomery and Kirsch, 1996, 1997; Benedetti et al., 1999; Price et al., 1999; Wager et al., 2004; Bingel et al., 2006). In addition, we also identified a group of placebo responders with significant reduction in pain on the sites where the cream was applied in both the conditioned and un-conditioned arms.

Voudouris (1990), Montgomery and Kirsch (1997), Price et al. (1999), Price (1999), De Pascalis et al. (2002), Charron et al. (2006) all asked their subjects to rate expectancy of pain reduction either before or after the administration of a placebo. In these studies, all subjects were told that they would receive an active and potent drug when infact they were given a placebo. The current study involved a degree of ambiguity with regard to the placebo, i.e. subjects may or may not receive a local anaesthetic. Because of this ambiguity we did not explicitly measure the expectation of pain reduction. Asking subjects about their expected reduction in pain intensity prior to stimulus delivery could alter their mind set and hence interfere with the actual expectancy or the perception of the stimulus. Therefore, if a measurement of expectancy is desirable, it would have to be a covert one. Given that the pain stimuli pre- and post-conditioning are physically the same, we would have to conclude that any observed changes in perception can only be modulated by a top-down process. A reduction in anticipation is therefore a likely explanation for such a change in perception (Wager et al., 2004).

The range of responders observed in the current study (Fig. 3) may be explained by reference to theories of machine learning and Bayesian statistics in which decisions (in this case a decision about intensity rating) are made on the basis of a combination of prior expectations and current stimulus experience (Brownstein, 2003; Wager, 2005). The integration of these components will influence the final decision on the intensity of the experience that is reported. On this basis subjects who did not show any reduction in intensity rating beyond the conditioning block could be more consistent with a decision that is more influenced by current experience (intensity of stimulation during and after conditioning) than expectation. On the other hand, subjects who reported intensity reduction in both arms may be more guided by their prior expectation of pain reduction.

The underlying mechanisms of expectancy have been proposed to play a role in placebo analgesia and pain perception (Fields, 2000; Fields and Price, 2005; Wager, 2005). Lorenz et al. (2005) and Koyama et al. (2005) have shown that when subjects are cued to expect a stimulus which they had previously reported as painful to be less painful, they actually perceive it as less painful.

The subjects that showed a reduction in intensity on both arms may have been influenced to a greater extent by expectation or prior information. The laser stimulus was positioned over the subject's arm approximately 5 s prior to each stimulus so it is possible that the subject had prior expectation or anticipation of the impending stimulus. Wager et al. (2004) have shown that placebo analgesia involves a change in expectancy processing. This modulation of expectation may be related to endogenous opioid system activation (Petrovic and Ingvar, 2002; Wager et al., 2004).

This rationale appears to provide a potential explanation for the inter-individual differences in placebo response. It also provides a potential explanation for the differences in site-specificity of placebo effects between our results and those of Benedetti et al. (1999), Montgomery and Kirsch (1996) and Bingel et al. (2006). In the absence of clear instruction as to which arm to expect an analgesic effect there is a well-defined group who will achieve a more expectation-driven non-site specific response (i.e. bilateral response). Whereas in our study there is also a well-defined group

of more experience-driven site-specific placebo responders (unilateral responders) who correspond more closely to the group within the study of Benedetti et al. (1999), Montgomery and Kirsch (1996) and Bingel et al. (2006) who were given site-specific information.

An alternative explanation is that the inter-individual differences are due to the demand characteristics of the experiment, i.e. the bias introduced where the individual reports an effect the experimenter expects them to report. In other words this could just be an effect of subject compliance. This is unlikely, as a preliminary study with a similar design, showing similar variability of bilateral responses, demonstrated that the intensity of pain report correlated with the amplitude of laser-evoked potentials during placebo response (Watson et al., 2005).

If the variability observed in the current study is proven to be reproducible, it may provide a way of establishing the physiological and pharmacological basis of the prior and current information-driven components of the placebo response. This may also have implications for the design of studies of different pharmaceutical agents. In this study, the control and treatment groups were not gender matched although there are reported gender differences in pain threshold and tolerance, there is no evidence of gender difference in placebo response in healthy subjects. However future studies should take into consideration the possibility that such a difference may exist. At present, it is only possible to speculate on the pharmacological basis of the variability of placebo response. Dopamine has been shown to be important in expectation and reward processing (Schultz, 1998, 2001, 2002; Zald et al., 2004) including expectations of therapeutic effect (Fuente-Fernandez and Stoessl, 2002) and may also be involved in the tonic and dynamic regulation of pain (Hagelberg et al., 2002). It is therefore possible that in individuals with more prior information-driven placebo responses (expectation and conditioning), their placebo responses may be more dopamine dependent. However, more current experience-driven placebo responders may be more susceptible to manipulation of the opiate system, which is likely to modulate both nociceptive processing (current experience) and reward. The latter would be consistent with the demonstration of partial naloxone reversibility of the site-specific responders (Benedetti et al., 1999).

This study shows that there are at least two patterns of placebo responses with some subjects showing a site-specific response and other subjects showing a more generalised response. However, when the temporal and spatial components of the responses are examined in individuals there appear to be distinctly different patterns of response that can be attributed to differences in cognitive styles. A better understanding of these different cognitive styles may aid the design of trials of pharmacological interventions that are less susceptible to the variability of placebo response.

Acknowledgements

We are grateful to Professor Fabrizio Benedetti for his comments during the preparation of this manuscript and Andy Vail statistician Research and Development, Salford Royal Hospitals NHS Trust, Salford, Manchester, UK M6 8HD. This work was funded by the Arthritis Research Campaign (ARC).

References

Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci 1999;19:484–94.

Benedetti F, Arduino C, Amanzio M. Somatotopic activation of opoid systems by target directed expectations of analgesia. J Neurosci 1999;19:3639–48.

Bentley DE, Watson A, Treede R-D, Barrett G, Youell PD, Kulkarni B, et al. Differential effects on the laser evoked potential of selectively attending to pain localisation versus pain unpleasantness. Clin Neurophysiol 2004;115:1846–56.

Bingel U, Lorenz J, Schoell E, Weiller C, Buchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 2006;120:8–15.

Borkovec TD, Nau SD. Credibility of analogue therapy rationales. J Behav Ther & Exp Psychiat 1972;3:257–60.

Brownstein AL. Biased predecision processing. Psychol Bull 2003;129:545–68.

Charron J, Rainville P, Marchand S. Direct comparison of placebo effects on clinical and experimental pain. Clin J Pain 2006;22:204–11.

De Pascalis V, Chiaradia C, Carotenuto E. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. Pain 2002;96:393–402.

Fields HL. Pain modulation: expectation, opioid analgesia and virtual pain. Prog Brain Res 2000;122:245–53.

Fields, Price. Placebo analgesia. In: Wall PD, Melzack R, editors. Churchill Livingstone, 2005.

Fuente-Fernandez R, Stoessl AJ. The biochemical bases for reward. Implications for the placebo effect. Eval Health Prof 2002;25:387–98.

Hagelberg N, Martikainen IK, Mansikka H, Hinkka S, Nagren K, Hietala J, et al. Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity 86. Pain 2002;99:273–9.

Koyama T, McHaffie JG, Laurienti PJ, Coghill RC. The subjective experience of pain: where expectations become reality. Proc Natl Acad Sci USA 2005;102:12950–5.

Kulkarni B, Bentley DE, Elliott R, Youell P, Watson A, Derbyshire SW, et al. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur J Neurosci 2005;21:3133–42.

Legrain V, Guerit JM, Bruyer R, Plaghki L. Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. Pain 2002;99:21–39.

Lorenz J, Hauck M, Paur RC, Nakamura Y, Zimmermann R, Bromm B, et al. Cortical correlates of false expectations during pain intensity judgments – a possible manifestation of placebo/nocebo cognitions. Brain Behavior Immun 2005;19:283–95.

Montgomery G, Kirsch I. Mechanisms of placebo pain reduction: an empirical investigation. Psychol Sci 1996;7:174–6.

Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. Pain 1997;72:107–13.

Petrovic P, Ingvar M. Placebo and opioid analgesia imaging a shared neuronal network. Science 2002;295:1737–40.

Price D. Psychological mechanisms of pain and analgesia. IASP Press; 1999.

Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. Pain 1999;83:147–56.

Rainville P, Feine JS, Bushnell MC, Duncan GH. A psychophysical comparison of sensory and affective responses to 4 modalities of experimental pain. Somatosens Motor Res 1992;9:265–77.

Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol 1998;80:1–27.

Schultz W. Reward signaling by dopamine neurons. Neuroscientist 2001;7:293–302.

Schultz W. Getting formal with dopamine and reward. Neuron 2002;36:241–63.

Voudouris NJ. Conditioned response models of placebo phenomena: further support. Pain 1989;38:109–16.

Voudouris NJ. The role of conditioning and verbal expectancy in the placebo response. Pain 1990;43:121–8.

Voudouris NJ, Peck CL, Coleman G. Conditioned placebo responses. J Pers Soc Psychol 1985;48:47–53.

Wager TD. Expectations and anxiety as mediators of placebo effects in pain. Pain 2005;115:225–6.

Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 2004;303:1162–7.

Watson A, Bentley DE, Boyle Y, Jones AKP, Vogt BA. Placebo induced reduction of pain intensity, unpleasantness ratings and laser evoked potentials. IASP, Sydney, Australia, 365-P342. 2005. Ref type: Abstract.

Zald DH, Boileau I, El Dearedy W, Gunn R, McGlone F, Dichter GS, et al. Dopamine transmission in the human striatum during monetary reward tasks. J Neurosci 2004;24:4105–12.

Zubieta JK, Yau WY, Scott DJ, Stohler CS. Belief or need? Accounting for individual variations in the neurochemistry of the placebo effect. Brain Behavior Immun 2006;20:15–26.