Is pain the price of empathy? The perception of others’ pain in patients with congenital insensitivity to pain

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Empathy is a complex form of psychological inference that enables us to understand the personal experience of another person through cognitive/evaluative and affective processes. Recent findings suggest that empathy for pain may involve a ‘mirror-matching’ simulation of the affective and sensory features of others’ pain. Despite such evidence for a shared representation of self and other pain at the neural level, the possible influence of the observer’s own sensitivity to pain upon his perception of others’ pain has not been investigated yet. The aim of this study was to explore how patients with congenital insensitivity to pain (CIP), who are largely deprived of common stimulus-induced pain experiences, perceive the pain of others. Ratings of verbally presented imaginary painful situations showed that CIP patients’ semantic knowledge regarding the pain of others did not differ from control subjects. Moreover, the propensity to infer pain from facial expressions was very similar between CIP patients and control subjects. On the other hand, when asked to rate pain-inducing events seen in video clips in the absence of visible or audible pain-related behaviour, CIP patients showed more variable and significantly lower pain ratings, as well as a reduction in aversive emotional responses, compared with control subjects. Interestingly, pain judgements, inferred either from facial pain expressions or from pain-inducing events, were strongly related to inter-individual differences in emotional empathy among CIP patients, while such correlation between pain judgement and empathy was not found in control subjects. The results suggest that a normal personal experience of pain is not necessarily required for perceiving and feeling empathy for others’ pain. In the absence of functional somatic resonance mechanisms shaped by previous pain experiences, others’ pain might be greatly underestimated, however, especially when emotional cues are lacking, unless the observer is endowed with sufficient empathic abilities to fully acknowledge the suffering experience of others in spite of his own insensitivity.

Keywords: empathy for pain; pain judgement; facial expression of pain; congenital insensitivity to pain

Abbreviations: BEES = Balanced Emotional Empathy Scale; CIP = congenital insensitivity to pain; HSAN = hereditary sensory and autonomic neuropathy; SAM = self-assessment manikin; SPQ = Situational Pain Questionnaire; STEP = Sensitivity to Expressions of Pain


Introduction

Empathy is a complex form of psychological inference that enables us to understand the personal experience of another person through cognitive/evaluative and affective processes (Ickes, 1997; Decety and Jackson, 2004). Research on the mechanisms of empathy in the context of pain has been stimulated by the observation that interpersonal judgements of the severity of pain are often inaccurate (Hodgkins et al., 1985; Prkachin et al., 2001; Marquié et al., 2003), and by acknowledgement that the distress of patients can be considerably increased by such inaccuracy (Morley et al., 2000; Herbette and Rime, 2004). Empathy for pain implies perception and judgement of the other’s pain, as well as
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self-oriented (e.g. distress or anxiety) and other-oriented (e.g. sympathy or compassion) affective responses (Batson, 1991). These components of empathy depend upon both bottom-up processes—driven by stimuli such as the observed person’s facial expressions and contextual pain cues—and on top-down processes, including the observer’s knowledge, learning experiences and beliefs about pain (Goubert et al., 2005).

In agreement with the Perception-Action Model, which postulates that perception of a given behaviour in another individual automatically activates representations of the personal experiences associated with that behaviour in the observer (Preston and de Waal, 2002), recent findings suggest that ‘mirror-matching’ simulation of the affective features of others’ pain might contribute to empathy for pain. Indeed, neuroimaging studies have shown that watching, hearing or imagining other individuals in pain triggers a neural network known to be involved in the affective component of self-pain processing (Morrison et al., 2004; Osaka et al., 2004; Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005, 2006; Saarela et al., 2006). Moreover, explicit inference about the intensity of others’ pain has been shown to be associated with selective embodiment in the observer’s motor system through a somatotopic mapping mechanism (Avenanti et al., 2005). Such evidence for a shared representation of sensory and affective aspects of self and others’ pain at the neural level raises the possibility that the observer’s own sensitivity to pain might in part shape his perception and affective responses to the pain of others. Previous behavioural studies have demonstrated that judgement of the severity of others’ pain can be biased by certain experiential influences (Prkachin et al., 2001), but the influence of the observer’s own sensitivity to pain upon his perception of others’ pain has yet to be investigated systematically.

Patients with congenital insensitivity to pain (CIP) offer a unique opportunity to explore the role of self-pain experience upon the perception of others’ pain. CIP is a rare clinical syndrome characterized by dramatic impairment of pain perception since birth, generally caused by an hereditary sensory and autonomic neuropathy (HSAN) involving the small-calibre nerve fibres, which normally transmit nociceptive inputs along sensory nerves (for a recent review, see Nagasako et al., 2003). Here, we used three different paradigms to explore whether CIP patients with diffuse sensory loss for pain differed from healthy controls in their judgements and affective responses to the pain of others. In a first experiment, participants were asked to estimate the level of self and others’ pain in a number of different imaginary situations, allowing quantitative evaluation of semantic knowledge about the pain of others. A second experiment evaluated participants’ pain ratings and affective responses to the view of various pain-inducing events seen on video clips. The ability of CIP patients and control subjects to infer the intensity of others’ pain from their facial expressions was assessed in a third experiment. Finally, the emotional empathy trait of CIP patients and control subjects was measured to explore whether the perception of others’ pain could be related to inter-individual differences in the ability to empathize.

Material and methods

Patients and controls

The study included 12 patients from 7 families (5 males, 7 females; mean age: 29.8 years, range: 16–50; mean education: 13.5 years, range: 9–18) with a diffuse form of CIP, presumably caused by an HSAN. The familial situation, social interactions and educational or professional status of the CIP patients included in this study did not differ from the general population (see Table 1). Inclusion criteria were (i) marked sensory loss for pain of congenital onset, affecting all the body (i.e. the four limbs, trunk and face) and (ii) age >15 years. Exclusion criteria were (i) mental retardation (which may be associated with certain types of HSAN) and (ii) a history of psychiatric disorder. All patients had a typical history of painless injuries from early childhood (see Table 1). A familial incidence was found in all cases, with autosomal recessive transmission in four families (six cases) and autosomal dominant transmission in the three other families (six cases). Self-mutilation during infancy or childhood had led to early diagnosis of CIP in five cases, while the diagnosis was established only at adult age in the seven other cases, despite evident lack of pain-related behaviour or complaint from birth at retrospective investigation. Although they showed a dramatic reduction of stimulus-induced pain, all the patients could still experience pain on some occasions, such as spontaneous electrical discharges or migraine attacks (see Table 1). The fact that CIP patients can experience pain despite marked sensory loss for pain has been previously documented (Dyck, 1993), and there are indeed several reports in the literature of CIP patients suffering headache or other stimulus-independent pain that may be of central origin (Dearborn, 1932; Jewesbury, 1951; Cohen et al., 1955; Magee et al., 1961; Comings and Amromin, 1974; Danziger and Willer, 2005).

All patients showed a complete lack of discomfort, grimacing or withdrawal reaction to prolonged pinpricks, strong pressure, soft tissue pinching and noxious thermal stimuli (0 and 50°C) applied to the proximal and distal parts of the four limbs and to the face. Warm and cold perceptions were impaired in six cases. Corneal reflex was absent in all cases. Other neurological impairments included mild autonomic dysfunction (four cases), anosmia (five cases) and aquaesia (one case). Muscle tone, power and coordination were normal in all patients, as were tendon reflexes and plantar responses. Light touch (static and dynamic) and vibration were felt normally by all patients. Postural sense, stereognosis and two-point discrimination were also normal in all cases. Nerve conduction study was normal in the nine cases examined. Additional neurophysiological investigations, including sympathetic skin response (three cases), nociceptive flexion reflex (six cases) and flare response to capsaicin (seven cases), showed marked impairment of small-calibre sensory nerve fibres in six patients, while a biopsy of the superficial peroneal nerve demonstrated nerve fibre degeneration in two other cases (see Table 1). Such heterogeneity in terms of severity, mode of inheritance, time of diagnosis and associated neurological dysfunction mirrors the variety of HSAN phenotypes reported in the literature. At present, five types of HSANs with different underlying genetic abnormalities have been identified as potential causes of CIP (Dyck, 1993; Thomas, 1993; Nagasako et al., 2003; Verpoorten et al., 2006). Although the lack of neuropathological and genetic data
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, gender</th>
<th>Genetic</th>
<th>Time of diagnosis</th>
<th>Major painless noxious events</th>
<th>Amount of experience in hospitals</th>
<th>Other neurological dysfunction</th>
<th>Residual pain experiences</th>
<th>Neurophysiology/nerve biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (YA)</td>
<td>32, F</td>
<td>12, shop assistant</td>
<td>R (pc) Infancy</td>
<td>Wounds, burns, bone fractures, deliveries</td>
<td>++</td>
<td>Impaired warm and cold perception, recurrent episodes of hyperthermia, anosmia, corneal reflex absent</td>
<td>A single episode of tension-type headache</td>
<td>NCS: normal; SSR: normal; RIII reflex threshold: greatly increased; flare response to capsaicin: absent</td>
</tr>
<tr>
<td>2 (EB)</td>
<td>50, F</td>
<td>12, shop assistant</td>
<td>D Adult</td>
<td>Wounds, burns, bone fractures, deliveries</td>
<td>++</td>
<td>Impaired warm and cold perception, recurrent episodes of hyperthermia, anosmia, corneal reflex absent</td>
<td>Occasional acute migraine attacks (3/year)</td>
<td>NCS: normal; SSR: normal; RIII reflex threshold: greatly increased; flare response to capsaicin: absent</td>
</tr>
<tr>
<td>3 (TA)</td>
<td>24, F</td>
<td>15, accountant</td>
<td>D Childhood</td>
<td>Wounds, burns, bone fractures</td>
<td>+++</td>
<td>Impaired warm and cold perception, recurrent episodes of hyperthermia, anosmia, corneal reflex absent</td>
<td>Occasional spontaneous electrical discharges</td>
<td>NCS: normal; RIII reflex threshold: greatly increased; flare response to capsaicin: greatly reduced</td>
</tr>
<tr>
<td>4 (DG)</td>
<td>20, M</td>
<td>15, engineer school</td>
<td>R Infancy</td>
<td>Wounds, burns, cellulitis, bone fractures, osteomyelitis</td>
<td>++</td>
<td>Impaired warm and cold perception, anosmia, corneal reflex absent</td>
<td>Low back pain when febrile</td>
<td>NCS: normal; flare response to capsaicin: greatly reduced</td>
</tr>
<tr>
<td>5 (AG)</td>
<td>16, F</td>
<td>11, high school</td>
<td>R Infancy</td>
<td>Wounds, burns, bone fractures</td>
<td>++</td>
<td>Abdominal pain when febrile</td>
<td>Occasional joint and muscular pain induced by cold weather, pain when teeth are drilled</td>
<td>NCS: normal; flare response to capsaicin: absent</td>
</tr>
<tr>
<td>6 (NH)</td>
<td>26, M</td>
<td>9, clerk</td>
<td>R (pc) Infancy</td>
<td>Wounds, burns, bone fractures</td>
<td>+++</td>
<td>Abdominal pain when febrile</td>
<td>Occasional spontaneous electrical discharges</td>
<td>NCS: normal; flare response to capsaicin: greatly reduced</td>
</tr>
</tbody>
</table>

Table 1: Main clinical and neurophysiological features of the 12 CIP patients
<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age, gender</th>
<th>Educ. (years) studies or profession</th>
<th>Genetic</th>
<th>Time of diagnosis</th>
<th>Major painless noxious events</th>
<th>Amount of experience in hospitals</th>
<th>Residual pain experiences</th>
<th>Other neurological dysfunction</th>
<th>Neurophysiology/nerve biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>7§ (FH)</td>
<td>27, F</td>
<td>9, sewing</td>
<td>R (pc)</td>
<td>Childhood (self-mutil)</td>
<td>Wounds, burns, corneal ulcers, dental abscess, osteochondritis, osteomyelitis</td>
<td>++</td>
<td>Low back pain during menstruations; occasional spontaneous electrical discharges</td>
<td>Impaired warm and cold perception, reduced lacrimation, anosmia, corneal reflex absent</td>
<td>NCS: normal; nerve biopsy; marked reduction of the number of large myelinated fibres with localized thickening of myelin sheaths</td>
</tr>
<tr>
<td>8 (SD)</td>
<td>48, F</td>
<td>17, consultant</td>
<td>R</td>
<td>Adult</td>
<td>Burns, bone fractures, cystitis, teeth extraction without anaesthesia</td>
<td>+</td>
<td>Occasional spontaneous pain at bone fracture sites, induced by humidity</td>
<td>Corneal reflex absent</td>
<td>NCS: normal; SSR: normal; nociceptive RIII reflex threshold: normal; flare response to capsaicin: normal</td>
</tr>
<tr>
<td>9* (MP)</td>
<td>24, M</td>
<td>18, medical school</td>
<td>D</td>
<td>Adult</td>
<td>Wounds, burns, bone fractures, joint strain, torsion of the testicle</td>
<td>+</td>
<td>Migraine attacks (~1/month)</td>
<td>Corneal reflex absent</td>
<td>NCS: normal; RIII reflex threshold: increased; flare response to capsaicin: absent</td>
</tr>
<tr>
<td>10* (GP)</td>
<td>24, M</td>
<td>17, engineer</td>
<td>D</td>
<td>Adult</td>
<td>Burns, wounds, joint strain, bone fractures, teeth extraction without anaesthesia</td>
<td>+</td>
<td>Mild pain when alcohol is applied on a wound</td>
<td>Corneal reflex absent</td>
<td>Not explored</td>
</tr>
<tr>
<td>11* (TP)</td>
<td>18, M</td>
<td>13, engineer school</td>
<td>D</td>
<td>Adult</td>
<td>Burns, wounds, bone fractures</td>
<td>+</td>
<td>Mild pain caused by strong impact when playing rugby</td>
<td>Corneal reflex absent</td>
<td>Not explored</td>
</tr>
<tr>
<td>12* (AP)</td>
<td>49, F</td>
<td>9, hairdresser</td>
<td>D</td>
<td>Adult</td>
<td>Burns, wounds, deliveries, gingival surgery without anaesthesia</td>
<td>+</td>
<td>Migraine attacks (~2/month) occasional low back pain</td>
<td>Corneal reflex absent</td>
<td>Not explored</td>
</tr>
</tbody>
</table>

#§ and * denote members of the same family; subjects no. 9 and 10 are monozygotic twins. educ: years of education; R: recessive; D: dominant; pc: parental consanguinity; self-mutil: self-mutilation; NCS: nerve conduction study; SSR: sympathetic skin responses. Methods for recording the RIII nociceptive flexion reflex and response to capsaicin are described in Danziger and Willer (2005).
precludes a definitive classification of our patients, early onset, lack of severe dyssautonomia and preserved sweating argue against HSAN types I, III and IV, respectively.

Control subjects (n = 286, mean age: 21.8 years, range: 18–60) were healthy undergraduate university students with no history of psychiatric disorder. To eliminate bias due to the gender, the male : female ratio (5 : 7) was the same in CIP and control groups in all experiments. Indeed, several studies have demonstrated a gender bias in judgment about others’ pain (Robinson and Wise, 2003), ability to detect facial pain expressions (Prkachin et al., 2004), emotional response to affective pictures (Brody, 1993; Lang et al., 1993) and the trait of emotional empathy (Mehrabian et al., 1988). Ninety-six controls (40 males, 56 females) completed the Situational Pain Questionnaire (SPQ) (experiment 1), 132 controls (55 males, 77 females) rated the pain-inducing events seen on video clips (experiment 2), 120 controls (50 males, 70 females) completed the Sensitivity to Expressions of Pain (STEP) Test (experiment 3) and 36 controls (15 males, 21 females) completed the Balanced Emotional Empathy Scale (BEES).

Patients and controls gave informed written consent, and the study was approved by the local Ethics Committee (Paris VI University) and conducted in accordance with the Declaration of Helsinki.

**Situational Pain Questionnaire**

To evaluate how CIP patients estimate their own pain sensitivity and the pain sensitivity of others, a French translation of the SPQ 30-Item Version (Clark and Yang, 1983) was used. The SPQ assesses the amount of stimulus-induced pain individuals think they would experience in a number of different imaginary situations involving various body regions. The questionnaire consists of 15 events that are considered to be relatively painful (signals) and 15 non-painful events (blanks). Items are rated by using a verbal scale of 1 not noticeable to 10 worst possible pain. Examples of painful items include ‘I get a tooth drilled without a pain killer’ and ‘I spill some boiling water on my hand.’ Examples of non-painful items include ‘I get out of breath trying to catch a bus’ and ‘I get a mosquito bite.’ Participants completed two versions of the SPQ on the same sheet: one version regarding their own pain sensations (SPQself), and another version regarding the pain sensations they think would correspond to the point on the subject’s rating scale at which, by interpolation, the sum of the hit and false alarm probabilities equals 1.0 \((P(S|s) + P(S|n) = 1)\); that is, the median response category) and indicates the degree to which the situations are considered as painful. The discrimination score \(B\) was computed by using the following steps: (i) find \(P(S|s) + P(S|n)\) for each response category; (ii) find the category for which that sum is \(\approx 1\); \(C_i\) is the size of the lower category in category units; (iii) compute \(B\) using the formula

\[
B = \frac{1 - \frac{1}{[P_f(S|s) + P_f(S|n)] - [P_f(S|s) + P_f(S|n) - C_i]}}
\]

Note that category values are reversed for this analysis in such a manner that the less painful the situations are considered, the higher the \(B\) score.

The discrimination scores will be termed \(P(A)_\text{self}\) and \(P(A)_\text{other}\) and the response bias scores will be termed \(B_{\text{self}}\) and \(B_{\text{other}}\) for ‘self’ and ‘other’ versions of the SPQ, respectively. Discrimination and response bias scores were compared between groups.

**Pain ratings and affective responses to the observation of pain-inducing events**

To assess how CIP patients estimate the amount of pain experienced by others during various pain-inducing events and to evaluate their affective responses to the observation of others’ pain, 22 video clips (duration: 5–15 s) showing individuals undergoing an injury were presented to the participants. Eighteen of these video clips were selected from the ‘Accident’ and ‘Injury’ categories of the web site ‘Stupidvideos.com’. Pain-inducing events ranged from very low to very high pain intensity and included different types of noxious stimuli—with a majority of falls—affecting various body regions (see Table 2). Most importantly, the pain-related behaviours of the injured individuals (including their facial expressions) were not visible or audible on the video clips. Participants estimated the amount of pain experienced by the injured individuals by using the same verbal scale as for the SPQ, ranging from 1 not noticeable to 10 worst possible pain. Participants also rated their affective response to the view of the pain-inducing events, using the self-assessment manikin (SAM) scales for valence and arousal (Lang, 1980). The valence scale shows SAM smiling at one extreme (1: most pleasant or funny), frowning at the other (9: most unpleasant or sad) and displaying a neutral expression in the middle (5: neutral). The arousal scale shows SAM completely calm at one extreme (1: no arousal) and strongly excited at the other (9: maximal arousal).

To avoid building up artificial correlations between pain and affective ratings, pain judgements and affective responses were assessed separately during two successive presentations of the whole 22-sequence set. During the first presentation, participants were asked to rate valence and arousal for each video clip, by making a mark on or between the SAM figures. During the second presentation, participants were asked to rate on a separate sheet the amount of pain they thought the injured person had experienced at the moment of injury. This order of rating was chosen because pilot experiments had suggested that the emotional impact of pain-inducing events could decrease at second view, while pain judgements did not seem to be significantly modified by repetition. Three pre-test video clips showing slight pain, moderate pain and high pain-inducing events, served as practice stimuli before the 22-sequence set began. The rating period was 15 s, allowing ample time for rating.
Different categories of video clips were defined according to the mean pain and valence ratings of the control group: ‘high pain’ videos (mean pain score > 6; n = 12); ‘low pain’ videos (mean pain score < 6; n = 10); ‘positive’ (i.e. pleasant or funny) videos (mean valence score > 5; n = 9) and ‘negative’ (i.e. unpleasant or sad) videos (mean valence score < 5; n = 13). Comparison between patients’ and controls’ pain ratings was performed (i) by computing the algebraic sum of the pain ratings of the 22 videos (TOTAL pain score); (ii) by computing the algebraic sum of the pain ratings separately for the 12 ‘high pain’ and the 10 ‘low pain’ videos (HIGH pain score and LOW pain score, respectively); and (iii) for each video separately. Comparison between patients’ and controls’ valence ratings was performed (i) by computing the algebraic sum of the valence ratings of the 22 videos (TOTAL valence score); (ii) by computing the algebraic sum of the valence ratings separately for the 9 ‘positive’ and the 13 ‘negative’ videos (POSITIVE valence score and NEGATIVE valence score, respectively); and (iii) for each video separately. As it made obviously no sense to compare arousal ratings associated with opposite affective valences, comparison between patients’ and controls’ arousal ratings was restricted to the videos (n = 7) that were considered as negative (valence < 5) by all patients and by >95% of control subjects. The arousal score was obtained by computing the algebraic sum of the arousal ratings of these seven videos.

**Sensitivity to Expressions of Pain Test**

Facial expressions of pain, which are socially the most prominent pain-related behaviour (Prkachin et al., 1983; Craig et al., 2001), consist primarily of four actions: brow lowering, orbit tightening (which narrows the eye apertures and raises the cheeks), levator tightening (which raises the upper lip, deepens the nasolabial furrow or may produce wrinkles at the side of the nose) and eye closure (Prkachin, 1992; Craig et al., 2001). Previous studies have shown that these actions are graded in intensity (Prkachin and Mercer, 1989) and convey evidence of the subjective intensity of pain experience (Prkachin et al., 1994). The ability of CIP patients to estimate the intensity of the pain of others from their facial expressions was assessed using the STEP Test (Prkachin, 2004). Participants viewed videotaped excerpts of the facial expressions of patients undergoing assessment of their shoulder injuries by active and passive range of motion tests. The excerpts were sampled from records taken in a previous study (Prkachin and Mercer, 1989), which had been coded for the amount of pain expression using Ekman and Friesen’s (1978) Facial Action Coding System.
Each of the four actions described above, with the exception of eye closure, can be graded on an intensity scale ranging from 'A' (a trace of the action) to 'E' (the action occurs at maximum intensity). For the purposes of assembling the STEP Test, the action 'eye closure' was excluded, as its occurrence is obvious. Excerpts were designated as displaying strong pain if at least one of the actions they contained received an intensity score of 'D' or 'E'. Excerpts were designated as displaying moderate pain if they contained a pain-related action that received an intensity score of 'B' or 'C'. Sixty 1-s-long filmed sequences were randomly divided into 20 depicting no pain, 20 depicting strong pain and 20 depicting moderate pain. Participants were asked to determine whether the sequence depicted 'no pain' (score 0), 'moderate pain' (score 1) or 'strong pain' (score 2). Three pre-test sequences served as practice stimuli before the 60-sequence set began. Answers were scored using a computerized scoring system based on a model of non-parametric sensory detection theory, which provided three scores for discrimination [P(A)] and three scores for response bias (B); between 'no pain' and 'strong pain' expressions [P(A)MS and BMS]; between 'no pain' and 'moderate pain' expressions [P(A)MM and BM]; and between 'moderate pain' and 'strong pain' expressions [P(A)MS and BM]. P(A) and B values were calculated in similar manner as those for the SPQ. In addition, the mean of these three discrimination scores and the mean of these three response bias scores [P(A)MEAN and BMEAN, respectively] were computed for each participant. The discrimination scores P(A) indicate the extent to which subjects are able to differentiate between different intensities of facial expressions and may vary between 0 and 1. A score of 0.5 is equivalent to chance and means no discrimination at all, while a score of 1.0 means perfect discrimination. The response bias scores B correspond to the point on the subject's rating scale at which, by interpolation, the sum of his/her responses to all 15 of the positively worded items and by subtracting from this quantity the algebraic sum of his/her responses to all 15 of the negatively worded items (Mehrabian, 1997).

**Balanced Emotional Empathy Scale**

To study whether the ratings of CIP patients and of control subjects were related to their general tendency to feel and vicariously experience the affective experiences of others, the participants’ emotional empathy trait was measured using a French translation of the full-length (30-item) BEES (Mehrabian, 1997). Participants used a 9-point agreement–disagreement scale to report the degree of their agreement or disagreement with each item. Examples of positively worded items include ‘The sadness of a close one easily rubs off on me’ and ‘I can almost feel the pain of elderly people who are weak and must struggle to move about.’ Examples of negatively worded items include ‘I cannot feel much sorrow for those who are responsible for their own misery’ and ‘The unhappiness or distress of a stranger are not especially moving for me.’ It may be noted that no item of the BEES assessed empathy for the physical pain of others. The total BEES score of each participant was computed by algebraically summing his/her responses to all 15 of the positively worded items and by subtracting from this quantity the algebraic sum of his/her responses to all 15 of the negatively worded items (Mehrabian, 1997).

**Data analysis**

Results are presented as mean ± standard deviation. Considering the small size of the CIP group (n = 12), all statistical comparisons between patients and controls were performed with a non-parametric test (Mann–Whitney U-test). Hartley’s test was employed to test homogeneity of variances between groups. Spearman correlation analysis was performed to study all possible correlations between BMEAN, pain, valence and arousal scores, BMEAN and total BEES score. Correlations between these scores and age or education level were also searched systematically, without any positive result. In addition to these quantitative data, noteworthy spontaneous reactions observed during the experiments as well as significant remarks made by patients during the following interview were recorded (see Discussion).

**Results**

**Ratings of imaginary situations**

As expected, CIP patients clearly differed from control subjects in their estimation of self-pain sensations on the ‘self’ version of the SPQ. Indeed, CIP patients showed a much lower discrimination score than controls [P(A)self = 0.70 ± 0.15 versus 0.92 ± 0.05 in controls, U = 48, P < 0.0001] (Fig. 1A), indicating that they were far less able to differentiate between painful and relatively non-painful situations. CIP patients also showed a much higher response bias score than controls (BMEAN = 8.32 ± 0.69 versus 6.04 ± 1.17 in controls, U = 47.5, P < 0.0001) (Fig. 1C), indicating that they were far less likely to consider imaginary painful stimuli as painful.

In contrast with these abnormal ratings regarding self-pain sensations, CIP patients did not differ from controls in their estimation of the pain of others. Indeed, P(A)other and Bother were not significantly different in CIP and control groups [P(A)other = 0.91 ± 0.05 in CIP patients versus 0.90 ± 0.05 in control subjects, U = 436, P = 0.2 (Fig. 1B); Bother = 6.20 ± 1.20 in CIP patients versus 5.91 ± 1.03 in control subjects, U = 487, P = 0.4 (Fig. 1D)].

**Pain ratings and affective responses to the observation of pain-inducing events**

**Pain ratings**

Pain ratings varied much more among CIP patients than among control subjects (Fig. 2), in such a manner that the variance of the TOTAL, LOW and HIGH pain scores was significantly higher in the CIP group than in the control group (P = 0.003, 0.02 and 0.003, respectively, Hartley’s test). Five patients (Cases 3, 4, 7, 10, 12) showed exceptionally low pain scores compared with control subjects (<5th percentile), while two patients (Cases 2 and 6) displayed on the contrary exceptionally high pain scores (>95th percentile) (see Fig. 2). Overall, the pain scores were lower in the CIP group than in the control group. Statistical analysis showed that this difference was close to significance when all videos were considered together (TOTAL pain score = 118.7 ± 27.8 in the CIP group versus 133.9 ± 12.8 in the control group, U = 538.5, P = 0.06), not significant when only ‘low pain’ videos
were considered (LOW pain score = 37.7 ± 14.0 in the CIP group versus 43.7 ± 7.9 in the control group, \( U = 626, P = 0.2 \)) and very significant when only 'high pain' videos were considered (HIGH pain score = 81.1 ± 15.0 in the CIP group versus 90.1 ± 6.8 in the control group, \( U = 439.5, P = 0.01 \)). Separate analysis of pain scores for each video clip showed that CIP patients underestimated significantly the level of pain evoked by 8 of the 22 pain-inducing events, compared with control subjects (see Table 2). Even when the differences were not significant, in all instances but two, patients gave lower ratings than controls.

**Valence and arousal ratings**

The TOTAL valence score was very similar in CIP and control groups (132.0 ± 14.4 in the CIP group versus 132.6 ± 13.2 in the control group, \( U = 780, P = 0.9 \)). Separate analysis of the valence scores for 'positive' and 'negative' videos, however, revealed significant differences between CIP and control groups (Fig. 3A). Indeed, CIP patients considered the 'positive' videos as more unpleasant than control subjects (POSITIVE valence score = 44.7 ± 7.4 in the CIP group versus 39.4 ± 8.0 in the control group, \( U = 486.5, P = 0.03 \)), while they considered the 'negative' videos as less unpleasant than control subjects (NEGATIVE valence score = 87.2 ± 9.0 in the CIP group versus 93.1 ± 9.3 in the control group, \( U = 514, P = 0.04 \)). Thus, the difference between valence ratings for 'negative' and 'positive' videos (NEGATIVE valence score minus POSITIVE valence score) was significantly lower in the CIP group than in the control group (\( U = 313.5, P = 0.0005 \)). Separate analysis of valence ratings for each video clip showed that CIP patients underestimated significantly the unpleasantness of three videos, while they overestimated the unpleasantness of one other video, compared with control subjects (see Table 2).

The arousal score was significantly lower in the CIP group than in the control group (35.1 ± 8.1 versus 43.4 ± 9.5, \( U = 377.5, P = 0.003 \)) (Fig. 3B). Moreover, separate analysis of arousal ratings for each video clip showed that CIP patients displayed significantly less arousal than control subjects for five of the seven videos selected (see Table 2).

Overall, a significant correlation was found between pain and valence ratings (22 video clips) in the CIP group (\( n = 264, r = 0.59, P < 0.0001 \)), as well as in the control group.
A significant correlation was also found between pain and arousal ratings (seven video clips), both in the CIP group \( (n = 84, r = 0.40, P = 0.0001) \) and in the control group \( (n = 924, r = 0.36, P < 0.0001) \). Note that these correlation coefficients were very similar between CIP and control groups.

**Sensitivity to facial pain expressions**

Overall, CIP patients’ ratings of the facial pain expressions were very similar to those of controls, whatever the intensities of pain compared (Table 3), suggesting that CIP patients were as able as controls to distinguish the different intensities of the facial pain expressions included in the STEP Test. Moreover, CIP patients and controls showed very similar response bias scores, whatever the intensities of pain compared (Table 3), indicating that the two groups did not differ in their tendency to infer pain from facial expressions.

Correlation analysis showed a strong correlation between the TOTAL pain score and the STEP Test mean response bias score \( (B_{\text{MEAN}}) \) in the CIP group \( (n = 12, r = 0.80, P = 0.008) \). This means that the pain scores attributed by CIP patients to the pain-inducing events seen in video clips were closely related to their propensity to infer pain from the facial pain expressions included in the STEP Test. In the control group, on the other hand, no correlation was found between the TOTAL pain score and the STEP Test mean response bias score \( (B_{\text{MEAN}}) \) \( (n = 26, r = 0.16, P = 0.4) \).

**Emotional empathy score**

No significant difference in emotional empathy (BEES) score was found between CIP and control groups \( (47.4 \pm 30.8 \text{ versus } 36.2 \pm 31.7, U = 180.5, P = 0.4) \). Within the CIP group, the BEES score was strongly correlated to the STEP Test mean response bias score \( (B_{\text{MEAN}}) \) \( (n = 12, r = 0.68, P = 0.02) \) (Fig. 4B) and to the TOTAL pain score \( (n = 12; r = 0.77, P = 0.01) \) (Fig. 4D). Thus, the propensities to infer pain from facial pain expressions and to rate pain-inducing events as painful were both related to the emotional empathy trait in the CIP group.

In the control group, on the other hand, no correlation was found between BEES and STEP Test \( B_{\text{MEAN}} \) scores \( (n = 32, r = -0.26, P = 0.1) \) (Fig. 4A), nor between...
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Table 3 Sensitivity to facial expressions of pain (STEP Test)

<table>
<thead>
<tr>
<th>Score</th>
<th>Controls</th>
<th>Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discrimination scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(A)_{NM}</td>
<td>0.76 ± 0.08</td>
<td>0.78 ± 0.09</td>
<td>0.5</td>
</tr>
<tr>
<td>P(A)_{MS}</td>
<td>0.82 ± 0.06</td>
<td>0.81 ± 0.07</td>
<td>0.5</td>
</tr>
<tr>
<td>P(A)_{NS}</td>
<td>0.95 ± 0.04</td>
<td>0.97 ± 0.03</td>
<td>0.2</td>
</tr>
<tr>
<td>P(A)_{MEAN}</td>
<td>0.84 ± 0.04</td>
<td>0.85 ± 0.04</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Response bias scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b_{NM}</td>
<td>1.10 ± 0.41</td>
<td>0.94 ± 0.27</td>
<td>0.3</td>
</tr>
<tr>
<td>b_{MS}</td>
<td>1.71 ± 0.26</td>
<td>1.74 ± 0.35</td>
<td>0.7</td>
</tr>
<tr>
<td>b_{NS}</td>
<td>1.29 ± 0.23</td>
<td>1.31 ± 0.32</td>
<td>0.8</td>
</tr>
<tr>
<td>b_{MEAN}</td>
<td>1.36 ± 0.22</td>
<td>1.33 ± 0.30</td>
<td>0.8</td>
</tr>
</tbody>
</table>

The discrimination scores, P(A), indicate the extent to which subjects were able to differentiate facial expressions, while the response bias scores, B, indicate their tendency to infer pain from the facial expressions. Three discrimination scores and three response bias scores were computed: NM = between ‘no pain’ and ‘moderate pain’ expressions; MS = between ‘moderate pain’ and ‘strong pain’ expressions; NS = between ‘no pain’ and ‘strong pain’ expressions. In addition, the mean of the three discrimination scores [P(A)_{MEAN}] and the mean of the three response bias scores [b_{MEAN}] were computed for each participant. The lack of significant difference between CIP and control groups for all the computed scores (Mann–Whitney U-test) is worth noting.

BEES and TOTAL pain scores (n = 36; r = 0.11, P = 0.5) (Fig. 4C).

Finally, no significant correlation was found between the BEES score and valence or arousal scores, either in the CIP group or in the control group.

Discussion

Summary of results

The aim of this study was to explore how patients who are largely deprived of common stimulus-induced pain experiences perceive the pain of others. Ratings of verbally presented imaginary painful situations showed that CIP patients’ semantic knowledge regarding the pain of others did not differ from control subjects. Moreover, the propensity to infer pain from facial expressions was very similar between CIP patients and control subjects. On the other hand, when asked to rate pain-inducing events seen in video clips without any visible or audible pain-related behaviour, CIP patients showed more variable and significantly lower pain ratings, as well as a reduction in aversive emotional responses, compared with control subjects. Interestingly, pain judgements, inferred either from facial pain expressions or from pain-inducing events, were strongly related to inter-individual differences in emotional empathy among CIP patients, while such correlation between pain judgement and empathy was not found in control subjects.

Semantic knowledge regarding other’s pain

The semantic difficulties in discussing pain with patients who have only little and atypical experience of it has been underlined previously by several authors (Magee et al., 1961; Thrush, 1973; Losa et al., 1989). For example, patients with CIP may adopt the same pain language as normal people to avoid being regarded as ‘strange’ or ‘abnormal’ (Thrush, 1973; Losa et al., 1989). Moreover, the learning of cues indicating potential damage (e.g. the sensation of warmth as a signal for a risk of severe burn) can lead some CIP patients to rate painless but threatening stimuli as ‘painful’. Such inevitable sources of confusion in communication about pain experiences could have biased CIP patients’ answers to the SPQ. However, the scores computed from patients’ ‘self’ and ‘other’ ratings suggested that, on the
whole, no major confusion had occurred about the signification of the word ‘pain’ and of the scaled descriptors used in this experiment. Indeed, in CIP patients the pattern of responses regarding self-pain attested to their great reduction of stimulus-induced pain sensitivity, already inferred from history and clinical examination. Moreover, the finding of similar discrimination and response bias scores between CIP and control groups regarding the pain of others suggested that CIP patients had managed to have access to a shared semantic knowledge about the level of others’ pain, despite the considerable impairment of their own experience of pain. One can suppose that the good intellectual capacities and relatively high level of education of this particular group of CIP patients might have contributed to such accuracy in judgement of verbally presented pain-inducing situations. The persistence of some residual personal experiences of pain might also have helped these CIP patients to build their knowledge from the observation of others’ pain-related behaviour in everyday life.

Judgements of pain-inducing events seen in video clips
In contrast with this intact ability to estimate others’ pain from verbally presented imaginary situations, CIP patients clearly differed from controls in their judgements of pain-inducing events seen in video clips. First, a dramatic increase of the inter-individual variability in pain ratings was observed in the CIP group, by comparison with control subjects. Moreover, as a consequence of the marked underestimation of others’ pain in almost half of the patients, pain ratings were, on the whole, significantly lower in the CIP group, especially for injuries inducing a high level of pain. This latter result fits well with the subjective experience reported by the majority of our patients during the interview that followed the experiments. Indeed, two-thirds of them acknowledged that they frequently suspected other people of exaggerating their pain and often considered others—including their friends or spouse—as ‘sissies’. Interestingly, this tendency
to challenge others’ pain experience systematically had been already noted by Magee et al. (1961) in their detailed psychological investigation of three CIP patients. How can we explain this propensity to discount others’ pain in our patients, despite normal semantic knowledge regarding the intensity of others’ pain experiences? Avenanti et al. (2005) have recently provided evidence of a pain somatic resonance mechanism, in which basic sensory aspects of someone else’s painful experience are automatically mapped with great somatotopic selectivity onto the observers’ motor system. Using transcranial magnetic stimulation, a consistent reduction of excitability of hand muscles was demonstrated during the mere observation of ‘flesh and bone’ painful stimuli delivered at the same site to a model, and the level of this inhibition was shown to be strongly related to the observer’s subjective rating of the intensity of the pain ascribed to the model. In our video clips, participants saw individuals suffering various injuries, while pain-related behaviours and other pain cues were deliberately omitted. In such conditions, embodiment of the painful stimulus in the observer’s own sensorimotor maps might be particularly required for an accurate estimation of others’ pain. The implementation of this embodiment process might crucially depend on previous personal pain experiences, and could therefore be greatly impaired in CIP patients. In a very similar perspective, Bosbach et al. (2005) showed that subjects lacking cutaneous touch and proprioception following complete deafferentation of large diameter sensory fibres displayed a selective deficit in interpreting another’s anticipation of weight when seeing him lifting boxes. In both cases, the lack of specific peripheral nerve fibres—nociceptive or proprioceptive—may have prevented the formation of internal sensorimotor representations of others’ sensation and/or action, and may thus have led the observer to make distorted inferences.

Deficiency in embodiment of others’ pain may also account for the miscalibration of CIP patients’ affective responses to the view of pain-inducing events seen in video clips. Indeed, although valence and arousal ratings were related to pain ratings in the same way in CIP and control groups, CIP patients showed comparatively attenuated aversive responses to negative videos, together with a decreased tendency to rate positive videos as funny, suggestive of an over-compensation mechanism. Overall, these results indicate that in the absence of visible or audible emotional cues related to pain experience, CIP patients may be, on average, less affected by the view of individuals suffering severe injury. Large inter-individual differences could be noted in this regard, however. Indeed, four patients displayed overt affective reactions (including non-verbal vocalisations such as ‘ouch!’) when viewing the most serious injuries, while six patients acknowledged a lack of emotional reaction to the view of severe wounds in others, in movies and in reality as well.

Inferences drawn from facial expressions of pain

Previous work has provided evidence that observers tend to underestimate the pain of others when making inferences based on facial behaviour (Prkachin et al., 1994). Moreover, several studies have shown that contextual variables, beliefs, judgement biases or even clinical experience with pain patients can degrade the quality of the observer’s pain estimation and result in an increased tendency to underrate facial expressions of pain (Poole and Craig, 1992; Prkachin and Craig, 1995; Hess et al., 1998; Prkachin et al., 2001; Williams, 2002). Such a propensity to ignore or downgrade facial evidence of pain in others could have been expected in CIP patients, as a consequence of the impairment of their own experience of pain. However, patients’ performances in inferring pain from facial expressions were similar to controls. As participants rated facial pain expressions on a scale consisting of only three verbal descriptors (‘no pain’, ‘moderate pain’ and ‘strong pain’), subtle differences between CIP patients and control subjects might have been overlooked. In any case, this result suggests that the sensitivity to variations in sufferers’ pain intensity and the weight placed on the facial evidence of pain in others do not depend crucially upon the observers’ own experience of pain, at least in this experimental setting. It has been noted that the parents of some CIP patients may systematically resort to miming facial expressions of pain to make their child understand that a particular stimulus might damage his body (P. Landrieu, personal communication). Such ‘teaching’ may have contributed to increased facial pain discrimination in some of our CIP patients.

Neuroimaging studies have shown that watching, hearing or imagining other individuals in pain activates some of the cortical areas known to be involved in the affective component of self-pain experience, such as the anterior cingulate cortex and the anterior insula (Morrison et al., 2004; Osaka et al., 2004; Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005, 2006; Saarela et al., 2006). Facial expressions of pain, cries and vocalizations signal a specific emotional experience and are therefore particularly suited to automatically triggering the affective component of the pain matrix in the observers’ brain (Osaka et al., 2004; Botvinick et al., 2005; Saarela et al., 2006). In contrast with the sensorimotor mapping mechanisms described above, such ‘mirror matching’ of the affective dimension of others’ pain might be relatively preserved in CIP patients. This could account for the intact propensity of CIP patients to detect suffering in others from emotional cues such as facial pain expressions. Interestingly, one-third of our patients stated spontaneously at the end of the experiments that they found it quite difficult to estimate the pain experienced by injured individuals without seeing their face or hearing them cry. In the absence of functional sensorimotor pain matching mechanisms, such emotional cues might indeed be crucial to CIP patients when they have
to estimate the pain experienced by someone else. In this regard, the subjective report made by patient MP was of particular interest. Indeed, this medical student had realized retrospectively that he had always considered the pain of the in-patients he had to look after as an abstraction, until he was confronted with wounded patients ‘crying out with pain’ in the emergency room: from then, by his own account, others’ pain became something real to him.

The role of dispositional empathy
Judgements of others’ pain made from facial pain expressions and from pain-inducing events seen in video clips were strongly correlated in the CIP group, but not in the control group. Moreover, only in the CIP group were these pain estimations related to inter-individual differences in the trait of emotional empathy, the highest pain ratings being found in patients with the highest empathy scores. These results suggest that CIP patients might rely partly on their emotional empathic abilities to estimate the pain of others, independently of the nature of the pain cues made available, while healthy subjects could make use of other strategies that could vary according to the modality of the task. Although CIP patients, on the whole, did not differ from controls in terms of emotional empathy, such interaction between empathy and pain estimation might have contributed to increase the inter-individual variability in ratings of pain-inducing events in the CIP group.

Methodological limitations
Several limitations to the present findings should be emphasized. First, the small number of patients—due to the rarity of HSAN cases with diffuse insensitivity to pain—and the use of a fairly uniform group of undergraduate men and women as control subjects, may limit the generalizability of the results. Secondly, the facial expressions of pain and the pain-inducing events were shown in the same sequence to all participants, precluding the evaluation of order effects. Thirdly, the present findings might not be necessarily transposable to situations of everyday life, in which additional judgement bias and pain-related cues could influence pain judgements. In this regard, subjective reports made by CIP patients suggested that their tendency to underestimate the pain of others might be more pronounced in real situations than in our experimental setting. Finally, some of the hypotheses inferred from these behavioural experiments should be tested with objective neurophysiological methods. For example, whether the same pattern of cerebral activation underlies the capacity of CIP patients and control subjects to decode facial expressions of pain remains to be determined.

Conclusion
In his novel Ingenious Pain, contemporary novelist Andrew Miller created a central character who is born unable to feel pain and who grows into a technically skilled but unfeeling surgeon (Miller, 1997). Contrary to the theory supported by the plot of this novel (Loeser, 2005), our results suggest that a normal personal experience of pain is not necessarily required for perceiving and feeling empathy for others’ pain. In the absence of functional somatic resonance mechanisms shaped by previous pain experiences, others’ pain might be greatly underestimated, however, especially when emotional cues are lacking, unless the observer is endowed with sufficient empathic abilities to fully acknowledge the suffering experience of others in spite of his own insensitivity.

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References
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