Clinical Neurophysiology 122 (2011) 1838–1845

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Effect of pain perception on the heartbeat evoked potential

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ARTICLE INFO

Article history:
Accepted 14 February 2011
Available online 10 March 2011

Keywords:
Pain perception
Heartbeat evoked potential
Interoceptive process
Alternative pain measure

HIGHLIGHTS

- We investigate the effect of tonic cold pain on the heartbeat-evoked potential (HEP).
- Tonic cold pain induces significant suppression of the HEP.
- The HEP suppression is correlated with subjective pain ratings.

ABSTRACT

Objective: To investigate the effect of acute tonic pain on the heartbeat-evoked potential (HEP) and to test whether or not pain perception can be reflected by the HEP.
Methods: Simultaneous electroencephalogram (EEG) and electrocardiogram (ECG) were recorded from 21 healthy young adults in three conditions: passive no-task control, no-pain control and cold pain. The HEP was obtained by using ECG R-peaks as event triggers.
Results: Prominent HEP deflection was observed in both control conditions mainly over the frontal and central locations, while it was significantly suppressed in the cold pain condition over the right-frontal, right-central and midline locations. A comparison of the data in the first and last 5 min of cold pain condition showed that lower subjective pain ratings were accompanied by higher HEP magnitudes. A correlation analysis showed that the mean HEP magnitude over the midline locations was significantly negatively correlated with subjective pain ratings.
Conclusions: Cold pain induces significant suppression of the HEP across a number of scalp locations, and the suppression is correlated with self-report of pain.
Significance: The HEP has the potential to serve as an alternative pain measure.

1. Introduction

Pain, an unpleasant sensory and emotional experience, if uncontrolled or undertreated, can seriously interfere with normal functioning and impair the quality of life. In many cases, the failure to adequately treat pain is due to the lack of accurate pain assessment tools (Rissacher et al., 2007), especially when subjective self-report methods are not applicable due to patients' inability to formulate their pain experience (e.g. young children, incapacitating brain conditions). Therefore, there is a need for measures of pain which do not rely on patients' ability to self-report.

Some recent studies (Edwards et al., 2001, 2002, 2008; Martins et al., 2009; McIntyre et al., 2006) have shown that pain-related evoked potential and pain rating can be modulated across the cardiac cycle, probably due to a close integration of the pain system and the neural network involved in cardiovascular regulation. There is also emerging evidence that afferent signals from the heart can modulate pain perception through the neural pathways including the periaqueductal grey matter (PAG), the thalamus, the hypothalamus, the amygdala and the prefrontal cortex (McCraty et al., 2009). There are therefore close neuronal links between pain perception and central processing of cardiovascular activity. Hence, it is reasonable to hypothesize that the brain electrical activity associated with the processing of cardio-afferent input, i.e. the HEP (Chen, 1993; Dirlich et al., 1998; Gray et al., 2007; Jones et al., 1986; Leopold and Schandry, 2001; McCraty et al., 2009; Montoya et al., 1993; Pollatos and Schandry, 2004; Riordan et al., 1990; Schandry and Montoya, 1996; Schandry et al., 1986), may reflect pain processing in the brain and offer potential use for pain assessment.

Chen and Dworkin (1982) in their pilot work attempted to link the HEP with pain perception. The study provides so far the only

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1388-2457/$36.00
doi:10.1016/j.clinph.2011.02.014

evidence of the relation between the HEP and pain. However, the study was performed on patients with chronic headache. It is known that the perception of acute and chronic pain involves different brain networks (Apkarian et al., 2005), and that chronic pain is usually associated with neuroplastic changes in the nervous system (Wilder-Smith et al., 2002). Hence, acute and chronic pain may reflect differently.

The study presented in this paper was performed to investigate the relation between the HEP and acute pain perception. In this study, ECG R-peak locked HEP was measured and compared in three conditions: a passive no-task control condition, a no-pain control condition and a cold pain condition induced by cold pressor test (CPT) (Mitchell et al., 2004; von Baeyer et al., 2005; Walsh et al., 1989). The aim was to examine the effect of acute tonic cold pain on the HEP.

2. Methods

2.1. Subjects

Twenty-one healthy young adults (12 males and 9 females, ages: 25.2 ± 3.6 years) participated in the experiment. They were recruited from the National University of Singapore (NUS). All the subjects were right-handed, not on medication, without any history of neurological, psychiatric and cardiovascular problems. Each subject was given a detailed explanation of the experimental procedure and each signed a consent form prior to the experiment. The study was approved by the NUS Institutional Review Board (also referred to as the Research Ethics Committee in some countries), which requires all experiments to comply with the Declaration of Helsinki, the Belmont Report and all relevant laws and regulations in Singapore.

2.2. Experimental procedure

In the experiment, each subject was comfortably seated in an upright chair in a brightly lit, sound attenuated and temperature controlled (24–26 °C) room, and participated with eyes open in three conditions: passive no-task control, no-pain control and cold pain induced by CPT. The three conditions were presented in a randomized order within a single session to remove potential confounds introduced by the task order, such as changes in anxiety levels due to adaptation to the experimental environment, the reaction to electrode application etc. The no-task control and no-pain control condition lasted for 5 min while the cold pain conditions lasted for 10 min.

In the no-task control condition, the subject was asked to relax and stay awake. In the no-pain control condition, the subject was required to immerse his/her non-dominant hand in cool water maintained at a temperature of 25 °C and count backwards mentally by 3's from a randomly determined 4-digit number throughout the test. In the cold pain condition, the subject was asked to immerse his/her non-dominant hand into cold water maintained at 10 °C. The subject was allowed to take the hand out of the water before the end of the 10-min recording block if the pain became unbearable. However, none of the subjects did so. In the cold pain condition, the subject was not required to perform a counting backwards task, but to verbally rate the perceived pain intensity/unpleasantness on a 0–10 point numerical rating scale (NRS) every minute. The NRS for the perceived pain intensity/unpleasantness was as follows: 0 = no pain/neutral, 1 = barely noticeable pain/barely unpleasant, 5 = mild pain/distressing and 10 = maximum pain tolerable/worst unpleasantness imaginable (Chen et al., 1998; Farrar et al., 2001).

Both the no-task and no-pain control conditions were considered as baseline conditions in contrast to the cold pain condition. The passive no-task control condition has been used as the baseline condition in many neurophysiological studies (see e.g. Backonja et al., 1991; Chang et al., 2001, 2002; Chen et al., 1989, 1998). Following the work by Dowman et al. (2008), the no-pain control condition was also included because, though being arguable, the no-pain control condition may represent a better baseline condition than the no-task control condition. The no-pain control condition was aimed to keep the subjects vigilant and focused on the experiment at constant level, and it controlled for innocuous pressure sensation associated with hand immersion in the water.

2.3. Data acquisition

EEG and Lead-II electrocardiogram (ECG) were simultaneously recorded using the Neuroscan NuAmps system (sampling rate: 250 Hz; bandpass filtering: 0.5–100 Hz) from a 32-Channel Quick-Cap™ (Compumedics Neuroscan, USA) with sintered Ag–AgCl electrodes and two surface ECG electrodes attached on the right arm and left leg, respectively. The scalp EEG was referenced to the average of A1 and A2, with AFz serving as the ground electrode.

2.4. Data preprocessing

EEG segments contaminated with strong muscle artifacts were manually rejected by visual inspection. The eye-blinking and eye-movement artifacts were removed from the EEG using an independent component analysis (ICA) based method developed earlier (Shao et al., 2009). The Hjorth method (Hjorth, 1975) was used to reduce the potential effect of cardiac field artifact (CFA) on EEG data (Montoya et al., 1993; Pollatos et al., 2005; Pollatos and Schandry, 2004). EEG signals were bandpass filtered (0.5–15 Hz) offline. The further offline bandpass filtering of 0.5–15 Hz was to further ensure the removal of DC drift and high frequency noise such as muscle activity. This would cause minimal loss of signal of interest, the HEP, a slow wave below 15 Hz as documented in the literature (see e.g. Montoya et al., 1993).

The R-peaks of ECG were detected as developed by Zhang et al. (2006) and used as the triggers for EEG averaging. EEG sweeps were defined as starting 100 ms before the ECG R-peaks to 900 ms after the ECG R-peaks, i.e. the time interval of −100 to 900 ms with respect to the onset of ECG R-peaks. The baseline mean was calculated by using the time window of −100 to 0 ms and subsequently subtracted from each sweep.

2.5. Data analysis

The HEP for each subject and the grand average of the HEP across all subjects, were computed separately for the first and last 5 min of the cold pain condition (denoted by Cold Pain 1 and Cold Pain 2, respectively), the no-pain control condition and the no-task control condition. For the analysis, the 30 EEG channels (excluding the reference channels A1 and A2) were grouped into seven anatomical scalp sectors (left-frontal: Fp1, F7, F3; right-frontal: Fp2, F8, F4; left-central: FT7, FC3, T7, C3, TP7, CP3; right-central: FT8, FC4, T8, C4, TP8, CP4; left-parietal-occipital: P7, P3, O1; right-parietal-occipital: P8, P4, O2; midline: Fz, FCz, Cz, CPz, Pz, Oz). The division into left and right scalp sectors was to facilitate the investigation of potential laterality effects. Analysis of variance (ANOVA) was performed for each scalp sector to evaluate between-condition differences in the mean HEP magnitude over all channels within the scalp sector,

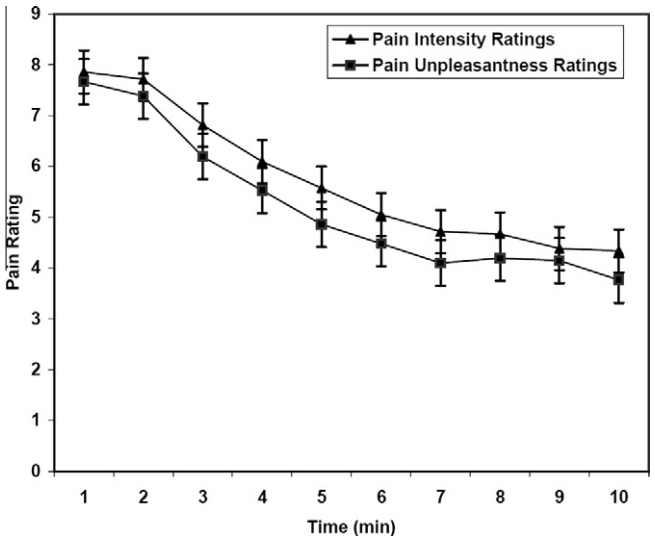

Fig. 1. Mean (±SEM) pain intensity and unpleasantness ratings of the 21 subjects obtained at 1 min interval throughout the 10-min cold pain recording block. Pain intensity/unpleasantness was rated on a 0–10 point numerical rating scale, where 0 = no pain/neutral, 1 = barely noticeable pain/barely unpleasant, 5 = mild pain/distressing, and 10 = maximum pain tolerable/worst unpleasantness imaginable.

where the HEP magnitude was computed as the average of absolute values of HEP amplitudes over the time interval with prominent voltage deflection shown (i.e. 200–600 ms post ECG R-peak in the present study).

3. Results

3.1. Pain ratings

Fig. 1 shows the mean (± standard error of the mean, SEM) of pain intensity and unpleasantness ratings given by the 21 subjects at 1-min interval during the cold pain condition. As can be seen, both the pain intensity and unpleasantness ratings decreased steadily until the 6th minute, and after that the pain ratings became almost constant.

3.2. The morphology and topography of HEP

Fig. 2 shows the across-subject grand averages of HEP over all EEG channels in Cold Pain 1, no-task control and no-pain control conditions. From Fig. 2, prominent HEP can be observed in both no-task control and no-pain control conditions. The HEP appeared as a positive or negative deflection (depending on channel location) in the latency range of 200–600 ms post ECG R-peak, mainly over the frontal and central scalp regions. This can also be seen from Fig. 3, the scalp maps of across-subject grand-average HEP at the latencies of 200 ms, 300 ms, 400 ms, 500 ms and 600 ms post ECG R-peak in the three conditions. In the figure, the absolute

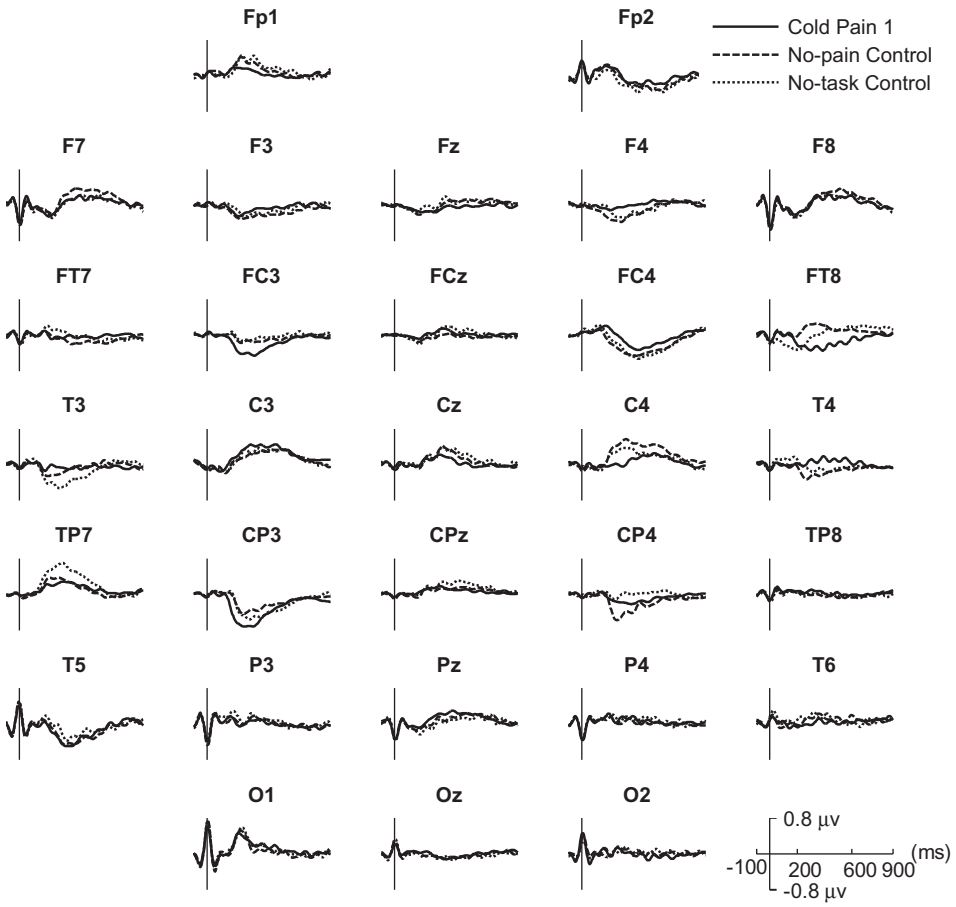

Fig. 2. Across-subject grand averages of HEP in Cold Pain 1, no-pain control and no-task control conditions over all EEG channels. Prominent HEP was shown in the control conditions as a positive or negative deflection (depending on channel location) in the latency of 200–600 ms post R-peak over the frontal and central EEG channels. The HEP was largely suppressed in the cold pain condition, especially over the right hemisphere. The vertical lines indicate the onset of ECG R-peaks.

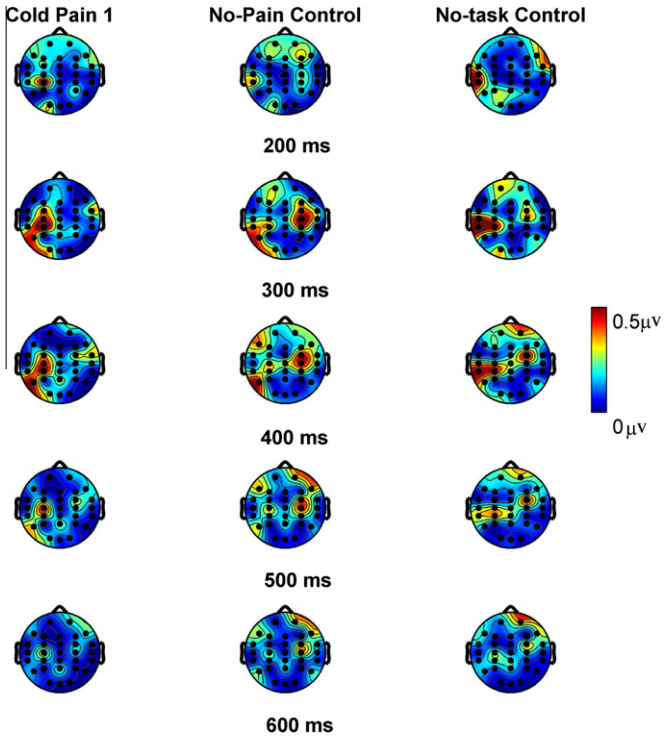

Fig. 3. Scalp maps of the across-subject grand-average HEP over each electrode in the Cold Pain 1, no-pain control and no-task control conditions at the latencies of 200 ms, 300 ms, 400 ms, 500 ms and 600 ms post ECG R-peak. The absolute value of HEP amplitude is color-coded, with a value of 0.5 μv represented by the red color and 0 μv by the blue color.

Table 1
Across-subject average of the mean HEP magnitudes over each scalp sector in Cold Pain 1, no-task control, no-pain control and Cold Pain 2 conditions. The symbol '∗' indicates statistically significantly higher mean HEP magnitude in no-task control, no-pain control or Cold Pain 2 than that in Cold Pain 1 ($P < 0.05$).

Scalp sectors	Mean HEP magnitude (μv)			
	Cold Pain 1	No-pain control	No-task control	Cold Pain 2
Left-frontal	0.48	0.65	0.72	0.51
Right-frontal	0.42	0.62*	0.66*	0.46
Left-central	0.51	0.59*	0.60	0.53
Right-central	0.40	0.66*	0.59*	0.41
Left-parietal-occipital	0.43	0.44	0.41	0.43
Right-parietal-occipital	0.28	0.33*	0.34	0.29
Midline	0.34	0.41*	0.41*	0.37*

value of HEP amplitude is color-coded, with a value of 0.5 μv represented by the red color and 0 μv by the blue color.

3.3. Pain and the HEP

3.3.1. Comparison of the HEP in cold pain and control conditions

The prominent HEP observed in both no-task and no-pain control conditions appeared to be largely suppressed in cold pain condition. Qualitatively, this can be seen from Figs. 2 and 3. The HEP suppression by cold pain can also be quantitatively evaluated by comparing the mean HEP magnitude for each scalp sector between different conditions (Cold Pain 1 vs. no-task control, Cold Pain 1 vs. no-pain control, and no-task control vs. no-pain control), as shown in Table 1. Each value in Table 1 represents the across-subject average of mean HEP magnitude for a specific scalp sector in a specific test condition.

ANOVA results showed that, there were significant differences in the mean HEP magnitude between cold pain condition and either control condition over several scalp sectors ($P < 0.05$, as indicated by the symbol '∗' in Table 1), but no significant difference between no-task control and no-pain control conditions over all scalp sectors. The HEP suppression by cold pain was more prominent over the right hemisphere, as evidenced by the significant mean HEP magnitude decreases over the right-frontal, right-central and midline scalp sectors in comparison to both no-task and no-pain control conditions. In order to provide a clearer picture of the HEP suppression, means (±SEM) of percent decrease in the mean HEP magnitude across all subjects in the cold pain condition as compared to both baseline conditions (i.e. [(baseline-cold pain)/baseline] × 100%) over the three scalp sectors were also computed and illustrated in Fig 4.

3.3.2. Subjective pain ratings and the HEP magnitude

As can be seen from Table 1, the across-subject average of mean HEP magnitude in Cold Pain 2 was larger than that in Cold Pain 1 over almost all scalp sectors. Especially for the midline scalp sector, the difference in the mean HEP magnitude was shown to be statistically significant by ANOVA ($P < 0.05$, as indicated by the symbol '∗' in Table 1). However, subjective pain ratings during Cold Pain 2 were generally lower than those in Cold Pain 1 (see Fig. 1). This indicates a potential negative association between the HEP magnitude and subjective pain ratings, or a positive association between the HEP suppression and subjective pain ratings.

In order to further evaluate the correlation between HEP suppression and subjective pain rating (i.e. self-reports of pain intensity or unpleasantness), Pearson's correlation analysis was performed, for each scalp sector, by using two sets of data: the standardized mean HEP magnitude and the normalized mean pain rating for each subject in a) Cold Pain 1 and b) Cold Pain 2. Herein, the standardized mean HEP magnitude was computed as the deviation in percentage from the average of mean HEP magnitudes over Cold Pain 1 and Cold Pain 2. The normalized mean pain rating was the mean of normalized pain ratings over Cold Pain 1 or Cold Pain 2, where the normalized pain ratings of a subject were the subject's pain ratings divided by the mean pain rating over the whole 10-min cold pain condition. The use of normalized pain ratings and standardized mean HEP magnitude was to reduce inter-subject variation in pain ratings and HEP magnitude. Significant negative correlations were found for both pain intensity ($r = -0.44$, $P < 0.05$) and pain unpleasantness ratings ($r = -0.50$, $P < 0.05$) to the mean HEP magnitude over the midline sector (see Fig. 5), but not over the other scalp sectors.

3.4. The potential effect of heart rate on the HEP

Cold pain tends to be accompanied by an increase in heart rate. In order to check for the potential effect of heart rate on the HEP, comparisons of the average heart rate and the mean HEP magnitudes over the three scalp sectors with significant HEP suppression shown (i.e. right-frontal, right-central, and midline sector) were made between Cold Pain 1 and either control condition (Table 2) for each subject. In nine subjects (highlighted in bold), the average heart rates did not increase with Cold Pain 1 as compared to either control condition. These subjects still showed decreases in the mean HEP magnitude. This suggests that the HEP suppression in the cold pain condition is not accounted for by changes in the heart rate.

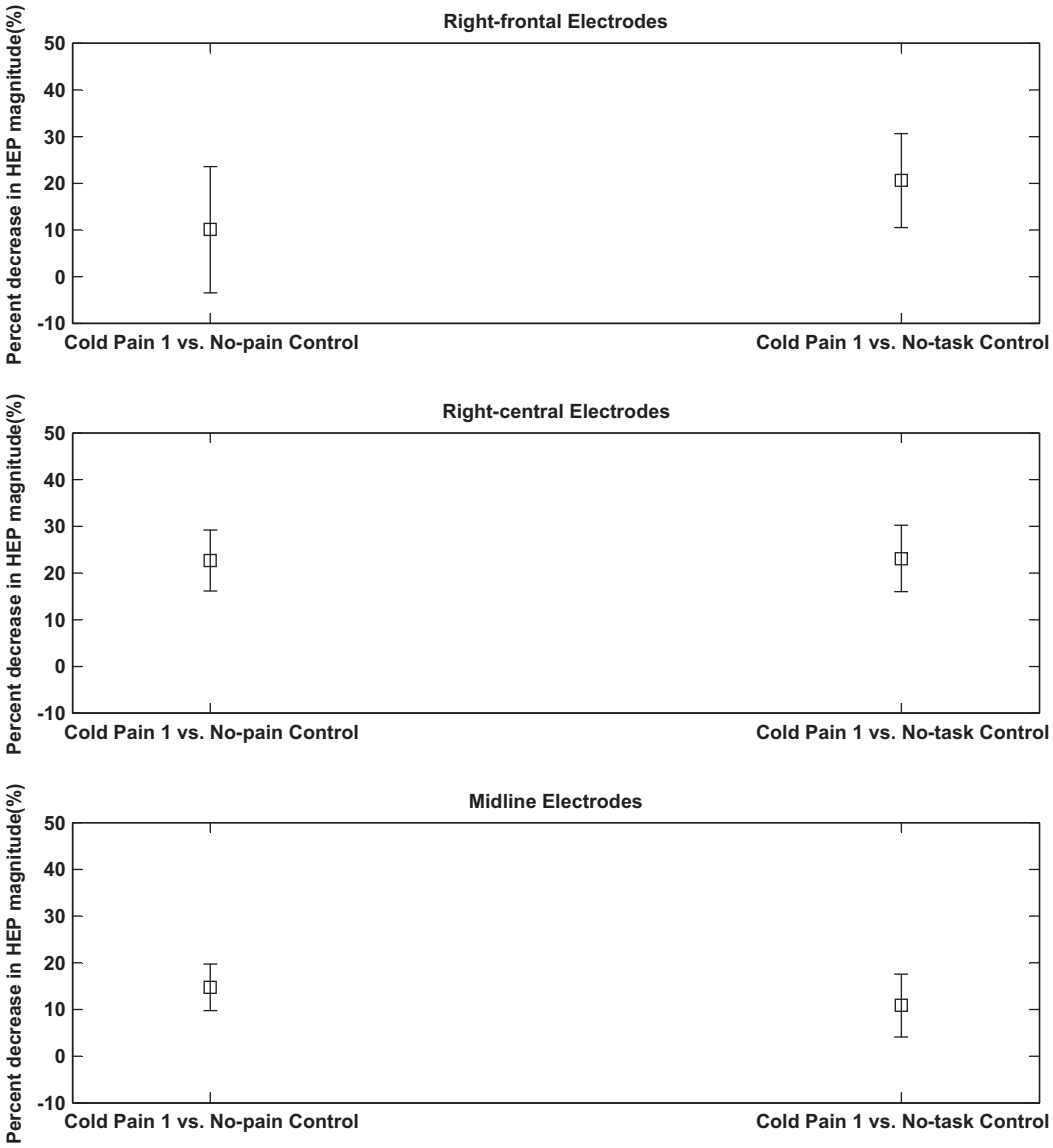

Fig. 4. Means (±SEM) of percent decrease in the mean HEP magnitude across all subjects over the right-frontal, right-central and midline scalp sectors in the Cold Pain 1 condition in comparison to the two control conditions (computed as [(control-cold pain)/control] × 100%).

4. Discussion

The present work examined the effect of acute tonic cold pain on the brain evoked potential accompanying cardio-afferent input (i.e. the HEP) through carefully controlled comparisons among cold pain, no-pain control and no-task control conditions. Prominent HEP was observed over the frontal and central scalp regions in both control conditions, as a deflection in the latency of 200–600 ms post ECG R-peak. The HEP was however significantly suppressed in the cold pain condition across several scalp regions.

4.1. Subjective pain ratings

The pain ratings given by the subjects in the present study were slightly different from those reported by most studies in the literature. In most of the past studies, the pain intensity ratings increased in the first several (usually <4) minutes and then declined steadily (see e.g. Chang et al., 2002) or became almost constant (see e.g. Dowman et al., 2008). The discrepancy between the subjective pain ratings in the present study and those in the past studies is probably due to the use of cold water with higher temperatures for CPT. According to Eccleston (1995), for low temperature (0 °C) CPT, there is a growing pain intensity (first pain) which reaches its peak between 2 and 4 min exposure, and if the subject is still exposed to the cold water at this temperature, there will be a second sharp increase in pain intensity (i.e. second pain) without numbness. For warmer temperature CPT (3–7 °C), the first pain tends to be of lower intensity and shorter duration, and there is usually no second pain. It is possible that for the CPT with even higher temperature (10 °C) in the present study, the first pain is even less intense and short, probably within one minute. As in the present study the first pain ratings were obtained from the subjects at the end of the first minute, the initial sharp increase in pain ratings resulting from the first pain was not captured.

4.2. The HEP

The HEP is believed to result from the central processing of cardio-afferent input, or the cardiac interoceptive process (Cameron, 2009; Dirlich et al., 1998; Gray et al., 2007; Leopold and Schandry,

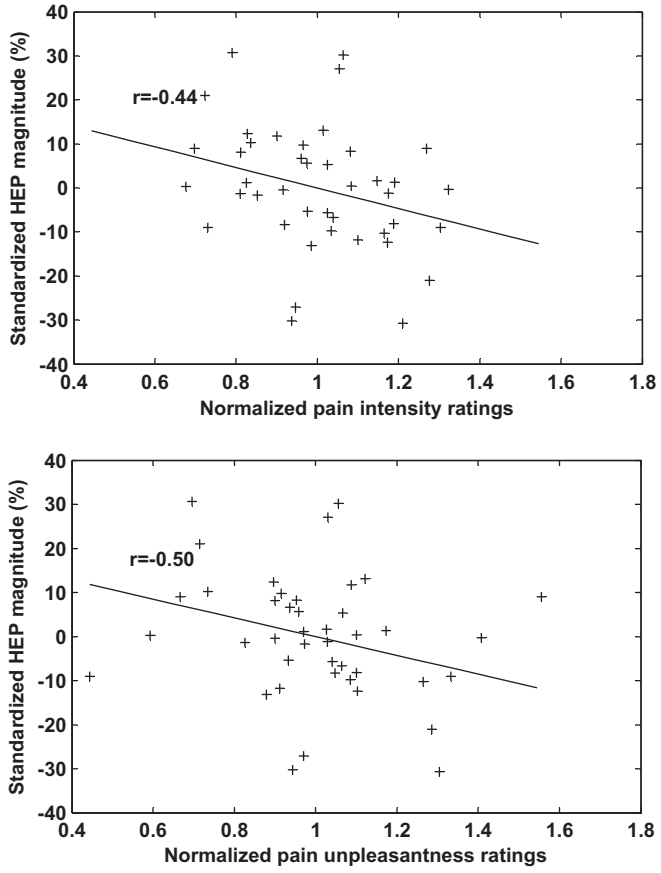

Fig. 5. Correlation between the standardized mean HEP magnitude over the midline sector and the normalized mean pain intensity/unpleasantness rating.

2001; Montoya et al., 1993; Schandry and Montoya, 1996). The presence of HEP has been shown to be independent of subjects' conscious heartbeat perception (Schandry and Montoya, 1996). This is understandable, as afferent signals from the body (i.e. interoceptive impulses) continuously reach the brain, and consciously or unconsciously, the brain is continuously monitoring interoceptive afferent information (Cameron, 2009; Schandry and Montoya, 1996; Sviderskaya and Kovalev, 1996).

In the present study, the HEP was obtained without requiring subjects to perceive their heartbeats and thus it was associated with un/sub-conscious cardiac interoceptive process. The deflection in the latency range of 200–600 ms post ECG R-peak for the HEP may be explained by the time interval for the brain to process the cardiac afferent input. According to McCraty et al. (2009), the period of 50–250 ms post ECG R-peak is the time interval for cardiac afferent signals to reach the lower brain areas, while the period of 250–600 ms post ECG R-peak is the time interval when the higher cognitive centers are processing cardiac afferent information. On the other hand, the scalp distribution of HEP, i.e. the dominance in frontal and central scalp regions, appears to suggest that the underlying network for the HEP involves extensive functional regions of the brain. This is consistent with the literature as it has been shown that the brain regions including the prefrontal/frontal cortex, the insular cortex, the somatosensory cortex, the amygdala, the thalamus, the hypothalamus, and the cingulate cortex, are all involved in interoceptive processing (Cameron, 2001, 2009; Pollatos et al., 2005).

4.3. The suppression of HEP by cold pain

It is interesting that HEP was largely suppressed in the cold pain condition in comparison with both the no-task control and the no-pain control conditions. The between-condition comparisons of each subject's heart rate and HEP magnitude convincingly show that the HEP suppression in the cold pain condition is not accounted for by changes in the heart rate.

The comparison between the two control conditions showed no significant difference in the mean HEP magnitude. This suggests that the HEP suppression is also not accounted for by an effect of counting backwards or innocuous pressure sensation associated with hand immersion in the water. During the no-task control con-

Table 2
The average heart rates and the mean HEP magnitudes over the right-central, right-parietal-occipital and midline scalp sectors for each subject in the Cold Pain 1, no-task control and no-pain control conditions. The values highlighted in bold show the cases when the mean HEP magnitude decreased while the subject's average heart rate did not increase in cold pain condition as compared to the control condition. bpm: beats per minute.

Subject No.	Cold Pain 1				No-pain Control				No-task Control			
	Heart Rate (bpm)	Mean HEP Magnitude (μv)			Heart Rate (bpm)	Mean HEP Magnitude (μv)			Heart Rate (bpm)	Mean HEP Magnitude (μv)		
		Right-frontal	Right-central	Midline		Right-frontal	Right-central	Midline		Right-frontal	Right-central	Midline
1	73	0.56	0.42	0.33	66	0.22	0.88	0.53	65	0.79	0.75	0.51
2	68	0.46	0.65	0.34	62	1.09	2.51	0.38	60	0.72	1.74	0.56
3	**74**	**0.74**	**0.53**	**0.41**	**76**	**0.98**	**1.16**	**0.51**	**76**	**0.83**	**1.32**	**0.54**
4	86	0.25	0.29	0.20	73	0.44	0.26	0.40	76	1.34	0.50	0.35
5	**68**	**0.83**	0.26	0.39	64	0.36	**0.66**	0.50	**72**	**0.88**	**0.63**	0.39
6	64	0.39	0.20	0.25	55	0.47	0.16	0.36	58	0.62	0.26	0.27
7	**67**	**0.23**	**0.31**	**0.20**	**69**	**0.42**	**1.28**	**0.55**	**70**	**0.70**	**0.83**	**0.42**
8	**56**	**0.44**	1.34	**0.59**	54	1.65	1.90	0.83	**57**	**1.50**	0.94	**0.87**
9	**71**	**0.51**	**0.70**	0.40	71	**1.24**	**0.81**	0.37	**71**	**1.20**	**0.91**	0.36
10	**80**	0.74	**0.37**	0.45	**85**	0.42	**0.54**	0.41	**81**	0.36	**0.69**	0.42
11	**66**	0.27	0.62	**0.60**	**67**	0.56	0.54	**0.73**	66	0.82	0.71	0.89
12	**66**	**0.34**	**0.26**	**0.48**	65	0.32	0.43	0.48	**67**	**0.39**	**0.34**	**0.60**
13	71	0.81	0.39	0.23	65	1.23	0.40	0.27	64	0.54	0.52	0.21
14	74	0.15	0.13	0.27	64	0.20	0.18	0.36	64	0.19	0.14	0.34
15	72	0.60	0.21	0.31	71	0.69	0.29	0.32	71	0.46	0.29	0.28
16	70	0.28	0.13	0.33	68	0.21	0.14	0.26	68	0.20	0.11	0.26
17	**50**	**0.28**	**0.52**	**0.25**	**54**	**0.38**	**0.68**	**0.29**	**52**	**0.37**	**0.74**	**0.30**
18	61	0.29	0.33	0.47	59	0.35	0.33	0.37	55	0.28	0.32	0.26
19	92	0.16	0.20	0.10	80	0.23	0.28	0.16	72	0.32	0.47	0.20
20	79	0.41	0.47	0.30	71	0.57	0.37	0.30	66	0.72	0.30	0.32
21	68	0.31	0.16	0.22	67	0.96	0.17	0.24	65	0.53	0.16	0.21

dition, the brain was in the resting state which is known to activate the brain default mode network (DMN) and embody interoceptive processes (Buckner et al., 2008; Nagai et al., 2004; Uddin et al., 2008). Thus, the un/sub-conscious cardiac interoceptive process which forms part of the functionality of DMN was active in the no-task condition. This may explain the prominent HEP shown in the no-task control condition. In comparison, under both the no-pain control and the cold pain conditions, the DMN was supposed to be largely deactivated with the attention-demanding mental calculation task or focused external attention and sensory processing demanded by pain (Buckner et al., 2008; Eccleston, 1995; Eccleston and Crombez, 1999; Elomaa et al., 2009; Nagai et al., 2004; Uddin et al., 2008). However, only the cold pain induced a significant suppression of the HEP. This indicates that the network involved in un/sub-conscious cardiac interoceptive process is linked closely to the pain pathways but likely not so to the network involved in mental calculation.

A plausible explanation for the HEP suppression by cold pain is the inhibition of un/sub-conscious cardiac interoceptive process by the perception of tonic cold pain through overlapping neural pathways. As stated earlier, the underlying network for HEP (or the network involved in cardiac interoceptive process) may include many cortical areas. These regions have also been shown to be involved in pain perception by functional neuroimaging studies (see e.g. Alkire et al., 2004; Apkarian et al., 2005; Ohara et al., 2005; Talbot et al., 1991). There is also evidence that pain is a significant interoceptive feeling, rather than an exteroceptive sense (Craig, 2002, 2003, 2009). These provide substantial evidence for close integration between the pain pathways and the network involved in the cardiac interoceptive process. Therefore, it is reasonable to believe that the two processes may interact with each other via overlapping neural pathways. This is supported by the work of Martins et al. (2009) showing that pain ratings vary across the cardiac cycle.

Moreover, it was found that the HEP magnitude was larger in the last 5 min of cold pain condition (with generally lower subjective pain ratings) than that in the first 5 min of cold pain condition (with higher pain ratings). That is, lower subjective pain ratings were accompanied by higher mean HEP magnitudes. Correlation analysis revealed a significant negative correlation between the mean HEP magnitude over the midline locations and subjective pain ratings.

The above results indicate that the HEP may be potentially useful in the measurement of acute tonic cold pain.

4.4. Implications for future study

There are several limitations with the present study. First, acute pain often leads to increased blood pressure and heightened sympathetic activity (e.g. increased heart rate). It has been demonstrated that the HEP suppression is not likely due to heart rate changes. However, the current study did not measure the blood pressure. Thus, it is not clear whether and how the changes of blood pressure would affect HEP. Before this is addressed, a firm conclusion about the specificity of the observed HEP suppression to pain should not be made. Second, this study examined the relation between HEP magnitude and subjective pain ratings by comparing HEP in the first and last 5 min of cold pain condition. However, the pain ratings were not constant but decreasing steadily in the first several minutes, and for some subjects, the pain ratings in the first and last 5 min did not differ significantly. This could be a reason why significant HEP difference between the two periods was only found over the midline scalp sector. Thus, a pain-induction method whose nociceptive input can be readily controlled to induce distinct levels of pain would be preferable in future studies. It should also be acknowledged that, the present study is limited to the test with painful stimulation applied to the non-dominant hand of right-handed subjects. A possible concern is that whether the observed HEP suppression is attributed to the mixing of sensory fibers from the left upper extremity with autonomic fibers with cardiac innervations. Thus, a fully controlled paradigm which includes pain stimulation of left as well as right upper extremity should be considered in future studies. However, it is worth noting that sensory fibers from the right upper extremity are also mixed to some extent (although less as compared to the left) with autonomic fibers with cardiac innervations. Therefore, there might be no obvious solution which can completely eliminate this confounding.

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