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Research Report

Temporal changes in cortical activation during distraction from pain: A comparative LORETA study with conditioned pain modulation

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ABSTRACT

Methods to cognitively distract subjects from pain and experimental paradigms to induce conditioned pain modulation (CPM; formerly termed diffuse noxious inhibitory controls or DNIC) have each highlighted activity changes in closely overlapping cortical areas. This is the first study, to our knowledge, to compare cortical activation changes during these 2 manipulations in the same experimental set-up. Our study sample included thirty healthy young right handed males capable of expressing CPM. We investigated brief consecutive time windows using 32-channel EEG-based sLORETA, to determine dynamic changes in localized cortical potentials evoked by phasic noxious heat stimuli to the left volar forearm. This was performed under visual cognitive distraction tasks and conditioning hot-water pain to the right hand (CPM), both individually and simultaneously. Previously we have shown that for CPM, there is increased activity in frontal cortical regions followed by reduced activation of the somatosensory areas, suggesting a pain inhibitory role for these frontal regions. We now observed that distraction caused a different extent of cortical activation; greater early activation of frontal areas (DLPFC, OFC and caudal ACC at 250–350 ms post-stimulus), yet lesser reduction in the somatosensory cortices, ACC, PCC and SMA after 350 ms post-stimulus, compared to CPM. Both CPM and distraction reduced subjective pain scores to a similar extent. Combining CPM and distraction further reduced pain ratings compared to CPM and distraction alone, supporting the dissimilarity of the mechanisms of pain modulation under these 2 manipulations. The results are discussed in terms of the differential functional roles of the prefrontal cortex.

1. Introduction

It is well known that cognitive attentional factors can reliably alter perceived pain intensity. Attending to a painful stimulus generally increases perceived intensity, whereas a sufficiently attention-demanding cognitive task (or distraction task) usually reduces pain perception by drawing attention resources away from pain processing. Such a distraction effect has been investigated in fMRI studies where attending to the cognitively demanding Stroop task attenuated the perception of pain

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stimuli, with increased activity observed in the periaqueductal gray (PAG), affective anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), and reduced activity in the thalamus, insula and cognitive ACC (Bantick et al., 2002; Valet et al., 2004).

Likewise, the human ability to endogenously modulate pain can also be revealed by the 'pain inhibits pain' test paradigms, typically when applying two concomitant remote noxious stimuli. This phenomenon, now termed 'conditioned pain modulation' (CPM; Yarnitsky et al., 2010) has been studied extensively (Moont et al., 2010, 2011; Pud et al., 2009; Roby-Brami et al., 1987; Treister et al., 2010; Wilder-Smith et al., 2010; Willer et al., 1984, 1989). Classically, such pain attenuation *via* 'diffuse noxious inhibitory control' or 'DNIC' (Le Bars et al., 1979) is considered to result from a spino-caudal medulla-spinal loop as evidenced by both animal (Bouhassira et al., 1992; Villanueva et al., 1986a, 1986b) and human DNIC studies (DeBroucker et al., 1990), who's descending influences reach the dorsal horn neurons (Willer et al., 1989). CPM, the psychophysical paradigm testing a DNIC-like effect, is usually measured either by reduced subjective pain ratings of the 'test' pain or more objectively by, for example, diminished pain evoked potential amplitudes (Fujii-Abe et al., 2010; Kakigi, 1994; Moont et al., 2011). Nevertheless, recent studies have shown some cortical influence under CPM; fMRI studies have found reduced activation in several areas such as the anterior insula, putamen and somatosensory, reported to be associated with pain perceiving and processing (Song et al., 2006), as well as in the ACC and supplementary motor area (SMA), along with increased activation in the OFC, thought to be engaged in pain modulation processing (Piché et al., 2009). Furthermore, using the EEG based standardized low resolution brain electromagnetic tomography (sLORETA) with its advantage of high time resolution, we have recently localized increased activity in the OFC and amygdala occurring prior to reduced activations in the somatosensory cortices, SMA, posterior insula and ACC (Moont et al., 2011).

Nevertheless, despite the close overlap of activated cortical areas during attentional manipulation of pain and under CPM, no study, to our knowledge, has investigated activity at the cortical level when comparing these 2 manipulations in the same experimental set-up. In an earlier psychophysical study measuring test pain under the conditioning effects of cognitive distraction, CPM or both cognitive distraction and CPM simultaneously, our group has suggested that CPM cannot be explained solely by a non-pain specific distraction effect (Moont et al., 2010). We therefore aim to compare, using sLORETA, the neurophysiological pattern of modulated cortical activity under continuous visual cognitive distraction tasks and CPM. In light of the results from our previous psychophysical study, we hypothesize that differences will be found between the patterns of cortical activity seen in these two types of pain modulation.

2. Results

2.1. Subjects

Fifty-one healthy male subjects were screened for the present study of which 30, aged 25±4 years (mean±SD), were included as being capable of CPM and completing both sessions.

2.2. Psychophysical results

The temperature of the test pain ranged between 51 °C and 53 °C (mean±S.D; 52.6 °C±0.7).

Mixed-model ANOVAs were conducted to examine any condition effect and any inter-train effect of the pain ratings. An overall condition effect was found (ANOVA: $F(3, 319) = 22.6$, $P<0.0001$) with post-hoc Tukey–Kramer tests revealing significant pain reduction of the test pain under both *CPM* and *Distraction* conditions; maximal pain intensity ratings (least squares mean±S.E.M. derived from ANOVA) were reduced from 60.4±4.2 to 54.7±4.2 under *CPM* and to 54.7±4.2 under *Distraction*. These attenuations were smaller than the minimum reduction of 10 NRS units required in the screening session. This may be due to a waning effect with repeated CPM testing. Furthermore, pain inhibition under the *Combined* stimulation was significantly greater ($P<0.05$) than either the *CPM* stimulation or *Distraction* stimulations alone; maximal pain intensity ratings were further reduced to 50.9±4.2 under *Combined* stimulation (Fig. 2). Thus there was a significant additive effect of pain inhibition when distraction was combined with tonic conditioning pain. No inter-train effect was found (ANOVA: $F(2, 319) = 1.70$, $P = 0.18$) suggesting no significant habituation or sensitization effects occurred with stimulation block repetition.

We found that the majority of subjects made no errors on the cognitive distracter task; for the total number of tasks completed by all subjects, performance was maximally accurate in 67%, one error was made in 19% and three or four errors were made in 4% of the tasks. Therefore, overall, performance on the distraction task was sub-maximal but above chance. This implies that the tasks were difficult enough to maximize continuous and cognitive attentional demand but not so hard as to discourage the subject from carrying out the tasks. There were no significant differences in the percentage of errors made between the different trains of experimental block (negative binomial regression, Wald chi-square (df 1) = 0.29, $P = 0.59$) or between *Distraction* and *Combined* stimulation blocks (NBR, Wald chi-square (df 1) = 0.26, $P = 0.61$), or their interaction (NBR, Wald chi-square (df 1) = 0.97, $P = 0.32$).

2.3. N_2P_2 evoked potential results

No inter-train effect was found on peak-to-peak vertex N_2P_2 amplitudes: ANOVA: $F(2, 228) = 0.27$, $P = 0.76$. Grand average pain EPs for both N_2 and P_2 peak latencies and N_2P_2 peak amplitudes were calculated by averaging the pain EPs from the vertex Cz electrode from all the three stimulation trains together for each of *Test* $Pain_{Baseline}$, *Test* $Pain_{CPM}$, *Test* $Pain_{Distraction}$ and *Test* $Pain_{Combined}$. There were no significant differences in the latencies of the P_2 peaks under the different conditions. Peak-to peak vertex N_2P_2 amplitudes of *Test* $Pain_{CPM}$, *Test* $Pain_{Distraction}$ and *Test* $Pain_{Combined}$ were significantly reduced from *Test* $Pain_{Baseline}$ (overall ANOVA: $F(3,62.7) = 8.05$, $P<.0001$ with Tukey–Kramer post-hoc tests showing $P<0.01$ for all the above pair-wise comparisons). This data is summarized in Table 1 and illustrated in Fig. 3. Regression analyses showed no correlation between the

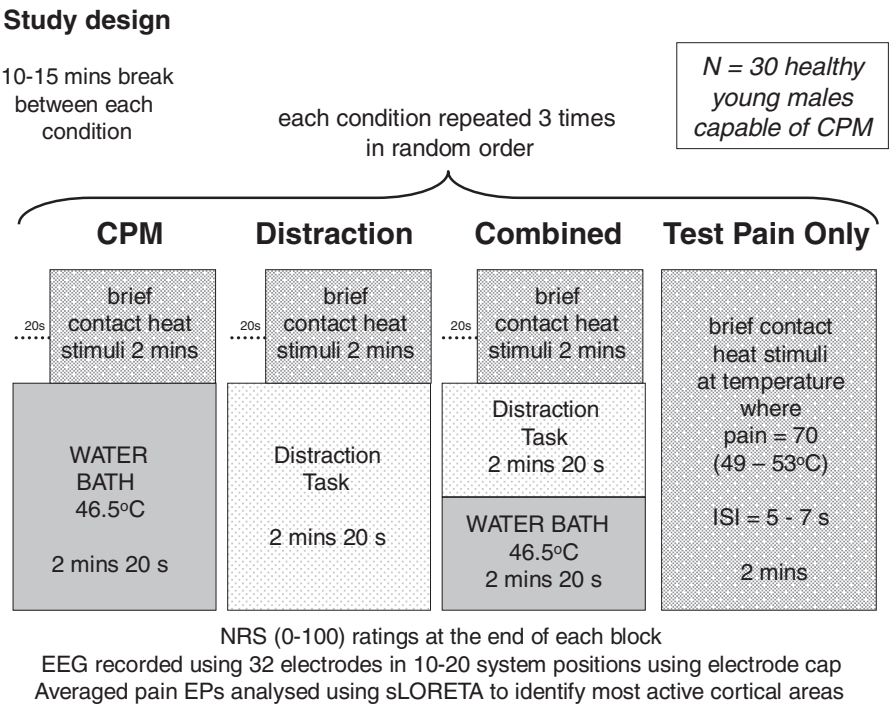


Fig. 1 – Study design.

pain ratings and the peak-to-peak N_2P_2 amplitudes. Specifically, a separate slopes model showed no interaction effect of the pain and condition ($F(3,66.9)=0.52$, $P=0.67$), no effect of condition ($F(3,64.8)=0.47$, $P=0.70$), and no effect of pain ($F(1,82.3)=0$, $P=0.97$). After averaging pain and EP amplitude across conditions, their correlation was not significant ($r=0.045$, $P=0.81$).

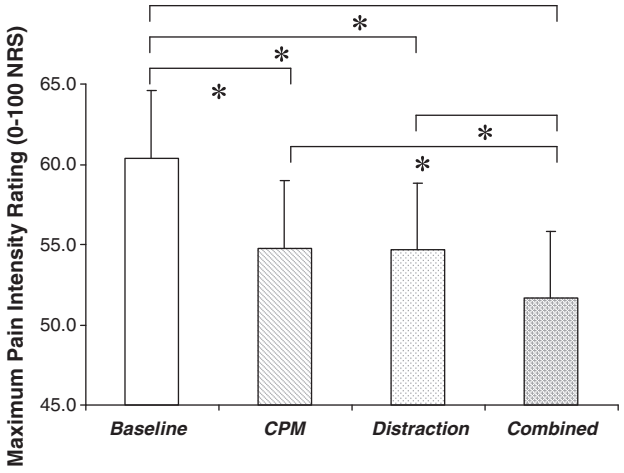


Fig. 2 – Maximal intensity pain ratings under Baseline, CPM, Distraction and Combined conditions (averaged across all 30 subjects). *The test pain was significantly reduced under all conditions compared to baseline. Also significantly greater pain intensity reduction was observed under the Combined condition compared to each of the CPM and Distraction conditions, $P<0.05$. Data are mean ± S.E.M.

2.4. *sLORETA based localizations of cortical activation changes under* **Distraction** *and CPM*

All the following comparisons relate to the Test pain under the various conditions *i.e. Test* $Pain_{Baseline}$, *Test* $Pain_{CPM}$, *Test* $Pain_{Distraction}$ and *Test* $Pain_{Combined}$.

2.4.1. *Distraction compared to baseline*

Increased cortical activations were observed in parts of the frontal cortex such as the OFC, DLPFC and ACC as well as in areas of

Table 1 – Table showing elicited pain evoked potential peak latencies and amplitudes.

Condition	N_2 latency	P_2 latency (ms)	N_2P_2 amplitude (μV)
Test $Pain_{Baseline}$	409 ± 8	542 ± 5	11.1 ± 0.9
Test $Pain_{CPM}$	416 ± 8	535 ± 9	9.0 ± 0.8 *
Test $Pain_{Distraction}$	427 ± 8	546 ± 5	9.2 ± 0.7 *
Test $Pain_{Combined}$	437 ± 7	541 ± 5	8.7 ± 0.7 *

Data are presented as least squares mean ± S.E.M. derived from the relevant ANOVAs.
N_2P_2 amplitude refers to the grand average peak-to-peak amplitude at the vertex.
* Significant reductions ($P<0.05$) in peak-to peak vertex N_2P_2 compared to *Test* $Pain_{Baseline}$.

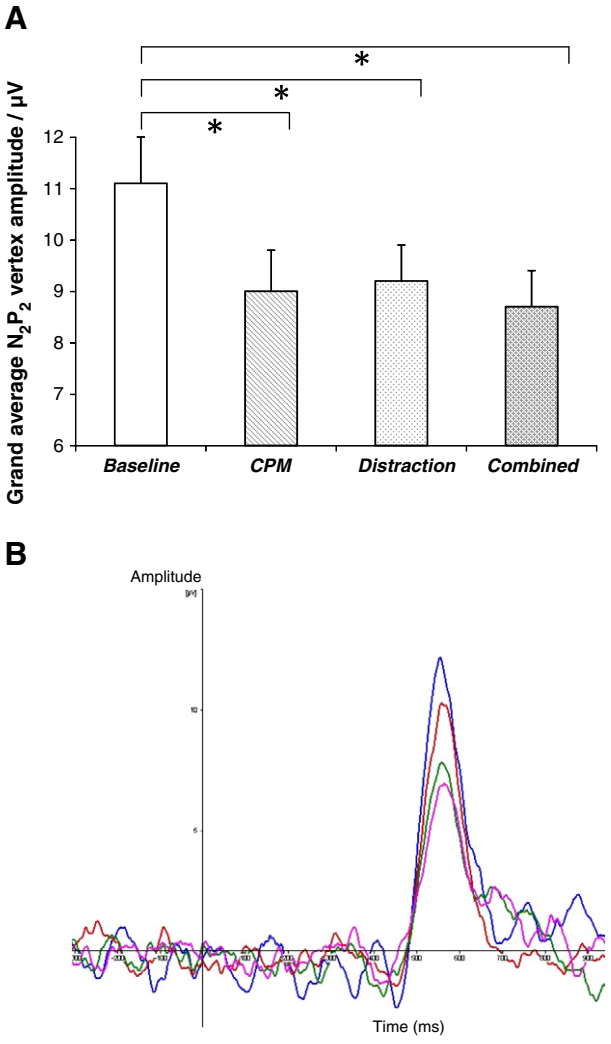


Fig. 3 – A. N_2P_2 peak-to-peak vertex amplitudes of the Test pain under Baseline, CPM, Distraction and Combined conditions (averaged across all 30 subjects). *The test pain N_2P_2 peak-to-peak vertex amplitude was significantly reduced under all conditions compared to baseline, $P<0.05$. Data are mean ± S.E.M. B. Grand averaged waveforms at the vertex evoked by the Test pain under Baseline, CPM, Distraction and Combined conditions. An individual subject example to illustrate the evoked N_2P_2 potential under the different conditions: *Test Pain*$_{Baseline}$ (blue); *Test Pain*$_{Distraction}$ (red); *Test Pain*$_{CPM}$ (green); *Test Pain*$_{Combined}$ (pink).

the occipital cortex (presumably due to the distraction task being in the visual modality). However these increased cortical activations did not reach significance under our strict statistical criteria. We did find significantly reduced left insula activity (two-tailed t tests where $P<0.05$) at 550–600 ms post-stimulus (Fig. 4A). Regression analyses performed to assess whether the activity changes in brain regions under *Distraction*, compared to baseline, correlated with the subjective maximum delta pain ratings yielded no significant results ($P>0.05$).

2.4.2. *CPM compared to baseline*

We located significantly increased initial activity in the OFC and amygdala 250–300 ms post-stimulus that were specifically correlated to reductions in pain ratings, followed by reduced activations in several cortical areas such as SI, SII, SMA, posterior insula and ACC from 400 ms onwards. (Refer to Moont et al., 2011 for further details).

2.4.3. *Distraction compared to CPM*

Test Pain$_{Distraction}$ was shown to have a significantly greater increased activation in the DLPFC and ACC between 250–350 ms post-stimulus and in the OFC and medial temporal gyrus 300–350 ms post-stimulus, compared to *Test Pain*$_{CPM}$. Interestingly, when estimating source localizations at later time windows, *Test Pain*$_{Distraction}$ also had a significantly greater activity, compared to *Test Pain*$_{CPM}$, in several areas associated with pain perceiving and processing. These included the somatosensory cortices, ventral ACC, PCC and SMA after 350 ms, with a marked increase in the volume or cluster size activated of these areas from 400 ms onwards. This data is summarized in Table 2 and Fig. 4B.

2.5. *Localized cortical activation reductions under the combined condition*

Cortical activations under *Test Pain*$_{Combined}$ were compared to cortical activations under *Test Pain*$_{Baseline}$ to estimate localizations of significantly different activity under the *Combined* condition compared to baseline. Significantly reduced activity in areas of the pain processing network such as the ACC and insula were observed under *Test Pain*$_{Combined}$ compared to *Test Pain*$_{Baseline}$ at 450–650 ms post-stimulus. Comparisons between *Test Pain*$_{Combined}$ and *Test Pain*$_{Distraction}$ showed reduced activity in the ACC in the time window of 500–550 ms post-stimulus (Fig. 3C). Comparisons between *Test Pain*$_{Combined}$ and *Test Pain*$_{CPM}$ showed no significant differential activity. However, when carrying out regression analysis correlating this last comparison to reductions in pain intensity ratings, significantly reduced activations in the somatosensory cortices were associated with reductions in pain scores under the *Combined* condition compared to *CPM* (at 600–650 ms post-stimulus, $P<0.05$, 1 tailed t-test comparison).

3. Discussion

This is the first study, to our knowledge, to investigate changes in cortical activity under both CPM and attentional manipulation of pain. Previous studies investigating each of these manipulations individually have highlighted changes in cortical areas that seem to overlap (Bantick et al., 2002; Moont et al., 2011; Piché et al., 2009; Song et al., 2006; Valet et al., 2004). This is reflected in the present study's results; our main finding was a significantly greater early activation (250–350 ms post-stimulus) of the frontal regulatory areas of DLPFC and OFC and of the caudal ACC when the subjects underwent our distraction task than when they underwent the CPM manipulation. However, attending to the distraction task was *less* effective than CPM at inhibiting pain, as revealed by greater activity under distraction compared to CPM of several areas related to pain perceiving

and processing including the somatosensory cortices, ACC, PCC and SMA after 350 ms post-stimulus.

3.1. *Different functional roles of the dorsolateral prefrontal cortex in attending to and modulating pain*

At the earliest significant time window of 250–300 ms post stimulus, we found increased activity in the DLPFC under the distraction task compared to CPM. The DLPFC is indicated in the cognitive and attentional processing of pain (Coghill et al., 1999; Peyron et al., 1999) and its activation is negatively correlated with pain intensity and unpleasantness (Lorenz et al., 2003), suggesting it exerts inhibition on the somatosensory areas. This implies that the distraction manipulation would be more effective than CPM in reducing pain perception. However there were no psychophysical differences in pain intensity reductions between the two manipulations. In fact, the neurophysiological findings indicate that the reverse is true; despite both CPM and distraction (relative to baseline) showing reduced activation in pain perceiving and processing-related cortical areas at later time intervals, CPM had a far greater extent of diminished cortical activity (in the SI, SII, SMA, posterior insula and ACC) compared to distraction (only in the posterior insula). Furthermore, comparing cortical activity under distraction *directly* to CPM indicated that the distraction manipulation was associated with *less* effective reduction of cortical activity in areas related to pain perception. Finally only cortical activity under CPM, showed specific correlations with reduced pain intensity scores.

The relatively increased DLPFC activation seen under the distraction manipulation may therefore be functioning in other known roles. Evidence suggests that the DLPFC is important for continuous monitoring of the outside environs, maintenance of information in short-term memory and ensuring efficient performance in the presence of interfering stimuli (Bunge et al., 2001; MacDonald et al., 2000; Sakai et al., 2002; Toepper et al., 2010). Brodmann Area 9 (BA9) is involved in classic working memory functions (Funahashi, 2006; Levy and Goldman-Rakic, 2000) where information is temporarily remembered to perform a task with sequential components. BA10 is implicated when one task must be momentarily suspended to attend to another task. Both these areas of the DLPFC have connections to the dorsal–caudal part of the ACC (BA 32) (Wang et al., 2009), which also showed early increased activation under distraction compared to the CPM manipulation. The ACC is important in resolving response conflict and its connections to the DLPFC help direct attention to new tasks while temporarily holding memory in another task (Orr and Weissman, 2009; Woldorff et al., 2004). It has been reported that the ACC, in particular its dorsal and caudal parts, and the DLPFC are both more activated and more functionally connected during recruitment of attentional processes (Fan et al., 2008; Wang et al., 2009). In the present study, the distraction task requires continual cognitive attention and working memory in the form of counting targets during sequential visual stimuli, in order to give an accurate total number of targets at the end of the task. These functions are likely to activate the DLPFC and ACC in order to sustain such attention. Accordingly, the DLPFC's role is likely to be mostly occupied with attending to the distraction task rather than modulating pain.

3.2. *Functional roles of the orbitofrontal cortex*

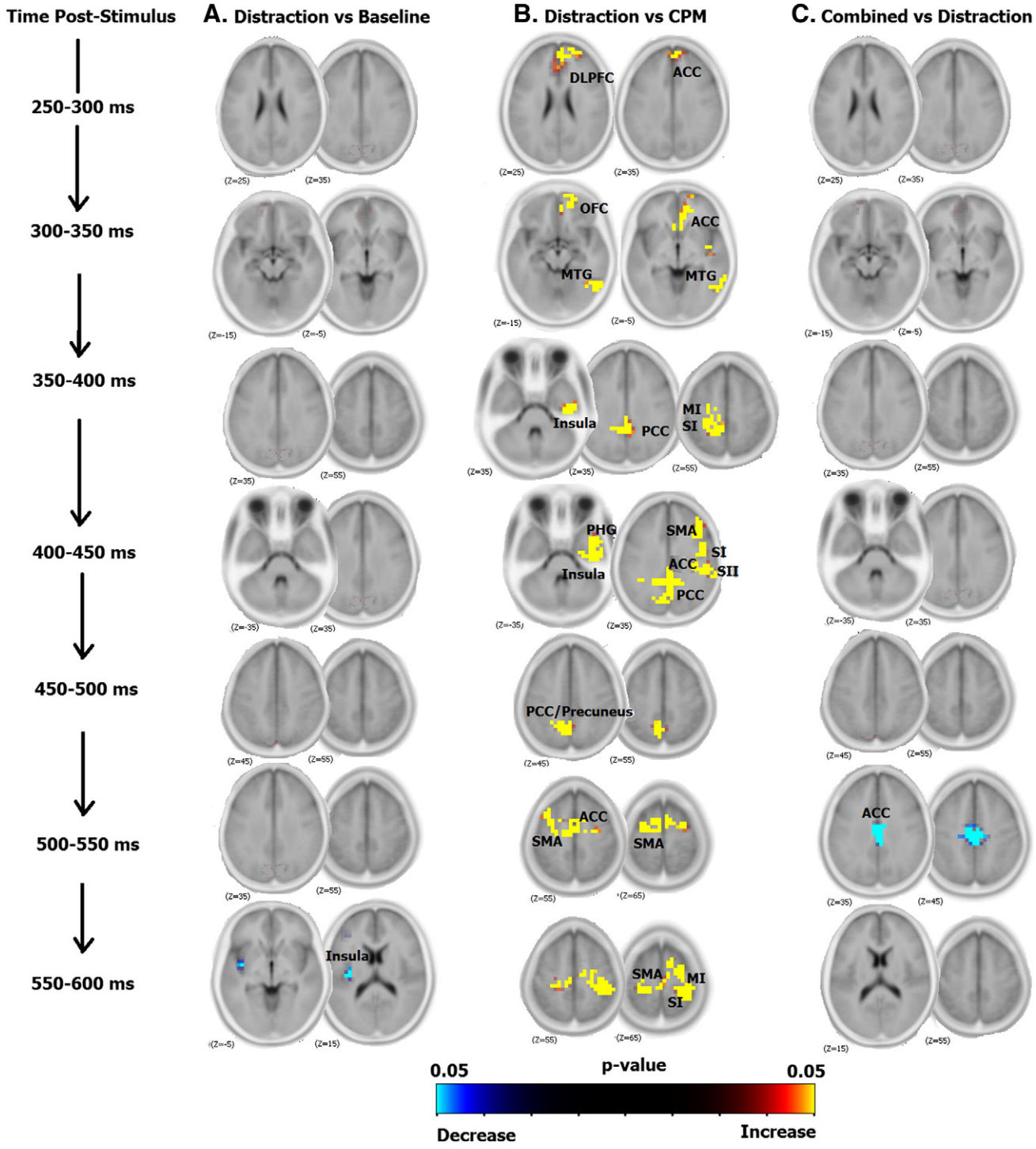
The OFC showed early increased activity under CPM compared to baseline at 250–300 ms post-stimulus. The OFC has extensive reciprocal connections to many brain areas, including SI, SII, ACC and insula (Carmichael and Price, 1995a,b; Price, 2007). Functionally, OFC plays an important role in goal-directed behavior and may act to inhibit an aversive stimulus, such as pain, by dynamically filtering nociceptive input and controlling emotional responses (Rolls, 2000; Rule et al., 2002; Shimamura, 2000). For further discussion, refer to Moont et al. (2011). In our study, OFC also exhibited greater early activity under distraction compared to CPM. We suggest that the OFC's role in goal-seeking behavior can also be applied to the desire to achieve high performance in the distraction task. The students who carried out this task inherently wanted to perform well as evidenced by the serious nature in which they carried out the task, their high performance and their subsequent desire to know their score level from the 'computer game' (although no feedback was given). Thus the OFC may act along with medial and dorso-lateral prefrontal cortices (Cho and Strafella, 2009) to ensure that attention is most efficiently directed towards satisfying the goal of high performance. Interestingly, a recent study (Park et al., 2010) showed that such reward-seeking can result in neurobiological plasticity, showing altered resting regional glucose metabolism in the OFC in young men who overuse internet games.

3.3. *Pain modulation by combination of painful conditioning stimulation and distraction*

Our study design also included a combined condition whereby the subjects underwent the CPM and distraction manipulations simultaneously. We found significantly reduced activity in the ACC and posterior insula, associated with pain perception and processing, in the combined condition compared to baseline. However, our results suggest that this is mainly due to the CPM manipulation, and not distraction, as evidenced by reduced activity in the ACC and insula with the addition of the CPM manipulation to distraction (*Combined vs Distraction*) but no cortical activation changes with the addition of distraction to CPM (*Combined vs CPM*). Nevertheless, although the distraction task may have been less effective than CPM in our study, that is not to say there is no pain modulation effect at all. Psychophysically, adding distraction to CPM in the combined condition showed greater reductions in pain scores than CPM alone. Furthermore, by quantitatively measuring the number of errors, our results showed that the task indeed required significant uninterrupted cognitive attention to compete with the painful stimuli for available attention resources (Eccleston and Crombez, 1999).

It is now recognized in both experimental (for review see Chen, 2009) and clinical (DePalma and Weisse, 1997) settings that distraction from pain can reduce subjective painful perception. fMRI studies where healthy subjects were required to carry out a cognitive task (counting, incongruent color/word or auditory Stroop tasks) whilst receiving painful thermal stimuli, resulted in reduced pain intensity scores, increased activation in the OFC and affective ACC and reduced activity in the thalamus, cognitive ACC and insula (Bantick

et al., 2002; Haupt et al., 2009; Valet et al., 2004). In the present study, our results similarly showed significantly reduced pain intensity scores when attending to the distraction task and reduced activation in the insula, compared to baseline. The insula is involved in encoding the intensity of pain (Baliki et al., 2009; Moayedi and Weissman-Fogel, 2009; Peyron et al., 1999) and has extensive links including to the ACC, prefrontal cortex and somatosensory cortices and receives spinothalamic input *via* the thalamic ventral posterior complex (Isnard et al., 2011). In the present study, it may be very likely that there are sub-cortical activation changes occurring during performance of the cognitive distraction task that are contributing to the observed pain modulation. Indeed, we found that reductions in pain intensity scores were associated with significantly reduced activations in the somatosensory cortex, a primary receiver of sub-cortical thalamic input, when adding the distraction condition to CPM (*Combined vs CPM*). Previous imaging studies have shown increased medial thalamic nuclei activity under painful stimulation (Tracey et al., 2000) with greater thalamic activity when attending to pain (Peyron et al., 2002) and less when cognitively distracted from the pain (Bantick et al., 2002). Thus, these studies support the role of



sub-cortical areas in the attentional manipulation of pain. A direct investigation of the spinothalamic input to the insula in the present study was not feasible since most sub-cortical areas are outside the analysis limits of LORETA.

3.4. *Study limitations*

There are several limitations within the present study. Firstly, this study recruited young healthy males who were capable of undergoing CPM. We decided on this population since we wanted a subject sample with the greatest likelihood of having a robust CPM in order to compare as truly as possible the underlying cortical neurological activity under CPM with that of cognitive distraction. Males may have a significantly more efficient CPM than females as demonstrated both psychophysically (Ge et al., 2004; Granot et al., 2008; Staud et al., 2003) and neurophysiologically (Serrao et al., 2004). While young healthy subjects ensures optimum CPM, as evidenced by CPM magnitude decreasing with age (Edwards et al., 2003; Riley et al., 2010), and a high ability to cognitively attend to the distraction task (for review on reduced cognitive attention with age see Greenwood, 2000). Therefore the ability to extend the results of the present study to the general population is somewhat limited. Secondly, we found no correlation between the measured evoked pain potentials with pain intensity scores. This may be due to the relatively high temperatures used for our test pain stimuli (ranging between 51 °C and 53 °C, mean ± S.D; 52.6 °C ± 0.7). A previous study in our lab has noted that the association of pain perception and N_2P_2 amplitudes evoked by such phasic test pain as used in the present study, while consistent for lower temperatures, failed at the highest temperature of 52 °C (Granovsky et al., 2008). They suggest that this may be related to a ceiling neuronal effect for SII responses, which contribute to the N_2P_2 potential, to attenuate pain EP amplitude at this painful intensity.

Although requiring caution in its interpretation when based on recordings from the limited spatial resolution of 32-channels, LORETA methodology has enabled us to localize cortical area activations within the same time window suggesting that they are activated simultaneously and also observe the time-course of changes in cortical activity following the phasic stimuli. Increasing the number of electrodes (excluding the reference electrode) from 31 to 63 may significantly improve the localization precision of cortical structures, as demonstrated in a study localizing epileptic sources (Michel et al., 2004). Future studies using fMRI or the emerging LORETA functional connectivity methodology in the frequency domain or using single trial data from the time domain (Mulert et al., 2011), would provide more substantial evidence of the connectivity or synchronicity in activations under CPM and distraction. Unfortunately the number of conditions and experimental blocks in this study did not allow feasible analysis of single trials. Although, such examination would not as yet be able to give information as to the direction of the connections, it would allow us to understand more clearly the regulatory functionality of the prefrontal cortex under both CPM and attentional modulation of pain.

4. Conclusions

The neurophysiological pattern of modulated cortical activity, as estimated by sLORETA, is significantly different between CPM and the continuous visual cognitive distraction tasks; our hypothesis is confirmed. This is further supported by our psychophysical results whereby combining CPM and distraction together reduced perceived pain intensity further than either CPM or distraction alone. Such an additive effect suggests differentiation in the activated nervous pathways during these endogenous analgesic processes.

5. Experimental procedures

5.1. *Subjects*

Fifty one healthy male right-handed paid volunteers were recruited mainly from the student body of our medical faculty by advertisement. They gave signed informed consent in accordance with full ethical approval by the local ethics board according to the Declaration of Helsinki (1964). Since the

Fig. 4 – sLORETA statistical maps showing locations and temporal sequence of significant decreases and increases in brain activity during distraction *vs* other conditions (2-tailed paired t-tests). A. sLORETA statistical maps of changes in cortical activity under Distraction compared to baseline, estimated by comparing cortical activations under *Test Pain*$_{Distraction}$ from cortical activations under *Test Pain*$_{Baseline}$ conditions for all subjects. The critical threshold for statistical significance of $P<0.05$ was automatically set, based on the data, to 3.2. Significant reductions (blue color) in cortical activations under Distraction were identified between 550 and 600 ms post-stimulus in the left insula. B. sLORETA statistical maps of changes in cortical activity under Distraction compared to CPM, estimated by comparing cortical activations under *Test Pain*$_{Distraction}$ from cortical activations under *Test Pain*$_{CPM}$ conditions for all subjects. The critical threshold was set for each time window to achieve a statistical significance of $P<0.05$. Significant increases (yellow color) in cortical activations under Distraction *vs* CPM were identified between 250 and 600 ms post-stimulus. DLPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; MTG = middle temporal gyrus; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; MI = primary motor cortex; ACC = anterior cingulate gyrus; PCC = posterior cingulate gyrus; SMA = supplementary motor area; PHG = parahippocampal gyrus. C. sLORETA statistical maps of changes in cortical activity under the Combined condition compared to Distraction, estimated by comparing cortical activations under *Test Pain*$_{Distraction}$ from cortical activations under *Test Pain*$_{CPM}$ conditions for all subjects. The critical threshold for statistical significance of $P<0.05$ was automatically set, based on the data, to 3.7. Significant decreases (blue color) in cortical activations under Combined *vs* Distraction were identified between 500 and 550 ms post-stimulus in the anterior cingulate gyrus (ACC). Please note that these maps use various transverse brain slices to highlight locations of changed cortical activity.

Table 2 – sLORETA statistical maps of regions with increased cortical activity during Distraction compared to CPM.

Post-stimulus time interval (ms)	Structure	BA	Side	X	Y	Z	Cluster size (voxels)
250–300	MFG/SFG	9	R	5	55	25	5
	DLPFC	10	R	5	60	25	15
300–350	OFC	11	R	15	48	−15	5
	MTG/fusiform	21, 22, 37, 39	R	50	−58	−1	13
	Dorsal ACC	32	R	10	33	−10	5
350–400	SI	3	L	−30	−32	48	14
	MI	4	L	−30	−27	47	10
	SPC	5	L	−20	−41	48	19
	SMA	6	L	−30	−12	56	15
	Precuneus	7	L	−15	−41	48	11
	PHG	20	R	40	−16	−20	28
	MTG	21	R	54	−15	−16	6
	Ventral ACC	24	L	−20	−17	42	6
	PCC	31	L	−20	−32	38	35
			M	0	−32	38	16
			R	5	−42	30	11
	SII	40	L	−30	−36	52	5
400–450 (N2 peak for test pain under CPM and under distraction was ~430 ms)	SI	2, 3	L	−35	−22	43	52
			R	30	−22	43	29
	MI	4	L	−40	−12	56	35
			R	30	−17	42	33
	SPC	5	L	−30	−41	57	27
			R	5	−36	48	28
	SMA	6	L	−40	−12	60	61
			R	30	−12	42	85
	Precuneus	7	L	−30	−46	48	94
			M	0	−37	43	18
			R	5	−32	43	37
	DMPFC	8,9	R	40	26	40	57
	Insula	13	R	30	−24	15	31
	PHG	19, 27, 28, 35, 36, 37	R	20	−44	−2	115
	Amygdala	20	R	30	−16	−24	104
	STG	21, 22, 38, 41	R	40	−15	−8	166
	PCC	23,31	L	−20	−32	38	70
			M	0	−47	25	31
			R	5	−37	43	55
	Ventral ACC	24	R	5	−32	34	9
			L	−20	−17	42	13
	IPL	40	L	−50	−46	48	55
			R	40	−32	34	49
450–500	Precuneus	7	L	−20	−51	44	32
			M	0	−51	44	7
	PCC	31	L	−20	−42	34	5
500–550 (P2 peak for test pain under distraction was ~515 ms; P2 peak for test pain under CPM was ~545 ms)	SMA	6	L	−40	12	50	81
			R	5	3	51	28
	SFG	8	L	−45	17	45	6
	Ventral ACC	24	L	−15	−7	46	14
			R	5	−3	46	9
550–600	SI	2, 33	L	−30	−31	66	35
			R	25	−31	61	38
	MI	4	L	−30	−26	66	17
			R	25	−22	52	15
	SMA	6	L	−25	−16	61	15
			R	10	−7	56	48
	SII	40	R	30	−36	57	17

L — left; M — middle; R — right; ACC — anterior cingulate cortex; DLPFC — dorsolateral prefrontal cortex; DMPFC — dorsomedial prefrontal cortex; IPL — inferior parietal lobule; MFG — medial frontal gyrus; MI — primary motor cortex; MTG — middle temporal gyrus; OFC — orbitofrontal cortex; PCC — posterior cingulate cortex; PHG — parahippocampal gyrus; SFG — superior frontal gyrus; SI — primary somatosensory cortex; SII — secondary somatosensory cortex; SMA — supplementary motor area; SPC — superior parietal cortex; STG — superior temporal gyrus. The threshold of the cluster size was set to 5 or more clusters, using 2-tailed paired t-tests. Significance was set at $P<0.05$.

purpose of the study was to compare the physiological basis of pain inhibition *via* distraction with that of CPM, and since many studies have demonstrated that not all healthy people express inhibition under CPM testing, potential subjects were only included if they demonstrated CPM in a screening session using our experimental task. Exclusion criteria consisted of any chronic or acute pain, taking medication, history of learning disabilities or neurological disorders.

5.2. *Instrumentation and recordings*

5.2.1. *Test stimuli*

Intermittent heat pulse stimulations were produced by a 27 mm diameter Contact Heat-Evoked Potential Stimulator (Pathway CHEPS, Medoc, Ramat Yishay, Israel). Stimuli were applied to the proximal left volar forearm, and the thermode repositioned slightly after each stimulus to reduce local thermal sensitization. Since the thermode was attached manually, attention was paid to maintaining relatively constant pressure on the thermode.

Uncued stimuli were delivered at randomized inter-stimulus intervals (ISIs) of 5–7 s in order to minimize expectancy effects. The thermode delivered stimuli perceived as discrete painful pulses (rapidly heating up at a rate of 70 °C/s and cooling at a rate of 40 °C/s), from a baseline temperature of 35 °C to a constant temperature between 49 °C and 53 °C depending on the subject's individual target temperature determined a priori (see below). The duration of onset to offset of the peaks ranged from 550 ms (49 °C) to 708 ms (53 °C).

5.2.2. *Conditioning stimulus*

The conditioning stimulus was delivered by immersion of the right hand to the wrist level in a hot water bath kept at a constant 46.5 °C during a 140 second long immersion (Heto Cooling Bath, Jouan Nordic A/S, Allerod, Denmark).

5.2.3. *Distraction task*

This was a non-invasive continuous cognitive visual task viewed on a standard IBM laptop monitor and designed and programmed in our lab using Presentation® (NBS Software, Albay, CA, USA) and Photoshop® (Adobe, San Jose, CA, USA) software. The stimuli consisted of 8 shapes in 3 colors; red, green and blue presented against a light gray background. Every 1.5 s, four random shapes with random colors were flashed on the screen in an equally spaced horizontal presentation across the center of the screen. The subject was instructed to concentrate on the 'computer game' and mentally count how many circle shapes and square shapes appeared at the same time within a group of four shapes during the time-course of the task (*i.e.* 2 targets and 2 non-targets at each stimulus presentation), and to give the total verbally only when requested to do so immediately following the end of the task. This type of distraction task was found in our previous psychophysical study using such cognitive tasks to be the most effective at reducing subjective pain scores of the test stimuli (Moont et al., 2010). The duration of the test was 140 s with the first 20 s allocated for familiarity purposes and showing no targets (although the subjects were not made aware of this). Correct responses were randomized between 8 and 14 (out of a total of 95 trials) to prevent subjects learning a correct response.

5.2.4. *Psychophysical recordings*

These consisted of pain intensity verbal ratings on a numerical rating scale (NRS) between 0 and 100. Zero was defined as "no pain felt whatsoever" and 100 was defined as "the worst imaginable pain".

5.2.5. *Neurophysiological recordings*

Pain evoked potentials (pain EPs) were recorded using an electrode cap (Easy Cap Q40, FMS Falk Minow Services, Herrsching, Germany) that contained 32 electrode positions according to the 10%-system with Ag/AgCl electrodes referenced to the chin. After analog-to-digital conversion, stimulus-linked EEG segments (sampling duration 2500 ms, 500 ms before and 2000 ms after the stimulus onset, sampling frequency 500 Hz, band-pass 0.15–40 Hz, notch filter of 50 Hz, impedance below 5 kΩ) were evaluated off-line, and manual artifact rejection (single responses contaminated by eye blinks or muscle artifacts) was applied before averaging (Brain Products GmbH, Munich, Germany).

5.2.6. *Electrophysiological cortical mapping tool*

Evoked potential data was obtained from the recording electrodes with the aid of Brain Products GmbH (see above) and was analyzed further using standardized low resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002) using the LORETA-KEY©® (publicly available free academic software at http://www.uzh.ch/keyinst/loreta.htm). sLORETA is a method to estimate the localization of brain function at specific time windows by providing a solution to the inverse problem. It can be used to compute statistical maps from EEG and MEG data that indicate the locations of the underlying source generators with zero error under ideal conditions. Numerous studies have supported the usefulness and validity of LORETA in localizing generators of scalp-recorded potentials, including recent research on pain processing and modulation, which have highlighted changes in cortical activity in areas of the pain matrix (Brown et al., 2008; Godinho et al., 2006; Moont et al., 2011; Nir et al., 2008; Stancák et al., 2006; Stern et al., 2006). Substantial congruence has been demonstrated between LORETA and fMRI localization (Mulert et al., 2005, 2010).

The sLORETA implementation incorporates a 3-shell spherical head model registered to a recognized anatomical brain atlas (Talairach and Tournoux, 1988), and makes use of EEG electrode coordinates derived from cross-registration between spherical and realistic head geometry (Towle et al., 1993). The solution space of sLORETA is restricted to cortical and some hippocampal and amygdala gray matter defined *via* a reference brain from the Brain Imaging Center at the Montreal Neurological Institute, and divided into 6239 cortical gray matter voxels at 5 mm resolution (Pascual-Marqui, 1999; Pascual-Marqui et al., 1994). In the present study, this analysis was applied to the average pain-EPs to identify the most active areas for baseline and under CPM, Distraction and Combined (CPM and Distraction together concurrently) conditions.

5.3. *Study design*

5.3.1. *Set-up*

The subjects were seated in a comfortable upright armchair in a quiet room. Prior to each experimental run, the procedure and

requirements from the subjects were explained carefully to them. We used a standardized set of instructions as a guideline and used the same surroundings and experimenter for all subjects for both sessions. In this way we aimed to reduce undue anxiety or fear and keep expectations or bias similar across all subjects.

5.3.2. *Session 1*

Since we only included subjects with CPM capability (a pain score reduction of ≥10 on the NRS under conditioning stimulus), a screening session was undertaken on a day prior to the main experimental session to determine which subjects to include on this basis. During this session, fifty-one healthy male subjects were first familiarized with the test stimulation by receiving four brief noxious pain stimuli of varying temperatures between 47 °C and 53 °C in randomized order applied to the volar part of the left forearm. Subjects were also familiarized with the conditioning stimulation by requesting them to place their right hand in the hot water bath for a few seconds.

The pain intensity of the test stimulus was then determined for each individual using a short series of ascending and descending test stimuli, culminating in identification of the temperature that induced a pain intensity score of 70 on a 0–100 numerical pain scale (NPS) as detailed in Moont et al. (2011). Subjects who found the test pain too painful or not sufficiently painful (consistently over 80 or below 20 on the 0–100 NPS, to avoid ceiling or floor effects) were excluded from the study.

After a break of 5 min, the subjects underwent a block of test pain stimuli for 2.5 min at the end of which they immediately gave ratings of the pain intensity they felt on average and at maximum during the stimulation block. This was followed by a break of 10–15 min before undergoing a block of test pain stimuli concurrently with the hot water conditioning stimulation. This block lasted for 2 min with a further initial 20 second period of the conditioning stimulus alone. This was to allow the subjects some initial familiarity of the conditioning stimulation, reduce surprise effects and to let the buildup of the conditioning take place. Again, immediately on finishing stimulation, the subjects reported average and maximum pain intensity ratings of the test stimulation as well as an average pain intensity rating felt from the hot water bath. Subjects who found the water bath too painful or not sufficiently painful (over 80 or less than 40 on the NRS) were excluded from the study.

5.3.3. *Session 2*

Firstly, the subjects were again familiarized with the pain stimulations by receiving four brief noxious pain stimuli of varying temperatures on their left volar forearm and placing their right hand for a few seconds in the hot water bath as in Session 1. An abbreviated distraction task was presented as a dummy run to verify that the given instructions were understood.

5.3.4. *Study protocol*

There were four separate experimental blocks as shown in Fig. 1. 1) The *Test Pain*$_{Baseline}$ stimulation block consisted of solely the test pain for 2 min and 20 s; 2) *CPM*: test pain stimulation concurrently with the hot water conditioning stimulation; 3) *Distraction*: test pain stimulation concurrently with the distraction task; 4) *Combined*: test pain stimulation concurrently with the hot water conditioning stimulation and the distraction task. The latter three blocks lasted for 2 min of concurrent stimulation with a further initial 20 second period of the conditioning stimulus (water bath, distracter task or both) alone. At the end of each stimulation block, the subject was immediately asked to give maximal pain intensity ratings of the test stimuli. Pain ratings were not requested during the stimulation blocks in order to prevent subjects having to divide their attention between the tasks and the pain. Each stimulation block was given three times to verify consistency and to test whether there was any significant habituation or sensitization to the pain stimuli. The stimulation blocks were run in a randomized sequence with 10–15 min interval between each block to allow for neural recovery.

5.4. *Statistical analysis*

CPM was calculated as the difference in pain ratings between the *Test Pain*$_{Baseline}$ and the test pain applied under the *CPM* stimulation (*Test Pain*$_{CPM}$). Similarly, distraction and the combined effect of CPM and distraction together, were calculated as changes in pain ratings between *Test Pain*$_{Baseline}$ and *Test Pain*$_{Distraction}$, and between *Test Pain*$_{Baseline}$ and *Test Pain*$_{Combined}$, respectively. Reductions in pain scores under *Test Pain*$_{CPM}$, *Test Pain*$_{Distraction}$ and *Test Pain*$_{Combined}$ compared to *Test Pain*$_{Baseline}$ indicated effective pain inhibition.

Mixed-model ANOVAs (analyses of variance) with repeated measures were conducted to examine any condition effect and any inter-train effect of the pain ratings. Models were comprised of full factorial tests of conditions (*Test Pain*$_{Baseline}$ *vs Test Pain*$_{CPM}$, *Test Pain*$_{Distraction}$ and *Test Pain*$_{Combined}$), and stimulus block trains (1, 2 or 3), or of one-way tests of condition effects themselves. Analysis consisted of first running several alternative models for each ANOVA, employing appropriate putative covariance structures. Resulting alternative models were assessed with regard to conventional ANOVA diagnostics, and choice of best model was made by evaluation of Akaike's corrected information criterion (AICC), and by evaluation of the raw covariances in an unstructured model for consistency. In addition, because they have been shown to be beneficial when dealing with small sample sizes, the Kenward–Roger method of estimation of degrees of freedom was employed, along with the appropriate adjustment for any subsequent post-hoc Tukey tests. PROC MIXED of SAS (SAS Institute, Cary, NC) was employed for statistical analyses.

Grand average pain scores were calculated by combining the pain scores from all the three trains together for each of *Test Pain*$_{Baseline}$, *Test Pain*$_{CPM}$, *Test Pain*$_{Distraction}$ and *Test Pain*$_{Combined}$ and calculating overall means and standard deviations of the pain ratings.

The above analyses were repeated using the peak-to-peak amplitudes of the N_2P_2 pain EP at the vertex Cz electrode. Regression analysis (separate slopes model) was performed to examine any correlation between the pain ratings and the peak-to-peak N_2P_2 amplitudes, controlling for condition.

The numbers of errors made by the subjects on the distraction tasks were calculated and performance assessed. Numbers

of errors across condition (*Test Pain*$_{Distraction}$ *vs Test Pain*$_{Combined}$), stimulus block train (1, 2 or 3) and their interaction was compared using Negative Binomial Regression (NBR) analysis. SAS PROC GENMOD was employed, utilizing an appropriate model for repeated measures.

All ANOVA results are represented as mean±S.E.M. Significance was taken at the 0.05 probability level.

For sLORETA, statistical differences between conditions were computed as images of voxel-by-voxel t-values. The localization of the differences in cortical activity was based on the standardized electric current density and resulted in 3-dimensional t-score images. In these images, cortical voxels of statistically significant differences were identified by a nonparametric approach thresholded at the 5% probability level determined by 5000 randomizations (Pascual-Marqui, 2002). A randomization procedure was implemented to control for Type I errors arising from multiple comparisons (Nichols and Holmes, 2002).

Changes in cortical activity under *Distraction* compared to baseline were estimated by comparing *Test Pain*$_{Distraction}$ from *Test Pain*$_{Baseline}$ conditions for all subjects at a time window of 250–700 ms post-stimulus. This is analogous to the estimation of cortical activity under CPM compared to baseline previously reported. Similarly changes in cortical activity under the *Combined* condition were estimated by comparing *Test Pain*$_{Combined}$ to *Test Pain*$_{Baseline}$, *Test Pain*$_{Distraction}$ and *Test Pain*$_{CPM}$. Cortical changes were also estimated when directly comparing *Test Pain*$_{Distraction}$ to *Test Pain*$_{CPM}$. The comparisons were computed using paired 2-tailed t-tests for consecutive 50 ms time intervals, within the specified above time window. Finally, regression analysis was performed, using the sLORETA tool, to assess whether the activity changes in brain regions under *CPM*, *Distraction* and *Combined* conditions compared to baseline, as tagged by the source analysis, correlated with the subjective maximum delta pain ratings. The correlation coefficient threshold used to create the functional maps was set at $P<0.05$, with the additional requirement of a cluster size of 5 or more voxels.

All analyses of the psychophysical and EP data employed Excel (Microsoft Corp., Redmond, WA, USA), JMP and SAS (both SAS Institute, Cary, NC, USA). All sLORETA analyses were performed using the sLORETA software package (Pascual-Marqui et al., 1994).

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