In contrast, there is a marked reduction in somatosensory evoked potentials (SEPs) during sleep, with a decrease in amplitude and prolonged latency (Addy et al. 1989; Naka et al. 1998; Nakano et al. 1995; Noguchi et al. 1995). In the case of noxious stimulation, several studies have shown that pain-related cortical SEPs (derived from electroencephalography) and somatosensory evoked magnetic fields (SEFs, derived from magnetoencephalography as described below) can be recorded using painful stimuli during wakefulness. The stimuli used were brief and were applied using surface electrodes (Miltner et al. 1989; Dowman et al. 1991; Becker et al. 1993; Naka and Kakigi 1998; Wang et al. 2003a,b), electrical intracutaneous needles (Bromm et al. 1984; Inui et al. 2002, 2003; Wang et al. 2004), or thermal CO_2 laser (see reviews by Kakigi et al. 2000a,b, 2004, 2005). During distraction and vigilance-oriented tasks there is a decrease in the amplitude of pain-related SEPs (Beydoun et al. 1993; Garcia-Larrea et al. 1997) and SEFs (Yamasaki et al. 2000), but only a few studies have attempted to investigate cortical responses to noxious stimuli during sleep (see review by Kakigi et al. 2003). One of the explanations why so few researchers have studied the effects of sleep on cortical activities evoked by noxious stimuli was the lack of an appropriate method by which to elicit clear cerebral activity without disturbing sleep continuity. To resolve this problem, Inui et al. (2002, 2003) developed a protocol using noxious intra-epidermal electrical stimulation. In comparison to other approaches using painful stimuli, which frequently wake the subject, this method selectively activates Aδ fibers and produces weak but well-defined sharp sensations similar to those induced with pinpricks. It is suitable for the study of sleep and pain perception because it does not interfere with the subject's sleep.

Another advance in methodology for the study of somatosensory processing, including that related to pain and sleep, was the introduction of magnetoencephalography (MEG). MEG makes it possible to study SEFs in humans during sleep (Kitamura et al. 1996) and has theoretical advantages over classical electroencephalography because it can localize the source of SEPs to a cortical-cortical or subcortical site. Fig. 1 illustrates, in a representative subject, the procedures of brain electrical source analysis to identify the multiple cortical sites in which SEFs were evoked by painful intra-epidermal electrical stimulation applied to the dorsum of the left hand (Inui et al. 2003; Wang et al. 2004). While awake, subjects were asked to count the number of stimuli silently (attention task) or ignore the stimuli (control task). Only a few sources were found in the contralateral primary somatosensory cortical area (S1), and bilaterally in the secondary somatosensory cortical area (S2) and insula, but the isocontour maps revealed two additional cortical sources—the ipsilateral medial temporal area and the cingulate cortex bilaterally. The peak latency of each source activity is

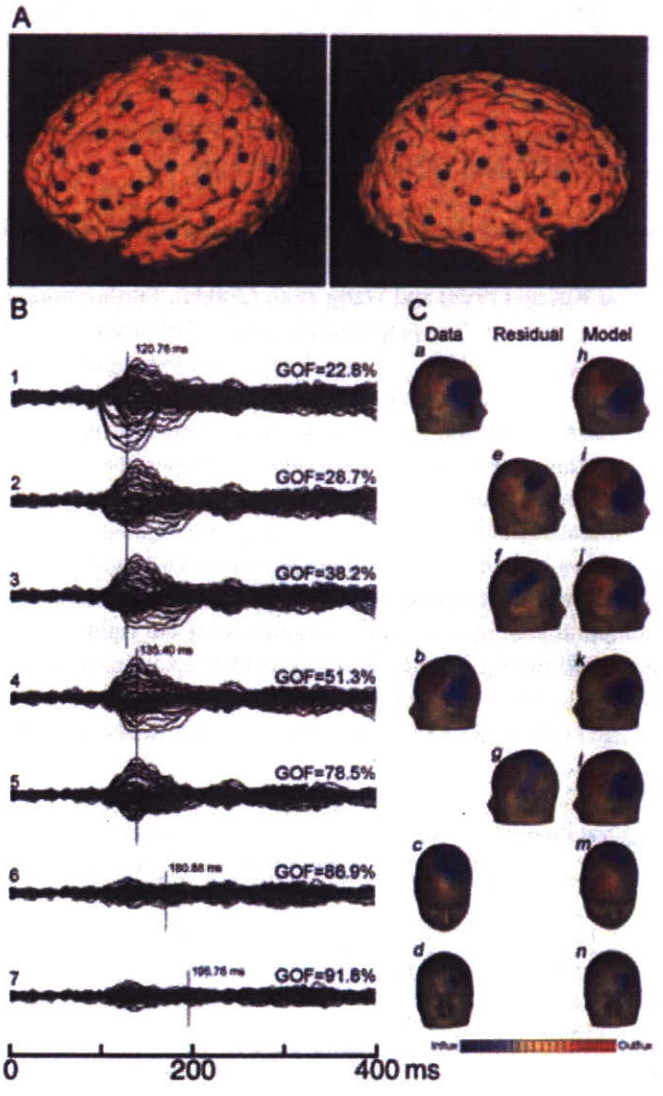

Fig. 1. Procedures of brain electrical source analysis for source location of somatosensory evoked fields (SEFs) in a representative subject using magnetoencephalography (for details see Wang et al. 2004). (A) Placement of probes. The center of the device was placed around the C3 and C4 positions according to the international 10–20 system. (B1) Superimposed waveforms recorded from 74 channels. (B2–B7) Magnetic fields obtained by the subtraction of a determined source model at each step from the recorded magnetic fields evoked by electrical stimulation. (Ca–Cn) Isocontour maps at the latency of selected deflection (vertical bars). (Ca–Cd) Isocontour maps of recorded magnetic fields. (Ce–Cg) Isocontour maps of the residual magnetic fields. (Ch–Cn) Theoretical isocontour maps of a model.

shown in Table I. Limitations of this source location method include the fact that some subjects may not present an activation in the contralateral cortex.

PAIN-EVOKED ACTIVITY IN VARIOUS CORTICAL AREAS IN RELATION TO ATTENTION AND SLEEP

Beydoun et al. (1993) were the first to report that pain-related SEPs are markedly decreased during light non-REM sleep, a finding later reproduced by Naka and Kakigi (1998) and Wang et al. (2003a). Furthermore, Wang et al. (2004) reported that no clear pain-related cortical SEF activity could be identified during sleep (e.g., Figs. 2, 3, and 4). Because the evoked magnetic fields during sleep were markedly attenuated, it was not possible to find any source activity in them. Therefore, the strength of each source activity was compared during the waking state between the attention and control tasks described above. The activities in the contralateral S1, the bilateral insula, the ipsilateral S2 and medial temporal area, and the cingulate cortex were significantly enhanced during the attention task in comparison to the control task, whereas in the contralateral S2 the difference did not reach significance (see Table I). The ipsilateral medial temporal activity evoked by stimulation of the right hand was significantly increased during the attention task (115.8 ± 45.9 nA) in comparison to the control task (69.6 ± 32.3 nA). The finding was supported by root mean square (RMS) calculations of the evoked magnetic fields (see Fig. 3), which

Table I
Latencies and strengths of cortical responses evoked by painful electrical stimulation in a representative subject during the waking state

	Control		Attention	
Site	Latency (ms)	Strength (nA)	Latency (ms)	Strength (nA)
S1 (c)	151.6 ± 18.2	6.6 ± 3.5	146.7 ± 13.3	11.5 ± 6.0*
S2 (c)	148.7 ± 17.3	7.0 ± 2.7	142.0 ± 12.1	10.2 ± 3.0
S2 (i)	158.6 ± 12.8	6.2 ± 2.8	156.6 ± 12.8	13.0 ± 3.2**
Insula (c)	144.9 ± 16.8	17.2 ± 6.5	138.9 ± 15.3	29.7 ± 12.0**
Insula (i)	154.9 ± 14.3	20.5 ± 8.6	152.3 ± 17.3	43.9 ± 19.5**
MT (c)	186.7 ± 15.4	96.1 ± 30.5	186.9 ± 13.9	139.7 ± 53.0
MT (i)	192.6 ± 15.1	78.2 ± 44.6	190.2 ± 10.2	138.4 ± 47.3**
Cingulate	192.7 ± 16.1	34.5 ± 15.3	198.1 ± 14.2	63.2 ± 17.2**

Note: Data are from Wang et al. (2004). Subjects were asked to silently count the number of painful electrical stimuli (Attention) or ignore the stimuli (Control). S1 and S2 = primary and secondary somatosensory cortex, respectively; MT = medial temporal area; (c) and (i) = hemisphere contralateral and ipsilateral to the stimulation, respectively. *$P < 0.05$, **$P < 0.01$ compared with control (Fisher's protected least significant difference).

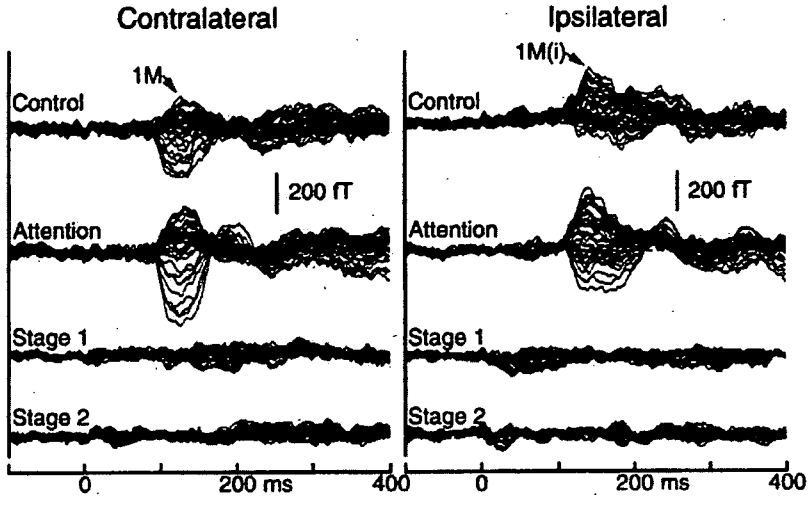

Fig. 2. Magnetic somatosensory evoked magnetic fields (SEFs) following noxious intra-epidermal electrical stimulation of the dorsum of the left hand in the awake state and in sleep stages 1 and stage 2 in humans. Superimposed waveforms were recorded from 37 channels at positions C4 and C3, corresponding to the hemisphere contralateral and ipsilateral to the stimulated hand. 1M and 1M (i) indicate the first components of the magnetic field in the hemisphere contralateral and ipsilateral to stimulation, respectively. Adapted from Wang et al. (2004).

showed that during the attention task, the responses were significantly greater than in the control condition in both hemispheres, at a latency of 130–180 ms. As seen from Fig. 4, the attention task was associated with more activity in the insula and cingulate areas. RMS values of 110–270 ms in stage 1 and stage 2 sleep were significantly smaller than those in the awake control task.

During wakefulness, electrically evoked cortical activities in the insula, cingulate cortex, and medial temporal area were greater than those in S1 or S2 (see Table I and Fig. 4). The processing of noxious events can be separated into sensory-discriminative and affective-motivational components in general, as noted by Sessle in this volume. S1 and S2 are especially involved in the discriminative aspect of pain, in which restricted numbers of specific neurons respond to stimuli, whereas the insula, cingulate cortex, and medial temporal area are involved in the emotional and behavioral aspects of pain, in which larger numbers of neurons specific to "warning" information may be activated by the same stimuli.

The MEG findings by Wang et al. (2004), showing a difference in source strength between S1 and S2 on the one hand and the insula, medial temporal area, and cingulate cortex on the other, could be explained by differences in

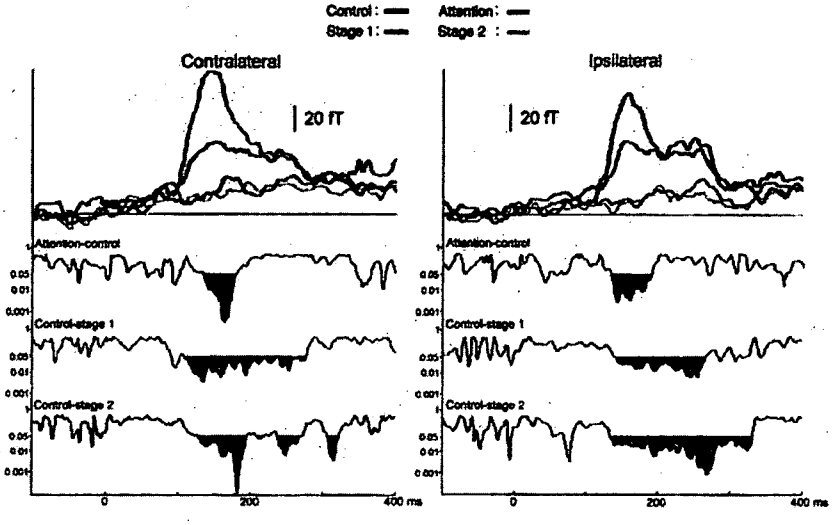

Fig. 3. The group-averaged root mean square of SEFs evoked by electrical stimulation in all subjects in the four conditions and the difference in each sampling point between the control task and each experimental condition (attention, sleep stage 1, and sleep stage 2). The scale for the paired *t*-test is a common logarithm. *P* values < 0.05 were considered to be significant. Adapted from Wang et al. (2004).

response properties among these cortical areas. The greater amplitude of the noxious stimulus-evoked activity in the cingulate cortex than in S1 and S2 is compatible with previous scalp SEP studies (Tarkka and Treede 1993; Xu et al. 1995), in which less activity was generated in S1 or S2 than in the cingulate cortex. Wang et al.'s findings are also consistent with the results of functional neuroimaging studies (Derbyshire et al. 1997; see also Nofzinger and Derbyshire, this volume). A recent intracranial pain-related SEP study showed that the amplitudes of laser-evoked potentials recorded in the cingulate region during wakefulness were greater than those recorded in S1 and S2 (Ohara et al. 2004). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies of cortical activation by noxious stimulation showed inconsistent activation in the medial temporal region, ranging from a significant increase (Bingel et al. 2002) to a significant decrease (Derbyshire et al. 1997) in blood flow in this region. However, previous SEP and SEF studies have demonstrated that medial temporal activation occurs during noxious stimulation (Valeriani et al. 1996, 2000; Watanabe et al. 1998). Sources in the cingulate cortex could not be estimated in half of the subjects in the Wang et al. (2004) study (see also Fig. 4). Therefore, in such subjects, it is possible that the estimated amplitude of the medial temporal source was larger than that of

the actual activity, because the estimated medial temporal source might have included the activities of the cingulate cortex as one dipole.

The involvement of S1 in nociceptive processing during wakefulness has been shown by anatomical and physiological studies in animals, as well as by functional imaging studies in humans (for review, see Bushnell et al. 1999; Schnitzler and Ploner 2000; also see chapters by Sessle and by Nofzinger and Derbyshire in this volume). S1 nociceptive neurons can encode the location,

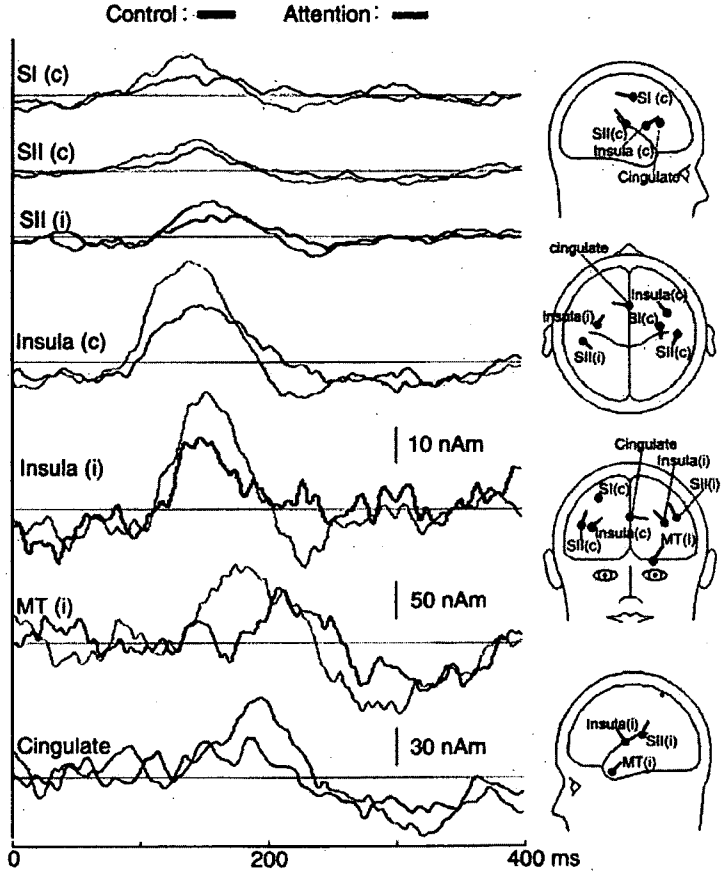

Fig. 4. The group-averaged waveforms of cortical activity (SEFs) evoked by electrical fields in the control and attention tasks and the mean source location. Waveforms obtained in the control and attention tasks are superimposed to clarify the differences in these two conditions. The figure presents the grand-averaged waveform in 10 subjects (except for the cingulate cortex, $n = 5$ subjects), and the source locations are shown in schematic head drawings. MT = medial temporal area; SI and SII = primary and secondary somatosensory cortex, respectively. Adapted from Wang et al. (2004).

intensity, and duration of a stimulus (Lamour et al. 1983; Kenshalo et al. 1988; Chudler et al. 1990; Iwata et al. 1998), and so S1 is considered to be involved primarily in the discriminative aspect of pain, as noted above. Nonetheless, noxious stimulation-related S1 activation is also regulated by cognitive factors (Bushnell et al. 1999). However, the early components of activity generated by noxious stimulation in S1 in humans did not show any significant change in latency and amplitude during sleep compared to the awake state (Wang et al. 2004).

Nociceptive neurons have also been documented in S2 in animals, but in contrast to S1 nociceptive neurons, S2 neurons have larger, bilateral receptive fields, and they encode stimulus intensity poorly (Robinson and Burton 1980; Dong et al. 1989). A large number of PET and fMRI studies (Coghill et al. 1994; Davis et al. 1998), as well as MEG studies (Hari et al. 1983; Watanabe et al. 1998; Ploner et al. 1999b; Kanda et al. 2000), have also documented S2 responses to noxious stimuli during the waking state in humans, and another study in a patient with cerebral infarction in the postcentral gyrus and the parietal operculum suggested that S2 is involved in pain perception (Ploner et al. 1999a). Wang et al. (2004) have found that during sleep, in comparison to the awake state, the long-latency components generated in S2 by noxious stimulation were abolished. This marked reduction of S2 activity during sleep supports the concept that S2 activity may be related to awareness of nociceptive inputs rather than to the magnitude of the nociceptive stimulus (Wang et al. 2003b, 2004; also see Nofzinger and Derbyshire, this volume).

Nociceptive neurons have also been described in the insula of animals, and activity can be evoked in the insula by noxious stimuli during wakefulness in human studies using SEF recordings (Inui et al. 2003), SEP recordings (Garcia-Larrea 1998), intracranial SEP recordings (Frot and Mauguière 2003), and functional imaging (Coghill et al. 1994; Davis et al. 1998). In clinical studies, patients with insular lesions show reduced feelings of pain and reduced reactions to painful stimuli but no changes in pain threshold (Berthier et al. 1988; Greenspan et al. 1999). These findings indicate that the insula may be involved in the affective and motivational aspects of pain, which is consistent with the MEG findings of Wang et al. (2003b, 2004). However, due to the attenuation of electrical-stimulation-evoked cortical potential during sleep, it was not possible to define the role of the insula in pain perception in relation to sleep.

During wakefulness, functional imaging studies (Talbot et al. 1991; Rainville et al. 1997) have consistently demonstrated activation in the anterior cingulate cortex (ACC) during noxious stimulation. Furthermore, single-cell recordings have revealed that the presence of nociceptive neurons in the ACC in humans and animals (Hutchison et al. 1999; Iwata et al. 2005) and that neurons in the ACC may be selectively active during a pain-avoidance behavior

(Koyama et al. 2000). Interestingly, a clinical study has reported that lesions of the cingulate cortex may relieve the feeling of persistent pain (Hurt and Ballantine 1974), and a study in which lidocaine was injected into this region in rats (Vaccarino et al. 1989) also indicates that the cingulate cortex is part of the affective component of pain. It is also noteworthy that an fMRI study (Sawamoto et al. 2000) reported that activation in the ACC was significantly increased even by expectancy of painful laser stimuli. These various findings in humans and animals suggest affective or attentional roles of this region that are consistent with the MEG findings of Wang et al. (2003 a,b). However, in the study from Wang et al. (2004), noxious stimulation evoked ACC activity in only 5 out of 10 subjects, perhaps because the ACC is located too deep for a response to be detectable or because the cingulate cortex is usually activated bilaterally when a noxious stimulus is applied to a part of the body, and so the ipsilateral and contralateral activity might conceivably cancel each other out. Also, as mentioned above, due to the attenuation of cortically evoked potentials during sleep, it was impossible to delineate the role of the cingulate cortex in responses evoked by noxious stimulation during sleep.

Activation in the medial temporal area has been demonstrated in humans following noxious stimulation during wakefulness in studies using SEF recording (Watanabe et al. 1998; Inui et al. 2003), SEP recording (Valeriani et al. 1996, 2000) and functional neuroimaging (Bingel et al. 2002). The MEG study of Wang et al. (2004) also found that noxious electrical stimulation of the left hand produced activation in the ipsilateral medial temporal area in all 10 subjects tested, whereas activation in the contralateral medial temporal area was documented in only two subjects, consistent with a previous report (Inui et al. 2003; Wang et al. 2003a,b). When the noxious stimuli were applied to the right hand, activation in the ipsilateral medial temporal area occurred in all subjects; these results are similar to results obtained from stimulating the left hand. In addition, medial temporal activity in both hemispheres was significantly enhanced during the attention task relative to the control task, whereas later magnetic activities, as well as the main component, were almost abolished during sleep. These MEG findings indicate that the medial temporal area may participate bilaterally in nociceptive processing, but it is unclear why the ipsilateral area was dominantly activated. Nonetheless, the study revealed that arousal level markedly influenced the bilateral activations in the MT. Other studies have also revealed that pain-related cortical potentials can be modulated by arousal and attention levels (Beydoun et al. 1993; Yamasaki et al. 2000). Thus, these findings collectively suggest that the medial temporal area is involved in the attentional and emotional aspects of nociception, consistent with the traditional concept that this area is part of the limbic system and is involved in the emotional aspects of pain.

Magnetic fields recorded by MEG reflect mainly excitatory postsynaptic potentials (EPSPs) in cortical pyramidal neurons. Therefore, Wang et al. (2004) suggested that their MEG findings indicated that the EPSPs generated in all cortical areas during the awake state were modulated by attention and sleep. Nociceptive signals might, for example, be blocked during sleep in each cortical area by presynaptic or postsynaptic inhibitory mechanisms, or could be modulated at the subcortical relays in the ascending somatosensory pathways (Lavigne et al. 2007; see also the Peever and McGinty plus Nofzinger and Derbyshire chapters in this volume). Activity of nociceptive neurons, at both the thalamic and the subthalamic levels, can be modulated by changes in the state of arousal or attention (Bushnell et al. 1985, 1987, 1989; Morrow and Casey 1992).

CONCLUSION

This chapter has examined whether nociceptive sensory inputs reach the cerebral cortex during sleep. Recent evidence suggests that little or no cortical activation occurs in response to noxious stimulation during sleep and that the manipulation of attention is associated with modulation of pain-related cortical activity. However, the sleeping brain remains capable of awakening if somatosensory inputs are potentially harmful.

ACKNOWLEDGMENT

Research of the authors is supported by the Japan Space Forum.

REFERENCES

Addy RO, Dinner DS, Luders H, et al. The effects of sleep on median nerve short latency somatosensory evoked potentials. *Electroencephalogr Clin Neurophysiol* 1989; 74:105–111.

Becker DE, Yingling CD, Fein G. Identification of pain, intensity and P300 components in the pain evoked potential. *Electroencephalogr Clin Neurophysiol* 1993; 88:290–301.

Berthier M, Starkstein S, Leiguarda R. Asymbolia for pain: a sensory-limbic disconnection syndrome. *Ann Neurol* 1988; 24:41–49.

Beydoun A, Morrow TJ, Shen JF, Casey KL. Variability of laser-evoked potentials: attention, arousal and lateralized differences. *Electroencephalogr Clin Neurophysiol* 1993; 88:173–181.

Bingel U, Quante M, Knab R, et al. Subcortical structures involved in pain processing: evidence from single-trial fMRI. *Pain* 2002; 99:313–321.

Bromm B, Meier W. The intracutaneous stimulus: a new pain model for algesimetric studies. *Methods Find Exp Clin Pharmacol* 1984; 6:405–410.

Bushnell MC, Duncan GH. Mechanical response properties of ventroposterior medial thalamic neurons in the alert monkey. *Exp Brain Res* 1987; 67:603–614.

Bushnell MC, Duncan GH. Sensory and affective aspects of pain perception: is medial thalamus restricted to emotional issues? *Exp Brain Res* 1989; 78:415–418.

Bushnell MC, Duncan GH, Dubner R, et al. Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. *J Neurosci* 1985; 5:1103–1110.

Bushnell MC, Duncan GH, Hofbauer RK, et al. Pain perception: is there a role for primary somatosensory cortex? *Proc Natl Acad Sci USA* 1999; 96:7705–7709.

Chudler EH, Anton F, Dubner R, Kenshalo DR Jr. Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval. *J Neurophysiol* 1990; 63:559–569.

Coghill RC, Talbot JD, Evans AC, et al. Distributed processing of pain and vibration by the human brain. *J Neurosci* 1994; 14:4095–4108.

Davis KD, Kwan CL, Crawley AP, Mikulis DJ. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. *J Neurophysiol* 1998; 80:1533–1546.

Derbyshire SW, Jones AK, Gyulai F, et al. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain* 1997; 73:431–445.

Dong WK, Salonen LD, Kawakami Y, et al. Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys. *Brain Res* 1989; 484:314–324.

Dowman R. Spinal and supraspinal correlates of nociception in man. *Pain* 1991; 45:269–281.

Frot M, Mauguiere F. Dual representation of pain in the operculo-insular cortex in humans. *Brain* 2003; 126:438–450.

Garcia-Larrea L. Multimodal approaches to laser-evoked potential generators. *Pain Forum* 1998; 7:216–220.

Garcia-Larrea L, Peyron R, Laurent B, Mauguiere F. Association and dissociation between laser-evoked potentials and pain perception. *Neuroreport* 1997; 8:3785–3789.

Greenspan JD, Lee RR, Lenz FA. Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. *Pain* 1999; 81:273–282.

Hari R, Kaukoranta E, Reinikainen K, Huopaniemie T, Mauno J. Neuromagnetic localization of cortical activity evoked by painful dental stimulation in man. *Neurosci Lett* 1983; 42:77–82.

Hurt RW, Ballantine HT Jr. Stereotactic anterior cingulate lesions for persistent pain: a report on 68 cases. *Clin Neurosurg* 1974; 21:334–351.

Hutchison WD, Davis KD, Lozano AM, Tasker RR, Dostrovsky JO. Pain-related neurons in the human cingulate cortex. *Nat Neurosci* 1999; 2:403–405.

Inui K, Tran TD, Hoshiyama M, Kakigi R. Preferential stimulation of A-delta fibers by intra-epidermal needle electrode in humans. *Pain* 2002; 96:247–252.

Inui K, Tran TD, Qiu Y, et al. A comparative magnetoencephalographic study of cortical activations evoked by noxious and innocuous somatosensory stimulations. *Neuroscience* 2003; 120:235–248.

Iwata K, Kamo H, Ogawa A, et al. Anterior cingulated cortical neuronal activity during perception of noxious thermal stimuli in monkeys. *J Neurophysiol* 2005; 94:1980–1991.

Iwata K, Tsuboi Y, Sumino R. Primary somatosensory cortical neuronal activity during monkey's detection of perceived change in tooth-pulp stimulus intensity. *J Neurophysiol* 1998; 79:1717–1725.

Kakigi R, Hoshiyama M, Shimojo M, et al. The somatosensory evoked magnetic fields. *Prog Neurobiol* 2000a; 61:495–523.

Kakigi R, Watanabe S, Yamasaki H. Pain-related somatosensory evoked potentials. *J Clin Neurophysiol* 2000b; 17:295–308.

Kakigi R, Naka D, Okusa T, et al. Sensory perception during sleep in humans: a magnetoencephalographic study. *Sleep Med* 2003; 4:493–507.

Kakigi R, Inui K, Tran TD, et al. Human brain processing and central mechanisms of pain as observed by electro- and magneto-encephalography. *J Chin Med Assoc* 2004; 67:377–386.

Kakigi R, Inui K, Tran TD, et al. Electrophysiological studies on human pain perception. *Clin Neurophysiol* 2005; 116:743–763.

Kanda M, Nagamine T, Ikeda A, et al. Primary somatosensory cortex is actively involved in pain processing in human. *Brain Res* 2000; 853:282–289.

Kenshalo DR Jr, Chudler EH, Anton F, Dubner R. SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. *Brain Res* 1988; 454:378–382.

Kitamura Y, Kakigi R, Hoshiyama M. Effects of sleep on somatosensory evoked responses in human: a magnetoencephalographic study. *Brain Res Cogn Brain Res* 1996; 4:275-279.

Koyama T, Kato K, Mikami A. During pain-avoidance neurons activated in the macaque anterior cingulate and caudate. *Neurosci Lett* 2000; 283:17–20.

Lamour Y, Willer JC, Guilbaud G. Rat somatosensory (Sml) cortex: I. Characteristics of neuronal responses to noxious stimulation and comparison with responses to non-noxious stimulation. *Exp Brain Res* 1983; 49:35–45.

Lavigne G, Zucconi M, Castronovo C, et al. Sleep arousal response to experimental thermal stimulation during sleep in human subjects free of pain and sleep problems. *Pain* 2000; 84:283–290.

Lavigne G, Brousseau M, Kato T, et al. Experimental pain perception remains equally active over all sleep stages. *Pain* 2004; 110:646–655.

Lavigne GJ, Okura D, Smith MT. Sleep and pain. In: Basbaum AI, et al. (Eds). *The Senses: A Comprehensive Reference,* Vol. 3. Elsevier, 2007, in press.

Miltner W, Johnson R Jr, Braun C, Larbig W. Somatosensory event-related potentials to painful and non-painful stimuli: effects of attention. *Pain* 1989; 38:303–312.

Morrow TJ, Casey KL. State-related modulation of thalamic somatosensory responses in the awake monkey. *J Neurophysiol* 1992; 67:305–317.

Naka D, Kakigi R. Simple and novel method for measuring conduction velocity of A delta fibers in humans. *J Clin Neurophysiol* 1998; 15:150–153.

Naka D, Kakigi R, Hoshiyama M, et al. Structure of the auditory evoked magnetic fields during sleep. *Neuroscience* 1999; 93:573–583.

Nakano S, Tsuji S, Matsunaga K, Murai Y. Effects of sleep stage on somatosensory evoked potentials by median nerve stimulation. *Electroencephalogr Clin Neurophysiol* 1995; 96:385-389.

Noguchi Y, Yamada T, Yeh M, et al. Dissociated changes of frontal and parietal somatosensory evoked potentials in sleep. *Neurology* 1995; 45:154–160.

Ohara S, Crone NE, Weiss N, et al. Attention to pain is processed at multiple cortical sites in man. *Exp Brain Res* 2004; 156:513–517.

Okusa T, Kakigi R. Structure of visual evoked magnetic field during sleep in humans. *Neurosci Lett* 2002; 328:113–116.

Ploner M, Freund HJ, Schnitzler A. Pain affect without pain sensation in a patient with a postcentral lesion. *Pain* 1999a; 81:211–214.

Ploner M, Schmitz F, Freund HJ, Schnitzler A. Parallel activation of primary and secondary somatosensory cortices in human pain processing. *J Neurophysiol* 1999b; 81:3100–3104.

Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997; 277:968–971.

Robinson CJ, Burton H. A high resolutioninterval timer and buffered storage system for neurophysiological experiments. *Med Biol Eng Comput* 1980; 18:731–740.

Sawamoto N, Honda M, Okada T, et al. Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. *J Neurosci* 2000; 20:7438–7445.

Schnitzler A, Ploner M. Neurophysiology and functional neuroanatomy of pain perception. *J Clin Neurophysiol* 2000; 17:592–603.

Talbot JD, Marrett S, Evans AC, et al. Multiple representations of pain in human cerebral cortex. *Science* 1991; 251:1355–1358.

Tarkka IM, Treede RD. Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a CO_2 laser. *J Clin Neurophysiol* 1993; 10:513–519.

Vaccarino AL, Melzack R. Analgesia produced by injection of lidocaine into the anterior cingulum bundle of the rat. *Pain* 1989; 39:213–219.

Valeriani M, Rambaud L, Mauguiere F. Scalp topography and dipolar source modeling of potentials evoked by CO_2 laser skin stimulation of the hand. *Electroencephalogr Clin Neurophysiol* 1996; 100:343–353.

Valeriani M, Restuccia D, Barba C, et al. Sources of cortical responses to painful CO_2 laser skin stimulation of the hand and foot in the human brain. *Clin Neurophysiol* 2000; 111:1103–1112.

Wang X, Inui K, Qiu Y, et al. Effects of sleep on pain-related somatosensory evoked potentials in humans. *Neurosci Res* 2003a; 45:53–57.

Wang X, Inui K, Qiu Y, et al. Effects of sleep on pain-related somatosensory evoked magnetic fields in humans. *Brain Res Cogn Brain Res* 2003b; 17:388-399.

Wang X, Inui K, Qiu Y, Kakigi R. Cortical responses to noxious stimuli during sleep. *Neuroscience* 2004; 128:177-186.

Watanabe S, Kakigi R, Koyama S, Hoshiyama M, Kaneoke Y. Pain processing traced by magnetoencephalography in the human brain. *Brain Topogr* 1998; 10:255–264.

Xu X, Kanda M, Shindo K, et al. Pain-related somatosensory evoked potentials following CO_2 laser stimulation of foot in man. *Electroencephalogr Clin Neurophysiol* 1995; 96:12–23.

Yamasaki H, Kakigi R, Watanabe S, Hoshiyama M. Effects of distraction on pain-related somatosensory evoked magnetic fields and potentials following painful electrical stimulation. *Brain Res Cogn Brain Res* 2000; 9:165–175.

Correspondence to: Ryusuke Kakigi, MD, PhD, Department of Integrative Physiology, National Institute for Physiological Sciences, Myodaiji, Okazaki 444-8585, Japan. Tel: +81-564-55-7815; fax: +81-564-52-7913; email: kakigi@nips.ac.jp.

PAIN

Pain xxx (2007) xxx–xxx

www.elsevier.com/locate/pain

Pain-related evoked potentials are modulated across the cardiac cycle

Louisa Edwards [a,*], Koji Inui [b], Christopher Ring [a], Xiaohong Wang [b], Ryusuke Kakigi [b,c]

[a] *International Centre for Health and Exercise Research, University of Birmingham, Birmingham B15 2TT, UK*
[b] *Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki 444-8585, Japan*
[c] *RISTEX, Japan Science and Technology Agency, Japan*

Received 27 April 2007; received in revised form 1 August 2007; accepted 8 October 2007

Abstract

Evidence suggests that the arterial baroreceptors modulate pain. To examine whether cortical processing of nociception is modulated by natural variations in arterial baroreceptor stimulation during the cardiac cycle, peak-to-peak amplitudes of the N2–P2 pain-related potential and pain ratings were recorded in response to noxious laser stimulation at different times during the cardiac cycle in 10 healthy males. Significant variations in the N2–P2 amplitudes occurred across the cardiac cycle, with smaller amplitudes midcycle, indicating that cortical processing of nociception was attenuated during systole compared to diastole. Pain ratings did not vary across the cardiac cycle. These data support the hypothesis that arterial baroreceptors modulate the processing of nociception during each cardiac cycle.

Keywords: Arterial baroreceptors; Cardiac cycle; Pain ratings; Pain-related evoked potentials

1. Introduction

The arterial baroreceptors are stretch receptors located in the aortic arch and carotid sinus that are naturally stimulated during systole by distension of the arterial wall by the pressure pulse wave [24]. Baroreceptor activation has been shown to inhibit sensory [18] and motor [23] processes. Mounting evidence indicates that pain and nociception also vary with baroreceptor activity. Using the nociceptive flexion reflex, a polysynaptic spinal reflex that facilitates withdrawal from noxious stimuli to avoid tissue injury [39], a series of studies found that nociception was attenuated during systole, when the baroreceptors are most active, compared to diastole [2,13–15,26]. In contrast, concurrent pain ratings did not vary across the cardiac cycle [13–15]. However, pain was attenuated when the carotid baroreceptors were artificially stimulated, beyond the normal physiological range, by neck suction (for review, see [33]).

Studies have also examined the effects of neck suction on pain-related evoked brain potentials comprising a negativity (N2) followed by a positivity (P2). These potentials correlate with both pain reports and stimulus intensity [9] and are attenuated by centrally-acting analgesics [41], and therefore, have been interpreted as reflecting the cognitive processing of a noxious stimulus [20]. Both N2 and P2 amplitudes [28] and the peak-to-peak N2–P2 amplitude [3] elicited by noxious intracutaneous electrical stimulation of the finger were found to be attenuated by neck suction. However, another study has reported that the N2–P2 amplitude was augmented by neck suction [5]. Accordingly, these studies indicate that stimulation of the arterial baroreceptors can modulate processing of noxious stimuli.

To date, no studies have investigated whether natural variations in baroreceptor stimulation across the cardiac

* Corresponding author. Tel.: +44 121 415 8785; fax: +44 121 414 4121.
E-mail address: L.Edwards@bham.ac.uk (L. Edwards).

0304-3959/$32.00
doi:10.1016/j.pain.2007.10.010

cycle, in the normal physiological range, influence cortical processing of noxious stimuli. The current study investigated the influence of the cardiac cycle, as an index of pulsatile variations in blood pressure, on the cortical processing of nociception. The study used thulium-evoked laser stimulation, that exclusively activates nociceptive nerve fibers, to evoke pain-related late brain potentials [22,29]. Based on previous findings that the nociceptive flexion reflex is attenuated during systole, it was hypothesised that the N2–P2 amplitude, an objective index of the degree of induced pain [6], would be smaller during systole than diastole.

2. Methods

2.1. Participants

Ten healthy male normotensive volunteers, with a mean age of 33 years (SD = 6), mean height of 171 cm (SD = 4), mean weight of 65 kg (SD = 6), mean systolic blood pressure of 120 mmHg (SD = 11), mean diastolic blood pressure of 77 mmHg (SD = 9) and mean heart rate of 63 bpm (SD = 11), participated in the study. All participants were free from neurologic and psychiatric diseases and psychiatric and analgesic medications. Participants were asked to refrain from alcohol, caffeine and smoking for at least 12 h prior to testing. The study was approved by the Ethics Committee at National Institute for Physiological Sciences, Okazaki; all volunteers gave informed consent to participate.

2.2. Laser stimulation

A thulium:YAG laser stimulator (Carl Baasel Lasertech, Starnberg, Germany) was used to produce noxious stimuli. Laser pulses (1 ms in duration, 2000 nm in wavelength, and 3 mm in spot diameter) were delivered to the dorsum of the right hand at an interval of between 15 and 20 s. The irradiated points were moved slightly for each stimulus to avoid tissue damage and habituation of the receptors. At the start of the session, 10–20 laser stimuli were delivered to determine the stimulus intensity required to produce a painful sensation. After each stimulus, the participants rated the stimulus using a visual analogue scale (VAS), with anchors of 0 (no painful sensation) and 100 (imaginary intolerable pain sensation). A stimulus intensity ($M = 158$, SD = 9 mJ), rated as approximately 50 on the VAS, was used to examine pain-related evoked potentials (see below). At this laser intensity, all subjects rated the stimulus as a pricking pain sensation. Trained subjects can discriminate the first and second pain sensations, however, no subjects in this study reported a sensation other than pricking.

2.3. Laser evoked potential recording

The laser evoked potentials were recorded with an Ag/AgCl disk electrode placed over Cz (vertex), referred to the linked earlobes (A1 + A2) of the International 10/20 System. A pair of electrodes placed on the supra- and infra-orbit of the right eye was used for recording an electro-oculogram. An electrocardiogram was recorded using a pair of disk electrodes placed on each forearm. The impedance of all electrodes was kept below 5 kΩ. The electroencephalographic signals were recorded with a 0.1 to 100 Hz bandpass filter and digitized at a sampling rate of 1000 Hz. The period of analysis was 800 ms before to 600 ms after stimulus onset; the pre-stimulus period was used as the DC baseline. Individual trials containing artifacts due to eye blinks were rejected before averaging.

2.4. Procedure

Each subject was seated in an armchair in a quiet, electrically shielded, and temperature controlled (24 to 26 °C) room. Laboratory systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm) were measured three times using a mercury sphygmomanometer and a brachial cuff attached to the participant's upper left arm. The experimental session consisted of 5 blocks of 12 trials. Each block was separated by a 10-min rest period. During the experiment, a fixation point (a white circle 2 cm in diameter) was displayed on a screen 1.5 m in front of the subjects from 10 to 15 s before until 2 s after each stimulus. Subjects were instructed to look at the fixation point when it was displayed. Two seconds after the onset of each stimulus, the fixation point disappeared and 'VAS' was displayed for 3 s, during which subjects rated the perceived sensation. Then the fixation point appeared again to prepare the next stimulus. The participants were instructed to rate the perceived pricking sensation associated with each laser stimulation by marking a 100 mm VAS.

2.5. Data reduction and analysis

The R-wave latency relative to stimulus onset (ms) and peak-to-peak amplitude (μV) of the N2–P2 component were measured in each trial. The peak of N2 and P2 was determined during a latency period of 180–240 and 280–400 ms, respectively, for each trial. To show the variability of N2/P2 components in each trial, the waveforms of 12 consecutive trials in a representative participant are depicted in Fig. 1. In addition, the amplitudes of each N2 and P2 component were measured, using a DC offset, from the prestimulus baseline of −100 ms to the peak negativity and positivity, respectively. Trials were then sorted into one of eight 100 ms wide intervals (each interval is labeled by its midpoint), whose minimum and maximum indicated the timing of the noxious stimulation after the R-wave: 0–99 ms (R + 50 ms), 100–199 ms (R + 150 ms), 200–299 ms (R + 250 ms), 300–399 ms (R + 350 ms), 400–499 ms (R + 450 ms), 500–599 ms (R + 550 ms), 600–699 ms (R + 650 ms) and 700–800 ms (R + 750 ms). The mean (SD) number of trials per R-wave to stimulation interval was 5.0 (1.6), 5.3 (2.8), 6.3 (2.8), 5.4 (2.8), 5.4 (1.8), 6.2 (1.9), 5.4 (2.9), 6.4 (2.2) for R-wave intervals R + 50 to R + 750 ms, respectively. All participants provided data for every R-wave to stimulation interval. Data were lost (25% of total number of trials) on trials with blink artifacts and trials when the R-wave occurred more than 800 ms before the onset of noxious stimulation. The mean N2, P2 and N2–P2 peak-to-peak amplitudes (μV) and pain ratings were calculated for each R-wave to stimulation interval. Repeated measures analyses of variance (ANOVAs) with R-wave to stimulation interval (i.e., R + 50,

Please cite this article in press as: Edwards L et al., Pain-related evoked potentials are modulated across the cardiac cycle, Pain (2007), doi:10.1016/j.pain.2007.10.010

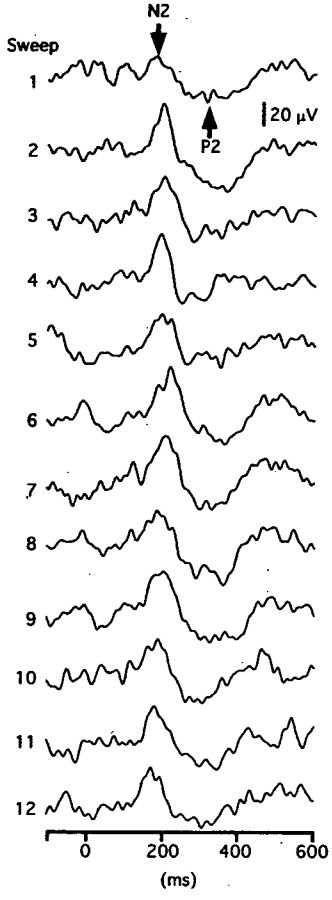

Fig. 1. Pain-related evoked potential waveforms of 12 consecutive trials, depicting N2 and P2, in a representative participant.

R + 150, R + 250, R + 350, R + 450, R + 550, R + 650, R + 750 ms) as a within-subjects factor were performed on the N2, P2 and N2–P2 amplitudes and pain ratings. ANOVAs were corrected for the assumption of independence of data points using the Huynh–Feldt correction (ε). Eta-squared (η^2), a measure of effect size, is also reported. A significance level of .05 was adopted. Significant results were followed by LSD post hoc tests. The data were analyzed using Statistica'99.

3. Results

3.1. N2–P2 peak-to-peak amplitudes

A repeated measures ANOVA (8 Intervals) revealed significant variations in the N2–P2 amplitude across the cardiac cycle, $\varepsilon = .74$, $F(7, 63) = 3.15$, $p = .02$, $\eta^2 = .26$, which were characterized by a quadratic trend, $F(1, 9) = 29.83$, $p = .0005$, $\eta^2 = .77$ (see Fig. 2). Post hoc comparisons confirmed that the N2–P2 amplitudes elicited by stimulation at R + 250, R + 350 and R + 450 ms were smaller than those elicited at R + 50, R + 150 and R + 750 ms. For illustrative purposes, the grand mean waveforms, averaged for the early (R + 50, R + 150 ms), middle (R + 250, R + 350, R + 450 ms)

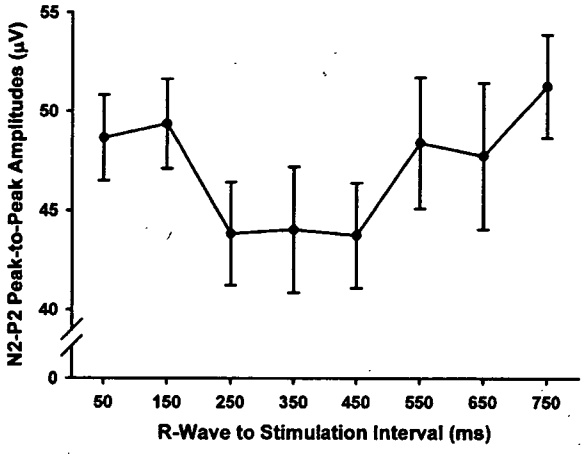

Fig. 2. Mean (SE) N2–P2 peak-to-peak amplitudes as a function of phase of the cardiac cycle. A repeated measures ANOVA revealed significant variations in the N2–P2 amplitude across the cardiac cycle ($p = .02$). Post hocs comparisons confirmed that N2–P2 amplitudes elicited by stimulation at R + 250, R + 350 and R + 450 ms were smaller than those elicited at R + 50, R + 150 and R + 750 ms. $N = 10$, Trials = 45. SE = SD ÷ $\sqrt{N}$.

and late (R + 550, R + 650, R + 750 ms) phases of the cardiac cycle, are presented in Fig. 3, where it can be seen that the amplitudes were smaller mid-cycle compared to early and late cycle.

3.2. N2 amplitudes

A repeated measures ANOVA (8 Intervals) revealed significant variations in the N2 amplitude across the cardiac cycle, $\varepsilon = .99$, $F(7, 63) = 4.13$, $p = .001$, $\eta^2 = .31$, which were characterized by a quadratic trend, $F(1, 9) = 25.43$, $p = < .001$, $\eta^2 = .74$ (see Fig. 4). Post hoc comparisons confirmed that the N2 amplitudes elicited by stimulation at R + 250 ms were smaller than those elicited at R + 50, R + 150, R + 650 and R + 750 ms. Stimulation at R + 350 ms produced smaller N2 amplitudes than R + 150, R + 650 and R + 750 ms. Finally, stimulation at R + 450 ms produced smaller N2 amplitudes than R + 650 and R + 750 ms.

3.3. P2 amplitudes

A repeated measures ANOVA (8 Intervals) did not reveal significant variations in the P2 amplitude across the cardiac cycle, $\varepsilon = .84$, $F(7, 63) = 0.73$, $p = .63$, $\eta^2 = .07$ (see Fig. 5).

3.4. Pain ratings

A repeated measures ANOVA (8 Intervals) revealed no significant differences in pain ratings across the cardiac cycle, $\varepsilon = .64$, $F(7, 63) = 1.10$, $p = .37$, $\eta^2 = .11$ (see Fig. 6).

Please cite this article in press as: Edwards L et al., Pain-related evoked potentials are modulated across the cardiac cycle, Pain (2007), doi:10.1016/j.pain.2007.10.010

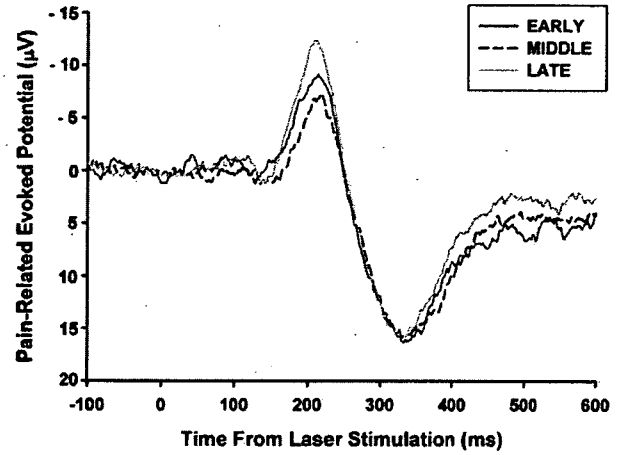

Fig. 3. Grand average pain-related evoked potentials waveforms grouped into early (R + 50 to R + 150 ms), middle (R + 250 to R + 450 ms), and late (R + 550 to R + 750 ms) phases of the cardiac cycle. $N = 10$, Trials = 45.

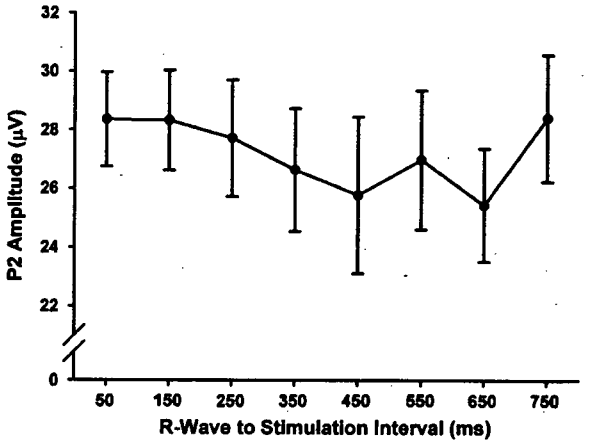

Fig. 5. Mean (SE) P2 amplitudes as a function of phase of the cardiac cycle. A repeated measures ANOVA did not reveal significant variations in the P2 amplitude across the cardiac cycle ($p = .63$). $N = 10$, Trials = 45. SE = SD ÷ $\sqrt{N}$.

4. Discussion

The present study found significant variations across the cardiac cycle in the amplitude of the N2–P2 pain-related components of the evoked potential elicited by noxious laser stimulation. The N2–P2 amplitude difference is believed to be an objective index of the degree of induced pain [6]. Indeed, positive relationships have been found between the intensity of noxious laser stimuli, the amplitude of the N2–P2, and the magnitude of pain sensation [7]. The observation of smaller amplitude N2–P2 waveforms during the middle of the cardiac cycle indicates that pain-related cortical responses were attenuated during systole compared to diastole. Accordingly, these data support the hypothesis that stimulation of the arterial baroreceptors by natural changes in blood pressure during the cardiac cycle has a dampening effect on the nociceptive system.

In the present study, we only recorded the N2–P2 components of the evoked potential from one electrode at Cz. Therefore, the data cannot reveal the precise mechanisms of N2–P2 modulation across the cardiac cycle. However, the grand-averaged waveform (see Fig. 3) suggests that the cardiac cycle effect was larger for N2 than P2. Indeed, separate analyses of the N2

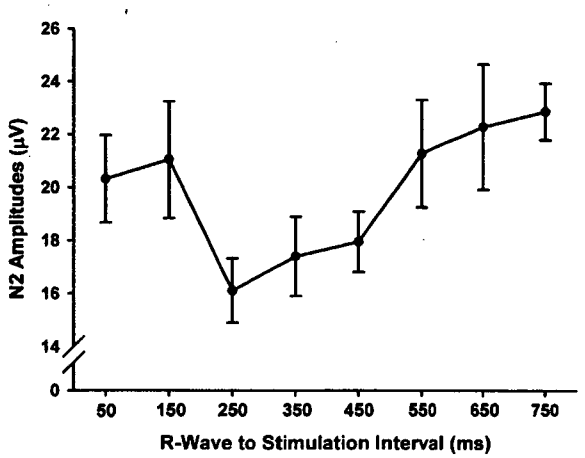

Fig. 4. Mean (SE) N2 amplitudes as a function of phase of the cardiac cycle. A repeated measures ANOVA revealed significant variations in N2 amplitude across the cardiac cycle, ($p = .001$). Post hocs comparisons confirmed that N2 amplitudes elicited by stimulation at R + 250 ms were smaller than those elicited at R + 50, R + 150, R + 650 and R + 750 ms. Stimulation at R + 350 ms produced smaller N2 amplitudes than R + 150, R + 650 and R + 750 ms. Finally, stimulation at R + 450 ms produced smaller N2 amplitudes than R + 650 and R + 750 ms. $N = 10$, Trials = 45. SE = SD ÷ $\sqrt{N}$.

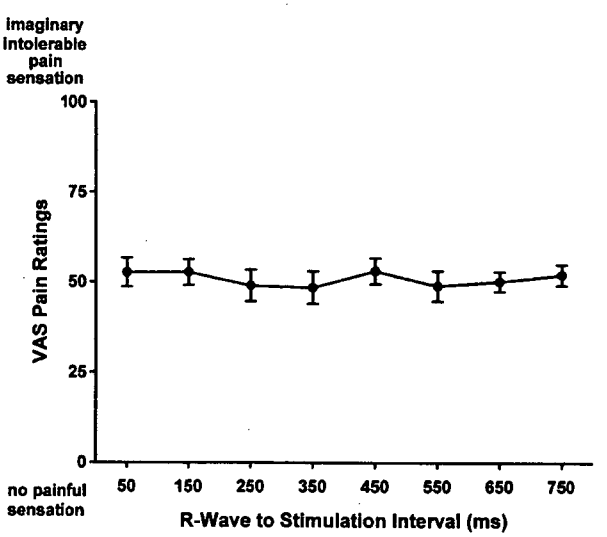

Fig. 6. Mean (SE) VAS pain ratings as a function of phase of the cardiac cycle. A repeated measures ANOVA revealed no significant differences in pain ratings across the cardiac cycle ($p = .37$). $N = 10$, Trials = 45. SE = SD ÷ $\sqrt{N}$.

Please cite this article in press as: Edwards L et al., Pain-related evoked potentials are modulated across the cardiac cycle, Pain (2007), doi:10.1016/j.pain.2007.10.010

and P2 components revealed cardiac cycle time effects for N2 and not P2. The N2 and P2 components are generated mainly in the anterior cingulate cortex [8,43,46]. In addition to anterior cingulate cortex, the secondary somatosensory cortex or insula cortex contribute to shape the N2 component [8,31,43,46]. Therefore, our findings are compatible with the hypothesis that the target site of the interaction between N2 and P2 and baroreceptor output is the somatosensory or insula cortex. Further studies employing multi-channel recordings are required to test this hypothesis.

This is the first study, to our knowledge, to describe modulation of the pain-related evoked potential with natural variations in baroreceptor activation across the cardiac cycle. The current findings broadly agree with previous research which has reported reduced N2–P2 amplitudes elicited by intracutaneous stimulation of the finger during artificial stimulation of the baroreceptors using neck suction [3,28]. In addition, the current data are in line with reports of dampened lower limb nociceptive flexion reflex responding during systole compared to diastole [13–15,26]. The modulating effect of the cardiac cycle on the brain appears not to be exclusive to nociception. Auditory and visual perception vary with the phase of the cardiac cycle: sensitivity is generally lowest at the start of the cardiac cycle and increases as the cycle progresses [37,40]. Further, modulation of visual and auditory event-related potentials has been demonstrated during systole and diastole: the P1 component of the visual evoked potential [47] and the N1 component of the auditory evoked potential [38] were smaller during systole. Previous research has demonstrated that rhythmic oscillations of the EEG, most notably in the alpha range, were time locked to the carotid pressure wave [48]. Other research has examined the effects of artificial baroreceptor stimulation on the brain. A classic study in cats showed that mechanical stimulation of the carotid sinus baroreceptors had an inhibitory influence on cortical excitability [4]. Further, artificial baroreceptor stimulation in humans has been shown to cause a substantial reduction in slow cortical negative potentials, particularly the contingent negative variation, an index of cortical arousal [17,34,35]. Accordingly, the current cycle time effect for the pain-related evoked potential adds to a compelling body of evidence for a relationship between the cardiovascular system and the brain.

Pain was not modulated across the cardiac cycle in the current study. This is in line with previous studies which found no differences in pain reports for electrocutaneous stimuli delivered at various intervals after the R-wave of the electrocardiogram [13–15]. These findings contrast with the results of other studies that employed artificial baroreceptor manipulations. These studies reported that pain was lower during systole compared to diastole during neck suction [2], during repeated neck suction and compression [28,32], as well as during single neck suction and compression pulses [13]. These contradictory findings may be due to differences between natural and artificial baroreceptor stimulation studies in terms of the level of baroreceptor stimulation achieved.

The mechanism by which pain-related cortical processing is attenuated by the cardiac cycle has yet to be determined. However, it is reasonable to assume that these effects might be due to natural fluctuations in arterial baroreceptor activity across the cardiac cycle (see [15,16]). The integrated baroreceptor output of aortic baroreceptors located in the aortic arch and carotid sinus can be estimated to extend from 90 to 390 ms after the R-wave. The current study found that the N2–P2 amplitude was attenuated when noxious stimuli were delivered to the hand during the 200–299, 300–399 and 400–499 ms intervals after the R-wave. The onset latency of cortical activity in SI and SII, the proposed site of interaction, following noxious YAG laser stimulation to the hand has been recorded at 90–110 ms [30,49]. Thus, as N2–P2 was modulated from 200 ms after the R-wave, the earliest time the SII must be affected by baroreceptor activity is 290 ms after the R-wave. Accordingly, the observed pattern of modulation of the N2–P2 amplitude is compatible with the pattern of baroreceptor activation when a sensory transduction and processing delay of approximately 150 ms is included. This 150 ms delay may be explained by neural transmission times within the brainstem. For example, electrical stimulation of baroreceptor afferents in dogs and cats has been shown to cause inhibition of sympathetic activity with a latency of 150–200 ms, dependent on the recording site at the spinal level [10,36]. Allowing 10–15 ms for transmission of nerve impulses from carotid sinus and aortic arch to the nucleus of the solitary tract [42], and approximately 30 ms from the rostral ventrolateral medulla to sympathetic preganglionic neurons [25], this leaves 100–150 ms for transmission in the lower brainstem from the nucleus of the solitary tract to the rostral ventrolateral medulla [11]. This 100–150 ms transduction latency could perhaps explain the 150 ms delay between baroreceptor activation and attenuation of the N2–P2 amplitudes found in the current study. Further, there is substantial evidence suggesting that structures involved in the baroreflex pathway could also influence the pain system (for review, see [19]). For example, stimulation of the nucleus of the solitary tract induces antinociception [1] and the A5 cell group and locus coeruleus are sources of descending noradrenergic fibers that modulate spinal nociceptive transmission [27]. Furthermore, other evidence shows that pain areas are involved in baroreflex control. The periaqueductal grey matter, which produces analgesia when stimulated, can modulate the arterial baroreflex [21]. The nucleus raphe magnus in the rostral ventrolateral medulla, which plays a role in pain modulation, is involved in

Please cite this article in press as: Edwards L et al., Pain-related evoked potentials are modulated across the cardiac cycle, Pain (2007), doi:10.1016/j.pain.2007.10.010

the baroreflex pathway mentioned above, and also contains neurons that respond to noxious stimuli that show spontaneous fluctuations in phase with both natural variations and experimentally-induced changes in blood pressure [44,45]. Accordingly, this evidence demonstrates a close integration of areas involved in pain modulation and cardiovascular regulation.

The current study should be interpreted in light of some possible limitations. Neither blood pressure nor vessel diameter was measured during laser stimulation. Accordingly, the extent to which the pulse pressure wave distended the aortic arch and carotid sinus was not characterized, and therefore, the precise timing and magnitude of arterial baroreceptor stimulation is not known. Further, respiration was not measured in the current study and therefore the potential moderating effects of the phase of the respiratory cycle on the effects observed across the cardiac cycle were not determined. Given that baroreceptor function can vary between inspiration and expiration [12], research is needed to explore these putative effects. The sample size may be considered a potential weakness. However, many pain-related evoked potential studies tested similar numbers of participants. This study only tested men and therefore the generalizability of the cycle time effect for the N2–P2 amplitude needs to be determined in female participants. Accordingly, firm conclusions regarding the influence of baroreceptor activation on pain-related cortical processing should not be drawn until the current findings have been replicated by larger studies of mixed gender.

In conclusion, variations in the N2–P2 amplitudes across the cardiac cycle, with smaller amplitudes mid-cycle, indicated that cortical processing of nociception was attenuated during systole compared to diastole. These data support the hypothesis that arterial baroreceptors modulate the processing of nociception during each cardiac cycle.

References

[1] Aicher SA, Randich A. Antinociception and cardiovascular responses produced by electrical stimulation in the nucleus tractus solitarius, nucleus reticularis ventralis, and the caudal medulla. Pain 1990;42:103–19.

[2] Al'Absi M, France CR, Ring C, France J, Harju A, McIntyre D, et al. Nociception and baroreceptor stimulation in hypertension-prone men and women. Psychophysiology 2005;42:83–91.

[3] Angrilli A, Mini A, Mucha RF, Rau H. The influence of low blood pressure and baroreceptor activity on pain responses. Physiol Behav 1997;62:391–7.

[4] Bonvallet M, Dell P, Hiebel G. Tonus sympathique et activite electrique corticale. Electroencephalogr Clin Neurophysiol 1954;6:119–44.

[5] Brody S, Angrilli A, Weiss U, Birbaumer N, Mini A, Veit R, et al. Somatotosensory evoked potentials during baroreceptor stimulation in chronic low back pain patients and normal controls. Int J Psychophysiol 1997;25:201–10.

[6] Bromm B, Lorenz J. Neurophysiological evaluation of pain. Electroencephalogr Clin Neurophysiol 1998;107:227–53.

[7] Bromm B. Laser-evoked cerebral potentials in the assessment of cutaneous pain sensitivity in normal subjects and patients. Rev Neurol 1991;147:625–43.

[8] Bromm B, Chen ACN. Brain electrical source analysis of laser evoked-potentials in response to painful trigeminal nerve-stimulation. Electroencephalogr Clin Neurophysiol 1995;95:14–26.

[9] Bromm B, Meier W. The intracutaneous stimulus – a new pain model for algesimetric studies. Methods Find Exp Clin Pharmacol 1984;6:405–10.

[10] Coote JH, Macleod VH, Fleetwoodwalker SM, Gilbey MP. Baroreceptor inhibition of sympathetic activity at a spinal site. Brain Res 1981;220:81–93.

[11] Dembowsky K, Mcallen RM. Baroreceptor inhibition of subretrofacial neurons – evidence from intracellular-recordings in the cat. Neurosci Lett 1990;111:139–43.

[12] Eckberg DL, Sleight P. Human baroreflexes in health and disease. Oxford: Clarendon Press; 1992.

[13] Edwards L, McIntyre D, Carroll D, Ring C, France CR, Martin U. Effects of artificial and natural baroreceptor stimulation on nociceptive responding and pain. Psychophysiology 2003;40:762–9.

[14] Edwards L, McIntyre D, Carroll D, Ring C, Martin U. The human nociceptive flexion reflex threshold is higher during systole than diastole. Psychophysiology 2002;39:678–81.

[15] Edwards L, Ring C, McIntyre D, Carroll D. Modulation of the human nociceptive flexion reflex across the cardiac cycle. Psychophysiology 2001;38:712–8.

[16] Edwards L, Ring C, McIntyre D, Carroll D, Martin U. Psychomotor speed in hypertension: effects of reaction time components, stimulus modality, and phase of the cardiac cycle. Psychophysiology 2007;44:459–68.

[17] Elbert T, Rockstroh B, Lutzenberger W, Kessler M, Pietrowsky R, Birbaumer N. Baroreceptor stimulation alters pain sensation depending on tonic blood pressure. Psychophysiology 1988;25:25–9.

[18] Gahery Y, Vigier D. Inhibitory effects in cuneate nucleus produced by vago-aortic afferent-fibers. Brain Res 1974;75:241–6.

[19] Ghione S. Hypertension-associated hypalgesia. Hypertension 1996;28:494–504.

[20] Handwerker HO, Kobal G. Psychophysiology of experimentally-induced pain. Physiol Rev 1993;73:639–71.

[21] Inui K, Murase S, Nosaka S. Facilitation of the arterial baroreflex by the ventrolateral part of the midbrain periaqueductal grey matter in rats. J Physiol 1994;477:89–101.

[22] Kakigi R, Shibasaki H, Ikeda A. Pain-related somatosensory evoked-potentials following CO_2-laser stimulation in man. Electroencephalogr Clin Neurophysiol 1989;74:139–46.

[23] Koch EB. Die Irradiation der pressorezeptorischen kreislaufreflexe. Klin Wochenschr 1932;2:225–7.

[24] Mancia G, Mark AL. Arterial baroreflexes in humans. In: Shepherd JT, Abboud FM, editors. Handbook of physiology. The cardiovascular system. Bethesda, Maryland: American Physiological Society; 1983. p. 755–93.

[25] Mcallen RM. Identification and properties of sub-retrofacial bulbospinal neurons – a descending cardiovascular pathway in the cat. J Auton Nerv Syst 1986;17:151–64.

[26] McIntyre D, Edwards L, Ring C, Parvin B, Carroll D. Systolic inhibition of nociceptive responding is moderated by arousal. Psychophysiology 2006;43:314–9.

[27] Miller JF, Proudfit HK. Antagonism of stimulation-produced antinociception from ventrolateral pontine sites by intrathecal administration of α-adrenergic antagonists and naloxone. Brain Res 1990;530:20–34.

Please cite this article in press as: Edwards L et al., Pain-related evoked potentials are modulated across the cardiac cycle, Pain (2007), doi:10.1016/j.pain.2007.10.010

[28] Mini A, Rau H, Montoya P, Palomba D, Birbaumer N. Baroreceptor cortical effects, emotions and pain. Int J Psychophysiol 1995;19:67–77.
[29] Mor J, Carmon A. Laser emitted radiant heat for pain research. Pain 1975;1:233–7.
[30] Nakata H, Inui K, Wasaka T, Tamura Y, Tran TD, Qiu YH, et al. Movements modulate cortical activities evoked by noxious stimulation. Pain 2004;107:91–8.
[31] Peyron R, Frot M, Schneider F, Garcia-Larrea L, Mertens P, Barral FG, et al. Role of operculoinsular cortices in human pain processing: converging evidence from PET, fMRI, dipole modeling, and intracerebral recordings of evoked potentials. Neuroimage 2002;17:1336–46.
[32] Rau H, Brody S, Larbig W, Pauli P, Vohringer M, Harsch B, et al. Effects of PRES baroreceptor stimulation on thermal an mechanical pain threshold in borderline hypertensives and normotensives. Psychophysiology 1994;31:480–5.
[33] Rau H, Elbert T. Psychophysiology of arterial baroreceptors and the etiology of hypertension. Biol Psychol 2001;57:179–201.
[34] Rau H, Elbert T, Lutzenberger W, Eves F, Rockstroh B, Larbig W, et al. Pavlovian conditioning of peripheral and central components of the baroreceptor reflex. J Psychophysiol 1988;2:119–27.
[35] Rau H, Pauli P, Brody S, Elbert T, Birbaumer N. Baroreceptor stimulation alters cortical activity. Psychophysiology 1993;30:322–5.
[36] Richter DW, Keck W, Seller H. Course of inhibition of sympathetic activity during various patterns of carotid sinus nerve stimulation. Pflugers Arch Eur J Physiol 1970;317:110–23.
[37] Sandman CA, McCanne TR, Kaiser DN, Diamond B. Heart rate and cardiac phase influence on visual perception. J Comp Physiol Psychol 1977;91:189–202.
[38] Sandman CA. Augmentation of the auditory event related potentials of the brain during diastole. Int J Psychophysiol 1984;2:111–9.
[39] Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. Prog Neurobiol 2005;77:353–95.
[40] Saxon SA. Detection of near threshold signals during four phases of the cardiac cycle. Ala J Med Sci 1970;7:427–30.
[41] Scharein E, Bromm B. The intracutaneous pain model in the assessment of analgesic efficacy. Pain Rev 1998;5:216–46.
[42] Seller H, Illert M. Localization of first synapse in carotid sinus baroreceptor reflex pathway and its alteration of afferent input. Pflugers Arch Eur J Physiol 1969;306:1–19.
[43] Tarkka IM, Treede RD. Equivalent electrical source analysis of pain-related somatosensory-evoked potentials elicited by a Co2-Laser. J Clin Neurophysiol 1993;10:513–9.
[44] Thurston CL, Randich A. Effects of vagal afferent stimulation on ON and OFF cells in the rostroventral medulla: Relationships to nociception and arterial blood pressure. J Neurophysiol 1992;67:180–96.
[45] Thurston CL, Randich A. Responses to on and off cells in the rostral ventral medulla to stimulation of vagal afferents and changes in arterial pressure in intact and cardiopulmonary deafferentated rats. Pain 1995;62:19–38.
[46] Valeriani M, Rambaud L, Mauguiere F. Scalp topography and dipolar source modelling of potentials evoked by CO_2 laser stimulation of the hand evoked potentials. Electroencephalogr Clin Neurophysiol 1996;100:343–53.
[47] Walker BB, Sandman CA. Visual evoked potentials change as heart rate and carotid pressure change. Psychophysiology 1982;19:520–7.
[48] Walker BB, Walker JM. Phase relations between carotid pressure and ongoing electrocortical activity. Int J Psychophysiol 1983;1:65–73.
[49] Wang X, Inui K, Kakigi R. Early cortical activities evoked by noxious stimulation in humans. Exp Brain Res 2007;180:481–9.

Cerebral Cortex May 2007;17:1139-1146
doi:10.1093/cercor/bhl023
Advance Access publication July 19, 2006

Inner Experience of Pain: Imagination of Pain While Viewing Images Showing Painful Events Forms Subjective Pain Representation in Human Brain

Yuichi Ogino[1], Hidenori Nemoto[1], Koji Inui[2], Shigeru Saito[1], Ryusuke Kakigi[2] and Fumio Goto[1]

[1]Department of Anesthesiology, Gunma University Graduate School of Medicine, 3-39-22 Showamachi, Maebashi 371-8511, Japan and [2]Department of Integrative Physiology, National Institute for Physiological Sciences, Myodaiji, Okazaki 444-8585, Japan

Pain is an unpleasant sensation, and at the same time, it is always subjective and affective. Ten healthy subjects viewed 3 counterbalanced blocks of images from the International Affective Picture System: images showing painful events and those evoking emotions of fear and rest. They were instructed to imagine pain in their own body while viewing each image showing a painful event (the imagination of pain). Using functional magnetic resonance imaging, we compared cerebral hemodynamic responses during the imagination of pain with those to emotions of fear and rest. The results show that the imagination of pain is associated with increased activity in several brain regions involved in the pain-related neural network, notably the anterior cingulate cortex (ACC), right anterior insula, cerebellum, posterior parietal cortex, and secondary somatosensory cortex region, whereas increased activity in the ACC and amygdala is associated with the viewing of images evoking fear. Our results indicate that the imagination of pain even without physical injury engages the cortical representations of the pain-related neural network more specifically than emotions of fear and rest; it also engages the common representation (i.e., in ACC) between the imagination of pain and the emotion of fear.

Keywords: brain, emotion, fMRI, IAPS (International Affective Picture System), pain, SII (secondary somatosensory cortex)

Introduction

Pain is an unpleasant sensation, but at the same time, it is always subjective and emotional (Fields 1999). Individuals learn of "pain" through experiences related to injury in their life, and they are able to imagine pain from their past experiences even without physical injury.

Recently, from the viewpoint of "empathy," some neuroimaging studies on pain processing have revealed a partial neural overlap between the experience of pain in self and the observation of pain in others (i.e., empathy for other's pain) (Singer and others 2004; Botvinick and others 2005; Jackson and others 2005). Although the actual experience of pain and the empathic feeling of the pain of other individuals involve similar brain regions such as the anterior cingulate cortex (ACC) and anterior insula, activations of the secondary somatosensory cortex (SII) and dorsal ACC were specifically attributable to receiving actual pain and were not detected from the observation of pain in others (Singer and others 2004). However, changing perspective taking, Jackson and others (2006) clearly differentiated the cerebral representation between the imagination of pain (i.e., a self-oriented aversive response that induces both empathy and distress) and imagining how others would feel pain (i.e., empathy for other's pain), showing that the imagination of pain activates the pain-related neural network (pain matrix) extensively including the SII, dorsal ACC (Brodmann Area [BA] 24), and insula. Furthermore, in a study of patients with phantom limb pain using a hypnotic suggestion that the missing limb was in a painful position, Willoch and others (2000) found a similar activation in the pain matrix including the SII, ACC, and insula in the absence of any noxious stimulation.

The aim of our functional magnetic resonance imaging (fMRI) study is to investigate the hemodynamic changes stemming from the inner experience of pain (imagination of pain) perceived from viewing images showing painful events in an intact body, in comparison with those stemming from another aversive emotion, that is, fear and rest emotion elicited by the International Affective Picture System (IAPS) (Lang and others 2005). This picture system includes images of several different emotional scenes; it is possible to use these images to elicit specific emotions. In a number of neuroimaging studies using the IAPS, various emotions, such as happiness, sadness (Lang and others 1998), and disgust (Schienle and others 2002), the anticipation of painful stimulation and aversive situations (Simmons and others 2004), the anticipation of aversion (Nitschke and others 2006), and their neural mechanisms have been shown. We focused on the emotions of pain and fear because these emotions have common features. Pain and fear belong to the category "negative affect," which is associated with the withdrawal from the emotion elicitor serving to protect the organism from being harmed and are also part of different warning systems dealing with different types of threat.

Materials and Methods

Subjects

Ten healthy, right-handed volunteers (10 males; mean age 26.3 ± 4.7 years [range 22-37 years]) participated in the fMRI study. The subjects were all fMRI-experienced males. The subjects had no history of head injury, learning disability, or psychiatric illness, including substance abuse/dependence or taking regular medications. All the subjects gave their written informed consent after the explanation of the experimental protocol, as approved by the local Institutional Review Board.

Task Design

The stimulus materials consisted of 45 images belonging to 3 emotional categories: images showing painful events (pain condition), images evoking fear (fear condition), and images evoking rest (rest condition) (15 each). Trials were blocked by the emotional categories. The block order was counterbalanced. In each block, 5 images of the same emotional category were presented for every 6 s (a 5-s presentation with a 1-s interstimulus interval). One run consisted of nine 30-s blocks and lasted 270 s. All the subjects performed 2 runs. Each pain, fear, and rest image was presented twice in the experiment. The stimuli were displayed through a shielded liquid crystal display panel mounted on the head coil.

The images were taken from the IAPS of Lang and others (2005), which includes images that have already been rated as representative examples on different emotional dimensions: mainly valence and arousal