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THE ROYAL SOCIETY

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Functional neuroimaging has fundamentally changed our knowledge about the cerebral representation of pain. For the first time it has been possible to delineate the functional anatomy of different aspects of pain in the medial and lateral pain systems in the brain. The rapid developments in imaging methods over the past years have led to a consensus in the description of the central pain responses between different studies and also to a definition of a central pain matrix with specialized subfunctions in man. In the near future we will see studies where a systems perspective allows for a better understanding of the regulatory mechanisms in the higher-order frontal and parietal cortices. Also, pending the development of experimental paradigms, the functional anatomy of the emotional aspects of pain will become better known.

Keywords: functional imaging; tomography; pain processing; cerebral cortex

1. INTRODUCTION

Pain is an unpleasant experience that involves the conscious awareness of noxious sensations, hurting and aversive feelings associated with actual or potential tissue damage (International Association for the Study of Pain 1994). The human pain experience is a multidimensional experience manifesting sensory–discriminative, cognitive–evaluative and affective–motivational components (Melzack & Casey 1968). Although the development of experimental models that mimic various clinical pain syndromes may provide a reasonable view of supraspinal mechanisms for the representation of nociception (for a review, see Bennett 1994), such models are of limited use when other aspects of the pain experience are studied. Indeed methods other than functional neuroimaging have provided the basic information on the supraspinal organization of the pain systems. Advanced anatomical electrophysiological methods have revealed numerous ascending tracts and nociresponsive supraspinal structures (Apkarian & Shi 1994; Brüggemann *et al*. 1994; Craig *et al*. 1994; Guilbaud *et al*. 1994). Functional neuroimaging allows the recording of functional activity across the whole brain simultaneously and with equal sensitivity. The functional neuroimaging methods have also provided means for the elucidation of the functional anatomy of the different components of pain. General methodological constraints for functional imaging are discussed elsewhere in the present issue (Petersson *et al*., this issue). However, there are some points that apply specifically to pain imaging and will be discussed here. Some of the imaging literature on pain may appear difficult to reconcile with information from other sources and the origin of such variations and the significant amount of variation in the results from imaging studies may be accounted for by differences in experimental paradigms and imaging technology or statistics.

The wide definition of pain recognizes that the experience of pain is modulated by a complex set of emotional, environmental and psychophysiological variables (Feuerstein 1989; Price 1988). Pain can therefore be expected to influence brain processing on many levels. This influence is not only expressed in terms of pain processing proper but also by competition for central mechanisms of consciousness such as attention, information selection, learning, avoidance and anticipation. This complexity represents a challenge in that most neuroimaging has a modular approach where isolation of singular cognitive components is sought.

2. METHODOLOGICAL CONSIDERATIONS IN PAIN IMAGING

It is of central importance to recognize that the different axes of the pain experience work on different time bases. While somatosensory information (of localizing nature) is processed in the sub-second range other aspects such as the motivational–affective axis pertains to slower processes. Some aspects of pain processing, such as coping, induce neural processing prior to actual pain stimulus. The most common methods for imaging brain function (positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) rest on the cerebral haemodynamic response to a change of the activity level locally in the brain. In many respects this is a relatively slow response in comparison with the actual neural events, but both the nature of the processing and optimization of the experimental paradigm make it possible to circumvent this potential problem. Even after a very brief and well-defined event this vascular response is delayed (approximately 5 s following the event) and biphasic in that it contains an early positive response followed by an undershoot that lasts up to 30 s. The relative tardiness of the response function has to be taken into account when designing experiments. In specific, the undershoot that follows a brief stimulus may introduce baseline shifts with an inclination that depends on the time between repeats of the stimulus (figure 1).

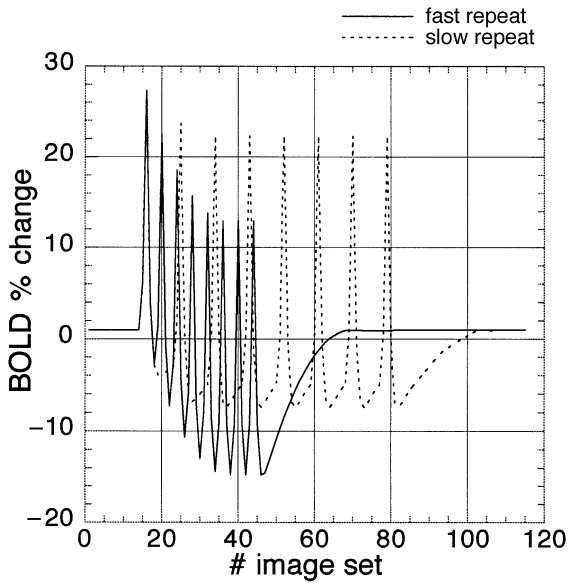

Figure 1. A simulation of the effect of the time between stimulus in fMRI and the baseline stability. Note that the baseline shift is nonlinear. The simulation is based on time between stimulus of 10 s versus 20 s.

Transient changes elicited by brief stimuli can be detected as event-related signals with both electrophysiological-based and regional cerebral blood flow (rCBF)-based methods (Friston *et al*. 1998*a*,*b*). Due to lack of sensitivity, repeated sampling is used in order to characterize the response. Such repetitions of stimulus are not trivial from the experimental point of view as repetitions always include both linear and nonlinear changes in response over time and repetitions on both the behavioural and the methodological levels. Event-related responses are detected based on their synchronicity with the triggering event. Thus, a brief event that is well defined in the time domain lends itself to detection with these methods. However, the central processes are organized in a parallel distributed manner (Rumelhart & McClelland 1986) with feedforward and feedback mechanisms amply represented (Carpenter & Grossberg 1989). Hence, any significant event will lead to changes longer than the initial electrophysiological event and hence these flow-based event-related methods will be suitable for detecting brain function at a systems level (Brewer *et al*. 1998).

Each picture element contains information on both location and function. The better the resolution, the higher the risk of contaminating the functional information with artefacts from morphology, especially if group or inter-group studies are performed. Inter-group studies entail specific problems of a statistical nature that must be accounted for in the imaging of clinical pain syndromes (Petersson *et al*., this issue).

PET methodology rests on the intravenous injection of a tracer that is distributed in proportion to the blood flow. This allows for a measurement of the CBF at a defined point in time, but does not allow the investigator to follow changes over time. Global blood flow changes may act as a confounder when detecting regional changes. Many pain paradigms will influence arterial carbon dioxide tension, which is the strongest regulator of global brain blood flow. A measurement of the arterial input function (the amount of radioactivity available for the brain) is necessary for the full quantification of the rCBF. However, this is seldom done since either flow normalization or covariance procedures can be used in order to account for variations in the global blood flow (Fox & Mintum 1989; Friston *et al*. 1990; Ingvar *et al*. 1994). Carbon dioxide tension in the blood may influence the activity in the limbic system and an interaction cannot be ruled out if a pain paradigm also induces changes in the $PaCO_2$ level in the blood (Corfield *et al*. 1995).

fMRI improves our possibilities of reaching functional imaging data on an individual basis. In pain imaging it will mean that individual diagnosis and treatment follow-up should be possible to achieve. The reasons are many.

First, imaging may be performed on regular clinically used instruments, which are present in many sites, at 1.5 tesla (T) (Schad *et al*. 1995). Seemingly successful studies have even been reported at 1.0 T (Jones *et al*. 1998). However, the trend is clear that several groups are taking advantage of higher field magnets in the urge to improve signal-to-noise characteristics of fMRI (Menon *et al*. 1993).

Second, fMRI has the advantage over PET that large amounts of data may be collected in each subject, and essentially it is only the time in the camera and changes of response over time (habituation, learning, fatigue etc.) that limit the time of study.

Third, it is possible to successfully use fMRI to study the functional response following single (but repeated) events (Buckner *et al*. 1998; Friston *et al*. 1998*a*; Rosen *et al*. 1998).

For obvious reasons, recordings of the electrophysiological responses seem to be the ideal way in the quest for understanding the organization of the working of the brain. The unsurpassed resolution in time combined with increasing accuracy of models for three-dimensional (3D) localization of activity makes these methods attractive candidates for the future (Fukushima *et al*. 1994; Hari & Kaukoranta 1985; Hari *et al*. 1997; Huttunen *et al*. 1986; Tarkka *et al*. 1995; Thatcher 1995). There still exist major problems, in that the models of detection of multiple sources do not carry a single solution. Modern algorithms together with a multitude of squids show great promise especially in the detection of cortically located pain responses, and reports on at least semiquantitive response evaluations have occurred (Hari *et al*. 1997). Also, the impressive resolution in time makes it possible to reveal the mechanisms underlying the sequencing of processing, as well as laterality in response to unilateral stimulation. Magnetoencephalography data suggest that S2 seems to receive bilateral input and respond synchronously to elicited pain (Kakigi *et al*. 1995).

EEG-based methods have now improved a lot with the use of multi-electrode arrays. The combination of different imaging methods shows great promise (Rosler *et al*. 1995). Realistic head models may provide further improvements and allow more than surface modelling of brain activity with spatial reliability (Babiloni *et al*. 1997).

The combination of electrophysiology with fMRI has great promise for future improvement of the description of brain events in the spatial and temporal domain (Menon *et al*. 1997). The importance of event-related fMRI is not only in the ability to time different events but also to reduce or even eliminate the problems with low-frequency physiological noise, since stimulus presentation

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can be randomized in the time domain (Friston *et al*. 1998*a*,*b*).

Of special importance in pain studies are problems with paradigm-synchronous movements. Pre-stimulus apprehension seems to induce slight movements and must be avoided even if parts can be removed in the post-processing by image realignment. Also, physiological noise from respiration and circulation should be accounted for as it provides a significant interference with the interpretation of results. While box-car designs are robust they may be difficult to use, since it is well known that the experience of pain changes rapidly during the initial period of stimulus. Event-related fMRI approaches tend to minimize the noise from physiological variables as the stimuli may be administered randomly over time and, hence, in a non-synchronous manner in respect to the biorhythms. However, the potential problem of stimulus-synchronous movements is still present.

(a) *Increases and decreases in rCBF*

Functional neuroimaging rests on the idea that cerebral work leads to increased energy metabolism and a disproportionate augmentation of CBF (Fox & Raichle 1986). Hence, the signal does not separate primary excitatory and inhibitory neural firing. It does not separate a net inhibitory effect from a net excitatory one. The cerebrovascular response only detects state-dependent changes in compounded activity of inhibitory and excitatory neurons. While increases in activity have been readily accepted as an expression of increased brain work, curiously, decreases have been less readily accepted as an index of the opposite. Experimental data suggest that an active inhibitory process may take place at the site of reduced rCBF (Freund & Antal 1988; Ghatan *et al*. 1995; Seitz & Roland 1992; Tsen & Haberly 1988). Changes in rCBF are tightly coupled to the level of regional neuronal activity (Raichle 1987). Therefore, an increase or decrease of rCBF indicates either an increased or a diminished net neuronal activity which is physiologically coupled and paradigm specific (Drevets *et al*. 1995; Ghatan *et al*. 1998; Haxby *et al*. 1994).

(b) *Mapping of pharmacology in pain paradigms*

Studies of different brain receptor systems during pain are theoretically very appealing. Basic studies of pain-relevant receptor system anatomy can be obtained with PET (Jones *et al*. 1991*b*). It would be of great interest to demonstrate changes in response to, for example, chronic pain. Indeed some successful trials have been reported demonstrating changes using diprenorphine as the probe. A group of patients with rheumatoid arthritis were examined to test the hypothesis that there is a change in the endogenous opioid system in the brain during inflammatory pain. Regional cerebral opioid receptor binding was quantified using the opioid receptor antagonist [^{11}C]diprenorphine and PET. In the patients studied in and out of pain, significant increases in [^{11}C]diprenorphine binding were seen in association with a reduction in pain. Increases were seen in most of the areas of the brain that were sampled apart from the occipital cortex. These findings suggest increases in occupancy by endogenous opioid peptides during inflammatory pain (Jones *et al*. 1994).

A possible difficulty is the contamination of the blood flow signal when extracting the information about binding potential and other more sophisticated receptor parameters when comparing receptor function in different brain states such as pain or pain-free states (Jones *et al*. 1991*b*) or rest versus mental activity (Koepp *et al*. 1998). Validation experiments seem to exclude a major influence of blood flow on the mentioned results. From a theoretical perspective it would be of value to develop the use of steady-state methods as the changes in CBF do not affect the results regarding the pharmacological parameters (Lassen 1992).

(c) *Imaging statistics*

The statistical treatment of imaging data is by no means trivial, and global searches are notoriously insensitive when properly corrected for multiple comparisons. Data from subtraction analyses are sometimes difficult to interpret since a proper analysis rests on the ability to control all experimental parameters in such a way that only relevant details differ between the studied states (Friston *et al*. 1996). However, in well-designed studies, there are several strategies at hand to improve both specificity and sensitivity. If the search volume is restricted to a few regions that can be anatomically defined, then the effect of correcting for multiple comparisons becomes negligible. In other words, if the study is made with the aim of understanding one mechanism with an underlying functional anatomical experience, then test only for that. A limitation of the anatomical search volume can be made by inferring results from another source (e.g. data from other scans in different or the same subjects) by a masking and conjunction approach (Price & Friston 1997). Following restricted searches a global search of exploratory nature can be performed. In pain imaging, it has proven very useful to regress the blood flow signal on external parameters such as behavioural measures of pain intensity or unpleasantness.

3. THE CENTRAL PAIN MATRIX

Many imaging studies have been performed and, in spite of sometimes very disparate study paradigms, a striking consistency seems to prevail about the functional neuroanatomy of the central pain matrix when examining main effects in subtraction designs (pain versus non-pain states). The supraspinal structures participating in processing nociceptive information include the reticular formation including the periaqueductal grey (PAG), the hypothalamus (HT), the thalamus, the limbic system, and several areas in the cortex (for a review, see Bonica 1990). The role of the cerebral cortex has been debated (Roland 1992*a*,*b*) but lately imaging has led to the firm conclusion that many cortical areas are involved in the experience of pain. The thalamus is the relay centre for cortical afferent information and can be broadly characterized into medial (palaeo-) thalamus and lateral (neo-) thalamus. Only the lateral systems seem to be somatotopically organized and project mainly to the primary and secondary sensory cortices (SI and SII). The medial thalamus receives input from multiple ascending systems of the spinal cord and the reticular formation. Pathways from the medial thalamus project diffusely to

wide areas of the cortex that together make up the 'medial pain system'.

(a) *The anterior cingulate cortex (BA 24/32)*

The anterior cingulate cortex (ACC) is the cortical region that is activated in almost every study of elicited pain starting with the first studies of PET and pain (Jones *et al*. 1991*a*; Talbot *et al*. 1991). The ACC can functionally be segregated into several parts and the loci of activation in the ACC varies between studies based on the construction of the imaging paradigm. It was known before the 3D imaging era that the ACC is involved in nociceptive processing in that lesions in the ACC reduced the reaction to nociceptive input (Vaccarino & Melzack 1989). The rostral section (perigenual part) has shown activation in almost all studies where the level of attention was unbalanced between the different states, which is analogous to the ACC activation in studies of executive attention (Bench *et al*. 1992; Ghatan *et al*. 1995; Pardo *et al*. 1990). In contrasts that are balanced for components of attention, the pain-elicited activation in the ACC is generally more caudal and more confined to the Brodmann area (BA) 24′ (Davis *et al*. 1997; Hsieh *et al*. 1995). Thus, it seems that the general stratification of the ACC into sub-regions of visceromotor, skeletomotor control cortex and nociceptive cortex, that was developed from animal studies and sparse human lesion data (Devinsky *et al*. 1995), has been confirmed by functional imaging in man. However, Vogt *et al*. (1996) have argued that activations in the perigenual ACC represent affective components of pain whereas the caudally situated activation more represents response selection like 'nocifensive reflex inhibition'. In a later paper, Derbyshire *et al*. (1998) made an attempt to stratify the different components of the ACC by using paradigms of either pain stimulus or challenge of attention mechanisms by means of the Stroop colour word interference test. The design was that of separate experiments in the same individuals and individual analysis suggested a separation of the functional anatomical representation for the two paradigms. In contrast to the studies on phasic pain, tonic stimuli of heat or cold seem less efficient in evoking rCBF changes in the ACC (Coghill *et al*. 1993; Di Piero *et al*. 1994; Jones *et al*. 1991*a*). However, with intense tonic stimuli there seems to be no difficulty in provoking ACC activations (Casey *et al*. 1996).

ACC is part of the medial pain system and the functional significance of the caudal ACC activation seems to be in the affective–evaluative dimension (Vogt *et al*. 1993). Robust activations are seen here in experimental conditions where acute pain is elicited (Davis *et al*. 1997; Guilbaud *et al*. 1994; Kakigi *et al*. 1995; Talbot *et al*. 1991; Tarkka & Treede 1994; Thierry *et al*. 1990). This seems also to be true for visceral pain (Aziz *et al*. 1997). In chronic pain states with habitual pain the activity is reduced upon pain alleviation suggesting a tonic increase in activity in this region in chronic pain states (Hsieh *et al*. 1995). In a study by Rainville *et al*. (1997) hypnotic suggestions were used to selectively alter the unpleasantness of noxious stimuli, without changing the perceived intensity level. The pain-evoked activity within the ACC was significantly reduced by this manipulation, whereas primary somatosensory cortex activation was unaltered, speaking for the selectivity of the ACC response. Reciprocally, it was possible by the experimental set-up of the thermal grill illusion to produce activation in the ACC. The illusion was created by touching warm (not painfully hot) and cool bars that were spatially interlaced and this produced a painful burning sensation resembling that caused by intense, noxious cold. The same area was also activated by noxious heat or cold but not by warm and cold stimuli (Craig *et al*. 1996).

As mentioned, in chronic pain states with habitual pain the ACC is chronically activated (Hsieh *et al*. 1995). In patients with ongoing pain a provocation of mechanical allodynia ('pain on pain') did not provoke an ACC activation, a finding that was interpreted as a different role of the ACC in chronic pain states (Peyron *et al*. 1998). An alternative explanation, given the presence of the spontaneous pain in the group of patients studied, would be that the variability in the ACC activity would be expected to be high thereby explaining the absence of significant difference between states. We performed a 'pain added to pain' study in a similar group of patients with peripheral mononeuropathy and mechanical allodynia and instead correlated the ACC activity to the reported pain intensity. Thereby, we accounted for the presence of different levels of spontaneous and elicited pain, and found a correlation in the ACC (Petrovic *et al*. 1998*b*). Hence, our data do not support an altered correlation between the suffering component of pain and activity in the ACC in chronic pain.

(b) *Thalamus*

As the relay centre for afferent input to the brain, the thalamus can be divided into medial (palaeo-) thalamus and lateral (neo-) thalamus. The former, which includes the medial and intralaminar nuclei, is not somatotopically organized. It receives input from multiple ascending systems of the spinal cord and the reticular formation. Pathways from the medial thalamus project diffusely to wide areas of the cortex and together make up the 'medial pain system'. On the other hand, the ventrobasal thalamus is somatotopically organized. It receives input from a somatotopically organized ascending tract and sends fibres to the primary (SI) and secondary (SII) somatosensory areas of the cerebral cortex, where refined localization and discrimination of stimuli occur. These areas make up the 'lateral pain system'. The activations of the thalamus elicited in experimental conditions seem less consistent than in the ACC. This could partly be explained by anatomical variations in a heterogeneous and complex structure where the actual representation of pain-elicited activity appears only in circumscribed areas (Craig *et al*. 1994). However, intra-individual direct comparison showed that a pain stimulus and not vibratory stimulation activated the thalamus (Coghill *et al*. 1994; Disbrow *et al*. 1998). The apparent lack of consistency probably stems from problems of methodological sensitivity (Di Piero *et al*. 1997). In chronic ongoing pain due to mononeuropathy, alleviation of the ailment by local injection of xylocaine led to pain relief and in parallel an increase in rCBF (Hsieh *et al*. 1995). This suggestion of a regulation of the thalamic activity in chronic pain was corroborated by a study where the contralateral thalamus was shown to have a decreased

blood flow in patients with chronic neuropathic pain (Iadarola *et al*. 1995).

(c) *SI and S2*

Currently, it is accepted that the medial pain system is mainly involved in motivational and affective aspects of pain; the lateral pain system is presumed to process and transmit spatially discriminative aspects of noxious stimuli (Chudler *et al*. 1990; Craig *et al*. 1994). It was for a long time regarded as a region with little importance for pain experience since surgical extirpation of S1 and S2 areas in humans provides little or no relief from chronic intractable pain (Head & Holmes 1911). Also, electrical stimulation of SI did not evoke painful responses in neurosurgical patients nor did ablation of SII cause detectable sensory deficits (Penfield & Jasper 1954). However, clinical (Greenspan & Winfield 1992; Young & Blume 1983), physiological (Chudler *et al*. 1990; Kenshalo *et al*. 1988; Kenshalo & Willis 1991), and functional brain imaging studies (Casey *et al*. 1994, 1996; Coghill *et al*. 1994; Talbot *et al*. 1991) suggest that the somatosensory cortex may participate not only in the spatial discriminative aspects of nociception but also in the further elaboration of the sensory experience.

Early imaging studies were inconclusive. In studies on experimental tonic pain, rCBF in SI has been shown to increase, remain unaltered, or vary individually (Coghill *et al*. 1993; Derbyshire *et al*. 1993; Di Piero *et al*. 1994). Some studies even reported decreases in contralateral S1 in response to a pain stimulus (Apkarian *et al*. 1992). Activation in SI has been reported when using the analgesic compound, capsaicin. This method reduces the possible tactile components of the pain stimulus to a minimum (Iadarola *et al*. 1993, 1998). The activity in the SI was found to be correlated to the intensity of tonic (heat) painful input, which suggests that the discriminatory role is not confined to the spatial domain but also entails intensity coding (Duncan *et al*. 1994). Very intense pain stimuli seem to activate the SI consistently (Hsieh *et al*. 1996*b*). The SI and motor area 1 (MI) have been demonstrated to be coactivated (either confluently or discretely) in imaging studies on sustained high-intensity (visual analogue scale: VAS $\geqslant$ 80%) tonic cold pain (Di Piero *et al*. 1994), and acute phasic heat pain (using fMRI) (Gelnar *et al*. 1994). We used a cognitive loading in trying to modulate to a standardized nociceptive input. In an analysis of interaction it was shown that cognitive loading by means of a computerized maze test concurrent with a standardized pain stimulus led to a relative decrease of activity, most prominently in SII combined with reports of lower experience of pain intensity from the subjects (Petrovic *et al*. 1998*a*).

The paucity of nociceptive neurons and the not well-demarcated receptive fields (Dong *et al*. 1989), suggest that the SII may not subserve the functions of precise spatial localization and intensity encoding. However, there are data suggesting that it is possible to detect a somatotopic representation in the pain response in SII with the foot region more posteriorly located than the hand (Andersson *et al*. 1997; Petrovic *et al*. 1998*b*). Also, the responses in SII seem often to be bilateral in response to a unilateral stimulus, but this trait is common to sensory stimuli that are also bilaterally represented in this region (Tarkka & Treede 1994).

The absence of significant cortical rCBF changes in SI and SII in chronic peripheral neuropathic pain (Hsieh *et al*. 1995) does not refute cortical responses below the sensitivity of this technique. The lack of detectable response may reside in the adaptive or learning mechanism that a familiarized mental task does not require the same degree of neuronal activity (magnitude of change and the amount of neurons) as in the naive situation (Jenkins *et al*. 1994; Petersson *et al*. 1997; Raichle 1997).

In cluster headache and visceral pain there seems to be less involvement of the SI region in line with the feature of poor spatial localization for these two entities of clinical pain syndromes (Hsieh *et al*. 1996*a*; Rosen *et al*. 1994). However, the paper by Aziz *et al*. (1997) and co-workers is at variance with this contention, since their model of oesophageal distension gave rise to a bilateral increase of the activity in S1. The authors speculate that the activation may hint at a possible mechanism for referred pain from the oesophagus.

(d) *Sensory–motor coactivations*

The SI and MI have been demonstrated to be coactivated (either confluent or discrete) in several imaging studies on sustained high-intensity (VAS $\geqslant$ 80%) painful electrostimulation (Hsieh 1995), tonic cold pain (using single photon emission computed tomography) (Di Piero *et al*. 1994), and acute phasic heat pain (using fMRI) (Gelnar *et al*. 1994). The activity in these two regions could also be correlated to the pain intensity (tonic heat pain) (Duncan *et al*. 1994). Thus the confluent activation of SI–MI may conform to the hypothesis that the pre- and post-central areas often function in concert (Libet 1973; Penfield & Jasper 1954). In fact earlier rCBF studies noted the dominance of sensory activations in some motor paradigms and called this the sensory–motor paradox (Ingvar 1975). It is therefore not a trivial task in any high intensity pain paradigm on what factor to account for activations in the motor and sensory cortices. If an intensive pain stimulus leads to the urge to move (withdraw) the stimulated limb and the subject is asked to be still during the scan, major parts may be due to cortical overriding of otherwise automatic movements initiated as lower level events. This may also, at least in part, be explained by the urge to move due to the pain stimulus, a component that is difficult to control in pain imaging (Hsieh *et al*. 1994; Petrovic *et al*. 1998*b*).

(e) *Brain defence system*

There is direct nociceptive input from spinal pathways to the limbic system and HT. These structures mediate the neuroendocrine 'stress response' (Kupfermann 1993). The HT has large, direct projections to almost all areas in the CNS that are involved in the autonomic control of visceral organs, including prominent direct projections to preganglionic neurons in the brainstem and the spinal cord (Swanson 1987). The PAG subserves various functions of the defensive behaviour and modulates the nociceptive transmission and integrates together with the HT many endocrine and autonomic responses associated with aggressive–defensive behaviours (Bandler & Shipley 1994). The phrase 'brain defence system' (BDS) has been

used to describe the concerted function of these anatomical structures and the amygdala.

The BDS system is most often not activated in controlled pain experiments where the subjects are well informed and the element of threat is reduced to a minimum. However, when acute pain was instigated based on a minimal skin lesion the BDS was activated (Hsieh *et al*. 1996*b*). A damaging stimulus that is threatening to the living organism often produces changes in affect or mood, and causes a host of somatic and autonomic reflexive responses (Cousins 1994). In a study of angina pectoris (visceral pain) the BDS was also activated. Angina signals cardiac ischaemia and thereby threat of tissue injury (Rosen *et al*. 1994). In induced cluster headache attacks it was shown that there was an activation in the HT that was not present in control subjects where the same provocation with nitroglycerine was instigated (May *et al*. 1998*a*,*b*). Possibly, different operational mechanisms are recruited in processing a potential or actual traumatic painful event versus non-traumatic painful challenge with a low level of affective response. The activity may also represent the function of this system in the descending inhibitory functions that seem to be important in the regulation of the pain input (Petrovic *et al*. 1998*a*).

(f) *Anterior insula*

The anterior-ventral insula is a polymodal convergence area that has extensive connections with orbitofrontal, temporopolar, anterior cingulate, olfactory, gustatory and autonomic structures whereas the posterior-dorsal insular is more closely connected to somaesthetic, auditory, motor, and high-order association areas (Mesulam & Mufson 1985). The anterior insula has consistently demonstrated activations in almost all studies of experimentally induced pain (Andersson *et al*. 1997; Casey *et al*. 1996; Hsieh *et al*. 1995, 1996*a*,*b*). Direct comparison between vibrotactile stimulus and painful stimulation showed that, whereas both these stimuli activated the S1/S2 region, a painful stimulus was significantly more effective in activating the anterior insula (Coghill *et al*. 1994). Chronic pain where the localizing and discriminatory dimensions are less evident and the affective or evaluative component seem to dominate activate the anterior insular region bilaterally (Hsieh *et al*. 1995).

(g) *Prefrontal cortex*

Converging evidence suggests the 'supervisory' and 'regulatory' role of the prefrontal cortex (PFC), since damage here leads to impairments in planning, personality, behavioural control, affective attachment, motor programming, and directed or sustained attention (Shallice 1982). Planning or suppressing a behaviour, or maintaining a cortically controlled behaviour, entails maintaining a neural representation of that behaviour. Such a neural representation includes not only static information but also sequencing information (information on the time domain) (Goldman-Rakic 1987). Such representations are sensitive to disturbance and critically reliant on patent mechanisms of attention. In the limited space of consciousness, pain makes its way by attention mechanisms that in turn rely on acute localization phenomena (domination for the lateral pain system), but also by means of emotional mechanisms (medial pain system). Emotion entails complex, organized psychophysiological reactions consisting of cognitive appraisals, action impulses, and patterned somatic reactions (Folkman & Lazarus 1991). Thus, being able to assess pain and feel unpleasantness reflect conscious awareness (LeDoux 1984). Controlled cerebral processing in the frontal lobes seems to be an integrated part of the creation of willed acts (Ingvar 1985) and the ACC involvement in behavioural control depends critically on a close interaction with the PFC (Cohen 1993, pp. 353–359; Paus *et al*. 1993). Nociresponsive neurons have also been demonstrated to exist in the PFC in animals (Snow *et al*. 1992) suggesting also a direct association of the PFC with pain processing. Psychosurgery to disconnect the frontal and the limbic cortex (PFC, ACC, etc.) has been performed successfully for relieving intractable pain (Bouckoms 1994).

Pain stimuli elicit reactions on all CNS levels from reflexes to intention-driven behaviour as well as changes in mood levels. It is therefore not surprising that experimental pain often leads to changes in activity in the frontal regions (Derbyshire *et al*. 1993, 1998; Hsieh 1995, p. 91; Di Piero *et al*. 1994; Hsieh *et al*. 1996*a*,*b*). The activation foci in the right dorsolateral PFC region (BAs 9, 10, 46) seems more related to acutely elicited pain with its preponderance for motor reactions of withdrawal or avoidance. It was possible to provoke activations in this region by provoking itch-sensation and asking the subjects not to move. This was understood as the urge to move elicited motor planning awaiting the possibility to scratch (Hsieh *et al*. 1994).

The inferior lateral PFC seems to be involved in cognitive emotional process and integrative regulation (George *et al*. 1994; Ketter *et al*. 1993). Chronic pain, with its impact on mood and emotion, seems to affect orbitofrontal cortices more (Gyulai *et al*. 1997; Hsieh 1995; Hsieh *et al*. 1996*a*; Peyron *et al*. 1998). The ventromedial PFC (BA 12), in conjunction with the ACC (BA 24′, 32) may exert inhibitory control on the pain-relevant affective signals from the limbic system (Davis *et al*. 1997; Peyron *et al*. 1998). It is very important to develop further experiments that address the specific roles of the prefrontal cortical sub-regions in pain processing.

(h) *Posterior parietal cortex*

The parietal lobes are also regarded as a polymodal association areas. The posterior parietal cortex (PPC) seems to process spatial representations (intrapersonal and extrapersonal space) (Deiber *et al*. 1991; Grafton *et al*. 1992). This includes a body scheme through which humans establish a physical sense of the self (Andersen 1987) and patients with lesions in the PPC, especially the right side, have severe attentional disturbances, designated as sensory neglect syndrome (Heilman & Watson 1977).

The PPC has nociceptive neurons with bilateral receptive fields, neurons that are also represented bilaterally in S2 (Dong *et al*. 1989). It has been demonstrated to be either activated in experimental pain (Coghill *et al*. 1994; Derbyshire *et al*. 1994), traumatic nociceptive pain (Hsieh *et al*. 1996*b*) and chronic neuropathic pain (Hsieh *et al*. 1995). A prominent activation has also been demonstrated in unpleasant itch (Hsieh *et al*. 1994), a situation

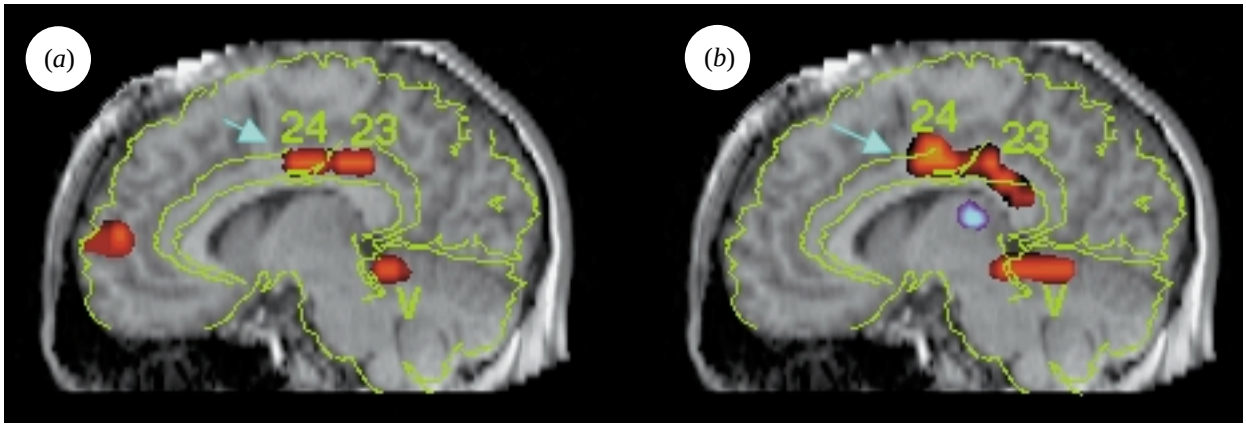

Figure 2. In peripheral neuropathy both right-sided (*a*) and left-sided (*b*) nerve affliction leads to a right-sided activation in the ACC. Sagittal slices through the right ACC in two subgroups with either right- or left-sided affliction. The omnibus significance maps (thresholded at $p<0.01$) were superimposed on a transformed MRI image and were colour coded into four levels defined by $0.001 \leqslant p<0.01$ (increase = red; decrease = blue) and $p<0.001$ (increase = yellow; decrease = light blue). Data from Hsieh *et al*. (1995).

with no pain but where the urge to scratch invokes body coordination. As part of the posterior attentional system, which has close anatomical connections to the anterior attentional networks and to the arousal or vigilance systems, the PPC may participate in orientating subjects to the sensory input (Posner & Raichle 1994, pp. 153–180). As with the frontal cortex, more specific paradigms are needed to delineate the subdominant regions of the PPC in response to pain.

4. CLINICAL VERSUS EXPERIMENTAL STUDIES

A critical factor in the quality of imaging studies is the sample size and it is unfortunately often necessary to limit the size of studies of clinical pain entities due to limited patient access (Frackowiak *et al*. 1997). In clinical studies, predefining the search volume can be used in order to increase the sensitivity. Another way of furthering understanding is to critically judge published studies and not accept results unless confirmed in an independent data set.

There is a possibility of differences in the cerebral activation pattern in chronic pathological pain and experimentally induced acute pain. The brain activation pattern in chronic pain emphasizes the emotional aspect whereas acute experimental pain seems to include localization or discrimination components. In painful mononeuropathy the ACC was activated in the habitual pain state with no concurrent activation of the lateral pain system (Hsieh *et al*. 1995). However, an acute pain exacerbation in allodynia leads to strong coactivations in the lateral pain system (Petrovic *et al*. 1998*b*).

Tonic pain stimulation with a cold pressor test of each hand in chronic cluster headache patients outside active headache periods showed a differential response depending on the side of stimulation. Stimulation of the contralateral side of the headache affliction led to a more expressed activation in the thalamus than ipsilateral stimulation (Di Piero *et al*. 1997). This could be taken as an account of aberrant pain processing in chronic pain but this is not yet established as a general principle in chronic pain.

(a) *Headache and migraine*

Vascular features are part of the headache family and this has made it natural to use rCBF methods in the search for pathophysiological mechanisms (Friberg *et al*. 1994; Hachinski *et al*. 1977; Olesen *et al*. 1990). In migraine there is to date no consensus of the significance regarding the changes in CBF that have been demonstrated, i.e. whether these changes are primary or secondary to the headache.

It was shown recently that in migraine without aura there was an activation in the brainstem during the headache state, but not in the headache-free interval (Weiller *et al*. 1995). It was suggested that this brainstem activation is inherent to the migraine attack itself and represents the so called 'migraine generator'. The same authors performed an experimental pain study in seven healthy volunteers. A small amount of capsaicin was administered subcutaneously in the right forehead to evoke a burning painful sensation in the area of the first division of the trigeminal nerve. Increases of rCBF were found bilaterally in the insula, in the ACC, the cavernous sinus and the cerebellum. No brainstem activation was found in the acute pain state as compared with the pain-free state. Hence, an externally elicited tonic pain did not lead to a brainstem activation as was reported from spontaneous migraine headache (May *et al*. 1998*a*, *b*).

Provocation of cluster headache leads not only to an activation of the central pain systems (both lateral and medial) but also an activation in the ACC that was right-sided irrespective of the afflicted side (Hsieh *et al*. 1996*a*). May and colleagues have also studied nitroglycerine-provoked cluster headache (May *et al*. 1998). As was previously demonstrated in acute severe experimental pain (Hsieh *et al*. 1996*b*), an increased activity was noted in the HT during the painful events. The authors gave the interpretation that this represented 'the primum movens' in the pathophysiology in this disorder. In the first PET study of provoked cluster headaches that was published there was no similar finding of an HT activation (Hsieh *et al*. 1996*a*). The conclusion of May *et al*. (1998*a*, *b*) merits further studies, since the literature on possible vascular origin of cluster headache seems so well established.

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5. MODULATION OF THE CENTRAL PAIN RESPONSE

(a) *Lateralization of the pain response*

There is evidence that the right hemisphere is more involved in emotional evaluation than is the left (Gainotti *et al*. 1993), and both experimental and clinical studies suggest that pain sensitivity is lateralized in humans with more expressed responses from the non-dominant hemisphere. Studies examining pain threshold or pain tolerance by means of various experimental pain-inducing procedures have revealed a lower pain threshold or pain tolerance when noxious stimuli are applied to the left side of the body in right-handed people (Heilman & Watson 1977). In several of the studies from our group (Hsieh 1995; Hsieh *et al*. 1995, 1996*a*,*b*) we demonstrated a preferential activation of the right ACC, regardless of the side of the painful input (figure 2). Other authors have made this finding but not commented upon it (Weiller *et al*. 1995). General discomfort also activates the ACC in a lateralized manner (Corfield *et al*. 1995).

The lateralization seems not to be confined to the ACC but rather both frontal and S2 lateralization has been shown to occur (Hari *et al*. 1997). Also in the frontal lobe there is a lateralization in that chronic pain seems to activate the right side preferentially.

(b) *Anticipatory events*

Hierarchical processing allows cognitive processes to be handled without competing for the limited space on consciousness (Posner 1990). In the establishment of priorities of the cerebral processing it is also of clear computational value to pre-process information to determine context and emotional or evaluative parameters in order to prepare behaviour. Itch can be defined as the urge to scratch. If itch is induced combined with the instruction 'do not move', imaging the brain will be an image of the urge to scratch, i.e. the network combined of sensory and motor regions necessary to perform the purposeful behaviour at a later stage (Hsieh *et al*. 1994). This is a significant finding when considering pain imaging, because most studies of experimental pain instigate a pain stimulus concurrently with the instruction of avoiding movements. This is a potential confounder in the interpretation of results from many studies since actual movements and suppressed movements activate the same mechanisms (Ito 1993). Also, many subjects tend to use movement as a way not only to avoid exposure to pain but also to alleviate the pain experience.

Anticipation of a pure sensory event invoked a decrease of activity in SI and SII ipsilaterally to the site of stimulation. Additionally, in the anticipatory states the SI displayed decreases contralaterally to the site of stimulation outside the primary projection area for the stimulus and such an inhibition may function as a gating mechanism and could facilitate focusing and localizing the somatic stimulus (Drevets *et al*. 1995; Hsieh 1995). Thus, the activity in the SI/SII can be modulated by a change of context, a phenomenon documented for other primary sensory cortices, e.g. the primary visual cortex (Corbetta *et al*. 1991), and may reflect top-down modulation of primary cortices (Ghatan *et al*. 1998; Shulman *et al*. 1997).

The anticipation of a harmful encounter involves cognitive appraisal and thereby anticipatory coping, which is a dynamic process that changes according to the person's perception of the consequences of an event (Folkman & Lazarus 1991). Thus the anticipation, or expectation, of pain can trigger the same emotional response as pain itself (Hsieh 1995). This is very important in designing pain studies. The setting and the information given to the subjects may crucially influence the results.

We did an experiment where subjects anticipated either an unknown (but per instruction not dangerous) painful event or a pre-trained known but unavoidable event (Hsieh 1995; Hsieh *et al*. 1999). On the behavioural level this experimental difference induces different responses. The unknown stimulus leads to apprehension whereas the other invokes avoidance. In line with this, the subjects self-reported that they promptly attended to the anticipated pain of unknown character or intentionally diverged attention from the source of distress when the upcoming stimulus was known. The unknown stimulus increased the activity in the PFC, ACC and PAG. On the other hand, the anticipation of the known pain stimulus led to decreases in the same regions. Hence, the anticipatory phase imposed changes in brain activity compliant with the two different reported reactions to the upcoming pain stimulus, reflecting either the vigilant (directing attention to the encounter) or avoidant strategies (diverting attention from the source of distress), respectively (Lazarus 1991).

(c) *Cognitive modulation of the pain response*

It is an everyday experience that it is possible to modify the experience of pain by means of attentional mechanisms. By actively disengaging the thoughts on the suffering component of pain it may become more bearable. Petrovic *et al*. (1998*a*) have tested this with a factorial design by means of exposing subjects to experimental pain (cold pressor test, left hand in ice-cold water) with and without cognitive loading. Indeed, the pain-evoked activations, especially in the lateral pain system, were less expressed during cognitive performance and the pain-evoked decreases in the basal forebrain were less expressed.

Pharmacological manipulations also demonstrate that the blood flow increase in the medial pain system and the reciprocal decrease in the basal forebrain parallel the reported level of pain discomfort (Gyulai *et al*. 1997). Hence, intentional diversion of attention from the pain stimulus decreases the intensity of the pain experience and this is paralleled by less expressed activations in the central pain systems.

Decreases of activity in areas outside a process-relevant network is a common finding in imaging studies (Ghatan *et al*. 1995). It has been questioned if it represents a real finding or rather reflects a top-down regulatory measure of attention mechanisms. Challenging these concepts, it was recently shown that process-relevant information handling coincided with the suppression of processing of potentially disturbing information concurrently present (Ghatan *et al*. 1998). Decreases in the medial temporal lobe in intense pain paradigms have been reported from some studies (Hsieh 1995; Hsieh *et al*. 1996*b*; Petrovic *et al*. 1998*a*,*b*). It can be speculated that this could represent a meaningful suppression of memory encoding during the

ongoing pain, as pain is known to interfere with memory function. The critical experiment remains to be performed.

6. FINAL REMARKS

The rapid developments of imaging methods over the past years have led to a decrease in variability in the description of central pain responses between different studies and have led to a definition of a central pain matrix with specialized subfunctions in man. In the near future we will see studies where the systems perspective allows for a better understanding of the regulatory mechanisms in the higher-order frontal and parietal cortices. Also, the emotional aspects of pain will become better known as experimental paradigms are developed that allow imaging studies of such aspects.

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