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Attentional modulations of pain perception:

evidence from laser evoked potentials

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List of Abbreviations

ACC Anterior cingulate cortex
AEP Auditory evoked potential
AIC Anterior insular cortex
aMCC Anterior middle cingulate cortex
ANOVA Analysis of Variance
BA Brodmann area
CC Cingulate cortex
EEG Electroencephalogram
EOG Electro-oculogram
ERD Event-related desynchronization
ERF Event related fields
ERP Event-related potential
ERS Event-related synchronization
fMRI Functional magnetic resonance imaging
GFP Global field power
HEOG Horizontal electro-oculogram
IASP International Association for the Study of Pain
ICA Independent component analysis
ISI Inter-stimulus interval
LEF Laser-evoked fields
LEP Laser-evoked potential
LFP Local field potential
MEG Magnetoencephalography
MEP Motor evoked potential
MCC Middle cingulate cortex
MMN Mismatch negativity
MRI Magnetic resonance imaging
Nd Negative difference
pACC Posterior anterior cingulate cortex
PET Positron emission tomography
pMCC Posterior middle cingulate cortex
PN Processing negativity
ROI Region of interest
SEP Somatosensory-evoked potentials
SI Primary somatosensory area
SII Secondary somatosensory area
SPN Stimulus preceeding negativity
TF Time-frequency

TMS Transcranial magnetic stimulation

VAS Visual-analogue scale

VEOG Vertical electro-oculogram

Chapter 1

Introduction

1 Nociception and pain

In our everyday interaction with the nearby environment, we try to avoid the experience of pain and at the same time we gratefully acknowledge it, as it provides alert and orientation reflexes towards possible dangerous stimuli in order to allow the evaluation, anticipation and avoidance of harm (Melzack & Casey, 1968; Loeser & Melzack, 1999). Nevertheless, pain is not just linearly related to the noxious stimulus, neither it always fulfills its protective function. Indeed, while on one hand even high discharge rates of nociceptive afferents are not necessarily perceived as painful (Bromm et al., 1984a), on the other hand pain may manifest without any external or internal tissue damage as consequence of an emotional condition like in psychogenic pain patients (Merskey and Spear, 1967).

In fact, the International Association for the Study of Pain (IASP) define nociception as 'unconscious activity induced by a harmful stimulus in sense receptors, peripheral nerves, spinal column and brain, that should not be confused with physical pain, which is a conscious experience. Nociception or noxious stimuli usually cause pain, but sometimes pain occurs without them'. Conversely, 'pain is an unpleasant multidimensional experience associated to actual or potential tissue damage or described in terms of such damage' (Merskey & Bogduk, 1994).

The study of pain is of capital importance given its invalidating nature, wherein a complex combination of mnestic, emotional, pathological, genetic, and cognitive factors interplay in determining an abnormal interpretation of the nociceptive information, as in

chronic pain patients (Tracey & Mantyh, 2007).

Pain, defined as a percept, is a complex and primarily subjective experience. Sensory-discriminative (e.g. evaluation of locus, duration and intensity of a noxious stimulus), affective-motivational (e.g. unpleasantness of the noxious stimulus) and cognitive-evaluative processes (e.g., catastrophizing, context appraisal) do characterize this fundamental mental function.

It is noteworthy that, past definitions of pain classified it either as an emotion (akin to pleasure), or as simply the extreme in a continuum of normal tactile sensation, such as temperature or pressure, rather than a specific sensory modality, such as vision or audition (e.g. see Dallenbach 1939 for a historical review). However, given the discovery of sensory receptors (nociceptors) specifically responsive to noxious stimuli, and the corresponding central nervous system segregations of this information, research community agrees that nociception should be considered as a specific sensory modality akin to vision, audition, olfaction, and taste (e.g. Melzack and Casey 1968).

Nonetheless, the understanding of the cortical processes underlying pain perception is well behind that of other sensory modalities. This has been likely due to the absence of an adequate and selective nociceptive stimulation up to the 1975, age in which Mor and Carmon introduced the infrared laser stimulator. This technology, allowed the brief, synchronous, and selective activation of cutaneous Aδ- and C-fiber nociceptors, laser heat stimulators, and since then, is extensively used to study time-locked nociception-related behavioral and electrophysiological responses.

The characteristics of infrared laser stimulators will be discussed in section 2. It will then be presented a brief introduction concerning cortical sources of vertex sensory event-related potentials in section

3. Chapter 2 will further narrow the discussion and interpretation of event-related brain activity (especially the nociceptive neural activity) according to attention-grounded mechanisms, and will present the reader with the objects of investigation. Chapter 3 and Chapter 4 will introduce the reader with the two thesis' studies, interpreted in the context of such attention-based mechanisms. Chapter 5 will offer a general discussion of the findings. In particular, the difference between nociception and pain perception will be addressed, and it will be shown how the present neuroscientific model ('pain matrix' model) has several interpretative weaknesses, to end with the proposal of a new integrated model of pain representation in the brain, in light of recent empirical and theoretical advances in in sensory neuroscience and philosophy of mind.

1.1 Event related potentials

A pertinent approach to the study of the sensory systems in humans implies the employment of non-invasive observational and experimental methods which give access to somatosensory, auditory, visual, both olfactive and gustatory, and nociceptive-related brain processes at an integrative level of the central nervous system.

Event-related potentials (ERPs) typically originates from exogenous and/or endogenous activation of central nervous system and consist of a series of voltage polarity changes, observed as peaks and depressions in the average waveform. These potentials can be classified according to their relative timing to stimulus onset, their polarity, and their magnitude. In most cases, each individualized ERP deflection corresponds to neural activity arising from several temporally overlapping sources. As ERPs provide a high temporal resolution, they can be used to distinguish and identify the different

neural processes involved in perceptual tasks. Indeed, depending on their modality, sensory stimuli elicit a series of sensory or exogenous ERP peaks which reflect the initial processing occurring in modality-specific cortical areas. Following these peaks, later components may be recorded, which are thought to reflect more integrative and endogenous aspects of perception.

2 Laser evoked brain potentials

Laser stimulators provide a narrow beam of nearly parallel monochromatic electromagnetic waves. Thus, high energy density (radiation per unit area) beams determine a fast rise of temperature on skin layers which in turn allows the brief, synchronous, and selective activation of cutaneous Aδ- and C- nociceptors (Plaghki and Mouraux, 2003). Compared to electrical stimulation used for standard somatosensory evoked potentials (SEPs), the main advantage of laser evoked potentials (LEPs) is the absence of concurrent involvement of tactile modality. Indeed, the excitation of the large diameter Aβ-fiber afferents to the lemniscal pathway, should be avoided as their activation could produce overlapping responses and, more importantly, modulate the nociceptive responses themselves (for a review see Plaghki and Mouraux, 2005). Such a detail is very relevant due to the higher amplitude and lower threshold activity of Aβ-fibres respect to Aδ- and C- small fibres. The specific activation of type-II A-mechano-heat nociceptors (Treede et al., 1998), small myelinated afferents, and spinothalamic neurons located in the anterolateral quadrant of the spinal cord (Treede et al., 2003a) made laser evoked potentials the best electrophysiological tool for assessing functionality of pain transmission in the central nervous system (e.g., Garcia-Larrea et al., 2002; Spiegel et al., 2000; Treede et al., 2003b).

2.1 Sensations mediated by Aδ- and C-fibers

Albeit it's nociceptive specificity, brief laser stimuli applied to the hairy skin (e.g. dorsum of the hand) do not necessarily evoke a painful sensation (Bromm and Meier 1984a; Svensson et al., 1997; Nahra and Plaghki 2003b). Indeed, at stimulus intensities slightly above detection threshold, perception is dominated by warmth and touch-like sensations which are detected with latencies above 800 ms. At higher intensities, the activation of Aδ- and C nociceptors produce a universal characteristic double sensation, reminiscent of the 'first' and 'second' pain described by Lewis and Ponchin (1937). First pain is often described as a localized, acute, and short-lasting 'pricking' sensation. It is related to the activation of small diameter myelinated Aδ-fibers which conduct the signal at a velocity of 4-30 m/s. On the other hand, second pain is often described as a 'burning' sensation which spreads beyond the spatial and temporal limits of the stimulus and is coupled to amyelinated C fibres conduction velocity of 0,4-1,8 m/s (e.g., Obi et al., 2007).

Although subjects clearly report sensations related to the activation of both Aδ- and C-fiber nociceptors, LEPs have only revealed components whose latencies are compatible with the conduction velocity of Aδ-fibers (i.e. the 'late LEP'; ~160–390 ms; Bromm and Treede, 1984b). Several methods allow narrowing the selectivity of the laser stimulator such as to activate C-fibers in isolation (Plaghki and Mouraux, 2003). Most curiously, all these methods have shown that avoiding the concomitant activation of Aδ-fibers not only resulted in the disappearance of first pain and its electrophysiological correlate, the late LEP, but also led to the appearance of an ultra-late LEP whose latency (~750–1150 ms) was compatible with the arrival time of C-fiber input (Mouraux et al., 2003; 2004) (see Figure 1-1).

From these observations, it appears that long-lasting tonic heat stimuli produce sensations which are mostly mediated by C-fibers, while brief phasic laser heat stimuli produce sensations which are mostly mediated by Aδ-fibers.

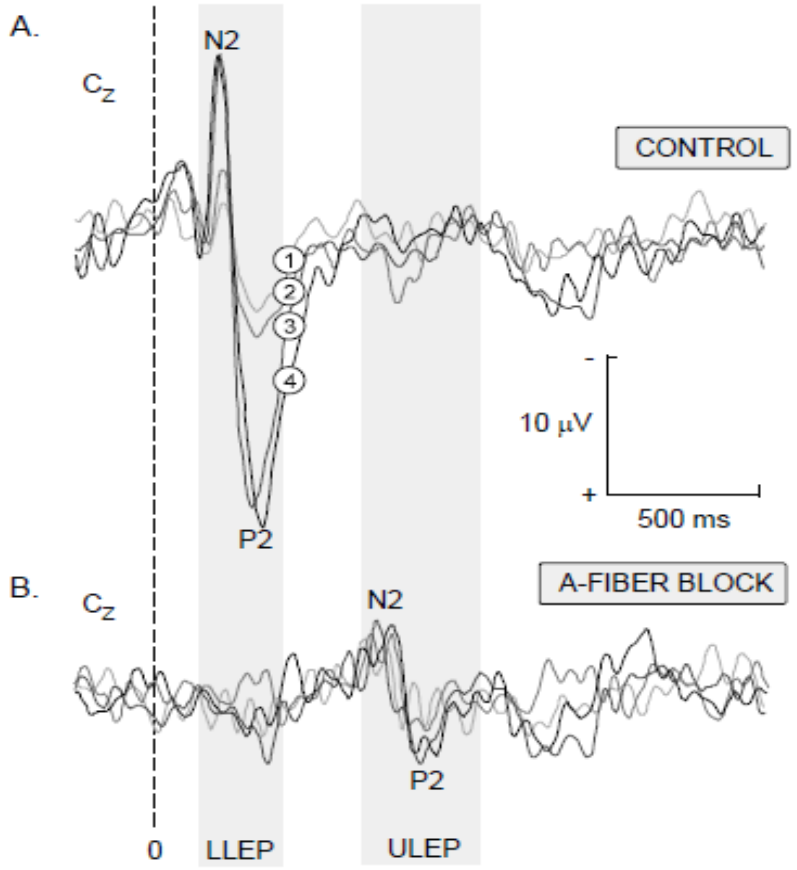

Figure 1-1. Laser-evoked potentials (LEPs) recorded in 9 subjects before (panel A) and after (panel B) applying an ischemic A-fiber pressure block to the superficial radial nerve (grand-average; A1A2 reference). Four different stimulus intensities, ranging from 5.8 to 10.6 mJ/mm2 were used (labeled '1' to '4). LLEP: the time-window within which Aδ-fiber related late LEP components are usually recorded after stimulation of the hand (160-390 ms). ULEP: the time-window within which C-fiber related ultralate LEP components are usually recorded (750-1150 ms). Note that unlike the amplitude of the late LEP recorded in the control condition, the amplitude of the ultralate LEP recorded in the A-fiber block condition was mostly uncorrelated with stimulus intensity (adapted from Nahra and Plaghki, 2003a).

2.2 The Aδ-fiber mediated late LEP

LEPs comprise a number of waves that are time locked to the onset of the stimulus. The largest wave is a negative–positive complex maximal at the scalp vertex (N2–P2; occurring at 160-390 ms when stimulating the hand dorsum) (Bromm and Treede, 1984b). This complex is preceded by a smaller negative wave (N1; accurring at 120-190 ms), that overlaps in time and space with the larger, subsequent N2 wave, and is described as having a distribution maximal over the temporal region contralateral to the stimulated side (García-Larrea et al., 1997). The most prominent component of the LEP response mediated by Aδ-fibers consists of a large, biphasic, negative-positive complex (N2-P2) culminating at the vertex. The P2 wave (Treede et al., 1988a; Miyazaki et al., 1994; Xu et al., 1995; Valeriani et al., 1996) displays a widespread central scalp topography whose maximum is recorded at the vertex (electrode CZ; see figure 1-2). Such as the P2, the N2 wave(Treede et al., 1988a; Kunde and Treede, 1993) is also maximal at the vertex.

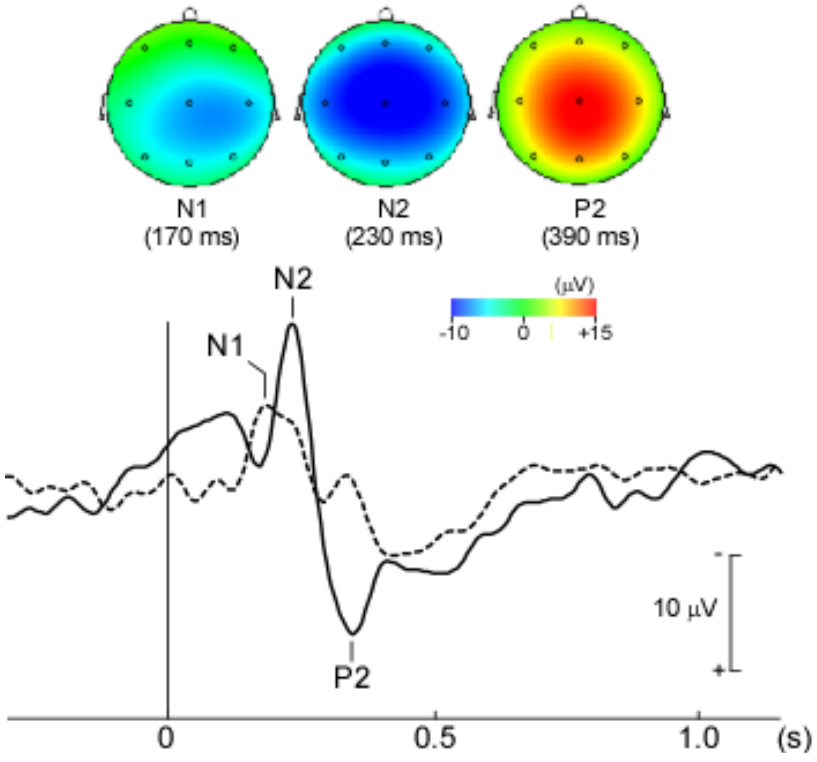

Figure 1-2. Laser-evoked potentials (LEPs) were recorded in 15 subjects.

Stimulus, applied to the dorsum of the left hand, was above the threshold of both Aδ- and Cnociceptors (9.5 ± 0.5 mJ/mm2; 40 ms duration; 10 mm diameter; ISI 10 – 20 s). Solid waveform: grand-average obtained at electrode CZ vs. A1A2. Dashed waveform: grand-average obtained at contralateral electrode T4 vs. FP1. Adapted from Kunde and Treede, 1993.

Several studies (Treede et al., 1988a; Kunde and Treede, 1993; Miyazaki et al., 1994; Xu et al., 1995; Spiegel et al., 1996) have shown that the laser stimulus can evoke an additional and earlier negativity, labeled N1 (see figures 1-1 and 1-2). The N1 component precedes the late vertex N2 component and is often described as 'riding on the ascending N2 negativity' (Treede et al., 1988a). When stimulating the dorsum of the hand, the latency of the N1component is approximately 170 ms. The topographical distribution of the N1 component is different from that of the N2 component. Indeed, the N1 component is lateralized, being maximal at temporal leads contralateral to the stimulation site. N2 and P2 components are usually best identified using nose or linked earlobes as reference. To identify the N1 component and dissociate it from the partially overlapping N2 component, a frontal median reference electrode is most often used (Kunde and Treede, 1993; Valeriani et al., 1996; Valeriani et al., 2000a). Indeed, the positive counterpart of the N1 component, sometimes labeled P1, may be recorded at such scalp locations. The significant correlations between N1 and P1 amplitudes and latencies is indeed a strong indication that this P1 component is the positive counterpart of the electrical brain activity underlying the N1 and not a distinct laser-evoked component. It should be noted that Spiegel et al. (1996) described an additional ipsilateral N1 component, of lower amplitude.

2.3 Electromagnetic dipole generators

A number of studies have applied source analysis methods to the

electrical scalp activity elicited by cutaneous laser stimuli. Most of these studies have used methods based on the optimization of a fixed spatio-temporal dipole configuration using a spherical head model (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996; Valeriani et al., 2000; Schlereth et al., 2003). These studies have repeatedly identified bilateral opercular (SII, insula) and anterior cingulate (ACC) cortical regions as significant contributors to the LEP waveform (see Garcia-Larrea et al., 2003 for a review). Nonetheless, the best insight on dipole localization of laser evoked potentials originates from few intracerebral recordings studies (e.g., Frot and Mauguiere, 2003; Frot et al., 2007; 2008; Lenz et al., 1998a,b).

2.3.1 Bilateral operculo-insular cortices

Tarkka and Treede (1993) were the first to apply source analysis methods to brain responses elicited by laser stimulation. Results of that initial study proposed that bilateral activity originating from operculo-insular regions largely contributed to the observed LEP waveforms. These activities were interpreted as arising bilaterally from secondary somatosensory cortices (SII). The earliest activity was recorded contralateral to the stimulation site, peaking at 160 ms after stimulation of the hand dorsum. As compared to the contralateral activity, the ipsilateral activity was delayed, peaking at 240 ms after stimulus onset.

Using a similar dipole-modeling Bromm and Chen (1995) provided additional results suggesting that bilateral operculo-insular sources participate in the generation of LEPs. There again, a slight delay between contralateral (peaking at 106 ms) and ipsilateral (peaking at 112 ms) responses was observed. The dipolar model proposed by Valeriani et al., (1996) also included two dipoles with a slightly

delayed time-course in the contralateral and ipsilateral opercular regions. In this study, it was initially proposed that bilateral hippocampal activity additionally contributed to the LEP responses. However, using a method to project coordinates from a spherical head model onto Talairach space, this activity was later reinterpreted as possibly originating from bilateral insular regions (Garcia-Larrea, 1998). In a successive study, Valeriani and colleagues (2000b) modeled sources located in the upper bank of the sylvian fissure to explain LEPs elicited by laser stimulation of both the hand and foot. This activity was interpreted as originating from SII cortices but a contribution of insular regions was not excluded. The body location of the eliciting stimulus did not modify the location of these sources. Such as in previous studies, the contralateral response (peak latency: 157 ms for hand stimulation, 217 ms for foot stimulation) preceded the ipsilateral response (peak latency: 180 ms for hand stimulation, 253 ms for foot stimulation). Schlereth et al. (2003) proposed that bilateral SII and insular cortical regions participate in the generation of LEPs. The magnitude of this activity, peaking at 155 ms after stimulation of the hand dorsum, was shown to be correlated with the intensity of the laser stimulus (see Figure 1-3).

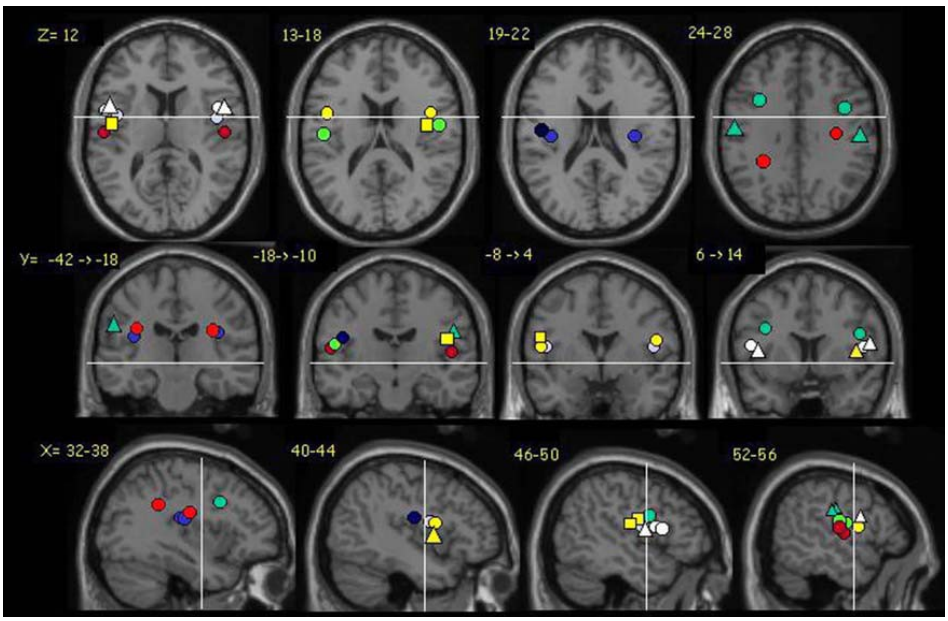

Figure 1-3. Anatomical locations of suprasylvian laser-evoked potential sources reported in twelve studies were projected onto a 3D-MRI normalised in Talairach space. White lines cross the anterior commissure in axial, sagittal and coronal slices. Although inter-study variability was important in the anterior-posterior axis, the overall distribution of sources closely followed the axis of the Sylvian sulcus. Pale blue circles and yellow triangles represent data from intracranial recordings. From Garcia-Larrea et al., 2003.

These source locations are compatible with signals originating from bilateral SII and deeper insular cortices as further confirmed by intracerebral recordings. Human intracranial recording of local-field potentials (LFPs), using either subdural or implanted electrodes, have brought direct proof of the involvement of the cortical regions pointed by source modeling studies in responding to laser stimuli. Lenz et al. (1998a) examined responses from six subjects to laser stimulation of the hand dorsum and face using subdural electrodes placed over left frontotemporal areas. The recorded potentials consisted of a negative-positive complex. When stimulating the hand, latency of the negative peak was approximately 220 ms for contralateral stimulation and 250 ms for ipsilateral stimulation. Latency of the positive peak was approximately 380 ms for contralateral stimulation and 440 ms for ipsilateral stimulation.

These responses were maximal over the parietal operculum, suggesting that their generators were located in SII and/or in the insula. This results were confirmed by Vogel and colleagues (2003) who recorded the nociceptive related activity from subdural grid electrodes in three patients. The LEP global field power (GFP), a measure of spatial variance, showed a first peak at about 150 ms latency, corresponding to the latency of the N1 recorded from the scalp. In contrast to scalp recordings, the amplitude of the first GFP peak recorded from the grid was larger than the second peak (P2). This finding suggests that the generator of N1, but not that of later LEP components, was close to the subdural grids. When a regional source was fitted to the first GFP peak, its location was within the frontoparietal operculum in all patients. The studies by Frot and co-workers (Frot and Mauguiere, 1999; Frot et al., 2001; Frot and Mauguiere, 2003, Frot et al., 2007; 2008) have brought definitive proof that laser stimulation evokes responses originating from operculo-insular regions. These studies examined laser-evoked responses recorded using deep implanted electrodes within SII and insula (figure 1-4). Laser stimuli were shown to evoke temporally distinct bilateral responses in SII and in the insula. The first response consisted in a negative-positive wave (N140-P170) recorded at the more lateral contacts, compatible with the location of SII. The second response consisted in a negative-positive wave (N180-P230) recorded at more medial contacts, compatible with the location of the insula. The insular response, beginning approximately 180 ms after stimulus onset, was delayed as compared to the SII response, beginning approximately 140 ms after stimulus onset. Furthermore, the ipsilateral responses from both the insula and SII were delayed by approximately 15 ms as compared to the contralateral responses.

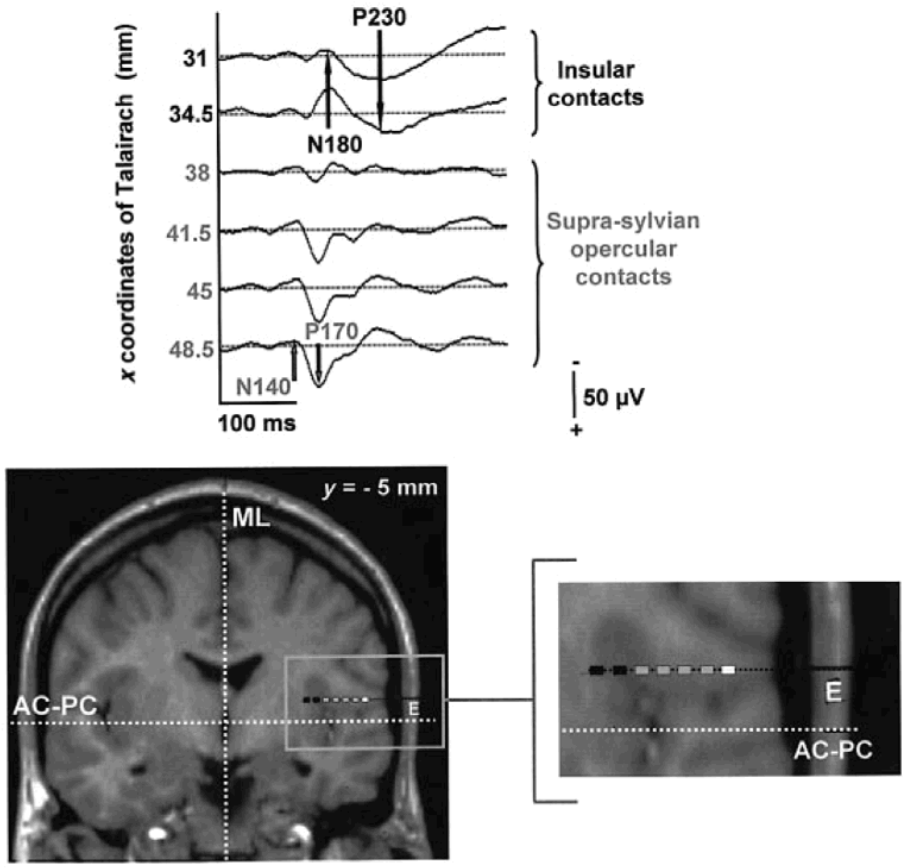

Figure 1-4. Contralateral laser-evoked potentials were recorded in the post-rolandic operculo-insular cortex of one patient (earlobe reference). The operculoinsular electrode (E) is represented on the patient's MRI slice. Contacts in black are located in the insular cortex. Contacts in grey are located in the suprasylvian cortex. ML = median line; AC-PC = horizontal anterior commissure-posterior commissure plane. Two distinct negative-positive responses were recorded. The first (N140-P170) was recorded at supra-sylvian contacts. The second (N180-P230) was recorded at insular contacts. From Frot and Mauguiere, 2003.

In conclusion, several studies have shown that changing the body location of the stimulus does not significantly modify the location or orientation of operculo-insular dipoles, suggesting the absence of clear-cut somatotopical organization of underlying cortical generators. However, the magnitude of this activity was shown to vary as function of stimulus intensity. Most of these studies have described the contralateral opercular activity as the earliest recorded signal in response to laser stimuli. Its latency was similar to that of

the LEP N1 component. However, the temporal patterns of SII sources suggest that they also contribute to the generation of the later N2 LEP component.

2.3.2 Cingulate cortex

In addition to identifying bilateral opercular sources, several authors (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996; Valeriani et al., 2000b) have repeatedly proposed that activity arising from locations within the cingulate cortex (CC) significantly contributes to the observed LEP responses (see Figure 1-5). The pioneer study by Tarkka and Treede (1993) proposed a four dipole model in which an area compatible with the anterior cingulated cortex (ACC) was suggested. After stimulation of the hand, onset of this activity was approximately 240 ms. Therefore, it was assumed that the ACC activity mostly contributed to the LEP P2 component. The four dipole model proposed by Bromm and Chen (1995) also included a dipole located in 'deep midline brain structures'. Activity of this dipole peaked 150 – 220 ms after stimulation of the temple. In the dipole model proposed by Valeriani et al. (1996), a frontal dipole, very close to the midline, and possibly corresponding to the anterior cingulate gyrus was also added to explain the later part of the LEP response. The first peak (~190 ms) was hypothesized to contribute to the earlier part of the N2 wave. The second peak (~290 ms) was coincident with the P2 wave. A similar biphasic ACC response was described in a study of the same group, comparing dipole configurations explaining LEPs evoked by stimulation of the hand to that evoked by stimulation of the foot (Valeriani et al. 2000b). When stimulating the hand, the peak latency of both activities were respectively 217 and 333 ms. When stimulating the foot, the peak latency of both activities were respectively 281 and 406 ms. In a

recent review Garcia-Larrea et al. (2003) showed how all these scalp recording studies can be grouped between the anterior and posterior commissures, thus definying a more dorsal location for late LEPs (see figure 1-5).

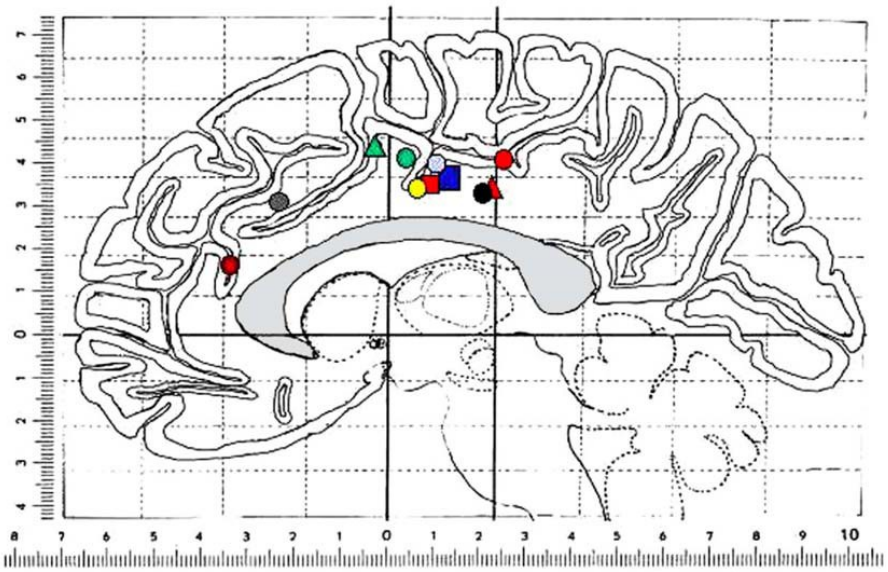

Figure 1-5. Laser-evoked middle cingulate sources reported in eleven different studies were projected onto Talairach space for inter-study comparison. All dipoles were projected onto the same parasagittal slice (x = 4 mm), even though their location in the x axis ranged from -1 to +8 mm. Note the posterior location of many sources within the cingulate, most of them lying at or between the anterior and posterior commissures. Grey circle: selective activation of C-fiber nociceptors. From Garcia-Larrea et al., 2003.

In another study, Lenz et al. (1998b) examined laser-evoked responses recorded in five patients using subdural electrode grids. After stimulation of the face, a biphasic response was recorded at locations 30 mm anterior to the central sulcus, i.e., over the middle cingulated cortex (MCC), compatible with the posterior region of anterior cingulate cortex (BA24). The first peak of activity occurred between 211 and 243 ms. The second peak of activity occurred between 325 and 352 ms. The most recent study (Frot et al., 2008) investigated the whole rostrocaudal extent of cingulate cortex using intracortical recordings in six humans. Only a restricted area in the

MCC region responded to painful stimulation, namely the posterior midcingulate cortex (pMCC), the location of which is consistent with the so-called 'motor CC' in monkeys. More importantly, cingulate LEPs showed two components, of which the earlier one peaks at latencies similar (120 – 195 ms) to those of SII LEPs (120 – 180 ms). Such an evidence induced the authors to claim the existence of a simultaneous early processing of pain information in the 'medial' and 'lateral' pain systems.

According to a better source localization of intracerebral recording studies, it is likely that cutaneous phasic painful stimuli can enhance activation of rostral cingulate cortex (area 24) after a fast activation of pMCC (for a precise anatomo-functional differentiation of CC, see Vogt, 2005).

2.3.3 Primary somatosensory cortex

Whether or not the primary sensory cortex (SI) participates in the recorded LEP responses is still unresolved. The four dipole model initially proposed by Tarkka and Treede (1993) included a source located in the contralateral SI. This activity was concomitant with that originating from bilateral SII areas. However, and unlike the other dipoles (bilateral SII, ACC), the contralateral SI dipole changed location when stimulating different body parts, suggesting a somatotopical organization of the underlying source. However, after this initial study, most studies have proposed dipolar modeling solutions of LEP responses, which did not include a contralateral SI generator (Bromm and Chen 1995; Valeriani et al., 1996; Valeriani et al., 2000b; Schlereth et al., 2003). It seems therefore that the bulk of recorded LEP responses may be explained without assigning a source into SI regions, as confirmed by intracortical recordings too. For instance, Kanda et al. (2000) examined responses to laser

stimulation of the hand using subdural electrodes placed over the contralateral primary sensory cortex. A signal was recorded at a latency of approximately 220 ms. The spatial distribution of this activity suggested that its source was probably not located in area 3b but rather in the crown of the post-central gyrus. This hypothesis was further supported by Valeriani and co-workers (2004). In this study, responses to electric stimuli activating large myelinated Aβ-fiber afferents and responses to laser stimuli selectively activating Aδ- and C-fiber afferents were examined using an electrode located in area 3b of the primary sensory cortex. Although approximately 20 ms after stimulus onset, a reliable signal was recorded in response to the electrical stimulus, no response could be recorded in response to the laser stimulus.

Therefore, these observations do not necessarily mean that the laser stimulus does not generate activity within the contralateral SI, but is likely that this activity does not significantly contribute to the generation of laser-evoked brain potentials.

3 Vertex potentials

Vertex potentials elicited by auditory stimuli were initially described by Davis (1939) in the raw unaveraged EEG. A similar vertex component, evoked by somatosensory stimuli, was also described in early EEG recordings (e.g., Bancaud et al., 1953). In fact, it appears that vertex potentials may be elicited by sensory stimuli regardless of their modality. Indeed, vertex potentials have been described in the auditory (reviewed in Naatanen and Picton, 1987), the somatosensory (Desmedt and Robertson, 1977; Goff et al., 1977; Josiassen et al., 1982; Michie et al., 1987; Desmedt and Tomberg, 1989; Garcia-Larrea et al., 1991; Garcia-Larrea et al., 1995), and the visual modalities (Simson et al., 1976; Simson et al., 1977;

Kenemans et al., 1993; Makeig et al., 1999; Hopf et al., 2000; Potts and Tucker, 2001; Potts et al., 2004).

As shown by Kunde and Treede (1993) some important signal features as topography and morphology of the N2-P2 complex evoked by the laser stimulus were very similar to those of the somatosensory evoked N140 and P250 vertex potentials (SEPs).

3.1 Vertex potentials in the auditory modality

Late auditory vertex potentials are formed by a negative component (N1) occurring approximately 75–150 ms after stimulus onset, followed by a positive component (P2), occurring with an approximate latency of 150–250 ms. The auditory N1 wave appears to be composed of several anatomically and functionally distinct sub-components. Naatanen and Picton (1987) identified three of them. Two of these are thought to originate from temporal cortical areas (respectively, negative peak at 100 ms and biphasic 100-150 ms complex). The third deflection would consist in a negative wave occurring approximately 100 ms after stimulus onset. This last wave, maximally recorded over the vertex, was interpreted as reflecting a widespread transient arousal facilitating subsequent stimulus detection, analysis, and response generation (Naatanen and Picton 1987; Picton et al. 1999). Giard et al. (1994) localized N1 activity. In the bilateral supratemporal plane of the auditory cortex but also in bilateral frontal regions hypothesized to be located either in cingulate or in supplementary motor areas.

On the other hand, earlier studies have considered the auditory P2 to be generated mainly in the vicinity of the auditory cortex, within the temporal lobe (Elberling et al. 1980; Hari et al. 1980; Perrault and Picton 1984). However, results from more resolute magnetoencephalography (MEG) and depth EEG recordings (Godey

et al., 2001) have suggested that the generators of the auditory P2 are located in the *planum temporale* as well as in BA22 (auditory association complex). However, other studies have speculated that the P2 component may also receive contributions from cortical areas in the upper lip of the sylvian fissure, at or near SII (Hari et al. 1990). Altough the number of studies investigating dipolar sources of auditory evoked potentials (AEPs) is scarce, up to date it seems that both the auditory N1 and the auditory P2 arises from multiple sources. The location of these sources would be centered around parietal and temporal opercular regions.

3.2 Vertex potentials in the somatosensory modality

Vertex potentials elicited by somatosensory stimuli are constituted by a negativity (often referred to as N1 or N140) followed by a positivity (often referred to as P2 or P250). Unlike the auditory N1 which displays a midline maximum whatever the stimulated ear, the topography of the somatosensory N1 is highly dependent of stimulus location and displays contralaterally to the stimulated side (Bruyant et al. 1993; Garcia-Larrea et al. 1995). Garcia-Larrea an co-workers (1995) proposed that such as the auditory N1, the somatosensory N1 is composed of at least two distinct sub-components: an earlier wave (labeled N120 or 'early N1') and a later wave (labeled N140 or 'late N1'). The N120 potential, displaying a contralateral temporal predominance, was hypothesized to be generated by bilateral SII sources and reflect modality-specific sensory processes. The N140 potential, displaying a symmetrical scalp topography maximal at the vertex, was hypothesized to reflect more endogenous and supramodal processes. In a study combining intracranial and scalp recordings, Allison et al. (1992) also described an early and lateralized N120 peak whose intracranial counterpart was

hypothesized to be an N100 recorded in suprasylvian regions. This early activity was differentiated from a subsequent N140 peak, recorded over both hemispheres, and hypothesized to correspond to a true 'vertex negativity'.

3.3 Common processes underlying vertex potentials

Vertex potentials appear to be elicited by stimuli whatever their sensory modality. As the topography of the N1 vertex potential varies across different sensory modalities, it could be considered that the N1 component reflects distinct processes, specific to each eliciting modality. However, studies within these different sensory modalities have indicated that the N1 cannot be reduced to a single component but rather that it reflects the activation of multiple subcomponents. Therefore, it could be hypothesized that some but not all of these subcomponents reflect more modality-specific processes. These could include the somatosensory N120 described by Garcia-Larrea and co-workers (1995), but also the first and second subcomponents of the auditory N1 as defined by Naatanen and Picton, (1987). Indeed, other later components such as the somatosensory N140 and the third subcomponent of the auditory N1 share similar scalp distributions and have therefore been proposed to reflect non modality-specific or supramodal processes. As suggested by Picton et al. (1999), these later processes could be related to exogenously-triggered orienting responses. Such as the later part of the N1, it is probable that, the P2 vertex potential reflects activities common to the processing of all sensory modalities. Indeed, the topography of the P2 appears to be similar across different sensory modalities. This relatively tardive potential has been hypothesized to reflect more integrative and cognitive aspects of sensory processing.

Chapter 2

Determinants of vertex potentials

1 An attentional modulation account

The determinants of neural processes of perception will be described and interpreted through the lens of information processing theory of cognition (Miller et al., 1960). The human information processing approach poses that relevant information in the environment must be selected and then assessed and further elaborated in a working memory. The mechanism of attention allows allocating resources for selection and integration of this process with working memory requirements. More in detail, cognitive science suggested that the attention mechanism can be divided into two categories: stimulus-driven (or 'bottom-up') and goal-directed (or 'top-down') (see Knudsen, 2009 for a review). 'Top-down' and 'bottom-up' are metaphors which are used to represent information processing in a hierarchy where lower levels of processing would rely on the physical features of the stimulus while higher levels would involve comparisons with information stored in memory, selection of relevant information in competition and respose to the stimulus. 'Bottom-up' (or sensory-driven) processing would lead to a progressive recognition and extraction of stimulus features while 'top-down' processing would allow previous experiences, expectations, homeostatic motivations, and task requirements to bias the processing and encoding of the incoming stream of sensory input. A recent attempt to apply these conceptual categories to a neurocognitive model of pain information processing has been put forward by Legrain (2009a) (See figure 2-2).

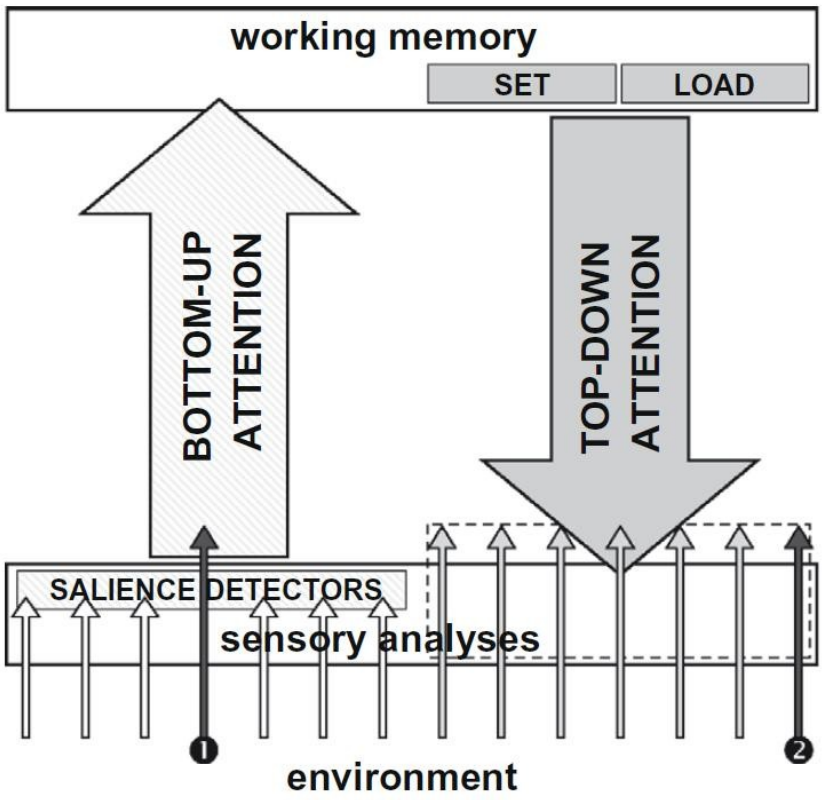

Figure 2-2. Constantly confronted with multiple competitive sensory signals (bottom arrows), the brain has to select signals that are most relevant for behavior and gives them priority access to working memory for conscious processing. Two forms of selection can be achieved. 'Bottom-up' selection stands for the capture of attention triggered by sensory stimuli themselves, and is initiated by pre-attentional detectors that identify salient stimuli (black arrow #1) and give them stronger neural responses to prioritize their processing. 'Top-down' selection is directed by cognitive goals activated in working memory. Goals define the stimulus features that are task relevant (attentional set) and the amount of attention deployed to achieve the task (attentional load). 'Top-down' selection increases the neural responses to goal relevant signals (grey arrows) and inhibits the responses to goal-irrelevant signals (white arrows). The model predicts that when we try to discard attention from pain, a nociceptive stimulus can still capture attention in two ways (1) when it is salient enough (black arrow #1) and (2) when it shares one of the perceptual features defined by the attentional set (black arrow #2). From Legrain, 2009a.

1.1 'Bottom-up' determinants: Stimulus intensity and intensity of perception

It is well known that the amplitude of auditory and somatosensory

vertex potentials is highly correlated with the intensity of the evoking stimulus. The influence of loudness of auditory stimuli on the N1-P2 peak-to-peak amplitude is a very consistent finding (Rapin et al., 1966; Beagley and Knight, 1967; Picton et al., 1970; Gerin et al., 1972). Such an increase appears to be linear, with a tendency to saturate or even reverse at high levels. Furthermore, the latencies of auditory N1 and P2 waves have been reported to decrease with increasing stimulus intensity (Rapin et al., 1966; Beagley and Knight, 1967). Such an effect has been individuated also on N100, P200, N200 and P300 visual evoked potentials (Convington and Polich, 1996; Polich et al., 1996). In the pain literature, numerous studies (Carmon et al., 1976; Bromm and Treede, 1984; Kakigi et al., 1989; Plaghki et al., 1994; Svensson et al., 1997; Timmermann et al., 2001; Nahra and Plaghki, 2003b; Schlereth et al., 2003) have shown a positive relationship between amplitude of the Aδ-fiber mediated late LEP P2 and the intensity of the evoking stimulus. These studies have also shown that increasing the intensity of the stimulus could reduce the latency of LEPs, such as for the latency of AEPs. However, studies examining intensity of perception and magnitude of late LEP responses under different attentional settings (Plaghki et al., 1994; Garcia-Larrea et al., 1997) have shown that the amplitude of late LEP responses may be more directly correlated to the subjective pain sensation than with the actual stimulus intensity. This proposition has been confirmed in a recent elegant experiment. Lee and co-workers (2009), by using a double pulse stimulation paradigm, showed late LEPs (N2 and P2 wave) being significantly reduced in amplitude when the second stimulus was reported as not perceived (figure 2-3).

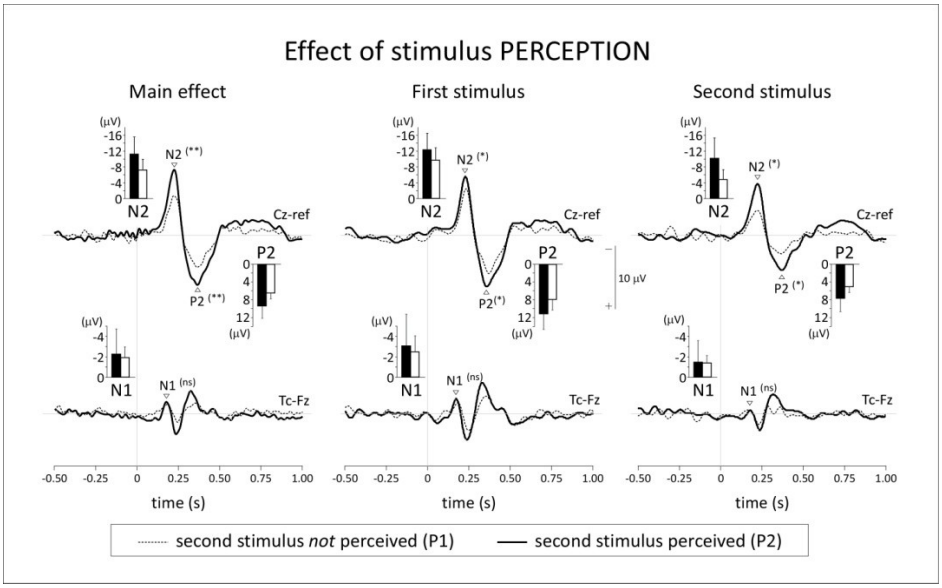

Figure 2-3. Effect of stimulus perception on LEPs elicited by two rapidly succeeding stimuli. *x*-Axis, Time (in seconds). Top graphs, N2 and P2 waves recorded at the vertex (Cz vs nose reference). Bottom graphs, N1 wave recorded at the temporal region contralateral to the stimulated side (Tc vs Fz). Full waveforms, LEPs obtained when the second stimulus was perceived. Dashed waveforms, LEPs obtained when the second stimulus was not perceived. The main effect of perception is shown in the left column. Note that the magnitudes of the N2 and P2 waves were significantly greater when the second stimulus was perceived, whereas the magnitude of the N1 wave was not significantly affected by whether or not the stimulus was perceived. The effect of perception on the LEPs elicited by the first stimulus is shown in the middle column, and its effect on the LEPs elicited by the second stimulus is shown in the right column. Note how the amplitude of the P2 wave elicited by both the first and the second stimulus was significantly greater when the second stimulus was perceived. The bar graphs represent the average (±SD) amplitudes of N1, N2, and P2 waves in each condition. *$p \leq 0.05$; **$p \leq 0.01$. From Lee et al., 2009.

1.2 'Bottom-up' determinants: Stimulus repetition and inter-stimulus interval

The effect of stimulus repetition and inter-stimulus interval (ISI) on the latency and amplitude of vertex potentials has been extensively studied in the auditory and somatosensory modalities (Ritter et al., 1968; Roth and Kopell, 1969; Fruhstorfer et al., 1970; Weber, 1970; Fruhstorfer, 1971; Ohman and Lader, 1972; Prosser et al., 1981; Angel et al., 1985; Woods and Elmasian, 1986; Bourbon et al.,

1987; Tomberg et al., 1989; Barry et al., 1992). Vertex potentials elicited by the first stimulus in a train are usually large in amplitude. When a constant presentation rate is used, their amplitude then rapidly diminishes with repetition, reaching a low asymptotic level after just few presentations of stimuli (for a review, see Naatanen and Picton, 1987). The amplitude decrement is faster and more pronounced when short and constant ISIs are used (Fruhstorfer et al., 1970; Angel et al., 1985). For example, Tomberg et al., (1989) showed that the somatosensory N1 vertex potential should disappear when ISI is reduced to 1.4 seconds. The same effect has been observed also for the visual P300 with an ISI of 1.2 seconds (Strüber and Polich, 2002).

According to some studies, the full recovery of the auditory N1 vertex potential could require up to 10 seconds (Davis et al., 1966; Ritter et al., 1968; Fruhstorfer et al., 1970; Naatanen, 1988). However, when variable rates of stimulation are used, studies have shown that the auditory vertex potential is not necessarily attenuated by repetition and may even be enhanced when sounds are presented within intervals shorter than 400 ms (Loveless et al., 1989; Budd and Michie, 1994; Loveless et al., 1996; McEvoy et al., 1997; Sable et al., 2003). This evidence has been recently extended to other modalities by Wang and colleagues (2008). The authors by delivering stimuli with ISI between 100 and 1000 found an enhancement of both auditory and somatosensory N1 amplitude and a decrease of P2 wave amplitude at ISI shorter than 200 ms.

These effects have been addressed by the two main following arguments:

I. *Latent inhibition*. When producing a first response, the neural populations that generate vertex potentials or LEPs could enter a transient state of 'refractoriness'. The ability of these neurons to

produce additional responses would be diminished and only gradually recover over time. The amplitude of a given response would therefore be directly related to the delay between the two response-eliciting stimuli. At high repetition rates, one would thus expect the response to the second stimulus to be minimal. This hypothesis was derived from the fact that following an action potential, single neurons display a 'refractory period'. It is assumed that the polysynaptic neural assemblies generating vertex potentials show a phenomenon similar to the 'refractoriness' of single nerve cells. In other words, the processes underlying vertex potentials and LEPs would be subject to temporal limitations (Naatanen and Picton, 1987; Budd et al., 1998). However, as complete recovery of the vertex potential amplitude may require up to ten seconds (Davis et al., 1966; Ritter et al., 1968; Fruhstorfer et al., 1970; Naatanen, 1988), it seems difficult to envisage that refractoriness of simple cellular mechanisms could fully account for the response decrements induced by repetition (Naatanen and Picton, 1987).

II. *Habituation*. The enhancement of vertex potentials elicited by the first stimulus in a train has been associated to an initial orienting-response (Kenemans et al., 1989). This stimulus would catch attention and therefore elicit a large vertex potential (Squires et al., 1975; Snyder and Hillyard, 1976; Alho et al., 1998; Escera et al., 1998). The response decrement of vertex potentials induced by stimulus repetition would thus result from a progressive loss of novelty associated with the repetition of the stimulus. The fact that stimulus repetition does not induce a similar response decrement when variable ISIs are used is a strong indication that the decrement observed when constant stimulation rates are used is indeed at least partially related to the loss of novelty or the higher expectancy of the subsequent stimulus. The response decrement following stimulus

repetition is a well-established phenomenon. However, while some studies have found the decrement to be maximal already for the second stimulus, suggesting that the decrement is related to refractoriness and not to habituation, other studies have suggested the opposite, showing the decrement to increase and reaching asymptote only at the third or fourth stimulus in the train (see Budd et al., 1998 for a review). In sum, response recovery of the vertex potential in response to a changing stimulus has been established in both auditory and somatosensory modality, both processes of habituation and refractoriness could explain such a recovery function.

In light of these observations, research on pain processing diplays no difference with respect to the other modalities. Indeed, It is widely accepted that even when care is taken to shift stimulus location, thereby avoiding peripheral habituation or sensitization of nociceptors, repeating the laser stimulus may induce an important decrease of late LEP amplitudes (Bromm and Treede, 1987a; Iannetti and Mouraux, 2008; Lee et al., 2009; Raij et al., 2003; Truini et al., 2004). Indeed, Bromm and Treede (1987a) reported that when two laser stimuli were applied with an inter-stimulus interval (ISI) of 900 ms, the amplitude of the LEP evoked by the second stimulus was significantly reduced. Raij and co-workers (2003) examined EEG and MEG responses evoked by trains of laser stimuli, using ISIs ranging from 0.5 to 16 seconds. In order to reduce stimulus expectancy, a 20% variation of ISI was introduced from trial to trial. This study showed that repetition induced an important attenuation of both LEPs and laser-evoked magnetic fields (LEFs) components. Truini and colleagues (2004) examined LEP responses to pairs of laser stimuli applied to the dorsum of the hand using a constant ISI, which ranged from 0.25 to 2 seconds. As compared to the LEP response elicited by the first stimulus, the amplitude of the second LEP

response was attenuated. At the smallest ISI (i.e., 0.25 s), the brain response was attenuated by 50%. At larger ISIs, the amplitude gradually recovered but a decrease of 20% was still observed at 1000 ms. The authors imputed this phenomenon to neural refractoriness. Nevertheless, a more recent research robustly demonstrated that this is not the case (Iannetti and Mouraux, 2008). Indeed, stimulus repetition at a short and constant ISI (1 second) led to a significant reduction of the magnitude of the laser-evoked N1, N2–P2, and the laser-induced event related synchronization (ERS). This reduction in magnitude occurred entirely between the first and the second stimuli, with no further reduction between the second and the third.

In the authors opinion two arguments act against an interpretation based on neural refractoriness or even on 'psychological refractoriness' mechanisms (see Pashler, 1984). First, stimulus repetition did not affect the magnitude of perceived pain (that would be expected according to the neural inhibition mechanism). Second, a previous study showed that when laser stimuli are delivered in pairs at unpredictable ISIs, thus ensuring that the occurrence of the second stimulus is as unexpected as the occurrence of a single stimulus, the amplitude of the laser-evoked N2–P2 is totally independent by the occurrence of the preceeding stimulus (Mouraux et al., 2004).

1.3 'Bottom-up' determinants: Saliency and behavioral relevance

In the aforementioned experiment Iannetti and Mouraux (2008) attributed the effect of neural activity suppression to a saliency-based mechanism: the first unexpected stimulus (relative to the second and the third of each triplet) that is perceived as more

salient, determines higher LEP amplitudes. Conversely, the reduction in the relative uncertainty of the following two stimuli along with the repeatition suppression effect, induced lower LEP magnitudes. Therefore, following this interpretation, saliency should be paralleled to temporal expectancy. Nevertheless, The authors applied a more general saliency definition provided by Downar and co-workers (2000): the "ability of the stimulus to disrupt the current cognitive focus and elicit an attentional or behavioural switch". This definition is implicitly susceptible to include other connotations of saliency besides the one that focuses on its temporal feature (e.g., magnitude, spatial position, modality). Nonetheless, defining the concept of saliency is not an easy task, as saliency is not only driven by the intrinsic physical features of the sensory stimulus, but also depends on the context within which the sensory stimulus is presented, and on the inner goals/objectives of the perceiving organism. In other words, saliency is associated both with 'bottom-up' properties of the sensory input and with 'top-down' factors related to behavioral goals.

The most advanced analysis of this concept in neuroscience can be tracked in the visual attention domain (Itti and Koch, 2001). Research in this field conceptualizes bottom-up saliency as a feature-based mechanism in which the strength of each characteristic is weighted and contrasted with others in the contextual surround (e.g., Koch and Ullman, 1985; Treisman and Gelade, 1980). This feature contrast computation is tought to converge in saliency maps, where stimuli of different quality, magnitude and scale (e.g, colour, contrast, luminosity, etc.) are computed and combined till only one pattern have access to working memory on the basis of its relative higher weight (see figure 2-4).

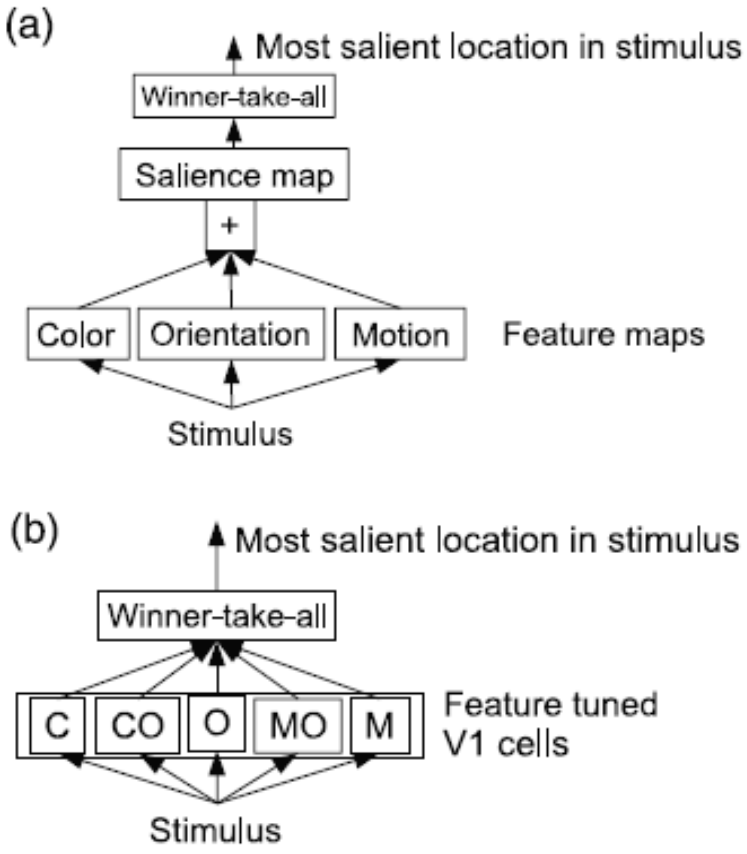

Figure 2-4. (a) **Feature summation hypothesis.** Visual inputs are first processed in separate feature maps tuned to different stimulus features (e.g., orientation, color, and motion). The output of these feature maps is summed to produce a single salience map. (b) **V1 hypothesis.** V1 cells tuned to different features interact through lateral connections. Activity in cells responding to uniform feature texture stimuli is suppressed through mutual inhibition. The most salient location is the receptive field location of the cell with the greatest firing rate. C = color, CO = color and orientation, O = orientation, MO = motion direction and orientation, M = motion direction tuned cells. Adapted by Koene and Zhaoping, 2007.

A similar model may be developed by research in neuroscience of pain perception to explain how nociceptive salience emerge from a set of different relative features as intensity, temporal pattern, and location. The relationship between stimulus intensity and magnitude of LEP responses has been hystorically interpreted as an indication that the processes underlying LEPs could subserve coding of the stimulus intensity (Svensson et al., 1997; Timmermann et al., 2001; Schlereth et al., 2003). However, although intensity of the

nociceptive stimuli contributes to LEP amplitude, the underlying brain areas are sensitive to others factors such as absolute novelty (i.e., when the stimulus is delivered in first position in repeated series) (Iannetti et al., 2008), contextual novelty (i.e., when 1 or more stimulus features are deviant relative to background) (Legrain et al., 2002, 2003a), the importance of the deviancy (Legrain et al., 2003b), the stimulus unpredictability (Clark et al., 2008), and the relevance according to ongoing cognitive/behavioral goals (Legrain et al., 2002). All these factors contribute to increased stimulus saliency. The role of saliency seems to be fundamental in all the perceptual system and especially in the nociceptive system, as it seems to be the main interface of bottom up processes with top-down attentional control even before the neural representation of the stimulus enters working memory.

1.4 'Top-down' determinants: Vigilance and arousal state

Vigilance, largely synonym to arousal, alertness, or sustained attention, would involve processes related to maintaining behavioral goals over time. These processes would also be implicated in the regulation of the sleep-wake cycle.

Both auditory and somatosensory vertex potentials have been shown to be modulated by the level of vigilance. Indeed, numerous studies have reported that an increase in the general level of attentiveness resulted in an increase in the amplitude of the vertex N1 component. On the contrary, it is well accepted that during the process of falling asleep, the auditory N1 vertex potential declines in amplitude (Ogilvie et al., 1991; Bastuji et al., 1995; Nordby et al., 1996). Furthermore, during non-REM sleep, the auditory N1 component is described as even more attenuated (Nielsen-Bohlman et al., 1991)

and may even reach near baseline levels (Paavilainen et al., 1987). This progressive decrease of N1 amplitude parallels a progressive slowing of behavioral response times (Ogilvie et al., 1991). For this reason, the decline in N1 amplitude observed during the process of falling asleep has often been interpreted as resulting from a progressive decline of the subject's arousal level. Similarly, an attenuation, or even a disappearance, of the auditory vertex potential complex has been described when sedation or drowsiness are pharmacologically induced by benzodiazepines or general anesthesia (Plourde and Picton, 1991; Rockstroh et al., 1991; Van Hooff et al., 1995). While it is commonly accepted that the amplitude of the auditory N1 is reduced during drowsiness and may even reach baseline levels during non-REM sleep, results concerning the auditory P2 vertex potential are more equivocal. Indeed, during the process of falling asleep, numerous studies (Nielsen-Bohlman et al., 1991; Ogilvie et al., 1991; Winter et al., 1995; Crowley and Colrain, 2004) have shown that the amplitude of the auditory P2 appears, paradoxically, to increase (see figure 2-5).

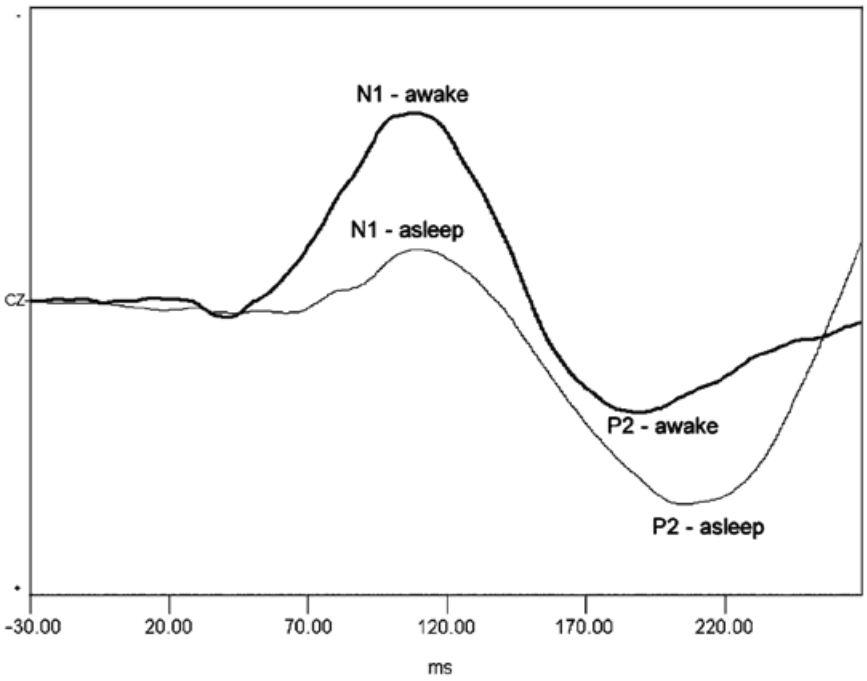

Figure 2-5. Grand average waveforms (CZ-A1A2) of auditory vertex potentials (N1-P2) during wakefulness and stage 2 sleep recorded at electrode CZ. From Crowley and Colrain, 2004.

However, it should be noted that this sleep-induced enhancement of P2 amplitude was not reported by all studies (Salisbury and Squires, 1993). For instance, De Lugt et al. (1996) revealed no differences across all sleepwake states from relaxed wakefulness to slow-wave sleep.

A strong attenuation of LEPs too, has been noticed following a decreases in arousal (Bromm and Treede, 1991; Arendt-Nielsen, 1994; Weiss et al., 1997; Bromm and Lorenz, 1998). Moreover, due to the long duration and monotony of experimental recordings, declines of vigilance most probably contribute to the often observed progressive amplitude decrement of LEP responses. Beydoun et al., (1993) compared late LEP responses under different states of arousal. LEPs were recorded in subjects after one day of sleep deprivation. Subjects were allowed to fall asleep during the experiment. When subjects were becoming drowsy (defined on the basis of a drop-out in EEG alpha-activity and the appearance of lateral eye movements), a marked decrease of N2-P2 peak-to-peak amplitude was reported. Furthermore, when subjects were in sleep stage 2 (defined on the basis of the appearance of sleep spindles on the EEG), the laser stimulus did not evoke quantifiable LEPs. These results were recently replicated both during sleep (Bastuji et al., 2008) and after sleep deprivation (Tiede et al., 2009).Similarly, decreases of LEP amplitude have also been shown to accompany sedation and drowsiness when induced pharmacologically. Indeed, Zaslansky et al. (1996a) showed that intravenous administration of benzodiazepines could induce a marked attenuation of the late laser-evoked P2 component.

Therefore, it appears that such as auditory and somatosensory vertex potentials, laser-evoked potentials are sensitive to the level of arousal. Both Aδ-fiber and C-fiber related LEP responses are strongly attenuated during drowsiness and tend to disappear completely during non-REM sleep.

However, the observation that the process of falling asleep leads to an apparent increase of the auditory P2 wave, If confirmed would contradict the disappearance of the nociceptive P2 potential elicited by laser stimuli, and would argues against the hypothesis that both components could be completely explained by the activation of common generators.

1.5 'Top-down' determinants: Selective and focused attention

Selective attention, also referred to as focused attention, would allow biasing or filtering relevant versus irrelevant sensory input. This attentional filtering is often considered as a 'regrettable necessity' required for limited processing resources to cope with the huge amount of sensory input arising simultaneously from different sensory modalities and locations (Desmedt et al., 1983; Desmedt and Tomberg, 1989; Garcia-Larrea et al., 1991; Eimer and Forster, 2003).

Studies which examine the effects of selective attention on event-related potentials typically compare responses elicited by attended stimuli to that elicited by unattended stimuli. In most of these studies, the effect of selective attention is then assessed by computing *unattended–attended* difference waveforms. Most studies have focused on the effect of selective attention within the same sensory modality (i.e. intra-modal selective attention; e.g. attending or ignoring the spatial location of the stimulus or a specific attribute

of the stimulus). A fewer number of studies have examined the effects of selective attention across different sensory modalities (i.e. inter-modal selective attention; e.g. attending or ignoring stimuli from a specific sensory modality).

The first pioneer finding described a consistent negative inflection occurring at latencies ranging between 50–150 ms after stimulus onset (e.g. Hillyard et al., 1973; Schwent and Hillyard, 1975; Hansen and Hillyard, 1980). This negative activity was described when subjects attended to the spatial location of the auditory stimulus but also when they attended to a specific acoustic frequency. This negative enhancement was initially interpreted as resulting from an increase of the auditory N1 wave elicited by attended stimuli as compared to that elicited by unattended stimuli (Hillyard et al., 1973; Schwent and Hillyard, 1975). Indeed, it is generally accepted that selective attention can enhance the receptivity of the cortical networks implicated in the processing of attended inputs (i.e., 'sensory gain' hypothesis). However, Naatanen and colleagues (1978) proposed that this negative enhancement does not reflect an increase of the auditory N1 per se but the increase of an independent overlapping electrophysiological component, originating from distinct cortical areas, and referred to as 'negative difference' (Nd). The Nd would reflect processes specifically related to selective attention and labeled 'processing negativities' (Naatanen et al., 1980; Naatanen and Picton, 1987; Naatanen, 1990). Processing negativities would involve the comparison of incoming inputs to an attentional trace formed by prior presentations of the attended stimulus (Naatanen et al., 1993). Inputs matching this attentional trace would be further processed while inputs mismatching this template would be fully or partially rejected from higher-order processing.

Similar negative enhancements have been evoked by somatosensory

stimuli as well (Desmedt and Robertson, 1977; Michie et al., 1987; Garcia-Larrea et al., 1995). Indeed, such as the auditory N1, selective spatial attention effects have been shown to modulate the somatosensory N1 component (Desmedt and Robertson, 1977; Josiassen et al., 1982; Desmedt et al., 1983; Michie et al., 1987; Desmedt and Tomberg, 1989; Papanicolaou et al., 1989; Garcia-Larrea et al., 1991; Ito et al., 1992; Garcia-Larrea et al., 1995). In fact, Garcia-Larrea and co-workers (1995) proposed that at least part of the enhancement of the somatosensory N1 observed when stimuli are presented at an attended location could be related to a 'processing negativity' similar to that described by Naatanen (1980) in the auditory modality.

With regard to the nociceptive modality, numerous studies have compared LEPs with attention directed either towards or away from the laser stimulus (Beydoun et al., 1993; Siedenberg and Treede, 1996; Zaslansky et al., 1996b; Garcia-Larrea et al., 1997; Yamasaki et al., 1999; Friederich et al., 2001). All these studies have consistently reported that attending to the laser stimulus could induce a strong enhancement of the vertex N2-P2 complex. Results of these studies have also suggested that the earlier N1 LEP was mostly unaffected by the focus of attention (see Garcia-Larrea et al., 1997). However, determining the exact causes underlying these LEP amplitude modulations is difficult due to the fact that, in most experimental paradigms, several attentional factors were concurrently manipulated. Indeed, in most of these studies (Beydoun et al., 1993; Plaghki et al., 1994; Siedenberg and Treede, 1996; Zaslansky et al., 1996b; Garcia-Larrea et al., 1997; Yamasaki et al., 1999; Friederich et al., 2001; Nakamura et al., 2002; Schlereth et al., 2003), LEPs were compared across different experimental conditions presented within different recording blocks. As tasks

requested within each experimental conditions differed (e.g., active counting of incoming stimuli vs. passively waiting for the recording sequence to end), use of such paradigms could have led to significant variations in the level of arousal. Such changes in arousal could therefore have contributed to the observed LEP differences. Furthermore, subjects were always asked to detect and react to the attended stimulus. Thus, observed LEP differences may have been related to the task-relevance or target nature of the attended stimulus. In addition, some studies (Beydoun et al., 1993; Towell and Boyd, 1993; Plaghki et al., 1994; Siedenberg and Treede, 1996; Zaslansky et al., 1996b; Garcia-Larrea et al., 1997; Yamasaki et al., 1999; Friederich et al., 2001; Nakamura et al., 2002; Schlereth et al., 2003; Boyle et al., 2008), required the attention to be shifted across both a different sensory modality and/or a different spatial location.

Under these conditions, both inter-modal and intra-modal selective attention effects could have modulated LEP responses. For instance, Friederich and colleagues did not observe significantly reduced late ERP components to painful stimulation while subjects were verbally suggested hypnotic analgesia but only while they were visually distracted from processing the noxious input. These authors found a significant reduction of N2 and P2 amplitudes during distraction condition as compared to the control condition. On the other hand, Boyle and co-workers (2008) investigated the effects of noise distraction (85 dB white noise) on the different components and sources of laser-evoked potentials (LEPs) whilst attending to either the spatial component (localisation performance task) or the affective component (unpleasantness rating task) of pain. These authors showed a selective modulation of the sole affective pain processing by noise distraction, indicated by a reduction in the

unpleasantness ratings and P2 peak amplitude, associated with the activity of the medial pain system. Finally, in a recent set of studies, Legrain et al. (2002; 2003a; 2003b) specifically examined the effect of the spatial direction of attention within the nociceptive modality. These studies showed that all LEP negativities, (i.e., the N2 but also the N1 component) were increased in response to laser stimuli at selectively attended body locations but independently by whether or not attended stimuli were targets (i.e. relevant to the task) (see figure 2-6). On the contrary, the laser-evoked P2 component was unaffected by the spatial location of the attentional focus.

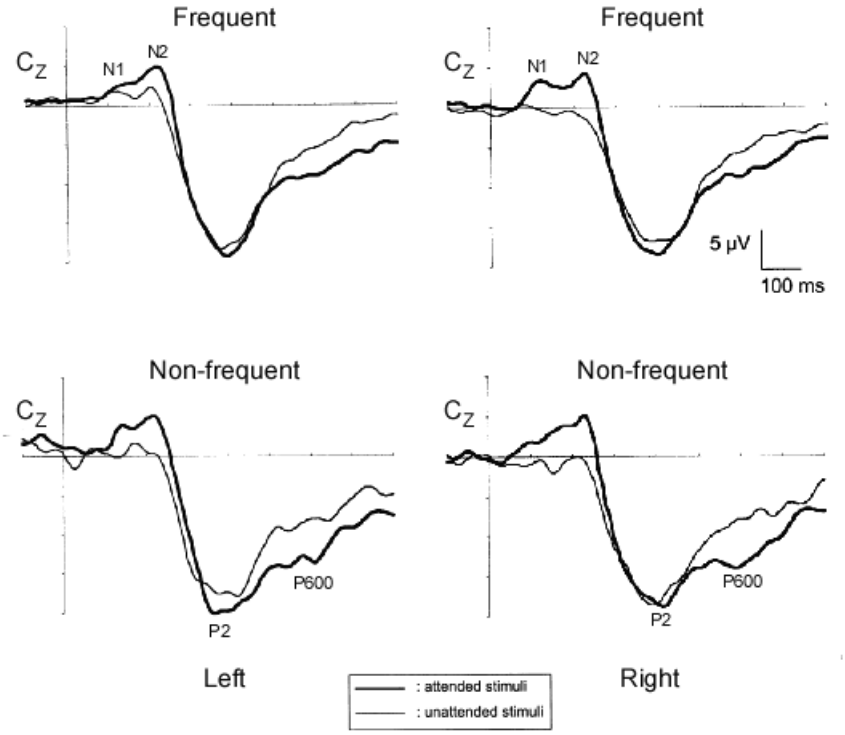

Figure 2-6. Grand-average of laser-evoked potentials recorded from left and right hand stimulation at electrode CZ. Frequent and non-frequent stimulus intensities were applied to the left and right hands. Subjects selectively attended either the left or right hand (subjects were requested to count rare targets occurring at the attended hand). Attending to the hand led to an enhancement of LEP N1 and N2 components but regardless of the fact the stimulus was a target, and regardless of probability of occurrence. Rare and attended stimuli elicited an additional P3b-like component (P600). Adapted from Legrain et al. (2002).

Therefore, LEP studies seem to report a top-down effect of selective attention (attending to specific features of pain) on late indexes (especially P2 wave). Whether the effects of selective (active) attention on the 50–150 ms range (N1) in other sensory modalities may be identified also in the nociceptive modality, is still to be further investigated.

1.6 'Top-down' determinants: Expectation and anticipation

Expectation about upcoming events enable an organism to adjust sensory cognitive and motor systems to provide a suitable neural activation and thus a 'fitting' behavioral response. It is a crucial mechanism to detect discrepancies between previously acquired information and new or changing features in the environment.

The number of ERP studies investigating the effect of pure expectation and anticipation of sensory and painful stimuli is limited. This is also probably due to the various levels of complexity engendered by these constructs. For instance, a general connotation of expectation may involve an automatic passive process similarly to those exerted by bottom-up processes. The 'priming effect' can be clearly interpreted as an effect of very fast-rising implicit expectation coupled to long term memory storage regardless of conscious appraisal.

The unique example of priming effect in LEPs literature is represented by the work of Dillman and co-workers (2000), whereby the authors studied whether different semantic primes could affect the processing of painful stimuli by pre-activating nociceptive nociceptive memory. Somatosensory pain-related, affective pain-related, and neutral adjectives were displayed for 5 seconds during which the laser pulse was delivered. LEPs obtained while subjects

processed pain-related primes (affective and somatosensory adjectives) resulted in larger LEP P2 compared to amplitudes of laser-evoked activities while subjects processed neutral primes. The authors proposed that such a top-down effect may reflect several affective-cognitive processes coupled to contextual stimulus meaning, temporal expectation, and attentional cognitive load, triggered by nociceptive memory of emotionally relevant past events. Other studies focused on the temporal connotation of expectation by manipulating the predictability of noxious events. Among the most recent, Babiloni and co-workers (2008) studied the hypothesis that the anticipatory cortical processes are stronger for painful thermal (biologically relevant) than electrical ('artificial') stimuli with similar intensity. Data from an array of 128 electrodes were recorded in a paradigm whereby expectation was manipulated by omitting a predictable target in a visual sequence. The electrical or laser stimulus was delivered at the instant in which the stimulus was omitted. The anticipatory stimulus preceeding negativity (SPN), thought to reflect motivational relevance of the stimulus, appeared before painful laser (shorter onset latency) but not prior to electrical stimulation. The same held true for the nonpainful stimulations. The authors interpreted this finding as a motivational priming of brain mechanisms coupled to the biological/ecological relevance of laser stimuli. In another study (Brown et al., 2008) laser heat stimuli at different intensities (low, medium or high) were delivered in a context where subjects viewed cues that either accurately informed (certain expectation) or not informed them (uncertain expectation) of forthcoming intensity. The SPN index increased with expectations of painful vs. non-painful heat intensity, suggesting the presence of neural responses that represent predicted heat stimulus intensity. These anticipatory responses also correlated with the amplitude of

the Laser-Evoked Potential (LEP) response to painful stimuli when the intensity was predictable. Source analysis revealed that uncertainty about expected heat intensity involved an anticipatory cortical network commonly associated with attention (left dorsolateral prefrontal, posterior cingulate and bilateral inferior parietal cortices). The analysis of how expectation can be relevant in dealing with immanent threat was addressed in a study that applied an auditory cue as signal of a subsequent painful laser stimulus (Hauck et al., 2007a). The duration of the cue-to-stimulus delay was systematically varied between 2, 4 and 6 seconds. The authors found an increase in evoked late potential (P2) according to longer cue-to-pain delays (enhanced expectation towards impending pain) that was coupled to a stronger cortical activation in limbic structures associated with pain expectation and focussing of attention (MCC). Seemingly, Clark and colleagues (2008) manipulated the duration of anticipation of laser-induced pain (3,6,9,12 seconds interval), yet they also provided one condition in which the elapsed time was predicted and one contition in which it was not, thus disentangling the net effect of predictability on expectation (see figure 2-7). Interestingly, the unpredictability in stimulus timing increased the amplitude of the P2 wave regardless the anticipation delay. This modulation was localized to midcingulate cortex (MCC) and ipsilateral secondary somatosensory (S2) areas. Greater anticipation duration instead, increased activity in a hippocampal-insula-prefrontal network but not in MCC areas, thus suggesting possible different patterns of activity for antipation/expectation and predictability of noxious events.

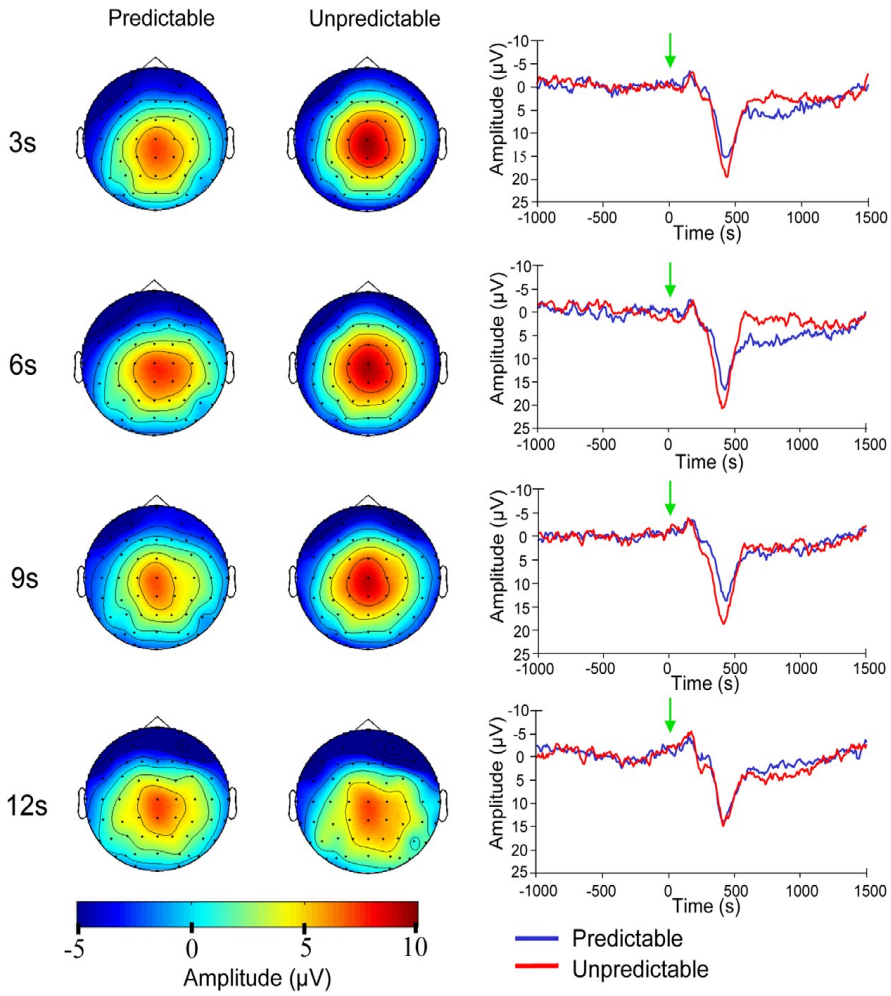

Figure 2-7. Modulation of P2 LEP by unpredictability of stimulus timing for each anticipation duration. Topographic maps showed the significant differences between predictable and unpredictable conditions at central electrodes (Cz) for each of the 3 s, 6 s, and 9 s anticipation durations, but not for the 12 s anticipation duration. Green arrows indicate onset of the laser stimulus. Adapted from Clarke et al., 2008.

Special attention should be directed also to those contribute of LEP technique to more complex experimental questions as those encountered in the study of the effects of social interaction on brain activity and behavior. Recently, Colloca and co-workers (2008) assessed the effects of both expectation (induced only by verbal suggestion) and conditioning on the N1 and N2–P2 laser-evoked potentials. An effect on the N2–P2 complex, but not the N1 potential was found when both verbal suggestions and conditioning were administered. Also, conditioning procedure produced a more robust

reduction of LEP amplitudes than verbal suggestions alone.

Future studies on the effects of expectation will still need to further elucidate whether pure expectation and anticipation (implicitly or explicitly triggered) may have an effect on early stage evoked brain activity and whether this effect may either be a general function of sensory integration (supramodal) or a function of specific modal activations in the brain.

1.7 At the crossroad: the Interaction of 'bottom-up' and 'top-down' mechanisms

'Bottom-up' and 'top-down' concepts are categories that help computational and biological sciences to disentangle the very complex processes related to how we build representation of external world and how this representation can affect our response to the world itself. However, as often happens when opposite taxonomies are used to analyse reality, we would not reach a clear understanding of brain functioning if we do not consider the massive interplay of 'bottom-up' and 'top-down' attentional mechanisms in the sensory systems, which is likely to be the rule (and not the exception) of brain dynamics.

The role of external stimuli in capturing attention does interact with the role of stored information in memory, subjective goals and motivations. A useful example of this interaction is represented by the mismatch negativity phenomenon or MMN.

In the auditory modality, numerous studies have shown that physically deviant sounds presented within a repetitive sequence (e.g., sounds differing in pitch intensity, duration, location, or timing) could elicit a negative inflection of the EEG, referred to as a 'mismatch negativity' (reviewed in Naatanen et al., 1992). The MMN is elicited even when the subject's attention is diverted from the

sound. For this reason, it has been suggested that the MMN reflects an automatic form of sensory analysis. To explain this phenomenon, Naatanen proposed that for the purpose of detecting changes in the auditory milieu, the brain automatically forms a short-term memory trace of auditory features which is then continuously compared to the incoming stream of sensory information. Detection of such changes would trigger processes reflected by the MMN component. Several studies have suggested that the greater part of the auditory MMN is generated in the auditory cortex (Alho, 1995). However, some investigators have proposed that bilateral frontal generators could also contribute to the MMN component (Giard et al., 1990). This frontal source was hypothesized to play a role in the initiation of an involuntary attention switch triggered by a sound change pre-perceptually detected in auditory cortices. In support of this hypothesis, it was shown that the signals generated by these frontal generators appear with a slight time-delay as compared to those generated by the bilateral temporal generators (Rinne et al., 2000). Whether deviant somatosensory stimuli may elicit EEG changes similar to the MMN component elicited by deviant auditory stimuli is still not clearly determined. Nevertheless, it should be noted that in a study examining event related potentials elicited by deviant and ignored vibratory stimuli, Kekoni and co-workers (1997) proposed that the earlier part of the vertex negativity (N120) could reflect a MMN-like activity. This somatosensory MMN component was hypothesized to originate from somatosensory-specific cortical regions. In addition, numerous studies (Courchesne et al., 1975; Squires et al., 1975; Yamaguchi and Knight, 1991; Escera et al., 1998; Katayama and Polich, 1998) have shown that deviant or intrusive auditory, visual, or somatosensory stimuli which occur outside the focus of attention may evoke an additional positive

component. This component, often referred to as P3a, has an earlier latency and a more frontal scalp distribution than the P3b component elicited by task relevant and infrequent stimuli. The P3a component is hypothesized to index an involuntary attentional-orienting reaction triggered by the detection of a sudden change in the environment. In the nociceptive domain too, Legrain and colleagues (2002) showed that rare intensity deviant laser stimuli presented within a stream of standard stimuli could elicit an additional positive deflection, occurring approximately 400 ms after stimulus onset (see figure 2-8). As this activity was elicited by deviant stimuli presented both within and outside the spatial focus of attention, it was hypothesized that it could reflect processes related to the P3a component described in other sensory modalities. In other words, the processes underlying this 'P400 effect' would be involved in an involuntary orientation of attention. In a later study comparing responses elicited by strong and weak deviant laser stimuli, Legrain et al. (2003b) showed that only laser stimuli of strong intensity could elicit this 'P400 effect'. This was interpreted as an indication that weak stimuli were not salient enough to induce involuntary attentional switching. This P3a-like component strongly overlapped with the later part of the LEP P2 component.

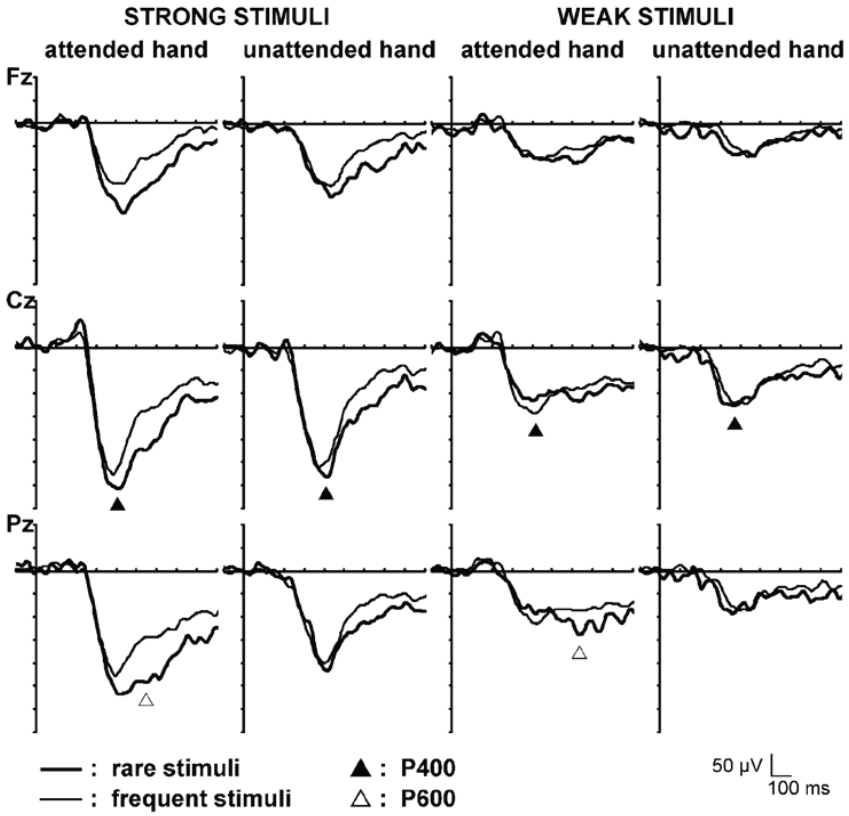

Figure 2-8. Grand-average of laser-evoked potentials recorded at three midline electrodes (FZ, CZ, PZ vs. A1A2). Strong and weak stimuli (either frequent or non-frequent) were applied to the left and right hands. Subjects were requested to count the nonfrequent stimuli occurring at the attended hand (target stimuli). The main positive peak, was larger in amplitude for non-frequent strong than for frequent strong stimuli (P400). It was not larger for non-frequent weak than for frequent weak stimuli. An additional parietal positivity was evoked at a later latency by both strong and weak target stimuli (P600). Adapted by Legrain et al., 2002.

When manipulation of task relevance and the occurrence probability of stimuli is introduced than an additional positive component can be elicited both in auditory modality (Sutton et al., 1965), and in the somatosensory modality (Desmedt et al., 1965). This response, often referred to as the P3b component, occurs approximately 300–350 ms after the onset of an auditory stimulus and 350–450 ms after the onset of a somatosensory or visual stimulus (Johnson, 1986; Picton, 1992). To elicit a P3b component, the evoking stimulus must be infrequent and subjects must be actively involved in its detection.

It is currently accepted that P3b waves represent late stages of information processing. To explain their functional significance, two leading hypotheses have been put forward. The first proposes that the P3b reflects the updating of working memory following the arrival of new information or 'context updating' (Donchin and Coles, 1988). The second proposes that the P3b reflects the closure of the processing of information or 'context closure', occurring when expectations are terminated (Desmedt, 1980; Verleger, 1988).

A number of studies have used oddball paradigms[1] to search for the presence of laser-evoked P3b-like responses (Towell and Boyd, 1993; Kanda et al., 1996; Siedenberg and Treede, 1996; Zaslansky et al. ,1996a; Legrain et al., 2002; Legrain et al., 2003a). In most of these studies, frequent and infrequent stimuli differed by their spatial location (Towell and Boyd, 1993; Kanda et al., 1996; Siedenberg and Treede, 1996; Zaslansky et al., 1996b). To allow dissociating between the effects of spatial attention and that of task relevance, some more recent studies have used different stimulus intensities to define stimulus deviance (Legrain et al., 2002; Legrain et al., 2003a; Legrain et al., 2003b). Task relevance was obtained by asking subjects to silently count or press a button when perceiving the infrequent target stimulus. The infrequent task-relevant laser stimuli elicited an additional positive potential (see figure 2-8) whose topography was similar to that of the P3b elicited by other sensory modalities. This wave, occurring approximately 600 ms after stimulation of the hand, could clearly be distinguished from the earlier P2 index.

[1] The oddball paradigm is the most used paradigm to evoke P300 responses. In this paradigm, two physically different stimuli are sequentially presented with contrasting probabilities. To focus the subjects attention towards the infrequent stimulus, subjects are usually requested to perform the detection of the infrequent 'target' stimulus.

More recently, Legrain and co-workers (2009b) in the context of oddball paradigm instructed subjects to ignore nociceptive stimuli while performing a task on visual targets. By changing location of laser stimuli in some trials (17%) (location-deviant) they questioned whether P2 wave could be sensitive index of attentional capture and whether involuntary orienting of attention to task-unrelated nociceptive stimuli could have detrimental effects on goal-relevant visual information. They observed that, as compared to frequent standard laser stimuli, deviant stimuli enhanced all nociceptive evoked brain potentials (laser N1, N2, P2a, P2b). Deviant laser stimuli also decreased the amplitude of late-latency evoked responses (visual N2-P3) to the subsequent visual targets and delayed reaction times to them.

These data can be interpreted as first proof of high competition of nociceptive processing with pain-unrelated cognitive activities for attentional resources, and that concomitant nociceptive events affect behavior by depressing attention allocation to ongoing cognitive processing. On the other hand, task-relevant and high-priority visual sensory processing was more preserved from interference by nociceptive distracters at early level of processing (N1-P1) than task-irrelevant and low-priority visual processing.

Up-to-date this experiment is one of the best examples on how to investigate the interplay of 'bottom-up' and 'top-down' attention between sensory systems, thus highlighting the functional significance of nociceptive processing in sensory binding and integration.

2 Aim of this thesis

The aim of the experimental work enclosed in this thesis was to further contribute to the understanding of respectively 'bottom-up'

and ‘top-down’ mechanisms of attention during nociceptive processing, with two distinct studies.

In particular, the focus of the present work will be centred on two features thought to be the most significant in determining the functional significance of nociception and pain perception. Indeed, the underlying commonality connecting the following two experimental works rests on the idea that ‘top-down’ expectation together with ‘bottom-up’ saliency may be the most relevant recursive mechanism whereby an organism builds percepts and updates the relevant information to be prioritized for further processing in working memory.

The literature in this field showed that late LEPs (N2-P2) appear to be equally modulated by experimental parameters such as stimulus intensity, general level of arousal, selective attention, task relevance, novelty or deviance of the evoking stimulus. Differently, the N1 wave seemed to be less susceptible to ‘top-down’ influences associated to expectation-anticipation and focused attention of the subject on the noxious context.

According to several investigators in this field, LEP-related processes could serve to trigger involuntary reorientations of attention (Garcia-Larrea et al., 1997; Lorenz and Garcia-Larrea, 2003; Iannetti and Mouraux, 2008; Legrain et al., 2009b). Consequently, one would expect these processes to be best triggered by the occurrence of salient (e.g., novel, sudden, threatening, rare, etc.) stimuli. However, exogenous and endogenous salient stimuli must be screened, directed and eventually manipulated on the basis of the individual cognitive beliefs on the current situation (also on the basis of a previous cognitive set and of memory traces). Thus, the expectancy related to upcoming changes in the ongoing stream of sensory inputs can deeply modify the perceptual outcome regardless

of the intrinsic peripheral physical saliency.

The challenge now lies in optimally understanding behavioral and neural effects of passive and active attentional processes related to both the emerging of a noxious stimulus in the sensory sourranding and to the intervention of affective and cognitive mechanisms adopted to monitor, select, and further process the emerging input.

Chapter 3 will present a study where we aimed at understanding whether the change of modality (from auditory to nociceptive rather than no change at all) could significantly modulate the evoked and event-related brain responses, no matter the subjects expectation of this change. The results of this study further increase the knowledge on LEPs determinants associated to saliency of noxious stimuli in the sensory environment.

Chapter 4 will introduce a study were hypnotic suggestions were used to draw subject's attention either on intensity or on unpleasantness of pain perception. Thus, I aimed to investigate whether this manipulation could induce a dissociation between this two measure of subjective experience and whether LEPs could reflect the role of focused attention and expectation in indexing behavioral changes. The results of this study further increase the knowledge on the effects of cognitive-affective processes in modulating LEPs during an altered state of consciousness known to heighten the fronto-parietal network of sustained attention.

Chapter 3

Contribution to the analysis of 'bottom-up' features

"Chasing the understanding of laser-evoked EEG responses: effect of expected and unexpected changes in modality"

1 Introduction

Brief radiant heat pulses selectively activate Að and C skin nociceptors and elicit transient brain responses (laser-evoked potentials, LEPs) in the ongoing electroencephalogram (EEG) (Carmon et al., 1976, Mouraux et al., 2003). LEPs are classically distinguished in a large bipolar vertex complex (N2-P2) which occurs 160-390 ms after the stimulation of the hand dorsum (Bromm and Treede, 1984b) and, in a smaller negative deflection called N1 which occurs after approximately 130-190 ms after the stimulus and is maximal over the temporal region contralateral to the stimulated side (Garcia-Larrea et al., 1997). Human EEG studies, magnetoencephalography (MEG) studies, or invasive intra-cerebral recordings, as well as hemodynamic studies using functional MRI (fMRI) or positron emission tomography (PET), all concur in outlining a large array of cortical structures devoted to specific processing of nociceptive inputs, the so called pain matrix (Apkarian et al., 2005; Garcia-Larrea et al., 2003; Kakigi et al., 2005; Peyron et al., 2000, 2002; Treede et al., 1999; Melzack, 1990). Among the structures involved in such a neural net, the primary and secondary somatosensory cortices (SI and SII), the insula, and the anterior cingulate cortex (ACC) seem to have a massive activity (Lenz et al.,

1998a,b; Ohara et al., 2004; Frot and Mauguiere, 2003; Frot et al., 1999, 2008).

However, as already pointed-out by Carmon et al. (1976) in their seminal work, as well as by Stowell (1984), the fact that the eliciting sensory stimulus is entirely selective for nociceptive peripheral afferents by no means implies that the elicited brain activity is nociceptive specific. As a matter of fact, non-nociceptive somatosensory stimuli (Garcia-Larrea et al., 1995; Goff et al., 1977), auditory stimuli (Naatanen and Picton, 1987; Picton et al., 1999), and even visual stimuli (Makeig et al., 1999; Vogel and Luck, 2000) may all elicit a large "vertex potential" whose shape, scalp topography, and sensitivity to various experimental factors closely resemble those of LEPs (Garcia-Larrea, 2004; Garcia-Larrea et al., 2003; Kunde and Treede, 1993; Mouraux and Plaghki, 2006). Therefore, although laser-evoked EEG responses are increasingly used to investigate nociceptive pathways, a full understanding of their functional significance has still to be achieved. We recently tackled this problem by investigating the single-trial behavioural and EEG responses to short trains (i.e. triplets) of nociceptive stimuli of identical energy, delivered to the hand dorsum at short (1 s) and constant inter-stimulus interval (Iannetti et al., 2008). By doing this we showed that the positive correlation between the magnitude of the laser EEG responses and the intensity of perceived pain, described both in the time domain (Arendt-Nielsen, 1994; Beydoun et al., 1993; Bromm and Treede, 1991; Iannetti et al., 2005; Ohara et al., 2004) and in the time-frequency domain (Mouraux et al., 2003; Iannetti et al., 2008), can be significantly disrupted. That is, while S1, S2 and S3 elicited a similar intensity of pain, virtually all EEG responses elicited by S2 and S3 were greatly reduced compared to those elicited by S1. Thus, we concluded that laser stimuli

perceived as more painful could elicit LEPs of greater magnitude simply because they were more salient (Iannetti et al., 2008).

In support of this interpretation, Legrain and coworkers showed that the laser-evoked waves are enhanced either by task-relevant novelty in nociceptive intensity (only P2; Legrain et al., 2003a,b) or by task-relevant shifting of attention (N1, N2; Legrain et al., 2002), and also by task-irrelevant novelty of nociceptive spatial deviancy (N1, N2, P2; Legrain et al., 2009b), thus suggesting both a 'top-down' attentional influence on somatosensory cortices (N1 and N2 waves) and 'bottom-up' stimulus-driven mechanism of arousal or attentional orientation likely coupled to cingulate and insular cortex activity (see also Lorenz and Garcia-Larrea 2003 for a review). Additionally, the conscious perception of painful stimuli has been associated with larger N2 and P2 waves (Lee et al., 2009). In the present study, by re-applying the 'triplet' paradigm, we aimed at testing whether the change in sensory modality could equally affect LEPs and auditory evoked potentials (AEPs). On a second thought, we wanted to further enquiry the role of expected or unexpected saliency by analyzing their interaction with the change in modality. Indeed, the ability to capture the attention can be underpinned by a variety of stimulus features, as its intensity, spatial location and modality. By holding constant both stimulus location and intensity, the purpose of the present study was to investigate if predictable or unpredictable modality change of the last stimulus in a triplet could equally affect evoked and event-related brain responses.

2 Methods

2.1 Subjects

Twelve healthy subjects (7 women) aged 22-35 years (mean 26.2 ±

4.2) participated in this study. The participants were recruited among research staff and students at the University of Oxford. All the participants gave their written informed consent. This study conformed to the standards required by the Declaration of Helsinki and was approved by the local ethics committee.

2.2 Nociceptive and auditory stimulation

Noxious radiant stimuli were generated by an infrared neodymium yttrium aluminium perovskite (Nd:YAP) laser with a wavelength of 1.34 μm (Electronical Engineering, Florence, Italy). At this wavelength the laser pulses activate directly the Aδ and C-fiber nociceptive terminals located in the superficial layers of the skin (Iannetti et al., 2006). The laser beam was transmitted via an optic fibre and its diameter was set at approximately 8 mm (50 mm^2) by focusing lenses. The duration of the laser pulses was 4 ms. Laser pulses were directed at the dorsum of the right hand, on an squared area (5x5 cm) defined prior to the beginning of the experimental session. To avoid nociceptors fatigue and sensitization, the location of the irradiated spot was shifted after each stimulus. The spot location was controlled by a computer that used two servo-motors (HS-422; Hitec RCD; angular speed, 60°/160 ms) to orient the laser beam along two perpendicular axes (see Lee et al., 2009 for details). To familiarize subjects with the nociceptive stimulus, a small number of low-energy laser pulses were delivered to the right-hand dorsum. The energy of the laser stimulus was then adjusted individually through the method of limits, in order to elicit a clear pricking pain sensation (3.1 ±0.3 J), related to the activation of Aδ nociceptors (Treede et al., 1995).

Auditory stimuli were brief 800 Hz tones (50 ms duration; 5 ms rise and fall times) delivered through a speaker (VE100AO, Audax,

France) placed in front of the right hand (~55 cm from the subject and ~50 cm from the midline). At the beginning of the experiment the intensity of stimulation was self adjusted in order to match the intensity of laser pulses. This calibration process was repeated at the end of each recording block. The average intensity of auditory stimulation was 85±5 dB.

2.3 Experimental design

A schematic illustration of the experimental design is shown in Figure 3-1. Four different blocks of stimulation were counterbalanced across subjects. In each block trains of both laser and auditory stimuli were presented. Each train consisted of three stimuli of identical energy (S1-S2-S3, a triplet) delivered to the hand dorsum at a constant inter-stimulus interval (ISI) of 1 second. The time interval between each triplet ranged between 6 and 12 s (rectangular distribution). While the first two stimuli were always belonging to the same sensory modality (e.g., nociceptive), the third stimulus was either belonging to the same modality of the first two stimuli (triplet s*ame*) or to the other modality (triplet *other*). Approximately 3 seconds before the onset of each triplet, subjects were verbally informed of the sensory modality of S1 and S2. In two out of four blocks the participants were also informed of the sensory modality of the last stimulus of each triplet (condition *certain*), while in the remaining two they were not (*uncertain* condition). Within each *uncertain* block, the occurrence of *same* and *other* triplets was balanced and pseudo-randomized. The maximum number of consecutive triplets belonging to the same pattern (i.e. *same* or *other*) was three. Before starting the recording, subjects were instructed to relax and equally attend all the stimuli of each triplet, independently of experimental condition and sensory modality.

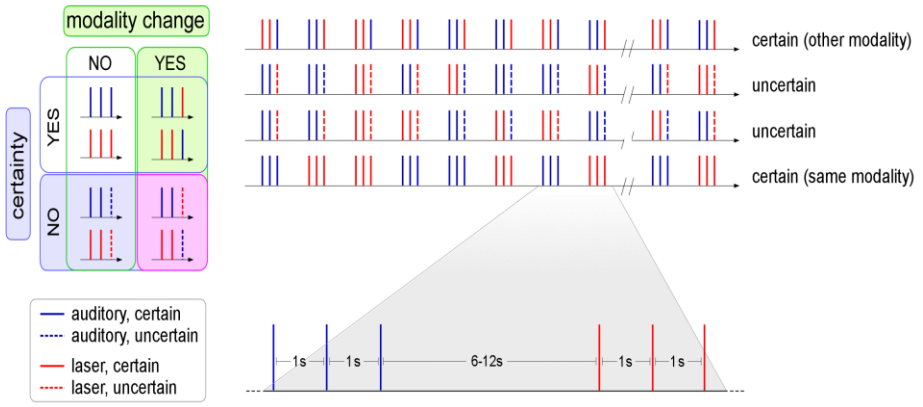

Figure 3-1. Experimental design. *Top right*: Event-related potentials (ERPs) were recorded in four different blocks of stimulation. The order of blocks was counterbalanced across subjects. In each block both laser (red) and auditory (blue) stimuli were presented at or around the right hand (see Methods for details). Stimuli were delivered in trains. Each train consisted of three stimuli (S1-S2-S3, a triplet) delivered at a constant inter-stimulus interval (ISI) of 1 second (*bottom right*). While the first two stimuli were always belonging to the same sensory modality (e.g., nociceptive), the third stimulus was either belonging to the same modality of the first two stimuli (*same* triplet) or to the other modality (*other* triplet). In two out of four blocks the participants were also informed of the sensory modality of the last stimulus of each triplet (condition certain), while in the remaining two they were not (uncertain condition). Within each uncertain block, the occurrence of same and other triplets was balanced and pseudo-randomized. This design allowed us dissecting the effect of 'modality change' and 'certainty' in determining the magnitude of the EEG response elicited by the third stimulus of the triplet.

In each block we delivered 40 trains of stimuli, for a total of 160 trains in the whole experiment. Between each laser pulse of a given triplet, the target of the laser beam was automatically displaced (by a motor, see previous section for details) by approximately 1 cm along a proximal-distal axis on the hand dorsum. The direction of this displacement was balanced in each block (20 stimuli in the proximal and 20 stimuli in the distal direction). This procedure aimed to minimize the variation in thickness and innervation of the irradiated skin and, consequently, the intensity of the somatosensory nociceptive input (Schlereth et al., 2001). Because variations in

baseline skin temperature could bias results (Tjolsen et al., 1988), an infrared thermometer was used to ensure that baseline skin temperatures were similar at the beginning of the blocks and within the blocks themselves.

At the end of each block participants were asked to rate verbally both the average intensity and the average saliency[2] of the sensation elicited by S1, S2 and S3, on a numerical scale ranging from 0 (no intense at all/no salient at all) to 10 (as much intense as possible/as much salient as possible, within the current experimental context).

2.4 EEG recording

Participants were seated on a comfortable chair in a silent, temperature-controlled room. They were asked to place their hands on a desk, and to keep their eyes open and gaze slightly downwards. A screen in front of the participants blocked the vision of the hands. The electroencephalogram (EEG) was recorded using 20 Ag-AgCl electrodes placed on the scalp according the International 10-20 system and referenced to the nose. The electro-oculogram (EOG) was recorded from two surface electrodes, one placed over the right lower eyelid, the other placed lateral to the outer canthus of the right eye. Signals were amplified and digitized at a sampling rate of 1,024 Hz and a conversion of 12 bit, giving a resolution of 0.195 μV (SD32; Micromed, Treviso, Italy).

[2] According to Downar (2000), saliency was defined as the stimulus ability to disrupt the current cognitive focus and elicit an attentional or behavioural switch'.

2.5 EEG analysis

2.5.1 Preprocessing

EEG data were pre-processed and analyzed using Letswave (http://amouraux.webnode.com) (Mouraux and Iannetti, 2008) and EEGLAB (Delorme and Makeig, 2004). EEG data were segmented into epochs using a time window ranging from 1 second before the first stimulus (S1) to 1 second after the third stimulus (S3) of each triplet (total epoch duration: 4s). Each epoch was baseline corrected using the interval from -0.5 to 0 s as reference. EEG epochs were band-pass filtered from 1 to 40 Hz, using a fast Fourier transform filter. EOG artifacts were subtracted using a validated method based on independent component analysis (ICA; Jung et al 2000). In all datasets, ICs related to eye movements had a large EOG channel contribution and a frontal scalp distribution. Epochs were then baseline corrected again using the interval from -0.5 to 0 as reference. Finally, epochs with amplitude values exceeding ±65 μV (i.e. epochs likely to be contaminated by an artifact) were excluded from additional analysis. These epochs constituted 6 ±0.2 % of the total number of epochs.

2.5.2 Analysis in the time domain

Epochs belonging to the same experimental condition were averaged together, time-locked to the onset of the first stimulus of each triplet. This procedure yielded four average waveforms (one for each experimental condition: certain same, certain other, uncertain same, and uncertain other) for each subject. For each average waveform, the latency and the baseline-to-peak amplitude of the ERP elicited by each stimulus of the triplet were measured. For LEPs, N1, N2 and P2 waves were measured as follows. The N1 wave was measured at the

temporal electrode contralateral to the stimulated side (T3), referenced to Fz. It was defined as the negative deflection preceding the N2 wave, which appears as a positive deflection in this montage. The N2 and P2 waves were measured at the vertex (Cz) referenced to the nose. The N2 wave was defined as the most negative deflection after stimulus onset. The P2 wave was defined as the most positive deflection after stimulus onset. For AEPs, N1 and P2 waves were measured at the vertex (Cz) referenced to the nose. The N1 wave was defined as the most negative deflection after stimulus onset. The P2 wave was defined as the most positive deflection after stimulus onset. Figure 3-2 displays group-level average ERPs elicited by both auditory stimuli and laser stimuli. Also, scatterplots of single-subject peak amplitudes of the N2 and P2 waves elicited by S3 are shown.

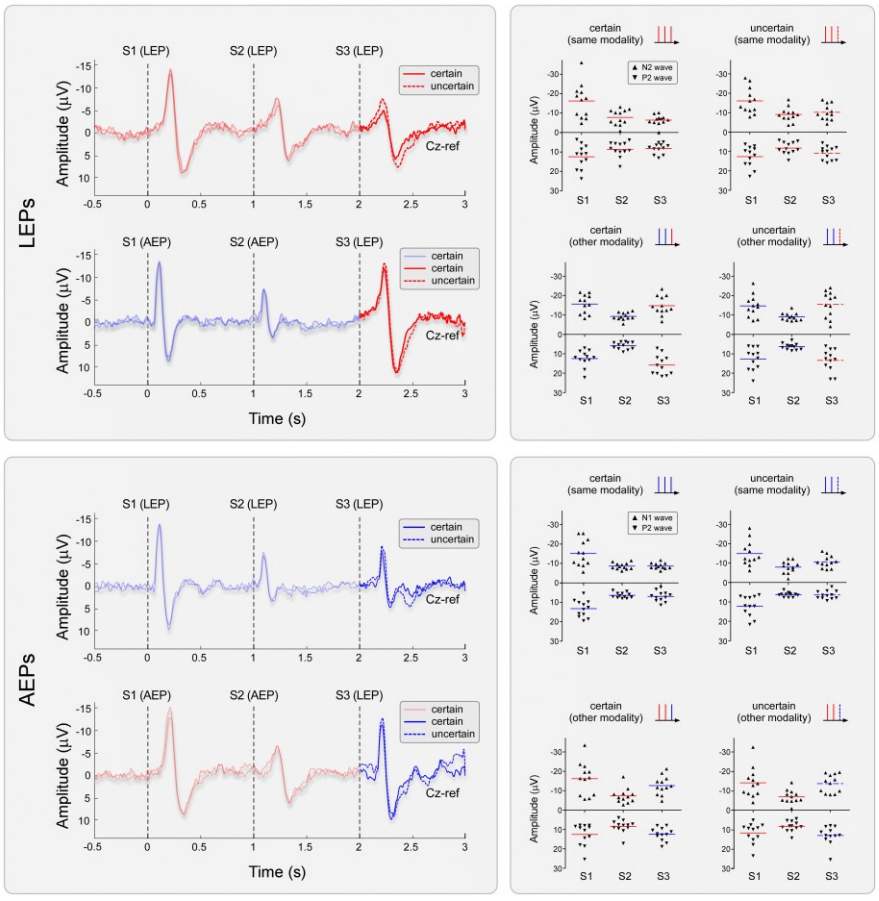

Figure 3-2. Left panels: Group-level average ERPs elicited by auditory

stimuli (blue) and laser stimuli (red). While the first two stimuli (S1 and S2) were always belonging to the same sensory modality, the third stimulus (S3) was either belonging to the same modality of S1 and S2 (*same* triplet, top waveforms of each panel) or to the other modality (*other* triplet, bottom waveforms of each panel). The modality of S3 was either certain (full line) or uncertain (dashed line). Displayed signals were recorded at electrode Cz (nose reference). x-axis, time (s); y-axis, amplitude (μV). The vertical dashed lines mark the onset of the three stimuli (S1–S3). Right panels: single-subject and group-level average peak amplitudes of the N2 and P2 waves elicited by S3. x-axis, stimulus number (S1–S3); y-axis, amplitude (μV). Coloured horizontal lines represent the group averages (red: LEPs; blue: AEPs; full lines: ERPs elicited by certain stimuli; dashed lines: ERPs elicited by uncertain stimuli). Note the significant amplitude reduction between S1-ERP and S2-ERP. Not also the larger amplitude of S3-ERP in triplets were there was a change of modality between S2 and S3.

2.5.3 Analysis in the time frequency domain

An estimate of the amplitude of oscillatory activity as a function of time and frequency was obtained for each EEG epoch. Because this estimate is a time-varying expression of oscillation amplitude regardless of its phase, averaging these estimates across trials discloses both phase-locked and non-phase-locked modulations of signal amplitude, provided that these modulations are both time locked to the onset of the event and consistent in frequency (i.e., the latency and frequency at which they occur are reproducible across trials). To obtain this estimate we used the continuous wavelet transform, which adapts the width of its window of analysis as a function of frequency, and thereby offers an optimal compromise for time–frequency resolution (Mouraux and Iannetti, 2008). We used a Morlet wavelet, consisting in a complex exponential function localized in time by a Gaussian envelope. The initial spread of the Gaussian envelope was set to $2.5/\pi\omega_0$ (ω_0 being the central frequency of the wavelet - for details of the method see Mouraux and Iannetti 2008; Mouraux et al. 2003). Across-trial averaging of these time–frequency

representations produced a spectrogram of the average EEG oscillation amplitude as a function of time and frequency. This time–frequency map was used to identify non-phase-locked, laser and auditory-induced modulations of ongoing EEG rhythms (ERS and ERD). For each estimated frequency, results were displayed as an increase or decrease of oscillation amplitude relative to a prestimulus reference interval (-0.5 to -0.1 s before the onset of S1), according to the following formula: $ER_{t,f}\%$ $[A_{t,f} - R_f]/R_f$, where $A_{t,f}$ is the signal amplitude at a given time *t* and at a given frequency *f*, and R_f is the signal amplitude averaged within the reference interval (Pfurtscheller and Lopes da Silva 1999).

2.5.4 Quantitative analysis of time-frequency spectrograms

To explore the differences between the brain responses elicited in the four different experimental conditions, three time-frequency regions of interest (ROIs) were defined in the spectrograms obtained at Cz. For laser-induced brain related activity, the time-frequency limits were defined based on previous work from our group: LEP (1-8 Hz and 100-500 ms), ERS (10-20 Hz and 100-500 ms) and ERD (7-13 Hz and 400-900 ms) (Iannetti et al 2008). For auditory-induced brain activity, the time-frequency limits were derived by Mayhew et al. (2009) and centered around the locations of the main foci of activity: AEP (1-10 Hz and 0-500 ms), ERS (10-25 Hz and 0-500 ms) and ERD (10-15 Hz and 400-900 ms). Within each time-frequency ROI, ER% values were extracted to compute the mean of the 20% of points displaying the highest increase (LEP/AEP and ERS) or decrease (ERD). This 'top 20%' summary measure reflects the higher ER% values within each window of interest, with the aim of reducing the noise introduced by including all points of the spectrogram, some

of which may display little or no response. This approach, which we have successfully used to analyze both ERP (Iannetti et al., 2008) and blood oxygen level–dependent fMRI data (Iannetti et al., 2005, Mitsis et al., 2008), shows several advantages for disclosing condition-specific effects (for a review Mouraux and Iannetti, 2008).

2.6 Statistical analyses

A two-way repeated-measure ANOVA was used to explore the main effect of 'modality change' (two levels: 'same', 'other') and 'certainty' (two levels: 'certain', 'uncertain'), as well as the possible interaction between these two factors, on the following responses: (1) N1, N2 and P2 peak amplitudes of the LEP elicited by S3; (2) N1 and P2 peak amplitudes of the AEP elicited by S3; (3) ER% summary measure of each ROI of the response elicited by S3 laser stimuli; (4) ER% summary measure of each ROI of the response elicited by S3 auditory stimuli. When main effects or their interaction were significant, *post-hoc* Tukey's tests were used to perform pairwise comparisons. These statistical comparisons were performed using Prism 5.0 (GraphPad Software, San Diego, CA). Furthermore, to disclose the time course of the effects of 'modality change' and 'certainty' on the ERP response in the time domain, we performed the same repeated-measures ANOVA, but using each time point of the averaged ERP waveforms, as implemented in LetsWave (http://amouraux.webnode.com). This analysis yielded two waveforms expressing the significance of the effect of each of the two experimental factors across time. A consecutivity threshold of 51 time points (approximately 50 ms) was chosen to account for multiple comparisons.

3 Results

3.1 Laser evoked brain activity

Grand average waveforms of LEPs in the four different conditions are shown in Figure 3-3a (top panel).

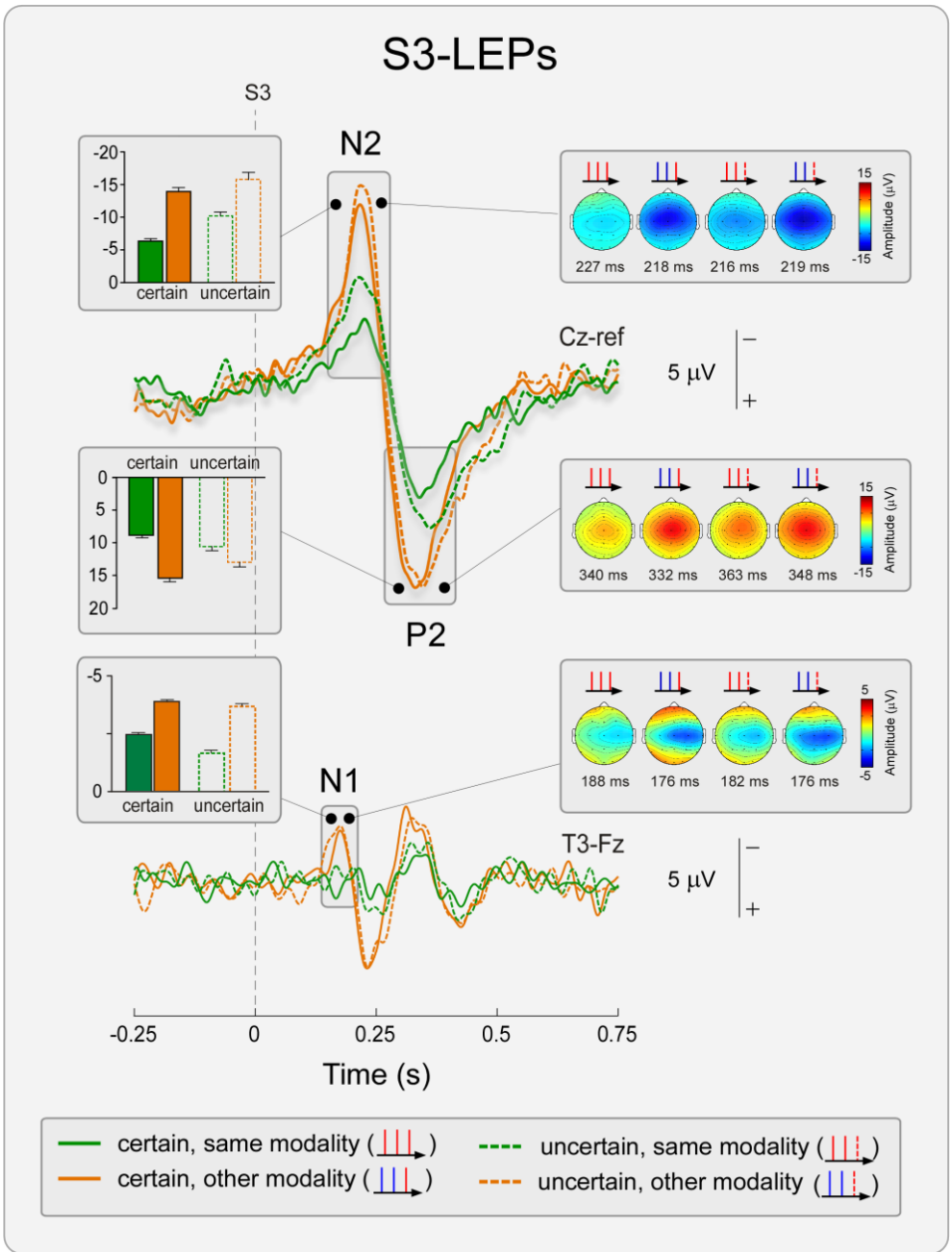

Figure 3-3a. Group-level average LEP waveforms elicited by S3 in the four experimental conditions are superimposed. Orange waveforms represent the S3-ERPs when there was a change of modality (triplets *other*). Green waveforms represent the S3-ERPs when there was not a change of modality (triplets *same*). Full and dashed lines represent the S3-ERPs elicited by certain and uncertain stimuli, respectively. The vertical dashed gray lines mark the onset of S3. Average peak amplitudes and scalp maps are shown

in the insets. Note the significant increase in ERP amplitude when a change in stimulus modality takes places.

Effect of 'modality change'. There was a significant main effect of the factor "modality change" on the amplitude of the N1, N2 and P2 waves elicited by S3. The LEP magnitudes were significantly larger when there was a change of sensory modality of the eliciting stimulus, i.e. they were larger when S3 was preceded by an auditory S2 (triplet other) than when it was preceded by a laser S2 (triplet same) (N1: F=12.268, p=.005; N2: F=56.456, p=.00001; P2: F=16.964, p=.002; Figure 4a). ***Effect of 'certainty'***. In contrast, there was a suggestion of significant main effect of 'certainty' only on the amplitude of the N2 wave (F(1,11)=6.230; p=.03;), but not on the amplitude of the N1 and P2 waves (N1: F(1,11)=.007; p=.93; P2: F(1,11)=1.528; p=.24). The magnitude of the N2 wave of the LEP elicited by S3 was significantly larger when the stimulus was uncertain, independently of the change of its modality (Figure 4a). ***Interaction between 'modality change' and 'certainty'***. Finally, there was a significant interaction between the factors 'modality change' and 'certainty' only on the amplitude of the LEP P2 wave of the LEP elicited by S3 (F(1,11)=16.216; p=.002). Post hoc comparison revealed that the change of sensory modality induced a significantly larger increase in P2 wave magnitude when S3 was certain than when S3 was uncertain (p=.001).

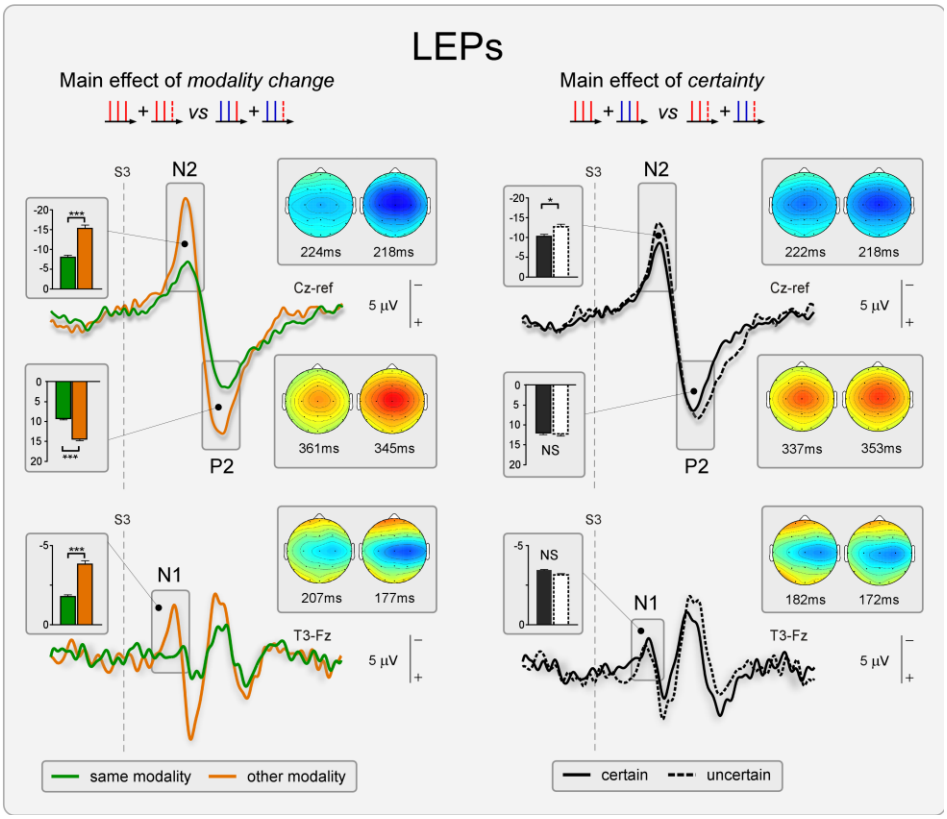

Figure 3-4a. Main effect of modality change (left waveforms) and stimulus certainty (right waveforms) on LEPs. Superimposition of orange and green waveforms represents the main effect of modality change (left). Superimposition of black full and dashed waveforms represents the main effect of the certainty of modality change (right). The vertical dashed gray lines mark the onset of S3. Average peak amplitudes and scalp maps are shown in the insets. Note the significant main effect of modality change in determining the response magnitude.

Time course of the effect of 'modality change' and 'certainty'. To follow the effect of these two experimental factors across time, in addition to peak amplitude analysis we computed a two-way repeated-measures ANOVA for each time point of the averaged LEP waveforms (Figure 5). At electrode Cz, the factor 'modality change' was a significant source of variance within two different intervals: 208–242 ms (coinciding with the latency of the N2 wave) and 275–394 ms (coinciding with the latency of the P2 wave) (Figure 5, left upper panel). The factor 'certainty' was a significant source of variance in the time interval 340–500 ms (coinciding with the latency

of the second half of the P2 wave). The interaction of these two experimental factors across time was not significant (p>.05)

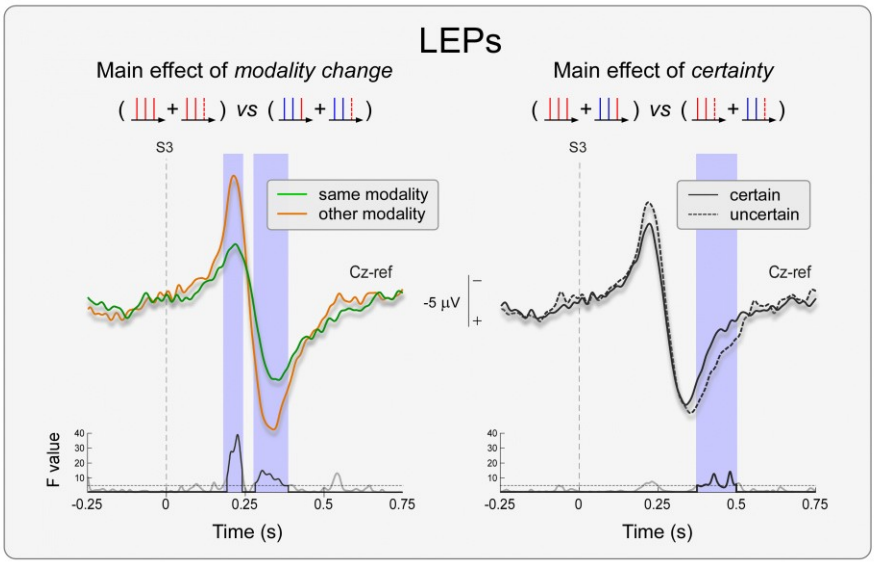

Figure 3-5a. Whole-waveform ANOVA. To assess the time course of the effects of "modality change" and 'certainty' on LEPs (top panel) and AEPs (bottom panel), we performed a repeated-measures ANOVA using each time point of the averaged waveforms (electrode Cz, nose reference). x-axis, time (s); y-axis, F values (F). Significant F-values obtained for each time point (above 4.80 for LEPs) Left graph: group-level LEP waveforms elicited by S3. The factor "modality change" significantly modulated the waveform in 2 distinct time intervals: 208–242 ms (coinciding with the latency of the N2 wave), 275–394 ms (coinciding with the latency of the P2 wave). Right graph: group-level LEP waveforms categorized according to the main effect of the certainty of modality change significantly modulated the waveform in the time interval 340–500 ms (coinciding with the latency of the second part of P2 wave).

3.2 Laser-induced ERS and ERD

Grand average spectrograms of time-frequency EEG responses in the four different conditions are shown in Figure 3-6a.

Effect of 'modality change'. There was a significant main effect of the factor 'modality change' on the ER% summary values of 'LEP' and 'ERS' time-frequency responses elicited by S3 ('LEP': $F(1,11)=22.357$; $p=.0006$; 'ERS': $F(1,11)=21.805$; $p=.0006$). The

magnitudes of the 'LEP' and 'ERS' responses were significantly larger when there was a change of sensory modality of the eliciting stimulus, i.e. they were larger when S3 was preceded by an auditory S2 (triplet other) than when it was preceded by a laser S2 (triplet same). The effect of 'modality change' on the magnitude of the 'ERD' response only approached to significance ('ERD': $F(1,11)=4.832$; $p=.05$). Nevertheless, it was Consistent with 'LEP' and 'ERS' effect direction: 'ERD' response was smaller when a change of sensory modality of the eliciting stimulus occurred, i.e. it was smaller when S3 was preceded by an auditory S2 (triplet other) than when it was preceded by a laser S2 (triplet same). ***Effect of 'certainty'***. There was no main effect of the factor 'certainty' on the ER% summary values of all three time-frequency responses elicited by S3 ('LEP': $F(1,11)=2.043$; $p=.18$; 'ERS': $F(1,11)=.058$; $p=.81$; 'ERD': $F(1,11)=.502$; $p=.49$;). ***Interaction between 'modality change' and 'certainty'***. There was no significant interaction between the factors 'modality change' and 'certainty' on the ER% summary values of all three time-frequency responses elicited by S3 ('LEP': $F(1,11)=.249$; $p=.63$; 'ERS': $F(1,11)=1.42$; $p=.26$; 'ERD': $F(1,11)=.852$; $p=.38$;).

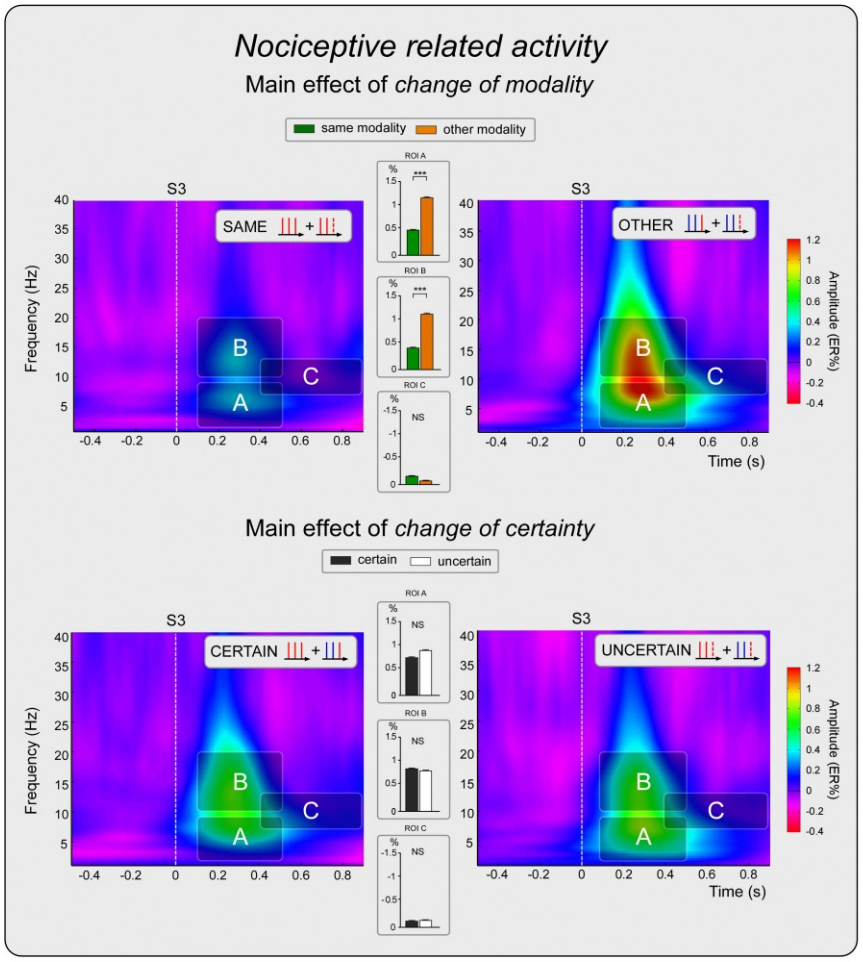

Figure 3-6a. An estimate of the amplitude of oscillatory activity as a function of time and frequency was obtained for each EEG epoch by applying the Morlet continuous wavelet transform. Three time-frequency regions of interest (ROIs) were defined in the spectrograms obtained at Cz. For nociceptive brain related activity, the time-frequency limits were the following: LEP (1-8 Hz and 100-500 ms), ERS (10-20 Hz and 100-500 ms) and ERD (7-13 Hz and 400-900 ms) (Iannetti et al., 2008). Within each time-frequency ROI, ER% values were extracted to compute the mean of the 20% of points displaying the highest increase (LEP and ERS) or decrease (ERD). Note the effect of modality change in determining the response magnitude of LEP. Also, note the effect on uncertainty of modality change in inducing a larger response in all the three ROIs.

3.3 Auditory-evoked brain activity

Grand average waveforms of AEPs in the four different conditions are shown in Figure 3-3b.

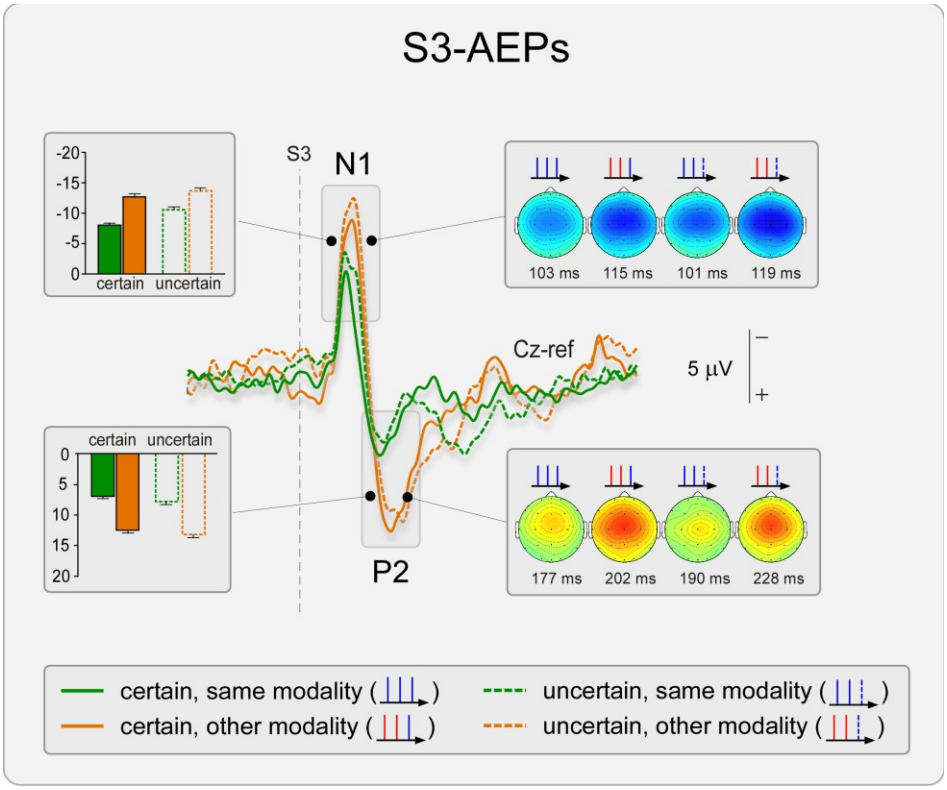

Figure 3-3b. Group-level average AEP waveforms elicited by S3 in the four experimental conditions are superimposed. Orange waveforms represent the S3-ERPs when there was a change of modality (triplets *other*). Green waveforms represent the S3-ERPs when there was not a change of modality (triplets *same*). Full and dashed lines represent the S3-ERPs elicited by certain and uncertain stimuli, respectively. The vertical dashed gray lines mark the onset of S3. Average peak amplitudes and scalp maps are shown in the insets. Note the significant increase in ERP amplitude when a change in stimulus modality takes places.

Effect of 'modality change'. There was a significant main effect of the factor 'modality change' on the amplitude of both the N1 and the P2 waves elicited by S3 (N1: $F(1,11)=15.006$; $p=.003$; P2: $F(1,11)=38.834$; $p=.0006$) (Figure 3-4b). The magnitudes of the waves of the AEP elicited by S3 were significantly larger when there was a change of sensory modality of the eliciting stimulus, i.e. they were larger when S3 was preceded by a laser S2 (triplet other) than when it was preceded by an auditory S2 (triplet same). ***Effect of 'certainty'***. Similarly to what observed in the LEP waveforms, a

trend to a main effect of 'certainty' could be observed only on the amplitude of the N1 wave (N1: F(1,11)=4.763; p=.05;), but not on the amplitude of the P2 wave elicited by S3 (F(1,11)=.442; p=.52). The magnitude of the N1 wave of the AEP elicited by S3 was significantly larger when the stimulus was uncertain, independently of the change of its modality (Figure 3-4b). ***Interaction between 'modality change' and 'certainty'***. There was no significant interaction between the factors 'modality change' and 'certainty' on the amplitude of both the N1 (F(1,11)=.219; p=.65) and the P2 wave of the AEP elicited by S3 (F(1,11)=.042; p=.84).

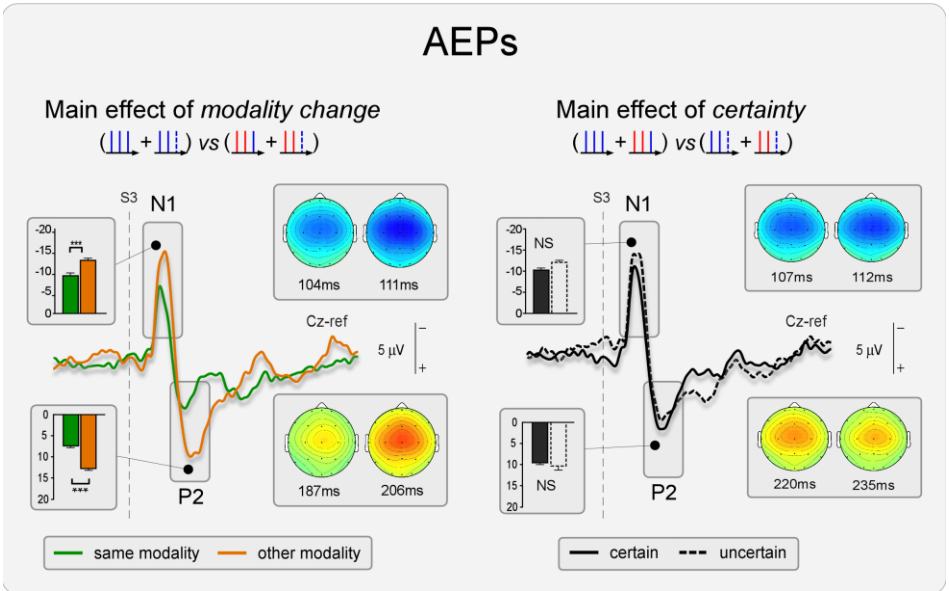

Figure 3-4b. Main effect of modality change (left waveforms) and stimulus certainty (right waveforms) on AEPs. Superimposition of orange and green waveforms represents the main effect of modality change (left). Superimposition of black full and dashed waveforms represents the main effect of the certainty of modality change (right). The vertical dashed gray lines mark the onset of S3. Average peak amplitudes and scalp maps are shown in the insets. Note the significant main effect of modality change in determining the response magnitude.

Time course of the effect of 'modality change' and 'certainty'. At electrode Cz, the factor 'modality change' was a significant source of variance of the AEP waveform within two different intervals: 75-

120 ms (coinciding with the latency of the N1 wave) and 180-295 ms (coinciding with the latency of the P2 wave) (Figure 3-5b). The factor 'certainty' was a significant source of variance in the time interval (-)25–38 ms and 267–322 ms (coinciding with the latency of the second half of the P2 wave). The interaction of these two experimental factors across time was not significant (p>.05).

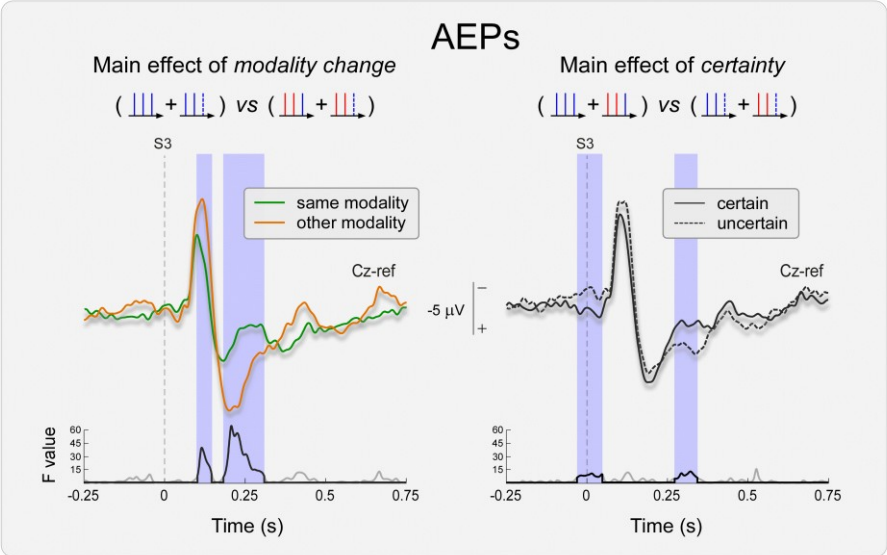

Figure 3-5b. Whole-waveform ANOVA. To assess the time course of the effects of "modality change" and 'certainty' on AEPs, we performed a repeated-measures ANOVA using each time point of the averaged waveforms (electrode Cz, nose reference). x-axis, time (s); y-axis, F values (F). Significant F-values obtained for each time point (above 4.40 for AEPs). Left graph: Group-level AEP waveforms elicited by S3. The factor "modality change" significantly modulated the waveform in 2 distinct time intervals: 75–120 ms (coinciding with the latency of the N1 wave), 180–295 ms (coinciding with the latency of the P2 wave). Right graph: group-level AEP waveforms as accounted for by the factor 'certainty' significantly modulated the waveform in two time intervals: -25–38ms and 267–322 ms.

3.4 Auditory-induced ERS and ERD

Grand average spectrograms of time-frequency EEG responses in the four different conditions are shown in Figure 3-6B.

Effect of 'modality change'. Similarly to what observed in the laser-induced time-frequency responses, there was a significant main effect of the factor 'modality change' on the ER% summary values of 'LEP' and 'ERS' time-frequency responses elicited by S3. The magnitudes of these responses were significantly larger when there was a change of sensory modality of the eliciting stimulus, i.e. they were larger when S3 was preceded by a laser S2 (triplet other) than when it was preceded by an auditory S2 (triplet same) ('AEP': $F(1,11)=12.357$; $p=.005$; 'ERS': $F(1,11)=10.850$; $p=.007$) Differently to what observed in the laser-induced time-frequency desynchronization ROI, auditory 'ERD' activity was not affected by modality change ('ERD': $F(1,11)=.093$; $p=.77$;). ***Effect of 'certainty'***. There was no main effect of the factor 'certainty' on the ER% summary values of all three time-frequency responses elicited by S3 ('AEP': $F(1,11)=3.300$; $p=.10$; 'ERS': $F(1,11)=.221$; $p=.65$; 'ERD': $F(1,11)=.209$; $p=.66$). ***Interaction between 'modality change' and 'certainty'***. No significant interaction between the factors 'modality change' and 'certainty' could be detected on the overall regions of interest ('AEP': $F(1,11)=.007$; $p=.93$; 'ERS': $F(1,11)=.0003$; $p=.99$; 'ERD': $F(1,11)=.371$; $p=.55$).

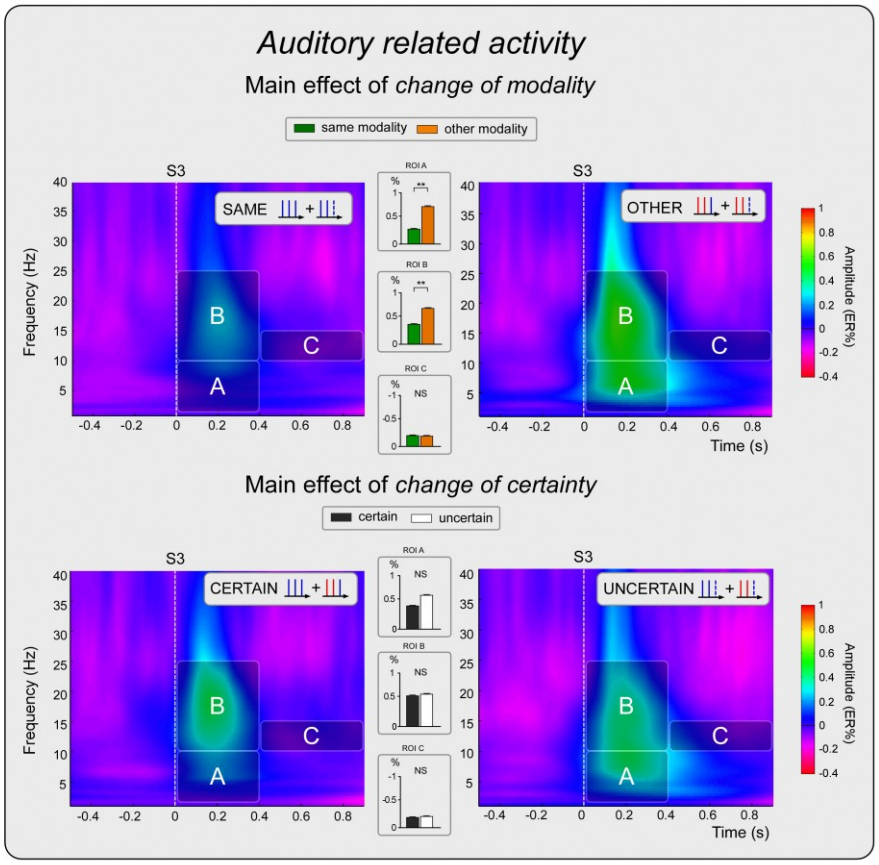

Figure 3-6b. An estimate of the amplitude of oscillatory activity as a function of time and frequency was obtained for each EEG epoch by applying the Morlet continuous wavelet transform. Three time-frequency regions of interest (ROIs) were defined in the spectrograms obtained at Cz. The AEP and ERS ROIs were centered in the 0-500 ms and respectively in 1-10 Hz (AEP), 10-25 Hz (ERS). The ERD was centered in the 10-15 Hz and 400-900 ms window. Within each time-frequency ROI, ER% values were extracted to compute the mean of the 20% of points displaying the highest increase (AEP and ERS) or decrease (ERD). Note the effect of modality change in determining the response magnitude of AEP. Also, note the effect on uncertainty of modality change in inducing a larger response in ROI A.

3.5 Discussion

By repeating sensory stimuli of identical modality, intensity and location, at short and constant inter-stimulus interval we showed that laser-evoked EEG responses do not reflect pain perception but are largely determined by stimulus novelty (Iannetti et al., 2008). Here we aimed to tease out the selective contribution of (1) the

change in stimulus modality and (2) the uncertainty of such a change in determining the magnitude of both laser and auditory EEG responses.

We observed four main findings. First, a change in stimulus modality importantly increased the magnitude of all the main peaks of both LEPs and AEPs. This finding indicates that sensory ERPs are very effective in detecting transient changes in the modality of the eliciting stimulus. Second, a change in stimulus modality also increased the magnitude of laser- and auditory-induced EEG responses in the time-frequency domain. This finding indicates that also event-related changes in ongoing EEG oscillations behave as transient detectors of changes in stimulus modality. Third, the uncertainty of a possible change in stimulus modality did not increase the peak amplitude of either LEPs or AEPs, but did increase the later part of their P2 wave. This finding indicates that the later neural components underlying the P2 wave might reflect the actual shift of attention towards uncertain stimuli, regardless of their modality. Fourth, the uncertainty of a possible change in stimulus modality did not alter the magnitude of laser- and auditory-induced EEG responses in the time-frequency domain. Altogether, these results indicate that the absence of change in the modality of a sensory stimulus, independently of the uncertainty of such a change, plays a major role in modulating the saliency of a sensory stimulus, and thus in determining the magnitude reduction of the EEG responses elicited by repeated stimulation.

3.6 Effect of change of modality

The effect of introducing a selective change of the modality of the repeated stimulus (Figures 3-1, 3-2) significantly reverted the response reduction caused by stimulus repetition (Figure 3-2).

Indeed, virtually all the EEG responses elicited by either nociceptive or auditory stimuli, both in the time domain (Figures 3-3,4,5 a and b) and in the time-frequency domain (Figures 3-6 a and b) were significantly larger when the eliciting stimulus (S3) was belonging to a sensory modality different from those of the two preceding stimuli (S1 and S2) (i.e., in the conditions AAL and LLA) than when belonging to the same modality channel (i.e., in the conditions LLL and AAA).

The observed similar modulation of all the main LEP and AEP responses by a change in the modality of the repeated stimulus brings further support to the idea that the most of the neural activity elicited by transient nociceptive stimuli is part of a neural system devoted to detect salient changes in the sensory environment (Downar et al., 2000; 2002). Indeed, both the cingulate cortex, which is thought to be the main generator of the N2 and P2 waves, and the operculoinsular cortex, which is thought to be the main generator of the N1 wave and to contribute to the N2 wave (Garcia-Larrea et al 2003), are part of the saliency-detector system identified by Downar (see also Downar et al., 2003). Crucially, all the responses generated in these areas were increased when the eliciting stimulus was more novel because of a change of its sensory modality. The saliency of a given sensory stimulus is also defined relative to the past experience (Itti and Koch, 2001; Kayser et al., 2005), and our results indicate that a change in the modality of a sensory stimulus significantly makes it more novel and, thus, more salient.

While the functional significance of the EEG responses elicited by nociceptive laser stimuli in the time domain is being clarified (Legrain et al 2005, 2009; Iannetti et al 2008; Mouraux and Iannetti 2009), the functional significance of the EEG responses elicited by

nociceptive laser stimuli in the time-frequency domain (Mouraux et al 2003) has not been investigated as such. Here we show that event related synchronization is index of change in modality as much as the evoked brain activity. Although we could not observe a significant difference in ERD activity, a trend to reduction of desynchronization was present when change in modality took place. This was possibly due by an indirect effect of large synchronization magnitude present in this condition.

LEPs are electrical brain responses to selective activation of nociceptive pathways by radiant heat stimuli (Plaghki & Mouraux, 2005). They are thought to index the nociceptive processes within the central brain underlying pain. Alternative views see the LEPs as reflecting the activity of a sensory-unspecific network that identified and orient attention to salient sensory events that can represent potential danger (Iannetti et al., 2008; Legrain et al., 2009b; Mouraux and Iannetti, 2009). One mechanism that was proposed to be involved as an initial component of the saliency-detector system is a change-detector (Legrain et al., 2005; Legrain et al., 2009). It is now older than 30 years the hypothesis of two discernible systems that scan the environment of an organism for potentially relevant events. One is known as transient-detector system and the other is a change-detector system (see Schroger, 1997). The first is activated by rapid changes in onsets or offsets of continuous stimulation, which may cause involuntary attentional capture (e.g., Jonides, 1981; Yantis and Jonides, 1990; Theeuwes, 1991; Folk, et al., 1992). The second is sensitive to violations of regularities in a sequence of discretely presented stimuli that may lead to involuntary orienting too (e.g., Sokolov, 1975; Ohmann, 1979, 1992).

With regard to transient detection, some previous studies using EEG or magnetoencephalography (MEG) have suggested that evoked

responses like auditory N1 and P3 are associated with the detection of change in a uni-sensory environment (Hari et al.,1980; Joutsiniemi et al.,1989; Loveless et al., 1994; Spackman et al., 2006; Yamashiro et al., 2008; 2009) and in multimodal environment (e.g., Gondan et al., 2004; Tollner et al., 2009). A transient detector approach to evoked nociceptive acitivity may also allow to interpret and re-interpret other facilitatory effects obtained in other modalities or in the somatosensory modality, as the facilitation of tactile processing through painful stimulation (Ploner et al., 2004). Pain-induced facilitation of tactile processing may rather reflect the spatially unspecific alerting function of attention (Corbetta and Shulman 2002; Posner and Petersen, 1990), which follows salient stimuli and may be mediated by a right-lateralized fronto-parietal-cingulate network (Corbetta and Shulman 2002; Downar et al. 2002, 2003).

The best representation of change detection in the sensory domain rests on the Mismatch Negativity (MMN) (Naatanen et al., 2007). The MMN reflect the activity of nervous structures able to register the features of recent sensory stimuli at very basic level and to form a memory template of past events. The MMN is evoked when a stimulus presents a breaking in regularities drawn by the memory template. The underlying brain structures are then involved in the detection of sensory event that differ from background and trigger orienting of attention to such environmental changes (Escera & Corral, 2007). Recent experiments suggested that such a mechanism might also be evoked by tactile stimuli (e.g., Kekoni et al.; 1997; Akatsuka et al., 2005, 2007; Restuccia et al., 2007) and visual stimuli (Maekawa et al., 2005; Kimura et al., 2009; Tales et al., 2009).

We suggest that a MMN like mechanism may be tracked in nociception too and though our study did not provided subjects with an oddball task where rare deviant stimuli could be detected, it clearly hints to the existence of a change detection mechanism which is independent by subject expectation about the change itself, and that this deviance can be detected through both phase-locked and non-phase locked synchronization.

3.7 Effect of uncertainty of a change in modality

However, it should be noticed that while the effect of change of modality was observed bimodally and was pervasive in all the different indexes of brain activity, the effects associated to the factor expectation were less influential though more evident in the nociceptive channel. Indeed, the main finding was related to LEP P2 amplitude increase specifically when the changes to noxious stimuli were certain. That is, knowing the occurrence of change to laser stimulus from auditory ones likely increased the excitability of P2 wave generators. Conversely, the observed increase of N2 peak amplitude and late P2 amplitude coupled to the uncertainty of both auditory and nociceptive stimuli occurrence.

The increase of P2 peak amplitude when change is expected may be counter-intuitive as one would expect uncertainty of stimulation being more effective in increasing cortical arousal and motor preparation through a mechanism of attentional resources allocation towards the noxious event (e.g., Macaluso and Driver, 2005; Kida et al., 2006). Nevertheless, it is well known that certain expectation of analgesic or hyperalgesic modulations of pain do respectively decrease or increase both subjective experience and related neural activations (e.g., Ploghaus et al., 1999; Price et al., 1999; Petrovic et al., 2002; Porro et al., 2002; Wager et al., 2004; Koyama et al.,

2005; Keltner et al., 2006; Brown et al., 2008). Therefore, it may conceivable the hypothesis that both certain and uncertain sensory stimulation could exert increase of behavioral and neural activity and that the modulatory balance of the two may be widely determined by procedural and task related factors. For instance, the experimental connotation of expectation is often implicitly manipulated and can be operationalized in several ways, that in turn, could differently contribute to the experimental outcomes. As already observed by other investigators (Brown et al., 2008), an event may be "absolutely" uncertain (no cue on its predictability) or "relatively" uncertain, that is one could infer to some extent (or even know) the probability distribution within which an event will occur. The latter was exactly the case of our experimental paradigm, as subjects could infer that in case of uncertainty the chances to receive a novel stimulus were always 1 out of 2 (either laser or auditory). It is then possible that increased level of unpredictability of change in sensory modality could have amplified the associated effects, as the observed increase of the late P2 amplitude. Interestingly, the increase of late P2 agrees with previous literature on neural effects on uncertainty (Legrain et al., 2002; 2003a; 2003b). Indeed, it was shown that when occurrence of the laser stimulus is unexpected, part of the signal within the latency range of the laser-evoked P2 could be explained by an additional component, an overlapping positivity (the P3a) interpreted as reflecting processes related to involuntary reorientations of attention triggered by salient and unexpected exogenous events (see also Legrain et al., 2009b). This index has been also reported in other sensory modalities (Courchesne et al. 1975; Squires et al. 1975; Yamaguchi and Knight 1991; Escera et al. 1998; Katayama and Polich 1998). Several studies have indicated

that the P3a component may originate from frontal regions near the anterior cingulate cortex (Baudena et al. 1995; Dien et al. 2003).

3.8 The importance of being novel in saliency

One may argue that the passive shift of attention that determined change detection in both nociceptive and auditory indexes could actually follow an active ('top-down') allocation of attention mainly related to certainty of stimulus change. Nevertheless, though we found an interaction between certainty and change in modality in the nociceptive P2, we could not identify any interaction in the other measures. This specific effect on the nociceptive channel may be related to the threatening meaning of laser pain as compared to the auditory stimulation. Indeed, though the stimuli were perceptually matched, it is possible that either the matching was not psychophysically balanced or not cognitively accessible in our subjects due to the instrinsic alerting nature of painful stimuli.

In light of future investigation of 'top-down' and 'bottom-up' interactions, these observations give rise of the importance of a matched sensory background in multimodal experiments and stress the relevance of studying contextual semantic associations between sensory stimuli and other environmental events or past memories in the experimental subjects.

The present findings further demonstrates that the response decrement of vertex potentials induced by stimulus repetition would results from a progressive loss of novelty and sensory significance associated with the repetition of the stimulus (see also Iannetti and Mouraux, 2008). The fact that stimulus repetition does not induce a similar response decrement when variable ISIs or when a stimulus with a new feature is presented (other modality) brings about further indication that the decrement observed when constant stimulation

rates are used is indeed at least partially related to the loss of novelty. However, it is not clear yet how important is the role of expectancy and active selective attention in determining neural modulations related to detection of regularities and deviancies within the stream of sensory stimuli. Conversely, we convey further evidence of the importance of saliency in probing sensory systems and we showed how the nociceptive system is sensitive to the same biological rules found in the other sensory systems. In this study we applied Downar and co-workers (2000) definition of saliency: the "ability of the stimulus to disrupt the current cognitive focus and elicit an attentional or behavioural switch". This definition of saliency refers to 'what' saliency is without claiming 'how' saliency produces its effects. Nonetheless, defining this concept is not an easy task as saliency is not only driven by the intrinsic physical features of the sensory stimulus, but also depends on the context within which the sensory stimulus is presented, and on the inner goals/objectives of the perceiving organism. In other words, saliency is associated both with 'bottom-up' properties of the sensory input and with 'top-down' factors related to behavioral relevance. Research in visual attention domain conceptualizes bottom up saliency as a feature based mechanism in which the strength of each characteristic is weighted and contrasted with others in the contextual surround (e.g, Itti and Koch, 2001; Koch and Ullman, 1985; Treisman and Gelade, 1980). This feature contrast computation is thought to converge in saliency maps, where stimuli of different quality, magnitude and scale (e.g, colour, contrast, luminosity, etc.) are computed and combined till only one pattern have access to working memory on the basis of its relative higher weight. A similar model may be developed by research in pain perception to explain how nociceptive saliency

emerges from a set of different relative features as intensity, temporal pattern, and location.

Chapter 4

Contribution to the analysis of 'top-down' features

"Dissecting the dissociation: unpleasantness and intensity of laser pain experience during hypnosis"

1 Introduction

The classical model of pain representation poses the existence of a network of cortical areas ("pain matrix") through which pain may emerge from nociception (Melzack, 1990).

At the level of the brain, this model anatomically distinguishes between "lateral" (somatosensory cortices - S1 and S2) and "medial" (anterior insula and mid-cingulate cortex – MCC, in particular its rostral part, the anterior cingulate cortex – ACC) components (Albe-Fessard et al., 1985). These two, should respectively code either sensorial-discriminative apects of pain (intensity, localization, duration) or the affective-cognitive (unpleasantness, predictability, anticipation) (Apkarian et al., 2005; Craig, 2003a; Garcia-Larrea et al., 2003; Ploner et al., 1999; Tracey & Mantyh, 2007)

Important evidence in favor of this view originated in particular by the contribute of two studies which reported a functional dissociation between the affective and sensory neural structures of the pain matrix, that is, between limbic ACC and S1-S2. Indeed, using positron emission tomography (PET) Rainville and co-workers (1997) showed that hypnotic suggestions for decreased and increased

unpleasantness of thermal stimuli cause an increase of activity in the ACC but not in the S1-S2. In a successive study by the same research group, the increase of metabolic activity in somatosensory cortices but not in the ACC was coupled only to hypnotic suggestions for decreased or increased intensity of pain sensation (Hofbauer et al, 2001).

However, other recent contributes question the notion of a clear-cut dissociation. Indeed, both ACC and the anterior insula (AIC) have been associated not only to a plethora of affective-cognitive processes, like empathy for others' pain (e.g., Singer et al., 2004, Saarela et al., 2006; Ochsner et al., 2009) and placebo and nocebo phenomena (e.g., Wager et al., 2004; Kupers et al., 2005; Craggs et al., 2007; Kong et al., 2008), but also to coding of suprathreshold pain intensity (e.g., Coghill et al., 1999; Büchel et al., 2002) and spatial discrimination of pain (Oshiro et al., 2009). These observation are complemented by the involvement in pure attentional phenomena as anticipation, expectation, predictability and controllability of pain (e.g., Porro et al., 2002; Solomons et al., 2004; Carlsson et al., 2006; Clark et al., 2008).

All these findings were obtained by applying neuroimaging techniques which are known to suffer a poor temporal resolution. Here, we tackled the temporal course of pain processing by applying the laser evoked potentials (LEPs) technique. By doing so we aimed at dissecting the interplay of sensory and affective aspects of painful experience by means of hypnosis in a single study, for the first time. According to the current knowledge about LEPs dipole localizations (see Frot et al., 1999, 2007, 2008; Garcia-Larrea et al., 2003; Vogel et al., 2003) and to recent advances in the understanding of LEPs (Lee et al., 2009), we assumed that the early N1 (100-220 ms) potential would have better indexed the sensorial-discriminative

aspects of pain, whereas the and N2 (150-280 ms) and P2 waves (240-420 ms) should have better informed the affective-cognitive dimension of noxious experience.

2 Methods

2.1 Subjects

Twenty-four healthy female subjects, mean age (±SD)= 22.7 (±2.3) were selected for the study. All participants were right-handed (Handedness Edinburgh Inventory: M= 16.2, SD=2.1). They had normal or corrected-to normal acuity in both eyes and were naïve as to the purpose of the experiment. None of the subjects had a history of neurological or psychiatric conditions or drug abuse thought to interfere with the pain sensitivity. Participants gave written informed consent and were paid for their participation. The procedures were approved by the local ethics committee and were in accordance with the standards of the Declaration of Helsinki.

2.2 Hypnotic induction and hypnotic suggestion procedure

In the first part of the study, we used an hypnotic induction test-retest procedure in which the twenty-four subjects were selected from a larger group (n=146) according to their scores on the standardized Stanford Hypnotic Susceptibility Scale, Form C (SHSS:C; Weitzenhoffer & Hilgard, 1962), Italian version (De Pascalis et al., 2000). Only subjects categorized either as High Hypnotizable (HH - N=12; M=9.8; SD=1.1; range=8-12) or as Low Hypnotizable (LH - N=12; M=1.5; SD=1.0; range=0-4) participated in the experiment. To control the reliability of the hypnotic scores,

two sex-different hypnotists (trained-psychology) performed the Hypnotic Susceptibility Scale. This allowed to control the influence of gender, personality and voice timber on the subject's performance. Furthermore, because of the possible existence of the instability of hypnotisability trait (Fassler et al., 2008), this procedure ensured to select subjects whose hypnotisability trait was utterly physiological rather than socially determined. According to this procedure, subjects demonstrating an extremely compliant behaviour and/or inducing discordances between hypnotists judgements were excluded. The order of the hypnotists was counterbalanced. Then, the two selected groups of subjects participated in the second part of the experiment in which three different suggestion protocols were administered according to the previous work by Rainville and co-workers (1999). The Italian version was obtained by a native English speaker.

2.3 Laser stimulation

Noxious heat stimuli were delivered to the dorsum of the right hand with an infrared neodymium yttrium aluminium perovskite (Nd:Yap) laser with a wavelength of 1.34 μm (EL.EN., Florence, Italy). At this wavelength the laser pulses activate directly the Aδ and C-fiber nociceptive terminals located in the superficial layers of the skin (Iannetti et al., 2006). The laser beam was transmitted via an optic fiber and its diameter was set at approximately 5mm. Laser pulses were directed at the dorsum of the right hand on a 5x5 cm2 area, defined prior to the beginning of the experimental session. To avoid nociceptors fatigue and sensitization, the location of the irradiated spot was manually shifted after each stimulus. The inter stimulus

interval (ISI) was set between 7 and 15 s. Overall mean intensity was 2.5±0.5 Joules (J) and the duration 3 ms.

2.4 Experimental design and procedure

The two experimental Groups were submitted to two hypnotic manipulation sessions, where the hypnotists separately manipulated either intensity or unpleasantness of laser pain ('Intensity' and 'Unpleasantness Focus'). The interval between the two experimental sessions was at least one week.

Within each experimental session three different suggestion protocols were administered, by means of a block design. Depending on the hypnotically-induced Focus, hypnotist focused the attention of the subjects on 1) the increase of intensity or unpleasantness of the pain sensation ("Up" suggestion) and 2) the decrease of perceived intensity or unpleasantness of the pain sensation ("Down" suggestion). As a control condition, a hypnotic state of relaxation ("Control" suggestion) was used. This was characterized by the suggestion of a pleasant warmth sensation, breathing function amelioration, deep muscle relaxation, increased sleepiness, and heightened perception of body parts. Both the order of the two hypnotic sessions and the three induction protocols were counterbalanced.

For each experimental block, thirty laser stimuli were delivered on the dorsum of the subject hand. After every five stimuli, subjects rated pain intensity and unpleasantness using a 10-point visual analogue scale (VAS) in which 0 represented no pain and 10 the worst imaginable pain. To maintain subject's attention and expectation high, suggestion protocols were repeated every 10 laser stimuli. In between stimulation blocks, hypnosis depth was ensured

by repeating the hypnosis relaxation protocol and checked by testing the subject's performance in at least two randomly chosen items of the SHSS:C. Furthermore, the effectiveness of hypnosis induction was visually inspected by controlling the presence of a typical eye movements pattern (slow movements with few saccades, see Faymoville et al., 2000). On the basis of previous findings, sensory and pain threshold were repeated after hypnotic induction in order to assess possible changes in perceptual threshold due to relaxation and hypnosis induction (De Pascalis et al., 1999; Emery et al., 2008; Langlade et al., 2002; Sharav and Tal, 2004).

Pre-post hypnosis induction pain threshold values (joules) were tested according to t-test for dependent samples in the two groups. Pre-post threshold were different in the two groups (HH= M=2.57±.51vs2.67±.50; t=-2.46; df=11; p=.03; LH= M=2.24±.47vs2.32±.47; t=-2.15(10); p=.05), simply proving the effectiveness of our hypnosis (HH)/ relaxation (LH) induction procedure on both groups of subjects and also post-hoc validating the rationale of pre-post threshold assessment.

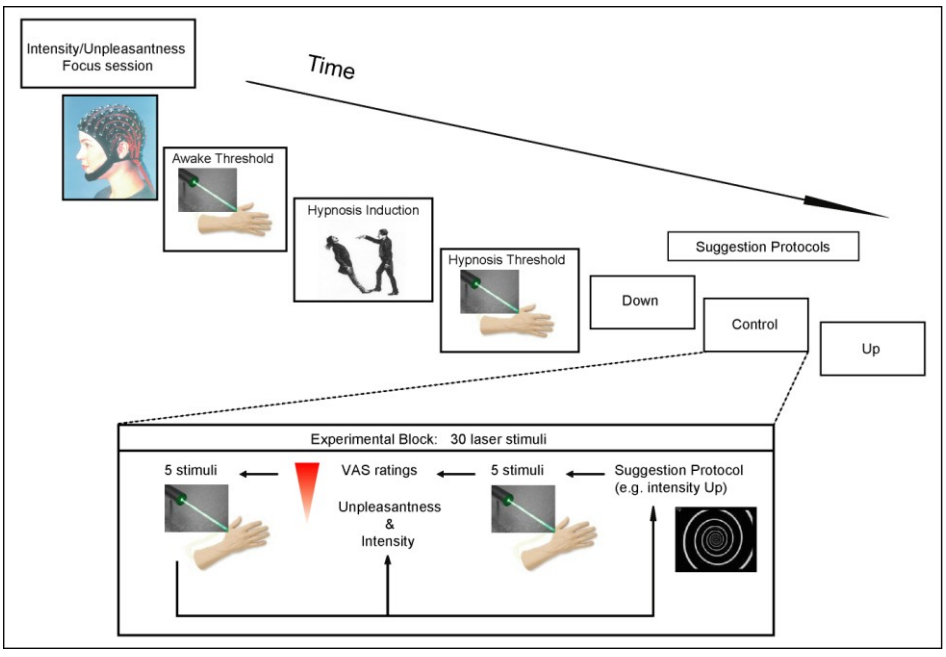

Figure 4-1. Schematic representation of experimental design and procedure. Each subject underwent two hypnosis sessions, where either intensity or unpleasantness of laser pain were manipulated. Sensory and pain threshold were repeated after hypnotic induction in order to check for changes in perceptual threshold due to relaxation and hypnosis induction. Within each experimental session control relaxation, decrease and increase of perceived intensity or unpleasantness were administered according to latin square design. Each recording block provided 30 laser stimuli partitioned in 6 subjective data collection stops (each 5 stimuli) and 3 suggestion protocols repetitions (each 10 stimuli). In between stimulation blocks hypnosis depth was checked by scoring in randomly chosen items from the SHSS:C.

2.5 EEG analysis

EEG data were analyzed using BrainVision Analyser 1.05 software (Brainproducts Co., Munich, Germany). EEG signal passed through an off-line 1-30 Hz band-pass filter (3 s time constant, 24 dB/octave). Pre-stimulus (200 ms) and post-stimulus (1000 ms) segments were extracted from the EEG, and the pre-stimulus baseline was corrected.

2.6 Statistical analysis: subjective reports

Subjective ratings were expressed as the difference (Δ) of increase and decrease hypnotic suggestions from control hypnosis condition . Δ mean ratings underwent a repeated measure four-way mixed ANOVA with Focus (2 Levels: Intensity, Unpleasantness), Rating (intensity, unpleasantness), Suggestion (Down, Up) and Group (between factor with two levels: LH,HH). To further disentangle possible difference related to the hypnotically-induced Focus we also performed two separate repeated measure three-way mixed ANOVAs with Ratings (intensity and unpleasantness), Suggestion (two Down, Up) and Group (between factor: LH, HH) Post-hoc comparison were computed by means of Scheffé test.

A "hypnotic modulation index" was calculated in each subject of each group, for both ratings of intensity and unpleasantness. according to the following ratio: (up - down suggestions/control hypnosis). This measure was conceived to obtain a clear-cut evidence of subjective modifications strength determined by either focus on intensity or Focus on Unpleasantness in both groups. Four distributions were obtained according to Focus (Intensity, Unpleasantness) and Rating (Intensity, Unpleasantness) factors. Each distribution was tested against the reference zero value by means of T-test in each group. In all the analyses differences were considered significant at $p<.05$.

2.7 Statistical analysis:laser evoked potentials

Preliminary analysis included visual inspection of epoched data. EOG artifacts were subtracted using a validated method based on independent component analysis (ICA; Jung et al 2000). In all datasets, ICs related to eye movements had a large EOG channel contribution and a frontal scalp distribution. Finally, epochs with amplitude values exceeding ±65 μV (i.e. epochs likely to be contaminated by an artifact) were excluded from additional analysis.

Epochs belonging to the same experimental condition were averaged together, time-locked to the onset of each stimulus in a recording block. This procedure yielded six average waveforms (one for each experimental condition: intensity control, unpleasantness control, intensity down, unpleasantness down, intensity up, unpleasantness up) for each subject. For each experimental condition, single-trial latency and baseline-to-peak amplitude of the evoked potential were measured.

Three LEP waveforms (N1, N2 and P2 waves) were investigated as follows. The N1 wave was measured at the temporal electrode

contralateral to the stimulated side (T3), referenced to Fz. It was defined as the negative deflection preceding the N2 wave, which appears as a positive deflection in this montage. The N2 and P2 waves were measured at the vertex (Cz) referenced to the nose. The N2 wave was defined as the most negative deflection after stimulus onset. The P2 wave was defined as the most positive deflection after stimulus onset.

LEPs N2, P2, (Cz electrode) and N1 (T7-Fz) amplitudes and latencies were expressed as the difference (Δ) of increase and decrease suggestions from control relaxation hypnosis. Mixed factorial ANOVA for repeated measures with 2 Within factors= Focus (Intensity, Unpleasantness), Suggestion (Down, Up) and 1 Between factor= Group (LH,HH) with Scheffe Post-hoc test, were performed on this index. Separated two-way mixed ANOVA per Focus session with 1 Within factor= Suggestion (Down, Up) and 1 Between factor= Group (LH,HH) were computed as further scrutiny of variance distribution.

A "hypnotic modulation index" was obtained for the three main waves too. Four distributions were obtained according to Focus (Intensity, Unpleasantness) and Suggestion (Decrease, Increase) factors. Each distribution was tested against the reference value zero by means of T-test in each group. In all the analyses differences were considered significant at $p<.05$.

Pre-post hypnosis induction pain threshold values (joules) were tested according to T-test for dependent samples in the two groups.

2.8 Correlational analysis

Pearson r correlations were computed separately on physiological and subjective indexes and also between them in order to examine

the behavioural relevance of LEPs outcomes. Differences were considered significant at $p<.05$.

3 Results

3.1 Subjective ratings

The repeated measures four-way ANOVA revealed a significant effect of Suggestion ($F(1,22)=39.33$; $p<.001$) as main factor. *Post hoc* test showed that this effect was entirely accounted for by higher subjective ratings of pain perception during Up with respect to Down ($p<.001$).

Furthermore, the Suggestion X Group interaction ($F(1,22)=17.94$; $p<.001$) revealed that the effect of pain perception enhancement was specific for the HH group ($p<.001$), being absent in the LH group ($p=.57$). Moreover, the HH group, specifically in the condition of Up suggestion, showed significant higher subjective ratings than LH for both the Up ($p=.02$) and Down ($p<.001$) suggestions. The hypnotic Suggestion for increasing or decreasing pain perception significantly modulated the intensity and unpleasantness scores as highlighted by the significant interaction Suggestion X Rating ($F(1,22)=6.26$; $p=.020$). Post hoc comparisons revealed that this effect was mainly accounted for by higher subjective ratings in the Up with respect to Down suggestion for both intensity ($ps<.001$) and unpleasantness scores ($ps<.001$). No significant difference was found between intensity and unpleasantness scores within both Up and Down suggestions ($ps>.05$).

Again, the effect was specific for Group, as highlighted by the interaction Rating X Suggestion X Group ($F(1,22)=7.98$; $p=.009$). Post hoc test revealed the significance of the effect only for the HH group, with higher subjective ratings during Up with respect to Down

suggestion for both intensity ($p<.001$) and unpleasantness ($p<.001$). No significant modulation of the subjective scores was found for the LH group ($p>.05$).

This pattern of results highlights that the hypnotically-induced Suggestion for increasing or decreasing of pain perception significantly modulates the subjective ratings, specifically for the HH group and concomitantly for both intensity and unpleasantness scores.

Importantly, the Focus X Rating X Suggestion interaction ($F(1,22)=12.51$; $p=.002$) showed a similar pattern of results for the hypnotically-induced Focus of Intensity and Unpleasantness, which was mainly accounted for by higher subjective ratings of intensity ($ps=.019$) and unpleasantness ($ps<.000$) in the Up relative to Down Suggestion. Crucially, however, the hypnotically-induced Focus of Intensity in the Up suggestion, evoked higher subjective rating of pain intensity with respect to the hypnotically-induced Focus of Unpleasantness ($p=.002$). Post hoc test performed on the interaction Focus X Rating X Suggestion X Group ($F(1,22)=7.89$; $p=.01$) revealed that results were specific for the HH Group, in which both for the Focus of Intensity and Unpleasantness, the Up condition induced higher subjective ratings of intensity ($ps<.001$) and unpleasantness ($ps<.001$). No significant modulation of the subjective scores was found for the LH group ($p>.05$).

To sum, higher subjective ratings of intensity and unpleasantness were found in suggestions of increasing pain and similarly during the hypnotically-induced suggestion of Intensity and Unpleasantness. Also, the effect was specific for the HH group.

This result was confirmed and further strengthened by means of separate ANOVAs (see Figure 4-2, panel A), which revealed a significant effect of Suggestion as main factor, during both Intensity

(F(1,22)=25; p<.001) and Unpleasantness (F(1,22)=26.1; p<.001) Focus. Post-hoc comparisons confirmed higher ratings during the suggestion of Up with respect to Down (p_s<.001). Moreover, the result was specific for Group as showed by the Suggestion X Group interaction, both for Intensity (F(1,22)=9; p=.007) and Unpleasantness (F(1,22)=10; p<.005) Focus. Scheffé post-hoc test highlighted higher ratings of intensity and unpleasantness in the Up with respect to Down condition (ps<.001), specifically for the HH group. It is noteworthy that in the Unpleasantness Focus, specifically in the condition of Up suggestion, the HH group showed significant higher subjective ratings than LH group (p=.027). The Ratings X Suggestion interaction was also confirmed, both for Intensity (F(1,22)=7.73; p<.01) and Unpleasantness Focus (F(1,22)=10; p<.004) with higher subjective ratings of intensity and unpleasantness during Up with respect to Down (ps<.000) suggestion. Crucially, however, while the interaction Ratings X Suggestion X Group was not significant for the Intensity Focus (F(1,22)=0.58; p<.45), the analysis revealed a different pattern of results for the hypnotically-induced Focus of Unpleasantness (F(1,22)=8.50; p<.008). Indeed, post-hoc comparison showed that the effect was mainly accounted for by higher subjective ratings of intensity and unpleasantness in the Up with respect to Down suggestion (ps≤.03), only in the HH group (see Figure 4-2, panel A, right graph). Thus, suggesting that the enhancement of pain significantly increased the subjective scores in the HH group during both Focus on Intensity and on Unpleasantness. In particular, both intensity and unpleasantness scores were significantly modulated. Crucially, the effect was specific for the HH group only for the Focus of Unpleasantness.

Hypnotic modulation index. HH subjects' modulatory effect on ratings was significantly different from the baseline (i.e., no change) in all the four conditions (see Figure 4-2, panel B): modulation of intensity rating increased during Intensity Focus (t=4.90; df=11; p<.001), modulation of unpleasantness rating increased during Intensity Focus (t=4.99; df=11; p=<001), modulation of intensity rating increased during Unpleasantness Focus (t=2.72; df=11; p=.02), modulation of unpleasantness rating increased during Unpleasantness Focus (t=3.90; df=11; p=.002). On the other hand, LH subjects showed a significance only for modulation of intensity rating during Intensity Focus (t=2.67; df=11; p=.02), whereas modulation of unpleasantness rating during Intensity Focus (t=2.03; df=11; p=.06), modulation of Intensity Rating during Unpleasantness Focus (t=-0.16; df=11; p=.87), and modulation of unpleasantness rating during Unpleasantness Focus (t=-0.39; df=11; p=.70) did no significantly change relative to baseline.

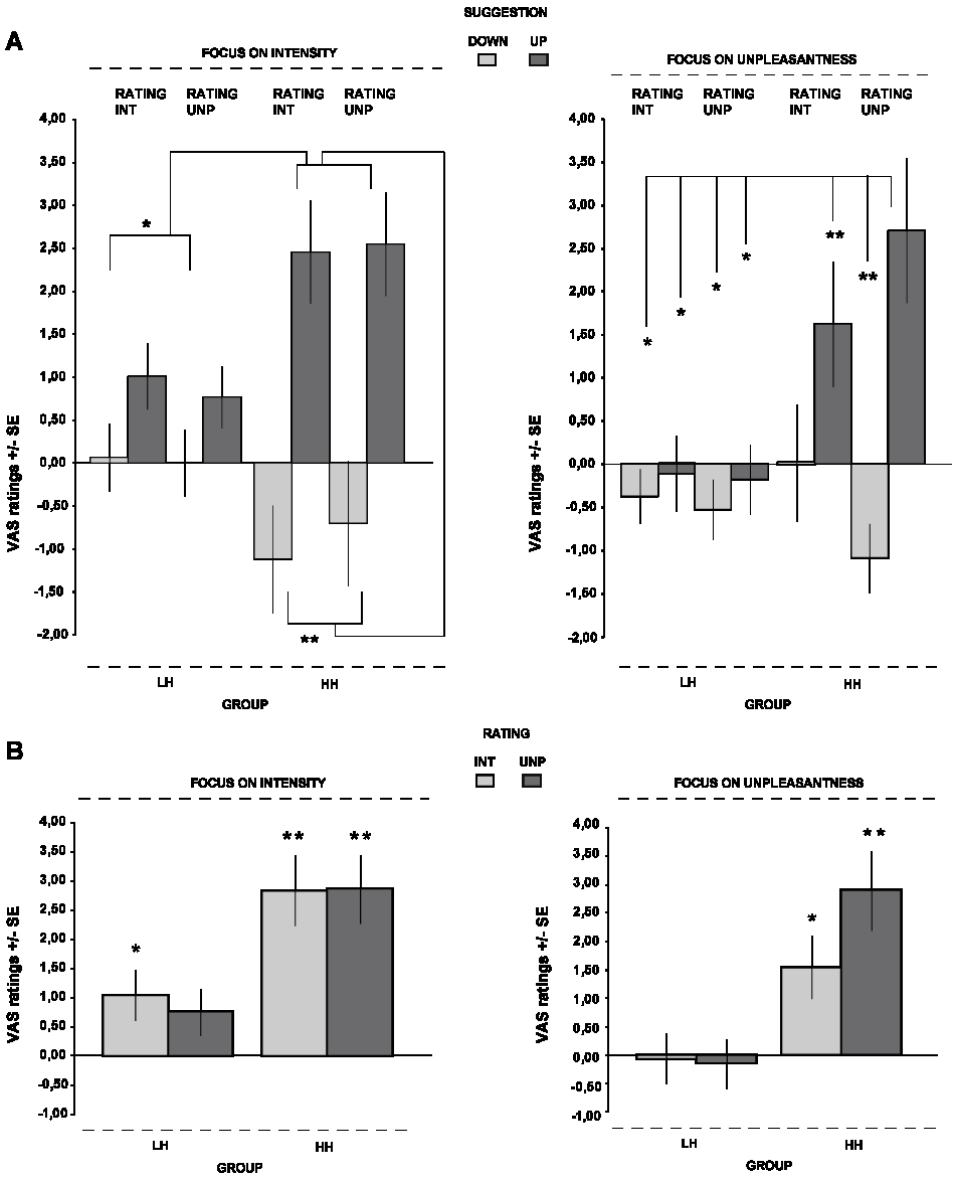

Figure 4-2. Statistical analysis of Subjective ratings of pain experience. Error bars represent SEM. One asterisk (*) indicates $p<.05$; two asterisks (**) indicates $p<.01$. Panel A shows results of ANOVA by intensity and Unpleasantness Focus sessions. Y axis represents Δ index (up or down suggestions – control hypnosis). Intensity manipulation does not determine decoupling of intensity and unpleasantness ratings, yet Up suggestions significantly increased ratings in both groups whereas Down suggestions significantly modulated only HH subjects ratings. Unpleasantness Focus does dissociate between groups: HH subjects show higher ratings of both perceived unpleasantness and intensity during Up suggestions whereas no effect is highlighted in LH subjects. Panel B illustrates T-tests results on each "hypnotic modulation index" per Focus session (Y axis: up - down suggestions/control hypnosis). A significant increase in perceptual modulation due to hypnosis suggestions is confirmed in HH subjects across Focus and Rating factors. Moreover, LH subjects show an increase in perceptual modulation when focus is on intensity.

3.2 Laser evoked potentials

ANOVA p-values of raw latencies were all non significant (p>.05).

Grand average waveforms of LEPs in the three different conditions, across Groups and Focus sessions, are shown in Figure 4-3.

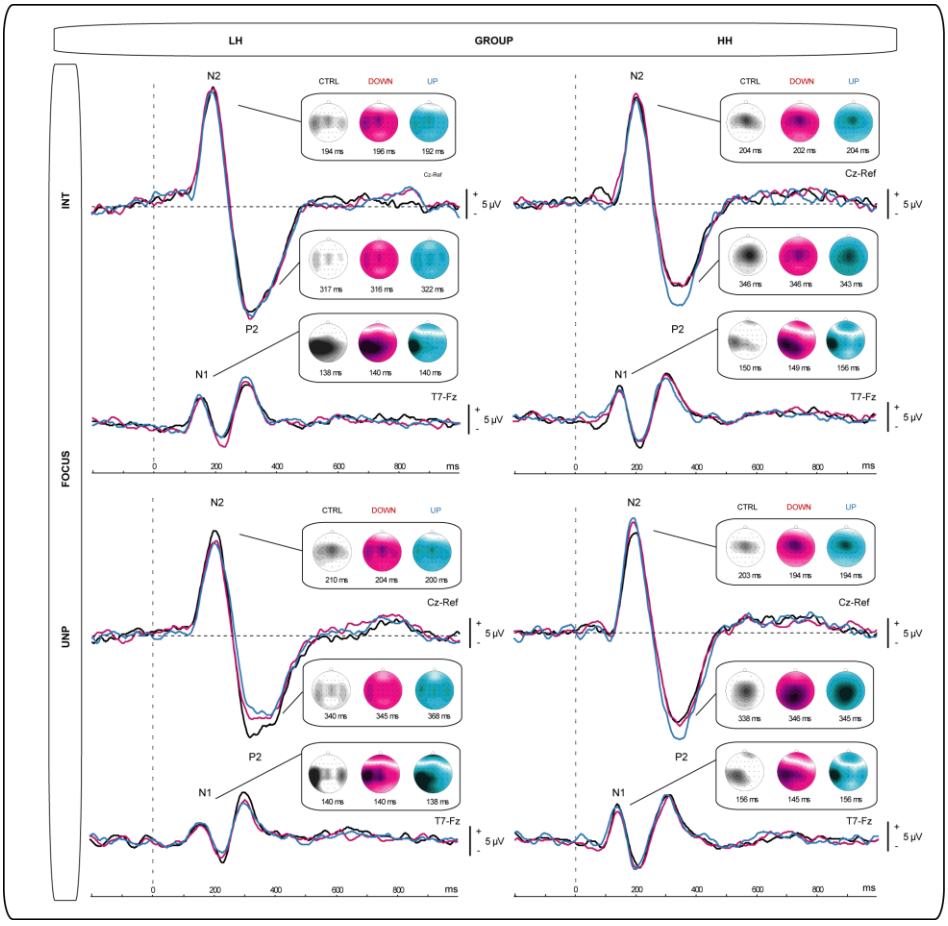

Figure 4-3. N1, N2 and P2 grand averages of the three experimental conditions recorded at electrode Cz (nose reference). Control hypnosis/relaxation treatment is represented in black whereas suggestion of increase in cyan, and suggestion of decrease is represented in magenta colour scale. Quadrants represent each Group in each Focus session. x-axis, time (ms); y-axis, amplitude (µV). Note the between groups dissociation in the P2 wave amplitude when Focus is on unpleasantness. Suggestions do not affect LH subjects while HH subjects show an increased P2 amplitude during Up suggestion.

General ANOVA outlined significant effects only for the P2 wave amplitude and the N2-P2 peak-to-peak amplitude index.

The ANOVA performed on normalized P2 amplitudes showed a significance of the main effect Group ($F(1,22)=10.38$; $p=.004$), which was mainly accounted for by higher P2 amplitudes in the HH with respect to LH Group ($p=.004$). Further, a significant modulation was also found for the main effect Suggestion ($F(1,22)=6.05$; $p=.02$) which was explained by higher amplitudes during Up with respect to Down ($p=.02$) suggestion. The interaction Suggestion X Group ($F(1,22)=10.77$; $p=.003$) revealed that the effect of enhancement was specific for the HH group ($p=.005$), being absent in the LH group ($p=.95$). Crucially, in the HH group, the Up suggestion related enhancement of P2 amplitude was also significantly different by P2 amplitude of the LH group both for Up ($p=.002$) and Down ($p=.004$) suggestions. It is worth noting that no significance of the main effect Focus or of its interaction with Rating or Group were found ($p>.05$).

According to results found for P2 amplitude, the analysis performed on the N2/P2 revealed a significant main effect Group ($F(1,22)=10.24$; $p=.006$) which was mainly accounted for by higher amplitude in the HH with respect to LH Group ($p=.006$). Moreover, a significant effect of the Suggestion X Group interaction ($F(1,22)=5.72$; $p=.031$) showed that the effect was linked to the hypnotic suggestion protocol. Scheffé post-hoc comparisons revealed a trend effect of enhancement in the Up suggestion with respect to Down ($p=.095$) only in the HH Group, being absent in the LH Group ($p=0.96$). Moreover, in the Up suggestion, the HH group showed higher N2/P2 amplitude with respect to LH group for both Up ($p=.007$) and Down ($p=.018$) suggestion.

ANOVA performed on normalized N1 and N2 amplitudes did not show any significance of the main effects, of their interactions or of the interaction with Group ($ps>.05$) as well no significant main effects or interactions were found for the LEPs latencies ($ps>.05$).

To sum up, higher P2 and N2/P2 amplitudes were found in the HH group with respect to LH. However, this effect did not reflect a modulation of the LEPs per se, as showed by the significance of the interaction Suggestion X Group. In other words, suggesting the enhancement of pain significantly modulated the P2 and N2/P2 amplitudes with respect to suggestion of pain decrease and the effect was specific for the HH group. Moreover, the analysis revealed that hypnotically-induced effect was specific for the late LEPs, being absent for the early and middle-latency N1 and N2. Thus, the hypnotic modulation significantly influenced the late component of LEPs leaving unaffected the early correlates of pain perception. The significant result found for the N2/P2 amplitudes likely reflects the hypnotically-induced modulation of the P2. Finally, no significant modulation was found for the LEPs latencies.

Although the three-way repeated measures ANOVA performed on the P2 amplitude did not show any significant effect related to the Focus of Intensity and Unpleasantness or of its interaction with Suggestion or Group, a different pattern of results was found by means of separate analysis performed on the hypnotically-induced Focus of Intensity and Unpleasantness. ANOVA on Intensity Focus highlighted a significant effect of Suggestion as main factor ($F(1,22)=5.47$; $p=.029$) which was mainly accounted for by higher P2 amplitude in the Up with respect to Down suggestion ($p=.029$). However, the interaction Suggestion X Group did not reach the significance ($F(1,22)=2.73$; $p=.11$) (see Figure 4-4, panel A). On the opposite, the main factor Suggestion was not significant in the hypnotically-induced Focus of Unpleasantness ($F(1,22)=1.97$; $p=.17$) whereas a significant Suggestion X Group interaction ($F(1,22)=9.47$; $p=.005$) was found. Scheffé post-hoc test showed that only for the HH group, the Up suggestion induced a significant enhancement of P2

amplitude with respect to Down (p=.037) suggestion. Furthermore, the Up suggestion increased the P2 amplitude in HH group with respect to the P2 amplitude found in the Up (p=.019) and Down (.077) Suggestion of the LH group. The separate ANOVA performed during the hypnotic-induced Focus of Unpleasantness on the N2/P2 amplitudes showed a significant main effect of Group F(1,22)=5.78; p=.025) which was mainly accounted for by higher N2/P2 amplitudes in the HH with respect to LH (p=.025) group. Moreover, the analysis revealed a significant interaction Suggestion X Group (F(1,22)=4.68; p=.041). Post-hoc test revealed that Up suggestion induced higher amplitude of N2/P2 in the HH group with respect to Up suggestion in the LH group (p=.041). On the contrary, a trend toward the significance was found between the HH N2/P2 amplitude in the Up suggestion, and LH N2/P2 amplitude in the Down suggestion (p=.07). However, the comparison between the Up and Down suggestion in the HH group failed to rich the significance (p=.117). The effect found on the N2/P2 amplitude did not show a strong effect of the hypnotic modulation because it likely reflects the effect of the P2 amplitude, thus hinting to a specific influence on the late P2 wave. Finally, the separate ANOVA performed during the hypnotic-induced Focus on Intensity did not show significant main effects or interactions on the N2/P2 amplitudes (ps>.05).

Hypnotic modulation index. T-test on "hypnotic modulation index" showed significant hypnotic modulation both upon the P2 wave and the N2-P2 index amplitudes (see Figure 4-3, panel B). Hypnotic modulation during Intensity Focus determined increased P2 amplitude only in the HH (t=4.33; df=11; p=.001) and not in the LH group (t=1.21; df=11; p=.25). No significant modulation of either N2 (HH: t=-.92; df=11; p=.37; LH: t=-.12; df=11; p=.91) or N1 (HH: t=.04; df=11; p=.97; LH: t=-.85; df=11; p=.42), and N2-P2

(HH: t=1.24; df=11; p=.24; LH: t=-.41; df=11; p=.69) was detected. Hypnotic modulation during Unpleasantness Focus was effective on HH P2 amplitudes (t=2.66; df=11; p=.02), while a trend to reduction in modulation was observed in LH (t=-1.81; df=11; p=.10). It was also effective on the N2-P2 peak-to-peak amplitude of HH subjects (t=2.55; df=11; p=.03) but not on LH subjects (t=-.50; df=11; p=.63). Again, No significant modulation of either N2 (HH: t=-1.14; df=11; p=.19; LH: t=1.64; df=11; p=.13) or N1 (HH: t=.002; df=11; p=1; LH: t=.73; df=11; p=.48) was found.

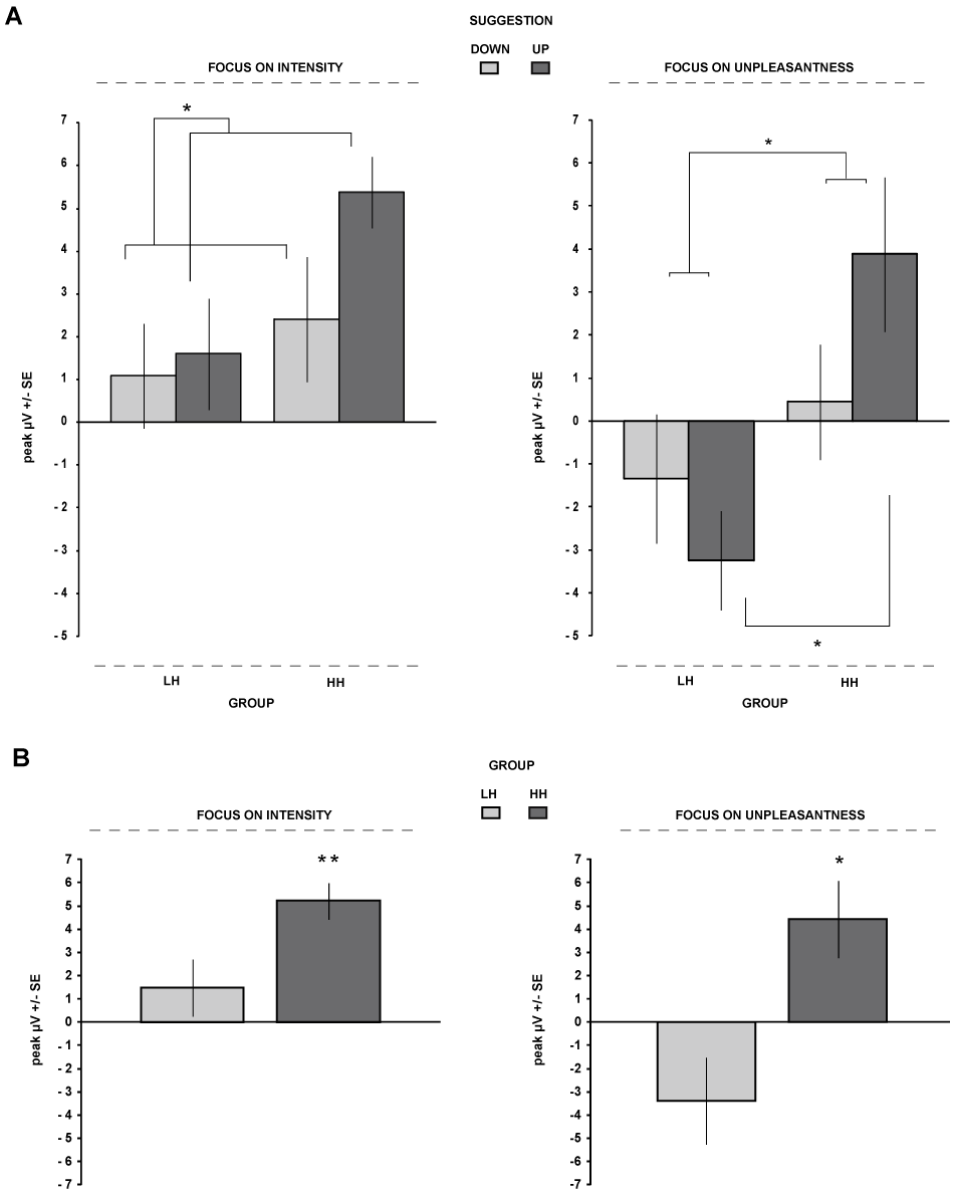

Figure 4-3. Statistical analysis of LEP P2 amplitudes. Error bars represent SEM. One asterisk (*) indicates $p<.05$; two asterisks (**) indicates $p<.01$. Panel A shows results of ANOVA by intensity and Unpleasantness Focus sessions. Y axis represents "hypnotic modulation index" index (up - down suggestions/control hypnosis). Intensity manipulation does not dissociate the two groups, yet P2 amplitude significantly increased during Up suggestions in both groups relative to Down suggestions. Unpleasantness Focus did dissociate between groups: HH subjects show higher P2 amplitude during Up suggestions whereas LH subjects display a trend to reduction of amplitude in this condition. Panel B illustrates T-tests results on each "hypnotic modulation index" per Focus session (Y axis: up - down suggestions/control hypnosis). P2 amplitude modulation was significantly increased during intensity and unpleasantness Focus in HH group. Noteworthy is the reduction of modulation of P2 activity in LH group when Focus is on unpleasantness though this pattern is not significant.

3.3 Correlation analysis

In the LH group, both during Intensity and Unpleasantness Focus, pearson r was found significant for intensity and unpleasantness ratings during Down suggestions (respectively, $r(12)=.90$, $p<.001$ and $r(12)=.74$, $p<.001$). Interestingly, in the HH group such a pattern of correlation was present only during Intensity Focus ($r(12)=.93$, $p<.01$) but not during the Unpleasantness Focus ($r(12)=.39$, $p=.22$). On the other hand, ratings reported during Up suggestions were highly correlated both in LH (ratings of intensity and unpleasantness during Intensity Focus: $r(12)=.90$, $p<.01$; ratings of intensity and unpleasantness during Unpleasantness Focus: $r(12)=.89$, $p<.01$), and HH (ratings of intensity and unpleasantness during Intensity Focus: $r(12)=.92$, $p<.01$; ratings of intensity and unpleasantness during Unpleasantness Focus $r(12)=.81$, $p<.01$) groups.

When subjective ratings were correlated to LEP amplitudes, significant correlations were found only for HH subjects to both P2 and N2-P2 amplitudes. In particular, when Focus was on

unpleasantness during Up suggestions, the increase of Unpleasantness ratings was positively correlated to both N2-P2 ($r(12)=.69$, $p=.01$) and P2 ($r(12)=.65$, $p=.02$) amplitudes (see Figure 4-4). No other correlations resulted significant.

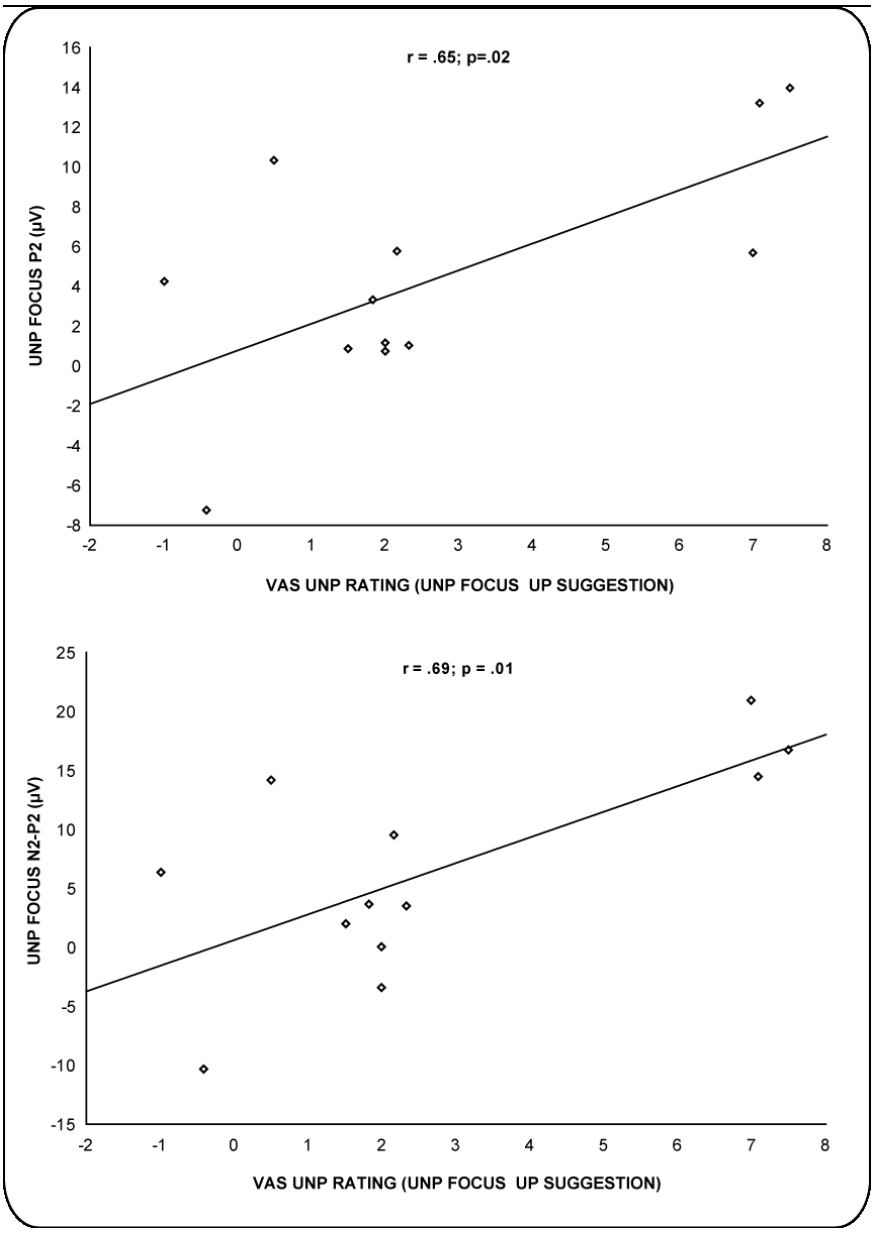

Figure 4-4. Correlational analysis. Top graph: scatter-plot of normalized P2 amplitude and ratings of pain unpleasantness when Focus was on unpleasantness in HH group. The P2 was maximal in subjects who rated the unpleasantness higher when the hypnotist suggested its increase during laser stimulation. Bottom graph: scatter-plot of normalized N2-P2 amplitude and ratings of pain unpleasantness when Focus was on unpleasantness in HH group. The N2-P2 complex increased progressively in subjects who rated the unpleasantness higher when the hypnotist suggested its increase.

4 Discussion

The phenomenon of hypnosis refers to "an interactive process in which one person responds to suggestions given by another person (the hypnotist), for experiences involving alterations in perception, memory, and the voluntary control of action" (Kihlstrom, 2008). The induced modifications are thought to be caused by an altered state of consciousness, commonly described as dissociative (Hilgard, 1975; Kirsch, 1995; Wagstaff, 1998).

Here we show three key findings strictly coupled to this phenomenon: First, hypnotic modulation of pain in HH subjects is strong and evident in both the unpleasantness and the intensity aspects of their experience while LH are modulated to a low extent and only when their attention is drawn to the intensity of stimulation. Second, P2 amplitude is the only feature of the electrophysiological response that reflect this subjective modulation, being higher in amplitude when HH are invited to focus both on intensity and on unpleasantness of pain. Such increased activity is especially due to the contribution of up rather than down suggestions. More interestingly, a specific dissociation between groups is evident when the attentional focus is on unpleasantness: P2 amplitude increases in the HH while tend to decrease in LH. Third, P2 wave amplitude increase during focus on unpleasantness positively correlate with the increase of unpleasantness ratings in HH group thus suggesting P2 as a behavioural marker of the affective modulation in these subjects.

4.1 Updating the dissociation between intensity and unpleasantness of pain experience

Hypnotic suggestions of hyperalgesia are more effective than suggestions of analgesia in modulating subjective reports. Hyperalgesia suggestions elicit a so pervasive experience of pain that its intensity and unpleasantness features cannot be untangle in both LH and HH individuals.

This pattern may be economically explained by applying a teleological perspective on biological function of hyperalgesia. Indeed, pain experience can limit immediate damage triggering flight as first reaction to avoid a harmful situation (Melzack & Casey, 1968; Loeser & Melzack, 1999). In this vein, the importance of current sensory information magnitude (intensity) is capital when individuals try to statistically interpret their feelings and define the quality of their perception on demand of external suggestions. Such a rationale helps to explain why hyperalgesia suggestions are effective in LH too, as they converge on pain intensity. Interestingly, the same does not hold true for analgesia suggestions: no *placebo* phenomenon was obtained in LH, whereas analgesia suggestions were compelling in HH. These data are in agreement with recent results obtained by Colloca and colleagues (2008) who found *nocebo* experience effective by verbal suggestions alone in naive subjects.

The self-reduction of pain experience was a more difficult task: analgesic suggestions significantly lowered both intensity and unpleasantness of pain perception but only in the HH group.

4.2 Laser evoked P2 as index of both intensity and unpleasantness of pain

Rainville et al. (1997) and Hofbauer et al. (2001) used hypnosis to respectively manipulate pain unpleasantness and pain intensity and

found that S1 and S2 brain responses coded pain intensity only, whereas the ACC was strongly correlated just with the unpleasantness of pain perception. They further stated that the ACC may also encode some intensity information. In fact, the author themselves detected an activation of ACC and IC when hypnotic manipulation was focused on intensity of pain though not significant with respect to SI activity.

In the present study three evoked brain activity indexes were investigated. The first was the early, lateralized, N1 potential originating from SI (Garcia-Larrea et al., 2003), and S2 (Frot et al., 1999, 2007; Vogel et al., 2003). The other two were the N2 and the P2 waves, which form a large, bipolar late vertex signal, known to occur in parallel in at least three brain areas: posterior, anterior insula and SII (N2), and MCC-ACC (P2) (Ohara et al., 2004, Frot et al., 2008, Perchet et al., 2008).

The increase of intensity in hyperalgesia experience is paralleled by enhanced laser evoked P2 amplitude in both groups while the increase of unpleasantness is targeted by P2 amplitude boosting only in HH. Thus, in a context were stimuli are unpredictable and physically matched (Clark et al., 2008), P2 wave seems to be measure of both intensity and unpleasantness dimensions of pain. Nevertheless, it may reveal a different functional meaning when verbal suggestions draw subjects attention on the affective attribute of noxious stimulation. Indeed, while LH seem to show no difference in their cingulate activity when they are required to "change" their feeling about current stimulation, hypnosis responders exihibit a hyperactivity of P2 dipole generators both when required to modulate the sensory and the affective dimension of their experience. The involvement of "medial pain system" in processing of sensory information is not just speculative. The mid-cingulate cortex does not

address only the processing of emotional representations, but progressively augment its activation accordingly to increase in stimulus intensity (Davis et al., 1997; Porro et al., 1998). This evidence stimulated the proposal of a "backup" theory of intensity coding (Coghill et al., 1999), which posits that redundancy of intensity coding in several neural structures may provide a compensatory mechanism to allow this information surviving the loss of neural tissue.

Moreover, a recent electrocorticography study showed a specific posterior mid-cingulate cortex (pMCC) fast rising activity during noxious laser stimulation (Frot et al., 2008), while EEG and magnetoencephalography (MEG) studies reported unaffected S2 activity (Hauck et al., 2007b; Yamasaki et al., 1999) or its saturation regardless the increase in relevance of painful stimuli (Nakamura et al., 2002). The posterior mid-cingulate cortex (pMCC) fast response to painful stimuli may be suitable to explain the highest P2 amplitude in HH when focus of suggestions is on intensity whereas a more rostral ACC activity could explain the specific increase in amplitude during focus on unpleasantness.

Following hypnotic modulation of both intensity and unpleasantness of pain perception, we cannot confirm the clear-cut existence of a physiological (as well as subjective) double dissociation between sensory and affective-cognitive processing. We rather observed a physiological and subjective dissociation in the cingulate cortex between LH and HH only when the focus was on unpleasantness. This evidence may be accounted for by either limitations related to the technique we used to measure brain activity (LEPs) or by an actual lack in relevant statistical differences among control hypnosis and suggestions conditions in the sensory indexes. Indeed, it is well known that N1 wave presents a very low signal to noise ratio and

very low variability in amplitude (absolute mean amplitude up to about 10 μV), features that make this signal prone to non experimental fluctuations in arousal and vigilance (Lorenz and Garcia-Larrea, 2003). It is also possible that the evoked activity was not enough phase-locked to the stimulus to be identifiable after averaging, though the YAP laser we applied in this study is possibly the best mean of synchronously recruiting Aδ and C fibres within the first 5 ms post-stimulus (e.g, Perchet et al., 2008).

As the physical parameters were maintained constant throughout the experiment, it is unlikely that SII and SI unimodal activity (thermo-nociceptive) was not modulated by the sensory stimuli. It is more likely that their overall level of activation did not change significantly during attentional modulation as well as during control relaxation (Downar et al., 2000).

It is noteworthy that the aforementioned seminal studies used hot water to induce painful sensation thus activating Aβ tactile fibres too. More importantly, in Hofbauer et al. (2001) SI activation was derived by comparing data obtained during suggestions (painful hot stimulation) with those obtained by subtracting data recorded during warm stimulation from those during painfully hot in the control conditions. These methodological discrepancies may hint to explain why somatosensory activity singled out during their experiment.

4.3 A "work in progress" neurocognitive model of sensory and affective mechanisms of pain processing

As we adopted the suggestion scripts used by Rainville and colleagues (1999), the present behavioral and neurophysiological results will be explained by a modified version of the successive model of pain processing (Rainville et al., 1999; Wade et al., 1996).

The weakest features of the previous version rely on the sequentiality of events and the lack of attention construct as driving force of sensory and affective modulation processes. Firstly, It is entirely plausible that affective and sensory processing happen in parallel (Frot et al., 2008; Ohara et al., 2004; Ploner et al., 2009; Weiss et al., 2008) though different weights may be assigned to the direction of interaction between "lateral" and "medial" pain structures (Oshiro et al., 2009). Secondly, this model neglects the pervasive role of attention as superimposed process influencing pain processing and specifically laser evoked potentials (Lorenz and Garcia-Larrea, 2003). Therefore, we were urged to integrate the successive stage model with a neurocognitive account of pain processing such as that proposed by Legrain et al. (2009a) (see Figure 4-5).

Legrain's model of attention to pain wisely adapts a *cognitivistic* account of attention to pain perception by introducing the concepts of bottom-up and top-down selection of information. In the context of our study the top-down mechanism is certainly the most involved given the externalized manipulation of sensory and affective information and due to the absence of both novel and infrequent stimuli in the design. As stated by the author "*top-down selection is directed by cognitive goals activated in working memory [...], it increases the neural responses to goal relevant signals and inhibits the response to goal irrelevant signals*". Though our experiment did not provide a proper task, this proposition may apply to the suggestions induced in HH subjects. Indeed, they explicitly provided the subjects with the goal of either reducing or increasing their pain. The increase of hypnotic modulation (both in analgesic and hyperalgesic conditions) is consistent with the increase of P2 neural response, while the highest P2 amplitude in the hyperalgesic

condition may be explained by a higher attentional load required by the most functionally relevant (harmful) situation for the subject.

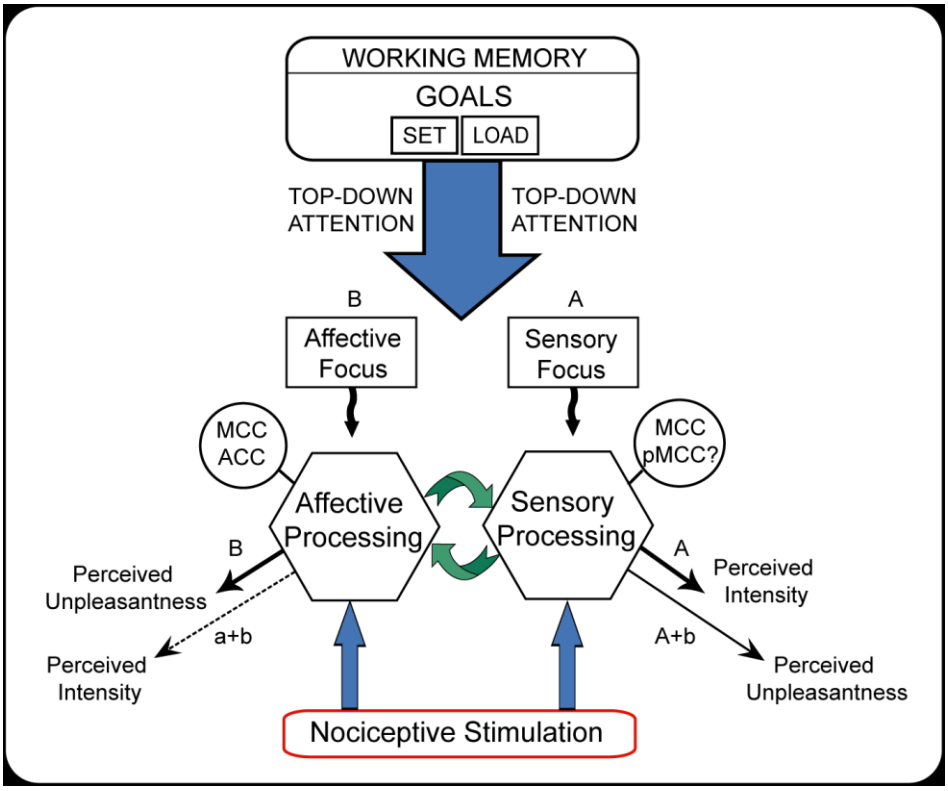

Figure 4-5. Integrated neurocognitive model of sensory and affective pain processing. In taking with a previous model (Rainville et al., 1999) when the focus of subject's attention was directed on intensity of sensation, modulation of pain intensity determined changes in sensory experience (A), and coupled changes of affective processing (unpleasantness) (A+b). Differently from what previously observed, when subjects' attentional resources were driven towards pain affect (B) we did not detect a strong influence of these suggestions on intensity experience (a+b), in particular when analgesic suggestions were applied. When a high attentional load is demanded and the attentional set is clearly defined, we suggest that such a psychological functions may implicate either different portions of the cingulate cortex or both the very same structures. Nevertheless, several variables besides intensity may differently relate to unpleasantness (e.g., localization – see Kulkarni et al., 2005; Oshiro et al., 2009), as much as different cognitive-affective processes may in turn affect the sensory experience (e.g, catastrophizing, anxiety – see Trecey and Mantyh, 2007). Therefore, some other structures as for instance insular cortex, posterior parietal cortex and dorsolateral prefrontal cortex will surely intervene to determine the emergence of pain perception from nociception.

Another explanation of our findings would call for the involvement of sole saliency enhancement mechanisms in determining behavioral and neural responses. Indeed, Downar and co-workers (2003) showed how a multimodal network of structures among which the ACC is meaningfully activated, is tonically responsive throughout the duration of a painful stimulus. The sustained response of ACC may infact represent the saliency of pain, which is widely know to be an experience able to remain salient for a prolonged period.

The hypothesis of a preeminent role of middle and rostral cingulate cortex (pMCC-ACC) in processing physical features of acute pain and in determining anticipatory allocation of neural resources to deal with it, is in agreement both with specific research on neural substrates of hypnosis (e.g, Rainville et al., 2002; Derbyshire et al., 2004; Horton et al., 2004; Vanhaudenhuyse et al., 2009) and on neuroanatomical models of cingulated function in pain and emotion (Vogt, 2005). Future research needs to fit the important integrative role of these structures in heuristic models able to couple neural functioning to subjective experience and behavior.

Chapter 5

General discussion

1 Nociceptive and pain processing specificity in the brain?

The sensory system producing pain perception, sometimes referred to as the 'nociceptive' system, is made by cutaneous and visceral nociceptors (present in all tissues except the brain), peripheral Aδ- and C-fiber afferent fibers, and spinal transmission neurons which modulate and project this peripheral input to supraspinal structures

such as the brain stem, the thalamus, the limbic system, and the cortex. A vital function of the nociceptive system is to provide immediate awareness of threats to the body's integrity, inciting the individual to react by producing an adequate protective response. Therefore, for noxious events to interrupt ongoing behavioral goals, nociceptive brain processes are expected to be strongly interlaced with attentional processes.

Based on this assumption, it is of paramount importance the understanding of the functional significance of LEPs as, up to date, they are the most selective and effective available technique able to activate nociceptive nerve endings. Thus, the investigation of how far the brain activity evoked by laser stimuli is nociceptive specific turns to be a general enquiry on how far pain processing in the brain is a specific modality mechanism versus a multimodal integration process with low or no amount of specificity.

Several lines of evidence from human electrophysiological studies (Hay and Davis, 1971; Greenwood and Goff, 1987; Barth et al., 1995; Okajima et al., 1995; Lam et al., 1999; Foxe et al., 2000; Lutkenhoner et al., 2002; Teder-Salejarvi et al., 2002; Gondan and Roder, 2006) have shown that the sum of the ERPs elicited by a stimulus occurring in one sensory modality significantly differ from the ERPs elicited by the simultaneous presentation of both stimuli, thereby providing evidence that significant interactions do underlie the cortical processing of multimodal sensory input. In support to this hypothesis, source localization studies proposed fronto-medial dipoles, probably originating from the ACC and MCC, as contributors to LEP, the SEP, and the AEP.

In most studies, these activities have been interpreted as reflecting non modality-specific processes related to stimulus-triggered orienting responses. Furthermore, as described in Chapter 2, all

vertex negativities have been hypothesized to receive significant contributions from signals arising around bilateral opercular regions, included those elicited by both laser and electric somatosensory stimulation. Nevertheless, unlike the somatosensory N1 potential, bilateral opercular sources of the auditory N1 wave have, more often, been ascribed to activity originating from the supra-temporal plane and the superior temporal gyrus.

It is thus conceivable that a partial differentiation in the level of unimodal specificity can be assigned to auditory and visual inputs on one hand, and somatosensory together with nociceptive inputs on the other hand, with the latter showing a weaker unimodal specificity at later stages of processing. Ground for this hypothesis originated by the observations of high similarity among all the vertex potentials topographies and between laser-evoked N1 and somatosensory evoked N1 topographies (Kunde and Treede, 1993). However, observing a difference in the scalp topography does not constitute any evidence that nociceptive-specific processing contributes to LEPs. This gap was filled only very recently in a study where LEPs recorded from both perceived and unperceived noxious stimuli were compared (Lee et al., 2009). The authors did not find any difference in the magnitude of early-latency N1 wave between perceived and unperceived stimuli, whereas the amplitudes of the later N2 and P2 waves were reduced when stimuli were unperceived (see figure 2-3, Chapter 2).

However, even though some extent of nociception specificity could be observed at the early stage of processing, this could be paralleled by some degree of concurrent multimodal contribution. Such a hypothesis was addresses in another recent study by the same research group (Mouraux and Iannetti, 2009). The authors applied a blind source separation algorithm (probabilistic independent

component analysis) to 124-channel event-related potentials elicited by a random sequence of nociceptive and non-nociceptive somatosensory, auditory, and visual stimuli, they showed how LEPs could be entirely explained by a combination of multimodal neural activities (i.e., activities also elicited by stimuli of other sensory modalities) and somatosensory-specific, but not nociceptive-specific, neural activities, especially in the very late P2 scalp potential (see figure 5-1). Regardless of the sensory modality of the eliciting stimulus, the magnitude of multimodal activities correlated with the subjective rating of saliency, suggesting that these multimodal activities were involved in stimulus-triggered mechanisms of arousal or attentional reorientation.

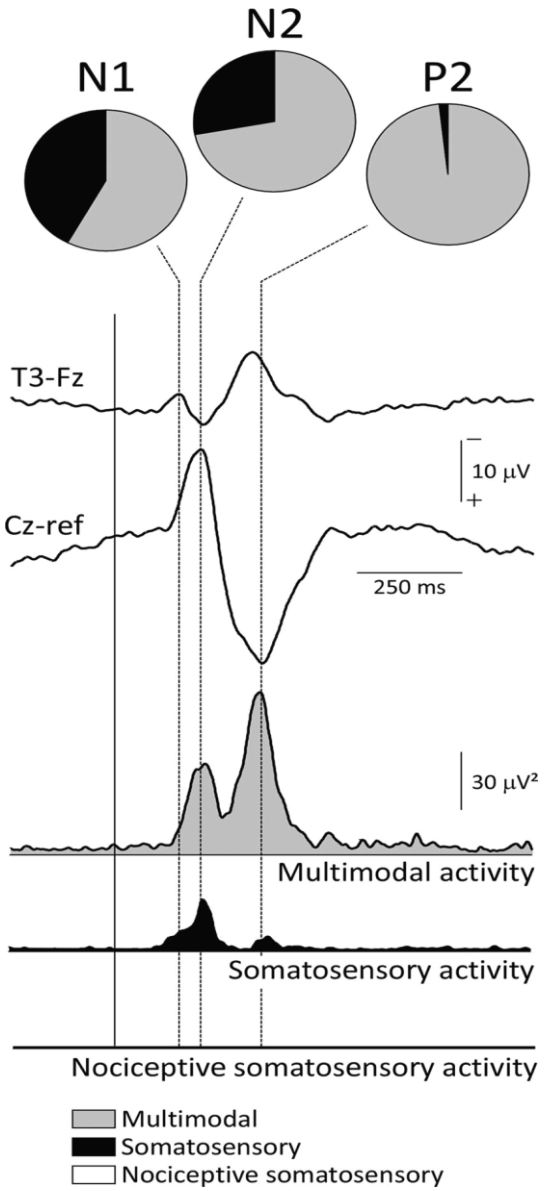

Figure 5-1. Multimodal and somatosensory-specific activities contributes to the laser-evoked potential (LEP) waveform. The time course of this multimodal activity, expressed as global field power (μV^2), is shown in gray. Note how multimodal activity explains much of the N1 and N2 waves and almost all of the P2 wave. Somatosensory-specific brain activity (i.e., activity elicited by both nociceptive and non-nociceptive somatosensory stimuli) also contributes to the LEP waveform. The time course of somatosensory-specific activity, expressed as global field power (μV^2), is shown in black. Note how its contribution is largely confined to the time interval corresponding to the N1 and N2 waves. Also note the lack of nociceptive-specific somatosensory activity contributing to the LEP. Adopted from Mouraux and Iannetti, 2009.

In agreement with this results is a MEG source analysis study (Inui et al., 2003) which compared the activity elicited by intracutaneous electrical stimuli selectively activating Aδ-fiber afferents to that

elicited by transcutaneous electrical activation of large Aβ-fibers. Indeed, results of that study suggested that nociceptive Aδ-fiber activation and non-nociceptive Aβ-fiber activation evoked similar responses in SI, SII, insula and anterior cingulate regions.

Therefore, how can this lack of nociceptive specificity be explained? One possibility is that the sparse and small number of nociceptive neurons in the brain (both nociceptive-specific and wide dynamic range) would provide a spatially indistinguishable response, with respect to tactile neurons in the same regions (Kenshalo et al., 2000). Nevertheless this explanation does not give rise of why, when LEPs are suppressed by the concomitant activation of non-nociceptive fibers, the nociceptive input still elicits a clear painful percept (Boulu et al., 1985; De Broucker and Willer, 1985; Garcia-Larrea, 2004). This last experimental evidence further proves that LEPs may be an indirect measure of pain perception, especially the late N2-P2 complex. In support of this notion, the topography of the vertex P2 positivity appears to be mostly invariant across auditory, visual, and somatosensory modalities. For these reasons, it could well be that the LEP vertex positivity reflects processes common to all sensory modalities. As a matter of fact, non-nociceptive somatosensory stimuli (Garcia-Larrea et al., 1995; Goff et al., 1977), auditory stimuli (Naatanen and Picton, 1987; Picton et al., 1999), and even visual stimuli (Makeig et al., 1999; Vogel and Luck, 2000) may all elicit a large 'vertex potential' whose shape, scalp topography and sensitivity to various experimental factors closely resemble those of LEPs (Garcia-Larrea, 2004; Garcia-Larrea et al., 2003; Kunde and Treede, 1993; Mouraux and Plaghki, 2006).

Taken together, these experimental observations question the suitableness of assuming that LEPs reflect neuronal activities uniquely or even preferentially involved in processing nociceptive

input. Rather, laser-evoked brain responses may represent an indirect readout of central nociceptive processing, being strongly affected by sensory-affective-cognitive integration processes which take advantage of neural information provided by brain structures also involved in other sensory modalities.

The results obtained in the studies presented in this thesis give further support to the notion of a saliency-driven modulation of brain nociceptive-related activity, which overlaps brain activities related to other modalities (Chapter 3), and to a fast, expectation-driven mechanism preferentially reflected by the late vertex positivity especially when the stimulus becomes affectively relevant, thus hinting to a strong attentionl-integrative role of P2 index in the internal and external elaboration of body representation.

2 How pain perception emerges from nociception

Nociception, which is initiated by the activation of peripheral nociceptors, may be defined as the afferent activity in the peripheral and central nervous system elicited by mechanical, thermal or chemical stimuli having the potential to inflict tissue damage (Albe-Fessard, 1985). However, nociception is not synonymous with pain, which is experienced as a conscious percept. Indeed, nociception can trigger brain responses without necessarily causing the feeling of pain (Lee et al., 2009). On the other hand, pain can occur in the absence of nociceptive input as in phantom limb pain (Nikolajsen and Jensen, 2006).

In the last decades, a very large number of studies have aimed to understand better how the cortex processes nociceptive stimuli and how the experience of pain may emerge from this processing. Human studies have shown that nociceptive stimuli may elicit activity within a very wide array of subcortical and cortical brain structures

(Ingvar, 1999; Peyron et al., 2000; Treede et al., 1999, Schnitzler and Ploner, 2000; Rainville, 2002; Garcia-Larrea et al., 2003; Porro, 2002; Apkarian et al., 2005; Tracey & Mantyh, 2007). Because some of these structures appear to be activated consistently across studies, they have been hypothesized to be preferentially involved in experiencing pain.

The classical model of neural representation of pain in the brain poses the existence of a network of cortical areas ('pain matrix') through which pain may emerge from nociception (Melzack, 1990). This model anatomically distinguishes between 'lateral' (somatosensory cortices, SI and SII) and 'medial' (anterior insula – AIC and mid-cingulate cortex – MCC, in particular its rostral part, the anterior cingulate cortex – ACC) components (Albe-Fessard et al., 1985). Human EEG studies, MEG studies, or intra-cerebral recordings, as well as fMRI or PET studies, all concur in describing a large array of cortical structures specifically devoted to process either the sensorial-discriminative ('lateral system') or the affective-cognitive ('medial system') aspects of pain (Ploner et al., 1999; Treede et al., 1999; Peyron et al. 2000, 2002; Craig, 2003a; Garcia-Larrea et al., 2003; Apkarian et al., 2005).

However, the strongest evidences in favour of this model are mostly related to the sensory discriminative node of the neuromatrix. For instance, non-human mammals studies demonstrated that SI and SII contain neurons suitable at coding spatial, temporal and intensive aspects of noxious stimuli (reviewed in Craig, 2003a). Clinical studies of brain damaged patients highlighted impairments of aware nociceptive discrimination skill following lesions of this area (Greenspan et al., 1999), or even no perception of pain accompanied by a non-localized and bad-defined unpleasantness sensation (Ploner et al., 1999). Studies using PET (Derbyshire et al., 1997; Coghill et

al., 1999; Tolle et al., 1999) and fMRI (Bornhövd et al., 2002; Büchel et al., 2002) have thereby shown that the magnitude of the hemodynamic responses in the Pain Matrix (i.e., SI, SII, AIC, ACC) can reliably predict the amount of pain perceived. Similarly, EEG/MEG studies have shown that the magnitude of the nociceptive ERPs and event-related magnetic fields (ERFs) may correlate with the intensity of nociceptive stimuli, and, even more, with the perceived intensity of pain (Arendt-Nielsen, 1994; Beydoun et al., 1993; Carmon et al., 1978; Frot et al., 2007; Garcia-Larrea et al., 1997; Iannetti et al., 2005; Ohara et al., 2004; Plaghki et al., 1994; Timmermann et al., 2001). For these reasons, the encoding of pain intensity has been suggested to constitute one, if not the main function reflected by the Pain Matrix.

On the other hand, the weakest side of the model is represented by the evidences coupled to the cognitive-affective node of the matrix. Indeed, the role of medial limbic pain structures as the anterior cingulate cortex (ACC) and the anterior insular cortex (AIC) seem to be more complex and less unambiguous. The implication of insular cortex in the subjective pain experience agrees with its role in homeostatic regulation processes (Craig, 2003b). Indeed, AIC lesions may produce a clinic condition labelled as 'pain asymbolia', where the patient can perceive pain but lacks of a proper emotional reaction to it (Berthier et al., 1988). Animal studies pointed out that ablations of cingulate cortex compromise the emotional response to pain (Cohen et al., 2001) and that the selective opioidergic activation of ACC do decrease affective dimension of pain (e.g., LaGraize et al., 2006).

In humans, its direct involvement in painful conscious experience has been demonstrated by a single cell study on patients undergoing cingulotomy (Hutchinson et al., 1999). This study showed a small

number of neurons in the anterior MCC (aMCC) responding only to heat painful stimuli. Furthermore, the authors found these neurons also firing for the observation of painful stimulation in the experimenter. This pushed the authors to claim that "*cells within ACC are involved in mediating the affective components associated not only with a painful sensory stimulus but also with attention, recognition and anticipation of an upcoming pain stimulus*".

Such a claim was confirmed and extended by neuroimaging studies which highlighted both ACC and AIC as associated not only to a plethora of affective-cognitive processes, like empathy for others' pain (e.g., Singer et al., 2004, Saarela et al., 2006; Ochsner et al., 2009) and placebo and nocebo phenomena (e.g., Wager et al., 2004; Kupers et al., 2005; Craggs et al., 2007; Kong et al., 2008), but also to coding of suprathreshold pain intensity (e.g., Coghill et al., 1999; Büchel et al., 2002) and spatial discrimination of pain (Oshiro et al., 2009). These observation are complemented by the involvement in pure attentional phenomena as anticipation, expectation, predictability and controllability of pain (e.g., Porro et al., 2002; Solomons et al., 2004; Carlsson et al., 2006; Clark et al., 2008).

However, two recent studies reported direct evidence of double dissociation between 'lateral' and 'medial' functions in humans (Rainville et al., 1997; Hofbauer et al., 2001). The double dissociation concerned the affective and sensory neural structures of the pain matrix, identified respectively in the limbic ACC and SI-SII. Rainville and co-workers showed that unpleasantness of pain is coupled to increase of activity in the ACC but not in the SI-SII (1997), whilst intensity of pain sensation is mainly associated to the the SI-SII activity, though ACC activity is likewise affected by the magnitude of sensation (Hofbauer et al, 2001).

In light of these observations, is not clear yet which is the contribute

of different neural structures in the emergence of pain experience from nociception.

At the state of art, several questions are to be answered.

First, what is the role of medial frontal structures in determining the emergence of pain from nociception? Second, is the 'pain matrix' model (as currently conceived) a useful device to explain how pain is represented in the brain? Is it the best model to account for the experimental evidence? Or, is there room to explain the findings according to a different model?

I will try to address these questions in the following paragraph.

3 A new model of pain representation in the brain

In support of the 'pain matrix' model investigators often put forward the following two arguments: (i) perceived intensity of pain highly correlates with the magnitude of neural responses in the 'pain matrix' (e.g., Coghill et al., 1999; Derbyshire et al., 1997; Tolle et al., 1999), and (ii) that factors modulating specific aspects of pain cuncurrently modulate the magnitude of the neural responses in specific structures of the 'pain matrix' (Hofbauer et al., 2001; Rainville et al., 1997). Therefore, the 'pain matrix' would constitue a '*representation*' (Treede et al., 1999) or a '*signature*' (Tracey & Mantyh, 2007) of pain in the brain, and thereby provides a window to study the neural processes underlying pain function and dysfunction in humans (Apkarian et al., 2005).

However, as already pointed-out by Carmon et al. (1976) in their seminal work, as well as by Stowell (1984), the fact that the eliciting sensory stimulus is entirely selective for nociceptive peripheral afferents by no means implies that the elicited brain activity is nociceptive specific. Indeed, the notion of specificity has been challenged by a number of recent experiments showing that the 'pain

matrix' responses (i) may be clearly dissociated from the perception of pain intensity (Clark et al., 2008; Dillmann et al., 2000; Iannetti et al., 2008; Lee et al., 2009; Mouraux et al., 2004; Mouraux and Plaghki, 2007; Seminowicz & Davis, 2007), (ii) are equally influenced by factors independent of nociceptive stimulus intensity (Hatem et al., 2007; Iannetti et al., 2008; Legrain, 2008; Mouraux et al., 2004), and (iii) can be evoked by non-nociceptive and non-painful stimuli (Downar et al., 2000, 2002; Lui et al., 2008; Mouraux and Iannetti, 2009; Tanaka et al., 2008).

Crucially, it has been shown that when laser stimuli are repeated at a short and constant ISI of one second, the relationship between intensity of the stimulus and intensity of pain perception is preserved, whereas the relationship between intensity of pain perception and magnitude of the N2-P2 is not (Iannetti et al., 2008). Chapter 4 showed how the use of hypnosis (as applied by Rainville and co-workers) while equally modulated both intensity and unpleasantness of pain sensation, it could not determine a dissociation of sensory (N1 wave) and cognitive-affective (P2 wave) aspects of painful experience. It was rather found an involvement of P2 potential (cingulate and insular sources) in both intensity and unpleasantness modulation of pain perception. The involvement of 'medial pain system' in processing of sensory information is not just speculative. The mid-cingulate cortex does not address only the processing of emotional representations, but progressively increases its activation according to increase in stimulus intensity (e.g., Davis et al., 1997; Porro et al., 1998; Buchel et al., 2002). This evidence stimulated the proposal of a "backup" theory of intensity coding (Coghill et al., 1999), which posits that redundancy of intensity coding in several neural structures may provide a compensatory mechanism to allow this information surviving the loss of neural

tissue.

Perceived intensity of pain and the magnitude of nociceptive ERPs are differently affected by the delay separating the visual cue and the nociceptive stimulus (Clark et al., 2008). Longer-duration delays lead to an increased intensity of perception. In contrast, the magnitude of nociceptive ERPs do not depend on the duration of the delay, but depended on whether the delay is predictable or not, being larger when the delay is unpredictable. Additionally, it is also noteworthy to mention a study having shown that when stimuli are presented in pairs with very short inter-stimulus intervals, the second stimulus of the pair is not perceived as a separate percept whereas both stimuli of the pair elicit separate and reproducible brain responses (Lee et al., 2009). Finally, others authors reported that nociceptive stimuli may elicit activity in the 'pain matrix' in absence of pain awareness, such as in sleeping subjects (Bastuji et al., 2008), patients in vegetative state (Boly et al., 2008), or anesthetized monkeys (Baumgärtner et al., 2006).

These results are clearly not accounted for by the classical model. as much as the evidence that when the inter-stimulus interval varies randomly and is, consequently, unpredictable, the magnitude of nociceptive ERPs is unaffected by stimulus repetition, even at very short intervals (e.g., 280 ms - Mouraux et al., 2004). This suggests that contextual information is a crucial determinant of the brain responses magnitude elicited by the nociceptive stimulus.

In particular the LEPs studies indicates that 'top-down' and 'bottom-up' attentional processes interact during pain perception to provide monitoring, planning and behavioral execution through a balanced activation of both somatosensory cortices (N1 and N2 waves) and cingulate along with insular cortex activity (see also Lorenz and Garcia-Larrea 2003 for a review).

Nevertheless, it is highly likely that somatosensory cortices are more susceptible to process relevant noxious information according to passive, automatic allocation of resources whereas cingulate and insular activity may be recruited by both conscious sensory-affective-cognitive integration and by unconscious detection of salient/behaviorally relevant information (Lee et al., 2009).

In support of this interpretation, numerous studies have consistently reported that attending to the laser stimulus could induce a strong enhancement of the vertex N2-P2 complex (e.g., Beydoun et al., 1993; Siedenberg and Treede, 1996; Zaslansky et al., 1996b; Garcia-Larrea et al., 1997; Yamasaki et al., 1999; Friederich et al., 2001). Results of these studies have also suggested that the earlier N1 LEP was mostly unaffected by selective attention and expectation (e.g., Friederich et al., 2001; Boyle et al., 2008; Clark et al., 2008; Garcia-Larrea et al., 1997). In addition, the two studies presented in the thesis are in agreement with this view. Indeed, while they confirm the modulation of N1,N2, P2 LEPs due to peripheral changes in saliency of sensory stimuli (i.e., change of modality), they also re-affirm the modulation of P2 wave due to selective attention and expectation (i.e., verbal suggestions) of cognitive-affective processing without concurrent modulation of N1,N2 potentials.

The most striking explanatory failure of the 'pain matrix' model supporters is represented by the repetition suppression phenomenon. When nociceptive stimuli are repeated using a constant and short inter-stimulus interval, a marked decrement of the elicited nociceptive ERPs is observed (Bromm & Treede, 1987; Raij et al., 2003; Truini et al., 2004, 2007; Iannetti et al., 2008). Some investigators have proposed that this repetition suppression results from refractoriness of the neural receivers of the nociceptive input (Raij et al., 2003; Truini et al., 2007). In this view, repetition

suppression would result from the fact that the neural receivers are in a state of refractoriness following their prior activation.

However, the finding that nociceptive ERPs are unaffected by stimulus repetiton when the time intervals are varied randomly from trial to trial rules out the hypothesis that repetition suppression is explained by neural refractoriness (Mouraux et al., 2004; Wang et al., 2008). Instead, this finding highlights that the context in which a nociceptive stimulus occurs strongly determines the responses that this stimulus induces in the brain. Varying the time interval disrupts habituation because it renders the occurrence of the repeated stimulus unpredictable and hence more salient.

Accordingly, it would be the absence of novelty to determine the lack of ERPs enhancement. In agreement with this view, in a recent experiment, Legrain et al. (2009b) showed that the occurrence of a novel nociceptive stimulus can impair the performance of the behavioural responses to a shortly-following visual stimulus and alter the brain responses elicited by that visual stimulus. It has been also shown that concurrent pain-unrelated processing was disrupted due to the shift of attention towards nociceptive input (Eccleston & Crombez, 1999). The described effects of stimulus novelty on magnitude of nociceptive ERPs closely resemble those observed in the other sensory modalities (Friedman et al., 2001). In addition, the effects appear to involve most of the components of nociceptive ERPs, i.e. components originating from operculo-insular, post-central and cingulate areas (see Chapter 1, paragraph 2.3). Accordingly, fMRI studies have identified also a cortical network involved in novelty detection, including cingulate and insular areas, regardless of the sensory modality of the eliciting stimulus: either nociceptive, tactile, visual or auditory (Downar et al., 2000, 2002).

In support with that, two recent studies (Mouraux & Iannetti, 2009;

Mouraux, submitted) showed, using EEG and fMRI respectively, that nociceptive, tactile, auditory and visual stimuli elicit spatially indistinguishable responses in the insula, the cingulate and the largest part of SII areas, indicating that the bulk of the Pain Matrix response reflects multimodal neural activity, (i.e., activity underlying brain processes that are independent of sensory modality). Furthermore, the only fraction of the 'pain matrix' response that was not explained by multimodal neural activity, originating from SI and a small portion of SII, was explained by non nociceptive-specific somatosensory neural activity, i.e. activity equalling involved in the processing of both nociceptive and tactile stimuli. Both in fMRI and EEG studies, the magnitude of the multimodal activity was correlated significanlty with the subjects' evaluation of how much the eliciting stimuli were able to capture their attention.

In fact, it is not surprising that brain structures composing the 'pain matrix' such as SII, the insula and the anterior cingulate cortex can be activated by various kinds of sensory stimuli and in various cognitive settings (Ackermann and Riecker, 2004; Augustine, 1996; Bamiou et al., 2003; Botvinick et al., 2005; Bush et al., 2000; Corbetta & Shulman, 2002; Macaluso & Driver, 2005; Uddin & Menon, 2009).

A view of sensory systems as a simple feed-forward relay of filtered sensory information from transducers to cortex is no longer appropriate. Instead, we must consider the statistics of the natural world, plasticity at multiple levels of sensory processing, and the consequences for encoding of sensory information at each stage. According to this, I believe that the understanding of pain processing would largely benefit from an integration of an (I) attention-driven interpretative framework (Legrain et al., 2009a), with several theoretical-epistemological views concerning (II) Bayesian inference

in perception (Friston, 2009), (III) a motivational account of pain monitoring and control (VanDamme et al., 2010; Auvray et al., 2010), along with a (IV) neuroanatomy of homeostatic feeling of body integrity (Craig, 2003b) and self-regulation (Posner et al., 2007).

(I) The experimental evidence in favour of the idea that the 'pain matrix' represents a multimodal processing network strengthen the idea that its activity may be determined by a general mechanism that is not only dependent on stimulus intensity and that is common to any stimulus regardless of sensory modality. This parameter is saliency (Iannetti et al., 2008; Legrain et al., 2009a, 2009b). Stimulus saliency is thought to constantly interact with top-down factors such as level of arousal/vigilance, selective attention and expectation/anticipation (see Chapter 2). A useful example of this interaction is represented by the mismatch negativity phenomenon or MMN. In the auditory modality, the MMN is elicited even when the subject's attention is diverted from the sound. For this reason, it has been suggested that the MMN reflects an automatic form of sensory analysis. To explain this phenomenon, Naatanen proposed that for the purpose of detecting changes in the auditory milieu, the brain automatically forms a short-term memory trace of auditory features which is then continuously compared to the incoming stream of sensory information. It is been argued (see Chapter 4) that changes and violations in regularities (e.g., Yantis and Jonides, 1990; Theeuwes, 1991; Folk, et al., 1992; Sokolov, 1975; Schroger, 1997), are tracked by neurally in-built change and transient detectors which contributes to direct processing resources (possibly through oscillatory phase reset) to the modality channel where is more highly likely the relevant information will come (attended source). This bottom-up mechanism would allow to initiate a new coherent

synchronized activity across unimodal and multimodal regions. All the saliency detectors, built to isolate and extract local physical dimensions by which a particular input contrasts from its neighbours (Itti and Koch, 2001), represent neural mechanism by which selective attention is captured and oriented towards the most relevant aspects of the exogenous/endogenous enviromnment in order to give them priority for processing, to improve their evaluation and to prompt action (Corbetta and Schulman, 2002; Desimone and Duncan, 1995; Egeth and Yantis, 1997; Schröger, 1997).

(II) However, to do this saliency detectors are to be interfaced with a bulk of other information related to the organism needs and goals, contextual appraisal, memories, and the level of cognitive-affective activation. According to the empirical Bayes perspective on perceptual inference (Friston, 2005; Friston, 2009) all these factors contribute to generate implicit expectations and anticipations (determining the top-down allocation of attention). This theoretical approach suggests that the role of backward connections (e.g., from ACC and AIC) is to provide contextual guidance to lower levels (SI and SII) through a prediction of the lower level's inputs. When this prediction is incomplete or incompatible with the lower areas input, a prediction error is generated that engenders changes in the area above until reconciliation. When (and only when) the bottom-up driving inputs are in accord with top-down predictions, error is suppressed and a consensus between the prediction and the actual input is established. This model would posit that early evoked responses such as N1 could be understood in terms of a failure to suppress prediction error when the peripheral salient information is incongruent with the global context, established by the surround. An example of this mechanism can be observed in the processing of

compound stimuli that have local and global attributes (e.g. an ensemble of L shaped stimuli, arranged to form an H). The posterior N2 visual evoked potential is enlarged when the incongruence between global and local letters is detected (Han and He, 2003). This result may be the electrophysiological correlate of the well known global precedence effect (faster behavioural response to a global attribute relative to local attributes and the slowing of local responses by incongruent global information). Thus the Bayesian minimising error prediction mechanism together with the saliency detectors could successfully explain also other phenomena such as the MMN in the auditory modality. If the MMN was observed in the nociceptive modality then there would be room for extending this theoretical framework to pain perception too.

(III) The cybernetics of neural communication is a fundamental component in a general theory of pain representation in the brain. Nevertheless, in order to understand the meaning of pain in real life and specially in clinical conditions, we need a phenomenological account that would attempt to address the reason why of pain in a human being. Everybody will confirm that pain is experienced as 'occurring to us' rather than as something which is intentionally pursued. The evaluation of threat to bodily tissues is often outside of our deliberate awareness and intentional control, and can be interpreted as a conscious manifestation of a preconscious evaluation of the potential danger to tissue (Moseley and Arntz, 2007). The identification of pain's most prominent qualitative property with a motivational force is is consistent with evolutionary considerations. It is highly adaptive for biological organisms to be motivated to act in ways that prevent further bodily damage. Adaptation gets even better if this motive is felt with the force of compulsion: If the organism could only not feel it in particular circumstances (such as

stress-induced analgesia, in which not feeling pain is more efficient than feeling it). The specification of a painful experience as linked to a compelling motivation to act might throw light on other case-limit phenomena, as the disappearance of phantom-limb pain. Patients who have had a limb amputated sometimes report being subjectively able to control the movements of their phantom. It is cristal-clear tha the causes of stress-induced analgesia and phantom-limb pain disappearance cannot be found only in the salient bottom-up characteristics of pain context, but they should be rather tracked at the level of the individual unintentional and intentional goals. Indeed, it is possible that attentional processing of pain is less prioritized when competing demands are associated with important or highly valued goals. Future research should focus on investigating the attentional competition of affective-cognitive tasks with real-life adaptive pain control/avoidance tasks. This might be particularly useful in understanding brain and behavioral dynamics of patients suffering from chronic pain.

(IV) The motivational account of pain processing requires to be grounded on a general anatomo-functional framework. It could be identified in the cortical interoceptive homeostatic integration system related to pain, temperature, itch, sensual touch and other bodily feelings, that contributes to determine a representation of the self, the main feature which distinguishes humans from non-human primates. This model (Craig, 2009) states that neural substrates of homeostatic emotions are coupled to the AIC, while affective motivations are thought to be engendered in the ACC. In most of the studies on pain perception, the AIC and the ACC are jointly activated, consistent with the idea that they serve as complementary limbic sensory and motor regions that work together, similar to the somatosensory and motor cortices. The role of AIC would be

essential for awareness on the basis of its afferent representation of the 'feelings' from the body, and the role of ACC would be essential for the initiation of behaviors. The emerging evidence from imaging studies that volitional cortical control in humans can directly modify homeostatic integration and the substrate of the feeling self (Frith et al., 1999; Ramautar et al., 2006; Dosenbach et al., 2007; Brass and Haggard, 2007) signifies the fundamental role of this interoceptive system in human consciousness. In particular, the role of insula as a multisensory region, in which perceptual information from different senses converges (Calvert, 2001), agrees with its putative role in participating to salience and change detection. Indeed, recruitment of the insula has been reported in audio-visual integration in communication sound processing (Remedios et al., 2009), and auditory-visual matching (Hadjikhani and Roland, 1998; Bamiou et al., 2003; Banati et al., 2000). On the other hand, the ACC is thought to play an important role in attentional control and self-regulation (Devinsky et al., 1995; Davis, et al., 2000; Botvinick, et al., 2001; see also Posner et al., 2007 for a review). The ACC is known to increase activation during performance of tasks that require subjects to selectively attend or inhibit response to a particular stimulus, and to orient attention to an unexpected or novel stimuli (Posner and Dehaene, 1994; Peterson et al., 1999; Bush et al., 2000). In agreement with these data are the studies by Downar et al. (2000, 2002) which identified a number of cortical areas sensitive to stimulus saliency. In the author's opinion these areas would constitute a "multimodal network for involuntary attention to events in the sensory environment". Interestingly, this network included all brain regions (e.g., ACC, bilateral operculoinsular cortices) that are commonly considered to contribute to scalp LEPs.

5 Conclusive remarks

A renewed concept of 'pain matrix' is based on its function of potential threat detector and action planner, in order to provide the integrity of the body.

Essentially, there is no reason why these mechanisms would not be involved in detecting non-nociceptive salient events. However, as compared to other sensory modalities, the nociceptive system could be more specifically involved in salience detection. In fact, because of their high threshold, peripheral nociceptors may be view as cutaneous receptors which react only to high-intensity, and hence, salient somatosensory stimuli (Belmonte and Vianna, 2008).

The interpretation of pain as homeostatic-motivational force naturally carries us to consider the 'pain matrix' not as a sensory-specific cortical network but rather as an action-specific network, representing the activity by which the individual identifies and responds purposefully to an immediate threat inside or outside of the body.

Furthermore, according to Wall (1995) it would be "*an act of faith to continue searching the brain [...] for some still-undiscovered nest of cells whose activity reliably triggers pain. The alternative [...] is to search for a temporal and spatial pattern of relative activity in sets of neurons that constitutes the signal pattern for pain or for touch*". Actually, this is the reason why the concept of a '*neuromatrix*' was originally introduced by Melzack (1990). Melzack's neuromatrix was defined as a widespread ensemble of neurons whose activity results in the feeling of the "*body-self*". This network integrates different sources of input in order to produce output patterns labelled "*neurosignatures*" (Melzack, 1990). Crucially, pain represents only one of the possible perceptual output patterns, i.e. one of the many neurosignatures that can be generated by the neuromatrix.

Therefore, it is conceivable that similar if not identical patterns (at least at the macroscopic level of fMRI or scalp EEG), can be generated and give rise to a comparable feeling of imminent threat for the body (Melzack, 2001).

Appendix

Personal Pubblications

Valentini E., Curcio G., Moroni F., Ferrara M., De Gennaro L., Bertini M. Neurophysiological effects of mobile phone electromagnetic fields on humans: a comprehensive review. Review. Bioelectromagnetics, 2007; Sep, 28(6):415-32.

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