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Behavioral and neural correlates of pain-related language

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GENERAL INTRODUCTION

The aim of this doctoral research project is to investigate the psycholinguistic, behavioural and neural correlates of pain-related language in healthy subjects. Specifically, we employed psycholinguistic, behavioural and brain imaging approaches in order to study (1) how pain-related language is semantically structured and organized, (2) how reading pain-related words affects the aversive motor response and (3) how reading pain-related words modulates brain activity compared to noxious stimuli. In the present dissertation we will discuss data from the psycholinguistic study and the behavioural experiments. Data from the neuroimaging experiment are still under analysis and will not be reported.

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Bonica, 1979; Merskey, 1964). The IASP definition reveals that pain is not a mere physical sensation, but it is the subjective result of sensory-discriminative, motivational-affective, and cognitive-evaluative dimensions. These dimensions are represented in separate nodes of a complex neural network referred to as the "pain matrix" (Avenanti & Aglioti, 2006; Price, 2000).

As a subjective experience, pain perception may be modulated by psychological variables such as cognitive and emotional states (Friederich et al., 2001; Johnson et al., 1991; Keltner et al., 2006; Miltner et al., 1999; Miltner et al., 1989; Price, 2000; Rainville et al., 2005) as well as more complex experiences like pain anticipation and empathy, which incorporate both emotional and cognitive factors (Anelli et al., 2012; Apkarian et al., 2005; Melzack, 1999; Morrison et al., 2007). These psychological variables and complex experiences may modulate pain perception for better or for worse, i.e., may decrease pain

perception or increase it. Moreover, a number of different stimuli, when associated with pain, e.g., faces, pictures and videos, can activate the pain matrix, or part of it, even in absence of a noxious peripheral stimulation. Only a few studies have employed words related to pain to investigate their effect on pain perception. Pain-related words were found to alter pain itself and to activate brain structures engaged in the processing of noxious stimuli (Ritter et al., 2016).

Pain is often one of the main complaints of patients. As a subjective experience, its evaluation must be a relevant element in the outcome assessment, which is a critical step to provide good pain management. Indeed, language is a means to create expectation of pain or pain relief. The pain evaluation in clinical setting has been dominated by the paradigm introduced by the McGill Pain Questionnaire (MPQ: Melzack, 1975), a word-based instrument for the multidimensional assessment of pain. The MPQ has been widely used in the research on pain as well and has significantly stimulated a large body of human research and methods of pain evaluation. Nevertheless, its predictive value on pain states remains to be demonstrated (Main, 2016). Moreover, its 78 pain descriptors do not report values for any of the psycholinguistic and emotional variables that are now known to affect comprehension processes.

Pain is a negative affective state. Its aversiveness, i.e., its negative affective-related nature, is important for self-preservation by promoting withdrawal from harmful or potentially harmful stimuli (Navratilova & Porreca, 2014). A fundamental assumption in emotion research is that emotions predispose the organism to act adaptively in a frequently changing environment (Kozlik et al., 2015). Many emotion theories postulate the existence of a motivational orientation, i.e., a link between emotion and action tendencies that prepare the organism to act adaptively. Specifically, positive stimuli were assumed to activate approach motivational circuits, which in turn trigger approach-related behavioral tendencies, whereas negative stimuli, such as pain-related stimuli, should activate aversive motivational circuits, which trigger avoidance-related behavioral tendencies (Kozlik et al., 2015). It is possible that the evolutionary relevance and

the salience of pain-related stimuli could differently affect the avoidance-related behavior compared to negative, pain-unrelated stimuli.

Interestingly, words used to describe physical pain-related experiences are also used to describe social pain, i.e., the unavoidable feeling of pain associated with being socially rejected, excluded or losing those closest to us (Baumeister & Leary, 1995; MacDonald & Leary, 2005; Eisenberger, 2015). From an evolutionary perspective, social bonds are a fundamental need and, like other basic needs, their lack represent a threat to survival and physical safety. Neurochemical, neurophysiological and brain imaging studies support the hypothesis that social pain processing might relay on the same mechanisms that process physical pain and that losing social connections may lead to a painful perception, allowing people to describe this experience with words typically used to report physical pain (e.g., a broken heart, a soul scars). Although such studies have involved the use of a number of different kinds of stimuli to induce social pain, e.g., pictures, memories, painting, no studies about the effects of social pain-related words have been carried out so far.

In the first part of this dissertation, theoretical and empirical background of the experimental questions investigated is described. This introductory part includes three chapters. In the first chapter we provide a description of the pain system, from nociceptors decoding noxious insults to cortical and subcortical processing of pain perception, and of the modulatory effect exerted by nocebo. We also outline the issue of the pain measurement in clinical setting. In the second chapter we review studies about the effect that pain-related words have on pain processing. In the third chapter, we describe what social pain is and why it is thought to relay on pain matrix. In the second part of the dissertation we describe the studies we carried out.

Study 1. The first study was designed to investigate how pain-related language[1] is semantically structured and organized. We employed an online, large-scale survey to collect data about several psycholinguistic and emotional variables that affect the recall of their semantic meaning Our hypothesis was that the semantic content of pain-related language differentiates its psycholinguistic and emotional structure from general emotional language. When it comes to study pain, psycholinguistic and emotional pain-related word databases are available neither in Italian nor in any other languages. This study also aims to fill this gap by creating a dataset of pain-related words with ratings for psycholinguistic and emotional variables available for research purposes. We also provided scores of words' pain-relatedness, i.e., the subjective estimate of the degree to which the word is generally linked to pain semantic domain, as well as the intensity and the unpleasantness they convey. Results showed that the semantic structure of pain-related language is partly different from the semantic structure of generic language, mainly because the modulatory effect of pain-related variables.

The second study includes three behavioural experiments designed to assess approach/avoidance tendencies toward pain-related linguistic stimuli in a healthy population.

Experiment 1. In this experiment we assessed if pain-related words, given their individual saliency and relevance, produced a different patter of results, with larger avoidance responses, than negative pain-unrelated words. We set up the experiment using an object-related reference that allows considering the withdrawal of the hand as avoidance and its movement on as approach. This frame would reproduce the adaptive automatic behavior that individuals experience with noxious stimuli. We asked participants to perform an explicit task to assess if the semantic content of pain words and its evolutionary relevance might affect the response when an explicit evaluation of the valence is required. We recorded the RTs of the movement initiation (release RTs) as well as the time

[1] Please note that from now on, with "pain-related" we will refer to relatedness to both physical and social pain.

requested to perform the complete arm movement (pression RTs). Results showed that pain-relatedness affects movements independently by the motivational orientation and does not trigger automatically approach/avoidance behaviors. Interestingly, social pain words exerted the strongest effect. A negative linear relationship between pain-related variables and RTs performing the movement emerged, regardless the direction of the movement itself.

Experiment 2. This experiment compared the implicit task to the explicit task of the Experiment 1. Participants performed a lexical decision on the same stimuli and with the same paradigm used in Experiment 1. Interestingly, the different, implicit task triggered a congruent approach/avoidance behavior. Again, social pain words exerted the strongest effect. However, pain affects pression RTs in an unspecific manner.

Experiment 3. This experiment involved the use of the Manikin Task in order to disambiguate distance-change (Krieglmeyer et al., 2010) in order to test effects on approach-avoidance responses independently of labeling the motor output in terms of approach-avoidance. Subjects had to move a manikin toward or far away a valenced word and to do it, the manikin must be moved either up or down, dependent by its position related to the word. Data confirm that the Manikin Task allows the stimulus valence to facilitate compatible approach-avoidance responses even though participants had no intention to approach or to avoid and the valence of the response labels was dissociated from the approach-avoidance movement. However, differences between negative, pain-unrelated and pain words do not emerged.

CONTENTS

1. THE PAIN SYSTEM

1.1. Nociceptors decode noxious insults

Nociception, from the Latin *nocere*, to injure, refers to the processing of signals in the central nervous system evoked by noxious stimuli. Nociception is mediated by nociceptors which are peripheral sensory receptors responding selectively to noxious, harmful stimuli, warning when a damaging or a potentially damaging stimulus is applied. Nociceptors, which are constituted by the endings of the axonal peripheral branch of primary sensory neurons, are widely distributed in the skin, deep tissues and viscera and can be activated by mechanical, thermal high-intensity stimuli or by specific chemical substances. Based on the stimulus they are sensitive to, they can be divided into five classes: thermal, mechanical, itch, polymodal and silent nociceptors. What differentiates them from other somatosensory receptors is the simpler morphology of their axon terminations that is just the free nerve ending. This is just one of several anatomical features along the nociceptive pathway that, together, produce a rougher spatial sense for pain than for touch (Grassi et al., 2015; Kandel et al., 2012).

The pain that people usually feel as a consequence of brief tissue damage, as for instance a puncture wound, is named nociceptive or physiological pain, indicating a transient, short-term pain. Persistent, long-term pain is named pathological or clinical pain and is not, or not simply, explainable as a response to tissue damage. Clinical pain is often due to an abnormal nociceptors' activity that may cause sensitization, a condition characterized by the onset of spontaneous activity and/or by an increased responsiveness to their normal or sub threshold afferent inputs and/or an increased duration of their activity after the end of the stimulus (Meyer et al., 1994; Thalhammer & LaMotte, 1982; Woolfe & Salter, 2006). Sensitization is usually associated with clinical conditions such as

hyperalgesia, an exaggerated subjective response to noxious stimuli, and allodynia, a feeling of pain following innocuous stimuli (Grassi et al., 2015; Kandel et al., 2012). Examples of clinical pain are inflammatory pain, which is associated with tissue damage and the infiltration of immune cells (e.g., strain, sprain), and neuropathic pain, which is associated with damage or disease affecting the somatosensory nervous system (e.g., peripheral neuropathy due to trauma, metabolic or neurological diseases, phantom limb pain) (IASP, 2015). The increased responsiveness, if extended in duration, may lead to chronic pain, a complex pathological condition in which pain is constantly perceived.

Nociceptive pain includes an initial sharp pain ("first pain") followed by a more prolonged aching and sometimes burning pain ("second pain"). These two sensations are mediated by two different groups of nociceptive afferent fibers with different conduction velocity: Aδ fibers, small-diameter, thinly myelinated, fast-conducting (5 to 30 m/s), carry information leading to the experience of the first pain whereas C fibers, small-diameter, unmyelinated, slow-conducting (0,5 to 2 m/s) are involved in the second pain (Grassi et al., 2015; Kandel et al., 2012).

Nociceptors may also be subdivided into four categories, based on the stimulus they respond to:

- Mechanical and thermal nociceptors (Aδ and C fibers) responding to mechanical and thermal stimuli, i.e., over 45°C and below 5°C;
- Polymodal nociceptors (C fibers) responding to mechanical, thermal and chemical stimuli;
- Itch nociceptors (C fibers);
- Silent nociceptors (Aδ and C fibers) responding to mechanical and thermal stimuli only in condition of sensitization.

1.2. Second order nociceptors convey information from the spinal cord to superior structures

Nociceptors' cell bodies of both Aδ and C fibers are located in dorsal root ganglia or, in the case of face, in the trigeminal ganglia (Gasser ganglion). Their primary afferent fibers connect with nociceptive interneurons and with projection neurons in the ipsilateral dorsal horn in a highly orderly somatotopic manner. Usually nociceptive fibers endings make synaptic contacts mainly in the corresponding spinal segment, depending on the body district they belong to, and send ascending and descending collaterals ending within a couple of segments above and below. Instead individual visceral nociceptors often terminate in more spinal segments; together with the low number of visceral nociceptors themselves and the thinned-out distribution of their peripheral axonal branch, the extensive spinal distribution of visceral C fibers appears to be responsible for the inability to well-localize visceral pain sensations (Grassi et al., 2015; Kandel et al., 2012).

Based on the differences in cell and fiber composition, the grey matter in each spinal segment is subdivided into 10 laminae or layers, numbered I to X from dorsal to ventral horns. Nociceptors terminate in dorsal horns where they establish synapses with three main classes of second-order neurons: projection neurons, sending information to the brain and local excitatory and inhibitory interneurons, connecting with projection neurons and thereby modulating the information flow. Projection neurons in lamina I receive input directly from myelinated nociceptive fibers (Aδ). Interneurons in laminae II to IV receive inputs from Aδ and C fibers and make excitatory or inhibitory connections to projections neurons in laminae I, IV and V. Neurons in lamina V and their dendrites in laminae III and IV are the main targets of the large myelinated sensory fibers (Aβ) from cutaneous mechanoreceptors and receive direct inputs from Aδ fibers as well. Aδ fibers also innervate motor neurons and interneurons in the ventral spinal cord. Visceral C fibers terminate ipsilaterally in laminae I, II, V and X. Some of them also cross

the midline and terminate in laminae V and X of the contralateral ventral horns (Grassi et al., 2015; Kandel et al., 2012).

Among projection neurons and interneurons, Two types of second-order nociceptors have been identified in projection neurons and interneurons: nociceptive-specific (NS) neurons, which respond only to noxious stimuli, and wide-dynamic-range (WDR) neurons, which respond to mechanical stimuli but increase their discharge when the stimulus intensity reaches a noxious level. Projection nociceptors in lamina V are an example of WDR neurons; indeed, they receive inputs from Aβ (mechanoreceptors) fibers as well as Aδ fibers (nociceptors). Moreover, WDR neurons may receive both visceral and somatic afferent fibers; this convergence may account for the phenomena of referred pain, a condition in which pain from injury to a visceral tissue is perceived as originating from a region of the body surface. Patients with myocardial infarction, for example, frequently report pain from the left arm as well as the chest. When nociceptive afferent fibers from the viscera and nociceptive afferent fibers from specific areas of the skin converge on the same WDR projection neuron, the brain has no way of knowing the origin of the noxious stimulus and mistakenly associates a signal from viscera to a skin area (Grassi et al., 2015; Kandel et al., 2012).

The convergence of nociceptive and non-nociceptive inputs on the same spinal neurons is thought to regulate pain processing, as hypothesized by Ronald Melzack and Patrick Wall (Melzack & Wall, 1965) in their gate-control theory. Here the activation of non-nociceptive sensory neurons closes a "gate" for central transmission of nociceptive signals that can be opened by the activation of nociceptive sensory neurons. In the original and simplest form of the gate-control theory, the interaction between large and small fibers occurs on second-order neurons in the dorsal horn of the spinal cord, e.g., at the first possible site of convergence, but we now know that such interactions can also occur at many supraspinal relay centers. Viewed in a broadest sense, the convergence of tactile and nociceptive inputs provides a plausible explanation for several empirical

observations about the perception of pain: the shaking of the hand that follows a hammer blow or a burn is a reflexive behavior and may alleviate pain by activating large-diameter afferents that suppress the central transmission of noxious stimuli, as well as the tongue pushing on the aching teeth and the massage we apply on the knee immediately after a hit. Nevertheless, the core concept of convergence of different sensory modalities has provided an important basis for the design of new pain therapies (Grassi et al., 2015; Kandel et al., 2012).

1.3. Ascending pathways

Most second-order nociceptors decussate and ascend in the anterolateral quadrant of white matter to reach superior structures giving raise to the anterolateral pathway of the spinal cord. Although multiple ascending pathways are involved in pain processing, five major pathways have been identified in the anterolateral pathway: the spino-thalamic, the spino-reticular, the spino-mesencephalic, the cervico-thalamic and the spino-hypothalamic tracts (Grassi et al., 2015; Kandel et al., 2012).

The spino-thalamic tract is the most prominent ascending nociceptive pathway in the spinal cord and is composed by axons from nociception-specific, thermosensitive and WDR neurons sited in laminae I and V to VII. Electric stimulation of its fibers elicits pain sensation and its ablation results in a deficit in nociceptive and thermal sensation. Spinothalamic tract fibers cross the midline just ventral to the central canal and ascend in the anterolateral white matter before terminating in lateral nuclear group of the thalamus (neo-spino-thalamic tract) and in the medial nuclear group of the thalamus (paleo-spino-thalamic tract). As a result of the decussation of spinothalamic fibers in the spinal cord, noxious and thermal information are transmitted controlaterally.

The spino-reticular tract is constituted by axons of second-order neurons in laminae VII and VIII of ventral horns. It ascends in the ipsilateral anterolateral pathway of the spinal cord and terminates mainly in the reticular formation and the thalamus. The spino-reticulo-thalamic tract is probably involved in the alert reaction and in aversive motor responses that may accompany pain.

The spino-mesencephalic (or spino-parabrachial) tract contains the axons of second-order neurons in laminae I and V. It projects through the anterolateral pathway to the mesencephalic reticular formation, the periaqueductal grey matter and the parabrachial nuclei. Neurons of the parabrachial nucleus project to the amygdala, a key nucleus of the limbic system that regulating emotional states; information transmitted along this tract seems to contribute to the affective component of pain.

The cervico-thalamic tract origins from laminae III and IV crosses the midline and ascends to the midbrain nuclei and in ventro-posterior lateral and posteromedial nuclei of thalamus. Other neurons in laminae III and IV send their axons directly into the dorsal columns and terminate in the cuneate and gracile nuclei of the medulla.

The spino-hypothalamic tract origins from neurons in laminae I, V and VIII and projects to hypothalamic nuclei that serve as an autonomic control centers involved in the regulation of the neuroendocrine and cardiovascular responses that accompany pain syndromes.

1.4. Thalamus nuclei relay nociceptive information to the cerebral cortex

Human brain-imaging studies have revealed consistent cortical and subcortical networks that are activated by pain, involving sensory, limbic and associative regions. One of the first sites in processing nociception is the thalamus. Among all the relay thalamic nuclei, two major subdivisions are

important for the processing of nociceptive information more than the others: the lateral nuclear group and the medial nuclear group (Kenshalo and Willis, 1991; Willis, 1985; Willis and Coggeshall, 2005). The lateral nuclear group includes the ventro-posterior medial, the ventro-posterior lateral and the posterior nuclei and receives inputs from nociception-specific and WDR neurons in laminae I and V of spinothalamic tract. The lateral thalamus is probably involved in processing information about the precise location of an injury, information that is usually brought to consciousness as acute pain. Consistent with this view, neurons in the lateral thalamic nuclei have small receptive fields, matching those of the presynaptic spinal neurons, and project to the primary and secondary somatosensory cortical areas (S1 and S2), which subserve sensory-discriminative functions. The tract terminating in the lateral thalamus is termed neo-spino-thalamic tract because it is most developed in primates. The medial lateral group includes the central lateral nucleus and the intralaminar complex and receives inputs from neurons in laminae VII and VIII. It is termed paleo-spino-thalamic tract because it is the first spinothalamic projection evident in the evolution of mammals. It is also referred as spino-reticulo-thalamic tract because it includes indirect connections through the reticular formation of the brain stem. Although the medial thalamic nuclei are not exclusively involved in processing nociceptive information, they contribute to non-specific arousal system and are thought to be involved in affective-evaluative aspects of pain through projections to the cingulate and frontal cortex.

1.5. Cerebral cortex is involved in the processing of noxious stimuli

Pain is more than nociception; it gives raise to several protective reactions, like alert, emotions, motor and autonomic responses, and is thought to emerge from the activity of a large distributed brain network involved in nociceptive processing often termed the “pain matrix” (Iannetti & Mouraux, 2010; Ingvar, 1999; Tracey, 2005).

Pain processing has long been considered to consist in a relatively simple connection directed to the first somatosensory cortex (Willis, 1985). However, the observation that patients with cerebral lesion involving this area are still able to feel pain casts serious doubts about this idea. More recently, Melzack and Wall (1965) changed the classic view of the pain system proposing the more plastic and integrative model to which we referred above. Since then, the emotional component has been recognized in pain sensation, processed in parallel with the sensorial one by distinct brain structures (Melzack & Casey 1968; see also Albe-Fessard et al. 1985; Backonja 1996; Price 1988). It has become commonly accepted that a pain matrix exists composed by a lateral component, related to sensory-discriminative pain aspects of pain such as quality, duration, location and intensity, and which includes areas such as lateral thalamus, first and second somatosensory cortices (S1 and S2) and posterior insula, and a medial component responsible for affective-evaluative pain aspects, which includes the anterior insula (AI), perigenual anterior cingulate cortex (pACC), mid-cingulate cortex (MCC) and prefrontal cortex (PFC) (Avenanti et al. 2005; Rainville et al. 1997; Vogt et al. 2003). The distinction between the two systems is likely to be a simplification of the networks involved but it helps in grouping brain areas with similar roles in pain perception. Indeed, because different brain regions play a more or less active role depending on intervening factors that involve, for instance, attention, expectation, mood, the pain matrix cannot be considered a static entity.

As brain-imaging techniques have been improved, the brain contribution to pain experience has been further clarified. Since then, brain-imaging studies on pain in response to acute nociceptive stimulation have most frequently reported the activation of S1 and S2, insula, ACC, PFC and thalamus (Apkarian et al., 2005; Bingel & Tracey, 2008; Casey, 2000; Davis, 2000; Duerden & Albanese, 2011; Farrell et al., 2005; Peyron et al., 2000; Price, 2000; Rainville, 2002; Treede et al., 1999). Recently, spinal cord activation in response to acute stimuli has also been described (Summers et al., 2010). Other brain regions, including

supplementary motor area (SMA), posterior parietal cortex (PPC), amygdala, hippocampus, basal ganglia, brainstem (including PAG), cerebellum and areas within the temporal cortices can also be active (Apkarian et al., 2005). Therefore, it is maybe more correct to refer to a "cerebral signature of pain" which is not necessarily represented by the conventional pain matrix (Tracey, 2008).

Primary somatosensory cortex. Earlier neuroimaging data do not provide a clear role for S1 in pain processing (Bushnell et al., 1999). It has been proposed that this inconsistency might be due to the tactile component of the sensory stimuli used in eliciting experimental pain. However, finally more recent and sensitive methods, e.g., studies designed to parse nociceptive activity from general, tactile-related brain activity, have clearly demonstrated that S1 may, indeed, be implicated in pain perception. In recent meta-analyses, Apkarian et al. (2005) and Duerden and Albanese (2011) identified S1 as a region that is activated in most of neuroimaging studies of acute pain. Several imaging studies in humans have found that S1, beyond other cortical areas, shows a somatotopic organization, even finer then the one originally identified (Bingel et al., 2004; Kenshalo et al., 2000), highly aligned with other non-painful somatosensory maps (Mancini et al., 2012; Mancini et al., 2013), and a haemodynamic graded activation in response to the increased intensity of experimental pain stimuli (Coghill et al., 1999; Derbyshire et al., 1997; Moulton et al., 2005; Porro et al., 1998). Interestingly, Rainville et al. (1999) reported that manipulating pain intensity and unpleasantness through hypnosis, S1 response correlated with perceived pain intensity but not with unpleasantness. Together, these findings suggest that S1 is implicated in the sensory-discriminative dimension of pain encoding the location and intensity of a noxious stimulus.

Secondary somatosensory cortex. According to Apkarian et al. (2005) and to Duerden and Albanese (2011), S2 is one of the regions most commonly activated in neuroimaging studies on experimental pain. What is not clear is how S2 reflects various aspects of the pain experience, e.g., its role in pain processing. It is also unclear whether S2 receives nociceptive information from the thalamus

through S1 (Allison et al., 1989; Hari et al., 1993) or directly, in parallel to information being sent to S1 (Liang et al., 2011; Ploner et al, 2006; Pons et al., 1992); evidence from laser-evoked potentials (LEP) and source localization studies seem to confirm this second hypothesizes (Frot et al., 2007; Valentini et al., 2012). Moreover, a nociceptive somatotopic map seems to exist in S2 as well, but not aligned with tactile somatosensory ones (Apkarian et al., 2005; Vogel et al., 2003).

Insula. The insula also has several somatotopic maps for different noxious stimuli and within different subregions (Baumgartner et al., 2010; Brooks et al., 2005; Henderson et al., 2007; Hua et al., 2005). This would prove its involvement in encoding sensory-discriminative components of pain (Craig, 2000); specifically, its posterior portion would encode pain intensity in a graded fashion (Coghill et al., 1999) and its laterality (Bingel et al. 2003; Brooks et al. 2002). Insula has been supposed to play a role in the affective-evaluative pain processing as well (Craig, 2003; Critchley et al. 2004; Seymour et al. 2004; Singer et al. 2004). Specifically, its anterior portion would be the area in which the sensorimotor, emotional, allostatic/homeostatic and cognitive components of pain are integrated (Brooks & Tracey, 2007; Craig, 2010; Critchley, 2004; Critchley et al., 2004; Devinsky et al., 1995; Peyron et al. 2002; Pollatos et al., 2005; Pollatos et al., 2007). Clinical data confirm this hypothesizes: the ablation of fibers that connect this area (e.g., cingulotomy) may alleviate strong emotional and anxious components in drug-resistant chronic pain syndromes. This hypothesis is also based on the convergence of the afferent pathways underlying the sensory-discriminative and the affective-evaluative dimensions of pain to the insula (Treede et al., 1999) and on the fact that its electrophysiological stimulation elicits pain perception (Ostrowsky et al., 2002) whereas its lesion elicits abnormal pain perceptions (Greenspan et al., 1999; Starr et al., 2009). However, because different subregions of insula are activated in many other cases, including gustation, emotion, olfaction, empathy, motor output, language, etc., and because these activations generally overlap with that of pain (Downer et al., 2003; Yarkoni

et al., 2011), insula has been considered a region that encodes behaviourally salient stimuli including pain (Downar et al., 2001; Downar et al., 2002; Downar et al., 2003; Iannetti & Mouraux, 2010; Legrain et al., 2011; Mouraux & Iannetti, 2009; Mouraux et al, 2011).

Cingulate cortex. The cingulate cortex is a large, heterogeneous brain region. Brodmann divided it into an anterior cingulate cortex (ACC) and a posterior cingulate cortex (PCC). Specifically, in Vogt's system, ACC refers to the rostral/ventral portion of the anterior cingulate cortex, whereas the dorsal/posterior section has been called middle cingulate cortex (MCC). These major sections are commonly further divided: MCC into a posterior and an anterior region (pMCC and aMCC, respectively) and ACC into a pregenual and a subgenual region (pACC and sACC, respectively). The different subregions of the cingulate cortex have been implicated in different dimensions of pain, including the affective, cognitive, modulatory and motor dimensions (Vogt & Sikes, 2009). Coghill et al. (1999) demonstrated that MCC shows graded responses to the increasing intensity of noxious stimuli. The area composed by aMCC and pACC seems to play a number of functions (Beckmann et al., 2009). For instance, this region has been identified as a node in the salience network and has been implicated in multimodal salience detection (Davis, 2011; Taylor et al., 2010; Weissman-Fogel et al., 2010), including detection of noxious stimuli (Lee et al., 2009; Mouraux et al., 2011; Wiech et al., 2010). The cingulate cortex has also been implicated in the cognitive and affective processing of pain (Semionwicz & Davis, 2007; Semionwicz & Davis, 2007; Wiech et al., 2008; Wiech & Tracey, 2009), the MCC in action selection and modulation of motor output in response to aversive stimuli (Shackman et al., 2011; Vogt, 2005), the sACC in pain modulation (Bingel & Tracey, 2008) and the pACC and sACC in emotional processing and depression (Etkin et al., 2011; Mayberg et al., 1997; Shackman et al., 2011).

Prefrontal cortex. There is no evidence suggesting that the PFC receives nociceptive information directly from the thalamus; it is more likely that it

receives it indirectly through other nociresponsive brain regions, e.g., the cingulate cortex, insula and the somatosensory cortex (Nieuwenhuys et al., 2008). Interestingly, no EEG or MEG studies reported PFC activation. It is thought that PFC reflects emotional, cognitive and interoceptive components of pain perception (Tracey, 2008) being implicated in the integration of cognitive and motivational dimensions of pain (Woolsey et al., 1979) and, through its connections to antinociceptive brainstem regions, in pain modulation. Evidence for these roles come from a number of studies that have investigated the interaction of pain and cognition of the brain (Baron et al., 1999; Iadarola et al., 1998; Lorenz et al., 2002; Lorenz et al., 2003; Salomons et al., 2004; Seifert & Maihofner, 2007; Valet et al., 2004;Wiech et al., 2006; Wager et al., 2004).

Cortical and subcortical motor regions. Motor regions are activated in acute pain in healthy controls, but less reliably than the aforementioned brain regions (Apkarian et al., 2005). Their activation has not always been observed during experimental pain induction (Halkjaer et al., 2006; Romaniello et al., 2000). It is believed that motor regions serve two purposes: to orient the body toward the source of pain and to initiate nocifensive behaviour (e.g., avoid the stimulus). The basal ganglia are a set of subcortical nuclei associated with motor function, but because they receive input from many nociresponsive regions (Nieuwenhuys et al., 2008), it has been proposed that they may have other functions as well (Haber & Knutson, 2009). Neuroimaging studies often have found activity in basal ganglia during experimental pain (Borsook et al., 2010). It is tempting to hypothesize that the basal ganglia are involved in determining a behavioural response to pain as a site of convergence of the different dimensions of pain (i.e., pain integration) (Borsook et al., 2010; Starr et al., 2011).

1.6. Cognition and emotion influence pain perception differently

Cognition and emotion are potent sources of pain modulation. The most extreme example of their effects has been documented by Beecher (Beecher, 1946) about excruciating damages without pain occurring in soldiers wounded during battles. Their effects on pain perception, for better or worse, it is not just a report bias but can be observed in neural activations as well. However, cognition and emotion are thought to affect pain perception through different modulatory ascending and descending systems, as has emerged from experimental studies on attention, mood and valenced stimuli (Villemure et al., 2003; Loggia et al., 2008; Roy et al., 2011). Attention seems to potentially intervene in modulating the intensity of pain and emotion in modulating the pain unpleasantness. This confirms clinical studies on women's VAS ratings of their childbirth experiences showing that affective VAS but not sensory VAS ratings of pain were considerably reduced when women in labor focused on the birth of the child as compared to when they focused on their pain (Price et al., 1987). Indeed, focusing on perceived pain increases its intensity but not its unpleasantness, whereas a negative mood increases its unpleasantness but not its intensity (Villemure et al., 2003; Loggia et al., 2008). Also the relation between pain evaluation and spinal reflex to nociceptive stimuli shows the dissociation between the modulatory effect of attention and emotion: whereas emotional valence influences pain ratings and a spinal nociceptive reflex in the same direction, distraction reduces pain but increases the reflex (Roy et al., 2011). Brain-imaging studies have revealed that varying the focus of the attention while controlling for the emotional state modulates the activity in S1 and in the insula (Villemure et al., 2009; Bushnell et al., 1999; Ploner et al., 2011; Dunckley et al., 2007). Similar studies that did not control for emotional state, varying arousal and/or negative emotions, have shown a modulation also in ACC, whose activity during pain processing seems to be increased by negative primes such as unpleasant music or odours (Berna et al., 2010; Phillips et al., 2003; Ploner et al., 2011; Roy et al., 2009; Valet et al., 2004). Therefore attention seems to intervene in modulating the intensity of pain and the

pain-evoked activity in S1 and insula, whereas emotion in modulating the unpleasantness of pain and the activity of ACC. The association of S1 and insula with cognition and pain intensity and the association of ACC with emotions and pain unpleasantness are consistent with the roles of these regions in pain perception.

However nociception is neither necessary nor sufficient to induce pain, despite being the most frequent cause of this condition. Complex experiences like empathy that incorporate both emotional and cognitive factors, have been found to alter the ways in which individuals feel pain and even perceive pain in absence of a noxious stimulus. These experiences are named *nocebo*.

The ability to understand others' pain experience may be fundamental to social cohesion (Preston & De Waal, 2002; Singer et al., 2004; Williams, 2002). Indeed, the merely observing, thinking about, or inferring that someone else is in pain may allow to the emergence of physical pain (Betti & Aglioti, 2016). This phenomenon known as *synesthesia* for pain (Fitzgibbon et al., 2010) and it has been described following trauma (Bradshaw and Mattingley, 2001) as well as in healthy subjects (Osborn and Derbyshire, 2010). Evidence suggests the existence of common neural substrates that map the perception of pain in self and in others (Betti & Aglioti, 2016). An alternatively hypothesis is that this common neural substrates might reflect neural processes associated with the salience of valenced stimuli that required the implementation of motor responses appropriate to specific circumstances (e.g., escape reactions). Several neuroimaging studies indicate that humans' neural system may recognize others' affective states primarily consisting of the anterior AI/IFG, ACC and MCC (e.g., Fan et al., 2011; Morrison et al., 2004; Morrison et al., 2007a; Singer et al., 2004). Betti and Aglioti (2016) reported single-neuron clinical cases of patients with cingulotomy provided direct evidence for the existence of a pain-related neuron in the dorsal portion of ACC (Broadmann area 24b) responding both to noxious stimulation and to the observation of the same stimulation delivered to the experimenter (Hutchison et al., 1999). Studies involving fMRI study supported the idea that the

empathic reactivity involves the affective-emotional node of the pain matrix when empathy is evoked through a number off different paradigms such as the observation of pictures depicting ordinary painful situations (Jackson et al., 2005), videos depicting hands being pricked by needles (Morrison et al., 2004) or faces expressing pain (Botvinick et al., 2005; Saarela et al., 2007). However, recent studies found activation in the sensory node of the pain matrix as well (S1, S2, but also motor regions) during the observation of others' pain (Avenanti et al., 2005; Avenanti et al., 2009; Avenanti et al., 2006; Aziz-Zadeh et al., 2012; Benuzzi et al., 2008; Betti et al., 2009; Bufalari et al., 2007; Cheng et al., 2008; Jackson et al., 2006; Valentini et al., 2012). Although both affective and sensorimotor pathways are called into action during empathy for pain, the specific involvement of the somatosensory cortex in this process is still questioned (Betti & Avenanti, 2016).

1.7. The evaluation of pain

Pain often is a major problem for many patients; therefore its evaluation is a key element in pain management and control (Anderson et al., 2000).

Although much can be inferred from measures of pain derived for instance by analyses of facial expressions, motor impairments, physiological indexes, they may be not sufficient to assess pain in the light of the nonlinear relation between the noxious insult and the perceived pain. Self-reports remain the standard by which all other measures are compared to and an important source of information from a clinical as well as a research perspective. Visual Analogue Scale (VAS; Woodforde & Merskey, 1971) and Numerical Rating Scale (NRS) have been developed to facilitate patient in explaining the multidimensional nature of their pain experience.

Visual Analogue Scale. The VAS is a simple and frequently used tool that allows patient to describe the intensity of the pain experience. It originated from

continuous visual analogue scales developed in psychology to measure well-being (Freyd, 1923; Aitken, 1969; Clarke & Spear 1964). The VAS consists, for instance, of a 10-centimeters horizontal line with the end-points defined by labels such as No pain at all on the left and Worst pain imaginable on the right. The patient is asked to mark his/her pain level on the line between the two endpoints. The score is determined by measuring the distance in millimetres between the left endpoint (Not pain at all) and the patient's mark, providing a range of scores from 0 to 100. The VAS is self-completed by the respondent in less than one minute. Several studies have shown that the VAS is sensitive to treatment effects (Jensen et al., 1986; Joyce et al., 1975; Kremer et al., 1981; Seymour et al., 1985) and positively correlates with other self-reporting measures of pain intensity (Jensen et al., 1986; Kremer et al., 1981). Limitations of the pain VAS are that it cannot be administered by telephone, limiting its use in research and scoring, at least when not in on a digital support, it is time-consuming and susceptible to measurement errors (Hawker et al., 2011; Jensen et al, 1996). Moreover, elderly with cognitive impairment may have difficulty in understanding and therefore completing the scale, so supervision during completion is recommended (Closs et al., 2004).

Numerical Rating Scale. The NRS is another simple and frequently used tool for pain intensity assessment. The NRS is a segmented numeric version of the VAS composed by a horizontal line with extreme labels and intermediate numbers, as a Likert scale. The anchor-terms describing pain severity are usually No pain at all: score of 0, on the left extreme, and Worst pain imaginable: score of 10, on the right extreme (Downie et al., 1968), and by intermediate numbers, for a total of 11 items (Farrar et al., 2001), even if 7-point and 5-point versions of the scale exist as well. The NRS can be administered verbally (therefore also by telephone) or graphically for self-completion in less than one minute. Respondents are asked to circle the number that fits best their pain intensity and this number represents the score. In contrast to the VAS, only the numbers are valuable answers, thus allowing a less sensitive distinction of pain levels.

Numerical Rating Scales are highly correlated with other pain assessment tools (Jensen et al., 1986; Kremer et al., 1981). Ease of use and good patient compliance have also been reported (Closs et al., 2004; Farrar et al., 2001). The advantages of NRSover VAS are the ability to be administered both in writing as well as verbally, therefore by telephone (Von Korff et al., 2000) and its simplicity of scoring, even if VAS is considered preferable to discontinuous methods (Carlsson, 1982).

In general, VAS and NRS may be used to assess the pain unpleasantness as well. However, to describe our own experience of pain we use words; traditional visual and numerical scales may not account for the multidimensionality of pain experience, according to Melzack (Melzack, 2005).

McGill Pain Questionnaire. In 1975, ten years later his gate-control theory, Melzack introduced the McGill Pain Questionnaire ("MPQ"; Melzack, 1975), a word-based instrument widely used to provide qualitative and quantitative measures of clinical pain. MPQ measures the sensory, affective and evaluative aspects of pain as well as pain intensity in adults (Burckhardt, 1984; Melzack, 1975). The scale consists of 78 pain descriptors divided into four subscales respectively evaluating the sensory (with further 10 subclasses), affective (with further 5 subclasses), evaluative (with further one subclass) and miscellaneous (with further 4 subclasses) aspects of pain, plus a 1-item pain intensity scale, a numeric-verbal combination that indicates overall pain intensity and includes six levels: none (0), mild (1), discomforting (2), distressing (3), horrible (4), and excruciating (5). The score associated with each descriptor is based on its position or rank order within the subclass word set. The MPQ is interviewer-administrated using paper and pencil and its completion may take up to 20 minutes. For each subclass of words, the respondent is instructed to select one word that fits their present pain, if it exists. Scoring of the MPQ takes 2 or 3 minutes and may be interpreted both in terms of quantity of pain, as evidenced by the number of words used and the rank values of the words, as well as of the quality of pain, as evidenced by the particular words that are chosen. The

innovation of the MPQ is reflected by its several translations 44 in total. Richard Gracely (Gracely, 2016) compares the pain to colors: if a single pain dimension is a variety of grey shades, MPQ and its subsequent shorter versions ("SF-MPQ", Melzack, 1987; "SF-MPQ-2"; Dworkin et al., 2009) provide a pile of pain color samples with many tints. Similar tints are grouped into categories and increasing color saturation provides a measure of magnitude for that shade. Discriminating between pain qualities is the plus-feature of the MPQs and both clinical practice and research on pain mechanisms benefit of it.

2. THE LINGUISTICALLY-DRIVEN ACTIVATION OF PAIN

2.1. Pain-related language modulates pain

"Sticks and stones can break my bones but worlds will never hurt me", says an English stock response children's rhyme to verbal bullying and name-calling, reported by the victim when ignoring the taunt. Beyond its metaphorical meaning, the effect of words on pain perception has been recently became a topic of interest. Researchers have found that words, when related to the semantic context of pain, may indeed act as a nocebo. Specifically, pain-related words may activate part of the pain matrix in the absence of a noxious stimulus (Gu and Han, 2007; Osaka et al., 2004; Richter et al., 2010) as well as modulate the pain perception, especially in patients with chronic pain (Richter et al., 2014).

The role of language in modulating pain perception is of fundamental importance from a clinical perspective. According to Brown (Brown et al., 2004), persistent and chronic pains may arise consequently to the continuous exposure of pain-related semantic information. Several sources for this continuous exposure have been hypothesized, mostly belonging to the pain-related illness behaviour, e.g., worrying and ruminating about one's own painful experience, being questioning about one's own pain from family and friends, being repeatedly exposed to pain-related report from hospital, physicians, and so on (Swannell et a., 2016). Considering the attentional bias that leads individuals with pain to increase attention to pain-related semantic material in the environment (Wilson et al., 2009), the relation between pain and pain-related language in patients with a condition of pain may led to a vicious, unconscious cycle.

The use (including the timing and the quantity) of negative words related to the output of a pain therapy from nurses to hysterectomy patients significantly

affected the output of patient-controlled analgesia compared to positive words, leading to the cortisol therapy failure and the need of further release of analgesic (Wang et al., 2008).

Two theoretical frameworks, not necessarily mutually exclusive, may account for the role of pain-related language on pain processing. According to the Embodied cognition framework (e.g., Gallese & Lakoff, 2005; Gibbs, 2006; Gibbs et al., 2004; Wilson & Gibbs, 2007), pain-related language could rely on sensorimotor simulation. This view predicts that processing a word activates the sensorimotor system typically associated with experiencing it. Therefore, during exposure to pain-related language, we simulate what we know about its meaning, drawing on past situations in which we have, directly or indirectly, experienced it and then we use that knowledge to map onto the semantic meaning of the word. On the other side, according to Hebbian cell assembly model (Hebb, 1949; Braitenberg & Schüz, 1991; Birbaumer et al., 1995; Pulvermuller, 2013), whenever we experience pain, its semantic and emotional representations are activated simultaneously with neural structures that process noxious events and constitute the experience of pain (Hebb, 1949; Ritter et al., 2016). Therefore, stimuli that are associated with the experience of pain might excite pain-related cell assemblies and consequently create a painful experience even in the absence of a painful stimulation.

In the last two decades, only a few studies investigated the role of pain-related words as a nocebo. The first approach to the investigation of this issue involved measuring laser-evoked potential (LEP) in an event-related potentials paradigm. Consequently this approach has been replaced by studies using the fMRI on both health subjects and patients.

Birbaumer and colleagues (1997) found that health control, prechronic pain patients and chronic pain patients detected the same number of pain-related words when subliminally presented compared with pain-related or neutral words. However, the two groups of patients showed an enhanced N100, and the group

with chronic pain an enhanced N200, that appear to be, together with P300, closely associated with the cognitive processes of perception and selective attention. This is congruent with the assumption that patients pay more attention to pain-related stimuli even when subliminally presented and not consciously recognized. Indeed, when receiving painful laser-heat stimulation, migraine patients and healthy controls showed larger LEP P300 amplitudes when primed with pain-related semantic stimuli compared to neutral semantic (Dillmann et al., 2000; Weiss et al., 2003). Moreover, migraine patients showed a stronger effect for affective than for somatosensory pain-related words. Similarly, enhanced positive event-related potentials to pain related words, especially when conveying the affective aspects of pain, were found in two EEG studies with chronic pain patients and patients with depression (Nikendei et al., 2005; Sitges et al., 2007).

These data together support the notion of abnormal information processing in chronic pain patients suggesting that pain-related semantic primes might pre-activate neural networks subserving pain memory and pain processing and that

2.2. fMRI studies on healthy subjects

Studies using the fMRI to investigate the neural correlates of processing pain-related language are a handful. Osaka et al. (2004) investigated the relation between unpleasantness of semantic pain-related stimuli and the affective component of pain using onomatopoeias. The role of onomatopoeia in the Japanese language is very common and important. Through onomatopoeias people may express feelings and thoughts with a salient affective component because of their power to project vivid imaginaries (Chang, 1990). Acoustically presented pain-related onomatopoeias are well suited to convey the unpleasantness of the affective dimension of pain. Researchers have found that listening and forming related mental images of pain-evoking onomatopoeias compared to non-sense syllables activate the left dorsal portion of ACC. The ACC

is involved in the attention-switching activity that allows controlling both the affective and cognitive component of pain. The dorsal portion of ACC has been considered the cognitive division of ACC, whereas its ventral portion has been considered the affective division of ACC (Bush et al., 2000; Rainville et al., 1997). Some studies reported that the dorsal ACC is activated during cognitive conflicts (Bush et al., 2000) and when performing high-load WM dual-tasks in which central executive attentional control is required (Osaka et al., 2003; Osaka et al., 2004). Osaka proposed that the reason why dorsal ACC, but not ventral ACC, was activated during the task could be that onomatopoeias have a salient affective component. Moreover, the authors found activation in the left ventrolateral prefrontal cortex (VLPFC). Because inferior frontal gyrus activation occurred next to Broca's area, it could represent the semantic retrieval of pain information from long-term memory from one's previous pain experiences. The circuit dorsal ACC-VLPFC may likely serve in generating imaginary pain closely regulated by the attention-controller system. Activations in the superior parietal cortex, thalamus and cerebellum were also found. Interestingly their activation is typically reported in response to physical pain stimulation (Hardcastle, 1999).

Gu and Han (2007) have investigated whether the pain matrix in general can also be activated by pain conveyed by semantically expressed actions. Starting from the observation that empathy for pain (Avenanti et al., 2006; Bufalari et al., 2007; Gu & Han, 2007; Jackson et al., 2005; Jackson et al., 2006; Singer et al., 2004) activates the ACC and the insula, Gu and Han hypothesized that reading about pain, as watching painful pictures, may generate empathic responses mediated by the pain matrix. Moreover, they tested whether this might be obtained only with explicit task (rating pain intensity) or also with an implicit task (counting Chinese ideograms). Interestingly, and differently from Osaka's study, they found activation in the S2, PFC and right anterior insula, but not in the ACC during the rating task in contrast to the counting task. Gu and Han's results suggested processing pain-related words might engage parts of both the sensory-discriminative and affective-motivational components of the pain matrix.

Moreover, authors proposed that the non-activation of ACC could be related to the lower salience of their stimuli compared to Osaka's onomatopoeia. It is also possible that verbs are more grounded on somatosensory areas than onomatopoeias (James & Maouene, 2009; Wellsby & Pexman, 2014). SII seems to be activated by a bottom-up painful stimulation. A possibility is that rating pain intensity of painful actions linguistically described could initially induce a high-level cognitive and emotional processing of pain in brain areas such as the insula and the PFC (Kong et al., 2006), then it could produce a feedback from these brain areas that modulates the SII activity. This hypothesis would be consistent with other studies reporting a top-down modulation of the somatosensory cortex activity. For example, Porro et al. (2002; 2003) found that the SI and the motor cortex, together with the insula and PFC, are activated by pain anticipation before that nociceptive stimuli are applied.

Similarly, increased activation within left dorsal ACC (BA32 Broadmann's area) and left inferior frontal cortex was found by Kelly et al. (2007) when retrieving pain-related memories in response to pain-related words compared to non-painful memories in response to pain-unrelated words. Similarly to Osaka et al., (2004), they hypothesised that activation of dorsal ACC may occur in the absence of peripheral sensory stimulation, but in contrast with them they identified in recalling painful episodes cued by pain-related words the source of such activation (Whalen et al., 1998). The task used by Osaka and colleagues did not explicitly require participants to recall memories; nevertheless it can have influenced subjects' memories. Activations of both inferior frontal gyrus and dorsal ACC have been found in experiments both with and without noxious stimulation (Maihofner et al., 2005; Osaka et al., 2004; Peyron et al., 2000; Derbyshire et al., 2004). These studies showed that dorsal ACC activation might be elicited through physically induced pain as well as mentally generated pain, through hypnoses, imagination or memory retrieval. The different brain response to pain-related and pain-unrelated words in the left inferior frontal gyrus may well

reflect the semantic processing of the words, whereas the activation of the dorsal ACC can mediate the pain component of the retrieved pain memories.

Weiss and colleagues have carried out several studies on the relation between pain-related words and pain processing. Whereas previous studies had a more exploratory approach, the work of Weiss and colleagues represents the first systematic attempt to investigate this issue. Their first work (Richter et al., 2010) tested whether the involvement of the pain matrix in processing pain-related semantic stimuli is attributable to the semantic meaning of the words or if it reflects a general effect of negative valence or greater arousal. Previous studies have shown that implicit processing of pain-related non-verbal stimuli (e.g., faces) affects the reaction times and activates the pain matrix (Andersson & Haldrup, 2003; Simon et al., 2006). Therefore, they wondered whether the pain matrix activation during the presentation of pain-related words was based on an explicit or implicit processing mode. To address these questions, they presented pain descriptors as well as negative pain-unrelated, neutral and positive words. A novelty in this study is represented by the control on verbal stimuli that were balanced for length and frequency as well as valence, arousal and pain-relatedness. Subjects went through two experimental conditions: in the imagination condition, they had to silently read the word and imagine a situation or a sensation associated to it, whereas in the counting condition, they had to silently count the vowels of the word and choose the correct response. In the imagination condition, they found increased activation within dorsolateral prefrontal cortex (DLPFC), inferior parietal gyri (IPG), and precuneus when processing pain-related words compared to other words. However, in the distraction condition, they found a decrease in activation within dACC and an increase in activation in sACC when processing pain-related words compared to other words. The comparison between the two conditions allowed authors to conclude that neural activation to pain-related words are strongly modulated by the attention demands of the task. Moreover, this activation cannot be explained by words' valence and arousal, but by their pain-relevance. Precuneus does not

contribute to the standard representation of pain in the brain, but recent research has demonstrated its role in pain sensitivity (Goffaux et al., 2014). Imagination task on pain-related words compared to other words strongly recruited the DLPFC and IPG. Therefore, their semantic content may have activated the attentional system. Gu and Han described a recruitment of the medial PFC, a sign of pain-specific allocation of attention resources (Gu & Han, 2007). Osaka et al. found activation within VLPFC and interpreted this in terms of attention-driven semantic retrieval and of generation of imagined pain (Osaka et al., 2004). This is confirmed by the fact that the meaning of pain-related words seems to produce a more consistent effect within attention-related regions as compared to pain-unrelated words, regardless of the arousal or valence of words (Kensinger & Schacter, 2006). Concerning the distraction task, the sACC activation and dACC deactivation observed during presentation of pain-related words might reflect the inhibition of salient pain-relevant information during the distraction task. Indeed the dACC is considered as the cognitive component of ACC that modulates attention and executive functions and monitors competition during task performance, whereas vACC/pACC is considered as an affective component involved in assessing the salience of emotional information (Bush et al., 2000).

The same experiment from Richter (Richter et al., 2010) has been replicated (Eck et al., 2011) on migraine patients, to assess if the presence of pain condition may affect the results. In the imagination condition, patients showed more pronounced pain-related activation in affective pain-related regions compared to health subjects. In the distraction task, no differential engagement of single brain structures in response to pain-related words compared to other words was found between groups. However, authors found an involvement of both the affective and the sensory components of pain in migraine patients when processing pain-related words, enhanced by past chronic pain experience.