Chapter 6
The Contribution of New Technological Breakthroughs to the Neuroscientific Research of Pain Communication

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> "You pain, my brain, I care" - EEVEE in the near future.

Abstract Pain is a universal experience of human distress but paradoxically eminently private. One can infer the level of pain in others based on varying sources of information making it difficult to accurately and systematically evaluate the actual experience of a person in pain. Yet, this is one of many difficult tasks healthcare professionals face every day. Assessing pain in others is further hindered by the fact that caregivers are humans, and humans cannot easily remain indifferent to other people's distress, and tend to avoid it. From the patient's point of view, available means of pain expression can be reduced, but they can also be voluntarily restricted when facing for instance distrustful professionals. From the healthcare professional's point of view, facing pain on a continual basis and communicating one's understanding and empathy can be difficult. Ultimately, beyond the individual feeling pain and another individual decoding the pain message, the patient-caregiver interaction itself crystallizes the complex phenomenon of pain communication. In this chapter, we discuss the perception of pain and its communication from the perspective of neuroscience. Firstly, we briefly review recent imaging studies on the cerebral responses to pain and pain in others. We point out neuroimaging evidence showing the varying involvement of regions of the "pain matrix" in the process of other's pain perception (also called pain empathy). Secondly, we discuss current neurocognitive models which provide a first step towards understanding pain communication at the level of the central nervous system, although they fall short at characterizing the interactive mechanisms

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S. van Rysewyk (ed.), *Meanings of Pain*,
DOI 10.1007/978-3-319-49022-9_6

underlying this complex process, as the traditional one-brain approach used to date has focused on either the observer or the person in pain. We also review more recent neuroimaging studies on the phenomena of interpersonal synchrony. We argue that examining both individuals of a dyad together, and their interactions, is becoming necessary to address pain communication fully. Finally, we present new perspectives in the study of pain communication through the field of affective computing, which is making steady progress towards designing machines capable of detecting and reacting to behavioural and physiological markers of human emotions, including pain. We propose that the use of avatars offers a highly controllable experimental set-up to explore the mechanism underlying pain empathy and pain communication from both the patient's and the caregiver's perspective, as well as their interactions. Beyond designing intelligent and empathic tools to detect patients' experiences, these research initiatives may help promote empathic behaviour and thus meet the challenge of preserving our humanness in the contexts of pain and suffering.

1 Introduction

Pain is a universal experience of human distress, which stems from the interaction of different sensory, affective, cognitive and social features. The communication of this complex experience is especially challenging due to its subjective nature. In general, one can only infer the level of pain in others based on bodily information (e.g. facial expressions, posture) or verbal report and paralinguistic features (e.g. crying, moaning, screaming), making it difficult to accurately assess the actual experience of a person in pain. Yet, pain assessment is only one of the many difficult tasks healthcare professionals face every day. Unfortunately, it is now acknowledged that caregivers, including physicians and nurses, often fail to adequately estimate and treat patients' pain, especially people with communication limitations such as children, people with disabilities, or seniors (for a review, see Prkachin et al. 2007).

In recent decades, this unfortunate fact was paralleled by a widespread reflection aiming at broadening the narrow biomedical model of pain to include essential psychological and social dimensions. This biopsychosocial perspective of pain has inspired naturalistic pain communication models (e.g. Hadjistavropoulos et al. 2011) that address how pain information is communicated to others in the social environment. Such models appear particularly relevant to capture the complexities of pain communication in clinical contexts [i.e. within a patient-caregiver relation; (Craig 2009; Hadjistavropoulos et al. 2011)]. In fact, pain assessment is far from precise; it can be influenced by numerous biases linked to the patient such as gender and race, the caregiver (e.g. his physical condition), or even the relation between the two (e.g. distrustful or confident) (Grégoire et al. 2012). Thus, the conceptualization of pain communication provides a framework to study clinically relevant sources of discrepancies between pain management and patient's actual pain experiences.

According to Craig's proposal (2009), pain communication includes four steps. It must begin with an experience of pain accompanied by tissue damage, injury or disease (*self-pain perception* or *internal pain experience*), which is then described to another person (*pain expression* or *encoding*). Next, this *pain message* is understood by the observer (*other's pain perception* or *decoding*) who chooses a response following his or her appraisal (*reaction to pain in others*, e.g. pain management in the clinical context). Distress accompanying pain is generally conveyed using intended and consciously produced acts, such as speech. Verbal information is also accompanied by unintended actions, i.e. language prosodics, facial expression and body language, which may or may not be recognized by the observer. This model also includes complex inter- and intrapersonal factors modulating the different steps of pain communication. Actually, the majority of studies in various disciplines (Sociology, Psychology, Physiology, Neurosciences) are based on this theory of pain communication. Beyond the promotion of theoretical knowledge on this topic, in the clinical context, the overarching goal of pain communication research is also to examine innovative solutions aimed at the improvement of pain appraisal and management (Drwecki et al. 2011; Padfield et al. 2015).

Herein, we address the contribution of recent technological tools to neuroscientific approaches of pain communication. The advent of neuroscientific technologies offers a new research avenue for the study of pain communication and the factors interacting with the transmission of pain messages, by measuring the neural correlates of pain perception (both in the person reporting pain and in the observer) in different experimental contexts. Neuroscience is particularly interested in studying non-conscious processes of pain communication, and complements behavioral findings [i.e. self-reported questionnaire or behavioral tasks in which participants have to evaluate pain intensity in visual stimuli (Price and Aydede 2006)]. Note that, as the lion's share of neuroscientific evidence is related to physical rather than social pain, and, to avoid slipping into the interesting debate about the *physical* versus *social pain* model (Eisenberger 2015), we deliberately limit the focus of this chapter to physical pain. Firstly, after a brief review of the cerebral correlates underlying *self* (i.e. the person in pain) and *other's* (i.e. the observer) pain perception, the different cognitive and social mechanisms implicated in the modulation of pain communication and their underlying neurological bases will be presented. In particular, neuroimaging evidence demonstrating variation of brain activations during pain observation in another person (*pain empathy*) will be discussed as a potential factor interacting with inaccurate assessment of other's pain. Secondly, we highlight the ecological impact of neuroimaging studies on pain communication, as they tend to fall short at characterizing the interactive mechanisms underlying this complex process. Recent neuroimaging studies on interpersonal synchrony may illustrate how pain communication may be scientifically studied using standard methods and instruments. Thirdly, new perspectives in the neuroscientific study of pain communication through the field of affective computing and virtual reality will be presented.

2 The Neural Basis of Pain Communication and its Modulation

As mentioned above, pain communication is highly influenced by psychological and social factors. In routine clinical contexts, if a patient fails to convincingly express pain, it might imply that they have limited/reduced physical means with which to express pain, but it could also mean that they voluntarily restrict their expression when facing distrustful professionals. By examining neural activation changes associated with pain experiences, neuroimaging studies can complement behavioral and qualitative findings, and help to understand complex processes underlying changes in pain communication. After a brief overview of the neural correlates of pain perception, from both an internal (*self-pain*) and a vicarious (*other's pain)* experience, the neuroscientific contribution to pain communication will be illustrated by referring to neuroimaging studies. Notably, we will refer to pain empathy studies, which were specifically interested in the *observer's* brain changes following psychological and social factors modulating the other's pain perception.

2.1 The Neural Structures and Systems Involved in Acute and Vicarious Pain

In the past decade, actual acute experiences have been observed using several brain imaging and brain mapping techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). The commonest regions for self-pain perception include the primary and secondary somatosensory (S1, S2), the anterior and posterior insulae, anterior cingulate (ACC), and prefrontal cortices (PFC), as well as the thalamus (Apkarian et al. 2005). S1 and S2, located on the postcentral gyrus, are usually known for their role in the sensory-discriminative dimension of pain (pain location and intensity). The insula, which receives input from S2 and the thalamus (posterior insula) and tightly connects to limbic structures and the ACC (anterior insula), is usually associated with the affective dimension (unpleasantness) of pain. The ACC, which also has bidirectional connections with regions of PFC [e.g. the medial PFC (mPFC)] associated with the cognitive dimension of pain, seems to integrate both affective and cognitive components of a painful experience (Shackman et al. 2011; Shenhav et al. 2013). Yet, posterior parietal and prefrontal areas also participate in the different temporal stages of pain processing (Garcia-Larrea and Peyron 2013). This network of brain regions, conventionally termed the *pain matrix,* is largely (see Apkarian et al. 2005 for a meta-analysis; Garcia-Larrea and Peyron 2013 for a review), but not universally, accepted within the field of pain as specific to pain (Iannetti and Mouraux 2010; Mouraux et al. 2011).

The neural circuitry underlying other's pain perception has stimulated a growing body of research interest since the early 2000s (for a review, see Lamm et al. 2011). The cerebral correlates of facing others in pain have been largely examined in neuroimaging studies aimed at exploring the neural correlates of empathy. Thus, although a recent debate was introduced about the distinction between *pain empathy* and *other's pain perception*, as the latter one would not necessary include a prosocial reaction to other's pain (Prkachin et al. 2015), we propose to define *pain empathy* as the natural ability to perceive, understand and react (or intend to) to the pain of others. Robust evidence showed that seeing another person in pain activated some regions within the hypothesized pain matrix (for reviews see Lamm et al. 2011; Jackson et al. 2006). More precisely, a core network consisting of the anterior insula (AI) and adjacent inferior frontal gyrus (IFG), the somatosensory cortex and a region including the anterior midcingulate cortex and dorsal anterior cingulate cortex (aMCC/dACC) is associated with pain empathy. However, the brain overlap between the representation of self and vicarious pain is not absolute, and substantial differences have been found in the precise areas activated in each form of pain. For instance, in the ACC, self-pain activations are more posterior and ventral, while pain related activations are more anterior when observing others in pain (Jackson et al. 2006). Moreover, pain empathy is not restricted to a spontaneous sharing of other's pain experience, but also engages cognitive processes such as *perspective taking* and *emotion regulation* (see Decety and Jackson 2004; for a neurophysiological model of empathy), which are known to be associated with activation in the temporoparietal junction (TPJ) and the posterior part of the superior temporal sulcus (pSTS) (Zaki and Ochsner 2012).

2.2 The Modulation of Neuronal Correlates of Pain Empathy

While some researchers have explored the cerebral basis of actual or vicarious pain, other neuroscientists have examined whether the neural correlates of pain empathy would be affected by the varied psychological or social biases well known to modulate pain communication. A neuroscientific perspective may be particularly useful to complement behavioral findings (i.e. subjective measures) about the modulation of pain communication, especially as these biases are innately unconscious and implicit. The factors modulating pain empathy are presented below according to their source and the interaction between the sources, i.e. those linked to the person in pain, the observer or the relation between the two individuals.

Variables related to the *suffering person* include personal characteristics such as age (Latimer et al. 2011), sex (Simon et al. 2006; Coll et al. 2012), the ethnic origin of the person in pain (Xu et al. 2009; Avenanti et al. 2010; Contreras-Huerta et al.

2013; Mathur et al. 2010; Riečanský et al. 2015) or even the level of incomes presumed (Guo et al. 2012). For instance, Xu et al. (2009) examined the neural empathic activity when Caucasian and Chinese participants watched video clips of Caucasian or Chinese persons receiving either painful (i.e. with a syringe needle) or non-painful (i.e. with a cotton-bud) stimuli touch their cheek. The results revealed a reduced empathic pain activity in the ACC and left AI when participants viewed painful touch to the faces of other-race people compared with people of the same race. Since the anterior insula (AI) is involved in the integration and representation of interoceptive and affective information, and the ACC is identified as its motivational and action-related counterpart (Bernhardt and Singer 2012), race bias in these areas suggests a decrease in the affective sharing to pain in other-race facial expressions. In the same vein, Guo et al. (2012) demonstrated greater activation in pain empathy related regions (i.e. aMCC, insula and TPJ) for poor people compared with people in a good financial situation. This finding suggests that the empathic neural responses for pain are likely inhibited by the belief that wealthy people have enough resources and confidence to cope with physical pain by themselves. Furthermore, the brain response to other's pain may be modulated depending on whether the person in pain is considered responsible or not for his/her suffering (Akitsuki and Decety 2009; Decety et al. 2010). Note that neural activation differences between experimental and control group were sometimes demonstrated in the absence of significant behavioural differences (e.g. ratings of other's pain, Xu et al. 2009), which strengthens the relevance of a neuroimaging perspective to complement and contribute new data (and hypotheses) to subjective measures of pain empathy.

The changes of brain responses related to *the observer* are also well documented. Notably, the neural responses to other's pain were shown to be affected by the observer's personal characteristics such as sex (Yang et al. 2009; Preis and Kroener-Herwig 2012; Preis et al. 2013), the propensity to be empathic (Avenanti et al. 2009), his/her physical state (Coll et al. 2012; Meng et al. 2013), or by contextual factors such as situation appraisal (Lamm et al. 2007), attention (Gu and Han 2007), the cultural environment (Cheon et al. 2011, 2013) or the relation to pain (e.g. over-exposure to pain, Coll et al. 2016) and prior pain experience (Cheng et al. 2007; Preis et al. 2013, 2015), or even whether participants had been exposed to short-term media violence (Guo et al. 2013). In a seminal study, Coll et al. (2016) examined the neural mechanisms underlying a repeated exposure to someone in pain. They measured behavioural (pain detection task) and Event-Related-Potential responses to facial expressions of pain in healthy adults who were either repeatedly exposed to intense expressions of pain or to neutral expressions. As in previous behavioral studies (Prkachin et al. 2004; Prkachin and Rocha 2010), the participants were less inclined to consider moderate expressions of pain as painful after observing expressions of intense pain. Most notably, this behavioral effect was associated with a reduction in the Late Positive Potential (LPP) response, measured at centro-parietal sites to pain expressions following exposure to intense pain compared with participants exposed to neutral expressions. These findings were interpreted as an alteration of cerebral responses to pain in others, which would indicate that repeated exposure to vicarious pain leads to a decrease in the perceived saliency of pain expressions. Besides extending previous behavioral evidence of the effect of over-exposure to vicarious pain (Goubert et al. 2009), these findings are particularly of interest in clinical settings as healthcare providers are exposed to patients in pain every day. Future investigations should test whether this effect cumulates and/or persists over time (e.g. several sessions).

Moreover, other neuroimaging studies have begun to describe neuronal changes associated with factors linked to *the connection between the two individuals making up the dyad*, e.g. their affinities (Singer et al. 2006; Hein et al. 2010), their social status (Feng et al. 2015), or in the clinical context (i.e. patient-physician relation), the expectancy for pain relief (Jensen et al. 2014). In a recent study, using fMRI, Feng et al. (2015) explored the influence of social hierarchies on the empathic neural response to pain in others. Social hierarchies were established based on contingent skills in a perceptual task, which allowed ranking of participants. Then, participants were scanned while watching inferior- or superior-status targets receiving painful or neutral stimulation. The results indicated higher activations in the AI and aMCC when viewing painful stimulation applied to inferior-status targets. In contrast, these brain activations were significantly reduced in response to pain seen in a superior-status individual. Moreover, this heightened response towards inferior-status targets was accompanied by stronger functional couplings between AI and brain regions important for nociceptive and emotional processing (i.e. thalamus) and cognitive control (i.e. middle frontal gyrus). Once again, these findings indicate that social biases may shape the emotional sharing with others' pain, shedding light on the modulation of the complex processes underlying empathy for pain.

In line with studies based on subjective reports, neuroscientific data referring to the *decoding stage* of pain communication (*the observer's perspective*) support the idea that empathy for pain is more complex than a mere resonance with the target's painful state, and is modulated by multiple social or psychological biases either linked to the suffering person, the observer, or the relation between the two individuals. Overall, neuroimaging findings suggest that multiple levels of neural mechanisms involved in affective sharing and sensorimotor resonance with someone in pain are modulated by individual characteristics and social relationships, and, thus, would mediate the contextual biases interfering in pain communication already shown in behaviours.

Interestingly, few neuroimaging studies have focused on the modulatory factors of pain empathy arising from the dyadic interaction compared to those assessing the person in pain or the observer. This observation may also apply generally to pain communication research as the traditional one person/one-brain approach used to date has focused on either the observer or the person in pain, without considering the dynamic influence of one on another. Without denying the great progress achieved so far in building a neuroscientific functional model of pain empathy and pain communication, the following discussion will address the non-ecological aspects of neuroimaging studies in this field. These studies often fall short in studying the social interaction component of this phenomenon in ecological or naturalistic terms. Recent neuroimaging studies interested in the phenomenon of interpersonal synchrony offer a more naturalistic approach by examining both individuals of a dyad together and their interactions, and appear as an interesting model for the study of pain communication in all its complexity.

3 Towards Interpersonal Interaction Experiments in the Neuroscience of Pain Communication

3.1 Pain Communication Research: A Challenging Compromise Between Controlled and Ecological Paradigms

The neuroscience of pain communication is still at its infancy. Yet, this exciting new field yields exponential findings from both the perspective of the person in distress and the person offering help or comfort. That said, at least two important methodological gaps observed in pain empathy studies must be pointed out and discussed.

The decoding of pain is generally based on *multimodal* and *dynamic* information, stemming from visual (non-verbal) and verbal-report information, which are contextually embedded (Hadjistavropoulos and Craig 2002; Hadjistavropoulos et al. 2011). With some exceptions, neuroimaging studies on pain empathy have used mainly simple visual stimuli, i.e. *picture-based* experimental designs based on a series of independent short events, without feedback to the participant; for instance, extracted from the UNBC-McMaster bank (Botvinick et al. 2005). In fact, as for most early study of any complicated psychological phenomenon, simplified stimuli and tasks were needed to first isolate specific processes and localize the cerebral response of pain empathy, and such precise and well-controlled localization was necessary before studying more complicated ecological designs, more aligned to achieving a holistic understanding of the neural circuitry underlying pain empathy. Thus, while the recurrent use of such simple and tractable stimuli has allowed researchers to disentangle the complex neuronal and cognitive processes underlying decoding another's pain; nevertheless, they are overly artificial and may limit the ecological significance of the data (Zaki and Ochsner 2012). We advocate the development of a more ecologic and realistic set of stimuli, e.g. video clips of individuals in real-life situations. For instance, Latimer et al. (2011) used video clips showing infants undergoing real medical procedures to examine whether repeated pain exposure would affect nurses' ability to be empathetic (Latimer et al. 2011). Naturalistic and controlled paradigms are fundamentally complementary and researchers should choose either one or the other depending on their theoretical issue. The cross talk between these two approaches would be a productive way to characterize the neural systems supporting the different steps of pain communication.

The second limit of the current literature on the neuroscience of empathy for pain is that, in the tasks used, no interaction is possible between the observer and the person in pain, even in a paradigm in vivo (Singer et al. 2004, 2006), as the person in pain sat to the side of the observer (positioned in the scanner) who only saw his/her hand reflection in mirrors. As already said, simplified experimental tasks were necessary to establish an evidence base. However, to be consistent with the scope of a biopsychosocial conception of pain, which draws specific attention to the social (*interpersonal*) factors characterizing pain experience, more ecological experimental designs must be also developed in the future. More simply, in real-life, the observer and the person in pain continuously interact, and thus, the resulting perception can only be predicted by a suitable combination of intrapersonal and interpersonal features. To make this point more concrete, imagine a physician hearing a patient who is describing his painful distress. The patient thinks his physician is not sensitive enough when he is talking about his pain, and suspects the physician to underestimate his suffering. As the conversation unfolds, he may amplify his pain expressions in order to receive desired treatment. From the physician’s point of view, when facing a patient who never complains about pain, he/she may pay close attention to unintended cues such as facial expressions when he/she is examining the patient, to perceive whether he/she should prescribe pain-killers to the patient or not. This scenario illustrates the complexity of pain communication, which entails constant interactions between the individual feeling pain and another individual decoding the pain message characterizing pain communication. Accordingly, neuroscientists cannot sensibly remain agnostic about the necessity to integrate the interaction between two individuals as the core of pain communication paradigms.

3.2 Interpersonal Synchrony

Albeit from a different field than pain communication, studies on *interpersonal synchrony* have demonstrated a key role of interactive processes in social exchanges, as well as the relevance of using alternative methodologies enabled by technological advances (including neuroimaging, physiological markers or even virtual reality) to pinpoint online changes during social interactions. Interpersonal synchrony refers to the temporal coordination of behaviours that appears naturally during dyadic interactions. In other terms, people spontaneously and unintentionally align their actions with others. For instance, the synchrony between the speech rhythms of a speaker and the bodily gestures of a listener in a conversation is well documented (Schmidt and O’Brien 1997). Moreover, during a conversation, gaze contributes to speech understanding as well as turn taking with eye contact, enabling persons to be coordinated and synchronized.

From the framework of pain communication, it has been suggested that shared pain may also involve facial expressions mimicry responses in the observer (Yamada and Decety 2009; Mailhot et al. 2012). Further, interpersonal synchrony likely is a foundation for effective social communication and enhanced sociality. Indeed, synchronized actions would result in an array of positive outcomes, increasing liking and rapport (Hove and Risen 2009), blurring self-other boundaries (Miles et al. 2010), facilitating person perception (Macrae et al. 2008) or enhancing altruistic behaviour and cooperation (Valdesolo and Desteno 2011). The social functions of interpersonal synchrony are important relative to pain communication, especially in medical settings, as the degree of synchrony between the observer (e.g. the caregiver) and the suffering person (e.g. the patient) could indicate the degree of his affiliative response toward the patient's painful distress; that is, whether he is "in tune" with his patient. In clinical contexts, interpersonal synchrony would be a potential lever to enhance empathic behaviour among health care providers, but also among patients (as critically pointed out in Jackson et al. 2015a, b), and thus, to help meet the challenge of successful decoding of the patient's pain.

The neural signature of interpersonal synchrony has been investigated by isolating reliable correlates of dynamical brain changes that occur during social interactions (Tognoli et al. 2007). In social neuroscience, scientists have developed a technique, called *hyperscanning*, which simultaneously records brain activity of two persons while they are engaged in a social exchange. This technically challenging brain-to-brain method has been applied using fMRI and EEG, and enables examination of interindividual neural synchronizations associated with behavioural synchronies at the intra- as well as the inter-brain level (Montagne et al. 2001; Dumas et al. 2011; Tognoli et al. 2015). To date, most neuroimaging studies have used conventional sensorimotor synchronization paradigms (e.g. synchronous or asynchronous finger-tapping movements realized with a partner) to assess interpersonal synchrony. For instance, Tognoli et al. (2007) used EEG hyperscanning in participants who were instructed to perform a rhythmic finger movement with or without the visual feedback of the other participant's movement. The authors focused on the alpha-mu band, which is conventionally considered as an electrophysiological correlate of the human mirror neuron system (MNS) functioning. The MNS refers to a set of brain regions which have been deemed important for some motor behaviours as well as the observation of the same behaviour in another individual (Rizzolatti and Craighero 2004). They observed that when participants could see each other they coordinated their behaviour. More interestingly, the results indicated a particular oscillatory component (*phi complex*) of brain activity that either favoured independent movement (*phi1*) or, behavioural synchronization (*phi2*). The topography of the phi complex was consistent with neuroanatomical sources within the MNS. The authors proposed that the phi complex might be a neuronal marker of social interaction. Although hyperscanning presents challenges for data collection and analysis, as well as the implementation of naturalistic and yet controllable paradigms (Schilbach et al. 2013), it seems to more naturalistically model the way the brain acts to convey and decode pain.

Another innovative media to further explore behavioural and neural synchronization of social exchanges is the avatar platform. Research in computer sciences using virtual reality, social gaming and *affective computing* (the study of computational machines and software that can display and process human emotions) is making steady progress towards creating sophisticated characters able to detect and react to behavioural and physiological markers of human emotions (Gaffary et al. 2014). The enormous advantage of animation tools is that they are fully controllable compared with a real partner, while still realistic enough to be ecologically valid. For example, features of avatars can be changed to control some social biases, such as sex or ethnic origin. In a recent study using a finger-tapping paradigm, Cacioppo et al. (2014) examined whether a person may perceive that a virtual partner is synchronized with his/her movements, and would experience affiliative feelings toward this partner (Cacioppo et al. 2014). Participants performed fingertip movements with no specific instruction to align their behaviour with virtual partners. Unknown to the participants, the timings of the avatars' movements were either synchronous or asynchronous with those of the participants. The authors also used fMRI to investigate how regional brain activity was modulated by differences in synchronous stimuli during the task compared with asynchronous stimuli. Behavioral results revealed that synchrony by the virtual partner enhanced the participant's ratings of perceived interpersonal synchrony and social affiliation with the virtual partner. Importantly, the fMRI results indicated greater brain responses of the synchronous condition compared with the asynchronous one in cerebral regions identified as neural correlates of interpersonal synchrony (Fairhurst et al. 2013) including, the left inferior parietal lobule, the left parahippocampal gyrus, the ventro-medial prefrontal cortex (vmPFC) and the ACC. This approach seems encouraging, as the development of specific virtual platforms may be an efficient solution to overcome the methodological limitations described above and to study pain communication in a more "real-life" way.

In this section, we observed that some neuroscientific research on pain communication fails to capture the personal interactive dimension inherent to human social exchanges. Based on the current research interest in interpersonal synchrony, a methodological and conceptual leap from an *individual* towards a *dyadic approach* of pain communication is now necessary to fully capture the human intimacy of this complex phenomenon. In the next section, we will argue how virtual reality procedures may be highly relevant to address the phenomenon of pain communication, and present research interventions that may contribute to improve pain assessment in clinical settings.

4 The Use of Virtual Reality in Neuroscientific Research on Pain Communication

Affective computing studies the recognition and simulation of human emotions; for example, through virtual characters (also called *avatars*) that can recognize and mimic human affects (Picard 2003). In research settings, affective computing technology offers a flexible and controlled set-up appropriate in experimental and therapeutic contexts because avatars can be easily animated and systematically varied according to the experimenter's needs (Dyck et al. 2008).

Virtual reality may provide realistic three-dimensional environments created by computer graphics. Virtual reality has been already used in the field of pain to standardize how pain may be expressed by a patient and assess differences in how people rate pain in others (Hirsh et al. 2008, 2009; Stutts et al. 2010) and, more recently, in empathy (Bouchard et al. 2013; Jackson et al. 2015a, b). Virtual reality can be applied to control pain (Hoffman et al. 2011; Garrett et al. 2014; Jin et al. 2016). In one study, a virtual frozen world were designed to distract patients from their painful burns while receiving wound care (Hoffman et al. 2007). This approach seems clinically promising, as the authors reported reduced pain ratings following the intervention. As a research method, virtual reality may be an efficient solution to overcome the limitations mentioned above for studying pain communication in a more meaningful way.

Recently, several groups have created virtual platforms for studying social exchanges, such as pain communication, and pain empathy (Jackson et al. 2015a, b; Romano et al. 2016; Wittkopf and Johnson 2016). For instance, the Empathy-Enhancing Virtual Evolving Environment (EEVEE), designed by Jackson et al. (2015b), can be used in combination with objective neurophysiological markers (e.g. heart rate, skin conductance, and cortical excitability) for online assessment of pain empathy at behavioral and neurophysiological levels. EEVEE was developed around three objectives: (1) to provide an ecological way to study social phenomenon such as pain empathy or communication, i.e. an interactive and naturally looking, yet highly controlled social environment, (2) to identify correlates associated with the social phenomenon studied, and, (3) to use this platform as a tool for improving social communication and empathy.

EEVEE uses human avatars to produce distinct sets of emotional expressions based on the Facial Action Coding System (FACS) (Ekman et al. 2002; Prkachin and Solomon 2008). The FACS encompasses 46 facial Actions Units (AUs), each AU corresponding to the encoding of the contraction and relaxation of different muscles or muscles groups. Most importantly, EEVEE enables real-time recording of behavioral and neurophysiological reactions, e.g. emotional face recognition, heart and respiration rates, skin conductance. Ultimately, the avatar can interact with the participant by changing its facial expressions based on participant's behavioral and neurophysiological measurements through a multimodal interface that creates different scenarios, and implements different settings for changing the behavioural and emotional response of the avatar. Currently, EEVEE allows the

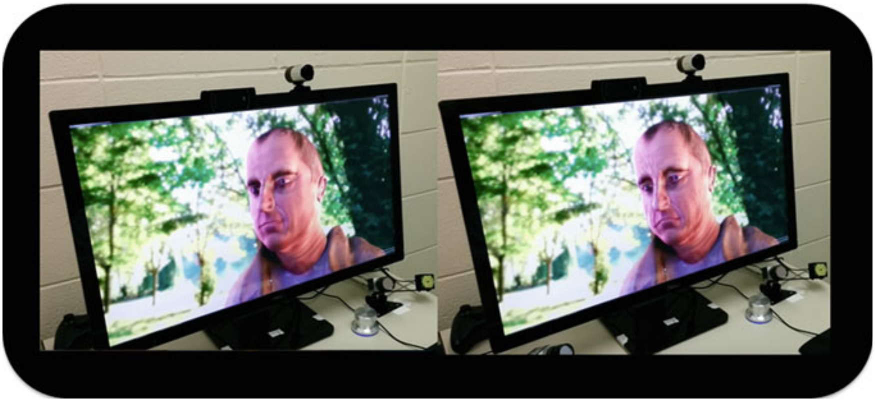

Fig. 1 Illustration of an avatar in a scenario configured with EEVEE. The avatar's facial expression can change based on a predetermined scenarios or the participant's behavioral and neurophysiological responses, including for instance gaze direction, facial expression, heart rate variability, changes in skin conductance and muscle contraction (EMG) (Jackson et al. 2015b)

production of varied avatars (i.e. different age, sex, ethnic origin) and has been validated for different intensities of facial expressions of basic emotions. Moreover, the platform actually proposes different environments in 3D (e.g. a hospital room and a park) (Fig. 1).

Future versions of EEVEE will allow users to change the avatar's gender, age, and ethnicity independently and yet to improve visual immersion. Actually, pilot experiments have been conducted to test the validity of the platform and examined whether the facial expressions of EEVEE's avatars are realistic to convey specific emotions (Jackson et al. 2015b). Preliminary studies were consistent with previous data (Kunz et al. 2012), confirming the validity of EEVEE. They also provided some key methodological information when using it for research on pain communication, discussed in the next section.

4.1 How Intelligent Avatars May Promote the Neuroscientific Study of Pain Communication

Virtual reality will certainly add value for research on pain communication. For instance, in the section above, we evoked the importance of the level of interpersonal synchrony in social exchanges as well as its positive outcomes, e.g. enhancing altruistic behaviour or facilitating the perception of another's mental state. Interactive avatars will enable researches to study whether the level of synchrony between the observer and the person in pain (e.g. matched gaze, facial and body expressions) may influence the empathic response to pain (*perspective of the observer*) or, pain perception (*perspective of the suffering person*), as well as their neural responses. It is reasonable to assume that a high level of synchrony of the observer's action with the suffering person may favour a better assessment of his or her pain; in other terms, may predict a better listening of the person's expression of pain. It seems of particular interest in the clinical context, as the level of temporal coordination of a caregiver with a patient may provide an objective marker of his or her capacity to empathize with the patient's pain, i.e. to recognize and share the pain in other. If the link between interpersonal synchrony, pain empathy and/or accurate pain assessment proves to be significant, intelligent avatars will make a suitable clinical and research tool to assess the ability of healthcare providers to synchronize with other's pain. Moreover, such virtual platforms could also help train caregivers to synchronize with others, improving their ability to detect and manage pain, especially in certain clinical populations (e.g. premature newborns, people with dementia). Concretely, different scenarios with the platform may be created using avatars with varied levels of facial expressions—as well as settings where avatars will change their level of expressions during the social exchange—to train healthcare professionals to detect and synchronize with *body-language of pain,* i.e. significant non-verbal clinical clues of pain (see Mantovani et al. 2003; Deladisma et al. 2007; Consorti et al. 2012; for prior research on this topic).

Another potential training exercise with intelligent avatars would consist in exploiting the neurophysiological and behavioral empathic responses of the caregivers to modulate the avatar's facial expression and communicative responses, to incite caregiver empathy. For instance, a caregiver could see a virtual patient, who suffers from chronic back pain, displaying different levels of facial expressions of pain (modulated according to a predetermined combination of neurophysiological parameters, e.g. gaze directed at meaningful facial areas, skin conductance showing elevated affective response). The avatar would then express relief only when the caregiver's responses would be compatible with a level of synchrony reflecting an empathic state. Other authors already tested practical interventions that may help nurses (Drwecki et al. 2011) or physicians to enhance their communication with patients. Adaptable avatar platforms like EEVEE provide a complementary tool to these cognitive approaches.

We have argued that methodological opportunities are offered by virtual reality to better understand the neuropsychological processes underpinning pain communication, and more generally social exchanges. Research on pain communication is now at a tipping-point and researchers should seek more ecological approaches to study this social phenomenon. Notably, new technological paradigms may help to uncover how behaviours may be modulated during dyadic interactions, as well as their neurophysiological basis. Such innovative initiatives as EEVEE should be encouraged in the future as they provide a rich experimental set-up to explore the mechanisms underlying pain communication from both the patient's and the caregivers's perspective, as well as their interactions. Note that a virtual platform should be developed in collaboration with scholars of artificial intelligence, who have expertise in machine learning paradigms allowing complex statistical analyses (Ashraf et al. 2009; Lucey et al. 2011; Bartlett et al. 2014; Girard et al. 2014; Sikka et al. 2015).

5 Conclusion

The inherent subjectivity of pain makes this experience difficult to access by others. Accurate pain evaluation is highly challenging but crucial for appropriate care delivery. Pain communication is highly influenced by psychological and social factors, linked to the suffering person, the observer, or the relation between them. Neuroscience provides a new window to increase awareness of how several psychological factors, either linked to the suffering person (e.g. age, visual quality, hands vs. facial expressions, visual perspective), the observer (e.g. age, gender, mental health, physical health, knowledge) or the interaction between them (e.g. link with the other [spouse, child], member of the same group, environment [hospital, war]), may separately shape pain communication. Until recently, neuroscience has focused either on the perspective of the person in pain (*self-pain perception*) or, on the perspective of the observer (*pain empathy*), and fell-short characterizing the interactive mechanisms underlying the transmission of a pain message. After 11 years of research on pain empathy, this field can continue to advance by promoting more ecological or naturalistic approaches that take into account both the perspective of the suffering person and the observer, as well as their interactions in relation to pain outcomes. While hyperscanning is a promising but exceedingly challenging method, technological tools such as affective computing and virtual reality appear as complementary and feasible methods. The use of intelligent avatars might provide an acceptable compromise between experimental control and ecological validity.

Overall, beyond designing intelligent and empathic tools to detect patients' experiences, these research initiatives may contribute to promote empathic behaviour in clinical contexts, helping caregivers to counteract the deleterious effects of over-exposure to pain; for instance, a tendency to underestimate the level of suffering. Ultimately, using naturalistic paradigms will be critical for modelling brain functioning during the course of pain communication, and thus help develop more ecological neurophysiological models of this complex phenomenon. The methodological adjustments towards more ecological experiments would also favour connections with other domains of research, especially the psychological literature, enabling evolution of current multidisciplinary models, and thus, contributing to our understanding of pain and the human mind.

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