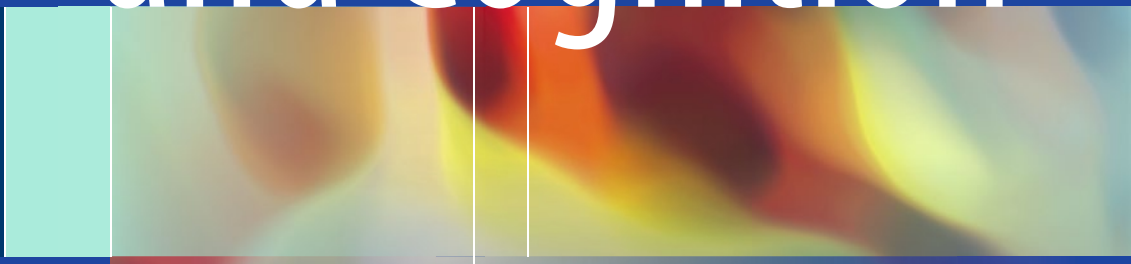
Pain, Emotion and Cognition



A Complex Nexus

Gisèle Pickering
Stephen Gibson
Editors

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Preface

Consciousness reigns but does not govern
—Paul Valéry "La conscience règne mais ne gouverne pas"
(Mauvaises pensées et autres, Tome II *Oeuvres*, p. 813)

This prophetic statement applies very appropriately to the pain, cognition and emotion nexus. Pain is a fundamentally conscious experience, but emotions and cognitions may govern the nature of that experience. For some time pain has been recognized as a complex biopsychosocial experience rather than a sensory circuit of unpleasant interoceptive transmission. As such there has been an ever increasing body of research into the emotional and cognitive factors that help to shape the perceptual experience of pain, as well as research into the way that pain can impact on these important aspects of the human condition. This book explores nodal intersections of the experience of pain and emotional and cognitive dysfunction that impair the quality of life of patients.

Pain, emotion and cognition aims to provide a comprehensive resource for health care providers and researchers alike, who seek a contemporary knowledge on this broad topic. It attempts to update our understanding of these areas by providing a state-of-the-art review of current literature and raises new questions and challenges in order to advance the field. The book contains 15 chapters, organized into 4 main sections. Part 1 of the book is devoted to the basic phenomenology of each domain including emotion, cognition and pain as well as a discussion of empathy and the underlying molecular and neurophysiological substrates. Part 2 deals with appropriate methods of measurement including psychometric tools, facial and behavioral markers, and assessment difficulties in those with dementia. Part 3 examines psychological, medical and physical treatment strategies that can be used to manage pain and its emotional and cognitive impacts. The final section considers the pain, emotion and cognition nexus in special populations including phantom limb pain, Parkinson's disease, psychiatric patients and in the elderly. All sections analyze the complex interrelationships between pain, emotion and cognition in the light of the complementary approaches of neurosciences, psychology, pharmacology, neuroimaging, physical rehabilitation and medical care.

All contributors to this book are internationally recognized by their research in this complex and fascinating field. They bring their own expertise and enthusiasm in fundamental or clinical research to furthering research in this domain.

Clermont-Ferrand, France — Gisèle Pickering
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Part I
Nociception, Pain, Emotion and Cognition Interconnections

Chapter 1
Cognitive Psychology and Neuropsychology of Nociception and Pain

Valery Legrain and Diana M. Torta

Abstract For a long time, pain research has focused on understanding the mechanisms underlying the unpleasant experience generated by a nociceptive stimulus. Cognitive theories emphasize the functional aspects of nociception by defining it as a warning process. Nociceptive inputs are processed in a multisensory processing system that prioritizes stimuli that are meaningful for the integrity of the body and integrates them into multi-frame representations of the body and the proximal space. The ultimate purpose of this multisensory system is to guide defensive behaviors. Recent experimental evidence supports the role that cognitive functions such as selective attention, spatial perception, and motor preparation play in nociceptive processing. In addition, the cognitive approach of pain offers new clinical perspectives by providing a framework for the treatment of chronic pain based on neuropsychological rehabilitation.

1.1 Introduction

Cognitive psychology is a theoretical and methodological framework which aims to study the architecture of mental processes (Neisser 1967). Unlike behaviorist psychology which focuses only on observable behaviors, cognitive psychology tries to infer knowledge about mental states from the observation of behavior. More specifically, cognitive psychologists are interested in the description of the processing steps through which sensory inputs are transformed into thoughts and actions. Research in cognitive psychology generally consists in observing the behavior of participants when they are involved in specific tasks such as perception, attention, memory, or language tasks. Most often, participants have to respond to the occurrence of stimuli. Their response depends on variations of the stimulus parameters and the experimental instruction, and these variations are systematically controlled by the experimenter. Experimental manipulation is aimed at disclosing the succession of

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operations from the processing of the incoming input to the computation of the output response during the task. Cognitive psychology mostly uses the experimental method, in the sense that variations of stimulus parameters and task instructions are deducted from theoretical hypotheses. The cognitive psychology method is based therefore on a principle: only one parameter of the task is changed at a time in order to measure its effect on participants' behavior. Cognitive psychology also tries to understand how cognitive processes are implemented in their material support, that is, the brain. Neuropsychology is a long-lived and yet still contemporary approach which aims to localize mental processing in regions of the brain, by inferring normal processes from brain lesions (among other methods). Neuropsychologists try to characterize the cognitive dysfunction produced by a lesion of a cortical area, with the aim to establish a link between a specific function and that cortical area. The underlying hypothesis is the following: *the way how the cognitive system is deconstructed is related to its structure and rules of normal functioning* (Seron 1994). The neuropsychologist is therefore especially interested in the knowledge of normal function that can be derived from the description of a pathological state. This classic top-down neuropsychological approach tries to characterize how cortical lesions, and the supposed changes in cognitive organization, affect the processing of sensory information. An alternative bottom-up approach can be used to understand how peripheral deficits such as impaired sensory transmission modify cognition due to maladaptive neuronal plasticity (e.g., Crollen and Collignon 2012; Jacquin-Courtois et al. 2012; Ramachandran et al. 1992).

1.2 Cognitive Psychology in Pain Research

Regarding nociception and pain, one of the first cognitive models was proposed by Leventhal and Everhart in 1979. The model describes four processing steps between the stimulus input, that is, the nociceptive stimulus, and the perceptual output, that is, the conscious experience of pain: (1) stimulus encoding, (2) motor elaboration and memory encoding, (3) perceptual elaboration, and (4) attentional amplification. These steps operate in two parallel pathways, one that elaborates sensory-discriminative aspects generating the perceptual knowledge about the stimulus features, and a second that codes the emotional aspects generating the experience of unpleasantness. The model predicts that the degree of pain experienced by an individual would depend on how much attention is paid to the nociceptive stimulus. However, because the model dissociates the sensorial and the affective aspects of pain (see Melzack and Casey 1968), both aspects are susceptible to be modified by attention in isolation. Conversely, the model developed later by Price and Harkins (1992) proposes an architecture of nociceptive processing during which sensorial and affective components are sequentially organized. Therefore, attentional control over the sensory-discriminative aspects of pain also modifies the processing of the emotional distress generated by the experience of pain. The two models predict a close interaction between attention and nociceptive processing. This has led to the

general idea that paying attention to pain makes it worse. It was then assumed that reducing the attention allocated to the experience of pain by modifying the focus of attention towards cognitive activities unrelated to pain would alter the salience of the experience and promote better coping with pain (see Van Damme et al. 2010). For instance, according to McCaul and Malott (1984), the elaboration of pain is made in a capacity-limited system in which selection is operated to reduce processing overload (see Broadbent 1958). As nociceptive processing is an effortful and subject-regulated processing mode (Shiffrin and Schneider 1977), the reduction of attention will affect the ability to transform sensory inputs into pain. Discarding attention from nociceptive stimulus can be used as a strategy to decrease pain, if pain does not draw too much attentional resources and if the distracting task also involves controlled processing components (McCaul and Malott 1984).

Other cognitive models highlighting the functional role of pain were recently put forward (e.g., Legrain et al. 2011, 2012b; Van Damme et al. 2010). Indeed, most of the current research on pain focuses on discovering brain mechanisms underlying the generation of the pain sensation and on characterizing the mechanisms involved in the descending modulatory control of nociceptive transmission. However, besides the unpleasant sensory experience associated with the noxious stimulation, pain can also be described as a warning signal allowing detection, localization, and reaction against a stimulus potentially meaningful for the physical integrity of the body. This definition proposes an important role in nociception for three cognitive processes, respectively: (1) selective attention to prioritize the processing of stimuli that are the most significant, (2) spatial perception to map their accurate position in space, and (3) action selection to prepare the most appropriate motor action in response to the nociceptive stimuli (Legrain et al. 2012b). It is worth noting that, despite the fact that these processes are not specifically involved in nociception (meaning they are not exclusively involved in the generation of pain in the brain), they are inherently involved in the elaboration of motivationally driven behaviors towards meaningful stimuli, such as physical threats. As nociception can be seen as an epiphenomenon of warning processes, the description of how selective attention, spatial perception, and action selection are involved in the processing of nociceptive inputs is of primary importance to understand how the brain adapts to meaningful changes and defends the body against potential harmful stimuli. In this perspective, the study of the sensation of pain can sometimes appear secondary to other responses such reaction times or perceptual judgments. In addition, the importance of these cognitive processes is emphasized by the fact that impairment of any one of them can be relevant for the understanding of clinical pain states (Moseley et al. 2012b; Haggard et al. 2013).

1.3 Salience Detection and Selective Attention

The role of selective attention is to prioritize the processing of some inputs at the expense of other inputs. Selective attention can be indeed defined as a *restricted focus of consciousness on one out of several objects physically present in the*

environment or one out of several mental representations of objects or ideas (James 1890). Such a selective prioritizing of perceptual, decisional, and, even, motor activity can be dissociated from phasic alertness, a general activation determining an unspecific state of readiness to external sensory events, and from alerting attention, a tonic alertness or readiness induced by the sensory events (Boisacq-Schepens and Crommelinck 1996). The concept of selective attention is grounded by the assumption that perception and action abilities are restricted, and, therefore, information flow has to be filtered in order to avoid processing overload (Broadbent 1958). However, this classic view of attention was challenged by theories that recognize the finality of attention is to prioritize and facilitate the perception of the information that enables one to select, among many possibilities, the most efficient action (Allport 1987; Hommel 2010; Rizzolatti and Craighero 1998). The selection of the meaningful stimulus and, consequently, the guidance of the appropriate action are based on the individual's aims and on the environmental context. Indeed, information processing is filtered based on a stimulus-driven (or bottom-up) selection and on a goal-directed (or top-down) selection (Egeth and Yantis 1997; Knudsen 2007). According to the first mode of selection, attention is captured by the stimuli themselves according to their salience, that is, their ability to stand out relatively to surrounding or preceding stimuli. This involuntary capture of attention allows the modification of processing priorities and cognitive goals to adapt behaviors to sudden changes in the environment or to tune to high-order motivational functions such as escape from a danger. According to the second mode of selection, the selection of information is voluntarily regulated by the relevance of the stimuli when compared to cognitive objectives and motivations.

The ability of a painful stimulus to involuntarily capture attention was firstly observed in studies showing that the performance in auditory discrimination tasks was impaired (increased reaction times) by the concomitant occurrence of a painful stimulus even completely irrelevant to the task goal (Crombez et al. 1994). This suggests that attention was transiently displaced from the auditory target to the painful distracter (see Eccleston and Crombez 1999). These studies showed that the ability of a nociceptive stimulus to attract attention and interrupt ongoing cognitive activities was more dependent on the context than on the perceived pain (Crombez et al. 1994, 1996, 1997). One can wonder how the salience of a stimulus can be established before the stimulus receives attention. Salience detection is supposed to rely on the existence of neurons particularly sensitive to contrasts and changes. In other words, those neurons would be activated by the occurrence of stimuli particularly contrasting relative to other surrounding stimuli (Itti and Koch 2001) or by the detection of transient changes in the afferent sensory flow (Näätänen 1992). Salience detectors, by responding more strongly and in a more sustained way to these kinds of stimuli, would give to salient sensory inputs greater cortical resources to ensure them a more complete processing (Desimone and Duncan 1995). Regarding nociceptive processing, it was suggested that responses of the cingulate cortex to nociceptive inputs play a pivotal role in the attentional selection by biasing the cortical activity to nociceptive stimuli (Bantick et al. 2002; Legrain et al. 2002; Peyron et al. 1999). More recent studies have demonstrated that most of the cortical responses to

nociceptive stimuli are sensitive to their salience, independent of the intensity of the perceived pain (Downar et al. 2003; Iannetti et al. 2008; Legrain et al. 2009a). For instance, Legrain et al. (2009a) showed that unexpected novel nociceptive stimuli, that is, stimuli irregularly presented, elicited event-related brain potentials (ERPs) of greater magnitude as compared to the ERPs elicited by nociceptive stimuli of the same intensity but presented more regularly and monotonously. Importantly, all components of the nociceptive ERPs were increased by stimulus novelty, including the earliest one supposed to be generated in somatosensory areas. In this experiment, nociceptive stimuli were made task irrelevant and participants were instructed to perform a task on visual stimuli that followed each nociceptive stimulus. Performance in the visual task was impaired by the occurrence of novel nociceptive stimuli. Iannetti et al. (2008) showed that the loss of novelty induced by the repetition of the stimuli at a constant rate decreased the magnitude of the elicited ERPs, whereas the perception of pain remained unchanged. Hu et al. (2013) identified in the ERPs elicited by nociceptive stimuli a component that could be interpreted as a neuronal change detector for nociception. In their experiment, they used a similar paradigm as Legrain et al. (2009a) during which nociceptive stimuli were delivered at a constant rate on a specific area of one hand (e.g., the lateral section). After a random repetition of stimuli, the area onto which the stimuli were then applied was switched to another section of the hand (e.g., the median section). Unexpected occasional changes in stimulus location induced increased ERP responses to nociceptive stimuli mostly around the ipsi- and the contralateral parts of the scalp, even when nociceptive stimuli were completely unattended by the participants. Conversely, a similar electrocortical activity was identified at the top of the scalp and was shown to be increased in magnitude when the nociceptive stimuli were actively attended. This seems to confirm that the median part of the cortical network activated by nociceptive stimuli (e.g., the mid-cingulate area) can be more consistently interpreted as reflecting the effective orienting of attention towards nociceptive stimuli (Legrain et al. 2002, 2009a).

In order to promote survival, evolution has naturally prompted individuals to escape from physical threats. Pain has then the potential to change cognitive goal and to override the effort to disregard attention from nociceptive information (Van Damme et al. 2010). However, since it was evidenced that the experience of pain is largely influenced by the attention paid to the nociceptive stimulation, both in experimental settings (e.g., Honoré et al. 1995; Miron et al. 1989; Van Ryckeghem et al. 2011, 2013) and in clinical situations (e.g., Hadjistavropoulos et al. 2000; Harvey and McGuire 2000; Johnson and Petrie 1997; Rode et al. 2001), the manipulation of attention, such as distraction, was proposed as a potential therapeutic strategy to alleviate pain (See Eccleston and Crombez 1999; Morley 2011). One may wonder how it is possible to direct attention away to a stimulus that has inherently the ability to capture attention. Legrain et al. (2009b) proposed that the capture of attention by nociceptive stimuli can be inhibited by three main ways (Fig. 1.1). First, attention should be focused to stimulus features that match task requests. Conversely, features of the unattended irrelevant distracter should be excluded from the selection and the searching set mode (attentional set hypothesis; Van Ryckeghem

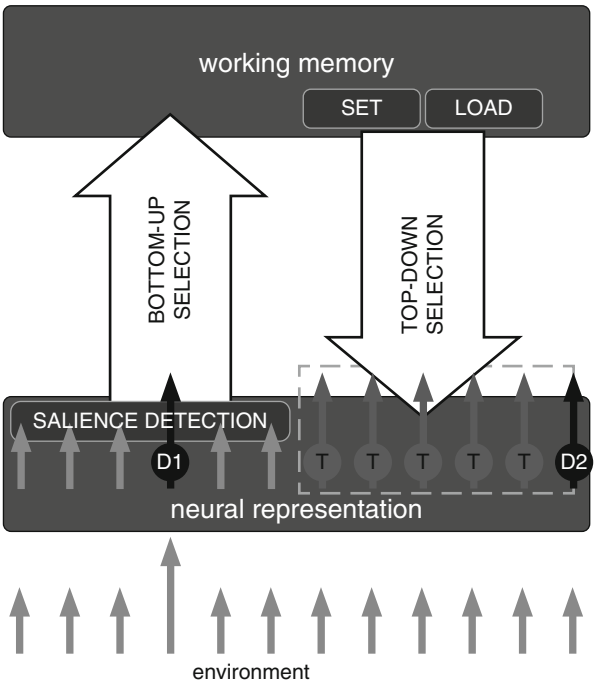

Fig. 1.1 Components of attention. Physical features of the information from the environment are *represented*, that is, encoded, into particular patterns of neural activations. The representations with the highest signal strength will be selected for further processing and access to working memory that holds active the representations of the information which are significant for ongoing cognitive processing. The selection is based on the salience of the sensory stimuli, that is, their ability to stand out relative to neighboring stimuli or relative to recent past events, or their relevance, that is, their pertinence for current cognitive and behavioral aims or for motivation. At the first level, information flow is filtered by salience detectors. These detectors weight the neural representations of sensory inputs relative to the representations of the sensory inputs from neighboring stimuli. These detectors modify the weight of the neural representations of sensory inputs relative to the representations of the sensory inputs from neighboring stimuli (Itti and Koch 2001). The stimuli that are the more distinctive receive then stronger representation signals (spatial salience detection). Other detectors increase the strength of neural responses to salient stimuli by identifying the stimuli that are novel or that represent a change according to recent past sensory events (Näätänen 1992) (temporal salience detection). On the basis of these mechanisms which translate physical salience into weighted neural representation (*black arrow* "D1"; "D" for distracter), the sensory inputs that receive the strongest neural response are those that are able to capture attention, even if these inputs are not explicitly attended by the individual (bottom-up or stimulus-driven selection). At the second level, processing prioritization is based on ongoing cognitive aims and high-order motivations, and the selection is then voluntarily controlled towards the sensory inputs that allow to achieve these aims and to satisfy motivations (*dark gray arrows* "T"; "T" for target) (top-down or goal-directed selection). The balance between top-down and bottom-up selection depends on several variables. First, top-down selection is under the control of working memory that maintains active the aims and the features of the to-be-attended information during the achievement of the task (Desimone and Duncan 1995). Second, the features of the targets are defined by the attentional set that helps attention to search and identify the relevant information in the environment. A consequence of the activity of attentional setting is that distracter stimuli that share one or more features with the attended targets (*black arrow* "D2") will also enter into the focus of attention (*dotted gray square*) (Folk et al. 1992). Third, attention abilities will be more or less loaded during selection (Lavie 2010). Under high-load selection, attention is narrowed on the processing of relevant information and distracters are rejected. To the contrary, under low selection, information processing is less selective; distracters will also be perceived, and their ability to gain control over cognitive activity will depend on the ability of executive functions to inhibit interference (Adapted from Legrain et al. (2009b))

et al. 2013). Second, searching and maintaining attention on the relevant stimulus should be effortful in order to avoid using attentional resources to process irrelevant distracters (attentional load hypothesis; Legrain et al. 2005; Roa Romero et al. 2013). Third, attention to the relevant stimulus should be controlled by executive functions in order to actively shield the processing of the attended stimulus from distraction (Legrain et al. 2013). The latter aspect emphasizes the role of working memory by allowing active maintenance of the goals of ongoing cognitive activities during the task in order to help attention to target the relevant stimuli (Desimone and Duncan 1995).

1.4 Spatial Perception

The role of the representation of space in the perception of nociceptive stimuli has been recently highlighted. For instance, a study has observed, in patients who showed hemispatial neglect syndrome after a stroke, that the perception of a nociceptive stimulus depends on the ability to localize stimuli in space and on the integrity of cortical structures such a posterior parietal and prefrontal areas (Liu et al. 2011). Some of these patients were able to report correctly the occurrence of a nociceptive stimulus only when this was applied on the hand contralateral to the lesion site. The perception of the same stimulus was extinguished when it was delivered concomitantly with another nociceptive stimulus on the ipsilesional hand (nociceptive extinction). Other patients were also able to identify correctly the occurrence of the nociceptive stimulus applied to the contralesional hand, but they localized it as if it has been applied to the ipsilesional hand (nociceptive allesthesia).

The ability to localize nociceptive stimuli is important because it allows the detection of which part of the body is potentially threatened. It is also of primary importance to identify in external space the position of the object that might be the cause of damage in order to prompt and to guide defensive motor responses towards the location of the threat. These considerations underline the importance of coordinating the representation of the body space and the representation of external space. The brain normally takes into account different frames of reference when coding the spatial position of sensory information (Fig. 1.2; see Vallar and Maravita 2009). One type of reference framework relates to the anatomical reference frames, which are based on the existence of a spatial organization of sensory receptors in receptive fields which project to separate populations of neurons. The primary somatosensory and motor cortices are somatotopically organized and contain a spatially organized representation of the cutaneous surface of the body (Penfield and Boldrey 1937). However, this type of frame of reference alone is unable to integrate the perception of which part of the body is stimulated and the perception of the position of external objects in contact with the body. In other words, defensive motor responses cannot be spatially guided towards the threat efficiently if the position of nociceptive stimuli is not remapped according to both the position of the stimulated body part and the position of the threatening object in external space. The peripersonal frame of reference is of particular interest because it allows integrating the body space and the space surrounding it. Indeed, this frame allows coding the position of

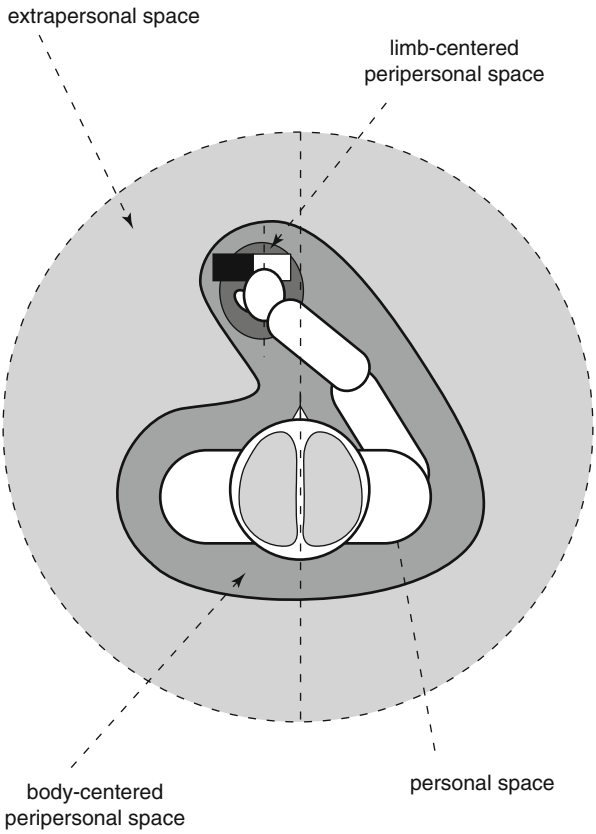

Fig. 1.2 Different frames of reference to perceive body and extra-body spaces. Three main reference frames can be dissociated. The personal reference frame corresponds to the space of the body. This frame can be dissociated into a somatotopic personal frame based on the anatomical projection of somatosensory receptive fields in spatially ordered groups of neurons and a spatiotopic personal frame using external space as a coordinate system. According to this second reference frame, as illustrated in the figure, we are able to recognize, eyes closed, that the right hand, that crosses the midline of the body, is touched by a right-sided object, despite the fact that somatosensory inputs are sent to the left hemisphere. Spatiotopic reference frames integrate therefore somatosensory and proprioceptive information. The peripersonal frame of reference corresponds to a coordinate system integrating body space and external space close to the body. This reference frame allows the integration of somatosensory information with visual and auditory information when visual and auditory stimuli occur close to the body. The peripersonal reference frame can be centered on the body; the sagittal midline of the body is used as a coordinate to separate the left and right parts of space. It can also be centered on each limb; the limb itself is then used as coordinate. Therefore, the peripersonal reference frame is considered as an interplay of body-part-centered coordinates mapping stimuli from the different senses and moving in space with the body part onto which these maps are anchored. The extrapersonal frame of reference corresponds to a reference frame used to perceive the far space, that is, to explore environment by movements of the eyes and the limbs. Finally, these reference frames were defined according to an egocentric perspective, that is, relative to the observer's own body. According to an allocentric object-centered perspective, spatial coordinates are defined relative the object itself (e.g., in the illustration the white part of the rectangle is in the right side relative to the black part, while both parts are in the left space of the observer) (Adapted from Legrain (2011))

somatosensory stimuli on the body space and the position of external stimuli (i.e., visual or auditory) occurring close to the body part on which the somatosensory stimuli are applied (see Holmes and Spence 2004; Maravita et al. 2003). The peripersonal frame of reference is specifically relevant to help guide direct manipulation of objects (Rizzolatti et al. 1997), unlike a more extrapersonal frame of reference which is more useful to explore the space by eye movements and to prepare reaching movements. Moreover, it is believed to be crucial for the organization of defensive motor actions (Graziano and Cooke 2006).

The existence of a peripersonal frame of reference to map the position of nociceptive stimuli supposes firstly the existence of multimodal interactions between nociceptive inputs and sensory inputs from other modalities. For instance, it has been suggested that vision of the limb onto which nociceptive stimuli are applied can modify the cortical processing of these nociceptive stimuli and the elicited pain (Longo et al. 2009; Mancini et al. 2011; Romano and Maravita 2014). In addition, Sambo et al. (2013) showed that the judgment about the occurrence of nociceptive stimuli could depend on the relative position of the limbs. They used a temporal order judgment task during which healthy blindfolded volunteers had to judge which of two nociceptive stimuli applied to either hand was perceived as being delivered first. The task was either performed with the hands in an uncrossed posture or with hands crossed over the sagittal midline of the body. This crossing-hand procedure is often used to induce a competition between somatotopic and spatiotopic frames of reference (when crossed, the left hand is right sided and the right hand left sided) (e.g., Shore et al. 2002; Smania and Aglioti 1995; Spence et al. 2004). The authors showed that judgments were much more complicated when the hands were crossed, suggesting that the perception of nociceptive stimuli was affected by a space-based frame of reference. It was also shown that crossing hands alters the processing of intensity of the stimuli and modifies brain responses to those stimuli (Gallace et al. 2011; Torta et al. 2013). These data support the idea that nociceptive inputs are integrated in multimodal representations of the body (Legrain et al. 2011; Haggard et al. 2013) in a brain network extending far beyond the classic nociceptive cortical network (Moseley et al. 2012b). More striking evidence was recently reported by De Paepe et al. (2014b) who provided data supporting the existence of a peripersonal frame of reference to map nociceptive stimuli. They used a temporal order judgment task with nociceptive stimuli applied to either hand and showed that the judgments were systematically biased by the occurrence of a visual stimulus in one side of space. Indeed, this visual cue facilitated the perception of the nociceptive stimulus applied to the ipsilateral hand, at the expenses of the stimulus applied to the opposite hand. Most important, this bias was significantly greater when the visual cue was presented close to the hand as compared to when it was presented 70 cm from the front of the hand. Using the crossing-hand procedure, additional experiments showed that this visuo-nociceptive spatial congruency effect was also influenced by the position of the limb (De Paepe et al. 2014a). For instance, the perception of a nociceptive stimulus applied to the left hand was facilitated by a proximal left-sided visual stimulus when the hands were uncrossed, but by a proximal right-sided visual stimulus when they were crossed. One important question

that remains to be addressed regards the neuronal mechanisms supporting such multimodal integration of nociceptive inputs. Animal studies have largely supported the notion that the peripersonal processing of tactile stimuli relies on the existence of multimodal neurons in the monkey's premotor and parietal cortices firing to the occurrence of tactile stimuli and visual stimuli when the latter are presented close to the adjacent somatosensory receptive fields (Graziano et al. 2004; see Macaluso and Maravita 2010 for a discussion about similar mechanisms in humans). Regarding nociception, only one study found similar multimodal neurons in the monkey's inferior parietal lobe (Dong et al. 1994).

The importance of the interaction between nociception, pain, and the representation of body space is also illustrated by the neuropsychological investigation of patients with chronic pain and more specifically in patients with complex regional pain syndrome (CRPS) (Moseley et al. 2012b; Legrain et al. 2012a). In addition to their sensory, motor, and vegetative symptoms, CRPS patients also suffer from unilateral cognitive deficits leading to impaired perception and impaired utilization of the affected limb. For this reason, CRPS patients were suspected to present with a "neglect-like" symptomatology (e.g., Förderreuther et al. 2004; Galer and Jensen 1999; Moseley 2004). Although the comparison to the symptomatology observed in poststroke patients with hemispatial neglect syndrome is still a matter of debate (see Legrain et al. 2012a; Punt et al. 2013), cortical changes observed in CRPS do not only affect areas involved in sensory and motor functions (Krause et al. 2006; Maihöfner et al. 2004) but also those involved in more complex and multisensory processing (Maihöfner et al. 2007). Several neglect-like symptoms were described such as asomatognosia (loss of body limbs' ownership) (Galer and Jensen 1999), hypo- and bradykinesia (movements are difficult to initiate and slower) (Frettlöh et al. 2006; Galer and Jensen 1999), impaired mental image (Moseley 2005), and impaired schema (Schwoebel et al. 2001; Moseley 2004) of the CRPS limb (see Legrain et al. 2012a for a review). Classic neuropsychological testing of neglect did not reveal major deficits in extra-body space (Förderreuther et al. 2004; Kolbe et al. 2012). Conversely, body space evaluations revealed phenomena of referred sensations such as allesthesia or synchiria in response to tactile stimuli applied to the CRPS limb (Acerra and Moseley 2005; Maihöfner et al. 2006; McCabe et al. 2003). Moseley et al. (2009) showed that temporal order judgments of tactile stimuli applied to either hand in a normal posture were biased at the expenses of the stimulus applied to the CRPS hand, suggesting a deficit similar to tactile extinction. But, surprisingly, the orientation of the perceptual bias was influenced by the position of the hands: when the hands were crossed, the perception of the stimulus applied to the healthy hand was in this case biased at the advantage of the stimulus applied to the CRPS hand. It was hypothesized that CRPS patients do not specifically neglect the perception of the CRPS limb but rather the part of the body placed in the side of space where the CRPS limb normally resides. The authors also showed significant changes of limb temperature when the limbs were crossed over the body midline (Moseley et al. 2012a). Finally, based on an experimental procedure aimed to misalign vision and proprioception using prismatic goggles, they suggested that the influence of spatial representation on body perception and temperature was mostly

driven by visual features rather than the proprioceptive perception of the position of the CRPS limb (Moseley et al. 2013). For these authors, the neglect-like symptoms observed in CRPS might reveal an altered representation of the body space organized along the sagittal midline of the body (Moseley et al. 2012b). The studies reviewed here above also show that CRPS-related symptoms can alter, not only somatotopic representations, but also spatiotopic representations of the body space (Moseley et al. 2009). These misaligned spatial representations would have been caused by maladaptive changes in cortical plasticity due to the initial musculoskeletal trauma (Moseley et al. 2012b) or implicit behavioral strategies to avoid limb provocation (Marinus et al. 2011). Altered body representations might in turn impair sensory perception and autonomic regulation of the pathological hemibody.

However, these assumptions were challenged by studies that showed that neglect-like symptoms cannot be locked to the side of space corresponding to the CRPS limb. Sumitani et al. (2007b) evaluated body representation in CRPS patients by means of visual estimates of the body midline. A visual stimulus was flashed and moved horizontally on a screen about 2 m in front of the participants. Patients were asked to guide verbally the visual stimulus until they estimated that the stimulus was positioned on the sagittal plane of their body midline. When the task was performed in the dark, their estimations were shifted significantly towards the side of space ipsilateral to their CRPS hand, as if, in the present case, they neglected the side of space corresponding to their healthy limb (for opposing results, see Kolbe et al. 2012; Reinersmann et al. 2012). As a consequence of nerve block following lidocaine injection, those estimates of the body midline tended to shift to the other hemispace, that is, the side of space contralateral to the CRPS hand (Sumitani et al. 2007b). These data suggest that the unbalanced body representation, as evaluated by visual body midline judgment task, is caused by attentional shifts due to excessive information coming from the affected limb, a hypothesis sharply in contrast with the assumption of a disownership of the CRPS limb (Moseley et al. 2012b). These discrepancies between the observed data across different studies emphasize that CRPS symptoms cannot be strictly paralleled to those observed in hemispatial neglect consequent to a stroke. Punt et al. (2013) argued that the CRPS-related motor symptoms such as hypo- and bradykinesia can be interpreted as a consequence to a learned nonuse consecutive to conditioned reduced attempts to move the pathological limb. Punt et al. (2013) added that representational and perceptual deficits were too subtle to be clinically relevant. Legrain et al. (2012a) suggested instead that neuropsychological testing performed until now was not adequate enough to reveal perceptual deficits specific to the CRPS pathophysiology. These authors recommended also a systematic investigation of spatial perception abilities across the different sensory modalities and, then, across the different frames of reference, using similar experimentally controlled procedures (see also Rossetti et al. 2013). In any case, the data reviewed in this paragraph suggest that chronic pain states such as CRPS can be useful to investigate the impact of pain on the abilities to represent and perceive the body and the surrounding space (Legrain et al. 2011; Moseley et al. 2012b) and the integration of nociceptive inputs in such cognitive representations (Haggard et al. 2013).

1.5 Action Selection

Peripersonal space is the privileged space for grasping and manipulating objects, but also for preparing defensive actions towards proximal objects that appear to be threatening. However, motor control and action selection have rarely been investigated in pain research. Yet, it is known that motor and premotor areas are activated by nociceptive stimuli (Gelnar et al. 1999; Frot et al. 2012). Using transcranial magnetic stimuli, Algoet et al. (2013) showed that nociceptive stimuli can modify motor excitability of the muscles of the arm and the hand onto which the stimulus is applied. It was also shown that the decision to move or to not move the hand onto which the noxious stimulus was applied altered the electrophysiological responses to this stimulus (Filevitch and Haggard 2012). But the neurophysiological mechanisms underlying the selection and the preparation of an action in response to nociceptive stimuli are still unknown. Recent studies suggest that reflex motor responses such as the eye blink reflex triggered by hand electrocutaneous stimulation can be controlled by high-order cognitive functions (Sambo et al. 2012a, b; Sambo and Iannetti 2013). These authors showed an increase of the magnitude of the eye blink reflex when the hand onto which the stimuli were applied approached the face. The authors concluded that this increase in the motor response could index the boundary of a defensive peripersonal representation of the face. However, because in these studies no external visual stimulus approaching the face was used as a control, the authors could not confirm the main role of vision nor exclude a causal role of personality traits such as anxiety. In this sense, any conclusion about a link between antinociceptive motor responses and spatial cognition is premature.

1.6 Neuropsychological Rehabilitation

Until now, the usefulness of clinical neuropsychology for the treatment of pain is still underestimated. However, some of the data reviewed above suggest a potential effectiveness for rehabilitation techniques based on cognitive neuropsychology. For instance, due to some similarities between CRPS and hemispatial neglect symptomatologies, Sumitani et al. (2007a) proposed to use in pain patients prismatic adaptation (PA), a noninvasive procedure which combines visual displacement induced by prismatic goggles and sensorimotor coordination to promote a reorganization of spatial cognition (Rossetti et al. 1998). This method allows misdirecting the brain by misaligning the real position and the visually perceived position of a target during a reach-to-point task and forces to compensate pointing movements during adaption by generating a realignment of sensorimotor coordination. PA has been shown to decrease neglect-related symptoms in poststroke patients (Rode et al. 2003). Sumitani et al. (2007a) used PA in five CRPS patients with prisms creating visual

displacement towards the side of space contralateral to the CRPS limb, that is, towards the side of space corresponding to the healthy limb. It is worth noting that Sumitani et al. (2007b) reported that CRPS patients neglected the portion of space corresponding to the healthy limb. Therefore, whereas PA in neglect patients is generally performed with prismatic displacement towards the non-neglected ipsilesional hemispace, Sumitani et al. (2007a) induced prismatic displacement towards the neglected hemispace. While body midline judgments were immediately shifted towards the hemispace ipsilateral to the healthy limb, the authors observed a reduction of pain and other CRPS-related symptoms only two weeks after PA. A follow-up of one single case showed that when PA was performed with a visual displacement towards the CRPS (non-neglected) side, the symptoms worsened. This suggests that the orientation of prismatic shift is a crucial feature for rehabilitation. Bultitude and Rafal (2010) replicated these results, again with PA promoting a visual displacement towards the hemispace ipsilateral to the healthy limb. They also showed that PA was effective in reducing CRPS symptoms only when the pointing task was performed with the CRPS hand, but not when PA was performed with the healthy hand. Despite the low number of cases, two conclusions can be proposed. First, PA seems effective in reducing not only body representation displacements but also CRPS symptoms. This suggests that sensorimotor misalignment during visually guided movements can have a role in CRPS pathophysiology. Second, the fact that the effectiveness of PA in CRPS depends on the specific displacement of vision towards the neglected hemispace and on the specific pointing with the CRPS hand suggests that impaired spatial cognition in hemispatial neglect and CRPS relies on different mechanisms.

1.7 Conclusion

Recent years have seen new interests for theoretical models of cognitive psychology in the field of pain research through analyses of behaviors such as reaction times and temporal order judgments. It is important to note that this approach does not deny the importance of the sensation of pain, nor the existence of neurophysiological mechanisms generating this feeling as specific qualia. Instead, this approach emphasizes the need to take into account the cognitive state of the subject receiving a painful stimulus at a given time and in a particular environment. It also emphasizes the functional role that pain has for adapting sensorimotor functions of the body to a perpetually unstable and potentially threatening environment. The cognitive approach of pain also emphasizes the need to go beyond the purely physiological conceptualization of nociceptive processing and to define a theoretical framework that incorporates pain as an epiphenomenon of a system which represents, perceives, and defends the body and its surrounding space. This approach also proposes a synergy between classical medical intervention and neuropsychological rehabilitation, towards what we would be tempted to call *cognitive physiotherapy*.

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Chapter 2
Emotional Aspects of Chronic Pain

Anne-Françoise Allaz and Christine Cedraschi

Abstract Emotions and chronic pain are deeply entangled. Emotions can predispose to or modulate pain. Various factors pertaining to negative affectivity can contribute to pain intensity and chronicity, as well as to its disabling consequences. In the last decade, advances in neurosciences have indisputably confirmed the clinical evidence of pain as an experience involving sensory and emotional components, emphasizing the essential role of brain structures related to motivation and emotions, pointing to central sensitization or to epigenetic influences on affect regulation disorder. Contemporary theories call upon integrative models that reflect the history and personal vulnerabilities as much as the emotional and cognitive factors that may influence pain. In patients with chronic pain, interpersonal dimensions also received renewed interest, and in particular attachment or somatization and alexithymia as specific modes of expressing emotions. Therapeutic approaches increasingly emphasize motivation as well as acceptance of pain and goal achievement despite the presence of pain.

2.1 Chronic Pain and Emotions in the Biopsychosocial Model

Pain and suffering are at the same time totally universal and strictly personal experiences; they are universal insofar as they are common to all individuals whatever the individuals' personal characteristics and social or cultural memberships, and they are personal because of their subjective characteristics and the difficulty in

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conveying them to others. Pain is thus somehow at the crossroads of the individual and the group. This sets into play physiological and psychological mechanisms, and it is also inserted within the social context to which the individual belongs. This context contributes to modulate variables such as the meaning and the expression of pain which in turn influence pain-related adjustment.

This review on the relationships between chronic pain and emotions is embedded within a biopsychosocial perspective on pain with a reference to clinical practice (Allaz 2003; Gatchel et al. 2007; Lumley et al. 2011). This relationship has been described as including dimensions of pain that have been termed "awareness," "expression," "experiencing," and "modulation" (Lumley et al. 2011). The biopsychosocial perspective requires a comprehensive concept of pain, including sensory, affective, and cognitive dimensions. In the biopsychosocial model, the somatic basis of pain is acknowledged, even if the cause of nociception cannot be identified. When pain becomes chronic, psychosocial factors become increasingly important so that a number of psychological, social, and physical traits are considered simultaneously. Such a multidimensional model acknowledges chronic pain as a dynamic process that results from an ongoing interplay between physical and psychological characteristics. It also stresses the multifaceted nature of pain as well as the considerable overlap that exists between variables and also the entanglement of psychological processes. This chapter is divided into categories that are to some extent artificial but that allow the reader to consider more easily the relative contribution of each factor. The review focuses on state-of-the-art knowledge as well as treatment and research current trends.

2.2 Depression and Affective Disorders

Depression is the dominant affective state associated with pain (Dersh et al. 2002; Gatchel et al. 2007). Its prevalence in most clinical surveys with chronic pain patients varies between 20 and 70 % that is three to five times more than in primary care patients (Bair et al. 2008; Demyttenaere et al. 2007). The prevalence is even higher in unexplained widespread chronic pain (Raphael et al. 2006). The association is demonstrated across different chronic pain syndromes and in all age cohorts (Egger et al. 1999; Lenze et al. 2000; McWilliams et al. 2004). Moreover, more than half of the patients suffering from a major depressive episode present with pain (Demyttenaere et al. 2006). A large international prospective cohort study showed that the initial presence of chronic pain predicted the occurrence of psychological disturbances as much as such disturbances predicted the occurrence of pain (Gureje et al. 2001). Hence, whereas chronic pain can undoubtedly cause a depression, the presence of depression also represents a predisposing factor to the onset and chronicity of pain (Jarvik et al. 2005). Depression has been shown to be predictive of chronicity and prolonged time to recovery in low back pain (Edwards et al. 2011), postherpetic neuralgia, rheumatic diseases (Goldenberg 2012), and in most if not all chronic pain syndromes (Garcia-Cebrian et al. 2006). Are pain and depression

distinct or common entities? The high prevalence of the association between the two syndromes and the many clinical and neurobiological similarities are consistent with the long-standing hypothesis of a single entity described as "affective spectrum disorder" (Hudson and Pope 1989) or more recently as "pain-depression dyad" (Goldenberg 2010). However, this unifying theory remains controversial (Garcia-Cebrian et al. 2006). For most clinicians and researchers, depression and pain are separate entities (Bair et al. 2003; Hennigsen et al. 2003; Katon et al. 2007). In the clinical setting, the central issue seems to be identifying and not trivializing the presence of depression. This may represent a challenge due to the frequent reluctance of chronic pain patients to give voice to their affective states. Whatever the difficulty, discussing the possibility of a depressive mood with chronic pain patients is central as the treatment of depression leads to undisputed benefits, including in elderly people.

2.3 Anxiety

Although anxiety has attracted less attention than depression, a growing body of research supports the association between the various clinical presentations of anxiety and chronic pain syndromes (Asmundson and Katz 2009; Kroenke et al. 2013). The presence of anxiety disorders or panic attacks is particularly documented in headaches, fibromyalgia (Raphael et al. 2006), and abdominal pain, including in children and elderly people (Lenze et al. 2000; McWilliams et al. 2004). The prevalence of anxiety may be as high as 35–50 % in chronic pain patients (Kroenke et al. 2013; McWilliams et al. 2004) or two to three times higher in people complaining from chronic back pain as compared to pain-free individuals (Demyttenaere et al. 2007).

Anxiety can be expressed in various ways. The documented effect in lowering pain thresholds (Rhudy and Meagher 2000) as well as the enhanced attention to experienced feelings and sensations (Carter et al. 2002) can account for pain amplification. A "hypochondria" dimension with its associated anxious concerns and focus on painful sensations often leads to repeated requests for additional consultations or investigations. Anxiety can also be manifested primarily in the form of physical pain states: tightness, constriction, or atypical chest pain, the latter especially during panic attacks (Huffman and Pollack 2003). In fact, the majority of patients with panic attacks report pain symptoms of one type or another (Schmidt et al. 2002). Post-traumatic stress disorder (PTSD) is often considered as an anxiety disorder. In this syndrome, the report of chronic pain is also very high (McWilliams et al. 2004) with prevalence up to 50–80 % in military veterans (Asmundson et al. 2002).

The co-occurrence of anxiety disorder is surprisingly high among patients with chronic pain. It should be systematically evaluated and taken into account, in view of its impact on the experience and presentation of the pain complaint and its repercussions on patients' distress and quality of life (Asmundson and Katz 2009; Kroenke et al. 2013).

2.4 Anxious Concerns and Negative Beliefs

Anxious concerns are far from uncommon; for example, they are apparent in the fears that evolve into paralysis in low back pain patients or the impression that the disease is gaining ground in patients suffering from fibromyalgia (Cedraschi et al. 2012). They can contribute to a significant decrease in quality of life. However, they may not always be expressed spontaneously, because they are seen as possibly too bizarre or disturbing to be verbalized.

Encompassed in the concepts of fear of pain, pain-related anxiety, or fear avoidance, expressions of fear and anxiety are known to contribute significantly to the development of chronic pain and of disability, even more than pain intensity itself (Crombez et al. 2012). The fear-avoidance model is a theoretical model that describes how psychological factors affect the experience of pain and the development of chronic pain and disability (Crombez et al. 2012). This model builds on the importance of the beliefs patients hold about their pain and their role in promoting disabling fear and avoidance. Beliefs have been defined as assumptions about reality which serve as a perceptual lens or a mental set through which events are interpreted, thus shaping an individual's understanding of his/her environment and influencing the individual's coping responses (Lazarus 1993). Inappropriate beliefs such as the belief that back pain is harmful or potentially severely disabling or an expectation that passive treatments rather than active participation will help have been described as warning signs ("yellow flags") of an increased risk of developing or perpetuating pain and long-term disability associated with low back pain (Nicholas et al. 2011) and thus are seen as barriers to adjustment and recovery.

In the fear-avoidance model, negative beliefs about pain lead to a catastrophizing response in which patients "imagine the worst possible result that could happen, but accept it as the given result" (Linton and Shaw 2011). This leads to fear of pain, fear of activity, and avoidance that initiate disuse and generate distress. This may in turn reinforce the primary negative appraisal and set into motion a vicious circle that inhibits patients' commitment and consequently eventual therapeutic progress. This model also theorizes that patients who do not display catastrophizing responses and fear-avoidance beliefs are more likely to confront pain problems and engage actively in the recovery process (Vlaeyen and Linton 2000).

2.5 Catastrophizing

Pain catastrophizing has been defined as an exaggerated negative cognitive set brought to bear during actual or anticipated pain experience (Sullivan et al. 2001). The conceptualization of catastrophizing is that of a unitary construct, comprising three dimensions: magnification, rumination, and helplessness. *Magnification* refers to the tendency to magnify or exaggerate the threat value or seriousness of the pain sensations; *rumination* refers to thought content reflecting worry, fear, and the inability to divert attention away from pain; and *helplessness* reflects elements of

pessimism and helplessness in relation to the ability to deal with the pain experience (Sullivan et al. 2001).

Catastrophizing has been associated with chronicity in various pain syndromes, including low back pain and fibromyalgia. A recent systematic review investigating the role of catastrophizing as a prognostic factor in patients with low back pain showed conflicting results about the association between catastrophizing and the future course of pain and disability. Interestingly, however, studies using cutoff values suggested the presence of a "dose-dependent" effect of catastrophizing (Wertli et al. 2014). Another review examining pain, catastrophizing, and depression in the rheumatic diseases including fibromyalgia stressed that catastrophizing and depression are risk factors for various adverse pain-related outcomes such as physical disability, increased pain severity, and pain sensitivity (Edwards et al. 2011). Indeed, pain-related catastrophizing has been shown consistently to be associated with greater pain and physical and psychosocial dysfunction among individuals with chronic pain (Linton and Shaw 2011; Nicholas et al. 2011). It has also been shown that pain-related catastrophizing thoughts tend to be stable rather than variable over time in the absence of an intervention targeting catastrophizing or a reduction in pain or depression (Turner et al. 2004). It is thus easily understandable that among the cognitive and affective factors influencing pain, catastrophizing has been termed a key determinant in different types of chronic pain syndromes (Smeets et al. 2006), associated with emotional and behavioral responses (such as pain-related fear and avoidance) that predict consequent levels of depression and disability (Leeuw et al. 2007).

The exact positioning of the concept of catastrophization is still debated; however, it is an independent factor, acting as marker of distress and of particular interest as it may provide a therapeutic target (Smeets et al. 2006). Recent developments in this concept also suggest a relational model ("communal model of pain catastrophizing") where pain catastrophizing is considered a way of expressing distress to one's significant others; however, while aimed at seeking empathy and support, pain catastrophizing often induces negative attitudes in the patient's social environment (Cano et al. 2009).

2.6 Perceived Injustice and Anger

Perceived injustice in the context of injury and pain is construed as an appraisal cognition encompassing the *severity of loss consequent to injury*, the *irreparability of loss*, *blame*, and a sense of *unfairness* (Sullivan et al. 2008). Although perceived injustice has been conceptualized as a construct distinct from catastrophizing, various studies have stressed that perceived injustice is highly correlated with pain catastrophizing, pain-related anxiety, and depression (Sullivan et al. 2012). Scott and Sullivan (2012) have shown that perceived injustice moderates the relationship between pain severity and depressive symptoms; drawing from their work, they also suggest that catastrophizing might be a precursor to perceiving injustice, such that individuals might first need to appraise pain as a catastrophe before viewing it as irreparable.

Recent research has also uncovered the impact of perceived injustice on pain intensity, physical and psychological recovery, and rehabilitation in general (Sullivan et al. 2012). Interestingly, it has been proposed that "just world" beliefs may have a buffering effect on psychological distress in chronic pain patients, so that patients with lower levels of pain, disability, and psychological distress may experience life events as more "just" than patients who experience more severe pain, disability, and distress (McParland and Knussen 2010).

Anger as an emotional aversive reaction contributes to the feeling of injustice. It has also been described as playing a significant mediational role in pain intensity, psychological distress, and disability as well as in the chronification process (Trost et al. 2012). Recent work indicates that anger intensity and anger inhibition mediate the relationship between perceived injustice, pain, and pain outcomes (Scott and Sullivan 2012; Scott et al. 2013), and in particular, it is suggested that both state anger, that is, a characteristic of the individual, and anger inhibition (i.e., an expression style referring to attempts to suppress feelings of anger) contribute to a large extent in explaining the impact of perceived injustice on pain intensity and may also be one of the mechanisms through which perceived injustice influences depressive symptoms (Scott et al. 2013). Attribution of blame is part of the process, as an antecedent of perceived injustice and anger reactions. The attribution of blame to external sources (e.g., to traumatic events) contributes to greater levels of anger and higher perceived injustice, eventually increasing feelings of hopelessness and helplessness and leading to the more or less conscious adoption of a victim role. The therapeutic alliance may be at risk when perceived injustice and anger lead to hostility or requests for compensation (Trost et al. 2012). Therefore, in clinical practice, identifying feelings of anger and injustice and working on anger regulation (i.e., on inhibition and expression of anger) can help prevent misunderstandings and maintain the therapeutic relationship. The difficulty of managing conflict and the repression of anger have been thoroughly described in patients with alexithymic traits (Nemiah and Sifneos 1970). This repression of emotions, and in particular of negative emotions, has also been associated with higher pain intensities, greater adjustment difficulties, and heightened physiological reactivity. Interestingly, it has been shown that while anger inhibition triggers greater sustained muscle tension than anger expression, the deleterious effects of inhibition are particularly salient in those individuals who report a predominant disposition ("trait-anger") to express anger in an outward fashion (Burns et al. 2008). These data cover a wide range of biopsychosocial reactions and thus testify to the importance of not neglecting anger and its correlates whose expression may vary from one individual to another.

2.7 Trauma

The association between pain and traumatic experiences has long attracted the attention of pain specialists. Indeed, traumatic experience often represents one of the very central dimensions of suffering in patients with chronic pain, way beyond

the classical association between chronic pain and PTSD. On one side, as described above, patients' attribution of their symptoms to traumatic events is far from exceptional (Cedraschi et al. 2013). This can elicit feelings of anger or injustice and lead to involvement in compensation claims. On the other hand, since Engel's description of the "pain-prone-patient" about 50 years ago, chronic refractory pain has often been associated with a history of abuse, neglect, or childhood trauma. From the epidemiological standpoint, data associating pain and abuse are very impressive (Davis et al. 2005). It is particularly prevalent in patients suffering from chronic unexplained pain syndromes like fibromyalgia (Imbierowicz and Egle 2003) or chronic pelvic pain in men (Hu et al. 2007) and in women (Lampe et al. 2003). Lately however, interest has shifted from abuse per se to emphasize the central importance of the dimension of neglect or abandonment (Landa et al. 2012). The importance of chronic stress has also been emphasized in this context (Van Houdenhove and Luyten 2005).

Traumatic experience such as child abuse or neglect has been linked with long-standing affective regulation disorders, being associated with difficulties with emotional disclosure and expression (Katon et al. 2007; Raphael et al. 2001). In the clinical encounter, reluctance to talk about personal history and difficulties in creating trusting relationships may point to the existence of such traumatic experiences, especially when a seemingly minor event leads to a perplexing intractable pain or disability.

2.8 Somatization and Alexithymia

The association between affect regulation disorder and the tendency to express distress by means of somatic symptoms has been consistently linked with the concept of *alexithymia*, literally meaning no words to express emotions (Nemiah and Sifneos 1970). Alexithymia is closely linked to the concept of somatization (Mattila et al. 2008). Lipowski (1988) has proposed a widely used, broad, and pragmatic definition of somatization: "the expression of an intrapsychic or psychosocial distress through bodily complaints (for instance pain), followed by medical consultation." In brief, emotional problems or mental suffering in general can be expressed in a somatic channel and take the "mask" of pain. Pain is the dominant mode of somatization in both primary care and specialized consultations, throughout different cultures (Gureje et al. 2001).

The process of somatization continues to challenge clinicians and researchers. Freud's masterly description of the "conversion" of an intrapsychic conflict into a bodily symptom (Strachey et al. 1955) has been followed by numerous developments especially in the psychosomatic field. The question of the origin and meaning of the symptom remains debated, whereas many models attempt to explain the process of somatization. The preferred expression of distress through bodily symptoms may be related to several different factors. We will only mention here the most relevant ones. The neurobiological and neuropsychological entanglement between

pain and emotions is now largely supported (Apkarian et al. 2005; Roy et al. 2009). Psychological factors are of major importance with alexithymia as a central phenomenon. The great difficulty with awareness and expression of emotions at the core of this concept makes the link with the frequently observed somatic expression of mood disorders and of depression in particular (Egger et al. 1999; Katon et al. 2007). As mentioned, a history of trauma or neglect during childhood is strongly associated with the presentation of multiple somatic symptoms and alexithymia (Joukamaa et al. 2008; Raphael et al. 2001). There is growing evidence that epigenetic factors, that is, the modulation of gene expression by environmental factors like affective deprivation or trauma, can be major contributors (Mehta et al. 2013). Behavioral and social factors emphasize the role of reinforcement to explain the presentation of distress through a bodily channel. Somatization may correspond to learned attitudes and behaviors (e.g., "painful families") who express any distress through painful complaints or to a social reinforcement, thereby facilitating entry in the healthcare system (Nettleton 2006). From an anthropological point of view, somatization can be understood as a culture-bound mode of communication. In psychodynamic terms, somatization is understood as a "shortcut of the psyche" acting as a protection or a defense against an unbearable suffering like grief or melancholy (McDougall 1989). To avoid the suffering related to a loss (real or symbolic), the individual unconsciously overinvests a body space that becomes difficult to cure (Nissen 2000). Globally, painful symptoms and pain behavior can be considered as a message of distress (Allaz 2003).

2.9 Attachment Styles

Bowlby's hypothesis that early experiences with caregivers are forming models of relationships later reproduced throughout life is widely known as "attachment theory" (Bowlby 1977). It comes of no surprise that affect regulation disorder associated with somatization and trauma is correlated with difficulties in interpersonal relationships, manifested as an "insecure attachment style" (Landa et al. 2012). Vulnerability in interpersonal encounters and high sensitivity to rejection associated with little ability to create trusting bonds are hallmarks of the insecure attachment style, mirroring observations made in clinical practice with chronic pain patients (Ciechanowski et al. 2002). The difficulties in creating interpersonal relationships can in turn contribute to the difficult construction of the therapeutic alliance (Allaz 2003).

The dimension of attachment has recently attracted renewed interest in the field of pain and has been the subject of recent reviews (Lampe et al. 2003; Meredith et al. 2008; Porter et al. 2007). Various studies have shown that an insecure attachment style contributes to high pain intensity and disability, to feeling pain as a threat, and to a higher degree of pain-related distress (Meredith et al. 2008). Insecure attachment is also correlated to high levels of depression, anxiety, and catastrophization and to a tendency to express distress in a somatic way, in children as well as in adults (Landa et al. 2012; Porter et al. 2007). Globally, attachment disorders

represent a strong vulnerability for difficult adjustment to pain as described in the attachment-diathesis model of chronic pain (Meredith et al. 2008).

Interestingly, in a related field, the hypothesis of a close neuroanatomical relationship between pain and suffering related to social rejection has recently attracted a lot of attention (Eisenberg 2012).

2.10 Clinical Evidence Strengthened by Advances in Neurosciences

For pain specialists, and in particular for psychotherapists, it is highly gratifying to see that major recent advances in neurosciences and neuroimaging have indisputably confirmed the clinical evidence of pain as an experience involving both sensory and emotional components. The essential role of brain structures related to motivation and emotions has indeed been widely demonstrated (Apkarian et al. 2005; Roy et al. 2009). Such advances as the evidence of central sensitization (Desmeules et al. 2003), epigenetic influences on affect regulation disorder (Mehta et al. 2013), and the neuroanatomical closeness of pain and social rejection (Eisenberg 2012), among others, reinforce evidence of the strong and mutual link between pain and emotions. Globally, the major advances of the neurosciences in the last decade not only allow for a better understanding of the complexity of pain experience but also of the development of personal vulnerabilities. Hopefully, these notions – when shared with the patients – will contribute to a common understanding of the complex modulation of emotions on pain chronification and to minimized misunderstandings in the therapeutic relationship. Taken together, contributions from the neurosciences brings as much a confirmation of the importance of emotional dimensions as new insights into the way we should acknowledge chronic pain patients. As Lumley et al. (2011) suggested: "At a minimum, we encourage clinicians working with patients who have persistent pain to at least inquire about – if not explore at length – [emotional] issues."

2.11 Coping with Pain: Toward a Shift in Paradigm?

Cognitive-behavioral therapy (CBT) has become the prevailing treatment for patients with chronic pain associated with psychological distress and disability (see also Chap. 10: Nicholas). Cognitive (e.g., reframing, examination of automatic thoughts, guided imagery) and behavioral (e.g., in vivo exposure, operant or respondent learning) techniques are used to modify thinking about and behaving with pain. There is evidence that CBT-based treatments are effective in various chronic pain disorders, with only moderate effect sizes, however (Veehof et al. 2011).

In recent years, therapies based on acceptance have received growing interest. In these therapies, the focus is on acceptance of pain and goal achievement (McCracken et al. 2004). Acceptance requires that the individual continues the activities he/she

values and keeps his/her commitment to his/her personal goals despite the presence of pain and that he or she stops devoting time and efforts to control or avoid pain and difficult experiences (McCracken et al. 2004; Sullivan et al. 2012). Acceptance of pain has been associated with lower pain intensity, lower degrees of pain-related fear, and avoidance of psychological distress and of disability (McCracken and Zhao-O'Brien 2010). It has also been evidenced that patients with higher levels of acceptance display less pain catastrophizing and that readiness to experience difficult personal events to pursue one's goals has a positive impact on the orientation toward present or anticipated pain experiences (de Boer et al. 2014).

This interest in pain acceptance may call for a paradigm shift toward approaches that better consider the patients' motivational capacities or, in some instances, resistance to treatment (Crombez et al. 2012). As such, these approaches take some distance with treatment strategies described hitherto as effective for all patients. This third-generation cognitive-behavioral therapies have been labeled acceptance and commitment therapy (ACT). ACTs are centered on acceptance, confrontation, and also mindfulness, that is, a state of intentional and nonjudgmental awareness and focus on the present moment (Veehof et al. 2011). It is noteworthy that recent publications bear witness to the development of studies and therapeutic options taking this dimension into account, and notably ACT. A topical systematic review and meta-analysis of acceptance-based interventions showed that mindfulness-based stress reduction programs and ACT have small to medium effects on pain, depression, anxiety, physical well-being, and quality of life; they are thus not superior to CBT but do provide good alternatives (Veehof et al. 2011).

2.12 Conclusion: Emotional Dimensions in the Clinical Encounter

In clinical pain practice, the importance of taking into account individual capacities, stages of life, as well as patient preferences, doubts, or resistance to treatment cannot be underestimated. The goal of treatment remains mainly rehabilitative in primary as well as specialized care. Due to frequent resistance to personal disclosure, referral of the patient to a specialist is not always indicated. Nevertheless, a recent systematic review emphasizes the beneficial effect of psychotherapy on psychological distress, disability, quality of life, and, to a lesser extent, pain (Williams et al. 2012).

An important emerging trend involves the development of integrative and developmental models of chronic pain (Landa et al. 2012; Meredith et al. 2008). Being aware of the documented consequences of a traumatic environment on the expression of distress, on the regulation of affect including feelings of anger or catastrophization, and on the capacity to create trusting relationships can help to better manage misunderstandings and interpersonal difficulties in the care of chronic pain patients. Therapeutic alliance remains sometimes difficult to build and requires a personal commitment of the pain therapist, whatever his/her specialty. The issue of emotional experience and of maintaining a good capacity for empathy in the therapists has not been discussed here. Yet, these issues deserve very close attention in the clinical context.

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Chapter 3
Cerebral and Spinal Modulation of Pain by Emotions and Attention

Mathieu Roy

Abstract In this chapter, the effects of emotions on the spinal and cerebral processes underlying nociception and pain perception are examined. Throughout the chapter, the effects of emotions will be compared with those of attention, and the potential interactions between emotions and attention will be discussed. The overall portrait that emerges from this literature review is that emotions and attention can exert their effects at multiple levels of pain processing, from the spinal cord to the cerebral cortex. Moreover, because of the highly integrated and dynamic nature of the neural processes underlying pain perception, it is difficult to identify the origins of emotions' and attention's effects on pain. Future research should therefore aim at probing the effects of emotions and attention at various levels of pain processing by combining different psychophysiological methods.

3.1 Introduction

The primary function of pain is to alert the organism that its corporal integrity has been compromised in order to attend to both the sources of the pain and its potential consequences. Contrary to purely exteroceptive senses (e.g., vision or audition) which function to gather information about the outside world, pain conveys information about the internal condition of the body. It is the last defense against life-threatening injuries, and in this sense, pain can be conceived as both an interoceptive sense, a homeostatic emotion, and a behavioral motivation (Craig 2003). The inherent survival value of pain shapes its processing at all levels of the neuraxis, from the spinal cord to the cerebral cortex. In this chapter, the influence of emotional factors on pain neural processing and subjective perception will be examined, as well as with attentional factors. First, a more general discussion of the relationship between emotional and cognitive sources of pain modulation will be undertaken. The modulatory effects influencing preconscious nociceptive processes versus modulatory effects affecting the cortical generation of the subjective experience of pain will also be considered.

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3.2 Emotional and Cognitive Sources of Pain Modulation

Emotions have been traditionally considered as qualitatively different from, and somewhat inferior to, cognitions (Descartes 1649). However, this view has been challenged within the field of psychology, where there is a long-lasting debate concerning the role of cognitive factors as determinants of emotions (Arnold 1960; Lazarus 1966). As the emerging field of cognitive neuroscience grew, this debate over the relationship between cognition and emotion rapidly spread to the neural systems underlying these two types of processes, with some researchers arguing that the neural processes underlying emotions are computationally inseparable from those underlying cognitions (Ledoux 2000; Pessoa 2008), while others made the case that emotions' subjective valence requires a separate explanation (Panksepp 2007). Within the field of pain research, a classical distinction is generally made between emotional and attentional sources of pain modulation (Villemure and Bushnell 2002). While redirecting attention away from pain seems to predominantly affect the sensory dimension, emotions appear to influence the affective dimension of pain (Villemure et al. 2003). Moreover, both sources of modulation seem to be associated with different neural systems. Whereas emotions seem to modulate ascending nociceptive signals through descending modulatory mechanisms centered around the periaqueductal gray (PAG) (Villemure and Bushnell 2009; Bushnell et al. 2013), attention appears to bias sensory processing in primary sensory (S1) and insular cortices through the frontoparietal attentional orienting system (Corbetta and Shulman 2011; Bushnell et al. 2013). In agreement with these findings, the effects of emotions on pain ratings have been repeatedly associated with a parallel modulation of spinal nociceptive flexion reflexes (NFRs; Rhudy et al. 2005, 2006; Roy et al. 2011, 2012a), which can be considered as an index of spinal nociception (Sandrini et al. 2005). By contrast, performance of a distractive task (McIntyre et al. 2006; Petersen et al. 2001; Edwards et al. 2007), or simply reorienting attention away from pain (Roy et al. 2011), seems to have facilitatory or null effects on NFRs, suggesting that attention and emotion have different effects on spinal nociception.

However, the boundaries between emotional and attentional sources of pain modulation may not be as clear as first thought. Indeed, decades of research in humans and animals have suggested that distraction also engages descending modulatory controls. Moreover, relatively recent evidence of increased PAG activity during distraction has been interpreted as a sign that distraction engages descending pain inhibitory mechanisms (Tracey et al. 2002), although this interpretation may constitute a case of abusive reverse inference (Poldrack 2006). More compelling evidence comes from earlier physiological studies showing increases in NFR thresholds during performance of a cognitively demanding task (Bathien 1971) or decreased activity in wide dynamic range (WDR) neurons when attention is directed away from pain (Bushnell et al. 1985). Finally, another line of evidence in support of descending modulatory effects comes from electrophysiological studies in humans showing that directing attention away from or toward the stimulated limb affects the earliest component of nociceptive event-related responses (ERPs; Legrain et al. 2002). This

suggests an upstream modulation of nociception at the spinal level. While these effects of attention on pain can be described in purely cognitive terms, they also reflect a fundamental motivational function: because pain is an alarm signal, it can be toned down when performance of a concurrent task is to be prioritized.

Thus, although cognition and affect may be ontologically distinct processes, they are in practice very difficult to disentangle at the neural level. Indeed, cognitive processes are ultimately at the service of one's goals and desires. Moreover, because cognitive systems have limited information-processing capacities, stimuli constantly have to compete for these limited resources as a function of their behavioral relevance. This competition, which is thought to occur at both the perceptual and executive levels (Pessoa 2008), has to be orchestrated by affective valuation systems. The neural architecture underlying this constant competition therefore requires a profound integration of affective/motivational and cognitive systems through parallel and reciprocal connections between the sensory, cognitive, and affective regions of the brain. For instance, in the visual domain, sophisticated visual information stemming from "late" visual areas is conveyed to emotional structures, such as the amygdala and orbitofrontal cortex (OFC), which then bias early visual processing through reciprocal connections with both late and early visual cortices. In parallel, visual inputs also reach components of the frontoparietal attentional network, such as the lateral prefrontal cortex (LPFC), which also projects back to early visual cortices. Therefore, visual cortical responses reflecting an item's significance will be a result of simultaneous top-down modulation from frontoparietal attentional regions and emotional modulation from the amygdala and OFC (Pessoa 2008). In this manner, the cognitive or affective origin of the modulation is lost, and the item's impact on behavior is a product of both cognitive and emotional influences.

The same level of integration between emotional, cognitive, and sensory/perceptual processes also applies for pain. As a matter of fact, this integration may even run a little deeper for pain since descending modulatory pathways can influence ascending nociceptive signals as soon as their first synapse in the dorsal horn of the spinal cord. When reaching the cortex, these signals are then integrated with multisensory inputs in order to produce a higher-order representation of the source of the pain in relation with the body-in-space (Haggard et al. 2013), thereby allowing finely coordinated responses to the source of pain. Finally, the whole episode is also evaluated as a function of the immediate context together with long-term goals and beliefs in order to judge the general aversiveness of the experience (Craig 2003; Roy et al. 2012b). In the next sections, the influence of emotions on pain processing at the spinal and supraspinal levels and how these effects may interact with attention will be examined.

3.3 Spinal Modulation of Nociception by Emotions

The principles governing the effects of emotions on nociceptive processing can be broadly characterized as a process of competition between nociception and other sources of motivation, which can either be congruent or incongruent with pain

(Fields 2007). Anything more important than pain should therefore exert inhibitory effects on nociceptive processing. For instance, tolerance to pain induced by the hot plate test is increased in rats for which the plate had been previously associated with delivery of chocolate versus regular food pellets (Dum and Herz 1984). Pain is also strongly inhibited when animals feed on palatable foods (Foo and Mason 2005), while the effects dissipate when the food is rendered aversive through pairing with a toxic substance (Foo and Mason 2009). Extremely aversive stimuli can also have important analgesic effects, such as when animals are subjected to intense and inescapable noxious stimuli or are put in the presence of a predator. In these cases, the importance of responding to the life-threatening situation surpasses the importance of attending to the pain (Butler and Finn 2009). By contrast, stressors of lower intensities, such as air puffs (Wagner et al. 2013) or pairing with aggressive cagemates (Andre et al. 2005), typically produce pain facilitation, probably to facilitate defensive responses in situations where injuries are likely (Gray and Mcnaughton 2000).

These pro- and antinociceptive effects of emotions appear to be implemented by descending pain modulatory mechanisms depending on endogenous mu-opioid (MOP) agonists and originating in the PAG, rostroventral medulla (RVM)/raphe magnus (RM), ventromedial medulla (VMM), and dorsolateral pontine tegmentum (DLPT) (Fields 2004; Mason 2012). These structures contain the following two distinct types of neurons with opposing roles: "OFF" cells are deactivated by noxious stimuli and activated by MOP agonists, while "ON" cells are activated by noxious stimuli and inhibited by MOP agonists. Most importantly, OFF cells can reduce responses to noxious stimulation while ON cells facilitate nociceptive processing. Conditions that produce analgesia should therefore be expected to exert their effects by deactivating ON cells and/or activating OFF cells. Consistent with this hypothesis, opioid antagonists (e.g., naloxone), given either systemically or directly into the PAG or RVM, have been shown to reduce the analgesic effects of appetitive (Dum and Herz 1984) or stressful stimuli (Butler and Finn 2009). Similarly, feeding on a pleasurable food has been shown to inhibit VMM ON cells and to activate VMM OFF cells (Foo and Mason 2005).

Interestingly, these circuits, and in particular those centering around the VMM, RVM, or RM, are also involved in nonemotional forms of pain inhibition, such as the analgesia accompanying sleep or urination (Mason 2001, 2012). The modulatory effects of emotions therefore seem to be exerted through descending systems, which have a general function to coordinate basic homeostatic processes. Whereas some of these modulatory effects may be mediated by relatively closed reflexive loops, such as those recruited during urination, others may involve top-down projections from forebrain structures capable of assessing the behavioral relevance of environmental stimuli. For instance, stress-induced analgesia critically depends on the amygdala (Watkins et al. 1993). By contrast, stress-induced hyperalgesia has recently been associated with the release of cholecystokinin (CCK) in the RVM through hypothalamic-medullary projections (Wagner et al. 2013). CCK is an endogenous peptide, which post-synaptically antagonizes the effects of endogenous opioids (Heinricher and Neubert 2004). It is therefore well positioned

to influence the balance of activation of ON/OFF cells in structures mediating stress-induced hyperalgesia, such as the RVM (Wagner et al. 2013) or PAG (Lovick 2008). Interestingly, the same mechanisms also seem to account for pain modulatory phenomena requiring more elaborate forms of cognitive processing, such as placebo analgesia or nocebo hyperalgesia. Indeed, the administration of MOP or CCK antagonists in humans has been shown to counteract the effects of placebo or nocebo instructions (Benedetti et al. 2005). Placebo effects constitute a good example of the close interactions between cognition and emotions during pain modulation because they require elaborate cognitive processing in prefrontal systems capable of processing placebo instructions (Wager et al. 2004; Atlas et al. 2010) before engaging the brainstem's motivational circuits responsible for descending pain modulation.

In humans, positively and negatively valenced emotions induced by odors (Villemure et al. 2003), tastes (Lewkowski et al. 2003), pictures (Rhudy et al. 2005), films (Weisenberg et al. 1998), music (Roy et al. 2008), hypnotic suggestions (Rainville et al. 2005), or sentences (Zelman et al. 1991) have also been shown to modulate pain. Pleasant emotions generally reduce pain ratings and increase pain perception thresholds, while unpleasant emotions increase pain ratings and decrease pain perception thresholds. These valence-dependent effects of emotion on pain ratings seem to be mediated by descending modulatory circuits, as evidenced by parallel modulations of the lower limb NFR (Rhudy et al. 2005; Roy et al. 2011, 2012a; Bartolo et al. 2013). This polysynaptic heterosegmental reflex, which is characterized by a flexion of the stimulated limb, occurs in a time window (approximately 90–180 ms) consistent with the conduction velocity of A∂ nociceptive afferents (Sandrini et al. 2005). Moreover, the threshold of the reflex also coincides with pain perception thresholds, and the amplitude of the reflex increases with perceived pain, suggesting that modulation of NFR amplitude by emotions may reflect spinal nociceptive processes (Sandrini et al. 2005). Additional indices of spinal modulation of pain by emotions come from measures reflecting processes occurring immediately downstream of spinal projections. For instance, emotions were shown to modulate the amplitude of the N150 component of nociceptive ERPs (Kenntner-Mabiala and Pauli 2005; Kenntner-Mabiala et al. 2008), the timing of which coincides with the NFR's temporal window. Moreover, sympathetic responses to nociceptive inputs, such as heart rate accelerations and skin conductance responses (Rhudy et al. 2005), which are controlled by homeostatic control systems receiving direct nociceptive inputs in the brainstem, are also modulated by emotions.

It thus appears that the same descending modulatory mechanisms mediating the effects of emotions on pain in animals are also involved in humans, though human advanced cognitive capacities may broaden the range of emotional stimuli influencing pain. However, evidence in favor of the involvement of endogenous MOP and CCK agonists in human models of pleasure-induced analgesia or stress-induced hyperalgesia remains equivocal. Indeed, only two studies have examined the effects of MOP antagonists on the analgesia induced by pleasurable pictures (Kut et al. 2011) or tastes (Lewkowski et al. 2003), and both failed to observe any effects of opioid receptor blockade on pain modulation. However, it is difficult to draw strong

conclusions from these negative findings, especially since both studies employed measures of pain tolerance that may only weakly reflect basic nociceptive processes. Therefore, a pressing concern for future research would be to examine the influence of MOP and CCK antagonists on the effects of emotions on pain ratings and NFR in humans. Alternatively, the lack of MOP receptor blockade effects could indicate the involvement of opioid-insensitive descending modulatory systems (Amanzio and Benedetti 1999; Flor et al. 2002).

Extremely aversive stimuli should also be expected to produce stress-induced analgesia in humans. However, because it is ethically difficult to expose human subjects to the same levels of fear used when experimenting with animals, the experimental paradigms employed in human studies of stress-induced analgesia complicate the interpretation of the results in terms of purely emotional processes. For instance, Rhudy and Meagher (2000) showed that the fear associated with the administration of painful electric shocks increases pain thresholds, whereas the anxiety associated with threats of electric shocks lowers pain thresholds. However, using pain to induce fear raises the possibility that the observed effects may be caused by the engagement of diffuse noxious inhibitory controls (DNIC; Millan 2002) rather than fear per se. Similarly, using a cognitively demanding task to induce stress (Yilmaz et al. 2010) introduces distraction as a confounding factor if pain is tested during the task and cognitive fatigue if pain is tested after the task. While it could be argued that counterirritation, stress, and distraction analgesia all share a common motivational basis in the sense that they all reflect a competition between pain and other sources of motivation, most experimental paradigms used in humans do not match the purely emotional forms of fear-induced analgesia observed in animals, such as that instigated by exposure to a predator.

One exception is found in studies of patients with post-traumatic stress disorder (PTSD), for whom traumatic reexposure produces an important, naloxone-reversible analgesia (Pitman et al. 1990). Another exception comes from studies using a classic protocol in human stress research in which participants are subjected to a public speaking task to induce social stress. Using this type of protocol, al'Absi and Petersen (2003) showed that public speaking produced a state of hypoalgesia that appeared to be mediated by task-induced increases in systolic blood pressure (SBP). Indeed, it has been shown that activation of arterial baroreceptors has widespread inhibitory influences on central nervous system activity, including pain perception, and these effects could mediate some of emotions' effects on pain. Interestingly, a recent study showed that in addition to abolishing the analgesia associated with a stressful cognitive task, naloxone also prevented stress-related increases in blood pressure and baroreflex sensitivity, suggesting that endogenous opioids modulate both nociceptive inputs and the interplay between stress, pain, and vegetative responses (Fechir et al. 2012). Finally, besides fear, anger constitutes another negative emotional state associated with an opioid-dependent hypoalgesic state (Frew and Drummond 2007), suggesting that anger-related hypoalgesia may be considered as another form of stress-induced analgesia. This is particularly interesting considering that the main purpose of stress-induced pain inhibition is to prioritize fight or flight reactions in the face of important threats or obstacles.

The fact that negative emotions can produce either hyper- or hypoalgesia also raises the possibility that both effects can sometimes compete with one another. For instance, al'Absi and Petersen (2003) observed that public speaking also induced increases in self-reported levels of distress that predicted increases in pain ratings independently from SBP-mediated analgesia. The resulting net analgesic effects of their public speaking task therefore appeared to have resulted from a competition between SBP-mediated hypoalgesia and negative mood-induced hyperalgesia. Although the net balance of hypo- and hyperalgesic effects resulted in a net hypoalgesia in al'Absi and Petersen's study, it is easy to imagine factors that could disrupt this balance in favor of hyperalgesic effects. While this could explain some of the discrepancies in the literature, it could also account for the important interindividual variability in the effects of negative emotions on pain. For instance, Rhudy and Meagher (2003) observed that participants who mostly reacted with fear to aversive electric shocks showed subsequent increases in pain thresholds, whereas those who responded with a mix of fear and humor showed no analgesic effects. Similarly, participants who have a heightened propensity to experience anger are more likely to experience hyperalgesia than hypoalgesia following acute anger induction, an effect which appears to be related to an unmasking of anger's proalgesic effects by reduced opioid-dependent analgesia (Bruehl et al. 2012).

A related phenomenon is the sudden transition from hypo- to hyperalgesia that can take place when the source of stress is abruptly removed. For instance, Cornélio et al. (2012) demonstrated that stressful exposure to open spaces (elevated plus maze task) had immediate antinociceptive effects that rapidly transitioned to hyperalgesia once the rats were removed from the stressful condition. Moreover, RVM lesions had no effects on the initial stress-induced analgesia but completely abolished the ensuing hyperalgesia, allowing the hypoalgesia to persist in time. Again, this confirms that the antinociceptive and hyperalgesic effects of stress are mediated by distinct and competing systems. Similarly, the results of a recent study showed that the stress-related release of endogenous opioids secondarily induces a long-lasting and latent pain hypersensitivity mediated by NMDA receptors (Le Roy et al. 2011). Thus, sustained stress may predispose individuals to develop chronic pain when exposed to injury, which could partially explain the important comorbidity between stress, chronic pain, and anxio-depressive symptoms observed in humans.

Emotions thus appear to have profound influences on spinal nociceptive processing. However, it is still unclear whether attentional and emotional sources of pain modulation can be differentiated on the basis of their effects on spinal nociceptive processing. First, distraction induced by performance of a difficult concurrent task also seems to have antinociceptive effects at the spinal level, as evidenced by lowered NFR amplitudes or heightened thresholds (Bathien 1971; Sandrini et al. 2005). However, as noted previously, these effects could also be caused by the stress induced by the difficult cognitive task. Using predictive cues to direct attention toward upcoming visual or nociceptive stimulations, Dowman (2001) observed a dissociation between pain ratings, which were reduced by invalid cues, and NFRs and somatosensory evoked potentials (SEPs), which were either unaffected or increased by invalid cues. This apparently paradoxical increase in SEPs was interpreted as

reflecting non-pain-specific processes, such as reorientation toward the source of pain. More recently, Roy et al. (2011) observed a similar dissociation between pain ratings and NFRs during the presentation of neutral pictures versus a fixation point, which reduced pain ratings but increased NFRs. By contrast with these paradoxical effects of attention, comparison of neutral pictures with pleasant or unpleasant pictures replicated the previously observed parallel modulation of pain and NFRs as a function of valence. These findings suggest that driving attention away from pain may produce increases in NFR amplitudes that are independent from pain perception and which could reflect the need to tune up defensive reflexes when attention is directed away from the source of pain. Although this may suggest separate mechanisms for attentional and emotional effects, there is also evidence of interactions between attentional and emotional effects that contradicts strong claims about their dissociability. Indeed, cueing shocks abolishes the effects of emotions on NFR but not on pain ratings (Rhudy et al. 2006), suggesting that the effects of emotions on NFRs may rather reflect a facilitation of defensive responses, which becomes unnecessary when pain is fully predictable. By contrast, modulation of pain ratings may reflect supraspinal processes that are relatively independent from spinal reflexes. Alternatively, the dissociation between NFRs and pain ratings during distraction may reflect a facilitation of spinal motor-neuron responses coinciding with an inhibition of nociceptive transmission in the dorsal horn, a proposition which is compatible with observations of modulation of early SEP components by emotions (Kenntner-Mabiala et al. 2008).

Finally, findings of differential effects of attention and emotions' effects on the sensory and affective dimensions of pain also raise interesting questions regarding the engagement of descending modulatory processes in these two forms of pain modulation. Using a 2×2 crossover design during which emotions were manipulated by pleasant or unpleasant odors and attention was manipulated by an odor or pain discrimination task, Villemure and Bushnell (Villemure et al. 2003; Villemure and Bushnell 2009) found that effects of attention were stronger on intensity ratings while emotions had a greater effect on unpleasantness ratings. This dissociation is difficult to explain through descending modulatory mechanisms, which in all likelihood should indiscriminately affect ascending nociceptive signals as a whole. However, upon closer examination of the reported effects, the relatively low statistical power of these studies does not allow strong conclusions about the absence of effects on intensity or unpleasantness ratings. Therefore, another possible interpretation of these effects could be that both attention and emotion influence nociception through common descending modulatory mechanisms but that in addition they have different effects at the supraspinal level, which could explain their preferential effects on the sensory and affective dimensions of pain.

3.4 Supraspinal Modulation of Pain by Emotions

So far, the focus of the discussion has been on the effects of emotions on spinal nociceptive processes. However, there is an important distinction to be made between nociception, which refers to the biological processes associated with tissue

damage, and pain, defined as the "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Spear 1967). According to this largely consensual definition, activation of peripheral nociceptors is neither sufficient nor necessary for pain to be experienced. Indeed, when entering the cerebral cortex, ascending nociceptive signals undergo an important multisensory integration process through which a higher-order representation of the source of the pain in relation with the body-in-space is generated (Haggard et al. 2013). At this stage, nociceptive signals from WDR and nociceptive-specific (NS) neurons are integrated with thermal, tactile, and proprioceptive information, as well as with visual representations of the body and of objects in peripersonal space. This early multisensory integrative process, which is implemented through interactions between somatosensory, parietal, and posterior insular cortices, constitutes a first perceptual stage of pain modulation where external stimuli can influence perception of pain localization and intensity (Haggard et al. 2013). It is also the stage where manipulations of attentional focus are mainly thought to exert their effects on the sensory dimension of pain (Villemure and Bushnell 2009; Bushnell et al. 2013).

The purpose of this integrative process is to provide motivational systems with sufficient information to evaluate the threat level of the situation and respond to it in a coordinated fashion. This initial emotional appraisal process seems to be implemented through projections from parietal and somatosensory cortices to anterior midcingulate and insular cortices (aMCC and aINS), which are involved in processing the affective salience of stimuli that are relevant to the organism. Lesion of these projections, or of their cortical targets, generally produces a state of pain asymbolia characterized by a selective loss of emotional reactions to otherwise preserved painful sensations. Interestingly, these patients also seem to be unreactive to all sorts of threats to their corporal integrity, such as a needle approaching their eye or a hammer menacing to crush their hand (Danziger 2006). By contrast, multisensory cues that are only suggestive of injury, such as a nail passing through one's boot without causing any actual injury, can sometimes generate an aversive experience that has all the characteristics of pain (Fisher et al. 1995). This suggests that the presence of actual nociceptive inputs is not necessary for a pain's primary affective dimension if multisensory inputs are sufficiently convincing. Therefore, if one accepts that what makes pain really "painful" is its intrinsic unpleasantness (Bushnell et al. 2013), then pain could be conceived as the specific emotion for which the "core relational theme" (Lazarus 1966) is "actual or potential tissue damage" (but see Fields 1999).

Consistent with this idea, manipulating the threat value of nociceptive stimuli by suggesting that they may cause injury increases pain through preactivation of the aMCC and aINS during anticipation of the nociceptive stimulation and of the aMCC during the actual stimulation (Wiech et al. 2010). Similarly, hypnotic suggestions to reappraise painful thermal stimuli as more or less unpleasant specifically affect ratings of pain unpleasantness, an effect which was linked to an up- or down-regulation of aMCC activity (Rainville et al. 1997). It therefore seems that the same reappraisal strategies proven to be efficient in reducing negative emotions (Gross 2002) also generalize to successful pain regulation. In support of that hypothesis, Lapate et al.

(2012) recently found that interindividual differences in successful regulation of pain and negative emotions were correlated with one another and with reductions in amygdala activations to pain and unpleasant pictures. This is particularly interesting since the amygdala is considered part of the brain's early appraisal system (Ledoux 2000) and is also involved in pain's affective dimension through nociceptive projections from the spinoparabrachial-amygdala pathway (Neugebauer et al. 2009). The similarity between the effects of reappraisal on pain and negative emotions therefore suggests that the two may rely upon the same lateral prefrontal- (LPFC) and medial prefrontal- (MPFC) subcortical pathways (Atlas et al. 2010; Leknes et al. 2013; Roy et al. 2012b; Salomons et al. 2007; Wager et al. 2004).

Pain can also be the object of other emotions, which can be considered as representing pain's secondary affect (Price 2000). For instance, pain may cause anger if it is considered unfair, whereas it may cause anxiety or even depression if it is perceived as recurring and inevitable. These secondary emotions may be particularly problematic in patients suffering from chronic pain. Fortunately, the same cognitive strategies proven to be effective for regulation of negative emotions also seem to have positive effects on pain-induced emotions. For instance, Jensen et al. (2012) recently showed that 12 weeks of cognitive-behavioral therapy in patients with fibromyalgia significantly reduced the anxio-depressive symptoms and self-reported levels of disability associated with the disorder. Interestingly, these therapeutic effects of CBT were associated with increases in LPFC activity during painful mechanical stimulation, confirming that reappraisal of secondary pain affect shares some of the same neuroanatomical substrate as reappraisal of negative emotions in general (Buhle et al. 2014). Finally, another therapeutic technique that is being increasingly used to ameliorate pain is mindfulness-based meditation (Ludwig and Kabat-zinn 2014). Contrary to reappraisal, mindfulness-based meditation encourages adoption of a non-elaborative stance, which has been shown to decrease pain unpleasantness in experienced practitioners (Grant et al. 2011; Gard et al. 2012; Lutz et al. 2013). Surprisingly, these decreases in unpleasantness ratings were associated with increases in the activity of structures processing pain's sensory and primary affective dimension (INS, aMCC), combined with decreases in prefrontal structures responsible for secondary appraisals (Grant et al. 2011; Gard et al. 2012). Although the inverse correlation between pain ratings and INS and aMCC activity may seem paradoxical, these findings are in striking correspondence with the psychological construct of mindfulness, which entails a nonjudgmental awareness of the present moment.

However, these results also raise questions about the sequential organization of primary and secondary pain affect. For example, how can downregulation of secondary appraisals during meditation decrease pain's primary unpleasantness? One possibility is that primary and secondary pain affect are subjectively difficult to separate, resulting in misattributions of secondary pain affect modulation to primary pain unpleasantness. Another possibility is that secondary emotions can have reciprocal effects on primary pain unpleasantness through various channels. This later possibility would be consistent with recent models of emotional processing stressing the high level of integration between various levels of appraisal during

the dynamic unfolding of emotional experiences (Sander et al. 2005). Within this framework, it becomes easier to understand how higher-order appraisals can impact pain perception, such as when the cause of pain is attributed to someone else's intentions (Gray and Wegner 2008), or when the same level of pain is judged as the worst versus best outcome in comparison with the alternative (Leknes et al. 2013).

This framework also provides a way to explain the supraspinal effects of emotions unrelated to pain, which could presumably also affect pain through increases in the activity of regions involved in secondary appraisals and primary and secondary pain affect. For instance, Berna et al. (2010) recently showed that induction of a sad mood increased pain unpleasantness ratings through increases in catastrophic thinking about pain accompanied by augmented pain-related activations in the insula, thalamus, hippocampus, amygdala, inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), and subgenual ACC (sACC). Similarly, Yoshino et al. (2010) found that painful electric shocks administered during the presentation of sad versus happy or neutral faces were associated with increases in pain-related ACC activations and enhanced ACC-amygdala connectivity in the context of sad faces. Finally, using yet another sadness induction technique, Yang and Symonds (2012) largely replicated these results by showing that the simultaneous presentation of pain and sad pictures produced higher activity in the bilateral subgenual anterior cingulate cortex (sACC), contralateral pINS/S2, contralateral PAG, and bilateral amygdala.

While these results are consistent with top-down effects of emotions on the cerebral processes by which nociceptive signals are interpreted as "pain," we previously saw that emotions can also have powerful effects on descending pain modulatory mechanisms. Therefore, brain imaging results of emotional modulation of pain paradigms may reflect a combination of both spinal and supraspinal modulation of pain. In order to disentangle these effects, Roy et al. (2009) performed a brain imaging study during which spinal nociceptive reflexes to painful electric shocks were recorded while participants observed pleasant, unpleasant, or neutral pictures. The effects of emotions on NFR amplitude correlated with pain-evoked activity in structures receiving direct or indirect nociceptive inputs, such as the brainstem, thalamus, cerebellum, amygdala, and MPFC. By contrast, the effects of emotions on pain ratings correlated with activity in the anterior insula. This was particularly interesting since recent theories of pain, emotion, and interception postulate that the anterior insula acts as an integrator of ascending interoceptive signals with the broader emotional/motivational context (Craig 2003). In support of this hypothesis, increases in anterior insula activity during the viewing of unpleasant versus pleasant pictures correlated with activity in visual and orbitofrontal cortices, suggesting that it reflected the perception of pain in the context of affective pictures (Roy et al. 2009). Finally, consistent with these brain imaging results, Godinho et al. (2006) also observed that presentation of unpleasant emotional pictures had predominantly late effects (270–500 ms) on shock-induced SEPs in the lateral prefrontal cortex/anterior insula, temporo-occipital junction, and right temporal pole, confirming that some of the effects of emotion on pain may reflect late integrative processes involving the binding of pain to the emotional/sensory context in which it occurs.

Finally, one last question concerns the potential interactions between emotional and attentional processes during modulation of pain by emotions. Indeed, recent cognitive theories of emotions (Sander et al. 2005; Lindquist et al. 2012) suggest that executive attention may be important for performing some of the higher-order appraisals influencing the affective dimensions of pain. Consequently, distraction induced by a concurrent task could decrease the primary and secondary dimensions of pain. By contrast, negative/positive emotions could also increase/decrease attention directed toward or away from pain (Salovey 1992) and thereby influence task performance in addition to pain ratings. Two studies directly addressed this question using 2×2 factorial designs where emotion and attention were manipulated independently from one another (Villemure and Bushnell 2009; Ploner et al. 2011). Villemure and Bushnell (2009) showed that the effects of attention and emotions on pain ratings were independent from one another. However, they reported an interactive effect on task performance whereby negative emotions interfered with redirection of attention away from pain. Using a substantially different protocol, Ploner et al. (2011) also observed independent effects of attention and emotions on pain ratings but did not report any interactive effects on task performance. Overall, these results suggest that it is possible to experimentally separate the effects of attention and emotions on pain perception.

However, these two studies diverge in the pain-processing structures identified as the targets of attention or emotion effects on pain. Whereas Ploner et al. (2011) identified the aINS as the common locus of modulation for both emotional and attentional effects, Villemure and Bushnell (2009) found that aINS was only affected by attention, but not emotions. In contrast, emotions influenced activity in a number of pain-processing somatosensory and affective structures, including the medial thalamus, S1, S2, and aMCC. Reports of emotions impacting on somatosensory activity were surprising because emotions did not significantly influence pain intensity ratings in that study. One explanation for the widespread cerebral effects of emotions could be that emotions directly affected ascending nociceptive signals, as discussed previously. Nevertheless, the results of these two studies, as well as those of Roy et al.'s (2009) study, overwhelmingly point toward the aINS as a hub for pain perception and supraspinal modulation. Most interestingly, Ploner et al. (2011) observed that what differentiated attentional and emotional effects were the patterns of aINS functional connectivity during attentional and emotional conditions: attentional manipulations increased aINS connectivity with the brain's attentional network (intraparietal sulcus, superior parietal lobule, frontal eye fields, frontal pole, aINS, MCC), while emotional manipulations increased aINS connectivity with emotional structures (medial temporal lobe, aINS). Hence, the flexible connectivity of regions associated with the affective dimension of pain, and in particular the aINS, seems to underlie the supraspinal effects of emotions and attention on pain processing.

3.5 Conclusion

The physiological and psychological mechanisms underlying the effects of attention and emotions on pain are summarized in Fig. 3.1 within a model of pain processing largely inspired from Price (2000) and described throughout this chapter.

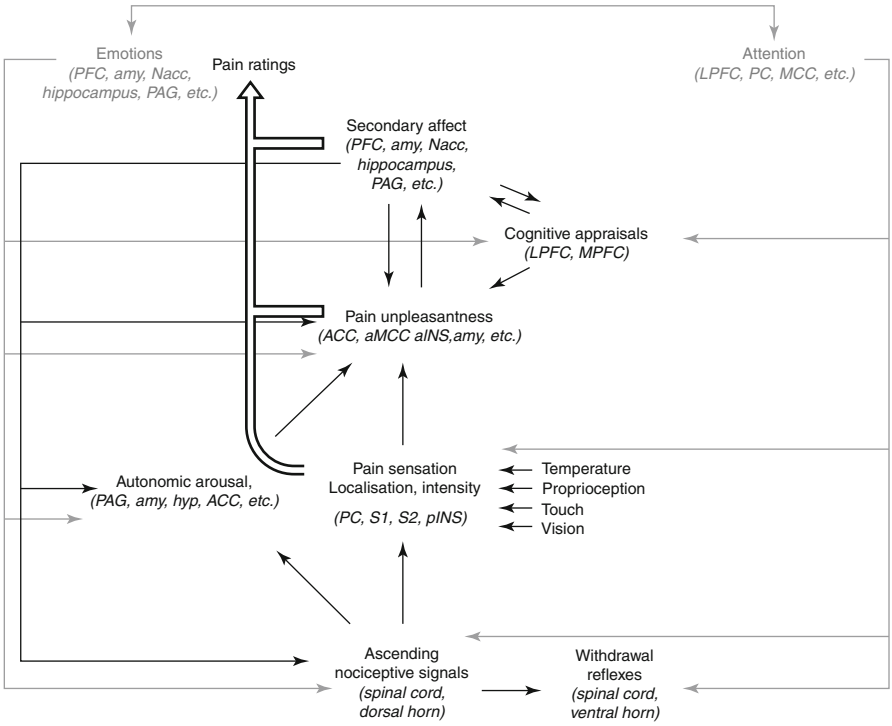

Fig. 3.1 Model of emotions' and attention's effects on nociception, pain sensation, and pain's primary and secondary affect. Neural structures likely to have a role in these dimensions are shown by abbreviations in adjacent parentheses. *PC* parietal cortex, *S1–S2* primary and secondary somatosensory cortices, *pINS* posterior insula, *ACC* anterior cingulate cortex, *aMCC* anterior midcingulate cortex, *aINS* anterior insula, *amy* amygdala, *PFC* prefrontal cortex, *Nacc* nucleus accumbens, *PAG* periaqueductal gray, *hyp* hypothalamus, *LPFC* lateral prefrontal cortex, *MPFC* medial prefrontal cortex

This model attaches considerable importance to the interactions between sensory, cognitive, and affective/motivational systems in the cerebral construction of the subjective experience of pain. As argued, interactions between attention and emotions during visual processing (Pessoa 2008) and the highly parallel and reciprocal nature of the neural architecture underlying pain perception make it difficult to differentiate the unique effects of attention and emotion on pain-processing structures (Ploner et al. 2011). Indeed, both attention and emotions can influence ascending nociceptive signals through descending modulatory pathways, which would cause largely indifferentiable patterns of modulation at the cerebral level. However, one potential difference between the effects of attention and emotion at the spinal level is the paradoxical increase in NFRs observed during distraction analgesia, which could reflect a disinhibition of spinal motor neurons when attention is directed away from pain. Still, this hypothesis remains to be confirmed with more specific measures of motor neurons' excitability in order to fully exclude alternative explanations.

Although the supraspinal mechanisms engaged by attention and emotions may substantially differ, their effects on pain-evoked activations appear to be difficult to disentangle due to the highly integrated nature of the pain-processing system. It has been suggested that one potential point of separation could be that attention preferentially affects the cerebral structures underlying the sensory dimension of pain, but recent neuroimaging findings are not perfectly congruent with this hypothesis (Villemure and Bushnell 2009; Ploner et al. 2011). It is also important to note that because of the partially sequential relationship between pain sensation and affect (Price 2000), modulation of pain sensation should also indirectly impact the affective dimension of pain, thereby blurring the boundaries between attentional and emotional effects. Another potential point of separation between attentional and emotional effects could be that emotions preferentially modulate pain affect, either directly or indirectly through a modulation of pain-related appraisals. However, distraction away from pain could also impact the affective dimension by interfering with the appraisal processes underlying pain's primary and secondary affect, which would be consistent with recent reports of selective effects of attention on aINS activity (Ploner et al. 2011). Finally, emotions could also influence pain perception through modulation of autonomic activity, which could be misattributed to pain (Schachter and Wheeler 1962), although this possibility has yet to be formally tested.

Moreover, emotional states can also alter the direction of attention (Salovey 1992) and be associated with different spinal and supraspinal effects that can either work synergistically or antagonistically. Therefore, in order to identify the origins of emotional effects on pain-related brain activity, it is necessary to try to probe as much as possible the various levels of pain processing by combining several methodologies, including NFR recordings, measures of autonomic activity, fMRI, EEG, etc. One interesting avenue for future imaging studies could be the use of cross-validated multivariate pain "signatures" in order to further characterize the nature of the modulatory effects of various interventions (Wager et al. 2013). Hopefully, a better understanding of the psychological factors that influence pain will lead to a better understanding of pain itself, including how it may become dysregulated in chronic pain syndromes.

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Chapter 4
Understanding the Suffering of Others: The Sources and Consequences of Third-Person Pain

Kenneth M. Prkachin, Kimberley A. Kaseweter, and M. Erin Browne

Abstract First-person pain (the subjective sensory and affective experiences that we associate with tissue damage) motivates changes in the sufferer's behavior that communicate the experience to others. The ability to infer features of another person's pain by observing a sufferer's behavior can be characterized as third-person pain. This chapter reviews research into the nature and determinants of third-person pain, focusing primarily on studies of the interpretation of facial expressions. Existing communication frameworks that attempt to organize thinking in this area are reviewed. Emerging conceptions of empathy and its role in third-person pain processes are described, including neuroimaging studies suggesting that first-person and third-person pain share common features of processing. Based on a review of the existing literature, a new organizing framework focused on the link between encoding of a pain signal by the sufferer and its decoding by the observer is developed. Components of this framework include preattentive processing, detection and registration, evaluation, differential responding (including the fact that the behavioral response to a sufferer may not necessarily be prosocial), and effects upon the observer. Finally, clinical implications of work in this field are considered.

4.1 Introduction

Pain is the clearest and most inescapable signal of threat to life, bodily integrity, effective functioning, and well-being. The adaptive significance of pain to the sufferer (first-person pain) is obvious. It is a signal of existential threat, and any capacity that confers the ability to avert that threat will support survival and reproductive fitness. The curious child who touches a hot stove and recoils in response to the consequent pain avoids the inherent danger of a burn. As humans are social

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animals that live in the proximity of others, this signal is not exclusively private; its experience is broadcast to others via automatic and controlled behaviors. Pain that occurs in a social context is relevant not only to the sufferer, but it has implications for others present during the pain episode.

Consider the case of Tom, a fluid transport driver whose load of volatile liquids exploded unexpectedly, causing life-threatening burns to a third of his body. For the other workers present, Tom's injuries and suffering likely generated fear as well as prosocial concern, at once causing hesitation and motivating their efforts to rescue him. Emergency response attendants may have faced a similar dilemma regarding the sometimes incompatible provision of pain relief and sustenance of vital functions, while processing their own vicarious emotional response. On the other hand, consider the military interrogator extracting information from a detainee. The detainee's suffering is critical to the execution of his role. The interrogator is no doubt sensitive to how the detainee communicates suffering, but mostly as a gauge of how close to the edge it is possible to go in performing his or her job. The response to suffering in others is by no means universally sympathetic, prosocial, or helpful.

The personal experience of pain that gives rise to behavioral adjustments can be called "first-person pain." First-person pain has multiple components (Melzack and Casey 1968). The sensory component allows the individual to perceive the location, intensity, and distinct qualities (burning, crushing, aching, etc.) of the experience. A cognitive-evaluative component arises from higher-order processing of pain, subserves active modulation of the experience, and enables adaptive functioning to the threat signaled by the pain. Pain is distinct among sensory systems in also having a prominent affective component that motivates changes in behavior. This affective dimension imparts the quality of unpleasantness, sometimes referred to as "suffering." For the purpose of clarity in the following discussion, we will use the term "sufferer" as a way of identifying the first-person experiencing pain, recognizing that the construct of suffering includes more than the affective dimension of pain.

Regardless of the internal experiences or the behavior of persons present during an episode of pain, all such experiences and behaviors are dependent, first, on the capacity to register that the other in the situation is experiencing pain—the ability to perceive another person's affective state. This capacity can be characterized as "third-person pain." In this chapter, we will describe and present empirical evidence for third-person pain and pain empathy processes, relate them to overarching models that have attempted to systematize the field, and propose a unifying framework that we think may be helpful in guiding future explorations of the determinants and implications of third-person pain processes.

4.2 Third-Person Pain Processes

The capacity to be influenced by the pain of others requires that the observer be able to perceive changes in the sufferer that covary with pain. In humans, these may include nociceptive flexion reflexes, adopting a guarded posture, facial expressions,

crying, groaning or complaining, describing, and requesting help. All of these changes can communicate information that an observer can use to draw inferences about the sufferer's experience, although they vary on certain underlying dimensions. Some (e.g., flexion reflexes) are communicative only indirectly, in the sense that their primary function is to protect the sufferer or provide relief from the pain. Others are communicative "by design," in the sense that they appear to be primarily adapted as signals to conspecifics while appearing to have no direct antinociceptive function. In humans, facial expression is one example (Williams 2002), homologues of which have been found in other animals, including mice (Langford et al. 2010), rats (Sotocinal et al. 2011), rabbits (Keating et al. 2012), and horses (Dalla Costa et al. 2014). Other behaviors of humans and animals, such as pain vocalizations, also fall into the directly communicative category.

Pain behaviors vary as well with respect to the degree to which they are reflexive and automatic as opposed to conscious and controlled (Craig et al. 2010). Because some cues can be subject to very precise, deliberate conscious control, they are in principle susceptible to distortion and bias on the part of the sufferer. However, as facial expressions appear to have evolved primarily to serve a communicative function and fall toward the automatic end of the continuum, it is likely that they have greater primacy and salience and are thus an advantageous medium for studies of third-person pain. There is now an extensive literature on the facial expression of pain, reviewed in Kunz et al. (2004). For our purposes, it is important only to note the following. First, extensive research has documented that pain is accompanied by distinct changes in facial actions that have been characterized as a "pain expression" (Craig et al. 2011; Prkachin 1992b, 2009). Second, the pain expression provides quantitative information that relates positively to the subjective experience of first-person pain (Kunz et al. 2004; Prkachin and Solomon 2008). Third, studies of first-person pain that have made use of facial expression as an outcome have provided video databases that are ideally suited to perform studies of the perception of this indicator of first-person pain by others.

As Williams (2002) points out, a distinctly communicative expression can only have evolved if the capacity among others to detect it coevolved along with it. The adaptive significance of third-person pain may seem obvious, but, as the examples we used to open this chapter illustrate, its beneficial features can be complex. Certainly, the ability to render aid to others whose welfare is threatened by bodily damage is dependent on the ability to recognize the need for such aid. To the extent that rendering aid promotes propagation of the genes of the person giving assistance, we would expect selection for this ability to take place. But for the observing individual, rendering aid may not be the wisest strategy when confronted with another experiencing pain. Pain to another arising from bodily injury may well signify threat to the observer, for example, when the sufferer's injuries are the consequence of predation that could just as easily affect the observer. In such circumstances, a mechanism that allows appreciation of the nature of the other's experience while maintaining personal autonomy provides a basis for flexible response choices.

While it is possible to imagine situations in which nonresponsiveness may be adaptive, evidence of the capacity to be affected by the suffering of others can

be found in several species. It has long been known that primates will perform an operant response to avoid exposure of a conspecific to painful stimulation (Miller et al. 1962). Rhesus monkeys will prefer a response that costs them access to food, even starving themselves to avoid presentation of a painful shock to a conspecific (Masserman et al. 1964). Likewise, rats display suppression of an operant response when a conspecific is subjected to electric shock (Church 1959). More recently, Langford et al. (2006) exposed mice to an experimental procedure that produced writhing pain. Other mice that observed them and were also exposed to the procedure evidenced more writhing pain than mice who did not observe pain, suggesting the existence of a complementary nociceptive response. The response was present only among animals that had been reared as cagemates and dependent primarily on information transmitted in the visual modality. The apparent existence of such resonating affective responses among several species suggests that the capacity to respond to evidence of others' suffering is part of the basic hardware of species whose life patterns involve a significant social component.

4.3 Frameworks for the Understanding of Third-Person Pain

Prkachin and Craig (1995) organized the processes involved in transmission of pain information from nociceptive input to social interpretation via facial expression in relation to Rosenthal's (1982) three-component (A → B → C) framework for nonverbal communication. According to this model, for pain communication to occur, an internal experience must first be encoded in expressive behavior. For example, if an individual experiences an injury (e.g., stepping on a nail), nociceptive processes culminating in brain activity are experienced as pain (Step A). The pain is then encoded in verbal or nonverbal behavior (Step B). This expressive behavior can then be decoded by an attending observer (Step C). From the perspective of third-person pain, the model emphasized the idea that decoding of pain expression involves the detection and interpretation of specific facial cues as a first stage in a process that determines how the observer will respond to the sufferer (e.g., helping behavior). Various inefficiencies in the process can lead to relative insensitivity to and biased utilization of evidence about pain. A particular phenomenon that the model was intended to address was what has been called the underestimation bias. The underestimation bias, reviewed below, refers to the widely documented tendency of observers to downgrade ratings of the intensity of others' pain relative to the ratings of the sufferers themselves. The model posited the existence of individual differences in "gain functions"—the relative weight observers attach to evidence of suffering in others—to account for varying degrees of underestimation (and, potentially, overestimation).

Hadjistavropoulos and Craig (2002), Craig (2009) and, later, Hadjistavropoulos et al. (2011b) elaborated on this initial model, which has evolved into a "sociocommunications model," by adding detail and supporting evidence. With respect to third-person pain—the transaction between sufferer and observer—these models

emphasize that some behaviors, such as verbal reports of pain, are primarily reliant on higher mental processes, whereas certain nonverbal reactions (e.g., some facial expression and nociceptive withdrawal reflexes) primarily reflect automatic processes. Expressive behavior can be modulated by numerous social factors such as context, social normative patterns, and display rules. For example, Vervoort et al. (2008) found that children were more likely to display facial pain expressions in the presence of their parent than in the presence of a stranger.

In considering the decoding of pain expressions (Step C), the pain communication model of Hadjistavropoulos et al. (2011b) emphasizes that an observer could fail to perceive the message, accurately perceive, or misinterpret it leading to an overestimation or underestimation of the painful state of the sufferer. The accuracy and interpretation of decoding can be influenced by numerous factors, including the clarity of the sufferer's expressions. For example, verbal messages have been found to be generally easier to interpret than nonverbal behaviors. However, observers are often aware of the potential for response bias with self-reported pain. Poole and Craig (1992) found that observers attributed greater importance to nonverbal as compared to verbal information when judging the credibility of pain expression. Additionally, observer characteristics, such as age, gender, and personality traits, have been shown to affect observer's decoding of pain. For example, Kaseweter et al. (2012) found a racial empathy and treatment bias, in which participants reported more empathy and prescribed more pain treatment for Caucasian patients than dark-skinned patients, regardless of the fact that the patients were displaying similar levels of pain expression.

4.4 Third-Person Pain and Empathy

The ability to perceive the suffering of others is necessary if one is to be influenced emotionally by that suffering. The perception of others' pain might simply be a cold, analytic process; however, much recent research links it to the phenomenon of empathy. Empathy is the process of being affected by the observable or inferred experiences of others. Batson (2009) cautions that the term is used in at least eight different ways, including (1) the sense of knowing another's internal state ("cognitive empathy"), (2) behavioral matching of the other's state (motor mimicry), (3) feeling an internal affective state that is similar to the other's, (4) imaginatively projecting oneself into the experience of another, (5) imagining how another is thinking and feeling (perspective taking), (6) imagining how one would think and feel in the other's place (role taking), (7) being distressed by another's suffering (personal distress), and (8) feeling for another person who is suffering (empathic concern). Goubert et al. (2005) characterized empathy as "…a sense of knowing the experience of another person with cognitive, affective and behavioural components."

Studies of human empathy suggest that the capacity to be affected by distress in others is present from the earliest moments of life. Neonates exposed to the crying of other newborns evince a crying response that is not shown to their own cries or

the cries of nonhuman primates (Martin and Clark 1982). This early form of emotional contagion is thought to be the precursor to later, more sophisticated types of empathic response (Hoffman 2001). By the age of five, children have the capacity to discriminate facial expressions of pain of different intensities (Deyo et al. 2004). It is likely that this capacity develops considerably earlier; however, studies that would reflect on this have not been performed.

4.5 Perception-Action Model

The growth in interest in empathy was strongly influenced by a conceptual framework developed by Preston and de Waal (2002). According to the perception-action hypothesis, perception of another's behavior automatically activates neural representations of that behavior in the observer; hence, the representation in the observer of the behavior in question can be described as "shared." The output from this shared representation automatically primes or activates motor areas of the brain linked to the initial representation, where responses are generated. This hypothesis evolved into the perception-action model (PAM) of empathy. According to the PAM, empathy is the result of a shared emotional experience that automatically occurs when an observer perceives another's state. These shared representations allow the observer to understand the mental state of the other. Thus, this model suggests that perception of pain in another would automatically activate neural mechanisms that are responsible for the experience of pain in the observer.

This general pattern of overlapping neural activation between a target and observer has been extensively documented in fMRI studies of perceived pain. Lamm et al. (2011) performed an image-based meta-analysis of nine independent functional magnetic resonance imaging (fMRI) investigations and a coordinate-based meta-analysis of 32 studies that had investigated empathy for pain using fMRI. The results indicated consistent activation in the bilateral anterior insula (AI) and medial/anterior cingulate cortex (ACC) during third-person pain. This finding remained across studies performed in different countries, using various paradigms. Activation in these areas overlaps with activation that occurs during the first-person experience of pain, supporting the theory that shared neural representations underlie empathy.

Danziger et al. (2006) examined responses to others' pain in a unique population: patients suffering from congenital insensitivity to pain who had had impairments in pain perception from birth due to sensory and autonomic neuropathy. Patients and healthy controls performed several tests, including rating the intensity of pain in videos depicting injuries (in the absence of behavioral reactions) and rating the intensity of facial expressions of pain. Patients' ratings of painful injuries were substantially more variable and significantly lower than controls'. Patients' and controls' ratings of pain expressions did not differ. Interestingly, however, patients' ratings of painful injuries and their willingness to judge pain expressions as painful were strongly correlated with their scores on a self-report measure of empathy, whereas controls' judgments were not. The results suggest that direct experience

with pain is not necessary to acquire an appreciation of the pain of others. In the absence of behavioral cues, however, patients may not have the benefit of the "mirror matching" activation of personal representations of the situations of others implied in the PAM. The results with respect to self-reported empathy suggest that an alternative mechanism, most likely involving direct learning from observation, can compensate for the absence of a functional somatic resonance mechanism.

In a subsequent neuroimaging study, Danziger et al. (2009) showed that patients with congenital insensitivity to pain and controls showed similar activation patterns in AI and ACC in response to pictures depicting injury and facial expressions of pain, challenging the mirror-matching notion that activation in these regions reflects automatic engagement of the observer's pain responses. They proposed the alternative interpretation that activation of these regions reflects general processing of aversive stimuli.

4.6 The Goubert et al. Model of Pain Empathy

Goubert et al. (2005) proposed a different perspective to account for pain-related empathy. According to their model empathy is a result of (1) bottom-up processes, (2) top-down processes, (3) contextual characteristics, and (4) relational factors. Bottom-up determinants include characteristics of the person in pain, such as their pain behavior. One of the most important bottom-up determinants of observers' pain judgments is believed to be the sufferer's facial expression of pain (Hirsh et al. 2008; Patrick et al. 1986; Prkachin et al. 1994; Williams 2002). Studies have repeatedly shown that activation of brain regions characterized as the "pain matrix" can be triggered by the perception of painful facial expressions (e.g., Botvinick et al. 2005). Top-down determinants of pain empathy include characteristics of the observer, such as knowledge and learning experiences. For example, Preis and Kroener-Herwig (2012) examined whether or not factors such as perceived similarity and prior exposure to pain are associated with empathy for pain. Results revealed that greater perceived similarity was associated with higher scores on an empathic emotional reaction scale, whereas previous exposure to pain was positively associated with a perspective-taking subscale. These results support the assumption that empathy can be modulated by observer characteristics. Contextual characteristics include such things as the presence of a wound or blood or the nature of the relationship between the sufferer and observer (Goubert et al. 2011). For example, Cheng et al. (2010) presented participants with animated stimuli depicting the hands or feet in painful and non-painful situations. Participants were instructed to imagine the scenarios from different perspectives, including that of a loved one and stranger. Functional MRI results revealed that adopting the perspective of a loved one elicited greater activation in the anterior cingulate cortex and insula than adopting the perspective of a stranger, demonstrating the modulating role of intimacy in pain empathy. Similarly, by analyzing heart rate changes among participants involved in a fire-walking ritual and spectators, Konvalinka et al. (2011) found that spectators who were related to participants showed greater synchrony of heart rate change during the ritual than unrelated spectators.

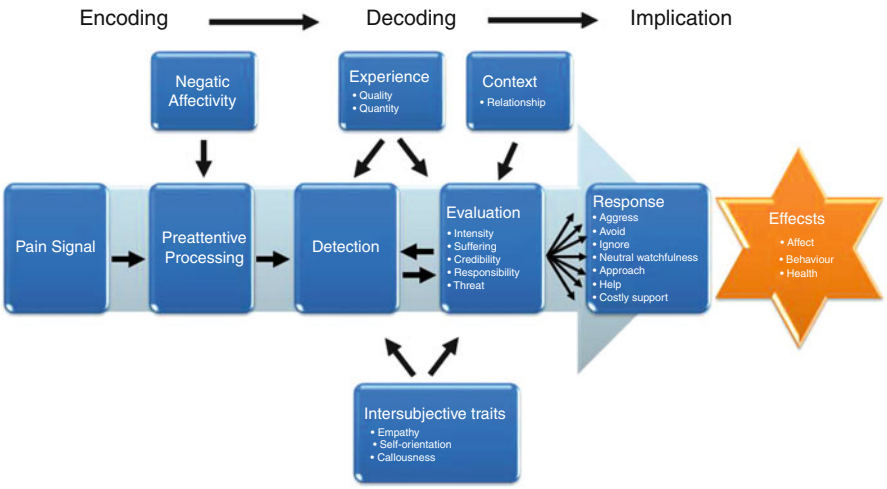

Fig. 4.1 An organizational framework for understanding the process of third-person pain from signal to outcomes. See text for details

4.7 An Organizing Framework for Third-Person Pain

Current theoretical conceptualizations of third-person pain processing place heavy emphasis on empathy as the fundamental mediator of third-person pain. The models invoke complex processes involving the automatic activation of shared representations and the modulation of empathic responses via bottom-up and top-down mechanisms contextual characteristics, and relational factors. There is reason to believe, however, that empathic processes represent but one of multiple pathways influencing the response to pain in others and that variables thus far linked indirectly to third-person pain through empathy may exert an independent influence.

The framework outlined in Fig. 4.1 represents our attempt to organize key concepts in the understanding of third-person pain, to update them in relation to the empirical literature, and to point to some priorities for future research. The framework focuses on the encoding → decoding pathway discussed in previous models of pain communication (Craig 2009; Prkachin and Craig 1995; Hadjistavropoulos et al. 2011b) emphasizing the processes involved in perceiving the other's suffering, subsequent behavior on the part of the observer, and implications of that behavior for the sufferer.

The framework begins with the pain signal—observable changes in behavior in any domain that are ordinarily reliable indicators of the experience of pain. That signal is broadcast into the social world where it may impinge on a receiver. Even before the signal undergoes perceptual transformation, preattentive processes—unconscious and effortless processing of information guided by preexisting schemata—can occur and activate emotional processes that affect subsequent

components. If the observer continues to orient toward the signal, it is processed in more detail such that it is detected and registered as an indication of pain. Once registered, evaluative processes take place along several dimensions that will bias the observer toward or away from different subsequent actions. Those actions, or response options, themselves vary along a continuum from antisocial to prosocial. Finally, the actions undertaken by the observer will have reciprocal effects on the sufferer in changes to her or his affective state, behavior, and health, both in the short and the long term. The framework also attempts to identify and locate points in the process that have been implicated as influential in third-person pain by evidence and theory, as reviewed below.

4.7.1 Preattentive Processing

Vervoort et al. (2013) examined eye-tracking patterns among people observing facial expressions displaying low, medium, or high levels of pain paired with neutral expressions. Participants' time to first fixation varied as a function of their self-reported levels of pain catastrophizing—the tendency to ruminate about, magnify the potential risks of, and feel helpless in the face of pain (Sullivan et al. 1995). Among participants low in catastrophizing, time to first fixation was more rapid to faces displaying pain and decreased with increasing intensity of pain expression. Among high catastrophizers, time to first fixation did not vary between neutral and pain expressions. This pattern suggests the operation, among people high in catastrophizing, of a (likely unconscious) preattentive process in which evidence of threat is rapidly processed and drives avoidance behavior. More generally, as catastrophizing is but one of a category of variables likely to prime a hypervigilant state (e.g., Yamada and Decety 2009), the framework includes this set of influences under the general rubric of negative affectivity. Future research is necessary to map and clarify the nature of such influences.

4.7.2 Detection and Registration

Detection is the process of determining that the behavior of the sufferer indicates pain. It is influenced by two variables: the magnitude of the evidence of pain and the observer's sensitivity to that evidence. The earliest work to examine perceptual processes involved in third-person pain demonstrated that naïve observers were capable of discriminating variations in others' pain intensity purely on the basis of facial expression (Prkachin and Craig 1985). Interestingly, the ability to discriminate differences in sufferers' experience was independently related to the physical intensity of the stimuli used to evoke pain and the sufferers' subjective reports of pain, suggesting that observers are sensitive to behavioral cues distinguishing sensory and affective dimensions. Although observers are sensitive

in general to behavioral cues of pain, they appear to rely primarily on the more salient indicators and to be relatively insensitive to subtle signs (Prkachin et al. 1994). Observers also appear to be sensitive to features of the display that indicate active modulation on the part of the sufferer, such as faking or exaggeration (Prkachin 1992a, 2005).

Sensitivity to pain expression appears to be a rather robust ability that does not vary substantially across people. There is evidence, however, that sensitivity to pain in others can be affected by what the proposed framework refers to as intersubjective traits and processes—personal characteristics and dynamic variables that influence how one registers the experiences of others. For example, groups known for their social impairments have been found to differ in their sensitivity to pain expression. Martins et al. (2011) compared schizophrenics with healthy controls in their ability to detect facial expressions of pain. Schizophrenic patients displayed consistent deficits in the detection of facial expressions of pain across a spectrum of pain intensity. Wojakiewicz et al. (2013) replicated this finding with a more homogeneous sample of patients diagnosed with paranoid schizophrenia. This study showed, in addition, that sensitivity to the pain of others was correlated with empathic characteristics of fantasy (the tendency to imagine oneself in hypothetical situations) and empathic concern among normal individuals, but not in the schizophrenic group, suggesting a decoupling of features of affective information processing and self-awareness in the latter. Caes et al. (2012) found that psychopathic traits were associated with a diminished perceptual sensitivity to others' pain. Lastly, pain judgments can be influenced by the sufferer's characteristics. The foregoing findings have been interpreted to imply that empathy deficits may underlie diminished sensitivity to others' pain. However, it is possible that other variables correlated with the characteristics under study are responsible for diminished sensitivity. Psychopathy involves multiple components (e.g., callousness) other than deficient empathy that could equally account for diminished sensitivity.

Another variable that has been shown to affect sensitivity to pain in others is likability (De Ruddere et al. 2011). Observers exposed to an evaluative conditioning procedure in which still photographs of pain patients were associated with adjectives reflecting positive (e.g., "faithful"), neutral (e.g., "conventional"), or negative (e.g., "arrogant") traits rated the intensity of the pain displayed by the patients during range-of-motion exercises. When viewing video recordings showing high levels of pain expression, patients whose images had been associated with negative traits were rated to be in less pain than patients associated with neutral or positive traits, with the latter two conditions not differing. This effect was attributable exclusively to reduced sensitivity to higher levels of pain.

In their pain empathy model, Goubert et al. (2005) note that instead of displaying sympathy and concern to the person in pain (characterized as an "other-oriented" response), "self-oriented" observers may experience personal distress. There is reason to believe that such an orientation may also diminish sensitivity to the other's pain by virtue of generating active avoidance of evidence, for example, by gaze aversion.

4.7.3 Evaluation

Having registered the occurrence of pain in another, the observer must ultimately make some kind of response, even if it is to do nothing but continue to observe. The process of response selection is dependent on elaborative and evaluative processes that relate evidence about the sufferer's pain to other information the observer has available. In the evaluation/elaboration phase, the observer makes judgments about what the pain display means in relation to certain key dimensions. These include pain intensity, suffering, the credibility of the sufferer's display, and personal characteristics of the sufferer or his or her circumstances, such as the degree to which they have been responsible for their misfortune. The degree to which the sufferer's pain poses a personal threat to the observer is also evaluated.

The most intensively studied of these dimensions is pain intensity. Observers' judgments about the pain of others are typically about how much pain the other is feeling or how unpleasant it is. In empirical studies, observers typically render judgments by using a quantitative scale. Observers have preferences for where they place their ratings on such scales. Some are conservative and tend to make lower ratings; some are liberal, distributing their ratings toward the higher end. These tendencies are called response biases. When observers make use of the same scales that sufferers have used to rate their own pain, it is possible to evaluate how closely third-person ratings match first-person ratings.

Prkachin and Mercer (1989) studied patients attending a physiotherapy clinic for treatment of injuries to their shoulders. As part of their assessment, the patients underwent a series of tests in which their affected shoulders were maneuvered through a range of motion. At the end of each test, the patients rated how much pain it caused. In a subsequent study, observers were shown video recordings of patients' facial expressions and rated how much pain they thought the patient experienced, using the same scale the patients had used (Prkachin et al. 1994). The results indicated that although judges' ratings tracked the patients' in terms of the painfulness of different tests, they were significantly and substantially lower than those of the patients. This effect has been termed an "underestimation bias." (It must be acknowledged that the term reflects the perspective of the sufferer and should not imply an ontological reality since it is really a reflection of the comparison of two subjective estimates.)

In a later study (Prkachin et al. 2001) a similar methodology was used to study groups of observers who differed with respect to the extent and nature of their experience with pain. One group consisted of people who had lived with a person who suffered from chronic pain, while another consisted of therapists whose practices involved treatment of people with pain conditions. A third group consisted of people with no significant experience with pain in others. All participants rated the video recordings of patients with shoulder pain, using the same scales the patients had used. Results indicated that all groups of observers displayed the underestimation bias. There were interesting differences in the rating patterns of the different groups, however. Relative to observers who had

little experience with pain in others, the ratings of people who had lived with a pain sufferer approximated those of the patients more closely. By contrast, people with substantial clinical experience working with pain sufferers showed an *enhanced* underestimation bias. The finding of an enhanced underestimation bias among health professionals when judging others' pain on the basis of pain expression is consistent with a broader literature indicating that various health professionals tend to underestimate the pain of others when relying on diverse sources of information (Prkachin et al. 2007; Solomon 2001) and with research showing that physicians give lower ratings of pain and fail to demonstrate electroencephalographic differentiation in frontal and centro-parietal regions when observing painful versus nonpainful stimulation to others (Decety et al. 2010). The implication is that something about the experience of health-care provision is responsible for a systematic alteration in processes for judging others' pain. Importantly, however, the finding that people who have lived with a pain sufferer show a diminished bias equally implicates experiential influences on pain judgment processes, but suggests that experiential effects can operate in different directions. Of critical concern is determining the kinds of influences that can shape judgments in either direction.

The classical perception theory of adaptation level (Helson 1964) provides one basis for explaining differences in pain estimation judgments. Adaptation-level theory holds that the evaluation an observer makes about a stimulus is determined in part by the context in which the stimulus is presented. The same stimulus judged in the context of weaker stimuli is perceived to be stronger than when it is judged in the context of stronger stimuli. In a study that bears on the adaptation-level concept, Prkachin et al. (2004) presented participants with very brief videos of the facial expressions of patients displaying no pain or moderate pain. Participants indicated whether they thought patients were displaying pain or not. Four experimental conditions manipulated the degree of exposure that each participant had to displays of strong pain. Exposure to 1, 5, or 10 displays of strong pain resulted in a reduced likelihood of judging people to be in pain, relative to no exposure, with the biasing effect evident at the lowest level of exposure and increasing with greater exposure. In short, experience with displays of strong pain led to a diminished likelihood of imputing pain to others. Prkachin and Rocha (2010) replicated this effect. The parallel with clinical scenarios is evident. Health professionals who work with pain sufferers are exposed to frequent and high levels of pain expression. The cumulative effects of such exposure are likely to set professionals' adaptation levels higher than those of people exposed to evidence of suffering to a lesser degree, making them more susceptible to underestimation.

Attitudinal factors reflecting observers' attributions about the motivations of sufferers have also been shown to influence third-person pain judgment biases. As emphasized by Craig et al. (2010), although they occupy an intermediate position on the automatic-deliberate continuum, nonverbal expressions of pain are under some degree of conscious control, and there is evidence that the topography of deliberately modulated expression differs in subtle ways from that of spontaneous

expression (Craig et al. 1991; Galin and Thorn 1993; Hill and Craig 2002; Prkachin 1992a, 2005). Williams (2002) emphasized that evolution should have prepared observers to be sensitive to this possibility in the form of a "cheater detection" algorithm. Kappesser et al. (2006) showed videos of shoulder pain patients displaying various levels of pain to health-care providers (primarily emergency room physicians and nurses) and had them rate the patients' pain using the same scales the patients did. Observers participated in one of three conditions. In one, they were told the actual rating the patient had given. A second group was also informed that the patients had been seeking opioid medication for pain relief. The control group was given no information. Results showed that providing information about the participants' own ratings partially diminished the usual underestimation effect; however, the addition of information indicating that patients were opioid seeking effectively eliminated the benefit attributable to learning of the patient's own rating. Furthermore, observers' estimates of the base rate of exaggeration of pain in patient populations were associated with enhanced underestimation, regardless of the condition to which they were assigned.

4.7.4 Responses

The judgments rendered in the evaluation/elaboration phase will, in principle, bias the observer toward or away from certain actions. The more intense the observer judges the person's pain to be, the more likely he or she is to be helpful. The observer who judges the sufferer to lack credibility may ignore or even engage in aggressive behavior toward him or her. In our framework, a series of response options, ranging from aggressive behavior on the one hand to engaging in behavior that is personally costly, is shown in a continuum. Unfortunately, detailed knowledge about the response options that people select is not available largely because of the difficulties entailed in studying them systematically. Nevertheless, some work has begun to address this component.

Hein et al. (2011) measured self-reported affect and skin conductance responses while participants were exposed to painful electric shocks. A confederate who was present was portrayed as receiving the same shocks as the participant. In a second session, the participant was given the choice of helping the other person by taking their shocks, watching but not helping the other or watching a video. Skin conductance responses while watching the other apparently receiving shocks were positively correlated with participants' ratings of the other's pain and predicted a greater likelihood of choosing the personally costly option of accepting pain for the other. Also, the more similar the participant's skin conductance responses while observing pain to the other person were to the participant's own responses, the more likely was costly helping.

Other research, while not directly measuring overt response choices, have has made use of proxy measures. Because most of this work has addressed issues of clinical relevance, it is reviewed below.

4.7.5 *Effects on the Sufferer*

Ultimately, we must be interested in how the process of third-person pain plays out for the sufferer. This will be a matter of the behavioral choices the observer makes in the face of evidence of suffering. Of particular interest are the long-term effects of observers' responses, such as those that would occur in the common scenario of a chronic, intractable pain condition. Although this is perhaps the most important issue of all, it is here where we have the least information and where research is needed the most. How, for example, is a tendency to underestimate another's pain likely to affect the sufferer in the short and long term?

The behavior of the observer, or observers, over time, will have implications for the sufferer's affective responses, their behavior and, in principle, their pain, and issues related to it. Anecdotal evidence, such as qualitative and survey studies, suggests that dismissive behaviors on the part of the observer might be predicted to follow from an extreme underestimation bias or judgments of diminished credibility produce negative emotional reactions (Herbette and Rime 2004; Morley et al. 2000). Anger, depression, and a sense of injustice have all been implicated as consequences of persistent pain, and plausible arguments can be constructed around how the responses of others to one's pain would contribute to them.

The sufferer's behavior might be affected positively or negatively by the behavior of others. From the perspective of the influential behavioral approach to pain (Fordyce 1976), withholding of positively reinforcing behavior on the part of an observer might be expected to diminish the sufferer's pain-related behavior. On the other hand, theories of treatment adherence would likely predict that any behavior on the part of an observer that diminishes satisfaction with care would be associated with noncompliance on the part of the sufferer.

Each of these speculative effects on the affect and behavior of the pain sufferer would be likely to affect the long-term outcome of the condition. This is an area in which there is virtually no empirical evidence to inform discussion. Given the importance of the issue and the fact that there are practical ways of addressing it, it should be a priority for future research.

4.7.6 *Clinical Implications*

The predominant realm in which third-person pain makes a difference is health care. Identification of pain in others is one of the most important responsibilities of health-care providers. For individuals who are not capable of communicating effectively verbally, such as infants and people with dementia, nonverbal expression is the only overt means by which their suffering can be conveyed (Craig 2006; Hadjistavropoulos et al. 2011a). Hence, the basic attentional, perceptual, and cognitive processes that give rise to third-person pain—sensitivity to the behavioral display and judgment criteria concerning how much evidence to identify pain is necessary—are a first line in the alleviation of suffering.

A different set of relevant circumstances involves clinical scenarios characterized by ambiguity. These include cases in which the underlying source of the pain is unclear, where situational, personality, or behavioral factors introduce the possibility that additional variables may be complicating the evidence at hand, or where the course of action may involve the risk of increasing pain or inflicting damage. Scenarios like this are common with many subacute or chronic conditions, such as low back pain.

The critical issues that arise in these circumstances are the response that is evoked in the health-care provider and the behaviors that he or she is likely to engage in. Behavioral evidence (Prkachin et al. 2007) suggests that the natural inclination to underestimate the pain of others is enhanced among health-care providers and that this exaggerated bias may be a direct consequence of high-density exposure to the suffering of others (Prkachin et al. 2004; Prkachin and Rocha 2010). Cheng et al. (2007) showed that, relative to inexperienced controls, acupuncturists with considerable experience with inflicting pain on others displayed virtually no hemodynamic signal change in the insular cortex, cingulate cortex, and other relevant regions when observing simulations of painful needle insertions. The authors suggested that these differences reflect an experientially based adaptation that inhibits empathic responding allowing experts to engage in practice without becoming emotionally overwhelmed.

Another clinical phenomenon to which third-person pain is relevant is the documented disparity that occurs in aggressiveness of treatment between people of different racial and ethnic groups, in particular among people of color seeking emergency care (Pletcher et al. 2008). Drwecki et al. (2011) examined the role of third-person pain processes in this phenomenon. In an initial study, undergraduate volunteers and registered nurses were asked to take the role of a treating physician while watching videos of the facial expressions of light-skinned and dark-skinned shoulder pain patients. The videos were matched for the amount of pain they displayed on the basis of measurements of the intensity of pain-related facial actions (Prkachin 1992b). After watching each video, observers completed a proxy measure of treatment aggressiveness by indicating how much treatment of various sorts they would recommend. Observers also completed an empathic concern scale for each patient viewed, indicating the extent to which they felt "warm," "compassionate," and so on. People of color were prescribed significantly less aggressive treatment on the proxy measure and received lower empathy scores. Treatment aggressiveness and empathy measures were strongly correlated. Kaseweter et al. (2012) replicated this finding in a Canadian sample, showing that the phenomenon is not isolated to the American culture and not attributable to potentially associated characteristics such as attractiveness or likeability. These studies suggest that findings that people of color are less likely to receive pain treatment, less appropriate management of chronic conditions, longer wait times for emergency care, and so on (Fiscella et al. 2002) reflect a basic process of downgrading evidence of suffering. In two follow-up studies, empathic processes were manipulated directly by encouraging the observers to imagine how the patients they were observing felt. Exposure to this "perspective-taking" intervention virtually eliminated the racial differences in both treatment

aggressiveness and empathy, suggesting, first, that the treatment aggressiveness disparities were indeed driven by the third-person phenomenon of pain empathy and, second, that it is possible to reduce differences in empathy with simple manipulations that have been identified in neuroimaging studies of pain empathy.

In another analog study, Lundquist et al. (2002) examined the influence of post-registration attributional processes and observers' attributional styles on social cognitive and emotional processes and treatment decisions. Observers were shown video recordings of shoulder pain patients displaying moderate and high levels of pain expression. Before viewing the recordings, observers read vignettes describing the patients' histories. The vignettes varied in terms of the degree to which the patient's pain was supported by medical evidence of pathology and the degree to which the patient was compliant with treatment recommendations. After viewing the recordings, observers rated the patients on a number of scales, including the amount of pain they thought the patient was in, the amount of distress and disability shown, and the degree to which the patient was responsible for his condition. Finally, observers were asked to recommend one of two treatments that were characterized as equal in effectiveness, although one was inherently more uncomfortable than the other.

Patients who were characterized as compliant with treatment were viewed much more favorably than those who were not. They were rated as less responsible for their condition. Observers saw them to be in greater distress and were more sympathetic and less angry toward them and more inclined to offer them support. Finally, observers who had an unsupportive attributional style were more likely to choose the more uncomfortable treatment to prescribe to patients seen to be noncompliant. The findings thus implicate both contextual variables (information about a patient's treatment compliance) and personal characteristics (the observer's attributional style) in observers' third-person pain processes and consequent behavior.

The foregoing studies provide reason to believe that third-person pain processes are relevant in clinical situations and could plausibly relate to patient outcomes through their influence on the nature of the interactions clinicians and pain sufferers are likely to have. Unfortunately, none of the studies have dealt with actual patient-provider interactions, and none have dealt with meaningful clinical outcomes. Consequently, we do not know whether the third-person pain processes implicated or the behavioral proclivities they engender augur well or poorly for clinical outcomes. From the perspective of at least one major model of pain and pain-related disability—the operant behavioral approach (Fordyce 1976)—one might expect some of the phenomena of third-person pain, such as the underestimation effect or diminished sensitivity to pain expression arising out of attitudinal or experiential factors to actually be associated with better outcomes because, in principle, they are likely to lead to diminished reinforcement of pain-related behavior. From the perspective of certain health communication theories (DiMatteo et al. 1980), they may well be associated with poorer outcomes mediated by the negative impact of third-person pain and associated responses on treatment satisfaction, provider satisfaction, and engagement with treatment. These are crucially important issues, with obvious implications not only for behavior in the clinical situation but also for training and selection of health-care personnel.

4.8 Conclusion

There has been steady growth in interest in the phenomenon of third-person pain. This progress has been stimulated by the development of conceptual models that have organized thinking about how socially transmitted information about an individual's internal experience is perceived and acted upon by others. Technological and methodological developments, such as advances in neuroimaging and the availability of databases for conducting studies of third-person pain, have also contributed to the rising interest. An advanced understanding of third-person pain, its determinants and consequences, requires that a series of phases in information flow between the broadcasting of a pain signal and the response to the sufferer be considered. In this chapter, we have systematized those phases into an organizing framework for reviewing existing literature on third-person pain. It is evident that there is a gap in research relating to the later phases of the framework. While further work to identify variables that play an important role in all phases of the framework is necessary, finding creative ways of studying the explicit behavioral changes evoked by observing pain in others and their consequences for the sufferer should be a high priority.

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Chapter 5
Neuroplasticity in the Pain, Emotion, and Cognition Nexus

Gisèle Pickering

Abstract Synaptic plasticity is at the heart of the cellular and molecular events involved in chronic pain, cognition, and emotion. Fundamental mechanisms of chronic pain development are largely studied at neuronal level, while the role of the glia and the neuroglia interactions constitutes an emerging domain. A number of challenges are discussed: May memory traces of pain be modified and even erased? May maladaptive pain be prevented? Does pain-induced plasticity produce plastic cognitive-affective changes? Chronic pain and associated cognitive-emotional plastic changes may in the long term leave pain, depression, and cognition scars that add to the burden of disease for patients and are important challenges for clinicians.

5.1 Introduction

Synaptic plasticity is central to a number of mechanisms and underlies physiological functions like learning and memory. It has also become clear that it is strongly involved in pathological conditions like chronic pain. Fundamental processes with specific cellular and molecular mechanisms are put into play in chronic pain genesis and some of these are also involved in cognition. In patients, the literature has widely reported that chronic pain is accompanied with cognitive and emotional impairment and a bidirectional causal relationship between chronic pain and cognitive disorders has been described (Apkarian et al. 2004; Vlaeyen et al. 1995; Abeare et al. 2010). In the clinic, the entanglement between these different domains is complex for clinicians, in chronic/neuropathic pain patients presenting with successive strata of cognitive and emotional dysfunction, central pain treatment and side effects, and

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traumatic life events. In fundamental and translational pain research, two domains are particularly fascinating and questioning in this nexus. The first domain concerns the molecular mechanisms and the plastic changes involved in the memory of pain and its resilience with time: is it possible to modulate synaptic plasticity in order to prevent maladaptive pain and to erase memory traces of pain? The second domain concerns the relationship between chronic pain-induced plasticity and cognitive/affective disorders: does pain-induced plasticity monitor or induce in some way plastic cognitive changes?

5.2 Synaptic Plasticity

Synapses are communication areas between neurons (or between a neuron and a muscle cell) where chemicals are transmitted through the cleft between the pre- and the postsynaptic membranes. Over the past 40 years, the concept of a synapse as a simple site of transfer of information that once established does not change along life has been revolutionized by the discovery of its extremely plastic properties (Bliss and Lomo 1973; Bliss and Collingridge 1993). This synaptic plasticity is central to understanding the mechanisms of learning and memory. The synaptic "strength" (Colgin et al. 2009; Ermentrout et al. 2008; Li et al. 2014) results from the sum of pre-and postsynaptic responses of stimulated neurons, in other words, action potentials firing. The sequence and the temporal precision of the spikes in the central nervous system (CNS) have been shown to be linked with the strength of long-term plastic changes (Rutishauser et al. 2010) and to be especially related to cognitive function of the brain and its regulation. Long-term potentiation is the predominant form of synaptic plasticity in the brain, has been shown in the amygdala, the hippocampus CA1 neurons, and has been described especially in learning and memory processes. It is also considered as serving as the cellular model for chronic pain (Zhuo 2004, 2007, 2008, 2013; Sandkühler 2007; Ikeda et al. 2006; Costigan et al. 2009). Peripheral noxious inputs in injured afferent neurons or associated cell bodies trigger LTP in dorsal horn neurons of the spinal cord and contribute to spinal sensitization (allodynia and hyperalgesia). Nociceptive information is then transmitted to the thalamus and to central structures (the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC)) where potentiation contributes to pain central sensitization and impacts on other brain functions including fear and emotion (Sandkühler and Lee 2012).

Ji et al. (2003) described striking similarities in the synaptic plasticity involved in pain central sensitization and memory. However, hippocampal LTP reflects only synaptic strengthening, whereas central sensitization might also reflect other cellular mechanisms. LTP has been mainly studied in the hippocampus and other cortical areas but may be induced in the spinal cord and has been reported in sensory pain-related central synapses, spinal cord, and cortical areas involved in pain perception (Zhuo 2007, 2008; Sandkühler 2007). It is complex and characterized by successive phases of induction, consolidation, and maintenance in the CNS.

It requires the synaptic activation (by glutamate, the main neurotransmitter in nociceptive pathways) of *N*-methyl D-aspartate receptors (NMDARs) (Collingridge et al. 1983), tetra-heteromeric assemblies made up of two GluN1 (NR1) and two GluN2 (NR2) subunits, but it is not a single process as thought for a long time (Volianskis et al. 2013). Different subtypes of NMDARs are involved during induction of different temporal phases of synaptic plasticity. High-frequency stimulation of NMDAR relieves the physiological magnesium block from the NMDAR, leading to an increase in calcium ions and to induction of potentiation (Bliss and Collingridge 1993). A number of other receptors (AMPA, kainate, G-protein-coupled metabotropic, neurokinin-1…) are involved and nociceptor inputs induce the phosphorylation of NR1, NR2A, and NR2B by serine/threonine and tyrosine kinases. Activation of the mitogen-activated protein kinase (MAPK) cascade leads to triggering in the nucleus of the cell of the transcription of genes that encode a number of related products (cAMP response element-binding protein CREB) that are critical for synaptic potentiation in central areas and in the ACC. The ACC is a key cortical region for pain perception and has been shown to be activated in brain imaging studies with healthy volunteers and with chronic pain patients. It is also involved in emotion, cognition, executive function, social pain, and in emotional pain situations and is a nodal point in pain and cognitive-affective domains (Chen et al. 2014).

5.3 May Memory Traces of Pain Be Modified and Even Erased?

Memory traces of pain result from neuronal mechanisms and plasticity. This memory aspect must be distinguished from the recollection of a painful experience (with its location, nature, intensity, duration, and environmental components) that is encoded in the explicit memory.

Erasure of chronic pain has been the center of interest of many papers and is the hope of patients suffering from long-standing pain and associated deleterious impact on everyday life. Sandkühler and Lee (2012) stress the importance of the balance between LTP and depotentiation of LTP (a less studied area of neuronal plasticity), a balance between the formation of new and the erasure of old memory traces, that is disrupted in chronic pain states. After the induction phase of plastic changes (including LTP) in response to noxious stimuli at the first synapse, the consolidation and the maintenance phases of LTP in nociceptive pathways will leave a long-term pain trace via de novo protein synthesis.

However, the development of lasting pain in the consolidation phase may be aborted if the insult is antagonized in an adequate time window that may range from a few hours (Dableh et al. 2011) to a few weeks (Eaton et al. 1999) depending of the type of trauma. Drdla-Scutting et al. (2012) succeeded to erase pain memory traces in animals with a very high dose of remifentanil (450 μg/kg for 1 h), a short-acting mu opioid receptor agonist, by modifying the phosphorylation

state of AMPA. Millecamps et al. (2007) showed in rats that neuropathic pain was reduced for weeks after injection of D-cycloserine (a partial NMDA receptor agonist) into limbic areas, with encouraging results in refractory orofacial pain (Antal and Paulus 2011).

Protein kinase M zeta (PKM ζ) has been shown to play an important role in LTP, in declarative, procedural memory, and also at some but not all synapses and not for all memory traces of pain (Migues et al. 2010; Laferrière et al. 2011). In the ACC, the presence of PKM ζ is required for the expression of neuropathic pain, and ζ pseudo-substrate inhibitory peptide (ZIP) may block its activity and erase some traces of pain (Sandkühler and Lee 2012; Price and Ghosh 2013). However, its deleterious disruptive effect on normal functions like fear responses may limit its interest in chronic pain.

Erasure of chronic pain is still a challenge and the use of compensatory mechanisms has been discussed (Sandkühler and Lee 2012), but from the model of fear memories, the competition between reconsolidation and extinction phases appears not to be helpful to complement pain erasure processes.

Another approach to prevent memory traces of pain is to prevent the whole process of LTP especially consolidation and maintenance. Preemptive/preventive analgesia before and at the time of surgery aim at aborting chronic pain development in the postoperative period (Kissin 2000). The large literature in this field gives different results for the prevention of chronic neuropathic pain, with positive and negative outcomes that depend on multiple factors (Katz et al. 2011; Dualé et al. 2009).

Focusing on the NMDA receptor, a novel hypothesis suggests that memantine administration long before the surgical trauma (rather than on the day of the trauma) might prevent the development of central sensitization in an animal neuropathic pain model (Pickering et al. 2014). Memantine, prescribed in Alzheimer's disease to maintain cognitive function, has minimal side effects at doses within the therapeutic range, probably because of its specific mechanism of action as it is an uncompetitive antagonist with moderate affinity, strong voltage dependency, and rapid unblocking kinetics (Morel et al. 2013). Prevention of neuropathic pain with memantine administered for 4 days before surgery was successful, with no mechanical hypersensitivity and tactile allodynia with no increase of de novo synaptic proteins (especially tyrosine kinases $pTyr^{1472}$NR2B), and was also efficient in maintaining spatial memory. In a translational approach, a recent clinical trial (Pickering et al. 2014) in postmastectomy patients confirmed these findings and suggests that the plasmatic presence of this NMDA receptor antagonist 2 weeks before and after surgery (and not only on the day of surgery) might be a promising strategy to abort central sensitization and diminish the burden of disease in oncology. This approach must now be studied in relation to the different phases of LTP.

Finally, neurons have been the focus of attention to understand how central sensitization and LTP may help to find therapeutic options to treat chronic pain; accumulating evidence demonstrates that glial cells (microglia and astrocytes of the CNS and satellite glial cells of the dorsal root and trigeminal ganglia) are not static entities and are activated in chronic pain (Ji et al. 2013) with neuroglial interactions. Glial cell activation is complex, may be different in different neuropathic pain

etiologies and timings. Considering that a human astrocyte is estimated to contact up to two million synapses (Oberheim et al. 2009) and that glial mediators modulate synaptic transmission, the role of the glia may have been so far underestimated: Ji et al. (2013) recently suggested that chronic pain could be a result of a "gliopathy at peripheral and central levels."

5.4 Does Pain-Induced Plasticity Monitor or Induce in Some Way Plastic Cognitive and Emotional Changes?

Zhuo (2013) underlines that the spinal dorsal horn and periphery are seen as "gold" targets for controlling pain yet it is also obvious from the literature that central changes in the ACC, the prefrontal cortex, the insular cortex, the amygdala, and the hippocampus occur immediately after injury. However, the molecular, cellular, and synaptic aspects of LTP and the possible existence of different types of LTP in these central structures and within the ACC when chronic pain develops are just emerging. A major question concerns the relationship between pain-induced plasticity and cognitive/emotional disorders in chronic pain conditions. Cardoso-Cruz et al. (2013) showed in a rat model of neuropathic pain that impaired spatial memory was associated with reduced hippocampus-prefrontal cortex connectivity. Connections between thalamus and prefrontal cortex are necessary for cognition (Parnaudeau et al. 2013). The temporal precision in the sequence of firing of action potentials (in the thalamic-cingulate-prefrontal cortex pathways) is known to regulate cognition (Rutihausher et al. 2010), and NMDA and AMPA receptors are involved in this process, but how this may be modified in the context of chronic pain is still under investigation. Li et al. (2014) studied the temporal precision of information coding within the thalamic-cingulate pathway during peripheral injury (inflammatory and neuropathic pain). They showed for the first time that the temporal precision of information coding within this pathway is decreased in these chronic pain conditions: this would suggest a possible causal link between peripheral injury and cognitive impairment in chronic pain states, a link that needs to be further investigated.

Taken together, preclinical (Morel et al. 2013) and clinical reports (Pickering et al. 2014) suggest that memantine, an NMDAR antagonist, prevented pain expression in spinal structures and in cerebral structures, but not at the level of the peripheral nociceptor. Patients were conscious of pain but were not bothered by its presence suggesting a sensori-limbic dissociation that has been described in pain asymbolia (Berthier et al. 1988). This may also suggest different types of LTP and synaptic plasticity in different areas of the neuraxis. Considering there are today no specific drug available to target synaptic plasticity, such a finding needs to be further explored. A similar observation has already been reported in patients suffering from neuropathic pain and administered with oral magnesium, the physiological blocker of NMDAR. Long-standing pain was not improved but they were coping better with pain, suggesting a specific action on central structures involved in emotional processes (Pickering et al. 2011).

5.5 Conclusion

Synaptic plasticity for central sensitization and LTP is challenging along the entire neuraxis and within the neuroglial interactions. From a singular process, plasticity has now evolved to entail several types of LTP probably depending on the etiology, intensity of pain, and also on the neuronal site and the connectivity between brain areas. Memory traces of pain are complex to interfere with and therapeutic erasure of these traces may impact on other brain functions. Chronic pain does induce cognitive/emotional plastic changes that may in the long term leave depressive and pain scars that represent difficult challenges for clinicians. Prevention of chronic pain as early as possible before injury is a strategy that must be explored further and pursued in the overall context of the patient having to face the burden of the disease, of pain, and of emotional dysfunction.

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Part II
Measurement Issues

Chapter 6
Tools That Should Be Considered in Pain Assessment: Cognitive Factors, Emotion, and Personality

Joukje M. Oosterman and Inti A. Brazil

Abstract In this chapter, an overview is provided of instruments to measure pain, neuropsychological domains, pain cognitions, emotion, and personality constructs. Interpretational and conceptual issues will be discussed that should be considered in pain assessment. For example, the interpretation of neuropsychological test results should be done with caution. These tests often rely on multiple cognitive functions for intact performance, and, hence, performance on a specific test can be impaired due to cognitive deficits other than the function targeted with that test. Also, emotional and personality factors are highly interrelated constructs; as such, it is advisory to examine them concurrently in relation to pain assessments. Finally, it is important to keep in mind that personality and psychological constructs and affective states and traits are used interchangeably to refer to different levels of explanation.

6.1 Introduction

The outcomes of pain assessments are determined by multiple factors. Next to cognitive functions, emotional and personality factors, such as depression and anxiety, also play key roles in determining these outcomes. In addition, it is crucial to consider the differences between pain assessment tools and the various pain constructs they target (e.g., clinical pain intensity, experimental pain tolerance) in relation to cognitive, emotional, and personality aspects.

In this chapter, a brief overview will be given of available instruments to measure neuropsychological domains, pain cognitions, and emotional and personality constructs, together with a short outline of tests for malingering or insufficient effort. The most commonly used pain tools will be summarized, and findings of pain assessments

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will be briefly discussed in relation to different pain components that can be distinguished. Finally, a short discussion of the interrelatedness between the neuropsychological, pain cognition, and emotional and personality constructs is provided.

6.1.1 Psychometric Properties

The decision to use a specific test or questionnaire relies on many factors. First, an instrument must be reliable, in that it yields similar outcomes when administered multiple times over different test sessions (test-retest reliability). Similarly, an instrument should have high interobserver reliability, that is, test assessment and scoring is standardized such that the same results are found by different examiners, and high internal consistency, indicating that different items within an instrument show consistent results. Furthermore, validity must be high, indicating that an instrument should correlate strongly with other instruments tapping the same psychological constructs (convergent validity) but not with instruments more sensitive to other psychological constructs (divergent validity); together, these two factors determine the construct validity of an instrument. In addition, content validity reflects validity of the items (in terms of formulation, selection, etc.) and is established by expert raters. Finally, criterion validity indicates the extent to which an instrument is associated with an external (non-test) criterion.

For many of the tools discussed in this chapter, comprehensive reference books exist with additional details regarding the instruments, norm scores, and their reliability and validity. These include, for example, Lezak et al. (2012) and Strauss et al. (2006) for neuropsychological tests and McDowell (2006) for an overview of health-related questionnaires.

6.2 Cognitive Functions

In this section, we will give an overview of various cognitive domains, together with examples of tests employed to measure these functions. Only a short overview of available tests will be given; for detailed test descriptions, see Lezak et al. (2012). Next, we will briefly discuss caveats that exist when interpreting these tests, in the context of chronic pain.

Cognitive function is a general construct encompassing multiple abilities, each relying on partially different brain circuits. While broad categories, such as memory, executive function, and processing speed, are commonly found in the literature, more recent studies have provided evidence in favor of further differentiation within these cognitive domains. Unfortunately, there is little consensus on the exact subdivision of these domains. Within the domain of executive functions, for example, it has been suggested that there may be as many as six different components (Testa et al. 2012). For the sake of clarity, we will follow commonly accepted theories

regarding the underlying structure of different cognitive abilities. Overall, it is generally accepted that intelligence, executive function, memory, and attention and speed of information processing form separate cognitive domains. Other domains can be distinguished, such as praxis and motor skills, visuospatial functioning, language, and perception; however, to date there is little evidence that these functions play substantial roles in relation to acute or chronic pain. Therefore, these latter domains will not be discussed in this chapter. Finally, a brief overview of suitable tests to measure insufficient effort and malingering is provided.

6.2.1 Intelligence

Intelligence is probably one of the most ill-defined constructs in psychology with many different operationalizations and subdivisions. It is a broad concept that aims to capture the integrity of various types of cognitive functions across different domains. One common distinction is that between crystallized and fluid intelligence. Crystallized intelligence refers to knowledge and skills, whereas fluid intelligence encompasses abilities such as reasoning, problem-solving, and flexibility. Multiple intelligence tests exist, including the National Adult Reading Test (NART) as an indicator of premorbid intelligence and the Raven Progressive Matrices (RPM) which primarily measures fluid intelligence. Alternatively, the Wechsler Adult Intelligence Scale (WAIS, currently the 4th edition is out) is an entire battery devised to get a comprehensive estimate of intellectual functioning. The fourth edition of this test contains both core and supplemental tests, which are used to measure four different domains as well as to obtain a full-scale IQ estimate. The domains are the Verbal Comprehension Scale, Perceptual Reasoning Scale, Working Memory Scale, and the Processing Speed Scale. Finally, the Kaufman Adult Intelligence Test (KAIT) is widely used as an indicator of intelligence. The core battery of the KAIT contains six subtests, three of which measuring crystallized intelligence and three measuring fluid intelligence.

6.2.2 Executive Functions

Executive function is another particularly heterogeneous concept that includes a variety of cognitive abilities. Previous studies have distinguished between numerous functions, such as flexibility, set switching, inhibition, working memory, abstract reasoning, planning, and even more. Factor analysis has shown that three constructs, inhibition, set shifting, and monitoring and updating account for a major part of performance on the more traditional executive function tests (Miyake et al. 2000).

There is general consensus that executive functions rely on frontal-subcortical pathways that include regions such as the prefrontal cortex and the basal ganglia; the prefrontal cortex, part of the anterior cingulate cortex, and parietal cortex are

neurocognitive resources commonly recruited during executive function tests (Niendam et al. 2012). However, the diversity and heterogeneous nature of executive functions and the tests employed is founded by the fact that differential activation patterns exist between various tests purportedly measuring executive function (Niendam et al. 2012). This is commonly interpreted as support for the existence of multiple different executive functions.

A major problem when measuring executive functions is that many of the so-called executive function tests are heterogeneous in nature. This is in part due to the large variety of functions grouped under the term executive function; as a result, correlations between these tests are often nonsignificant and/or small (Miyake et al. 2000). In addition, these tests tap multiple functions, and impaired performance may therefore be the result of cognitive deficits other than executive function loss. The most obvious one is processing speed; performance on many executive function tests is actually expressed in terms of completion time and is therefore particularly sensitive to reduced (motor and/or mental) processing speed. Whenever possible, it may therefore be appropriate to calculate proportion scores, since such scores successfully limit involvement of functions such as processing speed (Stuss et al. 2001; Oosterman et al. 2010b). Similarly, learning and memorization processes play important roles in rule induction tasks such as the Wisconsin Card Sorting Task (WCST), in which rules have to be induced based on feedback (Oosterman et al. 2014). Therefore, pure executive function tests are scarce, and caution is needed when making firm claims based on the results of tests that are reliant on multiple executive or cognitive functions.

Numerous test of executive function have been developed over the years. Some of the best-known and frequently used tasks are tests such as the Stroop Color/Word test and the Hayling Sentence Completion Test to measure inhibition of prepotent responses, the Trail Making Test to measure cognitive flexibility, the Digit Span Backward test to measure working memory, the Tower of London and the Tower of Hanoi test to measure planning ability, the WCST and the Brixton Spatial Anticipation Test to measure set shifting, and the Fluency test to measure speeded verbal production. Other, more extensive, test batteries have been developed in order to have a more comprehensive examination of various executive functions. The Behavioural Assessment of the Dysexecutive Syndrome (BADS) battery was developed to get a more ecologically valid indication of executive function. This battery contains six tests that mimic situations one can encounter in daily life; for example, the Zoo Map Test measures planning ability and consists of a route that has to be planned on a map of a zoo, while taking into account certain rules that have to be adhered to. Next to planning, this battery measures functions such as organization, problem-solving, mental flexibility, inhibitory control, and monitoring behavior and contains two questionnaires (DEX), one to be completed by the patient him- or herself and one to be completed by a significant other. The advantage of this battery is that these tests resemble daily life situations and may therefore be more sensitive in detecting problems a patient encounters in daily life, something that many of the more traditional executive function tests fail to do. One disadvantage is that detailed norm scores are only available for the entire battery; there are no norm

scores available for comparative purposes (other than a very rough profile score) when one wishes to use a single or some subtests of this battery. The Delis-Kaplan Executive Function System (D-KEFS) consists of nine subtests, each measuring different aspect of executive function, namely, flexibility of thinking, inhibition, problem-solving, planning, impulse control, concept formation, abstract thinking, and verbal and spatial creativity. Several of these tests consist of adjusted versions of preexisting tests. Normative scores are available, also for the individual subtests. Finally, the Cambridge Neuropsychological Test Automated Battery (CANTAB) contains several tests, some of which assess executive functions such as planning, set shifting, and working memory. Norm scores are stratified according to age and IQ estimates. The advantage of this battery is that it does not rely heavily on verbal abilities, making it particularly suitable for clinical assessment in patients with different cultural backgrounds or patients with reduced verbal abilities as is the case in patients suffering from conditions such as aphasia or dementia.

6.2.3 Memory

With regard to memory, a common distinction is that between *explicit memory*, which includes episodic and semantic memory, and *implicit memory*, which is concerned with procedural knowledge and priming. These two memory systems depend on functionally different brain systems, with explicit memory being mostly dependent upon the hippocampal formation and neocortical regions, whereas subcortical structures such as the basal ganglia play a crucial role in implicit memory processes. In this section, the focus will be on learning and episodic memory processes, as these have been implicated mostly in relation to pain. Commonly used measures of verbal episodic memory include the Rey Auditory Verbal Learning Test (RAVLT), the Hopkins Verbal Learning Test (HVLT), and the California Verbal Learning Test (CVLT), and the Benton Visual Retention Test (BVRT) and Location Learning Test (LLT) as measures of visual episodic memory. Some memory test batteries are also available, measuring different aspects of memory processes. For example, the Wechsler Memory Scale (currently the 4th edition has been published) consists of seven subtests. Index scores can be calculated representing auditory memory, visual memory, visual working memory, and immediate and delayed memory. Another widely used battery is the Rivermead Behavioural Memory Test (RBMT-3). This battery taps everyday memory functioning and was particularly designed for memory assessment in patients with acquired brain damage, although it is also used in other frail populations such as patients with dementia. This battery consists of 14 subtests, focusing on aspects such as verbal memory, memory for faces, and prospective memory, among others. For all tests, extensive normative data are available, making them of particular use in clinical practice.

When assessing memory functioning, it is important to consider the role of executive control processes in explicit memory performance, which facilitate memory performance through strategic encoding and retrieval processes. This is particularly

the case for encoding and free recall measures; cued recall and recognition tests are less sensitive to executive (dys)functioning. In current standard memory tests, these processes are difficult to segregate; one exception to this is the CVLT, which was specifically designed to measure processes and strategies that are part of learning and memorization stages. Apart from encoding and retrieval processes, this test measures abilities such as organizational capacities (e.g., semantic clustering) in storing information as well as pro- and retroactive interference between two word lists that have to be memorized. Hence, this test provides detailed information regarding the executive control processes involved in memory performance. Besides executive processes, reduced speed of processing and attentional dysfunction may impair performance on memory tests. For example, several studies suggest that reduced processing speed plays a significant role in age-related decline in memory performance (e.g., Lee et al. 2012). Hence, memory may be diminished for various reasons, and this should be considered when assessing memory performance.

6.2.4 Attention and Speed of Information Processing

Attention and speed of information processing are strongly related constructs and will therefore be discussed together. Traditionally, attentional functioning has been divided into sustained attention, selective attention, and divided attention. Inherent to these definitions, a large overlap is present with the so-called executive functions. For example, the ability to inhibit prepotent responses requires the ability to selectively attend to one aspect while ignoring other aspects and can be measured with tasks such as the Stroop Color/Word test. Similarly, flexibility as measured with the Trail Making Test requires the ability to divide attention between multiple sets of stimuli. Some validated tests to measure sustained attention are, for example, the continuous performance test, the d2-test, and subtests of the Test of Everyday Attention (TEA). This latter is a test battery with high ecological validity, containing eight subtests measuring functions such as selective attention, cognitive flexibility, sustained attention, and more. Norm scores are available for the TEA, and this battery is applicable to various clinical populations, from all ages. Additional information regarding attention and processing speed can be obtained from the Stroop Word and the Stroop Color cards, as well as from the Trail Making Test part A, or from simple and choice reaction time tests that are, for example, part of the CANTAB.

6.2.5 Insufficient Effort and Malingering

A clear distinction between insufficient effort and malingering is crucial. Lack of effort refers to performance that is worse than can be expected on basis of demographics (e.g., age, educational achievement) and condition (e.g., the deficits cannot be fully explained by a neurological, psychiatric, or developmental disorder).

Malingering denotes intentionally feigned or exaggerated cognitive deficits or psychological symptoms, in the context of an external motive. Tests of insufficient effort or malingering are strongly recommended in case of several situations, such as in case of litigation or when a financial incentive is involved. To diagnose malingering, the following four criteria have to be met: (1) presence of a substantial external incentive, (2) evidence from neuropsychological testing (e.g., negative or probable response bias, discrepancy between test data, and documented background), (3) evidence from self-report (e.g., self-reported symptoms are discrepant with known patterns of brain functioning or behavioral observations), and (4) criteria 1–3 cannot be fully accounted for by neurological, psychiatric, or developmental disorders (see Slick et al. 1999). Tests have been developed to get an indication of potential insufficient effort or malingering. These tests are designed to appear difficult but they are actually extremely easy to perform and can therefore even be validly administered to patients with conditions such as neurological disorders (e.g., Tombaugh 1997). Sometimes positive feedback is provided to the patients during task performance, which may trigger an even larger decline in performance in case of malingering. Normally, a cutoff score is used, and performance beyond this point is indicative of malingering. Well-validated tests include the Test of Memory Malingering (TOMM), the Word Memory Test (WMT), and the Rey 15-Item Memory Test (RMT) and questionnaires such as the Structured Inventory of Malingered Symptomatology (SIMS). Apart from these tests, other (sub)tests may be indicative of possible malingering of insufficient effort (e.g., from the WMS or from the WAIS or particular items from questionnaires such as the Minnesota Multiphasic Personality Inventory-II).

Even though these tasks are very simple, studies have shown that performance can no longer be interpreted validly in case of severe cognitive decline, such as is the case in dementia patients. A significant part of these patients perform below the cutoff point on malingering tests, a finding that is associated with disease severity as expressed with measures such as the Mini-Mental State Examination (Merten et al. 2007).

6.2.6 Interpreting Neuropsychological Test Performance in Chronic Pain Patients

Several studies have reported compromised cognitive functioning in chronic pain patients, and some studies additionally found inverse associations between pain reports and cognitive functioning, in that an increase in pain severity is associated with a decline in cognitive ability. Domains typically affected include executive function, attention, processing speed, and episodic memory (Moriarty et al. 2011). However, many studies focusing on executive function and attention actually relied on tasks that also place heavy demands on processing speed. Importantly, there is evidence that the executive impairments found in chronic pain patients can be accounted for by reduced processing speed (Oosterman et al. 2012; Veldhuijzen et al. 2012). Furthermore, whereas controlled memory performance is diminished in

these patients, more automatic memory processes are intact (Grisart and Van der Linden 2001). This illustrates the importance of task selection if one wishes to obtain reliable indicators of cognitive function performance in patients. More specifically, since attention and speed of information processing may be particularly affected in chronic pain, it is crucial that future studies isolate the genuine memory and executive function impairments in these patients.

Regarding the interpretation of malingering tests in chronic pain patients, it is crucial to consider whether an external incentive is present. Although studies have shown alarmingly high prevalences of malingering in over 30 % of patients with pain or somatoform disorders (Mittenberg et al. 2002), such high numbers appear to be directly related to those involved in litigation or compensation seeking (Gervais et al. 2001); in case there is no legal context or financial incentive, evidence for malingering in these patients is limited or even absent.

6.3 Pain Cognitions

Pain cognitions constitute a separate category, apart from cognitive functions measured with neuropsychological tests. These cognitions refer to aspects such as pain catastrophizing and pain control beliefs and determine in important part pain coping strategies and future development of emotional disorders associated with pain (e.g., depression and anxiety). In addition, these factors may be associated with metacognitions regarding pain-related thoughts (Yoshida et al. 2012). Traditionally, questionnaires are used to measure these cognitions, such as the Pain Catastrophizing Scale (PCS), the Beliefs about Pain Control Questionnaire (BPCQ), the Pain Beliefs Questionnaire (PBQ), the Pain Beliefs and Perception Inventory (PBPI), the Pain Cognition List (PCL), the Multidimensional Locus of Pain Control Questionnaire (MLPC), the Coping Strategies Questionnaire (CSQ), the Pain Attitudes Questionnaire (PAQ), and the Survey of Pain Attitudes (SOPA). Various studies have published on psychometric properties of these questionnaires; overall, these appear to be in order (e.g., Osman et al. 2000; Ter Kuile et al. 1993).

The importance of these cognitions is underscored by many studies. They are, for example, positively associated with experimental pain sensitivity (Forsythe et al. 2011) and may predict future pain following skeletal trauma (Vranceanu et al. 2014). Also, cognitions such as catastrophizing tend to be associated with pain intensity ratings and with pain interference or pain-related disability in various pain populations (e.g., Osborne et al. 2007; Turner et al. 2002).

6.4 Emotional Factors and Personality Traits

The notion that pain sensitivity is strongly associated not only to emotional factors but also to certain personality characteristics probably seems rather intuitive to most of us. Moreover, emotional factors such as high levels of anxiety are an integral part

of higher-order personality constructs such as neuroticism. Therefore, it is difficult to disentangle the unique roles of personality and emotions, respectively, in pain experience. Adding to this, some basic emotions, like fear and anxiety, are also often regarded to be personality traits (e.g., Spielberger 1970), and some personality constructs that encompass a collection of behavioral and affective features, like depression, are sometimes referred to as (transient) affective states (e.g., Sáez-Francàs et al. 2014). Therefore, it may be crucial to consider emotions and personality concurrently when examining pain and pain-related disability. This section will provide a brief outline of frequently employed questionnaires to measure emotion and personality in relation to pain. Next, personality factors and their interrelatedness with emotion and pain will be discussed. The focus will be on personality characteristics related to negative affectivity/neuroticism given the large amount of studies on pain experience in various conditions characterized by heightened (trait) anxiety and/or depression.

6.4.1 Questionnaires

Some of the most widely used scales to measure depression include the Beck Depression Inventory (BDI), the Hamilton Rating Scale for Depression (HRSD), the Depression Anxiety and Stress Scale (DASS), the Zung Depression Scale (ZDS), the Center for Epidemiological Studies Depression Scale (CES-D), the Hospital Anxiety and Depression Scale (HADS), and the Geriatric Depression Scale (GDS) for older adults. In general, studies show that these scales are quite capable of differentiating between chronic pain patients with depression and those without (e.g., Geisser et al. 1997; Turk and Okifuji 1994). Note it has been suggested that the use of higher cutoff scores may be more suitable for these patients, such as a score of 19 instead of 16 on the CES-D (Turk and Okifuji 1994), as these questionnaires contain questions addressing somatic symptoms and patients are more likely to give positive responses on these items.

There are also various questionnaires to assess anxiety personality constructs. For instance, the State-Trait Anxiety Inventory (STAI) is one of the best-known instruments used to measure trait and state anxiety and has often been used in pain studies. Other commonly used measures include the Beck Anxiety Inventory (BAI), the Hamilton Anxiety Rating Scale (HARS), the DASS, and the HADS. Finally, pain-related anxiety or fear of pain can be measured with the Pain Anxiety Symptom Scale (PASS) or the Fear of Pain Questionnaire (FPQ), respectively.

Several instruments have been developed to measure personality and individual differences. The Minnesota Multiphasic Personality Inventory (MMPI) is one of the best-known instruments and has often been used to study pain as a function of personality. The MMPI assesses personality profiles based on ten clinical scales. The first three scales are hypochondriasis, depression, and hysteria (the so-called neurotic triad), and patients suffering from chronic pain generally tend to score relatively high on these scales (Gough 1946). Among these three classifications of personality, depression has received a relatively large amount of attention in the empirical

literature, and many (self-report) scales have been developed for its assessment. Other well-known instruments are the NEO-PI, the Eysenck Personality Inventory (EPI), Cattell's 16PF, and the HEXACO Personality Inventory, among others.

While most studies on negative affectivity/neuroticism, personality, and pain have employed self-report instruments measuring the relative *presence* of negative traits, a handful of questionnaires have been developed to measure the relative *absence* of traits such as fear and anxiety. These (self-report) measures are readily found in research on psychopathy. For instance, it has recently been shown that fearlessness and low anxiety are comprehensively captured by the Psychopathy Checklist-revised (PCL-R (Neumann et al. 2013)), a semi-structured interview used to assess psychopathy based on maladaptive behavioral tendencies. Other instruments, such as the Psychopathic Personality Inventory (PPI; (Lilienfeld and Andrews 1996)), include subscales targeting lack of fear and anxiety. For an overview of emotion and personality questionnaires, see McDowell (2006).

6.4.2 *Anxiety and Depression as Clinical Conditions: Negative Affectivity as a Common Factor*

In general, many have focused on depression and various anxiety-related conditions as more or less discrete psychiatric classifications representing a collection of behavioral and psychological features rather than moods and emotions. However, there is evidence that many personality disorders share genetic vulnerabilities and can be described in terms of overarching dimensions representing the commonalities between the disorders (Vaidyanathan et al. 2009). Indeed, there is a growing body of evidence highlighting a link between higher prevalence of pain conditions and personality constructs encompassing a heightened predisposition to experience aversive states such as fear and anxiety (i.e., *negative affectivity*; (Watson and Clark 1984)), often combined with feelings of depression (i.e., *neuroticism*, (Sáez-Francàs et al. 2014)). For instance, McWilliams and colleagues (2003, 2004) found relatively large associations between chronic pain and various anxiety disorders in a (non-institutionalized) sample. More specifically, individuals diagnosed with an anxiety disorder were more likely to suffer from chronic pain conditions. This positive association has also been found in relation to other personality constructs such as alexithymia (Shibata et al. 2014), depression, and increased trait anxiety (Celiker et al. 1997), thus suggesting that negative affectivity might be a common denominator in explaining the relationship between personality facets and pain. Such an approach could also partly account for the high comorbidity between depression and anxiety disorders, which are clinical conditions characterized by high negative affectivity.

In contrast, recent (neuroscientific) findings point out that pain experience is reduced in individuals scoring unusually *low* on personality traits such as fear and anxiety. These studies often measured diminished negative affective reactivity as a function of psychopathy. From a clinical perspective, psychopathy is a personality disorder characterized by abnormalities in the interpersonal-affective domain

combined with antisocial personality styles (Hare 2003). The interpersonal-affective component includes personality characteristics positing reduced negative affectivity, such as callousness and lack of empathy, a lack of feelings of guilt or remorse and shallow affect. Therefore, studying pain in relation to psychopathy provides insight into personality correlates of pain in those scoring low on personality traits related to reduced negative affectivity. Earlier studies in offenders with psychopathy used painful shocks to study reduced fear reactivity in offenders with psychopathy (Hare 1965a, b). While these studies showed that pain elicited less fear reactivity in psychopathy, they were not primarily concerned with pain itself. More recent neuroscientific studies are beginning to elucidate how the interpersonal-affective disturbances found in youth and adults with psychopathic tendencies are related to various aspects of pain. These studies were primarily focused on empathic pain, and, taken together, the findings indicate a negative relationship between empathic pain and interpersonal-affective functioning (Decety et al. 2013; Lockwood et al. 2013; Marsh et al. 2013). That is, the increased presence of personality predispositions capturing reduced negative affectivity is related to reduced neural responses to stimuli depicting other individuals experiencing pain.

6.4.3 Extraversion

In addition to neuroticism, some researchers have argued that extraversion is also an important personality factor when it comes to pain. Extraversion is a personality dimension that includes sub-components such as sociability, high activity levels, and positive emotionality. Thus, extraversion encompasses personality facets related to positive psychological adjustment to pain. It has been suggested that individuals scoring high on extraversion should show higher pain thresholds and tolerance (Lynn and Eysenck 1961). This notion has received some empirical support, and there is evidence that extraversion is related to the employment of more efficient strategies to cope with pain, while increased negative affectivity/neuroticism is linked to the use of maladaptive coping strategies (for a more extensive discussion, see Ramírez-Maestre and Esteve 2013; Ramírez-Maestre et al. 2004). Unfortunately, there are relatively few studies on the role of extraversion in populations suffering from chronic pain, and future studies should aim to incorporate measures of extraversion (Table 6.1).

6.5 Pain Tools and Different Components

Different tools are currently employed for pain assessment purposes; for an overview, see McDowell (2006). The most widely used include the McGill Pain Questionnaire (MPQ), Brief Pain Inventory (BPI), the Chronic Pain Grade (CPG), the Oswestry Low Back Pain Disability Questionnaire, visual analogue scale (VAS),

Table 6.1 An overview of available instruments

Domain		Instrument
Neuropsychology[a]	Intelligence	KAIT, NART, RPM, WAIS-IV
	Executive function	BADS, Brixton Spatial Anticipation Test, CANTAB, Digit Span, D-KEFS, Fluency, Hayling Sentence Completion Test, Stroop Color/Word test, TMT, Tower of London/ Hanoi, WCST
	Memory	BVRT, CVLT-II, HVLT, LLT, RAVLT, RBMT 3, WMS-IV
	Attention processing speed	CPT, d2, TEA, TMT-A, Stroop Word and Color cards
	Malingering and insufficient effort	MMPI, Rey 15-item Memory test, SIMS, TOMM, WMT
Pain Cognitions[a]	Catastrophizing, control beliefs, attitudes	BPCQ, CSQ, MLPC, PAQ, PBPI, PBQ, PCL, PCS, SOPA
Emotion[a]	Depression	BDI-II, CES-D, DASS, GDS, HADS, HRSD, ZDS
	Anxiety	BAI, DASS, FPQ, HADS, HARS, PASS, STAI
Personality[a]	Extraversion, neuroticism, depression	Cattell's 16PF, EPI, HEXACO Personality Inventory, MMPI, NEO-PI
	Lack of anxiety and fear, coldheartedness	PCL-R, PPI

BADS Behavioural Assessment of the Dysexecutive Syndrome, *BAI* Beck Anxiety Inventory, *BDI* Beck Depression Inventory, *BPCQ* Beliefs about Pain Control Questionnaire, *BVRT* Benton Visual Retention Test, *Cattell's 16PF* Cattell's 16 Personality Factor Test, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *CES-D* Center for Epidemiological Studies Depression Scale, *CPT* Continuous Performance Test, *CSQ* Coping Strategies Questionnaire, *CVLT* California Verbal Learning Test, *DASS* Depression Anxiety Stress Scale, *D-KEFS* Delis-Kaplan Executive Function System, *EPI* Eysenck's personality Inventory, *FPQ* Fear of Pain Questionnaire, *GDS* Geriatric Depression Scale, *HADS* Hospital Anxiety and Depression Scale, *HARS* Hamilton Anxiety Rating Scale, *HRSD* Hamilton Rating Scale for Depression, *HVLT* Hopkins Verbal Learning Test, *KAIT* Kaufman Adult Intelligence Test, *LLT* Location Learning Test, *MLPC* Multidimensional Locus of Pain Control Questionnaire, *MMPI* Minnesota Multiphasic Personality Inventory, *NART* National Adult Reading Test, *NEO-PI* NEO Personality Inventory, *PASS* Pain Anxiety Symptom Scale, *PAQ* Pain Attitudes Questionnaire, *PBPI* Pain Beliefs and Perception Inventory, *PBQ* Pain Beliefs Questionnaire, *PCL* Pain Cognition List, *PCL-R* Psychopathy Checklist-revised, *PCS* Pain Catastrophizing Scale, *PPI* Psychopathic Personality Inventory, *RAVLT* Rey Auditory Verbal Learning Test, *RBMT* Rivermead Behavioural Memory Test, *RPM* Raven Progressive Matrices, *SIMS* Structured Inventory of Malingered Symptomatology, *SOPA* Survey of Pain Attitudes, *STAI* State-Trait Anxiety Inventory, *TEA* Test of Everyday Attention, *TMT* Trail Making Test, *TOMM* Test of Memory Malingering, *WAIS* Wechsler Adult Intelligence Scale, *WCST* Wisconsin Card Sorting Test, *WMS* Wechsler Memory Scale, *WMT* Word Memory Test, *ZDS* Zung Depression Scale

[a]The functions within each domain represent a selection of those aspects relevant in relation to pain assessments; naturally, each domain encompasses more aspects than currently denoted in this table

numerical rating scale, Short Form 36 Bodily Pain Scale (SF-36 BPS), Faces Pain Scale (FPS), Verbal Descriptor Scale, and Self-Rating Pain and Distress Scale. When distinguishing between the different pain components, scales such as the MPQ are useful. In case of cognitive impairment, scales such as the FPS and VAS may be less reliable; additional information from observation tools is advisable then.

The literature on factors contributing to pain reports and experience is extensive. Sometimes, controversial findings have been reported, which may be due to factors such as differences in study design and the different pain components that have been assessed. Next to a distinction between findings that result from either clinical or experimental pain assessment methods, a crucial differentiation is one between different pain components, such as sensory and cognitive-evaluative or affective-emotional aspects, since the processing of these aspects relies on different neural pathways. For example, whereas the processing of sensory-discriminative pain component relies on more posterior brain structures as well as the primary and secondary somatosensory areas (the "lateral pain system"), the cognitive-evaluative and affective-emotional aspects are primarily being processed by frontal-limbic brain regions (the "medial pain system"). This system includes brain regions also heavily involved in cognitive functions (e.g., dorsolateral prefrontal region, anterior cingulate cortex, hippocampal formation) as well as in the processing of affective information such as fear and anxiety (e.g., orbitofrontal and ventromedial prefrontal cortex, amygdala). This overlap is evident in studies showing interrelatedness between pain reports and cognitive, psychological, and personality measurements.

In experimental pain studies, consistent patterns of results have been observed showing particular overlap between medial pain aspects on the one hand and emotional or cognitive aspects on the other. In patients with fibromyalgia, for example, depressive symptoms were found to be associated with neural activation patterns in those brain regions associated with affective pain processing, but not with the more sensory-discriminative pain pathway (Giesecke et al. 2005). Similarly, several studies showed that mood induction alters pain tolerance, but not pain intensity levels (e.g., Loggia et al. 2008; Kut et al. 2011; Villemure et al. 2003). Cognitive inhibition is also significantly associated with pain tolerance levels, but not with pain threshold (Oosterman et al. 2010a). Some studies do not, however, support this overlap, in that emotion induction has also been associated with both altered pain intensity and unpleasantness ratings in healthy controls (Kamping et al. 2013).

6.6 The Overlap Between Cognition, Emotion, and Personality in Relation to Pain

From the previous sections, it is evident that both personality/emotional and cognitive factors are significantly associated with clinical and experimental pain reports. The extent to which these factors are interrelated is unclear as the

evidence is unequivocal. For example, in fibromyalgia patients, neuroticism and conscientiousness are associated with catastrophizing, whereas neuroticism, agreeableness, and openness relate to pain anxiety. Similarly, another study showed that factors such as fear and catastrophizing are strongly associated with negative personality constructs (e.g., neuroticism, Lee et al. 2010). Catastrophizing may mediate the relationship where higher dispositional optimism is associated with reduced endogenous pain facilitation responses (Goodin et al. 2013). Finally, significant associations have been reported between pain cognitions and personality constructs such as neurotic traits, depression, and anxiety (Williams et al. 1994).

On the other hand, evidence regarding the relationship between cognitive functioning and emotional/personality constructs is less conclusive. For example, both cognitive inhibition and fear of pain may independently contribute to experimental pain tolerance (Oosterman et al. 2010a). It has furthermore been shown that the effects of mood on pain processing may be independent from attentional factors (Villemure and Bushnell 2009). On the contrary, catastrophizing may increase the distractive effects of pain on concurrent task performance, in both pain-free volunteers and in chronic pain patients (Crombez et al. 2002; Vancleef and Peters 2006). High catastrophizers may further have a heightened attentional focus on pain (Seminowicz and Davis 2006). In addition, depression and, to a lesser extent, anxiety and catastrophizing predict self-reported memory problems in chronic pain patients (Muñoz and Esteve 2005). Catastrophizing and coping may also be associated with memory functions as assessed with neuropsychological tests (Jorge et al. 2009). However, relationships of catastrophizing or depressive symptoms with processing speed, attention, and executive function may be less clear (Oosterman et al. 2012; Veldhuijzen et al. 2012), and, overall, not much support exists for the notion that psychological and pain cognition scores are related to cognitive test performance in chronic pain patients (see Moriarty et al. 2011, for a review).

6.7 Recommendations for Clinicians

When deciding which tools to use, several points are important to consider. Pain can be reliably assessed with measures such as the NRS, assessing pain from a unidimensional point of view, or with more generic tools assessing multiple dimensions of pain, such as the MPQ and CPG. It is advisable to assess cognitive functioning, since many patients suffering from chronic pain report cognitive problems (mostly memory and concentration) and display mild cognitive decline. When one wishes to have an extensive assessment of cognitive functioning, batteries such as the WAIS-IV (full-scale IQ), D-KEFS (executive functioning), TEA (attention), and WMS-IV (memory functioning) can be employed. For brief examinations of cognition, the NART or WAIS-IV subscales (IQ estimate), WMS-IV subtests (e.g. story recall), or word list learning paradigms such as the RAVLT, HVLT, or CVLT-II (memory functioning) and the TMT, Stroop test, or WCST (executive functioning)

can be administered. Subtests of the TMT and Stroop may also be used to measure psychomotor speed and attention.

Regarding pain cognitions, catastrophizing measured with, for example, the PCS or PCL and pain beliefs measured with lists such as the PBPI or CSQ are recommended since catastrophizing behavior and pain beliefs have been repeatedly associated as important factors influencing (or even moderating) pain processing and treatment success in chronic pain patients. Lists such as the BDI-II, CES-D, STAI, and PASS are useful to measure the level of depressive symptoms and anxiety. HEXACO and NEO-PI, as well as the PPI, are suitable to measure personality traits and negative affectivity, respectively.

6.8 Summary and Conclusions

This chapter focused on interpretational and conceptual issues that should be considered in pain assessments and also provided a comprehensive overview of neuropsychological tests, pain cognitions, and emotional and personality constructs. One conclusion is that the interpretation of neuropsychological test results should be done with caution, bearing in mind that neuropsychological tests require multiple functions for intact performance. Also, emotional and personality factors are highly interrelated constructs, suggesting it is important to examine them concurrently in relation to pain assessments. Finally, it is important to keep in mind that personality and psychological constructs and affective states and traits are used interchangeably to refer to different levels of explanation.

Future studies are needed in which the diverse pain components are compared in relation to cognition, emotion, and personality. Not only does this imply a distinction between experimental indices such as pain threshold and pain tolerance levels, but it is also crucial to differentiate between sensory-discriminative, affective-motivational, and cognitive-evaluative aspects. Particularly little is known about potential differences between these latter two aspects in relation to cognitive and emotional/personality factors. It has been suggested that brain regions involved in cognitive-evaluative aspects (e.g., prefrontal cortex) are compromised in irritable bowel disease, whereas feelings of anxiety and depression may be primarily associated with diminished gray matter density in brain regions involved in processing the affective-motivational pain aspects (Seminowicz et al. 2010). Therefore, a differentiation between the medial pain aspects may be pivotal when examining associations with cognitive and emotional factors; hence, a further examination of these different pain aspects in relation to neuropsychological performance, pain cognitions, and emotional and personality constructs is warranted. The independent contributions of each factor should be investigated when possible, preferably within mediation models that concurrently integrate these distinct functions.

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Chapter 7
Pain Evaluation in Patients with Cognitive Impairment

Patricia Schofield

Abstract This chapter will explore the issues surrounding pain assessment in the older population. It is well known that we are facing increasing challenges in the future around the world with the potential ageing demographic. With this demographic, we anticipate an increase in the numbers of older adults who may be in chronic pain. Alongside this we have a potential increase to 66 million older adults with dementia worldwide by 2030, and there is a clear and growing need for aged care staff to adequately identify pain in this population despite the difficulties involved. Nevertheless we have the facilities that can help us to identify pain in this population and some tools have a fairly strong evidence base, while others have a strong clinical utility. Following recent systematic reviews of the literature, recommendations will be made regarding the assessment tools that can be used to measure pain intensity along with the other factors that should be considered. A demonstration of how technology can be applied to enhance the assessment process will also be presented. A particular emphasis will be placed upon the tools that can be used for the assessment of pain.

7.1 Introduction

In recent decades, we have seen many great advances into the assessment and treatment of pain around the world. For example, there has been an increased acceptance of pain being recognised as the fifth vital sign and a strong move towards the implementation of pain self-management (Jenson et al. 2003). However, in spite of the recommendations made by the International Association for the Study of Pain in 2007 with the year against pain in older adults, care of the older adult in pain remains suboptimal in many countries with estimates of at least 50 % of older adults in pain living in the community and an increase to as high as 80 % when we

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examine the long-term care sector (Elliott 2013). This suggests that our most frail, most vulnerable adults have the poorest pain management. In terms of the research, again this remains incomplete and lacking in many areas, with some studies applying the findings from research in the younger population and simply "translating" the findings across to the older age cohorts. So much still needs to be done for the older population. Even more worrying is the fact that when dealing with older adults with cognitive impairment, this cohort has been demonstrated repeatedly to be missing in the academic literature or research studies (Barry et al. 2014). Where older adults with cognitive impairment are discussed or researched, we tend to see the same findings emerging repeatedly, in that problems identifying or assessing pain in this group are constantly highlighted. This chapter will aim to discuss the issues around pain evaluation amongst the older population, and in so doing, we will address the following objectives:

- Highlight the size and nature of the problems associated with pain in the older population.
- Identify the recognised pain assessment tools for older adults and recommend those with the strongest evidence base and those most accepted in clinical practice.
- Discuss the factors which could indicate pain in adults with cognitive impairment.
- Demonstrate the behavioural pain assessment tools and the evidence underpinning their use.
- Make recommendations for future practice and research in the field of pain evaluation.

7.2 Pain in the Older Population: The Issues

Many of the epidemiological studies have suggested that pain exists in 50 % of the community dwelling older population. This represents half of the older population living at home. Furthermore, similar epidemiological studies highlight that this number increases up to 80 % when we look at adults living in nursing or residential homes. Thus, many of our frailest, most vulnerable population are likely to be in moderate to severe, poorly controlled pain (Gibson 2006). However, recent work by Elliott (2013), who systematically reviewed the literature on prevalence, suggests that these averaged prevalence figures do not really provide an accurate picture of the literature and that prevalence estimates vary between 0 and 93 %. The problem with the studies to date is that there is great variation between the definitions of pain used and they do not take into account the gender differences. For example, women report more pain (Fillingim et al. 1999) and women are overrepresented in the older population.

We know that the population is ageing and that we are facing a significant demographic shift in the older versus younger generations (Crook et al. 1984). There is going to be an increase in the older population which is significantly higher than

what we expect to see in the younger generations. So the over 65s and the over 80s around the world are going to be proportionately higher than their younger counterparts. Furthermore, with this ageing demographic, a rapid increase in the numbers of older adults with dementia is expected. In the UK, the number is currently around 850,000, and on a worldwide scale, the number is around 36 m and expected to increase to 66 m in the next 15 years (Prince 2014).

It is widely acknowledged that pain is poorly managed in the older population and so it may be useful to consider some of the factors that can be attributed to this poor pain management (Crook et al. 1984). Furthermore, a recent study by Lukas et al. (2013b) demonstrates in a sample of 4,156 residents living in nursing homes across Europe that pain management remains suboptimal. They highlighted a number of predisposing factors such as dementia, large nursing home facilities, above-average and high turnover rates of nursing staff, low physicians' availability and severe pain intensity were negatively associated with adequate treatment.

A recent UK report by Help the Aged highlighted a number of attitudes and beliefs held by healthcare professionals and older adults themselves. Some of the commonly held views include the following:

Stoicism – "we don't make a fuss, I regard myself as stoic" (Raynor 76 years pg 8).
Older adults do not want to complain – "sometimes I feel like I am a bother to people" (Uddin 70 years pg 20).
It is to be expected at my age – "pain is part of growing old" (Allcock 76 years pg 16).

Such attitudes and beliefs amongst healthcare professionals and the older adults themselves lead to a general acceptance that pain is inevitable and incurable (Cowan et al. 2003; Cousins et al. 2004) with many older people feeling let down by the healthcare providers (Sofaer et al. 2007) and many healthcare providers reluctant to prescribe due to fears of tolerance, addiction, unwanted side effects and pre-existing co-morbidities (Cousins et al. 2004) (Fig. 7.1).

Many healthcare professionals and patients themselves tend to assume that pain is a natural part of the ageing process and so there is no need to do anything about it (Crook et al. 1984; Herr and Mobily 1997; Hofland 1992; Morrison and Siu 2000).

Fig. 7.1 A classic comment in the literature

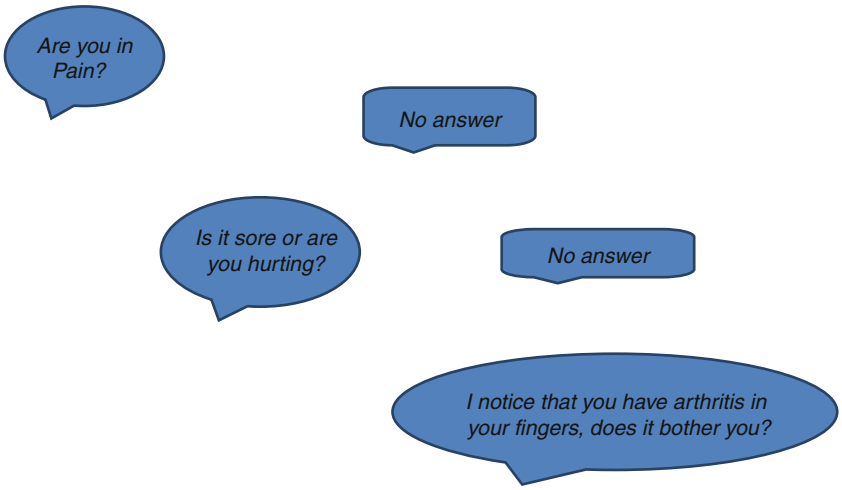

Fig. 7.2 Asking about pain

Add into this mixture the fact that the individual may not communicate their pain in a language that is easily understood by healthcare professionals.

It is worthwhile to remember that pain is a complex phenomenon and can be influenced by psychosocial and cultural factors, so individuals may choose not to report their pain. But asking the question in various formats may provide an opportunity for those in pain to be able to report their pain. It may be appropriate to ask the question in different ways (Feldt et al. 1998). For example, (Fig. 7.2).

7.3 Pain Evaluation: Types of Scales for Assessing Pain

1. Self-report – Numerical rating scale (0–10) or verbal rating scale (none, mild, moderate, severe) has high validity and reliability in older people (Herr and Mobily 1993; Herr et al. 2007). They can be used in mild/moderate cognitive impairment (Weiner et al. 1999). Vertical as opposed to horizontal orientation may help to avoid misinterpretation in the presence of visuospatial neglect, e.g. in patients with stroke.
2. Older people with moderate to severe cognitive impairment – Pain thermometer or coloured visual analogue scale is easy to use in those with cognitive/communication impairment (Herr et al. 2007). Validity has not been fully evaluated but is well understood in early- and mid-stage Alzheimer's disease.
3. Observational pain assessment – Older people with severe cognitive/communication impairment: Abbey pain scale (Abbey et al. 2002), Doloplus (Wary and Doloplus 1999; Pickering et al. 2010), PAINAD (Warden et al. 2003), and Algoplus (Rat et al. 2011).

4. Multidimensional assessment – Older people with minimal cognitive impairment: Brief Pain Inventory is a 15-item scale assessing severity, impact on daily living, impact on mood, and enjoyment of life (Auret et al. 2008).

As discussed earlier, it is anticipated that there will be a significant proportion of the older population experiencing dementia in the future, and this will impact upon our ability to identify and subsequently manage pain. Often behaviour in adults with dementia is perceived as "challenging", and historically, such behaviour has been treated with antipsychotic medications. Certainly, in the UK, there has been a move away from prescribing such drugs, and healthcare professionals are becoming more aware of changes in behaviour associated with other problems such as pain or distress. In fact recently, the work by Hyochol and Horgas (2013) proposed that "challenging" behaviour can be reduced when treated with analgesic drugs. This study evaluated the minimum data set measures taken in all nursing homes within the USA and demonstrated that residents with more severe pain are less likely to display wandering behaviours, but more likely to display aggressive and agitated behaviours. The authors concluded that the "relationship between pain and disruptive behaviours depends on the type of behaviours". Pain is positively correlated with disruptive behaviours that do not involve locomotion (e.g. aggression and agitation), but negatively related to disruptive behaviours that are accompanied by locomotion (e.g. wandering) (Hyochol and Horgas 2013). Some of the common behavioural signs reported in the literature include the following: Verbal communication – shouting, screaming, crying; Nonlanguage-based verbal – grunts, groans, aggression, agitation, withdrawal, facial expression, protecting an area; Physiological signs – pallor, sweating, blood pressure, pulse (not always present).

Such signs do not necessarily require a "trained eye"; they are signs that could be observed by any person. Nevertheless, they are signs that have often been incorporated into behavioural pain assessment tools. These will be discussed further below.

A recent systematic review of the literature was carried out in 2007 for the UK National Pain Assessment Guidelines (Collett et al. 2007). Within this guidance, two self-report pain intensity scales were recommended as appropriate for the measurement of pain in older adults with mild to moderate dementia. The scales were *verbal descriptors* (none, mild, moderate, severe) and *numerical rating scale* 0–10 scale.

It may be necessary to use both scales, if one does not work. But these are the two scales with the most evidence underpinning their use. Furthermore, a recent systematic review in 2013 was carried out to update the UK National Pain Assessment Guidance, and these scales continue to be the recommended with the strongest evidence (Schofield et al. 2014).

If severe dementia is present or language skills are lost, then it may be necessary to use one of the behavioural scales. In total, there are around 12 scales within the literature and all are fairly similar in terms of the behaviours that they attribute to pain. In 2007, the scale that had the most evidence was the Abbey scale.

7.4 Use of the Abbey Pain Scale

The Abbey pain scale is best used as part of an overall pain management plan (Collett et al. 2007). The Pain scale is an instrument designed to assist in the assessment of pain in residents who are unable to clearly articulate their needs. The scale does not differentiate between distress and pain, so measuring the effectiveness of pain-relieving interventions is essential. Recent work by the Australian Pain Society recommends that the Abbey pain scale be used as a movement-based assessment (Australian Pain Society 2005). The staff recording the scale should therefore observe the resident while they are being moved, e.g. during pressure area care, while showering, etc. The scale should be completed immediately following the procedure and record the results in the resident's notes. Include the time of completion of the scale, the score, staff member's signature, and action (if any) taken in response to results of the assessment, e.g. pain medication or other therapies. A second evaluation should be conducted 1 h after any intervention is taken in response to the first assessment, to determine the effectiveness of any pain-relieving intervention. If, at this assessment, the score on the pain scale is the same, or worse, consider further intervention and act as appropriate. Complete the pain scale hourly, until the resident appears comfortable, then 4 hourly for 24 h, treating pain if it recurs. Record all the pain-relieving interventions undertaken. If pain/distress persists, undertake a comprehensive assessment of all facets of resident's care and monitor closely over a 24-h period, including any further interventions undertaken. If there is no improvement during that time, notify the medical practitioner of the pain scores and the action/s taken.

An update of the UK National Pain Assessment Guidelines has revealed that there has been some more recent work using the Abbey scale which shows use of the observer scales such as Abbey, PAINAD, and NOPAIN improves assessment of pain in older adults with cognitive impairment (Lukas et al. 2013a). Furthermore, in the UK, Abbey scale is most widely accepted in practice. However, the recent systematic review due to be published in 2014 has identified that other scales have now overtaken the Abbey scale and perhaps the most credentialed and recommended behavioural pain assessment tool is now the PAINAD (Schofield et al. 2014).

As discussed earlier, in 2007 we identified 12 behavioural pain scales (Abbey, PAINAD, PACSLAC, DisDAT, PADE, PAINE, Doloplus, NoPain, CNPI, ADD, Mobid, and COOP). The recent update of the UK guidelines has identified 15 scales (Schofield et al. 2014). A further few scales have since been developed. In 2007, the Abbey, PAINAD, and Doloplus scales were recommended based upon the best evidence at the time. More work has been carried out using PACSLAC (Cheung and Choi 2008; Schiepers et al. 2010; Zwakhalen et al. 2012; Lints-Martindale et al. 2011) and PAINAD (Horgas and Miller 2008; Jordan et al. 2009; Lane et al. 2003; DeWaters et al. 2008). The PACSLAC scale has good inter-rater reliability (Cheung and Choi 2008) and is the scale most valued by nurses (Zwakhalen et al. 2012) but does need a short form and more testing in larger-scale studies. PAINAD is a sensitive tool for detecting pain in adults with dementia but does have a high false-positive rate (Jordan et al. 2009). The PAINAD has a high sensitivity (92 %) but low specificity for pain (62 %). It is easy and simple to use, although further research with larger

sample sizes is required. The Doloplus scale has been translated in five languages (Pickering et al. 2010) and the Doloplus team recently developed the Algoplus scale. This scale has been developed specifically for acute pain measurement in adults with dementia (Rat et al. 2011). It was developed using expert opinion, caregiver interviews, and video recordings of patients. It is currently being validated in 5 languages and translated in 20 languages. The advantage of this scale is the very brief rater time (1 min). Therefore, it certainly shows a great deal of potential for clinical and research settings (Rat et al. 2011). It has become so popular in France that it has now overtaken the use of the Doloplus scale. Therefore, the Doloplus team is currently finishing a concordance study between both scales and data will be available soon. Moreover work by Schofield and colleagues within the COST collaborative on pain and dementia demonstrates that there is great inconsistency across European care homes in terms of the types of pain assessment scales being used and whether any pain assessment is undertaken at all, largely attributed to lack of education of aged care staff. The COST Action on pain and dementia will make future recommendations regarding pain assessment and implementation of assessment scales (http://www.cost.eu/COST_Actions/isch/Actions/TD1005 accessed 11th Nov 2014).

7.5 The Pain APP

Following the UK National Pain Assessment Guidelines, it was found that pain was not being widely assessed in adults with cognitive impairment across all care settings. Therefore, the pain assessment application was developed for Android or iPhone use. This follows the pain algorithm developed for the national guidelines in 2007.

http://cms1.gre.ac.uk/gwizards/pain-app/

7.6 Main Guidelines

In summary, pain assessment and management continues to be suboptimal across many countries (Lukas et al. 2013a, b; Schofield et al. 2014). This is in spite of a proliferation of pain assessment tools, many of which have been developed for older adults with communication difficulties including dementia. It is widely recognised that there is huge shift anticipated in the age cohort across the world with increased numbers of older adults compared to diminishing numbers of younger adults. Furthermore, it is anticipated that there will be a significant increase in the numbers of older adults with dementia over the next 20 years (Prince 2013) which further complicates the pain assessment process. A number of factors need to be considered when assessing pain in older adults with or without cognitive impairment as follows:

7.6.1 Pain Awareness

All healthcare professionals should be alert to the possibility of pain in older people and to the fact that older people are often reluctant to acknowledge and report pain (Herr and Gerand 2001).

7.6.2 Pain Enquiry

Any health assessment should include enquiry about pain, using a range of alternative descriptors (e.g. sore, hurting, aching) (Feldt et al. 1998).

7.6.3 Pain Description

Where pain is present, a detailed clinical assessment of the multidimensional aspects of pain should be undertaken including the following:

- Sensory dimension: the nature, location, and intensity of pain
- Affective dimension: the emotional component and response to pain
- Impact: on functioning at the level of activities and participation (Katz and Melzack 1999)

7.6.4 Pain Location

An attempt to locate pain should be made by asking the patient to point to the area on themselves or the use of pain maps to define the location and the extent of pain (Herr and Gerand 2001).

7.6.5 Pain Intensity

Pain assessment should routinely include the use of a standardised intensity rating scale, preferably a simple verbal descriptor scale or a numeric rating scale, if the person is able to use these (Schofield et al. 2014).

7.6.6 Communication

Every effort should be made to facilitate communication particularly with those people with sensory impairments (use of hearing aids, glasses, etc.). Self-report assessment scales should be offered in an accessible format to suit the strengths of the individual (Herr and Gerand 2001).

7.6.7 Assessment in People with Marked Impaired Cognition/Communication

People with moderate to severe communication problems should be offered additional assistance with self-report through the use of suitably adapted scales and facilitation by skilled professionals. In people with very severe impairment, and in situations where procedures might cause pain, an observational assessment of pain behaviour is additionally required. Pain behaviours differ between individuals, so assessment should include insights from familiar carers and family members to interpret the meaning of their behaviours (AGS 1998; Schofield et al. 2014).

7.6.8 Cause of Pain

Careful physical examination should be undertaken to identify any treatable causes. However, staff should be aware that pain can exist even if physical examination is normal (AGS 1998; AHCPR 1992).

7.6.9 Re-evaluation

Once a suitable scale has been identified, serial assessment should be undertaken using the same instrument to evaluate the effects of treatment (Schofield et al. 2014).

7.7 Conclusion

In conclusion, pain experienced by older adults is no different to that of their younger counterparts. There is no clear evidence to suggest that pain is diminished with either ageing or dementia. So we must assume that pain is experienced in the same way across the age cohorts. We need to remember, however, that the impact of pain upon the individual may vary. For the older adult, pain may affect ability to maintain independence and subsequently cause social isolation (Herr and Gerand 2001). Measurement of pain may require some special attention, in terms of language of assessment tools. But the important thing to remember is that it must be appropriately measured and managed using a multidisciplinary approach. As Melzack once said:

To describe pain solely in terms of intensity is like specifying the visual world only in terms of light flux without regard to pattern, colour, texture and many other dimensions of the visual experience (Melzack 1975: 278)

Appendix 7.1: Scales

PACSLAC

Pain Assessment Checklist for Seniors with Limited Ability to Communicate-II (PACSLAC-II)	
Date of Assessment: _____ Time: _____	Check if present
Facial Expressions	
1. Grimacing	
2. Tighter face	
3. Pain expression	
4. Increased eye movement	
5. Wincing	
6. Opening mouth	
7. Creasing forehead	
8. Lowered eyebrows or frowning	
9. Raised cheeks, narrowing of the eyes or squinting	
10. Wrinkled nose and raised upper lip	
11. Eyes closing	
Verbalizations and Vocalizations	
12. Crying	
13. A specific sound for pain (e.g., 'ow', 'ouch')	
14. Moaning and groaning	
15. Grunting	
16. Gasping or breathing loudly	
Body Movements	
17. Flinching or pulling away	
18. Thrashing	
19. Refusing to move	
20. Moving slow	
21. Guarding sore area	
22. Rubbing or holding sore area	
23. Limping	
24. Clenched fist	
25. Going into foetal position	
26. Stiff or rigid	
27. Shaking or trembling	
Changes in Interpersonal Interactions	
28. Not wanting to be touched	
29. Not allowing people near	
Changes in Activity Patterns or Routines	
30. Decreased activity	
Mental Status Changes	
31. Are there mental status changes that are due to pain and are not explained by another condition (e.g., delirium due to medication, etc.)?	
TOTAL SCORE (Add up checkmarks)	

Doloplus-2

DOLOPLUS-2 SCALE

BEHAVIOURAL PAIN ASSESSMENT IN THE ELDERLY

NAME : Christian name : DATES

Unit :

Behavioural records

SOMATIC REACTIONS					
1• Somatic complaints	• no complaint	0	0	0	0
	• complaints expressed upon inquiry only	1	1	1	1
	• occasional involuntary complaints	2	2	2	2
	• continuous involuntary complaints	3	3	3	3
2• Protective body postures adopted at rest	• no protective body posture	0	0	0	0
	• the patient occasionally avoids certain postures	1	1	1	1
	• protective postures continuously and effectively sought	2	2	2	2
	• protective postures continuously sought, without success	3	3	3	3
3• Protection of sore areas	• no protective action taken	0	0	0	0
	• protective actions attempted without interfering against any investigation or nursing	1	1	1	1
	• protective actions against any investigations and nursing	2	2	2	2
	• protective actions taken at rest, even when not approached	3	3	3	3
4• Expression	• usual expression	0	0	0	0
	• expression showing pain when approached	1	1	1	1
	• expression showing pain even without being approached	2	2	2	2
	• permanent and unusually blank look (voiceless, staring, looking blank)	3	3	3	3
5• Sleep pattern	• normal sleep	0	0	0	0
	• difficult to go to sleep	1	1	1	1
	• frequent waking (restlessness)	2	2	2	2
	• insomnia affecting waking times	3	3	3	3
PSYCHOMOTOR REACTIONS					
6• Activities of daily living (washing &/or dressing)	• usual abilities unaffected	0	0	0	0
	• usual abilities slightly affected (careful but thorough)	1	1	1	1
	• usual abilities highly impaired, washing &/or dressing is laborious and incomplete	2	2	2	2
	• washing &/or dressing rendered impossible as the patient resists any attempt	3	3	3	3
7• Mobility	• usual abilities & activities remain unaffected	0	0	0	0
	• usual activities are reduced (the patient avoids certain movements and reduces his/her walking distance)	1	1	1	1
	• usual activities and abilities reduced (even with help, the patient cuts down on his/her movements)	2	2	2	2
	• any movement is impossible, the patient resists all persuasion	3	3	3	3
PSYCHOSOCIAL REACTIONS					
8• Communication	• unchanged	0	0	0	0
	• heightened (the patient demands attention in an unusual manner)	1	1	1	1
	• lessened (the patient cuts him/herself off)	2	2	2	2
	• absence or refusal of any form of communication	3	3	3	3
9• Social life	• participates normally in every activity (meals, entertainment, therapy workshops)	0	0	0	0
	• participates in activities when asked to do so only	1	1	1	1
	• sometimes refuses to participate in any activity	2	2	2	2
	• refuses to participate in anything	3	3	3	3
10• Problems of behaviour	• normal behaviour	0	0	0	0
	• problems of repetitive reactive behaviour	1	1	1	1
	• problems of permanent reactive behaviour	2	2	2	2
	• permanent behaviour problems (without any external stimulus)	3	3	3	3
		SCORE			

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PAINAD

Pain Assessment IN Advanced Dementia- PAINAD (Warden, Hurley, Volicer, 2003)

ITEMS	0	1	2	SCORE
Breathing Independent of vocalization	Normal	Occasional labored breathing. Short period of hyperventilation	Noisy labored breathing. Long period of hyperventilation. Cheyne-stokes respirations.	
Negative vocalization	None	Occasional moan or groan. Low- level of speech with a negative or disapproving quality	Repeated troubled calling out. Loud moaning or groaning. Crying	
Facial expression	Smiling or inexpressive	Sad, frightened, frown	Facial grimacing	
Body language	Relaxed	Tense. Distressed pacing. Fidgeting	Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out	
Consolability	No need to console	Distracted or reassured by voice or touch	Unable to console, distract or reassure	
			TOTAL*	

*** Total scores range from 0 to 10 (based on a scale of 0 to 2 for five items), with a higher score indicating more severe pain (0="no pain" to 10="severe pain").**

Instructions: Observe the older person both at rest and during activity/with movement. For each of the items included in the PAINAD, select the score (0, 1, or 2) that reflects the current state of the person's behavior. Add the score for each item to achieve a total score. Monitor changes in the total score over time and in response to treatment to determine changes in pain. Higher scores suggest greater pain severity.

Note: Behavior observation scores should be considered in conjunction with knowledge of existing painful conditions and surrogate report from an individual knowledgeable of the person and their pain behaviors.

Remember that some patients may not demonstrate obvious pain behaviors or cues.

Algoplus Scale

SCALE ALGOPLUS

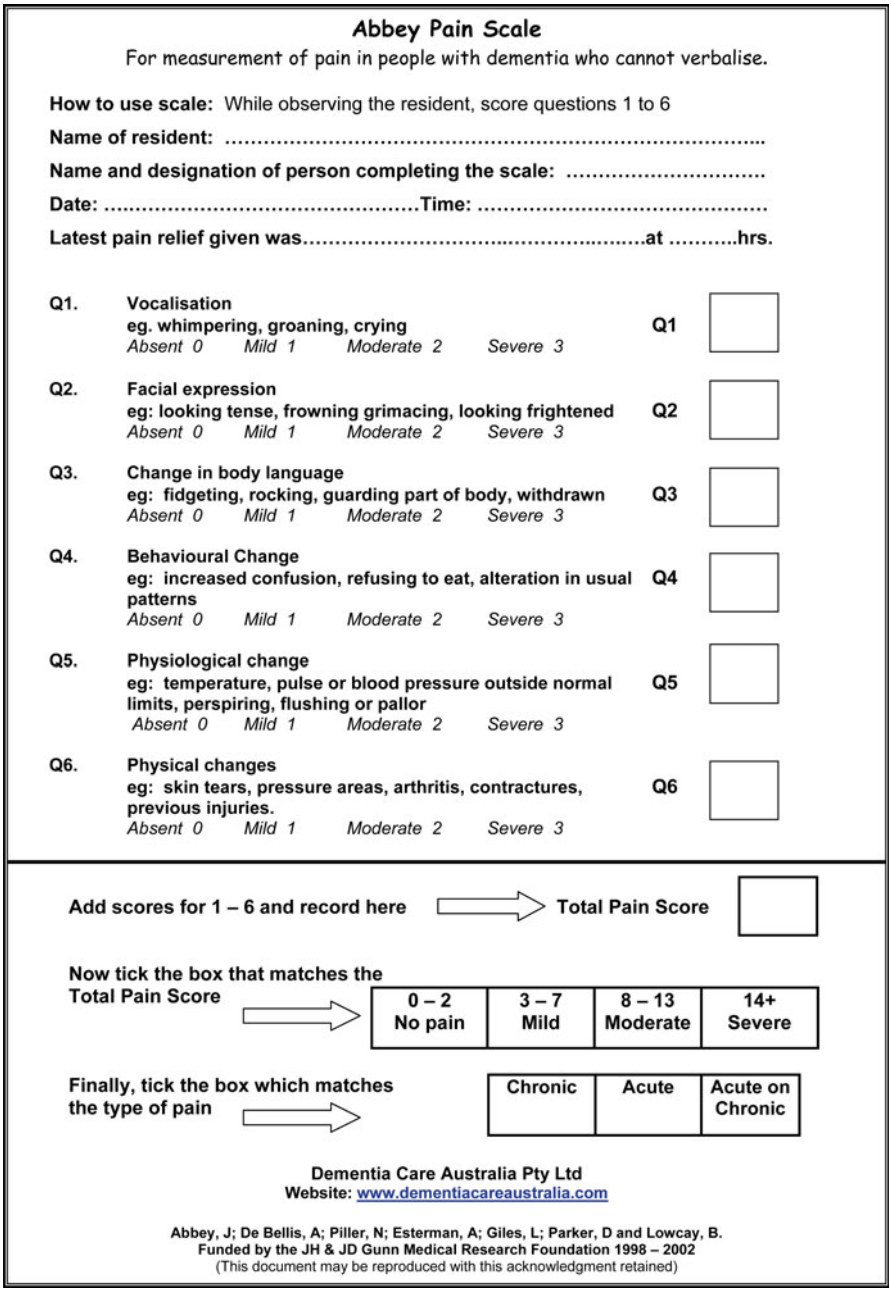
Pain assessment

acute pain-behavior assessment scale for the elderly with limited ability to communicate verbally

Patient identification

Date pain assessed	...../...../.....		...../...../.....		...../...../.....		...../...../.....		...../...../.....		...../...../.....	
Time	.....		.....		.....		.....		.....		.....	
	YES	NO	YES	NON	YES	NO	YES	NO	YES	NO	OUI	NO
1 • Facial expressions Frowning, grimacing, wincing, clenched teeth, unexpressive.												
2 • Look Inattentive, blank stare, distant or imploring, teary-eyed, closed eyes.												
3 • Complaints "Ow-ouch", "that hurts", groaning, screaming.												
4 • Body position Withdrawn, guarded, refuses to move, frozen posture.												
5 • Atypical behaviors agitation, aggressivity, hooking onto something or someone.												
Total YES	/5		/5		/5		/5		/5		/5	
Health professional who conducted the assessment	❑ Doctor ❑ Nurse ❑ Care assistant ❑ Other Initials		❑ Doctor ❑ Nurse ❑ Care assistant ❑ Other Initials		❑ Doctor ❑ Nurse ❑ Care assistant ❑ Other Initials		❑ Doctor ❑ Nurse ❑ Care assistant ❑ Other Initials		❑ Doctor ❑ Nurse ❑ Care assistant ❑ Other Initials		❑ Doctor ❑ Nurse ❑ Care assistant ❑ Other Initials	

Abbey Pain Scale



Abbey Pain Scale

For measurement of pain in people with dementia who cannot verbalise.

How to use scale: While observing the resident, score questions 1 to 6

Name of resident: .....

Name and designation of person completing the scale: .....

Date: .....**Time:** .....

Latest pain relief given was.....at .....hrs.

Q1. **Vocalisation**
eg. whimpering, groaning, crying **Q1**
Absent 0 Mild 1 Moderate 2 Severe 3

Q2. **Facial expression**
eg: looking tense, frowning grimacing, looking frightened **Q2**
Absent 0 Mild 1 Moderate 2 Severe 3

Q3. **Change in body language**
eg: fidgeting, rocking, guarding part of body, withdrawn **Q3**
Absent 0 Mild 1 Moderate 2 Severe 3

Q4. **Behavioural Change**
eg: increased confusion, refusing to eat, alteration in usual patterns **Q4**
Absent 0 Mild 1 Moderate 2 Severe 3

Q5. **Physiological change**
eg: temperature, pulse or blood pressure outside normal limits, perspiring, flushing or pallor **Q5**
Absent 0 Mild 1 Moderate 2 Severe 3

Q6. **Physical changes**
eg: skin tears, pressure areas, arthritis, contractures, previous injuries. **Q6**
Absent 0 Mild 1 Moderate 2 Severe 3

Add scores for 1 – 6 and record here ⇨ **Total Pain Score**

Now tick the box that matches the Total Pain Score ⇨

0 – 2 No pain	3 – 7 Mild	8 – 13 Moderate	14+ Severe

Finally, tick the box which matches the type of pain ⇨

Chronic	Acute	Acute on Chronic

Dementia Care Australia Pty Ltd
Website: www.dementiacareaustralia.com

Abbey, J; De Bellis, A; Piller, N; Esterman, A; Giles, L; Parker, D and Lowcay, B.
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DOLOPLUS-2 SCALE : LEXICON

Somatic complaints
The patients expresses pain by word, gesture, cries, tears or moans.

Protective body postures adopted at rest
Unusual body positions intended to avoid or relieve pain.

Protection of sore areas
The patient protects one or several areas of his/her body by a defensive attitude or gestures.

Expression
The facial expression appears to express pain (grimaces, drawn, atonic) as does the gaze (fixed gaze, empty gaze, absent, tears).

Investigation
Any investigation whatsoever (approach of a caregiver, mobilization, care procedure, etc.).

Washing/dressing
Pain assessment during washing and/or dressing, alone or with assistance.

Mobility
Evaluation of pain in movement: change of position, transfer, walking alone or with assistance.

Communication
Verbal or non-verbal.

Social life
Meals, events, activities, therapeutic workshops, visits, etc.

Problems of behaviour
Aggressiveness, agitation, confusion, indifference, lapsing, regression, asking for euthanasia, etc.

DOLOPLUS-2 SCALE : INSTRUCTIONS FOR USE

1 • Scale use requires learning

As is the case with any new instrument, it is judicious to test it before circulating it. Scale scoring time decreases with experience (at most a few minutes). Where possible, it is of value to appoint a reference person in a given care structure.

2 • Pluridisciplinary team scoring

Irrespective of the health-care, social-care or home structure, scoring by several caregivers is preferable (physician, nurse, nursing assistant, etc.). At home, the family and other persons can contribute using a liaison notebook, telephone or even a bedside meeting. The scale should be included in the 'care' or 'liaison notebook' file.

3 • Do not score if the item is inappropriate

It is not necessary to have a response for all the items on the scale, particularly given an unknown patient on whom one does not yet have all the data, particularly at psychosocial level. Similarly, in the event of coma, scoring will be mainly based on the somatic items.

4 • Compile score kinetics

Re-assessment should be twice daily until the pain is sedated, then at longer intervals, depending on the situation. Compile score kinetics and show the kinetics on the care chart (like temperature or blood pressure). The scale will thus become an essential argument in the management of the symptom and in treatment initiation.

5 • Do not compare scores on different patients

Pain is a subjective and personal sensation and emotion. It is therefore of no value to compare scores between patients. Only the time course of the scores in a given patient is of interest.

6 • If in doubt, do not hesitate to conduct a test treatment with an appropriate analgesic

It is now accepted that a score greater than or equal to 5/30 is a sign of pain. However, for borderline scores, the patient should be given the benefit of the doubt. If the patient's behavior changes following analgesic administration, pain is indeed involved.

7 • The scale scores pain and not depression, dependence or cognitive functions

Numerous instruments are available for each situation. It is of primary importance to understand that the scale is used to detect changes in behavior related to potential pain.
Thus, for items 6 and 7, we are not evaluating dependence or independence but pain.

8 • Do not use the DOLOPLUS 2 scale systematically

When the elderly patient is communicative and cooperative, it is logical to use the self-assessment instruments. When pain is patent, it is more urgent to relieve it than to assess it ... However, if there is the slightest doubt, hetero-assessment will avoid underestimation.

PAINAD Item Definitions

(Warden et al., 2003)

Breathing

1. *Normal breathing* is characterized by effortless, quiet, rhythmic (smooth) respirations.
2. *Occasional labored breathing* is characterized by episodic bursts of harsh, difficult, or wearing respirations.
3. *Short period of hyperventilation* is characterized by intervals of rapid, deep breaths lasting a short period of time.
4. *Noisy labored breathing* is characterized by negative-sounding respirations on inspiration or expiration. They may be loud, gurgling, wheezing. They appear strenuous or wearing.
5. *Long period of hyperventilation* is characterized by an excessive rate and depth of respirations lasting a considerable time.
6. *Cheyne-Stokes respirations* are characterized by rhythmic waxing and waning of breathing from very deep to shallow respirations with periods of apnea (cessation of breathing).

Negative Vocalization

1. *None* is characterized by speech or vocalization that has a neutral or pleasant quality.
2. *Occasional moan or groan* is characterized by mournful or murmuring sounds, wails, or laments. Groaning is characterized by louder than usual inarticulate involuntary sounds, often abruptly beginning and ending.
3. *Low level speech with a negative or disapproving quality* is characterized by muttering, mumbling, whining, grumbling, or swearing in a low volume with a complaining, sarcastic, or caustic tone.
4. *Repeated troubled calling out* is characterized by phrases or words being used over and over in a tone that suggests anxiety, uneasiness, or distress.
5. *Loud moaning or groaning* is characterized by mournful or murmuring sounds, wails, or laments in much louder than usual volume. Loud groaning is characterized by louder than usual inarticulate involuntary sounds, often abruptly beginning and ending.
6. *Crying* is characterized by an utterance of emotion accompanied by tears. There may be sobbing or quiet weeping.

Facial Expression

1. *Smiling or inexpressive*. Smiling is characterized by upturned corners of the mouth, brightening of the eyes, and a look of pleasure or contentment. Inexpressive refers to a neutral, at ease, relaxed, or blank look.
2. *Sad* is characterized by an unhappy, lonesome, sorrowful, or dejected look. There may be tears in the eyes.
3. *Frightened* is characterized by a look of fear, alarm, or heightened anxiety. Eyes appear wide open.
4. *Frown* is characterized by a downward turn of the corners of the mouth. Increased facial wrinkling in the forehead and around the mouth may appear.
5. *Facial grimacing* is characterized by a distorted, distressed look. The brow is more wrinkled, as is the area around the mouth. Eyes may be squeezed shut.

Body Language

1. *Relaxed* is characterized by a calm, restful, mellow appearance. The person seems to be taking it easy.
2. *Tense* is characterized by a strained, apprehensive, or worried appearance. The jaw may be clenched. (Exclude any contractures.)
3. *Distressed pacing* is characterized by activity that seems unsettled. There may be a fearful, worried, or disturbed element present. The rate may be faster or slower.
4. *Fidgeting* is characterized by restless movement. Squirming about or wiggling in the chair may occur. The person might be hitching a chair across the room. Repetitive touching, tugging, or rubbing body parts can also be observed.
5. *Rigid* is characterized by stiffening of the body. The arms and/or legs are tight and inflexible. The trunk may appear straight and unyielding. (Exclude any contractures.)
6. *Fists clenched* is characterized by tightly closed hands. They may be opened and closed repeatedly or held tightly shut.
7. *Knees pulled up* is characterized by flexing the legs and drawing the knees up toward the chest. An overall troubled appearance. (Exclude any contractures.)
8. *Pulling or pushing away* is characterized by resistiveness upon approach or to care. The person is trying to escape by yanking or wrenching him- or herself free or shoving you away.
9. *Striking out* is characterized by hitting, kicking, grabbing, punching, biting, or other form of personal assault.

Consolability

1. *No need to console* is characterized by a sense of well-being. The person appears content.
2. *Distracted or reassured by voice or touch* is characterized by a disruption in the behavior when the person is spoken to or touched. The behavior stops during the period of interaction, with no indication that the person is at all distressed.
3. *Unable to console, distract, or reassure* is characterized by the inability to soothe the person or stop a behavior with words or actions. No amount of comforting, verbal or physical, will alleviate the behavior.

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Chapter 8
Behavioural/Facial Markers of Pain, Emotion, Cognition

Miriam Kunz

Abstract Behavioural/facial markers of pain refer to a variety of responses that typically accompany the experience of pain. They serve the purpose to communicate the inner state "pain" to others and thus play a crucial role in social interactions. Moreover, they can also serve the purpose to protect affected body areas from pain and hereby promote healing. This chapter will give an overview of these behavioural markers of pain, with a specific focus on facial activity. Descriptions on what these responses look like, how they can be analysed, which aspects of pain they encode and how they can be differentiated from behavioural responses to other types of emotional affective states will be given. Moreover, since behavioural markers of pain are of special importance in patients with cognitive impairments (who are often not able to report about their pain), the impact of cognition on behavioural responses to pain will be discussed.

8.1 Introduction

The experience of pain is typically accompanied by a certain set of behavioural responses. A comprehensive conceptual framework for these behavioural responses is provided in Chap. 2. Some of the pain-related behavioural responses can be nicely observed in football matches (aka soccer), where football players who are hit by an opposing player can often be seen falling to the ground, clutching the affected body part, rolling about, grimacing and groaning. Commonly these behavioural responses are divided into three groups, namely, facial expressions, body postures/movements and paralinguistic vocalisations (Craig et al. 2010). This chapter will mainly focus on facial expressions, given that facial expressions of pain have been studied extensively, whereas little is known about the two other groups of pain behaviours. It is believed that the broader domain of behavioural responses accompanying the experience of pain serves two purposes, which are (1) a communicative function and (2) a pain management function (Prkachin 1986; Williams 2002). Facial

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expressions and vocalisations both seem to have a primary communicative function by rapidly informing others that one is experiencing pain and thus warning others and/or eliciting empathy and solicitous behaviours in others. In contrast, body postures/movements are believed to have a primary pain management function. For example, rubbing or holding the affected body part seems to mainly serve the purpose of protecting the self from pain and promoting healing. However, even if pain management might be the primary function, pain-related body postures/movements do of course also have a communicative value, given that certain postures and movements can easily be detected as pain indicative by observers (Prkachin 1986). Likewise, facial expressions and vocalisations – although having a primary communicative function – might also have a pain management function. For example, closing of the eyes – a movement often occurring in the context of pain – might shield the individual from the noxious and physically threatening stimulus. Therefore, behavioural markers of pain seem to have evolved to serve communicative as well as pain management functions.

The aim of this chapter is to give an overview of behavioural responses (with a special focus on facial expressions) occurring in the context of pain and to describe what they look like, their variability, which aspects of pain they encode, how they can be differentiated from behavioural responses to other types of affective states and whether they are altered in those with impaired cognitive functioning.

8.2 Facial Responses to Pain

Amongst the three categories of non-verbal behavioural responses to pain, namely, facial expressions, vocalisations and body movements, the *facial expression* of pain has been studied most extensively. Especially in the last two decades, a considerable number of studies have been conducted that try to analyse the "characteristic" features of facial expressions of pain and which bio-psychosocial factors might impact the way we facially express pain (Hadjistavropoulos et al. 2011). The reason why research on pain behaviour has mostly focused on the facial expressions of pain is that facial expressions are readily accessible, are highly plastic, and are believed to be the most specific, encodable form of pain behaviour in humans (Williams 2002).

8.2.1 Which Methods Can Be Used to Analyse Facial Responses?

One of the first instruments developed for the assessment of non-verbal behaviour is the Facial Action Coding System (*FACS*), which is still considered the gold standard (Ekman and Friesen 1978). The FACS is based on anatomical analysis of visible facial movements which are categorised as action units (AUs). The FACS lists 44 different AUs, each AU being based on discrete movements of specific muscles.

FACS analyses of facial expressions are not carried out in real time, but instead the videotaped facial expressions are coded in slow-motion and stop-frame feedback, thus making the coding very time-consuming and not suitable for use in clinical settings. For research purposes, however, the FACS has enabled us to better describe and understand facial responses occurring during the experience of pain. Another method to analyse facial responses is the electromyogram (*EMG*). However, so far, very few studies have used facial EMG to assess facial responses to pain (Mailhot et al. 2012; Wolf et al. 2005) because despite EMG being able to pick up even subtle muscle activities, only a limited number of facial muscles can be assessed simultaneously. Moreover, the ability to isolate a facial muscle is much poorer when using surface EMG (due to *EMG crosstalk* amongst neighbouring muscles) compared to FACS analyses (Hess 2009). Apart from FACS and EMG analyses, new developments in visual computer techniques have rendered the possibility of developing *automated recognition systems* for facial expressions of pain. Several attempts in this direction have been made (e.g. Bartlett et al. 2014; Hammal et al. 2008). However, the development is still at its beginning and not ready to be used in clinical or most research contexts. The most important shortcoming so far has been that the majority of attempts to develop automatic recognition systems for facial pain displays have used video material with posed facial expressions that depict prototypical "caricatures" of pain expressions that lack naturally occurring variations (only intensified pain-prototypical facial expressions are shown). However, in order for such a system to validly decode actual pain displays, it is crucial that such a system is capable to detect pain despite the occurrence of variations in facial displays. Nevertheless, the developments in this area are promising and might render an automatic analysis of facial responses to pain possible in the next decades.

8.2.2 What Do Facial Expressions of Pain Look Like?

It is acknowledged that facial responses to pain are not unspecific grimacing but convey pain specific information (Hadjistavropoulos et al. 2011; Williams 2002). There seems to be a subset of facial movements that repeatedly occur across different types of pain (ranging from different types of experimental pain induction procedures to clinical pain (Prkachin 1992; Prkachin and Solomon 2008)) as well as across individuals (male/female (Kunz et al. 2006); young/old (Kunz et al. 2008b)). This subset includes as the most prominent facial movements: tightening of the muscles surrounding the eyes, furrowed brows, raising the upper lip/nose wrinkling and eye closure (Prkachin 1992; Prkachin and Solomon 2008). In addition, opening of the mouth has also been frequently observed (Craig et al. 2011). Images of these facial movements are displayed in Fig. 8.1. The combination of these facial movements is often referred to as the "prototypical facial expression of pain".

It is, however, important to keep in mind that despite the evidence that these key facial activities reliably occur during pain, this does not imply only one uniform facial expression of pain that can be observed at all times and in all individuals (Craig et al.

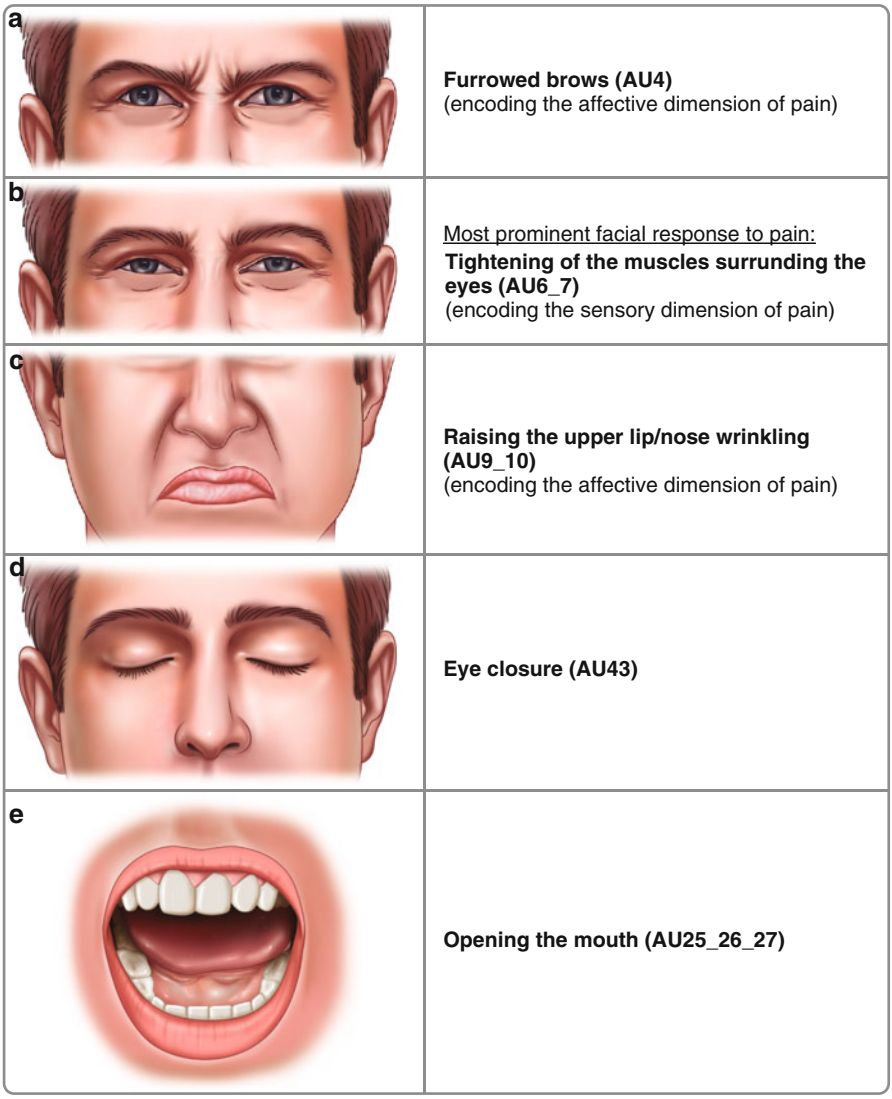

Fig. 8.1 (**a**–**e**) Pain-indicative facial movements: shown are those facial movements that are frequently displayed in the context of experimental as well as clinical pain conditions. Facial responses to pain have mostly been analysed using the FACS which categorises facial responses in different action units (AUs). Each picture illustrates a different AU that has been found to be pain indicative

2011). Instead, the frequencies of occurrence of these key movements during pain usually range from 10 to 60 % (Kunz et al. 2011a, b; Kunz and Lautenbacher 2014). Therefore, the likelihood that all four key facial movements occur simultaneously or in other words the likelihood that an individual displays the complete "prototypical

expression of pain" is very low. Rather, individuals often display only parts of this subset, sometimes even blending it with a limited range of other facial activities (e.g. smiling; Hale and Hadjistavropoulos 1997; Kunz et al. 2009, 2013a, b). Recently it has been shown that it is more helpful to differentiate between at least three different facial activity patterns of pain that are displayed in the context of pain and which are composed of different combinations of facial movements (Kunz and Lautenbacher 2014). These were as follows: (a) tightening of the muscles surrounding the eyes with furrowed brows and wrinkled nose (pattern I, combination of A + B + C of Fig. 8.1), (b) furrowed brows with tightening of the muscles surrounding the eyes (pattern II; combination of A + B of Fig. 8.1) and (c) opened mouth with tightening of the muscles surrounding the eyes (pattern III; combination of B + D of Fig. 8.1).

These different facial activity patterns all have one facial movement in common, namely, the tightening of the muscles surrounding the eyes (AU 6_7). This facial movement is indeed the most frequent and, thus, possibly the most important marker that occurs during pain (Craig et al. 2011). Interestingly, this facial movement encodes the sensory dimension of pain (giving information on the intensity of pain) (Kunz et al. 2012b) and perhaps the information on the sensory dimension of pain might be the most important aspect that needs to be communicated to onlookers (in order to warn them for potential danger). In contrast, furrowed brows and wrinkled nose – encoding the affective dimension of pain (Kunz et al. 2012b) – occur much less frequently. Thus, facial expressions of pain are a multidimensional response system, encoding the sensory aspects as well as the affective dimensions of pain, however, with an emphasis on the sensory aspects.

It is also important to mention that a considerable percentage of individuals (approximately 15–25 %) do not show any visible facial responses during the experience of pain, although they do report moderate to even strong pain intensities (Kunz and Lautenbacher 2014). This is especially true for chronic pain patients, since chronic or long-lasting pain is most often not accompanied by facial expressions of pain. Only if there is an acute exacerbation of pain, facial expressions will be elicited. For example, a patient with chronic back pain might experience constant pain of moderate intensity while he/she is sitting at a table for an hour, and this constant pain level will likely not be accompanied by facial expressions. However, if the patient gets up, the moderate pain might increase to a strong intensity and this exacerbation will elicit facial expressions of pain. It is important to keep in mind that that a "stoic face" is not necessarily incompatible with the experience of pain and individuals might be experiencing pain although they do not show any pain-related facial activity (Craig et al. 2011; Kunz and Lautenbacher 2014).

8.3 Body Postures/Movements

Although it is unquestionable that the experience of pain is typically accompanied by body postures/movements, little research has been conducted so far that aimed at classifying or describing body movements accompanying pain using objective

assessment tools. Reasons for the lack of research might stem from the complexity and variability of bodily movements and the lack of instruments to objectively assess them. Moreover, given that body movements are believed to have a primary pain management and not a primary communicative function (Prkachin 1986), they do not need to be as distinct or as definable as facial expressions. Given that the origin of pain, the quality of pain, and the body areas/body parts being affected can vary immensely, body movements aiming at reducing or controlling the pain can also be expected to vary immensely. Nevertheless, despite this enormous diversity, there seem to be some body postures/movements that have repeatedly been observed across different types of pain and that might be pain indicative for various types of pain. These body movements are guarding (abnormally slow, stiff, interrupted or rigid movement), bracing (a stiff, static position) and rubbing the painful area (Labus et al. 2003).

8.4 Paralinguistic Vocalisation

So far, even less is known about vocalisation changes occurring during pain. Although it is acknowledged that pain experiences are accompanied by paralinguistic vocalisations – such as crying, shouting, groaning – studies are lacking that have tried to investigate these pain-indicative vocalisations using specialised voice analyses tools. Using voice analyses tools, the following parameters should be assessed in order to better characterise pain-indicative vocalisations: frequency, voice intensity, formants and voice quality as well as temporal characteristics (Scherer et al. 2003). Only when assessing and analysing these parameters we will be able to characterise pain-indicative vocalisations and possibly differentiate them from paralinguistic vocalisations of other types of emotional states.

8.5 Differentiating Behavioural/Facial Markers of Pain from Behavioural Responses to Other Emotions

Observers are able to differentiate behavioural markers of pain (especially facial expressions) from behavioural responses to other types of affective states (e.g. anger, joy, surprise) well above chance level (Simon et al. 2008; Kappesser and Williams 2002), and this ability to differentiate is already developed by the ages of 5–6 years (Deyo et al. 2004). Even though these findings seem promising, there are also several studies demonstrating substantial shortcomings in pain recognition (e.g. mistaking pain for disgust, underestimation of pain; Chambers et al. 1989; Kappesser et al. 2006; Kunz et al. 2013a), and compared to almost all of the six basic emotional states (anger, disgust, fear, happiness, sadness and surprise), the recognition accuracy for facial pain expressions seems to be the lowest (Simon et al. 2008; Kappesser and Williams 2002). The reasons why behavioural/facial markers

of pain can be confused with other emotions are that each single marker by itself does not exclusively occur during pain but also during other emotional states. For example, each of the single facial movements displayed in Fig. 8.1 can also be found during other emotional states, such as happiness (contraction of the muscles surrounding the eyes), during disgust (nose wrinkle) and anger (furrowed brow). Thus, none of the single facial movements by itself can differentiate between pain and other emotional states, but the combinations of facial movements, their temporal patterns and context information, as well as the combination of facial expressions, body posture and paralinguistic vocalisations help us to correctly interpret these behavioural/facial markers of pain.

Interestingly, experience with pain diagnostic and/or pain management by itself does not improve the ability to correctly infer pain from facial expressions (e.g. Lautenbacher et al. 2013); however, a training procedure specifically targeting the facial expressions of pain has been shown to be successful. Solomon et al. (1997) developed such a training procedure to improve recognition accuracy for pain. Based on the finding that pain is accompanied by a specific set of facial movements (Prkachin 1992; Prkachin and Solomon 2008), observers were trained to recognise these facial movements (see Fig. 8.1 where these facial movements are displayed). And indeed, those observers who received this training showed better decoding accuracy compared to a control group (Solomon et al. 1997). Given the clinical importance of correctly interpreting behavioural/facial markers of pain, such a training seems to be a promising approach.

8.6 Impact of Cognition on Behavioural/Facial Markers of Pain

Based on empirical findings, it is acknowledged that behavioural/facial markers of pain are a mixture of biological dispositions as well as of social learning (Hadjistavropoulos et al. 2011). As for their biological dispositions, it has been shown that infants (including neonates) (Craig et al. 2011) and congenitally blind individuals (Kunz et al. 2012a) display the same patterns or the same types of facial movements in response to pain as sighted adults do (see also Fig. 8.1 for a list of the most frequent pain-indicative facial movements). These findings clearly suggest that facial expressions of pain are “hard-wired”. As regards body movements and vocalisations, empirical findings are lacking so far. Despite facial expressions of pain having been shown to be “hard-wired”, it is also acknowledged that facial responses become modifiable across early and late childhood through social learning experiences and cognitive capacities (Hadjistavropoulos et al. 2011). One very important modification relates to the degree/intensity to which we express pain via our face. Whereas young children tend to show vigorous facial expressions of pain, older children and adults seem to have learned to effectively downregulate their facial expressions of pain (Larochette et al. 2006). In line with this finding, a recent neuroimaging study demonstrated that a low degree of facial expressiveness to pain

was associated with higher activation in fronto-striatal structures (Kunz et al. 2011a). Given that these fronto-striatal structures are known to be involved in motor inhibition, this finding suggests that low expressive individuals actively suppress their facial display of pain (Kunz et al. 2011a). When trying to interpret these findings, it has been argued that individuals learn to intentionally suppress the facial display of negative affect (including pain) following culturally/socially learned "display rules". These display rules represent social norms about when, where and how one should express affective states (Ekman et al. 1969) and are learned already at a young age. Based on this theory, facially responding to pain would be the "default" that individuals learn to suppress due to social/cultural demands (e.g. "big boys don't cry", "one mustn't be oversensitive to pain"). In accordance with this theory, it has been demonstrated in previous studies that social learning and social context indeed influence the degree of facial expressiveness to pain. The presence of others can reduce (e.g. when being together with a stranger) as well as increase (when being together with a loved one) the amount of pain-indicative facial responses depending on the nature of the relationship between observer and sufferer (Karmann et al. 2014; Vervoort et al. 2008). Furthermore, it has been shown that the degree of facial expressiveness to pain can be effectively modulated by different types of learning, with operant conditioning techniques leading to an increase (positive reinforcement of facial expressions of pain) or decrease (positive reinforcement of a neutral expression) in facial expressiveness to noxious stimulation, respectively (Kunz et al. 2011b). This learned ability to mostly downregulate facial expressions of pain seems to depend on the cognitive status of the individual.

Not surprisingly, given the involvement of prefrontal structures in the inhibition of facial displays, patients with cognitive impairments (dementia) have been found to display elevated facial expressions when experiencing pain (Hadjistavropoulos et al. 2000; Kunz et al. 2007, 2008a). It is possible that facial responses to noxious stimulation are increased in patients with dementia because the cognitive ability to control the impulse to facially display their inner state is impaired in demented patients. As discussed above, we mainly learn in the course of childhood to inhibit the facial display of negative affective states, such as pain, owing to certain display rules, and this ability to suppress facial responses to pain might be impaired in patients with dementia. However, it is also possible that the increased facial responses are due to the fact that patients with dementia lose the capacity to anticipate the pain and when it will end or exercise adequate cognitive control over the pain experience.

The cognitive capacity of an individual does – however – have no impact on the types of facial markers being displayed during pain. It has been found that facial expressions occurring during pain are composed of the same types of facial movements as found in non-demented elderly individuals in response to pain (Kunz et al. 2007). These findings are very promising for clinical settings, given that they clearly suggest that the face seems to specifically encode the experience of pain and that this specific encoding does not change in the course of dementia.

The findings for body movements being affected by cognitive decline in patients with dementia might be less promising. Many researchers seem to believe body

movements/postures remain pain indicative, given that "guarding", "bracing" and "rubbing" are included in most of the observational scales for pain assessment in patients with dementia (Herr et al. 2006; Zwakhalen et al. 2006). Nevertheless, some authors have issued the concern that these body movements might be less discriminant in frail elderly patients with dementia (Weiner et al. 1999). Indeed, elderly patients with dementia may have difficulties in moving or may show stiffness due to arthritis or due to Parkinson's disease, and therefore, these changes in body movements might be completely unrelated to pain per se. This could mean that pain can be wrongly diagnosed even though the patient is pain-free (and is "only" functionally impaired) or that pain is overlooked because health-care professionals interpret these behaviours simply as age-related impairments (Weiner et al. 1999). More research is needed in this area.

8.7 Conclusions

The experience of pain is typically accompanied by a certain set of behavioural responses including facial expressions, body postures/movements and paralinguistic vocalisations. These behavioural markers are of great clinical relevance, especially in cognitively unimpaired individuals and infants who are not able to provide self-report of pain. Consequently, pain becomes what the observer/health-care professional/caregiver/parents decides it is. Such a decision is usually based on the individuals' behaviour responses.

So far, research has mainly focused on facial expressions of pain. Here, some key facial movements have been described that occur frequently in the context of pain (see Fig. 8.1). These movements are rather seldom displayed together simultaneously when individuals are experiencing pain, but instead individuals most often show different combinations of these single facial movements. Most frequently, tightening of the muscles surrounding the eyes is paired with one or two of these other pain-indicative responses. These movements are also able to encode different aspects of pain, with the eyes primarily encoding the sensory dimension whereas the eyebrows and nose movements encoded the unpleasantness of pain. With regard to body movements and vocalisations occurring during the experience of pain, objective and reliable descriptors are mostly lacking so far but are urgently needed.

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Part III
Management Issues

Chapter 9
Pharmacological Pain Management: For Better or for Worse?

Gisèle Pickering and David Lussier

Abstract Although taking advantage of the synergistic effect of non-pharmacological and pharmacological approaches for the treatment of pain is always recommended, drugs remain the first and sometimes the only line of available treatment. Analgesics as well as pain itself do have an impact on cognitive and emotional processes. The cognitive/affective central effect of analgesics prescribed for chronic pain treatment is well documented in the literature, but the causal relationship of pain to cognitive and emotional disorders remains to be explored. In order to provide satisfactory pain alleviation, analgesic treatment in frail patients and in patients with preexisting cognitive/affective impairment is particularly difficult. Considering the large array of adverse events of orally administered analgesics, topical analgesics may be an interesting option for pain treatment. Non-pharmacological therapies should always be included in a comprehensive pain management plan.

9.1 Introduction

Pain requires cognitive processing and is also an emotional experience. Neural systems involved in cognition, emotion, and pain overlap and may modulate each other reciprocally (Peyron et al. 2000; Lumley et al. 2011). Moreover, cognitive functioning and emotions are dysregulated by chronic pain (depression, anxiety, stress, fear) (Apkarian et al. 2004; Baliki et al. 2006), and a large literature has been published on consequences on health-related quality of life and on the burden of chronic pain

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in everyday life (Pickering and Leplege 2011). On the treatment side, positive emotional states (Lumley et al. 2011) and cognitive interventions (hypnosis, meditation, distraction, cognitive training (Kesler et al. 2013)) have given interesting results and may reduce pain. Non-pharmacological approaches are indeed recommended in synergy with pharmacological treatment, but the first line of treatment of chronic pain remains predominately pharmacological (Pickering 2012). In that context, analgesics used for chronic pain have a number of cognitive and emotional side effects, and the role played by analgesics on cognitive function and emotional status is difficult to dissociate from the impact of chronic pain itself, clinically but also fundamentally. "Symptom clusters" where pain, depression, fatigue and impaired cognition happen concomitantly may influence each other in a downward spiral.

Observational studies on large cohorts do not always consider the adverse effects of analgesics and their negative impact on neural systems. Indications on pain treatment are often not clearly or analytically reported in the literature. Several issues remain open: What is the cognitive/affective impact of analgesics that are commonly used and recommended for chronic pain treatment? What is the impact of analgesic treatment in patients with preexisting cognitive/affective impairment? Are nonsystemic routes of administration a viable option to prevent drug-induced cognitive-affective impairment?

9.2 What Is the Cognitive/Affective Impact of Chronic Pain Treatment?

Commonly prescribed drugs for chronic pain include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant drugs recommended for neuropathic pain treatment.

9.2.1 Paracetamol

Paracetamol has not been demonstrated to have any specific deleterious effects on cognitive processing. A recent functional magnetic resonance imaging study has shown that paracetamol reduced neural responses to social rejection in brain regions previously associated with distress caused by social pain and the affective component of physical pain (dorsal anterior cingulate cortex, anterior insula). Thus, paracetamol reduces behavioral and neural responses associated with the pain of social rejection, demonstrating a substantial overlap between social/emotional and physical pain (DeWall et al. 2010).

9.2.2 Aspirin and NSAIDs

Aspirin is widely used in stroke prevention, and atrial fibrillation is associated with a decline of cognitive function. A randomized controlled trial (Mavaddat et al. 2014) recently compared the effect of anticoagulation (warfarin) versus aspirin on cognitive function in elderly patients with atrial fibrillation and showed no superiority of aspirin over anticoagulation against cognitive decline. Several epidemiological studies (Imbimbo et al. 2010) have suggested that long-term use of NSAIDs may protect subjects carrying one or more ε4 allele of the apolipoprotein E against the onset of Alzheimer's disease (AD). However, a Cochrane study (Jaturapatporn et al. 2012) assessed the efficacy of aspirin, steroids, traditional NSAIDs, and COX-2 inhibitors in AD and concluded that their efficacy is not proven and that these drugs cannot be recommended to prevent cognitive decline of AD. It is interesting to note that inflammation is at the heart of a number of degenerative pathologies and pain states and has also been incriminated in depression, although inflammation as a cause or consequence of depression has been questioned for a number of years. A recent study showed no significant relationship between inflammatory markers and symptoms of depression and anxiety during aging in patients with NSAID use, suggesting no particular influence of this medication on depression (Baune et al. 2012).

9.2.3 Opioids

Over the last two decades, the clinical use of opioids for chronic pain treatment has become widespread with the development of immediate- and extended-release formulations for acute and chronic pain including cancer pain. Opioid analgesics do relieve pain and remain first-line drugs for severe, chronic pain. The continued increase in their medical use (Atluri et al. 2014) has led to concerns of misuse, abuse, and addiction in chronic pain patients (CDC 2011). Indeed the abuse liability during opioid therapy for pain treatment has been noted as a concern for a certain percentage of chronic pain patients (Fishbain et al. 2008). This point is important as opiate dependence contributes to cognitive impairment in the domains of attention and executive function, with comorbid depressive symptoms negatively affecting reaction times (Loeber et al. 2012). In general, the scientific literature devoted to the impact of opioids on cognition and emotion in chronic pain patients is poorly documented. Adverse events of opioids per se are well known, with mental dullness, somnolence, sedation, sleep disturbances, and even delirium due to opioid excess. Analgesic efficacy and side effects may however be quite heterogeneous among patients with variable pharmacological mu-opioid responses. It has also been shown that the kappa-opioid receptor modulates synaptic strength and controls neuroplasticity in different brain regions associated with cognition and emotion (Pasternak et al. 1999). The success of opioid therapy often depends on achieving a balance between analgesic effectiveness and acceptable side effects.

Current evidence for a lack of appreciable effect, benefit, or harm of a long-term stable opioid treatment on cognitive functioning in noncancer pain patients (Kendall et al. 2010) or in cancer pain patients (Kurita et al. 2009) is still limited (Ersek et al. 2004). It is interesting to note that the best-quality randomized clinical trials showed no deleterious effect on cognition and even some cognitive improvement with opioid treatment (Kendall et al. 2010). The discrepancy between studies may be linked to the different methodologies used to evaluate cognitive domains in the studies, as subjective cognitive complaints are not always associated with objective (neuropsychological tests) measures of cognitive function and may give different results. A large meta-analysis (Lindner et al. 2014) focused on cognitive impairment in cancer patients (but with no report on opioid consumption) and concluded that the likelihood to identify cognitive impairment rests on the type of design employed, as memory and attention impairments were only detected in cross-sectional studies. Repetition of cognitive neuropsychological testing (attentional capacity, psychomotor speed, information processing speed, short-term memory, semantic memory, decision-making) may bias the findings of longitudinal studies. There is a real need to establish a consensus concerning reliable assessment of cognition in patients, especially with those on opioid treatment. In the clinic, it is important to inform the patient that long-term treatment with opioids may not be harmless and may even marginally interfere with cognitive function; however, this potential side effect should not hinder clinicians from increasing opioid dosing and optimizing opioid therapy. Overmedication and undertreatment can both have detrimental consequences. Overmedication may lead to addiction, hyperalgesia and worsening of negative emotional state. Undertreatment may maintain emotional distress, depression, sleep, and anxiety disorders. A rational use of opioids for chronic pain will avoid allostatic emotional behavior and maintain or restore homeostatic regulation of emotional behavior (Shurman et al. 2010).

9.2.4 Antidepressants

Antidepressants are recommended as first-line treatment for neuropathic pain (Finnerup et al. 2005; Dworkin et al. 2010). However, the mechanism of action of antidepressants in pain alleviation is complex; the safety profile of tricyclic antidepressants (TCAs) must be carefully taken into account as they may impair cognition. Newer classes of antidepressants, duloxetine and venlafaxine (serotonin and norepinephrine reuptake inhibitors SRNIs), may be less analgesic but they have less adverse effects although fatigue is frequently reported. Depression and chronic pain share a number of common mechanisms (Nekovarova et al. 2014; Blackburn-Munro 2001; Chou 2007), and depression may precede or follow after chronic pain. Chronic pain and depression are both conceptualized as stress and all three modulate brain and synaptic plasticity. Pain and depression may influence the functions of the brain default mode network (Baliki et al. 2008; Marchetti et al. 2012), a network of interacting brain regions activated during "resting" states. Plastic changes induced by pain or/and depression at synaptic, cellular, and molecular levels modify

connectivity within the neuronal circuitry and contribute to structural and functional changes in the brain. Not surprisingly, an additive effect of depression and chronic pain has been shown in cancer patients in several domains of quality of life (Kroenke et al. 2010). Cognitive dysfunction accompanies depression (McIntyre et al. 2013) and pain, and this cognitive dysfunction often persists after remission of the depressive symptoms (Conradi et al. 2011). This suggests that currently used antidepressants, selective serotonin (5-HT) reuptake inhibitors (SSRI), and SNRIs may not be all that adequate to improve cognition in depressive patients (McClintock et al. 2011; Pehrson et al. 2014). We recently showed in patients with long-standing postzoster neuropathic pain (with mild depressive symptoms) that antidepressants (mainly TCAs) prescribed for pain impaired several cognitive domains (spatial memory and semantic memory) when compared to neuropathic pain patients without antidepressants (Pickering et al. 2014a) These findings confirmed reports of an association between memory disorders and TCAs/SSRIs antidepressants (Chavant et al. 2011), but antidepressants do not always induce cognitive impairment. They seem to display a dose-dependent and etiology-dependent pluripotent action. In depressed patients, SSRIs and SNRIs may improve executive functions and attention (Herrera-Guzman et al. 2010). In nondepressed patients with Alzheimer disease, TCAs and SSRIs diminish the severity of cognitive decline (Archer et al. 2007). Animal studies show that amitriptyline (a TCA) ameliorates neuropathic pain-induced deficits in abilities of spatial learning and memory (Hu et al. 2010) and cognitive function in Alzheimer rats (Chadwick et al. 2011). Considering the complexity and heterogeneity of these results, there is a need for larger clinical trials to study cognitive dysfunction in chronic pain with or without depressive symptoms. The cognitive deficits observed in chronic pain patients receiving antidepressants could be due to the chemical properties of the prescribed antidepressant or because of inappropriate dosing. They could also be linked to residual non-alleviated pain and to the combination of pain-induced and depression-induced cognitive loads. It is also plausible to suggest that the type of antidepressant, its mechanistic action on the opioidergic system (Wattiez et al. 2011), the etiology of the pain syndrome, the duration of pain, the comorbidities, the severity of the depressive symptoms, and the extent of the memory traces of depression and pain may all contribute to the complexity of cognitive homeostasis in chronic pain. Finally, as mentioned before, there are also methodological difficulties concerning the cognitive evaluation of patients using neuropsychological tests or via self-report (Amado-Boccara et al. 1995), and isolation of the specific effects of antidepressants on cognition in a patient suffering from chronic pain remains to be established.

9.2.5 Antiepileptics

Gabapentin and pregabalin are also recommended first-line neuropathic pain treatment. Adverse events of gabapentin related to cognition (somnolence (27.4 %) and falls, dizziness (23.9 %), and ataxia (7.1 %)) may lead to discontinuation of

treatment in 10 % of patients and are particularly important in older persons (Pickering 2014). In a recent study in the context of postherpetic neuropathic pain (Pickering et al. 2014a), antiepileptics induced less cognitive impairment than antidepressants, but the impact of antiepileptics on depression and cognition in the context of pain must be explored further.

9.2.6 Other Drugs

9.2.6.1 Hypnotics

Benzodiazepines are frequently prescribed in patients suffering from chronic pain, as anxiety and sleep disturbances are very common: a bidirectional association between sleep disturbances and chronic pain has been frequently discussed in the literature (Smith and Haythornthwaite 2004). There are common brain structures (periaqueductal gray matter, reticular nucleus of the thalamus, raphe magnus) involved in pain and in sleep (Demarco et al. 2003), and although benzodiazepines are widely used, their effects on cognition, mood, alertness, anxiety, or depression may or may not be independent of their analgesic properties. Benzodiazepines may have beneficial effects on pain-related anxiety, and cognitive disorders have been described with reports of memory disorders and increased reaction time (Pickering et al. 2014a; Chavant et al. 2011), confusion, and a potential risk of dependence and abuse with a long-term use.

9.2.6.2 *N*-Methyl-D-Aspartate Receptor as a Therapeutic Target

N-Methyl-D-aspartate receptors (NMDAR) are ubiquitous and are not only involved in the establishment of central sensitization (Dingledine et al. 1999) and in pain-related synaptic plasticity but also in many pathophysiological processes such as memory, learning, and neurological disorders (Begon et al. 2000; Niewoehner et al. 2007). NMDAR antagonists, such as ketamine, dextromethorphan, or memantine, are possible therapeutic options after failure with other recommended treatments for neuropathic pain and could prevent or treat painful symptoms (Zhou et al. 2011; Tawfic 2013). However, there is some heterogeneity among clinical trials with different efficacies according to the doses used, routes of administration, and type of pain pathology (postherpetic neuralgia, postamputation pain, phantom limb pain, diabetic neuropathy). The efficacy of ketamine in neuropathic pain has been reported (Eide et al. 1994; Jørum et al. 2003), although it may lessen with time, and ketamine is well known for its psychodysleptic and cognitive adverse events (Cvrcek 2008; Niesters et al. 2013). It prevents windup and improves pain and also depression. The parallel of ketamine effect in pain and in depression is striking as not all patients are responders to ketamine: ketamine improves pain in 65 % of patients (Rabben et al. 1999; Jackson et al. 2001) and improves depression in 64 % of patients within 1 day

of administration (Murrough et al. 2013). The duration of the analgesic effect of ketamine varies among studies and among patients, so does its antidepressant effect (Gálvez et al. 2014).

With a similar mechanism of action on NMDAR, dextromethorphan and memantine have less adverse events. They have been routinely prescribed for the antitussive properties and moderate to severe Alzheimer's disease, respectively. The influence of memantine and dextromethorphan on cognitive function in patients suffering from neuropathic pain is not currently known and is still under investigation (Pickering et al. 2014b). Activation of NMDAR is an essential step in pain central sensitization and "windup" (a temporal summation of C-fiber response in the spinal cord) and is also involved in memory formation and cognition processes. Such a windup phenomenon has also been demonstrated in depressive patients independently of pain (Klauenberg et al. 2008) underlining once more common aspects of chronic pain and depression.

Magnesium (Mg^{2+}) is a physiological blocker of the Na^{+}/Ca^{2+} channel of the NMDA receptor and is able to modulate NMDAR (Nowack et al. 1984). Mg homeostasis is proposed to be involved in biochemical dysregulations contributing to psychiatric disorders (Murck 2002). A significant association between Mg imbalance and cognitive impairment has been shown in hospitalized patients (Corsonello et al. 2001), and Mg therapy in animals is effective in facilitating cognitive recovery following brain injury in a task- and dose-dependent manner (Hoane 2007). A randomized, double-blind, controlled trial with patients suffering from neuropathic pain showed a diminution of the frequency of pain paroxysms and of the emotional impact of pain (Pickering et al. 2011). Despite experiencing background pain, patients were less bothered by it, suggesting a beneficial sensori-limbic dissociation that allowed an improvement of quality of life and of affect. More clinical studies are warranted on all NMDAR antagonists and on their anti-inflammatory effect that could also impact on their antidepressant potential, as demonstrated recently for ketamine (Hayley and Litteljohn 2013).

9.3 What Is the Impact of Pain Treatment in Patients with Preexisting Cognitive or Emotional Disturbance?

The challenges surrounding pain treatment are amplified in the presence of frailty and impaired cognition (McLachlan et al. 2011) and there are few data to support evidence-based decisions in such patients. Frailty (also associated with pain (Shega et al. 2012)), medications, and impaired cognition may impact on the pharmacokinetics and pharmacodynamics of analgesics in this population ranging from physiological age-related cognitive decline to severe psychiatric disease. The judicious clinical mantra of "start low and go slow approach" to analgesic dosing in frail older persons may lead to undertreatment of patients, but inappropriate dosing may conversely result in serious adverse events. In the absence of rigorously controlled trials in frail older people and those with cognitive impairment, a pharmacologically

guided approach can be used to optimize pain management which requires a systematic understanding of the pharmacokinetics and pharmacodynamics of analgesics in frail older people with or without changes in cognition. It is difficult from the existent literature to evaluate the positive or negative impact of analgesics on cognitive/affective domains in patients with preexisting cognitive/affective disorders and the biases of comorbidities and associated medications.

Patients suffering from dementia often present noncognitive symptoms (behavioral and psychological symptoms of dementia (BPSD)) that occur in 40–60 % of individuals living in care home settings (Ballard and Corbett 2013) and 60–98 % of patients with dementia (Sink et al. 2005). BPSD includes agitation, aggression, delusions, hallucinations, repetitive vocalizations, wandering, depression, apathy, anxiety, and disinhibition. However, most of these symptoms could also be due to pain or dehydration. Such a clinical presentation may be confusing as pain is frequent in patients with dementia who often cannot communicate their discomfort: pain should always be considered as a possible cause of agitation or aggression and should be adequately attended to and treated. Despite the poor evidence base and although non-pharmacological treatment is recommended in these patients, it has been a common practice for a number of years to use drugs acting on the central nervous system (Kamble et al. 2009). Antipsychotics, cholinesterase inhibitors, anticonvulsants, antidepressants, anxiolytics, and *N*-methyl-D-aspartate-receptor modulators (Schulze et al. 2013) are often prescribed without clear evidence-based efficacy. Administration of a non-opioid drug, paracetamol, 3 g per day, in a cluster randomized clinical trial showed in 352 patients a significant improvement in agitation accompanying parallel reductions in pain (Husebo et al. 2011).

9.4 Could Topical Administration of Drugs Be an Option to Prevent Drug-Induced Cognitive-Affective Impairment?

Topical analgesics often have a comparable efficacy to oral agents, with a good tolerability and safety profile. They may be an alternative or be added to oral treatments. They are particularly relevant for elderly patients who suffer from comorbidities and/or taking multiple medications. It allows the reduction of concomitant treatments and the risk of adverse events, as elderly patients are often prescribed oral combination therapies including drugs with central side effects (dizziness, sedation, impairment of cognition).

Topical NSAIDs seem to be the safest choice among all options for localized pain in superficial joints and have demonstrated efficacy similar to oral NSAIDs, with a low incidence of adverse events (Baraf et al. 2011). A randomized clinical trial with ibuprofen foam dressing has also shown a significant pain relief in five types of wound: arterial, venous, and mixed arterial-venous leg ulcers, vasculitis, and traumatic ulcers (Arapoglou et al. 2011). Transdermal fentanyl in non-naïve patients has been used for a number of years, with improved pharmaceutical forms

and dosages. Taken together, studies have shown no negative impact on cognitive function in patients with a stable opioid treatment for pain (Sabatowski et al. 2003; Menefee et al. 2004).

All patients with neuropathic pain are candidates for treatment with antidepressants and anticonvulsants, whereas localized neuropathic pain can benefit from topical treatment (Gloth 2011). Two drugs have been approved, 5 % lidocaine medicated plaster (Baron et al. 2009) and 8 % capsaicin patch (Haanpää and Treede 2012). In older patients suffering from postherpetic neuralgia, the 5 % lidocaine medicated plaster resulted in a reduced use of antidepressants and opioids (Clere et al. 2011). In another study, elderly patients with postherpetic neuralgia of several years duration had a significantly better cognitive performance with 5 % lidocaine patch than patients with orally administered drugs and their cognition was not altered when compared to healthy controls (Pickering et al. 2014a).

Although the number of available topical treatments is still limited, topical analgesics represent a very innovative pharmacological field with the potential of combining several mechanisms of action and therapeutic targets. With their oral analgesics sparing effects and their lesser deleterious impact on cognitive function, topical analgesics present advantages for optimization of pain treatment, especially in the elderly and in patients taking multiple medications acting on the central nervous system.

9.5 Non-pharmacological Therapies for Pain Management

Pain, especially when chronic and persistent, is better managed when a multidimensional and interdisciplinary approach is implemented. Although scientific evidence on the efficacy of non-pharmacological techniques is limited, these should also be part of a comprehensive pain management plan. They offer the advantage of being denied of any adverse effects on cognition, and some have been shown to improve cognition and emotion states. Non-pharmacological therapies are developed in Chaps. 10 and 11 and include psychological and physical/rehabilitative approaches.

9.5.1 Psychological Approaches

Psychological approaches have been categorized as cognitive-behavioral therapy, strategies based on emotional disclosure and mind-body interventions (e.g., yoga, mindfulness) (Keefe et al. 2013).

Cognitive-behavioral therapy (CBT) approach to pain management combines stress management, problem solving, goal setting, pacing of activities, and assertiveness. Its efficacy in reducing pain has been demonstrated numerous times, for various types of pain (Turk et al. 2008). A Cochrane review however failed to confirm positive effects of CBT on reducing pain, except for a small effect when

compared to "usual" treatment, and no difference with an "active control" (Williams et al. 2012). While the effect of CBT on mood in patients with chronic pain appears to be mild and of limited duration (Williams et al. 2012), it seems to be effective in reducing highly anxious thinking about pain and future pain (Eccleston et al. 2013). It therefore appears that, while its effect on general pain is limited, CBT is especially effective in improving problems arising from long-lasting disabling chronic pain.

Emotional disclosure interventions aim to reduce pain and pain-related mood impairment by working on negative thoughts and feelings triggered by pain. The response is highly variable between individuals, depending on personality and pain characteristics.

Mind-body interventions aim to cultivate awareness and acceptance of physical and emotional experiences. They include modalities such as mindfulness meditation and yoga. Evidence on their effectiveness on reducing pain, as well as pain-related disability and mood impairment, is mostly limited to open-label, nonrandomized studies. This limited evidence should however not discourage their inclusion as part of a multimodal and interdisciplinary pain management plan.

9.5.2 Physical Approaches

Evidence on response of pain to passive physical approaches such as TENS, ultrasounds, or massage is mostly limited to anecdotal experience and open-label, nonrandomized studies. No effect on pain-related mood impairment has been reported. Exercise however seems to be effective in relieving pain in a variety of pain conditions, sometimes with resultant mood improvement. Exercise can also prevent cognitive deterioration in older patients, whether they have or do not have premorbid cognitive impairment. The effect on cognition and emotions in patients with chronic pain needs to be explored.

9.6 Conclusion

Recommendations for chronic pain treatment support a more tailored approach based on the patient individualized risks, an optimization of the treatment strategy, and a multimodal therapeutic regimen. However, most analgesics, with their central mechanism of action, have cognitive and emotional adverse events that may be amplified in the presence of comorbidity, multiple medications use and aging. Evaluation, in the specific context of chronic pain, of the beneficial or deleterious effects on cognitive and emotional processes, and of drugs commonly used, needs to be explored further. While clinicians are aware of common side effects to be expected with recommended analgesics, the impact of these drugs in patients with long-standing chronic pain and emotional and cognitive dysfunction is not well

known. The impact of analgesics on the relationship between chronic pain and cognitive and affective impairment also remains to be elucidated. To avoid deleterious effects of analgesics on cognition in patients with chronic pain and to improve pain-related mood impairment, non-pharmacological therapies should always be included in a comprehensive pain management plan.

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Chapter 10
Psychological Approaches to the Management of Pain, Cognition and Emotion

Michael K. Nicholas

Abstract Psychological approaches to managing chronic pain have evolved considerably since the 1970s when pioneers like Fordyce first described applications of behaviour change principles to pain and its behavioural manifestations. The settings in which these approaches have been applied have also been greatly extended since Fordyce's original work in a rehabilitation hospital. This chapter reviews current psychological approaches to the management of persisting pain and associated cognitive, emotional and behavioural changes. This chapter considers primarily cognitive behavioural therapy (CBT) approaches as they have the most empirical support in this field. The theoretical and experimental underpinnings for CBT approaches are described, and this is followed by: (1) a description of the characteristics of CBT methods, (2) the available evidence supporting the use of these approaches in the management of persisting pain and (3) a consideration of the implementation of psychological approaches and their effects on outcomes. There is general agreement in the research literature that the question of 'does it work?' has been answered (in the affirmative), and the task now for both clinicians and researchers is to refine our questions. In particular, we need to consider questions like which versions of psychological treatments, for which problems, and how these can be done most efficiently and effectively. An emerging issue is to do with the quality of treatment and that, in turn, raises the question of training. This is starting to be addressed but it is likely to become a much larger issue than was the case even 10 years ago.

10.1 Introduction

Psychological treatments for people with disabling or bothersome chronic pain are based on the understanding that psychological factors contribute to the experience, impact and maintenance of such pain, regardless of original cause. Psychological

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factors that have been found to influence severity of pain, its impact and maintenance include cognitions (e.g. maladaptive beliefs), mood states (e.g. anxiety or depression) and behaviours (e.g. excessive guarding or avoidance behaviours) – all of which may be influenced by the context in which they occur and their history (e.g. reinforcement history) (Flor 2012). Accordingly, psychological treatments are usually aimed at addressing one or more of these contributing psychological and environmental (or psychosocial) factors (e.g. Jensen 2011). By changing the identified contributing psychosocial factors, it is expected that chronic pain will be less disruptive or bothersome and that psychological and physical well-being will be improved. Specifically, cognitions will be more adaptive, mood will be less distressing and function (e.g. normal activities of daily life) will be enhanced or largely restored. Associated with these gains, it is expected that there will be reductions in treatment seeking for pain and in the use of unhelpful medication.

Historically, reduction in pain severity has typically not been seen as a focus for psychological treatments of chronic pain. This seems largely due to the perspective that as these treatments are not addressing the cause of the pain, they are unlikely to abolish it (Fordyce 1976). However, this perspective has come under some doubt in recent years, especially with the evolution in thinking about chronic pain as being driven more by central nervous system processes (especially higher cortical activities associated with functions like learning and memory) than peripheral ones (Flor 2012). Certainly (mostly small) reductions in pain severity following psychological treatments have often been reported (see Morley et al. 1999), but these findings have not been given much emphasis in the pain literature. In addition to doubts about possible causation, many have argued that pain severity measures themselves do not adequately capture the multidimensional experience of pain (Turk and Melzack 2001). Partly in response to this concern, many clinical researchers have sought to describe the effects of treatments (psychological or not) on pain in terms of reductions in the degree to which pain is troublesome or bothersome (Dunn and Croft 2005). This position is buttressed by the evidence from epidemiological research that when people in the community report having persisting pain, those who find it more troubling are more likely to seek treatment for it (Blyth et al. 2005).

Psychological interventions often occur in the context of multidisciplinary treatments or programs; however, they can be performed in isolation (by individual practitioners) and all healthcare professionals can (and arguably, should) incorporate psychological principles into their respective interventions in this area (e.g. Indahl et al. 1995; Lindstrom et al. 1992; Nicholas and George 2011). One of the constraints in discussing different psychological treatments for people with chronic pain is that randomised controlled trials (RCTs), or even in studies using single case designs (e.g. Kazdin 2003), have largely been limited to different versions of cognitive behavioural therapy (CBT). This chapter will concentrate on psychological approaches that have been widely supported in the research outcome literature and it is divided into three sections: (1) a description of the characteristics of the most widely used psychological treatments, (2) a commentary on the available evidence supporting the use of these approaches in the management of persisting pain and (3) a consideration of the implementation of psychological approaches and their effects on outcomes.

10.2 Characteristics of Commonly Used Psychological Approaches

The most extensively studied psychological treatments for chronic pain come from the broad spectrum of operant-behavioural, respondent-behavioural and cognitive methods. These are normally used in combination (Turk et al. 1983), so reference is typically made to cognitive behavioural therapy (CBT) methods (e.g. Eccleston et al. 2013). Within the framework of CBT treatments, clinicians and researchers typically employ multiple components depending upon the population being treated. These can include increments in activities of daily life (walking, driving, shopping, cooking, etc.), regular exercising (stretch, strengthening, fitness), medication withdrawal, self-regulation strategies (relaxation, meditation, mindfulness), cognitive strategies (identifying unhelpful ways of thinking and changing them, distraction techniques, problem-solving), communication skills training, self-reinforcement, self-monitoring and so on.

The primary distinguishing characteristic of CBT approaches is that the learning or behaviour change principles informing CBT are utilised through all (or most) facets or components, such as exercises, activity upgrading, reducing medication, dealing with flare-ups in pain, sleep problems, etc. (see Nicholas and George 2011; Williams et al. 1999). As mentioned earlier, CBT for pain is also heavily reliant on models of pain that emphasise interactive relationships between the experience of pain, thought processes, mood, behaviours and their environmental contexts or contingencies (see Turk et al. 1983, for an early outline of this perspective). In recent years, these interactive relationships have been conceptualised in terms of moderators and mediators (Vlaeyen and Morley 2005). In this perspective, unhelpful beliefs about pain, for example, are thought to mediate the relationship between pain and effects like depression or disability. Accordingly, the psychological treatment is targeted at changing the unhelpful beliefs. In practice, the principles of operant and respondent learning (conditioning) are employed alongside cognitive methods aimed at processes like thoughts, worries, reactions, beliefs and expectations. The nature and emphasis of psychological approaches to chronic pain have evolved since Fordyce's (1976) seminal work based on operant methods, but most continue to reflect this history. Most recently, what have been described as 'third-wave' versions of CBT, particularly acceptance and commitment therapy (ACT) (e.g. McCracken and Vowles 2014) have been promoted, but despite the input from relational-frame theory (Hayes 2004), these approaches still reflect their fundamental origins in learning principles (Vlaeyen 2014). Accordingly, rather than a completely new approach, this chapter will consider ACT-based approaches as lying within the framework of the broader CBT 'family'.

Operant methods (Fordyce 1976) emphasise a focus on the graded performance (activity pacing) of agreed (and clearly specified) activities (towards goals desired by the patient) that are reinforced (by therapists and patients), contingency management (e.g. undesirable behaviours, like excessive resting, are not reinforced where possible), the use of modelling (demonstration of new skills or adaptive behaviours), rehearsal (of these behaviours), feedback (from therapists and self-monitoring) and structured plans (usually time limited), as well as application of

specific self-management skills in normal life contexts (i.e. not just at clinic). For example, a patient might be taught a relaxation technique, and their practice of this would be reinforced by the patient charting his/her practice and by the therapist verbally (see Nicholas and George 2011).

Respondent methods emphasise repeated exposure to cues or indicators for increased pain or avoidance of activities expected to be painful (e.g. de Jong et al. 2005). Thus, the patient is encouraged to repeatedly perform a previously avoided behaviour (such as lifting an object of a certain weight) until the patient is able to perform the activity without distress.

Cognitive methods typically include self-monitoring of thoughts and emotions to gain awareness of their relationships (e.g. whether certain ways of thinking might mediate the relationship between pain and distress). Once these unhelpful thoughts or patterns of thinking, such as catastrophic beliefs (e.g. 'this pain is killing me'), are identified, the treatment involves helping the patient work out more helpful alternatives and then applying them as needed. Some semi-structured methods for dealing with setbacks or obstacles (problem-solving) are often included as well (Van den Hout et al. 2003).

Exponents of ACT-based methods typically use different terms to describe this approach, but fundamentally they target experiential avoidance using exposure methods as well as recognising unhelpful or self-defeating thoughts that are challenged indirectly by the use of metaphors and disengagement. In these respects, these approaches are analogous to respondent-behavioural and cognitive therapy approaches.

In practice, elements of all three methods are often employed in an integrated manner. Thus, while a patient is engaging in a specific behaviour that she/he may have previously avoided due to worries about pain, she/he can reinforce the attempt by recording it in a diary (i.e. subsequently acknowledged by the clinician) and simultaneously the patient can also be dealing with any unhelpful thoughts using the cognitive therapy strategies. The fundamental goal of CBT for chronic pain is to enable treated patients to lead their lives with as little interference due to pain as possible. This means that they must employ effective pain self-management strategies to combat the experience of pain on their daily lives. From a CBT perspective, these treatments entail the strengthening of new, more helpful behaviours and the weakening of older, less helpful behaviours.

10.3 Commentary on the Available Evidence Supporting the Use of These Approaches in the Management of Persisting Pain

Two main lines of evidence are available – one refers to treatment programs that include multiple components and disciplines and the other refers to specific modalities that may be used in isolation, like relaxation, biofeedback or behavioural exposure by single practitioners.

10.3.1 Comprehensive Treatment Programs

An early systematic review of 35 randomised controlled studies on cognitive behavioural treatments for chronic pain patients, excluding those treating headache patients, concluded that the high-quality studies demonstrated large and sustainable changes for the targeted outcomes (e.g. increased activity levels, improved mood, reduced use of analgesic medication) but less impressive results in lower-quality studies (McQuay et al. 1997). Subsequent meta-analyses of high-quality randomised controlled studies within the Cochrane Collaboration framework by Morley et al. (1999), Eccleston et al. (2009) and Williams et al. (2012) concluded that there was good evidence that cognitive behavioural treatments were effective relative to placebo and no-treatment controls but weaker evidence of their superiority over alternative active treatments (though there were far fewer of these studies available). However, it needs to be understood that the so-called 'no-treatment' controls category does not mean the patients were receiving no treatment – in most cases that used wait-list controls, for example, the wait-list patients were typically receiving treatment as usual (mostly drugs) (e.g. Williams et al. 1996; Nicholas et al. 2013). Nevertheless, the overall effect sizes from these systematic reviews and meta-analyses were predominantly in the small to medium range (0.2–0.5) (Eccleston et al. 2013). While these effect sizes are respectable, they also leave room for improvement.

The challenge of improving effect sizes for psychological treatments for chronic pain has been the subject of considerable debate and thought over the last few years. One line of thought has been to argue for different approaches – and this perspective has underpinned the development of acceptance-based methods (e.g. McCracken and Vowles 2014). Others, like Williams et al. (2012), concluded that we should acknowledge that CBT has been established as a useful approach to the management of chronic pain, but in order to improve outcomes, we should move away from RCTs of CBT that report group means, and instead we should explore different types of studies and analyses. These include studies aimed at identifying which components of CBT work, for which type of patient and on which outcomes, as well as why they work.

While both positions have their merits, an important issue to keep in mind is that they have as their starting point the modest outcomes reported to date with systematic reviews (like Williams et al. 2012). In this context, it is important to bear in mind that when examining the results of systematic reviews of psychological treatments for chronic pain, it must be recognised that unlike trials of drug treatments, where the drugs have known properties of content and quality that allow for considerations of dose-response effects, the psychological treatments in these reviews are much more heterogeneous. This applies not just to the nature of the treatment, but also to the amount (e.g. length of time, comprehensiveness) of treatment and experience of the treatment providers. In the Williams et al. (2012) Cochrane review, for example, treatment content ranged from 120 h over 4 weeks with a highly trained multidisciplinary team and a comprehensive (in content) program (Williams et al.

1996) to 6 h over 6 weeks with trainee psychologists and a very limited program (Litt et al. 2009). Not surprisingly perhaps, the longer and more comprehensive programs (with highly trained and multidisciplinary teams) were generally more effective than the lighter programs conducted by less qualified/trained, single discipline providers (e.g. compare Williams et al. 1996, with Litt et al. 2009).

In the Williams et al. study, relative to both the treatment as usual (wait-list group) and a briefer outpatient version of the inpatient program (one 3.5 h session per week for 8 weeks), the intensive treatment group made significantly larger gains for mood, disability, physical performance measures, medication reduction, the bothersomeness of pain, cognitions (pain catastrophising and pain self-efficacy beliefs) and reduced use of health services. At 1-year follow-up, the differences between the more intensive program and the less intensive version were maintained. In contrast, the Litt et al. study revealed that relative to standard treatment for temporomandibular pain, the group that received a CBT component as well as standard treatment reported some benefits for pain but no statistically significant benefits for depression and interference in activities at posttreatment.

In evaluating these interventions, it is also important to consider the people being treated as they can be quite heterogeneous within and between studies. For example, the Williams et al. (1996) study employed a heterogeneous sample of patients with a range of chronic pain conditions, and their level of pain interference (in daily activities) at pretreatment was in the moderate to high range. In contrast, the Litt et al. sample of a fairly homogeneous sample of patients with chronic temporomandibular pain rated their pain interference (in daily activities) at pretreatment as relatively low. In addition to patient characteristics, the social context of the treatment is also likely to influence outcomes. For example, it is well-established that the presence of a worker's compensation claim (where an injured person might expect to receive some financial gain if they remain disabled) can be a risk factor for poorer outcomes, regardless of treatment (Waddell et al. 2002). These sorts of differences in treatment samples, treatment contexts and treatments provide a cautionary note against assumptions of equivalence between treatments of the same name and patients treated, and these sorts of differences need to be considered when evaluating the value of treatments.

A broadly similar perspective on the clinical and research agenda for future psychological treatments for pain was provided by Jensen (2011) who argued that while there was some evidence supporting a range of psychological treatments, many were narrow in scope and not equally applicable in broader contexts. Instead, he proposed that researchers and clinicians should take a more strategic perspective (than promoting their favoured treatment) and consider identifying the contributing factors in any one case and then using the most appropriate intervention for specific facets of the individual case. This would require that clinicians become competent in several psychological modalities to enable them to utilise them according to the analysis of the individual case. Like the case proposed by Williams et al. (2012), Jensen directs the focus of clinical and research efforts away from simply testing more treatment packages against each other or against 'usual care' and towards identifying aspects of each case and evaluating the best options for addressing those. Once again, that means identifying what works for whom and under what circumstances.

These attempts to shift the focus of the research and clinical agenda for psychological treatments are important developments as they not only raise the prospect of advancing our understanding of the key mechanisms contributing to clinical presentations but also identifying the best ways (or combinations of ways) of changing these contributors and hence, better outcomes. Such an approach could reduce the wasted cost (in time and money) on more small studies on variants of psychological treatments that are rarely substantially different from the broad family of treatments encapsulated by CBT methods, for example (Eccleston et al. 2013). The reality is that due to the (almost inevitable) common features of interventions that attempt to help patients change their cognitions, mood, pain and level of daily functioning, these treatment variants are unlikely to demonstrate they are substantially better than CBT generally. This was clearly found in a systematic review of treatments based on acceptance and commitment therapy (ACT) which found that the benefits were not superior to those found with no greater CBT, with which they share many features (e.g. Veehof et al. 2011).

Even within multidisciplinary CBT programs varying a theoretically important component, like attention towards (exposure) or away from pain (distraction), was recently found to yield no difference in outcome, either at posttreatment or 1-year follow-up, especially in those who adhered to other parts of the program as well (Nicholas et al. 2014). Findings such as these suggest a degree of robustness in the case of multicomponent, multidisciplinary pain programs for heterogeneous groups of patients. Alternatively, they could also suggest the possibility that meta-constructs are involved, beyond the immediate methods being evaluated. For example, these complex, multicomponent programs (whether they be called CBT or ACT or whatever) may share some common feature that accounts more for their effects than their ostensible content. As Nicholas et al. (2014) found that adherent patients did better than non-adherent patients, a possible explanation is that the adherent patients could have activated positive rather than negative representations of their pain. Brewin (2006) proposed this as a core element that could account for effects of different versions of CBT in many clinical conditions. Another possibility is that adherence enhanced a belief in ability to control pain. Vancleef and Peters (2011) found that this belief promoted greater pain relief in experimental settings, while Tan et al. (2002) reported similar findings for reduced disability in chronic pain patients. It is also possible that the attention strategies evaluated in the Nicholas et al. study allowed patients to disengage from their pain, as proposed by McCracken et al. (2007) as a key element in acceptance-based methods. Also, as both conditions emphasised remaining active despite pain, it could be argued they had a similar degree of exposure to the feared stimulus anyway (De Peuter et al. 2011). Thus, it's possible that any psychological treatment (or even any intervention) that activated these sorts of mechanisms was likely to influence outcomes in pain, mood, cognitions and function. The most recent accounts of placebo mechanisms would be consistent with this perspective (e.g. Geers and Rose 2011).

In trying to evaluate these complex, multicomponent treatment programs, it might also be worth considering the perspective taken by researchers dealing with other complex health problems for which complex interventions have been pro-

posed (e.g. diabetes, stroke, etc.). The (UK) Medical Research Council (MRC) published an early foray into this domain in 2000 with its '*Framework for the development and evaluation of randomised controlled trials for complex interventions to improve health*' (Campbell et al. 2000), and this has been followed by other papers that have gradually refined this perspective (e.g. Hawe et al. 2004; Craig et al. 2008). A review by Grimshaw et al. (1995) also raised questions about the value of systematic reviews for treatments of complex health problems. What these researchers have proposed is that we should not rely completely on systematic reviews to evaluate the treatment of complex health problems. To date, however, these views have had relatively little airing in the pain treatment literature.

10.3.2 Single-Modality or 'Micro' Psychological Treatments

Leaving aside the broader psychological treatment packages that contain multiple components, it is also important to consider the available evidence for the more micro-level treatment modalities. These are often used as components within a broader CBT or ACT framework (as described by many authors, such as Jensen 2011; Turk et al. 1983; McCracken et al. 2005; Morley 2011; Nicholas et al. 2014; Turner et al. 2007). They include treatments like self-hypnosis, relaxation, meditation, mindfulness, exposure, problem-solving, education, distraction and cognitive challenging. These modalities have often been used singly, especially in acute pain settings such as postsurgical pain (e.g. Patterson and Jensen 2003), but in chronic pain treatments, many are typically integrated into a combination of behavioural and cognitive components as mentioned earlier. The reason for this is that chronic pain patients referred to tertiary level pain services often have complex problems that, besides persisting pain, can include a mixture of depression, anxiety, anger, medication dependence, substantial disability in daily normal daily activities (including work), sleep disturbance, social isolation and interpersonal difficulties (especially with other family members and employers) (e.g. Breivik et al. 2006). To expect a single treatment or a single healthcare provider to address all these problems in isolation is clearly unrealistic. Thus, Williams et al. (1996) described their CBT-based multidisciplinary pain management programs as containing: exercising and stretch, goal setting, activity pacing (as a means of achieving many functional goals), education, problem-solving, identifying and changing unhelpful thoughts, self-reinforcement for achievements, drug withdrawal, relaxation training, sleep management, family engagement and relapse prevention.

There is some supporting evidence for many of these 'micro' methods when used in isolation, but their use in isolation is mainly restricted to cases with only a limited range of problems. For example, behavioural exposure (to feared or avoided activities) has tended to be used only with those patients where high fear avoidance has been identified but no other major problems. In de Jong et al.'s (2005) study, for example, patients with low back pain and high fear-avoidance scores were selected, but those with major depressive disorder and posttraumatic stress disorder were

excluded. The behavioural-exposure treatments have typically been evaluated using single-case ($n=1$) designs and multiple measurements (e.g. de Jong et al. 2005). These provide good evidence at the single case level for an intervention, or sequence of interventions, but not their generalisability.

Another way these individual modalities have been evaluated is through designs that involve combining the specific modality with another treatment (like a CBT-based activity program) for one group and comparing the combined intervention with another group which gets only the CBT-based treatment, for example. In this vein, Jensen et al. added self-hypnosis to a CBT program and compared that combination with another group who received only the CBT program. The results indicated there was a benefit for the combined treatment, suggesting that the addition of hypnosis to CBT was superior to CBT alone. An earlier meta-analysis reached a similar conclusion (Kirsch et al. 1995). However, it remains the case that hypnosis tends to be used more in cases of acute pain, especially pain associated with invasive procedures or burns care (e.g. Accardi and Milling 2009). Van den Hout et al. (2003) also tested the value of adding problem-solving to graded activity with sick-listed workers with low back pain and found that those who received the combined intervention had better return to work outcomes in the 12 months following, relative to those who received graded activity training and education. These sorts of studies have indicated that multicomponent interventions tend to be more effective than single-modality approaches, at least in the more complex chronic pain patient samples tested.

Some researchers have also promoted the idea of using dismantling designs to evaluate the contribution of components of multicomponent CBT-based treatments (Jensen et al. 2001; Turner et al. 1990), but others have cautioned that as attractive as this option might seem, 'component dismantling studies offer an illusion of identifying active ingredients but cannot achieve sufficient power to calculate the effects of each component on each outcome' Morley et al. (2013). Morley et al. noted that others have pointed to similar difficulties within the field of psychotherapy generally (Ahn and Wampold 2001).

Currently, there seems a general recognition that single-modality treatments can be effective for specific (but limited) outcome goals, but broader and more sustainable effects are likely only when multiple aspects of a case are targeted using several modalities in a coordinated manner (e.g. Jensen 2011). It might be expected that there could be synergistic benefits (i.e. over and above the sum of the individual parts) from combining several modalities (like activity pacing, behavioural exposure and cognitive coping strategies) in a single case, but this is difficult to demonstrate and has not been clearly established to date. At present then, we are not in a position to confirm that one intervention is superior to another for a specific clinical target. Rather, there are theoretical reasons why one approach may be preferable to another, but the weight of available evidence is that likely outcomes will be influenced by a combination of factors including: the amount (dose) and nature of the treatment (e.g. comprehensive or narrowly targeted), the characteristics of the patients being treated, their social context (e.g. compensable versus non-compensable injuries) and the qualifications (training and competence) of the treatment providers. These considerations raise important implementation issues and these are considered next.

10.4 Implementation Issues

The variance in outcome results is not likely to be solely due to the treatments provided; by their very nature, psychological treatments are very 'operator dependent'. This means they rely heavily on the skills of the practitioners involved and their ability to consistently apply these skills. For example, Eccleston et al. (2009) noted that while the methodological quality of trials had improved (since the Morley et al. 1999 review), they had some concern that too little attention was being paid to the quality and training of treatment staff and the length of programs seemed to be getting shorter (or less intensive). These developments may be due to factors like staffing changes and resource limitations, but they appear likely to have implications for outcomes in many programs, especially those dealing with patients who have more complicated and enduring conditions (e.g. Robbins et al. 2003). Fortunately, in recent years, a number of studies have been reported describing more detailed accounts of more systematic training for treatment staff in the implementation of CBT pain management (see Nicholas 2014). This development can only help to improve the outcomes of these interventions.

While psychological treatments can be seen as very operator dependent, it is equally true to say they are also very responder dependent – that is, unless the recipients of the treatments (the patients or clients) actually engage in and employ the methods taught, they are unlikely to benefit (Nicholas et al. 2012). This is the nub of the adherence literature, which of course, applies to pharmacological treatments just as much. Somewhat remarkably, the topic has received relatively little attention in the psychological treatment literature for chronic pain (Nicholas et al. 2014). In part, this may be due to relatively primitive methods for measuring adherence, but there is clearly a need to not only develop the evaluation methodology; if we could improve adherence, generally the available evidence suggests we could get much better and more consistent results than any 'new' treatment is likely to produce. Enhancing communication skills by clinicians seems a key issue here, and there is a growing number of papers on this in the pain and behavioural medical literature (e.g. Butow and Sharpe 2013, Feldman and Berkowitz 2012).

An additional implementation issue concerns the social context of treatment. It was noted earlier that the presence of a compensation claim for an injury can impede better treatment outcomes. In the case of an injured worker (with or without a compensation claim), the goal of treatment typically includes return to work. This is now widely recognised as important for both psychological and physical good health (Black and Frost 2011). But how this might be achieved, when treating a person in a clinical context, is rarely reported. Despite that, there is growing evidence that if the healthcare provider is able to liaise with their patient's workplace as part of the treatment process, they may well improve their chances of returning to work. For example, a systematic review of the quantitative literature on this topic by Franche et al. (2005a) found strong evidence for this position. Attempts to pursue this in practice have often met resistance, but a research agenda is evolving to develop and evaluate possible ways of overcoming these obstacles (Franche et al. 2005b).

10.5 Conclusion

In summary, psychological approaches to managing chronic pain have evolved considerably since the early days of Fordyce and colleagues. But despite successive waves of evolution, many aspects of the original approaches described by Fordyce persist as they remain helpful. Changes to the ways in which psychological treatments are conducted, and by whom, have been a major feature of the developments since the 1970s. It is increasingly recognised that there is no need to continue asking if this broad group of treatments are effective (they are), but we now need to shift focus to more specific questions on which treatments for which problems and how these can be done efficiently and effectively.

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Chapter 11
Physical Therapy and Exercise: Impacts on Pain, Mood, Cognition, and Function

Maureen J. Simmonds, Catherine Ortega, and Kent P. Simmonds

Abstract Pain is multidimensional, common, complex, costly, and challenging. It has a pervasive effect on the individual with frequent co-occurrence of mood disorders, cognitive problems, movement dysfunction, activity limitation, fatigue, and clusters of comorbid health problems. The extent to which these problems are separate entities, different expressions of a central pain problem, or a consequence of pain or of physical inactivity is unclear. Regardless, the allostatic load associated with pain is cumulative and substantive. Physical activity appears to be a positive mirror image of pain. Strong evidence supports the positive and generalized role of physical activity/exercise to improve pain, mind (emotions and cognitions) movement, and social function. However, there appears to be no evidence supportive of any specific type of exercise or activity regimens. Unfortunately and regardless of proven health benefits, many individuals have difficulty initiating and/or maintaining exercise programs or even assuming a more active lifestyle. People with pain, depression, and psychomotor slowing have even greater challenges to overcome. Effective physical therapies for patients with pain require the therapist to understand the complexity of the problem of pain and its pervasive impact, in order to help individuals with pain, mood, movement and cognitive disorders address and overcome perceived barriers to and challenges of exercise. This must be done in the context of social and environmental determinants of health and health behavior change.

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11.1 Introduction

Pain is a common, complex problem that is costly in human and economic terms but can be frequently managed with physical therapies. Despite its prevalence, pain is also incompletely understood and remains a challenge to measure and to manage. A number of factors account for the poor understanding and management of pain, but an important component includes the complex multidimensional nature of the problem. This complexity is observed in clinical practice as heterogeneity in pain presentation, impact, and trajectory from apparently similar injuries or health conditions, the frequent co-occurrence of mood disorders and movement dysfunctions, and clusters of comorbid health problems.

In its chronic state and for some individuals, pain is associated with significant emotional distress, movement dysfunction, social disability, and cognitive impairment. Like pain, each of these problems is multidimensional and complex. Indeed, there are shared neurobiological mechanisms and overlapping impacts on the person that appear to be bidirectional and additive in terms of cause and consequence (Clauw and Ablin 2009; Clauw 2010, 2014; Clauw and Chrousos 1997; Dominick et al. 2012). For people with pain, chronic emotional distress and movement and cognitive dysfunction add to the allostatic load (van der Windt 2012), increase the cumulative burden of pain, and essentially have a substantive aging effect on function (Simmonds and Turner 2014).

Pain-related movement dysfunction is particularly problematic. Pain is among the most commonly cited reason for activity limitation, and limited activity aggravates the negative impacts of pain on mood and social engagement contributing to secondary disability and also an increased risk for comorbid health conditions (e.g., cardiovascular disease, obesity, depression, cognitive dysfunction, and some cancers). On the other hand, a preponderance of research across a range of health conditions including chronic pain has shown that physical activity has a myriad general and specific benefits for physical, mental (emotional and cognitive), and social health and well-being.

Although pain is associated with movement dysfunction and physical inactivity, and may be cited as a key reason for reduced physical activity, the relationship between pain and movement dysfunction is not straightforward because pain and movement are individually experienced and characterized by variability, respectively. In addition, both pain and movement are influenced by many different negative and positive emotions as well as by cognitions – beliefs and misbeliefs. The relationship between pain and physical activity is even more complicated because physical activity not only includes activity preferences and experiences but also social, cultural, and environmental determinants (e.g., access to a socially acceptable, safe, and enjoyable place to exercise).

The beneficial effects of exercise and activity on physical and mental health for individuals with pain are not in dispute; however, questions remain as to the comparative effectiveness of any specific exercise interventions and/or whether and how specific interventions should be tailored for subgroups or individuals with chronic pain. In essence, there remains a need at a population and individual level to better understand how to decrease distress and disability and/or enhance positive emotions and well-being in order to enable people to self-manage and engage in and maintain a healthy and active lifestyle, despite their persistent pain.

In this chapter, research that addresses the multidimensional complexities of pain, mind, movement, and physical activity will be reviewed as well as the clinical implications of this work as it relates to expanded conceptual models that include self-management and that optimize overall (physical, emotional, cognitive, and social) function and that reduce a dysfunctional dependence on a health-care system that may itself be dysfunctional.

11.2 Expanded Conceptual Framework of Pain and Pain Impact

Pain remains a challenge and a source of frustration for the individual to live with and a challenge and often a source of frustration for the health-care provider to manage. Within physical therapy, it has long been recognized that the traditional biomedical approach to understanding and managing chronic pain was incomplete. Primarily based on a presumed tissue or structural abnormality, the biomedical model did not explain the myriad problems that patients with pain experience and neither did it explain the lack of pain in those with similar tissue and structural abnormalities.

A more contemporary model has emerged whereby chronic pain is recognized as a primary disorder of the central nervous system expressed as widespread pain and which can include cognitive, mood, and movement dysfunction (Tracey and Bushnell 2009; Murphy et al. 2011; Schweinhardt et al. 2008). This understanding includes the recognition that shared mechanisms across chronic pain conditions can account for how pain is generated and maintained in the CNS, irrespective of the underlying structural pathology (Clauw 2010, 2014; Murphy et al. 2011, 2012; Phillips and Clauw 2011). To date, this understanding and its application in clinical practice are not well disseminated outside of pain specialty practice.

However, an expanded biopsychosocial model of pain has become more prevalent within physical therapy. This model takes into consideration traditional biomedical factors but also considers negative psychological factors such as fear, anger, or depression that may amplify the pain experience, have a disproportionate effect on movement and activity, and contribute to poor outcomes (Simmonds et al. 2008).

This negative emotional component of pain is exemplified within the fear-avoidance model (FAM) (Vlaeyen et al. 1995) which was advanced to explain persistent pain, distress, and disability. Although the FAM model has been expanded to incorporate motivation and self-regulation theories, it currently does not include physical impairments (which may appropriately limit some activities) nor does it account for social/environmental factors that contribute to distress and disability. Finally, it does not incorporate more recent neurobiological and neuroanatomical findings that explain severe persistent pain, depression, and distress. Perhaps most importantly, research that has examined the central tenet of the FAM model, that is, the recursive and sequential series of fear-related cognitive, affective, and behavioral processes, is not supported (e.g., Wideman et al. 2009, 2013; Pincus et al. 2010). Regardless of the validity of the FAM and the fact that it stems from psychopathology, the simplicity of the model was seductive, and its widespread utilization has helped to keep the explanatory focus of poor outcomes on the individual patient

rather than the provider, the treatment, or the health-care system. Thus, although pain and disability is acknowledged as a biopsychosocial problem, the primary focus has been on the presumed psychopathology of the patient with little emphasis and thus management of social determinants of distress and disability.

The International Classification of Functioning, Disability, and Health (ICF) framework (Cieza and Stucki 2008) is an expanded model of rehabilitation that is outcome oriented, biopsychosocially based, person focused and empowered, and best-evidence and activity driven. The ICF model recognizes that pain and disablement are influenced by sets of variables that include predisposing risk factors, for example, psychosocial attributes (e.g., anxieties and coping skills) but also extra-individual physical and social factors that can affect the presence, severity, and persistence of disability (see Fig. 11.1). This framework specifically recognizes the impact (positive or negative) that the health-care provider can have on outcome. And indeed in some instances, the quality of the therapeutic relationship through nonspecific mechanisms that may be the single most important factor for improving function, promoting well-being, and enabling self-management of chronic pain. It is a fundamental tenet that the therapist not only delivers but is indeed the therapy.

Finally, the chronic care model (Fig. 11.2) is a relatively recent model that further expands the conceptual framework of chronic health conditions. When applied to pain and disability, the model recognizes that social community (Kelly et al. 2010; Mozaffarian et al. 2012; Parra-Medina and Hilfinger 2011) (physical and personnel – assets and barriers) (Baruth et al. 2014; Bopp et al. 2009), as well as the health-care system, influences the patient's pain experience as well as their outcome.

In summary, it is a fundamental truism that better management of pain and its impact will require a better understanding of neurobiological mechanisms, development and appropriate interpretation of more sensitive measurement tools (i.e. assessment and outcome measures) as well as the conduct of more comparative effectiveness trials (Lundberg et al. 2011). However, it is also true that a laser-like focus on the pain and the patient may not serve to illuminate some of major determinants of problematic outcomes that reside within the community and within social and health-care education and delivery systems. Complex, challenging, multidimensional problems require a systems thinking approach and frequently require behavioral and systems change by many individuals and groups within and between health and community systems; this is clearly a much more complex and challenging problem than just understanding and managing the patient, their pain, their mood, and their movement. However, that too is important.

11.3 Pain, Mind, Movement, and Physical Therapy

Physical therapy is a cornerstone non-pharmacological treatment for individuals with pain and especially for individuals with pain and movement dysfunction. Movement is inevitably changed in pain conditions. It appears that regardless of the original injury or illness, pain is associated with a generalized *psychomotor slowing* and a "stiffening" during movement that is both fatiguing and akin to

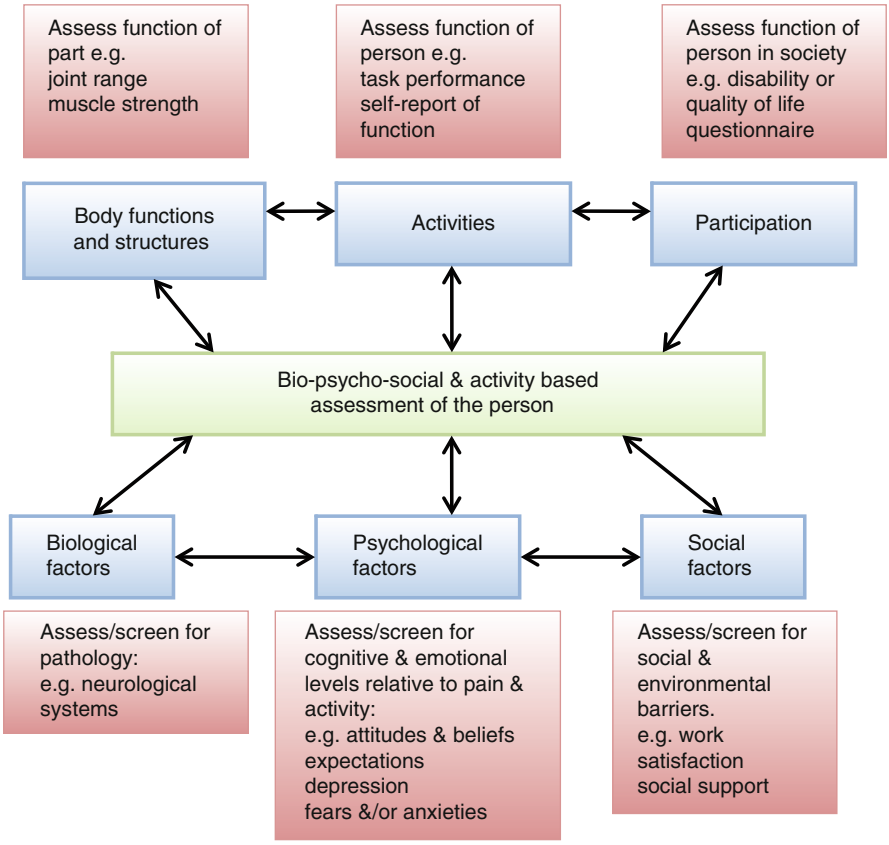

Fig. 11.1 The ICF model that recognizes that pain and disablement are influenced by sets of variables that include predisposing risk factors, for example, psychosocial attributes (e.g., anxieties and coping skills), and extra-individual physical and social factors that affect the presence, severity, and persistence of disability

age-related movement patterns (Simmonds 2002, 2007; Simmonds et al. 2005; Giralt et al. 2007; Montoya et al. 2006; Lee et al. 2007).

11.3.1 Pain, Emotion, and Movement

Slow movement patterns are inefficient in terms of the time taken to complete a given activity; they are also physiologically inefficient and therefore associated with higher levels of fatigue. Essentially, the energy cost required to complete a standardized physical task will be relatively high for patients with pain compared to their age and gender-matched cohort because of slow inefficient movement patterns (Lee et al. 2002, 2007). For example, in a group of 50 patients with back pain in primary

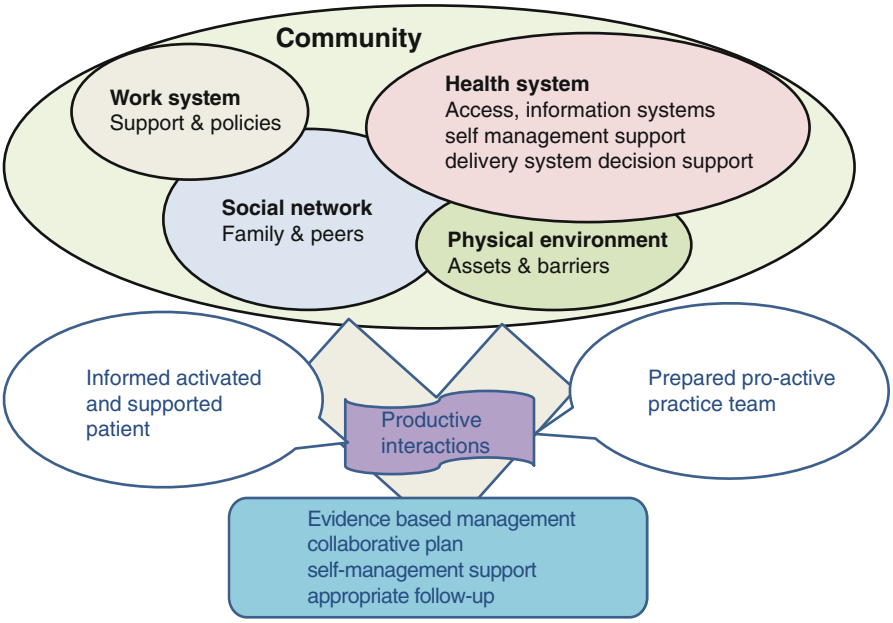

Fig. 11.2 The conceptual framework for a chronic care model of chronic health conditions. When applied to pain and disability, it recognizes that social community (physical and personnel – assets and barriers) and the health-care system influence the patient's pain experience as well as their outcome

care, when compared to an age- and gender-matched cohort, it was found that the patients not only had a mean compromise in walking performance of approximately 20 % but also had a 20 % higher level of effort associated with the performance of that task (Lee et al. 2002). For patients with pain and illness ($n = 100$ patients with pain and HIV), walking task performance was compromised by 50 % (Simmonds et al. 2005). The high level of perceived effort and physiological inefficiency during task performance may be partially explained by the relatively greater magnitude and duration of all muscle activity during any task performance in people with pain. Figure 11.3 shows the relatively high magnitude and duration of muscle activity throughout the gait cycle in individuals with back pain and/or leg pain, compared to a pain-free cohort. This overall "stiffening effect" compromises movement efficiencies and is relatively fatiguing. Moreover, for individuals with pain, because movement is slower and task performance takes longer, this relatively high and fatiguing level of muscle activity persists for a relatively longer period of time.

The presence of depression as well as pain compounds the magnitude of psychomotor slowing. In a group of 24 individuals with chronic pain and depression (as measured by scores greater than 5 on the Patient Health Questionnaire) (PHQ9), a 60 % compromise in walking performance was found. The subjects in this study had a mean age of 54 years but had a mean movement speed equivalent to that of an

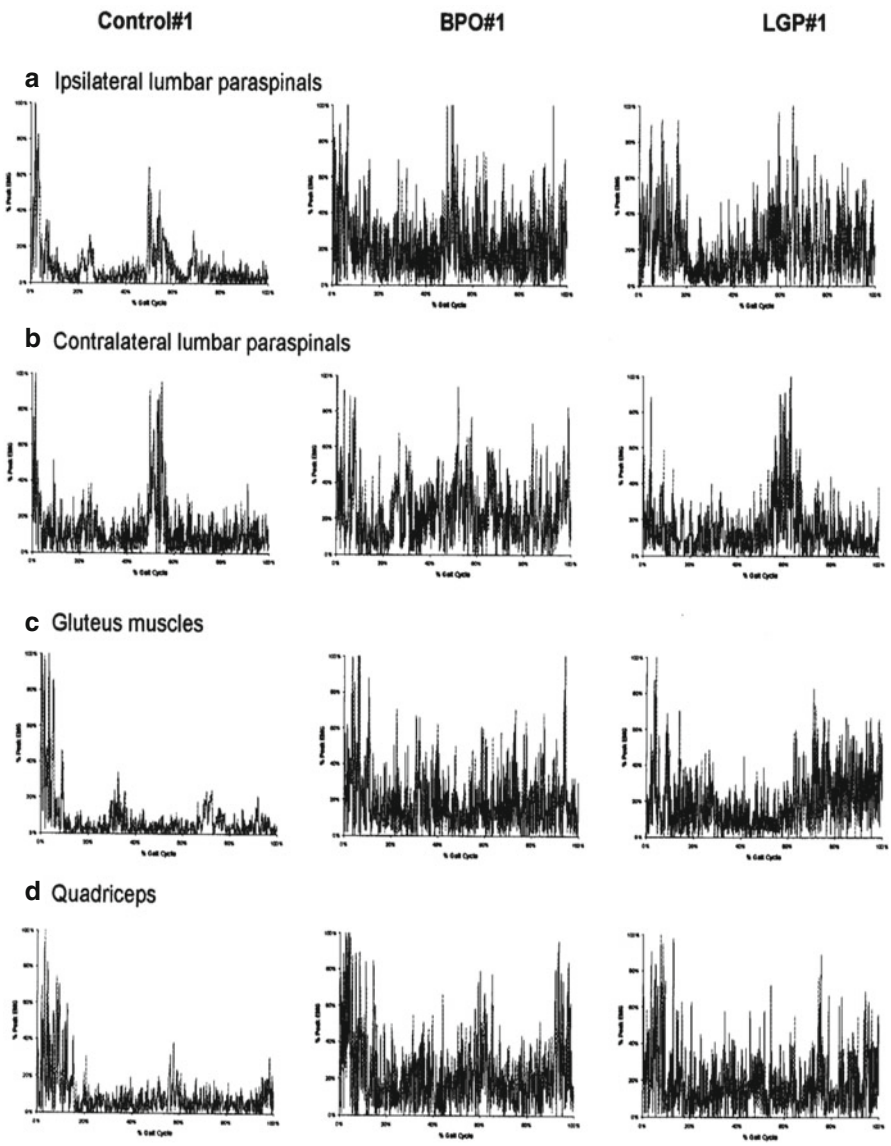

Fig. 11.3 The relatively high magnitude and duration of muscle activity throughout the gait cycle typical for an individual with back pain and back and leg pain, compared to a control subject

80–89-year-old person (Simmonds and Turner 2014). Clearly patients with pain and especially those with illness or depression have major mobility burdens that are incredibly fatiguing.

In an effort to improve movement without increasing pain or effort, we conducted a series of experiments to test the use of interval "sprint training," music, and also

different visual and audio cues in a virtual reality environment (Wilson et al. 2008; Song et al. 2011; Wang et al. 2013; Prasanna et al. 2010, 2013; Powell and Simmonds 2014; Simmonds and Zikos 2014). The details of the experiments have been reported elsewhere, but in essence, it was found that at the group level, "something" is generally better than "nothing," that is, control condition to improve physical performance and specifically movement speed, but there is no evidence to support any single optimal approach. For example, in a repeated measure single-case series of individuals with fibromyalgia, the effectiveness of fast versus slow music versus no music on walking speed was tested and found that average gait speed was higher with fast music and lower with slow music, as compared to baseline (Prasanna et al. 2010, 2013). More importantly, the increase in performance was not matched with any increase in pain. This suggests that music could be a simple cost-effective intervention that translates easily to a clinical or lifestyle situation.

Within a virtual reality environment interfaced with a treadmill, audio cues (audible footsteps at slow, normal, and fast speeds) and visual cues (fast, slow, and no optic flow) were manipulated as individuals with musculoskeletal pain walked on an instrumented treadmill (Powell et al. 2006; Powell et al. 2010a, b). Essentially, both audio and visual cues led to individuals walking faster compared to baseline and a control (no cue) condition. Again, there was no increase in pain despite an increased level of activity. It has also been shown that in patients with fibromyalgia, computer game play can improve mood and also physical performance (Simmonds et al. 2012a, b; Simmonds and Zikos 2014).

Taken together, the results suggest that although patients with pain have generalized psychomotor slowing, speed of movement can be manipulated in a variety of simple ways without any aggravation of pain or symptoms. The mechanisms underlying this manipulation have not been specifically tested but could include focused attention to the stimuli with secondary distraction from pain since "busy" virtual reality screens appear to have a greater effect on reducing pain and increasing movement speed (unpublished data). Nevertheless, it remains to be seen whether the change in movement speed persists and faster movement speeds transfer to overground walking, during daily life, and maintained over the long term.

11.3.2 Pain, Cognition, and Movement

Accumulating evidence indicates that pain is associated with compromised cognition that includes reduced processing speed and mental flexibility as well as attentional and working memory deficits sufficient to impact daily activities (Wilson et al. 2008; Hart et al. 2000; Karp et al. 2006; Dick and Rashiq 2007; Abeare et al. 2010). The adverse impact of chronic pain on executive function may be due to the interruptive effect of pain and perceived pain-related threat on attentional processing (Dick and Rashiq 2007), but it is likely to be more complex than that and is probably linked to emotional state, as well as physical and social function. This problem of cognitive compromise in pain conditions adds to the therapeutic

management challenge. Chronic pain, by its name and nature, is a chronic condition, and effective self-management is an ultimate goal. This often requires patients with pain to unlearn their misunderstandings about pain; self-regulate their thoughts, feelings, and behaviors; and learn new skills that enable effective self-management of chronic pain. Unlearning and relearning can be a challenge in ideal circumstances; unlearning and relearning in the context of unpleasant and distracting pain, emotional distress, and cognitive compromise adds to the challenge for patients and needs to be understood and taken into consideration by practitioners.

11.3.3 Exercise and Activity: Pain, Mood, and Cognition

Numerous studies have demonstrated the benefits of physical exercise and activity for health promotion, disease prevention, disability management, and overall quality of life (Cepada and Carr 2006; Lønkvist et al. 2013; Burzynska et al. 2014; Bradt and Dileo 2014; Brocki et al. 2014; Klasnja et al. 2014). The mechanisms that underlie these effects are not completely clear and are most likely due to multiple physical, psychological, and social factors. To state the obvious, the beneficial effects of exercise or activity will only accrue if the exercise or activity is done and is maintained, hence the value of simple and enjoyable activities such as walking or dancing. Unfortunately and regardless of proven health benefits, many individuals have difficulty initiating and/or maintaining exercise programs or even assuming a more active lifestyle. Identifying perceived barriers to physical activity at an individual level is an essential component of physical therapy. The ten most common reasons for not engaging in physical activity are presented below (Centers for Disease Control (CDC) 2010). Noteworthy is that even at a general population level, fear of injury or reinjury is among the top ten barriers to physical activity. Among patients with pain, fear of injury will probably rank the highest, but other barriers will also play a role.

To date, a preponderance of evidence supports exercise and activity-based interventions for the improvement of physical, emotional, cognitive, and social function. Indeed the overriding gestalt from the exercise and activity literature suggests that no matter what variable is measured at baseline, it improves with exercise and/or activity. Activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, whereas physical exercise is planned, structured, repetitive, and purposive in that improvement or maintenance of one or more physical fitness components is the goal (Caspersen et al. 1985).

There is also evidence to suggest that the nuances of exercise prescription are somewhat moot and that acute bouts of exercise versus chronic exercise, resistance exercise versus aerobic exercise, high intensity versus low intensity may be of less importance to impact long-term outcomes in a patient-centered approach to chronic pain than has been previously considered suggesting a primarily generalized and/or nonspecific effect of exercise/activity. This is an interesting contention that is in keeping with recent research supporting central and overlapping mechanisms that

contribute to persistent pain states, for example, fibromyalgia, dysautonomia, chronic fatigue, and irritable bowel syndrome (Clauw and Ablin 2009).

Barriers to physical exercise and activity: "Just do it" is a reasonable tenet. However, the problem is how to best tailor guidance to physical activity interventions so that patients may overcome their barriers to exercise and activity. Initiation and adherence to continued movement and activity is important as initial improvements decline when exercise/activity is discontinued (Hooten et al. 2012; Häuser et al. 2010).

From a population standpoint, the Centers for Disease Control (http://www.cdc.gov/physicalactivity/everyone/getactive/barriers.html) reports that the ten most common reasons why people do not engage in physical activity are as follows:

- Do not have enough time to exercise
- Find it inconvenient to exercise
- Lack self-motivation
- Do not find exercise enjoyable
- Find exercise boring
- Lack confidence in their ability to be physically active (low self-efficacy)
- Fear being injured or have been injured recently
- Lack self-management skills, such as the ability to set personal goals, monitor progress, or reward progress toward such goals
- Lack encouragement, support, or companionship from family and friends
- Do not have parks, sidewalks, bicycle trails, or safe and pleasant walking paths convenient to their homes or offices

These reasons obviously apply to people with chronic pain and need to be considered and addressed within physical therapy while noting that individuals are likely to have unique circumstances that also need to be addressed. A patient-centered model focuses upon exercise/activities that are relevant to the patient and are enjoyable (Abdulla et al. 2013). This approach enhances the effectiveness of rehabilitation but more importantly promotes long-term adherence (Farrell et al. 2004). Where appropriate, clinicians should encourage early involvement of the entire family to increase physical activity, as this improves exercise adherence and non-activity-related family commitments are perceived as a barrier to physical activity http://www.cdc.gov/physicalactivity/everyone/getactive/barriers.html.

With regard to exercise frequency, the recommended training effect dose is a minimum of 15 min for aerobic activity and a recommended "30 min most days or ≥5 days per week" (Garber et al. 2011). Though this recommendation is for healthy individuals, it was included in the American College of Sports Medicine consensus statement, and the recommendation probably applies to most individuals with chronic pain. The difference lies in the intensity of exercise that the individual can engage in based on their baseline level of physical condition. For example, deconditioned patients may need to engage in more frequent but short bouts of exercise/activity to accumulate a daily or weekly training effect. Likewise, the intensity of exercise/activity can be adjusted so that individuals work at a lower level of exertion but for a longer period of time.

A number of researchers have examined the relationships among measures as well as the predictive value of measures of mood, movement, and emotion across different patient groups. The findings show that the relationships are complex and enmeshed in both healthy pain-free individuals as well as those with chronic pain and chronic illness (Brunet et al. 2013). For example, Sabiston et al. (2008) examined the association between pain symptoms and affect and depression indicators of mental health among 145 breast cancer survivors over a 3-month period during which activity level was also monitored. Not surprisingly, they found that pain was negatively correlated with positive affect and physical activity and positively correlated with negative affect and depression. In addition, physical activity was positively correlated with positive affect and negatively correlated with depression. They also found that physical activity significantly mediated the relationship between pain and depression as well as between pain and positive affect (Sabiston et al. 2012, 2013).

In a series of clinical studies, the relationships among measures of physical performance, mood, and cognition were examined as well as the predictive value of physical performance on outcome (e.g., (Simmonds et al. 1998, 2005; Novy et al. 1999, 2002; Lee et al. 2001, 2003; Filho et al. 2002; Simmonds 2002, 2006, 2007; Shelton et al. 2009). Physical performance is measured with simple timed tests of function that include a timed 15 m fast walk and 5 sit-to-stand repetitions and a 6 min distance walk (6MDW). These tests have robust levels of reliability and strong validity (Simmonds et al. 1998, 2005; Lee et al. 2001; Novy et al. 2002; Simmonds 2002). The 6MDW was found to be the single best predictor of 5-year survival in patients with lymphoma, regardless of age or stage of disease. Moreover, in 47 patients with advanced non-small cell lung cancer, fatigue and the 6MWT distance were the strongest predictors of change in mental health-related quality of life, accounting for 13 and 9 % of the variance, respectively (unpublished data).

It is not surprising that the 6MDW is a good predictor of outcome and is negatively associated with depression and positively associated with social function. The ability to walk is fundamental to function, and the ability to walk a reasonable distance in a reasonable time enables one to potentially engage in social and recreational activities that are also associated with emotional health and well-being as well as improved cognitive function. The ability of simple quantitative measures of waking to predict outcome across a range of health conditions has led some to promote gait speed as the sixth vital sign.

In a recent meta-analysis, the effect of acute aerobic exercise on positive activated affect (PAA) was evaluated (Reed and Ones 2006). PAA included the affective component of well-being, energy, and positive activation. Key results showed that exercise was associated with increased PAA (d_{corr} = .47), while no exercise showed a negative association with PAA (d_{corr} = –.17). Moreover, within investigations of individuals with lower pre-exercise PAA scores, there were greater increases in PAA postexercise than with those that had mid and high PAA pre-exercise scores. Finally, this meta-analysis suggested that low-intensity exercise increases positive affect and that neither moderate nor higher intensity bouts of exercise have any significant additive effect.

Thus although exercise bouts of 20–30 min are recommended as a duration threshold for improved fitness levels (ASCM 2011; Berger and Motl 2000), conclusions from this meta-analysis show that shorter doses may suffice in improving affect, but the activity level must be maintained (Reed and Ones 2006). Notwithstanding the important contribution of physical fitness for overall physical health, level of fitness or change in fitness level is not necessary for activity to have beneficial effects on emotional state and cognitive function. For example, Loy et al. (2013) conducted a meta-analysis to identify parameters of exercise that promoted well-being. They found that a single bout of exercise (21–40 min of moderate intensity aerobic exercise) had a positive effect on affect (mean energy positive effect size change of .47 (95 % CI = .39–.56) but not surprisingly did not reduce perceived fatigue (mean effect size .03 (95 % CI = –.08–.13).

Several systematic reviews and meta-analyses have addressed the effect of exercise on depression. For example, a *Cochrane Review* by Cooney et al. (2013) evaluated 35 trials (1,356 participants) that compared exercise with no treatment or a control; the standardized mean difference for depression at the end of treatment was –.62 (95 % CI = –.08 to –.42), a moderate clinical effect. The authors further reported that there appeared to be little difference in effect between exercise therapies compared to pharmacological or psychological therapies. This suggests that individual treatment preferences should be considered by health-care providers but so also should the cost and the potentially negative consequences of specific treatments. For example, pharmacological therapies may have many more physiological and psychological consequences and little benefit other than on depressive symptoms. Exercise on the other hand can reduce depressive symptoms and has side effects that are positive in that they contribute to overall physiological, psychological, and social well-being.

Rethorst et al. (2009) conducted a meta-analysis of 58 trials ($n = 2{,}982$) on the effects of exercise on depression. The authors reported that exercise improved depression scores (0.8 SD units). There is also a suggestion that within a clinically depressed population, more frequent exercise (i.e., five times a week as opposed to two–four times a week) has a stronger treatment effect. There is also a suggestion of a U-shaped response to exercise bouts, that is, 30–40 min bouts of exercise appear optimum compared to shorter or longer exercise bouts. Whether optimal frequency and timing of exercise/activity that decreases depressive symptoms more effectively will contribute to better long-term adherence remains to be seen.

Adherence is a difficult issue that is not fully understood and often not managed well. However, there is evidence that shows at least for some patients a lifestyle approach to increasing physical activity may not only be beneficial but also adhered to (Stuifbergen et al. 2010). In a randomized trial of 84 participants with fibromyalgia that compared a fibromyalgia education program and a physical activity lifestyle program, the authors showed that the lifestyle physical activity program improved physical activity (daily activity counts increased by 54 %), reduced pain, and improved function (Fontaine et al. 2010).

Research on the effects of exercise on cognition and the mechanisms that underlie potential effects has burgeoned in recent years (Hötting and Röder 2013; Guiney

et al. 2015; Law et al. 2011; Niemann et al. 2014). In a randomized trial by Hogan et al. (2013), an acute bout of moderate exercise, 15 min of stationary cycling, with healthy participants between the ages of 19 and 93 were compared with a control condition, and measures of cognitive function were included and compared across age ranges. The authors reported baseline differences on memory ($b = -.28$, $p < .0001$) and reaction time tests (.38, $p = .001$) as a factor of age but that exercise improved reaction time irrespective of age ($b = .20$, $p = .014$) but not accuracy of memory ($b = -.09$, $p = .274$).

Recent imaging research has contributed to major understandings of the brain and the mind under a variety of different conditions including pain, stress, illness, and aging. Although the implications are not clear and it is important not to over-interpret imaging findings, for example, it is known that chronic pain is associated with a reduction in gray matter in pain processing areas of the brain (Kuchinad et al. 2007) and that chronic aerobic exercise increases brain volume, at least in healthy elders (Colcombe et al. 2006). However, it must be emphasized that the mechanistic links between change in gray matter and pain, distress cognitive function, and exercise although seductive are also speculative at present.

Nevertheless, it is interesting that in a randomized controlled trial of elders ($N = 59$), ranging in age from 60 to 79 years, a 6-month aerobic training regimen compared to a low resistance and stretching intervention and control resulted in increased gray and white matter in the prefrontal and temporal cortices. By comparison, a control group of 20 younger, neurologically intact individuals (18–30 years) did not demonstrate any changes in brain volume. The reason for this is not clear, but it seems to reflect a limited capacity for change that may be age, pathology, or dose response related.

A meta-analysis by Colcombe and Kramer (2003) on exercise and cognition demonstrated that cognitive changes due to exercise primarily impacted executive function but the impact of exercise was moderated by the length and type of intervention as well as the duration of training sessions.

With regard to individuals with chronic pain and in one of the few studies that have measured cognitive function in patients with pain, a 4-week residential exercise program of 108 persons with chronic pain was administered that also included cognitive behavioral treatment. Ninety-five individuals were followed at 4 weeks and 9 months, and improvements were noted in physical and cognitive performance. Specifically, improvements at 4 weeks in physical performance (timed walk, repeated sit-to-stand, and stair climb) and cognitive performance (Stroop test) ranged between 40 and 100 %, and these improvements were maintained at follow-up (Wang et al. 2013).

Finally, a body of research has addressed the direct hypoalgesic effects of acute exercise on healthy pain-free individuals as well as those with pain. In a recent meta-analytic review of this literature Naugle et al. 2012 evaluated studies that had addressed three types of exercise (acute isometric, aerobic, or dynamic resistance exercise). The authors found a differential effect based on the subject sample, that is, healthy pain-free participants versus those with chronic pain, and the type of exercise. In healthy pain-free subjects, resistance exercise – isometric and dynamic – had an analgesic effect as measured by experimental pain threshold ($d_{thr} = 1.02$ and $d_{thr} = .84$), respectively, indicative of a large analgesic effect, whereas aerobic

exercise had a moderate analgesic effect (d_{thr} = .41). The results in chronic pain populations were much more variable in direction and magnitude of effect. A number of factors contribute to the variability in these findings but the overriding explanation must be the gestalt, that is, the complex multidimensional nature of pain and its heterogeneous clinical impact at neurobiological, psychological, and social levels. And questions remain as to whether in patients with pain, changes in experimental thresholds impact function or well-being.

11.4 Clinical Implications

Evidence from a number of clinical trials and systematic reviews support the notion that maintenance or resumption of activity is important, for individuals with pain to promote and maintain general health and well-being, reduce the level of disability, and increase quality of life (Koes et al. 2006). However, there is little evidence and no consensus as to whether any particular type of exercise or activity is substantially better in terms of effectiveness as measured by pain, disability, or quality of life. It is plausible that for the majority of individuals with pain, simply increasing activity is enough. And therefore, identifying patient preference for exercise or activity and addressing key barriers to physical activity is of most importance.

That said, it is clearly appropriate to tailor specific exercise interventions for individuals with specific physical impairments, for example, joint stiffness or muscle weakness that are limiting their overall function and quality of life. In such a situation, it would be expected that a strengthening exercise regimen would lead to a greater change in muscle strength than a flexibility exercise regimen. And if the impairment was correctly identified as an important limitation to function, then improvement in muscle strength or joint flexibility should result in an improvement of physical function. If it does not, then the primary limitation to physical activity may have been misidentified. However, the comparative effectiveness of these different exercise regimens may be similar on outcome measures of pain, depression, or quality of life because of the generalized effects of exercise and activity.

For individuals with chronic pain, the overall aim of therapy is to improve function and increase social engagement often despite persistent pain (Airaksinen et al. 2006; Chou et al. 2007). This requires a broad conceptual model to understand and address any major concerns (beliefs and behaviors) that are contributing to distress and disability. Therapists should promote education and self-management, work with the patient to ensure a good understanding about the positive effects of activity, establish concrete and achievable activity related goals, identify and address perceived and actual barriers to activity, and facilitate social and activity support from friends, family, peers, and potential employers (Airaksinen et al. 2006; Chou et al. 2007).

Educational information includes information booklets, one-on-one sessions, group classes, and online forums, but a key message should be to de-medicalize and demystify the problem of pain and emphasize the benefits of an active healthy

lifestyle on chronic pain. It is important that the therapist explicitly elicits and addresses any concerns related to pain and activity, and this will probably require several conversations to reiterate key elements (Liddle et al. 2007).

A key component of effective physical therapy is based on encouraging patients with pain to exercise and/or resume physical activity. Several symptoms associated with chronic pain, including fatigue and depression, are characterized by reduced motivation to initiate or complete goal-directed tasks. Helping patients with pain *and* depression participate in an exercise regimen is challenging because the exercise will likely be non-appetitive and will also require relatively high energetic costs. However, if a therapist understands the psychological and physiological context and is empathetic, they are more likely to be effective. This is important because exercise can improve depression as well as pain and can increase movement speed (e.g., Wang et al. 2013).

Finally, therapists should also be mindful of their personal beliefs and biases and how these may influence the therapeutic relationship. Research suggests that therapists with elevated fear-avoidance beliefs have an increased tendency to recommend passive coping strategies for pain reduction, such as bed rest (Linton et al. 2002). Also, therapists who have a strong biomedical focus or are intolerant of ambiguity tend to recommend and deliver passive rather than active therapies (Derghazarian and Simmonds 2011; Simmonds et al. 2012a, b). It is obviously important that educational messages and treatments delivered to patients are consistent with best evidence-based practice.

As noted, there is good evidence in support of physical activity for chronic pain but no evidence supporting any specific regimen of exercise or specific physical activity. In this regard, therapists should work with the patient to see how to best address perceived barriers and increase participation in a physical activity routine that can be adhered to over the long term. This may require addressing pain levels, confidence, fears, social support, time and financial resources, and transportation, as well as assessing readiness for change. The activity program itself might also influence participation. Accessibility to the required venue and equipment, personal interest in the selected activities, and group versus individual activities are all factors that may influence patients' levels of motivation and participation in activity as well as maintenance of activity participation (Turk and Okifuji 2002).

Therapists can improve their treatment efficacy by using a cognitive-behavioral approach and helping patients become aware of and potentially modify maladaptive thoughts and behaviors (George et al. 2003; Sullivan et al. 2006). They can also facilitate patients' reintegration into pre-injury social roles. This will require addressing social factors such as family and friends who can be instrumental in supporting participation in a physical activity regimen and may even take part themselves. It may also require addressing employers regarding modified work schedules for a return-to-work plan. Social and health-care system factors can also contribute to self-management and activity through policies and payment systems, and therapists may need to play an advocacy role in this regard to optimize outcome in a cost-effective manner.

11.5 Summary

In summary, pain is complex and multidimensional and a myriad factors influence outcome. Strong evidence supports the positive and generalized role of physical activity/exercise to improve pain, mind (emotions and cognitions) movement, and social function. However, there appears to be no evidence supportive of any specific type of exercise or activity regimens. Unfortunately and regardless of proven health benefits, many individuals have difficulty initiating and/or maintaining exercise programs or even assuming a more active lifestyle. Understanding the complexity of the problem, the perceived barriers to exercise as well as the challenges of exercise for individuals with pain, mood, and movement disorders in the context of social and environmental determinants of health behavior change are key to making progress in this field.

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Part IV
Special Populations

Chapter 12
Phantom Pain: The Role of Maladaptive Plasticity and Emotional and Cognitive Variables

Xaver Fuchs, Robin Bekrater-Bodmann, and Herta Flor

Abstract Phantom pain is a frequent sequel of the amputation of a limb or another body part and must be differentiated from residual limb pain, postoperative pain, and other chronic pain problems such as back pain that may occur simultaneously. In this chapter, we first discuss how maladaptive plasticity of the central nervous system in interaction with peripheral variables may contribute to phantom pain and then examine how emotional and cognitive variables modulate the phantom pain experience. We show that anxiety, depression, stress experiences, body representation, and memory processes as well as psychosocial variables are associated with both the development of phantom limb pain and its maintenance. In examining this issue, pain and disability-related emotional and cognitive factors must be differentiated. An integration of the described physiological changes with the psychological variables is still missing. We propose a model that integrates psychological and physiological variables in phantom limb pain and discuss implications for both pain assessment and treatment.

12.1 Introduction

The amputation of a limb or another body part such as the breast represents a breach of one's body integrity, which requires several adjustments. First, amputees have to adapt to the altered physical conditions, including postural adjustments and the development of new behavioral strategies to cope with the loss of the body part. Second, the amputees have to come to terms with their new role in their social environment. And third, the majority of amputees have an additional challenge to cope with: phantom pain, that is, painful sensations located in the lost body part, which

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are a common consequence of an amputation. The latter consequence of an amputation is of special clinical importance, since its presence is accompanied by psychological distress and causes high costs for the healthcare system. The transition from health to disability is influenced by individual cognitive and emotional factors, and, on the other hand, amputation and post-amputation experiences can act upon cognition and affect. Since phantom pain is an important clinical feature in limb amputees, the question arises how cognitive and emotional variables modulate its presence and strength and how phantom limb pain itself affects emotional and cognitive functioning. Although a large number of studies in the last decades have dealt with the physiological alterations after limb amputation that are associated with the development of phantom limb pain, the relationship between phantom limb pain and cognitive and emotional variables is less well understood. This chapter will review the evidence reported in the literature, relate emotional and cognitive factors to alterations in maladaptive plasticity, and discuss the implications of these findings for the assessment and treatment of phantom pain.

12.2 Amputation and Post-Amputation Experiences

Despite great progress in health care, amputations are still frequent. In the United States, more than 185,000 persons undergo an amputation each year, resulting in almost two million people that are currently living with loss of a body part (Ziegler-Graham et al. 2008). The causes of amputations are diverse and differ considerably for arms and legs. Traumatic amputations are most frequent for the upper extremity (80–90 %), whereas vascular disease secondary to diabetes accounts for more than 40 % of the leg amputations (Johannesson et al. 2009; Ephraim et al. 2005). The neuronal mechanisms after limb amputation in adults seem to differ from those in childhood or in congenital limb amputees (Montoya et al. 1998; Melzack et al. 1997), where no or little phantom pain is present (Wilkins et al. 1998). As a result, the following data relate to amputations in adulthood, and almost all focused on limb amputation.

Almost all amputees report some awareness of the phantom (Kern et al. 2009; Kooijman et al. 2000), that is, the persistent perceived presence of the missing limb. Size and shape of the phantom limb can be similar to or different from the former limb, and its posture can be distorted into physically impossible positions (Cronholm 1951; Ramachandran and Hirstein 1998; Giummarra et al. 2010). The phantom limb can be immobile or subject to voluntary or involuntary movements. In addition to phantom limb awareness, amputees report various types of non-painful phantom sensations, such as tingling or thermal perceptions (Kern et al. 2009; Kooijman et al. 2000). The prevalence of non-painful phantom sensations is between 70 and 90 % (Kooijman et al. 2000; Jensen et al. 1983; Kern et al. 2009).

Painful experiences after an amputation refer to postoperative pain, that is, pain related to the wound, residual limb pain present in the remaining body part adjacent to the amputation line, and phantom limb pain, which refers to pain in the missing

body part. Of these pain types, post-amputation pain is present in almost all amputees during the days up to weeks after amputation and can often not be well differentiated from residual limb and phantom pain. Residual limb and phantom pain frequently become chronic and continue to exist after the physical wound healing process. Residual limb pain is very common after an amputation with a mean prevalence rate of 60 % (Ehde et al. 2000; Ephraim et al. 2005; Kern et al. 2009; Kooijman et al. 2000; Schley et al. 2008). Phantom limb pain (PLP) is heterogeneous in terms of the development, frequency, intensity, and quality of pain, ranging from occasional slight painful sensations to constant severe pain. Some amputees can precisely determine the location of the perceived pain, while others report diffuse pain that cannot be located with certainty. Mean PLP rates of about 75 % have been reported in epidemiological studies (Ehde et al. 2000; Ephraim et al. 2005; Hanley et al. 2009; Houghton et al. 1994; Kern et al. 2009; Kooijman et al. 2000; Pohjolainen 1991; Sherman et al. 1984; Wartan et al. 1997). The incidence of phantom limb pain in the first 6 months after the amputation ranges from 50 to 80 % (Carlen et al. 1978; Jensen et al. 1983; Jones and Davidson 1995; Shukla et al. 1982b; Richardson et al. 2006). Although most studies have focused on phantom pain related to the loss of an upper or lower extremity or parts thereof, phantom pain has also been reported after mastectomy or tooth extractions.

In addition to residual limb and phantom limb pain, a considerable proportion of amputees report comorbid chronic pain in other body parts, such as the intact limbs, buttocks, neck, shoulders, and back, with prevalence rates of 20–50 % (Ephraim et al. 2005; Ehde et al. 2000; Hanley et al. 2009; Smith et al. 2008). Some of these pain problems may be a result of the disability and postural adjustments related to the amputation; other numbers are comparable to those in the general population (Breivik et al. 2006).

12.3 Neuronal Alterations Related to Phantom Limb Pain

The large variation in prevalence, symptoms, and development described above suggests a multifactorial origin for phantom limb pain. The removal of an extremity, especially in a non-clinical context like an accident or during combat, is a severe disruption of the body's integrity with negative effects on peripheral and central physiological mechanisms.

12.3.1 Peripheral Changes

After peripheral nerve section, the disconnected endings start to grow towards each other, and this regrowth of the remaining nerve can lead to the formation of tangled knots of neural tissue (Watson et al. 2010). These so-called neuromas are known to show spontaneous and unpredictable activity (Fried et al. 1991), display changes in

sensitivity to various noxious stimuli (Gorodetskaya et al. 2003), and might contribute to pain in some amputees. Since they are located in the residual limb, neuromas are usually seen as a cause of residual limb pain rather than PLP, although there are contrary findings reported in the literature (e.g., Wiffen et al. 2006; Bek et al. 2006). In addition to neuromas, functional alterations of the dorsal root ganglia have been related to phantom pain phenomena (Devor and Wall 1990). In fact, elimination of input from the residual limb or the dorsal root ganglion seems to eliminate phantom limb pain in some amputees (Birbaumer et al. 1997; Chabal et al. 1989; Vaso et al. 2014).

12.3.2 Maladaptive Plasticity in the Central Nervous System

Hyperexcitability and reorganization in spinal cord neurons after nerve damage has been shown to occur after amputation (Devor and Wall 1978). In addition, interneurons may be destroyed by ectopic discharge or other consequences of axotomy (Woolf 2004) or might change from an inhibitory to an excitatory mode (Nitzan-Luques et al. 2011). Even though the spinal cord alterations could account for some of the variations in PLP, the intensity and frequency of this type of pain has also been found to be connected to alterations in the somatosensory and motor cortices, brainstem, and thalamus, which show massive functional alterations after limb amputation (Flor et al. 2006; Kaas 2000). The primary somatosensory cortex might play a key role in phantom pain after deafferentation since it reorganizes as a consequence of an amputation, and this reorganization is positively related to phantom pain intensity. After the loss of input, the vacated areas start to process sensory information from the adjacent nerves, and this might be perceived as phantom pain. Makin et al. (2013) showed that the presence of phantom limb pain was enhanced when more input from the preserved representation of the former hand in SI was present in amputees. Although controversial (Flor et al. 2013), there are clearly interactions between peripheral and central changes in PLP. Moreover, it is likely that emotional and cognitive processes interact with both peripheral and central maladaptive changes involved in PLP.

12.4 Emotional Factors

Since phantom limb pain is a pervasive disorder, comorbid mental disorder can be expected in line with its high prevalence in chronic pain, where it mainly involves anxiety and depression (cf., Fishbain et al. 1997; Flor and Turk 2011; Gatchel et al. 2007). Annagür et al. (2014) reported comorbid depression at a rate of 50 % and anxiety at a rate of 33 % in a sample of 108 chronic pain patients. In order not to draw wrong conclusions about the association of PLP and comorbid mental disorders, comorbidity rates in samples of amputees have to be interpreted with great

caution with respect to certain characteristics of the sample such as age, cause of amputation, and the time passed since amputation. Some studies on mental disorders in amputees have reported extremely high rates of depression (50 %) and anxiety (above 35 %) in the postoperative phase (e.g., Shukla et al. 1982a). Other studies have reported lower rates in samples that are heterogeneous with respect to cause of amputation and age, for example, 19 % for depressive symptoms and 31 % for post-traumatic stress disorder (Mall et al. 1997) or 24 % for both depression and anxiety symptoms (Singh et al. 2009). Despite variation of rates depending on sample characteristics, depression and anxiety symptoms are common in recently amputated subjects. However, recent amputations are a special case, and, in fact, there is evidence that depression in a post-amputation phase is more strongly correlated with concerns about disability rather than with PLP (Whyte and Niven 2011a; Mall et al. 1997; Trivedi et al. 1997). This suggests that studies examining early stage amputees give little information about the interplay of mental disorder and PLP and that more valid information can be drawn from studies with amputees in a later stage. However, it is worth noting that PLP is always confounded with disability and that even in amputees in later stages it is important to consider both disability-related and pain-related issues. Finally, anger has not been examined in amputees although it is known to be important in chronic pain (Fernandez 2005).

12.4.1 Depression

There is evidence that depression or "depressive symptoms" are common in amputees in the first years following amputations, but that they decline afterwards. In their review, Horgan and MacLachlan (2004) come to the conclusion that, after 2 years, depression rates decline to rates comparable to the general population and that depression within the first years is most strongly linked to disability. Whyte and Niven (2011a) showed that the correlation of PLP and depression as assessed by the Beck Depression Inventory was mainly mediated by items that assess performance or somatic symptoms that are common in chronic pain. The issue that the Beck Depression Inventory overestimates depression in samples with physical disease and chronic pain has been noted before (Peck et al. 1989). It is therefore important to take into consideration the depression measure used in amputee studies. Desmond and MacLachlan (2006) found elevated values in depression and anxiety as measured by the Hospital Depression and Anxiety Scale and post-traumatic stress, measured with the Impact of Event Scale. They used a large ($N=582$) sample comprised of only older male former military members with long-standing traumatic amputation (at least 10 years). In this homogeneous sample, values above a criterion indicating potential clinically relevant depression were observed three times more often than it would be expected in the normal population. In addition, this study found associations between psychological distress and chronic pain: amputees with either residual limb pain or residual limb pain and PLP showed higher values in depressive symptoms, avoidance and intrusions. However, this was not the case in the group

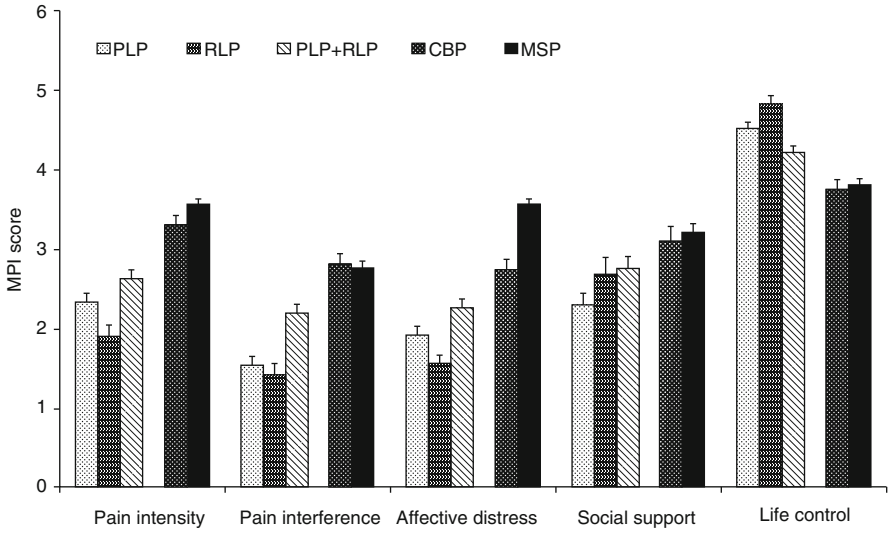

Fig. 12.1 Data on subscales of the Multidimensional Pain Inventory (*MPI*) for amputees suffering exclusively from phantom limb pain (*PLP*, $N=190$), residual limb pain (*RLP*, $N=100$), or both (*PLP+RLP*, $N=191$). For comparison, data from a sample of chronic back pain patients (*CBP*, $N=101$) as well as norm MPI data of a sample of 250 patients with chronic musculoskeletal pain (*MSP*) are given. *Error bars* indicate standard error of the mean (SEM). The age of amputees and CBP patients ranged from 18 to 70, and the mean duration of pain presence in these samples was more than 10 years. Chronic post-amputation pain sufferers reported less pain, pain-related interference, and affective distress and more life control compared to CBP sufferers. The only exception is the social support subscale, which is similar to CBP patients in RLP sufferers (exclusively or in combination with PLP) ($p<.05$, Bonferroni corrected for multiple *t*-tests)

with only PLP and no residual limb pain (for a comparison with our own data see Fig. 12.1). The reasons for this differential effect are not clear. Desmond and MacLachlan assume that residual limb pain might be a health concern more conflicting with prosthesis use and more strongly linked to activity restriction resulting in negative affect (e.g., Marshall et al. 2002). The study by Desmond and MacLachlan suggests that there is no or only a weak association of PLP and depression. However, it can be argued that observations made with former military service members cannot be generalized to other populations. Darnall et al. (2005) conducted a survey using a stratified sample of more than 900 amputees, which might provide norms that are more representative of the general population. Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale, a screening instrument especially suitable for people with chronic health problems. In addition, it was assessed how much the amputees were bothered by their phantom pain, residual limb pain, and back pain using a Likert scale, ranging from 0 ("no pain") to 3 ("extremely bothered by pain"). This study found a significant association between how much the subjects were bothered by pain and depressive symptoms. Subjects who were "extremely bothered" by PLP were almost three times more likely to have depressive symptoms than subjects reporting not to be bothered. However, the

associations of depression and chronic back pain and residual limb pain were even higher. The overlap between both types of pain was high.

Taken together, these studies suggest that there is a positive association of PLP and depression. However, this association might be weaker than in other chronic pain conditions, including residual limb pain. A direct comparison of depression and anxiety in PLP sufferers and other chronic pain patients was made by Kazemi et al. (2013). In this study, amputees with PLP showed fewer symptoms in both depression and anxiety compared to a sample with non-phantom neuropathic pain caused by trauma or surgery.

In a larger sample of persons with chronic back pain compared to three groups of amputees (only PLP, only residual limb pain, and both, PLP and residual limb pain), the mean values of the subscales of the German version of the Multidimensional Pain Inventory (Flor et al. 1990) are shown in Fig. 12.1. For comparison, normative data for persons with musculoskeletal pain were included (Flor and Turk 2011). In line with Kazemi et al. (2013), persons with PLP showed less affective distress and pain interference when compared to chronic back pain or musculoskeletal pain patients.

12.4.2 Anxiety

Anxiety is generally discussed as a factor associated with the aggravation and maintenance of chronic pain, related to avoidance of activity and perceived disability (Turk 2002). As it is the case for depression, anxiety symptoms are common immediately following amputation (Shukla et al. 1982a; Singh et al. 2009) but, in that early stage, do not chiefly concern PLP. In their review, Horgan and MacLachlan (2004) state that anxiety following amputation commonly relates to a changed body image, social functioning and social discomfort, and adaptation to a new identity. However, they also state that too few empirical data exist about the process of adaptation of the amputees' identity to being disabled and concomitant anxiety themes. Rather than being associated with PLP, anxiety is correlated with somatic symptoms (e.g., exhaustion, insomnia) in the early phase after amputation (Whyte and Niven 2011a). Similar to the course of depression, anxiety levels decline within the first years (Horgan and MacLachlan 2004; Singh et al. 2009). Little is known about the association of anxiety and PLP in a later stage, after the consequences of an acute amputation have subsided. Desmond and MacLachlan (2006) found that anxiety was higher in long-term amputees with chronic pain (PLP or residual limb pain) compared to pain-free amputees, but anxiety scores were within the range of the normal population. As mentioned above, their sample also consisted only of former military service members with traumatic limb loss. Castillo et al. (2013) showed that in a late, chronic phase of pain following lower-extremity trauma, anxiety—not depression—predicted subsequent pain. However, their sample was heterogeneous and contained amputees and non-amputees, and no distinction was made between PLP and other types of pain. Finally, fear of pain and movement have been

identified as important predictors of pain and interference in other chronic pain populations, for example, in musculoskeletal pain (Leeuw et al. 2007; Vlaeyen and Linton 2000), but have not been systematically analyzed in amputees with PLP.

12.5 The Role of Stress and Tension in PLP

It has been proposed that stress plays a role as a trigger of pain episodes in PLP and other types of chronic pain (Sherman et al. 1987; Flor and Turk 2011). However, the concepts of stress referred to in the literature are diverse and range from more broad constructs of general psychological distress (as used in Desmond and MacLachlan 2006), which bears similarities to anxiety and depression, to more situational and transient concepts like emotional and physiological arousal (as used in Angrilli and Köster 2000).

In a series of studies, Sherman (1994) and Sherman et al. (1989) examined the relationship of physiological alterations of the residual limb and PLP and proposed that local changes as well as autonomic system responses might contribute. For example, Sherman et al. (1987) showed that the temperature of the residual limb as compared to the intact limb is decreased in persons with PLP, most likely related to decreased near-surface blood flow. For burning, tingling, and throbbing pain, there was a significant relationship between the extent of the temperature difference and the intensity of PLP. Discharges of peripheral input can be mediated by autonomic nervous system activity, which could explain why situational components (like external stress) and internal states (like tension and anxiety) interact and trigger PLP episodes. Sherman et al. (1992) showed a close temporal relationship between (involuntary) contractions of the residual limb muscles and PLP. In this study, bursts, as recorded by surface electromyography signals, preceded the PLP experience. These rather involuntary contractions of residual limb muscles can be related to anxiety, tension, and stress.

Angrilli and Köster (2000) induced stress in amputees with and without PLP by having them report about memories of the amputation in a free speech and applied a cold pressor pain test and mental arithmetic as control tasks. Heart rate and blood pressure were recorded as a measure of sympathetic stress responses. Amputees with PLP showed a stronger psychophysiological stress reaction compared to amputees without PLP in the free-speech task. This study also supports the notion that distressing pain memories play a role in PLP (Katz and Melzack 1990; Flor 2002; Giummarra et al. 2011a).

An interesting question is how these findings on the relationship between physiological stress and PLP in the laboratory relate to a more naturalistic context and to more general ("everyday") stressors. Giummarra et al. (2011b) had amputees complete a structured questionnaire on experienced triggers of PLP episodes. Most commonly reported (50 %) were behavioral triggers, like "forgetting" that the limb is amputated and trying to use the phantom. Thirty-seven percent reported triggers related to stimulation of the residual limb, such as movement, touch, or pressure.

Emotional triggers such as emotional distress, exhaustion, or thinking of the missing limb were reported by 23 %. Additionally, 20 % reported influence by the weather, and 11 % reported referred sensations from the intact limb. These findings support the notion that PLP episodes follow emotional distress and that input from the residual limb is an important factor. However, these data are based on subjective reports and may follow preconceived notions rather than actual events. Rather than using a survey, Arena et al. (1990) conducted a longitudinal study employing pain and stress diaries acquired from 27 male amputees with PLP who completed them four times a day for 6 months. A cross-lagged correlational analysis was used to detect relationships between stress and PLP over time. In 74 % of the amputees, a significant relationship between stress and PLP was found. In 63 % of this sample, a simultaneous covariation of stress and pain was observed, in 44 % a change in pain preceded a change in stress, and in 37 % a change in stress preceded a change in pain. This study supports the interpretation that there is a bidirectional link between PLP and stress.

12.6 Cognitive Factors

Cognitive factors such as anticipation, expectations, beliefs, interpretations, appraisals, and coping strategies have been found to modulate chronic pain (Turk et al. 1983; Turk 1999; Flor and Turk 2011). In PLP little is known about the role of cognitive factors (Hill 1999), although catastrophizing, coping styles, memory processes, and body representation have been examined.

12.6.1 Body Representation in PLP

The amputation of a limb is accompanied by alterations in body representation such as a changed perception of the missing limb. Amputees in general (Nico et al. 2004) and especially those experiencing PLP (Reinersmann et al. 2010) show an increase in reaction time when asked to mentally rotate a hand representing their missing limb. This delayed response has been viewed as indicative of a dysfunction in the processing of the body schema, which refers to more implicit aspects of body representation compared to the body image, which has been viewed as an explicit, conscious percept. As implicit and explicit aspects of body representation are dynamic and closely interwoven and cannot always be separated, we prefer the term body representation. Other basic processes involved in body representation, however, seem to be less affected. Thus, amputees can be induced to perceive a rubber hand as belonging to their body, when the seen rubber hand is synchronously touched together with the hidden residual limb (Ehrsson et al. 2008). The underlying neuronal principles in amputees (Schmalzl et al. 2014) appear to be similar to those in healthy controls (Ehrsson et al. 2004). No significant differences between

amputees with and without PLP related to the responsiveness to this so-called rubber hand illusion have been found (Ehrsson et al. 2008). The intact ability of amputees with PLP to perceive an artificial limb as belonging to their body might be useful for the treatment of PLP. For example, functional prosthesis use has been found to be negatively associated with both dysfunctional cortical reorganization and PLP intensity (Lotze et al. 1999; Weiss et al. 1999), indicating that restoring the amputee's body integrity might alleviate or prevent PLP. There is evidence that the perception of ownership of the prosthetic device plays a mediating role in this process, with more intense ownership experience of the prosthesis being associated with lower levels of PLP (Kern et al. 2009). Similarly, sensory feedback from the prosthesis (Dietrich et al. 2012) might enhance perceived ownership. However, amputees who report a telescopic distortion of their phantom stated less often the occurrence of ownership sensations for the prosthesis (Giummarra et al. 2010), suggesting that the presence of a telescope might influence the effectiveness of PLP treatment as well. In line with this, Foell et al. (2014) reported that the presence of a telescope is an important predictor for the effectiveness of mirror therapy. During mirror therapy, patients perform movements with their intact limb in front of a mirror and have to mentally combine the seen movements with the self-executed movements of the phantom. Amputees who experienced a telescope failed to relate the seen movement to the felt movement and did not benefit from the mirror intervention (Foell et al. 2014). Since the sensation of a telescope is associated with similar reorganizational processes like PLP (Grüsser et al. 2001), this finding highlights the importance of body perception and its neural correlates for the treatment of PLP.

12.6.2 Memory for Pain

It has been proposed that "somatosensory memories" of non-painful and painful sensations in the missing limb play a role in phantom limb awareness and PLP (Katz and Melzack 1990; Katz 1992; Flor et al. 2006). Anderson-Barnes et al. (2009) proposed that "proprioceptive memories" could explain sensations in a phantom limb and that there might exist learned associations between proprioceptive memories and pain perceived before amputation. Before amputation, pain in the affected limb is common, for example, due to a tumor, vascular disease, or injury. Katz and Melzack (1990) suggested that these types of pain are encoded and can later be triggered, for example, by peripheral input from the residual limb, and experienced as PLP. Support for this comes from retrospective reports showing a relationship between reported memories referring to the phase before or during amputation and later phantom sensations (Katz and Melzack 1990; Giummarra 2011a). In Katz and Melzack's (1990) study, almost 60 % of amputees who reported some kind of pain before the amputation also reported that painful sensations continued or recurred in the phantom limb. It has been proposed that neural plastic changes following long-term nociceptive input can be seen as a neuronal mechanism underlying pain memories (Flor 2003, 2008). Maladaptive plasticity associated with PLP might be more

severe if chronic pain precedes the amputation. The concept of pain memories and pain prior to the amputation is closely linked to the question whether the formation of pain memories and subsequent PLP can be prevented if nociceptive input is blocked before amputation, for example, by the use of anesthetic drugs. However, the evidence on this is controversial (Ypsilantis and Tang 2010; Jensen and Nikolajsen 2000). In a prospective study, Jensen et al. (1985) and Nikolajsen et al. (1997) showed that PLP during the first 6 months but not long-term PLP was predicted by pain before amputation. However, usually long-standing pain was not taken into account.

12.6.3 Catastrophizing

Pain catastrophizing is an exaggerated, negative orientation towards pain and has been found to predict chronic pain and impairment (Flor et al. 1993; Sullivan et al. 1995; Linton and Shaw 2011) as well as a negative outcome (Linton and Shaw 2011; Wertli et al. 2014). In several studies, catastrophizing has been shown to be significantly positively correlated to the magnitude of PLP in amputees (Hill 1993; Hill et al. 1995; Jensen et al. 2002; Hanley et al. 2004; Richardson et al. 2007; Vase et al. 2011, 2012). Jensen et al. (2002) and Hanley et al. (2004) showed that catastrophizing 1 month after amputation was correlated with concurrent PLP and depression. However, high catastrophizing was associated with an improvement of PLP and depression at 6 months or 2 years later. This finding seems contradictory. However, these results might be related to regression to the mean: due to the high correlation of PLP and depression with catastrophizing at the first time point, subjects with high values in catastrophizing show high values in depression and PLP as well, leaving subjects little chance to further aggravate. Hence, the lagged relationships in these two studies should not be interpreted in a way that catastrophizing predicts improvement but rather that the initial magnitude of pain needs to be taken into account as well. Richardson et al. (2007) showed that catastrophizing before the amputation predicted PLP 6 months after the amputation such that a high degree of catastrophizing was associated with more PLP. Catastrophizing has also been examined with respect to coping with disability, showing that catastrophizing predicted physical and psychosocial disability in amputees (Whyte and Carroll 2004). Vase et al. (2011) showed that catastrophizing accounted for 35 % of the variance found in PLP even after statistically controlling for depression and anxiety. Moreover, catastrophizing also correlated with wind-up-like pain, elicited by pinpricks at the residual limb. The wind-up test is a dynamic pain measure in which moderately painful stimuli of the same intensity are repetitively presented at the same site. Usually, stimuli are perceived as increasingly painful. This measure is seen as an indicator of amplification of peripheral nociceptive input. The authors assumed that both catastrophizing and wind-up interact and contribute to PLP and that, given the trait-like nature of catastrophizing and the fact that it precedes PLP, catastrophizing might lead to wind-up. In another study (Vase et al. 2012), electroencephalography was used to record

cortical responses to noxious and non-noxious stimuli presented at the affected and non-affected limb. For the affected side, there was a correlation between catastrophizing and the root mean square power of the N/P135 dipole, which was located in the area of secondary somatosensory cortex, known to play a role in attentional processes. The authors interpret this finding as an indicator that catastrophizing relates to hypervigilant attention for noxious and non-noxious stimuli.

12.6.4 Coping Strategies

Pain coping strategies describe various ways to "deal" with pain after it has been attended to and interpreted (appraised) as being a threat (Rosenstiel and Keefe 1983; Linton and Shaw 2011) and can be divided into cognitive and behavioral strategies. Examples of cognitive coping strategies are distracting attention from a sensation or reinterpreting pain (Hill 1993). Behavioral coping refers to strategies like increasing or decreasing social or physical activity or seeking social or medical support (Hill 1993; Linton and Shaw 2011). Coping with PLP was first systematically been studied by Hill (1993) who used the Coping Strategies Questionnaire in 60 male amputees with PLP. A principal component analysis in the amputee sample revealed a factor structure that was similar to the one originally discovered for chronic back pain patients (Rosenstiel and Keefe 1983). Three main components were found which the authors called "cognitive coping," "helplessness," and "pain denial." They explained about 20 % of the variance in both PLP and psychological distress. An analysis of subscales revealed that catastrophizing was by far the most powerful factor accounting for most of the variance explained by the "helplessness" factor. The authors concluded that PLP sufferers use a limited amount of coping strategies that help to alleviate distress and pain and that "successful" coping rather means not to catastrophize. In another study, Hill et al. (1995) found that catastrophizing explained 26 % of the variance in pain as opposed to other strategies that only explained 3 %. Whyte and Niven (2011b) examined 89 amputees with pain diaries assessing PLP and coping strategies. Unlike other studies, strategies were captured in a free format without standardized questions. Diary entries were made once per hour for 1 week. The participants used a limited number of strategies falling into the categories of distraction, relaxation, seeking support, exercise, manipulation of the residual limb, and drug or alcohol use. Interestingly, none of the reported strategies turned out to be effective in reducing PLP. This study confirms that PLP sufferers have few effective coping strategies.

12.7 Prediction and Prevention of PLP

Prospective studies have examined factors in the pre- or early post-amputation phase that might predict PLP. Parkes (1973) predicted PLP 13 months after amputation by a set of variables assessed in the first weeks after amputation. In

addition to pain in the residual limb or phantom and health-related predictors such as having suffered from a life-threatening physical illness before amputation, "rigidity" and "compulsive self-reliance" were significant. However, other researchers have found no association of personality types and PLP (e.g., Sherman et al. 1987). Castillo et al. (2013) examined depression, anxiety, and pain in a sample of subjects with lower limb trauma at 3, 6, 12, and 24 months after injury. In this study, not all subjects were amputees, and the study did not differentiate between PLP and other types of pain. Pain predicted depression, but depression did not predict pain. However, anxiety predicted pain, especially in the later, chronic phase. The relationship between PLP, depression, and cognitive and social factors was studied by Jensen et al. (2002). Between 1 and 6 months after amputation, the change in PLP and depressive symptoms could be predicted by catastrophizing and lack of social support and overly solicitous responses from family members. In a later study (Hanley et al. 2004), these results were replicated for a period of 1 and 2 years following amputation. Hunter et al. (2008) examined skin temperature and tactile spatial acuity of the residual limb within the first 6 months and 1–3 years following amputation. There was no clear relationship between these measures and PLP or residual limb pain. The use of a functional prosthesis was associated with vivid phantom limb awareness, but not with decreases in PLP at follow-up.

Other studies predicted PLP by variables assessed before the amputation. Richardson et al. (2007) showed that catastrophizing predicted PLP 6 months after the amputation, whereas pain before the amputation was only weakly related. Prediction of PLP by means of pain before amputation was also investigated by other researchers (Jensen et al. 1985; Nikolajsen et al. 1997) who found a relation only 6 months, but not later after the amputation. Similarly, the sensitivity to pressure pain stimuli at the residual limb before an amputation predicted PLP at 1 week, but not at 6 months after amputation (Nikolajsen et al. 2000).

12.8 Plastic Changes and the Role of Emotional and Cognitive Factors

So far, an integration of physiological and psychological factors in PLP is lacking although it can be assumed that these factors interact. We have previously summarized important peripheral and central factors involved in PLP (see Fig. 12.2). We suggest that they influence both the representation of pain in the central nervous system and specifically in cortical areas and also the peripheral input that contributes to these changes, for example, through sympathetic activation. Flor and Turk (2011) and Simons et al. (2014) have summarized additional factors such as motivation or learning and conditioning processes that are important in the understanding of chronic pain, but these have not yet been examined in PLP. For example, Diesch and Flor (2007) showed that Pavlovian fear conditioning alters the map in primary somatosensory cortex such that the conditioned stimulus that predicts pain occupies

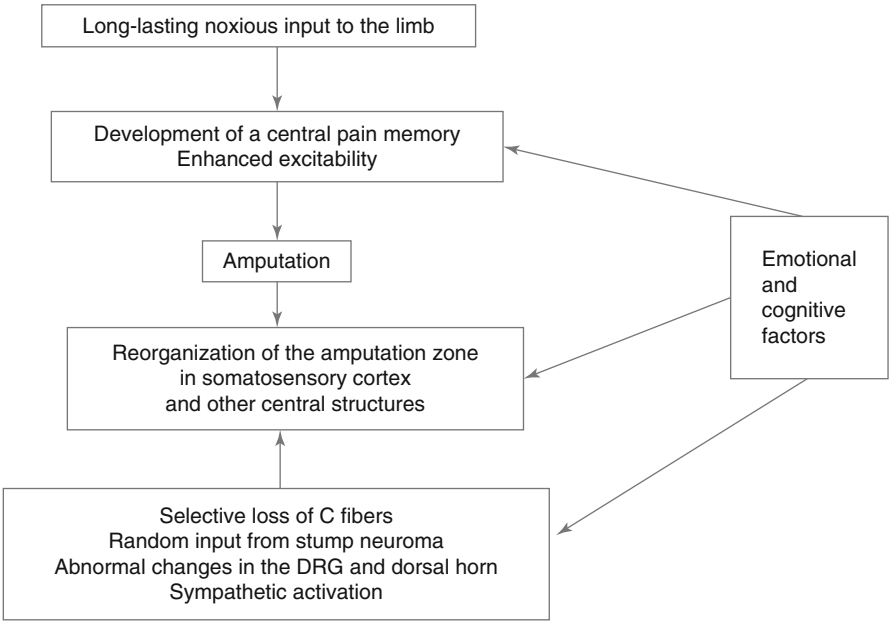

Fig. 12.2 Central and peripheral factors assumed to contribute to phantom limb pain and their interaction with emotional and cognitive factors

a larger area and shifts the activation map towards the representation of the unconditioned stimulus.

12.9 Implications for Assessment and Treatment of PLP

Although emotional and cognitive factors may play a less dominant role in PLP than in other types of chronic pain, there seem to be at least subgroups of PLP sufferers where these factors importantly contribute to pain and disability. Psychological factors also seem to contribute significantly to the development of phantom limb pain. Thus, emotional and cognitive variables must be considered in the assessment of PLP. In addition, treatments of PLP must take them into account. Thus, in addition to treatment strategies aimed at pharmacological or behavioral interventions to reduce pain, treatments should focus on affective and cognitive variables such as depression, body perception, catastrophizing, and individual coping strategies. More work is needed to determine how psychological factors interact with peripheral and central changes related to PLP and how this translates into improved treatment.

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Chapter 13
Pain in Parkinson Patients

Martina Amanzio

Abstract Pain is one of the most important non-motor symptoms in Parkinson's disease that should be taken into consideration carefully in these types of patients. Indeed, it is the most bothersome symptom ranked after slowness, tremor, and stiffness that is extremely distressful for patients. Pain often remains undetected, and it is a major cause of heath reduction related to the quality of life. Cognitive-impaired patients may have a compromised self-pain evaluation that does not allow them to objectively report their discomfort, and as result the physician is not able to select the most suitable therapy. Recent neuropsychological studies have underlined the importance of evaluating the cognitive status of the patients in order to identify those who have greater risk of cognitive impairment to facilitate intervention studies. Importantly, pain in PD is frequently under-recognized and is often undetected in about 40 % of patients.

Experimental pain studies are also an important challenge in order to analyze the functioning of pain-related areas and to understand the target of neuropathological changes in order to address individualized approaches.

13.1 Introduction

Parkinson's disease (PD), a neurodegenerative disorder which is very often associated with comorbid pain (figured as an important non-motor symptom), will be the discussed in this chapter. The prevalence of pain, the clinical categories of pain associated with PD, its clinical predictors, the processing, and pain sensitivity will be described here. However, the exact relationship between PD and pain has not been clearly established, and there is also little research in this area (Rana et al. 2013), even though pain is frequent and disabling and is significantly more common in Parkinson's patients compared to the general population. Unfortunately, only a minority of Parkinson's disease patients with pain received analgesic medication.

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Moreover, pain in PD is increasingly recognized as a major cause of reduced health related to the quality of life (Martinez-Martin 2011) and sleeping disturbances (Skogar et al. 2012; Lökk 2012). All these elements call for improved attention to assessment and treatment of pain in the follow-up of Parkinson's disease patients (Beiske et al. 2009). As far as illness duration is concerned, a survey evaluating patients' perception of their most troublesome symptoms found that pain ranked high in all stages of disease (Politis et al. 2010). Considering early and advanced stages of the disease, it is worth mentioning that pain, on the one hand, was rated as the most bothersome non-motor symptom, ranked after the three motor symptoms of slowness, tremor, and stiffness. Overall, pain was perceived as the sixth most troublesome symptom. The onset of pain in PD differs with respect to age at the beginning of the disease (Nègre-Pagès et al. 2008) and can vary in relation to motor symptoms and in a few cases precede the appearance of motor symptoms or occur after the diagnosis of PD has been made.

As far as experimental pain is concerned, research into neurophysiology provided evidence of disturbed sensory processing in patients with PD. However, future studies will be important to further analyze the mechanisms underlying pain and altered sensation in PD. In particular, even though an increased understanding of basal ganglia pathways has provided further insights into the pathogenesis of pain in PD, the exact mechanism of pain processing and modulation remains unexplained.

Finally, the early detection of cognitive decline in terms of mild cognitive impairment (MCI) should be considered as an important strategy to understand heterogeneity of clinical and experimental pain. Further studies will be important to analyze, in depth, the role of cognitive and behavioral dysfunctions on self-reported pain in patients with PD.

13.2 Clinical Categories of Pain, Prevalence, and Risk Factors

Pain in PD is frequently under-recognized and is often undetected in about 40 % of patients (Chaudhuri et al. 2010). The classification of pain for clinical proposes (Ford 2000) is often subdivided into four categories: central/ primary pain, dystonic pain, musculoskeletal pain, and radicular/neuropathic pain. Standard etiologic categories were first proposed by Goetz et al. (1986). A fifth category (akathisia) that is not experienced as pain is justified to be inserted here as it is distressful for patients with PD (Ford 2000). In particular, in the study by Ford (2000), akathisia was recorded as a fifth type of pain. It is worthy to mention that other authors do not categorize akathisia and symptoms of the restless legs syndrome as subtypes of pain but as sensory complaints (Beiske et al. 2009).

These categories should be considered in relation to the cardinal motor symptoms of tremor, rigidity, akinesia, and dystonia and to the antiparkinsonian therapy as inducing/exacerbating/relieving PD-associated pain (see Table 13.1).

In most studies on pain in PD patients, the cause of this symptom is inferred from subjective descriptions of discomfort, without an objective diagnostic assessment.

Table 13.1 Standard etiologic categories proposed by Goetz et al. (1986)

Category (Etiology)	Subjective description	Diagnostic considerations and therapy related effects
Akathisia (Under off period or drug induced)	Feeling of restlessness often accompanied by an urge to move, crawling sensations, *burning* or *tingling*	May fluctuate with medication therapy and improve with levodopa. It may occur as an off-phenomenon
Central/primary pain (Related to antiparkinsonian medication)	Feeling of *burning/tingling* pain. Characterized by bizarre, disagreeable painful sensations such as stabbing, *burning*, scalding, formication. Vague sensations of tension and discomfort	The painful sensations may have an autonomic, visceral aspect that fluctuate with the levodopa cycle
Dystonic pain (Related to antiparkinsonian medication)	Spasms	It may fluctuate with medication dosing. It can be subclassified into: off-pain period; beginning/peak/ end-of-dose dystonia. Levodopa-related dystonia may respond to manipulation of dopaminergic medication
Musculoskeletal pain (Due to parkinsonian rigidity, rheumatological disease or skeletal deformity)	Aching, cramping, arthralgic, myalgic sensations. Dull, shoulder stiffness/frozen, back pain	It may improve with medication dosing, especially levodopa and with exercise
Radicular/neuropathic pain (Due to a root lesion, focal or peripheral neuropathy)	As *tingling*	

Interestingly, the description of pain provided by patients pooled by different surveys may always overlap among different categories (see the second column of Table 13.1). In Table 13.1, it is possible to find the same description overlapping two different categories (i.e., burning, *tingling*). This aspect makes it difficult to know whether the painful complaint may be caused/aggravated/incidental to PD (Nègre-Pagès et al. 2008).

It is important to underline, despite these limitations, that the pain clinical description may be used as a framework to understand, classify, and treat painful symptoms.

A proposed classification separated PD pain (which included motor fluctuation, dyskinesia-related pain, and central pain) from non-PD pain, with some overlapping among categories (Chaudhuri and Schapira 2009). These classifications are not always easily applied because of the lack of clear objective measures and poor understanding of the mechanisms of the pain syndrome (Ha and Jankovic 2012).

Patients with PD may experience several types of pain, depending on the etiology (Table 13.1). A study on 95 outpatients found that 46 % experienced pain that they directly attributed to PD (Goetz et al. 1986). In one study that investigated 176 home-living PD patients, it was demonstrated that 53 % reported one type of pain, 24 % reported two types, and 5 % experienced three types. In particular, musculoskeletal pain was reported by 70 %, dystonic pain by 40 %

(Beiske et al. 2009), radicular–neuropathic pain by 20 %, and central neuropathic pain by 10 % (Ha and Jankovic 2012). Back pain has been reported to occur in up to 74 % of 101 PD patients, and 38 % had also suffered from radicular pain (Broetz et al. 2007). In line with these findings, another study analyzed the prevalence of pain in the PD population and underlined the most common pain types as musculoskeletal and dystonic pain (Ford 2009). Despite the high frequency of occurrence, only 38 % of PD patients with pain used medications for relief (Beiske et al. 2009).

As far as the risk factors were concerned, the studies carried out revealed some discrepancies that may be related to a number of factors that include small sample size, patient populations, and self-rating data collection. In particular, pain was associated with female gender (Beiske et al. 2009; Zambito Marsala et al. 2011), disease severity (Zambito Marsala et al. 2011), depression (Ehrt et al. 2009), and young age in some studies (Nègre-Pagès et al. 2008); on the contrary negative studies involving age, gender, disease duration, Hoehn and Yahr stage, levodopa dosage, sleep disturbance, and the presence of depression or anxiety have also been reported (Lee et al. 2006; Hanagasi et al. 2011).

Levodopa dosage is a crucial factor to be carefully considered in these types of patients. Dysregulation in dopamine signaling may modulate the experience of pain both directly, by enhancing or diminishing the propagation of nociceptive signals, and indirectly, by influencing affective and cognitive processes, which affect the expectation, experience, and interpretation of nociceptive processing (Jarcho et al. 2012). Since cognitive and affective symptoms associated with depressive and anxiety disorders affect the perception of chronic and acute pain and are associated with negative treatment outcomes, it is important to study these patients through an overall assessment of the cognitive status and to carefully evaluate motivation and also look for any psychiatric disorders (see the Movement Disorder Society Task Force guidelines Litvan et al. 2012).

These affective symptoms, along with the deficits in attention (Czernecki et al. 2002) and motivation-based processes (Chaudhuri et al. 2006), are common in patients with PD and may contribute to enhanced pain sensitivity. Finally, coping styles related to the prediction of positive or negative outcomes play an important role in severity of symptoms in chronic pain patients. For example, a coping style that assumes a high probability of worst outcomes (also referred to as catastrophizing) is highly correlated with pain symptom severity in a variety of chronic pain conditions (reviewed by Quartana et al. 2009).

13.3 Experimental Pain in Parkinson's Disease

Some studies demonstrated specific changes in psychophysical measures of pain in Parkinson's disease. A recent study by Tykocki et al. (2013) has demonstrated that pain threshold in patients with PD is significantly lower than pain threshold in non-parkinsonian patients.

Patients with central pain had lower thresholds for heat pain and laser pinprick than patients with no central pain or control subjects. These effects were attenuated with levodopa treatment (Schestatsky et al. 2007). Similarly, another study reported that L-DOPA increases the pain threshold in Parkinson's disease as assessed by the RIII nociceptive flexion reflex (Gerdelat-Mas et al. 2007). Lower activation thresholds of spinal reflexes—reflecting spinal nociception—were also detected by Mylius et al. (2009). Moreover, increased spinal nociception as well as increased sensitivity toward various experimental stimuli was diminished by dopaminergic therapy (Brefel-Courbon et al. 2005; Tinazzi et al. 2008).

PD patients also showed facilitation of temporal summation, a process where the response to repeated painful stimuli is greater than to the administration of single stimulus of the same intensity. Temporal summation is frequently increased in chronic pain and is often considered as an indicator of central sensitization. PD patients are more sensitive than controls to the administration of repeated painful stimuli, suggesting supraspinal input alteration to pain modulatory systems (Perrotta et al. 2011). Moreover, when examining experimental pain sensitivity and spinal nociception, it was demonstrated that alterations of pain sensitivity worsen during the course of the disease (Mylius et al. 2009; 2011). As the authors highlighted (Mylius et al. 2011), when summarizing experimental pain studies on PD patients, alterations in different parts of the pain pathway were reported in the literature. In particular, at central level, increased pain processing was elicited by laser-evoked potentials (Brefel-Courbon et al. 2005; Tinazzi et al. 2008). At the peripheral level, nociceptor alterations were noticed, and at the spinal level, dorsal horn layer I involvement within the pathological process was observed (Braak et al. 2007; Nolano et al. 2008).

PET data demonstrated L-DOPA-dependent activation of the right insula and prefrontal left and left anterior cingulate cortices, suggesting pain processing alterations within the medial pain pathway (Brefel-Courbon et al. 2005). It is worth mentioning that medial pain system plays a crucial role in the motivational–affective and cognitive–evaluative components, in the memory of pain and in the autonomic–neuroendocrine pain-evoked responses.

As far as deep brain stimulation was concerned, it is interesting to report the results obtained in two different groups of Parkinson's disease patients with or without neuropathic pain (Dellapina et al. 2012). The authors compared pain-induced cerebral activations during experimental nociceptive stimulations using $H_2{}^{15}O$ positron emission tomography in both deep brain stimulation off and on conditions. Correlation analyses were performed between clinical and neuroimaging results. Deep brain stimulation significantly increased subjective heat pain threshold and reduced pain-induced cerebral activity in the somatosensory cortex (BA 40) in patients with pain, whereas it had no effect in pain-free patients. There was a significant negative correlation in the deep brain stimulation OFF condition between pain threshold and pain-induced activity in the insula of patients who were pain-free but not in those who had pain. There was a significant positive correlation between deep brain stimulation-induced changes in pain threshold and in pain-induced cerebral

activations in the primary somatosensory cortex and insula of painful patients only. The authors underline that subthalamic nuclei deep brain stimulation raised pain thresholds in Parkinson's disease patients with pain and restored better functioning of the lateral discriminative pain system.

13.4 Possible Integration Through a Neurocognitive Approach

A neurocognitive approach may represent the best theoretical procedure to study pain in patients with PD. Most importantly, it highlights how pain is linked to brain pathology, particularly concerning focal lesions, motivational and emotional factors, and concomitant cognitive disturbances. Indeed, understanding pain in patients with different levels of cognitive impairment, by studying the neuropsychological and psychophysiological parameters, should represent an endeavor that has strong clinical implications. This is a very important issue to be taken into account as patients in mild to moderate stages of dementia may be unable to indicate pain perception through verbal or behavioral reports of pain. As dementia progresses to more severe stages, people lose the ability to communicate verbally, leaving them at a greater risk of experiencing untreated pain.

Importantly, a major aspect of future advances in pain research on PD patients will be to demonstrate linkages between behavior, brain, and bodily responses by combining research findings from neuropsychobiological and neuroimaging methods. Moreover, it would be extremely useful for the immediate clinical and prognostic implications to investigate pain from the very early prodromal stages of dementia. Unfortunately, up till now no study has addressed all these important issues while considering PD patients with MCI (PD-MCI).

The concept of MCI was initially suggested by Petersen et al. (1999) to detect cognitive changes in preclinical Alzheimer's disease. The construct of MCI was applied to PD patients to identify a transitional state between a normal cognitive status to the presence of mild cognitive dysfunction by Janvin et al. (2006) and Caviness et al. (2007) that is not related to normal age decline. In particular, MCI is a condition that frequently occurs in PD even in the early stages, and it is associated with demographic and clinical factors such as age and disease duration. It does not significantly interfere with functional independence. MCI predicts that patients may develop dementia (Litvan et al. 2011), and over 80 % of them are at risk of PD-D (Hely et al. 2008). Early detection of PD-MCI has implications for prognosis and treatment; it is therefore important to assess the presence of MCI in order to identify those patients at risk of developing a form of dementia associated with PD (PD-D). It is also important to emphasize that the cognitive impairment was associated with a more rapid involution phenotype and with increased severity of symptoms in numerous studies. Recently, a task force commissioned by the Movement Disorders Society (MDS) has proposed and outlined the diagnostic criteria for the

identification of MCI associated with PD (Emre et al. 2007; Litvan et al. 2012). These criteria use an operational scheme based on two assessment levels of cognitive profile. These two levels differ in the methods of evaluation and the level of diagnostic certainty and are characterized by an abbreviated assessment (level 1 criteria) or a comprehensive assessment (level 2 criteria), respectively.

It is being increasingly recognized that PD-MCI is heterogeneous (Litvan et al. 2011) and that many PD patients without dementia may show cognitive deficits not only in executive function due to dopaminergic degeneration but also in other domains including memory, visuospatial function, psychomotor speed, and attention (Marras et al. 2013; Broeders et al. 2013). The prototypical PD-MCI pattern is a predominant dysexecutive syndrome with visuospatial impairment, attentional deficits, and slowed processing speed (Taylor et al. 1986). When the pattern is atypical, it may reflect a greater burden of comorbid pathologies such as Alzheimer's disease or cerebrovascular disease. Given this heterogeneity, clinicians require specific tools to assess the pattern and severity of cognitive impairment and to follow its progression (Marras et al. 2014). In particular, since executive dysfunction has been associated with declines in instrumental activities of daily living (IADL) that do not allow a person to live independently in the community (Cahn et al. 1998), specific assessment tools should be used at this level. In this direction, the relatively few studies that have investigated the connection between functional and cognitive abilities in pre-dementia stages of PD (Sabbagh et al. 2005, 2007; Shulman et al. 2008; Kulisevsky et al. 2013) have shown that when accurately measured, a certain degree of functional impairment in IADL can also be identified in PD-MCI subjects.

An aspect that should be considered when studying pain in PD patients is the important concept that dopaminergic treatment influences cognitive performance. An exemplification of this concerns the role of dopaminergic treatment on the executive functions (EFs). The findings of a systematic review and meta-analysis on PD patients supported the view that EF impairments are evident even at the beginning of the disease (Kudlicka et al. 2011). As the exact pattern of executive impairment remains unclear and the clinical significance still has to be clarified (Kudlicka et al. 2011), the research results show that PD patients performed poorly in cognitive flexibility and, more specifically, in set switching and inhibition tasks. Only the performance of these particular tasks was impaired, but the whole spectrum of executive abilities was not compromised (Goldman et al. 2013). The results obtained by the authors (Kudlicka et al. 2011) should be explained taking into account the different effects of dopaminergic stimulation on cognitive functions at the dorsolateral prefrontal level, on one hand, and on the medial prefrontal–ventral striatal circuitry (orbitofrontal and cingulated frontal–subcortical loops), on the other hand. In particular, it was demonstrated that dopaminergic stimulation improved EFs related to the cortical–subcortical network, from the dorsolateral prefrontal cortex (DLPFC) to the dorsal caudate nucleus, which is dopamine depleted. On the contrary, the same dopaminergic treatment impairs functions connected to the medial prefrontal–ventral striatal non-depleted circuit (Cools et al. 2001), such as on tasks of attentional set-shifting and response inhibition (Dirnberger and Jahanshahi 2013;

Dujardin et al. 2001; Lewis et al. 2012; Muslimovic et al. 2005; Werheid et al. 2007; Amanzio et al. 2010, 2014). Importantly, while studying the different roles of dopamine on those different loops, motivational and reward behavior should be carefully taken into account.

Since thresholds of painful stimuli may be dopamine dependent and the integrity of dopamine terminal function can be measured with PET and SPECT, these can be correlated with executive task performance in PD patients. Moreover, the functional effects of dopamine deficiency and its replacement can be monitored by studying patterns of brain activation, as evidenced by regional blood flow changes (Brooks 2006).

Using statistical parametric mapping (SPM) to compare mean dopamine storage capacity at a voxel level between early PD cases and age-matched normal subjects reveals early motor cortex and anterior cingulate terminal dysfunction. This emphasizes that even early PD is not a pure lesion model for basal ganglia dysfunction (Brooks 2006). The author interestingly suggested that this naturally raises the question—how great an influence does frontal compared with striatal loss of dopamine have on behavioral functions in PD? One approach to answering this question is to correlate scores on behavioral tasks with regional levels of brain 18 F-DOPA uptake in PD.

Importantly studying experimental pain in PD is a matter of challenge since these kinds of patients, as already pointed out, experience a range of painful sensations some of which are related to dopamine deficiency, such as "off" dystonia and others to associated musculoskeletal and autonomic problems. Moreover, pain thresholds were significantly lower in PD patients withdrawn from medication than in healthy controls (Brefel-Courbon et al. 2005). These aspects represent the most important evidence that may explain the paucity of studies conducted so far.

13.5 Conclusion

Future work will be useful in order to develop both data from clinical and experimental pain studies and neuropathological information in patients with Parkinson's disease using a neurocognitive approach. Indeed, the provision of neuropsychological testing and neurological examination to pain assessment in dementia should also be carefully examined. In particular, both approaches might offer greater knowledge of any possible changes in an individual's experience of pain providing further information about the functioning of the pain-related brain area. As an example to be taken into account is that any memory disabilities should alert physician and health-care operators that patients may not preserve their memory of pain.

It seems reasonable to suggest that early detection of cognitive decline is an important strategy to understand heterogeneity of clinical pain in order to provide targeting therapies. Unfortunately, up till now there have not been any studies focused on these important aspects.

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Chapter 14
Clinical Pain in Schizophrenia: A Forgotten Area

Gwenda Engels and Erik Scherder

Abstract Results from several studies suggest that pain experience is diminished in people with schizophrenia. A reduced sensitivity for pain would have implications for treating people for painful conditions in clinical practice. In this chapter, a short overview of pain in schizophrenia is provided along with discussion of some theoretical suggestions concerning the neuropathology of schizophrenia in pain-processing areas. Additionally, we mention possible confounders for pain research in persons with schizophrenia.

14.1 Clinical Pain in Schizophrenia: Old Question, New Insights?

During the past two decades, the amount of literature on pain in specific patient groups has grown substantially. Several studies suggest a disturbed pain experience in neurodegenerative diseases such as Alzheimer's disease (Benedetti et al. 1999), vascular dementia (Scherder et al. 2003), multiple sclerosis, and Parkinson's disease (Scherder et al. 2005b). An example of disturbed pain experience can be found in patients with Alzheimer's disease, who appear to have an increased tolerance to pain compared to healthy subjects (Benedetti et al. 1999) although other more recent studies have failed to replicate this finding (Jensen-Dahm et al. 2014). This could be explained by reduced neural functioning of brain structures involved in pain processing, such as the anterior cingulate cortex, hippocampus, and insula (Scherder et al. 2003). Insight into possible alterations in pain experience in specific patient groups is essential for adequate pain treatment (Scherder et al. 2005a).

Nevertheless, the amount of literature in the field of pain in psychiatry remains sparse. Based on the hypothesis of altered prefrontal and medial temporal functioning in schizophrenia (Harrison 2008; Keshavan et al. 2008), a disturbed pain experience is plausible as well. Indeed, various case studies have described how persons with schizophrenia appear unaffected by severe medical conditions (e.g., appendicitis,

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abdominal surgical emergencies, fractures) and have put forward the possibility of reduced sensitivity to pain (Murakami et al. 2010; Murthy et al. 2004; Rosenthal et al. 1990). The question whether patients with schizophrenia are indeed "insensitive" to pain has been addressed in experimental studies in persons with schizophrenia. Thermal (de la Fuente-Sandoval et al. 2011; de la Fuente-Sandoval et al. 2010; Dworkin et al. 1993), electrical (Blumensohn et al. 2002; Collins and Stone 1966; Kudoh et al. 2000), cold (Atik et al. 2007), reflex (Guieu et al. 1994), and tactile stimulations (Girard et al. 2011; Karst et al. 2005) have been utilized to assess pain threshold and pain tolerance in schizophrenia. Several experimental pain studies found persons with schizophrenia to be less sensitive to pain compared to healthy controls, as measured by pain threshold or tolerance (Atik et al. 2007; Blumensohn et al. 2002; de la Fuente-Sandoval et al. 2010; Kudoh et al. 2000). A reduced reactivity to pain, instead of an "endogenous analgesia," has been proposed as a possible alternative explanation for this finding (Bonnot et al. 2009). Merely considering experimental and case studies might not fully represent pain in schizophrenia. Abilities such as a fast response and an adequate expression of pain might be impaired in people with schizophrenia, consequently biasing results (Girard et al. 2011). Pain reaction might also depend on the type of experimental manipulation. For example, in people with major depression disorder, hypoalgesia for heat and electrical pain was present compared to healthy controls, but *hyper*algesia was present for ischemic muscle pain compared to healthy controls (Bär et al. 2005).

The goal of this chapter is to explore possible alterations in the experience of pain in people with schizophrenia. Possible interactions based on theoretical considerations of the underlying neuropathology in schizophrenia will be discussed as well as examination of a few possible confounders of pain research in schizophrenia.

14.2 Pain in Schizophrenia: Evidence from Clinical Studies

A recent review of the literature regarding clinical pain in schizophrenia (Engels et al. 2014) examined clinical pain without experimental provocation. Intensity and prevalence of clinical pain appeared to be diminished in people with schizophrenia compared to control subjects in medically severe situations, such as headache after a lumbar puncture or post-surgery pain. For less severe situations, intensity and prevalence of pain appear to be similar. For a detailed description, see Engels et al. (2014). A recent meta-analysis concluded that prevalence of clinical pain was similar to controls for everyday pain (Stubbs et al. 2014).

14.3 A Theoretical Consideration of Pain in Schizophrenia

The sensory-discriminative, motivational-affective, and cognitive-evaluative aspects of pain (Melzack and Casey 1968; Scherder et al. 2003) are processed in two neural pain systems (Vogt and Sikes 2000; Willis and Westlund 1997). The lateral pain

system comprises the spinothalamic tract, which reaches to primary and secondary somatosensory areas, insula, and parietal operculum through the lateral thalamus (Scherder et al. 2003). The lateral pain system entails the sensory-discriminative aspects of pain experience (Sewards and Sewards 2002).

The medial pain system encompasses the spinothalamic tract, projecting to the medial and intralaminar thalamic nuclei, the spinoreticular tract, and the spinomesencephalic tract. These tracts reach to areas such as the amygdala, anterior cingulate cortex (ACC), hypothalamic nuclei, and hippocampus. The medial pain system mainly processes motivational-affective and cognitive-evaluative aspects of pain. A schematic view of the neural processing of pain, as well as a more detailed description of the pain systems, can be found elsewhere (Scherder et al. 2003; Willis and Westlund 1997).

A number of areas play a crucial role in pain processing, such as the prefrontal cortex (PFC), the hippocampus, and the thalamus. These areas also appear affected in schizophrenia, although the neuropathology remains elusive (Harrison 2008). Nonetheless, several neurobiological substrates show changes in schizophrenia quite consistently. The most robust findings on affected brain areas have been found on the prefrontal cortex and the medial temporal lobe (Harrison 2008; Keshavan et al. 2008) and, more specifically, the hippocampus (Harrison 2004). Activity in the dorsolateral prefrontal cortex (DLPFC) (Perlstein et al. 2001) and connectivity between the DLPFC and the hippocampal formation are thought to underlie certain cognitive deficits such as working memory impairment (Meyer-Lindenberg et al. 2005). An impaired connectivity between the prefrontal cortex, hippocampus, and thalamus has been proposed as an underlying neuropathological mechanism in schizophrenia (Lewis and Lieberman 2000), and variability in the dysconnectivity within prefrontal areas strongly correlates with cognitive deficits in schizophrenia (Cole et al. 2011). It has also been suggested that hubs (i.e., most highly connected brain regions) which are frontally located in controls are replaced by inferior temporal, insular, and anterior cingulate areas in schizophrenia (Bassett et al. 2008), emphasizing the deviant-functioning PFC in schizophrenia.

Gray matter deficits have also been found in the insular cortex (Sigmundsson et al. 2001), and a reduction in neuronal number has been found in the mediodorsal thalamic nucleus and in the anterior nuclei of the thalamus (Lewis and Lieberman 2000; Young et al. 2000). This reduced thalamic volume appears to be present already in early stages of the disorder, before any effects of medication can be detected (Gur et al. 1998). The mediodorsal nucleus forms the major projection from the thalamus to the prefrontal cortex, and the anterior nuclei additionally project to the ACC (Popken et al. 2000), an area which shows anatomical abnormalities (Fornito et al. 2009). Thalamic volume has been found to correlate with prefrontal white matter volume in persons with schizophrenia (Portas et al. 1998), indicating that prefrontal white matter is decreased as well.

With regard to the experience of pain, impairment of the mediodorsal thalamus and hippocampus, which are both part of the medial pain system, suggests an alteration of motivational-affective and cognitive-evaluative aspects of pain in schizophrenia. The ACC is part of the medial pain system and plays an

important role in attentional control (Tracey and Mantyh 2007; Willis and Westlund 1997). Since this structure exerts its inhibition by projecting to, among others, the pain suppressing periaqueductal gray (PAG) (Valet et al. 2004), a change in pain could be anticipated.

Impairment in the insula might not be confined to one single aspect, since the insula is part of both the medial and lateral pain system (Treede et al. 1999). Impairment of the (anterior) insula therefore suggests an alteration of the sensory-discriminative and the motivational-affective and cognitive-evaluative aspects of pain.

A close relation exists between the DLPFC, the midbrain-medial thalamic pathway, and the anterior insula. A strengthened flow of neural information in the DLPFC coincided with a decreased activity between midbrain and medial thalamus, as well as between midbrain and perigenual ACC, suggesting that the DLPFC inhibits the medial pain system (Lorenz et al. 2003). Consequently, impaired functioning of the DLPFC may cause an *increase* of the affective component of pain: dysfunctioning of the DLPFC might additionally result in a stronger association between insular activity and pain (Lorenz et al. 2003), resulting in an increase of pain. It must be noted, however, that an fMRI study found a significant correlation between unpleasantness and insular activity in healthy controls but not in persons with schizophrenia, where activity in primary somatosensory cortex correlated with unpleasantness (de la Fuente-Sandoval et al. 2011). The perigenual ACC is the part of the ACC associated with the affective experience of pain (Vogt and Sikes 2000). This additionally suggests that the affective aspect of pain is altered in schizophrenia.

14.4 Variables Affecting Pain in Schizophrenia

14.4.1 Medication

The use of antipsychotic medication might have a confounding influence on pain in schizophrenia (Guieu et al. 1994). The use of antipsychotics appears associated with several neurobiological changes (Keshavan et al. 2008). Consequently, neural processing of pain might be altered as a result of these medication-induced changes. Several studies have addressed this possibility. When pain in schizophrenia was assessed by an experimental paradigm, antipsychotic medication appeared not to influence pain (Jochum et al. 2006). A systematic review confirmed that hypoalgesia as measured by experimental pain studies in schizophrenia is independent of antipsychotic medication (Potvin and Marchand 2008). Pain was assessed in patients receiving depot injections of antipsychotics, where a difference in pain perception emerged depending on the type of antipsychotic (Bloch et al. 2001). A possible attenuating effect of the antipsychotics on pain experience in persons with schizophrenia cannot be ruled out.

14.4.2 Symptoms of Schizophrenia and Comorbid Psychiatric Symptoms

It has been suggested that positive symptoms, such as hallucinations and delusions, have been associated with pain in schizophrenia (Bloch et al. 2001; Hooley and Delgado 2001). Expression of these symptoms may make a person less *able* to adequately describe pain (de Almeida et al. 2010). Negative mood symptoms, for example, avolition or anhedonia, may make a person less *likely* to express their pain. Pain has been related to negative symptoms, such as affective flattening (Dworkin et al. 1993). Reduced pain expression (which might be mistaken for reduced pain sensitivity) has also been put forward as a marker of "hypofrontality" in schizophrenia (Bonnot et al. 2009; El-Mallakh et al. 2005). However, the association between clinical symptoms of schizophrenia and pain has not *consistently* been found (Girard et al. 2011).

Comorbid psychiatric complaints might also be of influence on pain experience (McWilliams et al. 2003). Depression and anxiety appeared to be associated with pain scores at five minutes after depot injection of antipsychotics (Bloch et al. 2001). This is not surprising, considering the extensive association between pain and depressive symptoms (Bair et al. 2003).

14.4.3 Age

Pain is a common complaint in the general population in persons over 60 years (Brown et al. 2010). Age is associated with an increase in pain threshold (Gibson and Farrell 2004; Lautenbacher et al. 2005), and at the same time, the endogenous pain-suppressing systems decline in strength, starting in middle-aged people (Larivière et al. 2007). Additionally, pain tolerance appears to decrease with age (Gibson and Farrell 2004). This change in pain experience, which is apparent in healthy middle-aged and elderly persons, leads one to suspect that old age in schizophrenia might place an additional burden on the pain system. An effect of age was found in psychotic patients with surgical disorders, where absence of pain was reported twice as often in the group of persons over 60, as those under 60 (Marchand et al. 1959). When pain thresholds increase, pain is no longer an early sign for underlying diseases.

14.4.4 Cognition

Cognition is affected in people with schizophrenia, and cognition has been associated with pain experience (Pickering et al. 2002). Indeed, cognitive performance depends on brain structures which are also part of the pain systems (e.g., ACC, PFC,

hippocampus, and amygdala). When pain was tested with experimental thermal manipulation, the difference in pain perception between the persons with schizophrenia and those without was attributed to an impaired information processing (Jochum et al. 2006). Cognitive inhibition, as regulated by PFC, is an important factor for inhibition of pain in healthy subjects (Oosterman et al. 2010). Neurobiological changes in prefrontal areas suggest that this additionally burdens pain perception in schizophrenia.

14.4.5 Use of Pain Questionnaires in Schizophrenia

Sensory-discriminative aspects of pain have been measured most often in schizophrenia. However, the complete experience of pain also includes motivational-affective and cognitive-evaluative aspects of pain. In one study, a difference was found between complaints of headaches and the experience of pain. This might be due to a difference between the lateral and medial pain system, whereby they might complain (medial) of headache but do not experience it (lateral). The McGill pain questionnaire is an example of a tool which investigates these aspects. When asked to describe the quality of pain, persons with schizophrenia experiencing chronic pain make use of the same descriptive terms the McGill pain questionnaire uses, which suggests that this questionnaire can be utilized in this group (Almeida et al. 2010). This also suggests that the lack of verbalizing is not a reason for refraining from expressing qualities of pain, a reason which has been mentioned before (Bonnot et al. 2009).

Persons with schizophrenia might be impaired in recognizing their own feelings of pain. A study which investigated empathy toward pain expression found that people with schizophrenia have problems recognizing pain expressions in other people (Martins et al. 2011). The extent to which people have these problems might also impair the ability to indicate their own pain, for example, when using a faces pain scale, which makes use of facial pain expressions.

14.5 Conclusions

- There is a paucity of studies on clinical pain in persons with schizophrenia, even though this population suffers more often from physical illness than the general population (Leucht et al. 2007). Moreover, diseases occur more often in persons with schizophrenia, and evidence exists that their lifetime is shortened compared to that of the general population (Leucht et al. 2007). This emphasizes the need for knowledge on pain in schizophrenia.
- Results from clinical studies suggest that the alterations in pain experience in schizophrenia depend on the severity of the medical cause, for example, myocardial infarction or lumbar puncture headache (Engels et al. 2014).

- Based on the neuropathology of schizophrenia, it is hypothesized that pain experience may increase or decrease. Further studies are needed to examine this hypothesis.
- The relationship between antipsychotic medication and pain experience needs further clarification.
- Persons with schizophrenia might have difficulties in expressing their pain, irrespective of the nature of their symptoms (i.e., mainly positive or negative symptoms).

Similar to the general population, comorbid psychiatric symptoms such as depression and anxiety may show a positive relationship with pain in people with schizophrenia.

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Chapter 15
The Pain, Emotion and Cognition Nexus in Older Persons and in Dementia

Stephen J. Gibson

Abstract With the rapid ageing of the worlds' population, it becomes increasingly important to recognise and understand the complex nexus between pain, mood and cognition in this specific age group. A particular focus should be on any age-related differences in pain prevalence and the impacts of pain on mood and cognitive functions as this will influence assessment and treatment options. Pain prevalence increases with advancing age predominantly due to the rise in degenerative musculoskeletal disorders, such as osteoarthritis. However, the atypical presentation of pain in many medical conditions (i.e. cardiac, gastrointestinal, malignancy, post-surgical pain) has also shown to increase with age. Conversely, the prevalence of psychopathology (depression, anxiety) decreases in older cohorts except when comorbid with persistent pain, where similar rates are seen across the entire adult lifespan. The lack of age differences in psychopathology in those with persistent pain might suggest that older persons are more vulnerable to the negative impact of pain on mood. The cognitive mediators of pain (beliefs, attitudes) also show some clear age differences, and older age may moderate the impacts of pain on cognitive functioning and performance. The special nexus of pain and emotion in persons with dementia has also attracted increased interest in recent years. It remains unclear whether the pain experience itself is altered by dementia, but findings do emphasise some differences in the types of behavioural and psychological impacts of pain in persons with dementia.

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15.1 Epidemiology of Pain, Mood Disturbance and Cognitive Difficulties in Older Persons

15.1.1 Prevalence of Pain Across the Adult Lifespan

There is a consistently demonstrated age-related increase in the prevalence of chronic pain at least until the age of 70, although the nature and type of pain may differ from younger adults. In particular, pain due to degenerative diseases, cancer and neuropathic conditions such as diabetic neuropathy, post-herpetic neuralgia and post-stroke are much more common (Helme and Gibson 2001; Miranda et al. 2012). Prevalence rates of chronic pain vary widely between studies (from 7 to 80 %) and depend upon a number of methodological factors. These include the time interval sampled (days, weeks, months, lifetime), the time in pain during this interval (pain always, most days, weekly or any pain during the period), how severe the pain needs to be for inclusion (mild, moderate, severe, bothersome, activity limiting) as well as the assessment technique (telephone, interview, questionnaire). Despite the differences in absolute prevalence, a consensus view across almost all studies suggests a progressive increase in pain prevalence throughout early adulthood (7–20 %) with a peak prevalence during late middle age (50–65 years; 20–80 %) followed by a plateau (65–85 years; 20–70 %) or decline in very advanced age (85+ years; 25–60 %) (Gibson and Lussier 2012; Abdulla et al. 2013 for review).

The high pain prevalence seen in older segments of the community has important implications for resourcing pain management services. Nonetheless, not all persistent pain will be bothersome or of high impact or require active treatment. The elderly with mild aches and pain often will not seek treatment and will manage pain symptoms without professional help. Perhaps it is better, therefore, to focus on pain that is considered as 'clinically relevant' or 'clinically significant'. Within this context, studies have shown that approximately 14 % of adults over 60 years suffer from moderate-severe or 'clinically significant' pain, defined as continuous, needing professional treatment and occurring on most days throughout the past 3 months (Breivik et al. 2006; Smith et al. 2001). Adults over 75 years were found to be four times more likely to suffer from a significant pain problem when compared to younger adults. On the basis of these studies, it appears that pain requiring clinical assistance also shows a major age-related increase in prevalence, albeit at much lower rates than for pain of any type.

Chronic pain is thought to be even more common in residential care facilities and nursing homes. Several studies demonstrate an exceptionally high prevalence of pain in residential aged care facilities, with as many as 58–83 % of residents suffering from some form of persistent pain complaint (Abdulla et al. 2013; Takai et al. 2010). Approximately 15 % of nursing home residents were reported to have 'clinically significant' pain of moderate or severe intensity, and 3.7 % had

excruciating pain on at least 1 day in the previous week (Teno et al. 2004). These estimates come from the minimum data set from all nursing homes in the USA, representing almost 2.2 million residents.

15.1.2 Prevalence of Mood Disturbance as a Function of Age

Depression is an important psychopathological condition that can interact with pain and cognitive functioning. In common with the trends noted for pain prevalence, the likelihood of a major depressive disorder and the level of depressive symptoms have been reported to peak in late middle age and decline thereafter (Gibson 1997; Beyer 2007). It is estimated that approx. 1–4 % of older persons living in the community (Charney et al. 2003), 5–12 % of older patients in primary care settings (Lyness et al. 2002) and up to 25 % of those in residential aged care (Smalbrugge et al. 2005) have a diagnosed major depressive disorder. When compared to the elderly, the reported rates of clinically diagnosed major depression are more than double in most studies of late middle-aged adults (45–60 years) (Mojtabai and Olfson 2004; Jorm 2000). Reasons for the age-related decrease in depression are multifactorial and include decreased emotional responsiveness, age-associated alterations in salient risk factors and possible changes in the phenomenology and measurement of depressive symptoms (Jorm 2000; Beyer 2007). For instance, depressive symptom severity may be inflated in older persons because many of the somatic-based symptoms, such as feelings of fatigue, sleep problems and memory complaints, and could be endorsed due to the increased frequency of comorbid medical problems rather than psychopathology, per se. The type of depressive symptoms endorsed by older adults has also been shown to differ, with decreased reports of anhedonia or sadness, being less likely to hold negative views about themselves and the future but more likely to contemplate death, report helplessness and endorse somatic features (Brodaty et al. 2005; Beyer 2007; Husain et al. 2005). These findings underscore the different symptomatology of depression in older age and the potential increased difficulty in diagnosing this condition.

Anxiety disorders are also reported to decrease in frequency with advancing age (Wolitzky-Taylor et al. 2010) and this is consistent with a general decrease in the reporting of negative emotional states by older persons (Gibson 1997). In representative community-dwelling samples, the prevalence of clinically diagnosed anxiety has been reported at 5.5 % for older adults, compared to 8.3 % in middle-aged populations (Flint 1994; Regier et al. 1998). As might be expected, the prevalence of psychometric measured symptoms of anxiety is considerably higher than estimates based on clinical diagnosis, occurring in approx. 15 % of healthy older adults (Mehta et al. 2003), but these rates are still 25–30 % lower than in middle-aged cohorts. The prevalence estimates jump significantly in samples with comorbid medical illnesses, most of which are more common in older adults. For instance,

anxiety symptoms in patients with cancer, cardiac issues, chronic obstructive airway disease or diabetes occur in 36–85 % of cases (Wolitzky-Taylor et al. 2010). It is, therefore, somewhat difficult to reconcile the consistently reported age-related decline in anxiety disorders with the higher burden of disease and associated anxiety. Clearly anxiety disorders are still quite common in the elderly, even in the absence of medical comorbidity, and any age-related decrease is of relatively modest proportions.

15.1.3 Prevalence of Cognitive Impairment and Dementia

Dementia can result from more than 100 different disease states, including Alzheimer's disease, vascular dementia, Lewy body dementia, frontotemporal dementia, Creutzfeldt-Jakob disease and a range of less common metabolic, infectious and neurodegenerative disorders. Dementia of any type is diagnosed in 1.5 % of adults aged 65–70 years and rates approximately double for each additional 5 years of life, affecting 22.2 % of those aged 85–89 years and 44.8 % of those aged 90–95 years (Ritchie and Kildea 1995). More than 35 million people worldwide are estimated to have dementia (WHO 2012), and this number is expected to increase exponentially with the rapid demographic shift towards an ageing population. Alzheimer's disease is the most common type of dementia, accounting for 65–75 % of cases, followed by vascular dementia (5–10 %), Lewy body dementias (7 %) and assorted others (10 %) (Small et al. 1997). Most dementias are neurodegenerative, showing progressive deterioration in cognitive, emotional and behavioural dysfunction over time and a typical life expectancy of approximately 10 years from time of first diagnosis. When considering the impacts of dementia, it is always important to recognise the stage of disease as the severity of symptoms varies widely across the time course of illness.

In recent years there has been a greater recognition of cognitive impairments seen in pre-clinical stages of dementia. Modern characterisations of Mild Cognitive Impairment (MCI) include a spectrum of impairments in both memory and non-memory cognitive domains (Roberts and Knopman 2013). Prevalence estimates range between 16 and 20 % in most studies of representative population-based samples and show a strong age-related increase in MCI from age 60 onwards. Some studies report much higher prevalence estimates and this is thought to reflect peculiarities in the specific sample, including multiethnic cohorts, clinic-based studies and large urban centres (Roberts and Knopman 2013). Several risk factors have been identified for MCI including age, sex, education, vascular and cardiovascular outcomes, diet and lifestyle factors, neuropsychiatric conditions and abnormalities in structural neuroimaging and spectroscopy (Campbell et al. 2013; Roberts and Knopman 2013). There is a demonstrated increased risk of progression to clinically diagnosed dementia in persons with MCI. Most studies report that 20–40 % of those with MCI progress to dementia (Campbell et al. 2013; Roberts and Knopman 2013). However, approximately 20 % of those with MCI will revert back to normal cognitive functioning at subsequent evaluation, suggesting a more complex relationship between these entities.

15.2 Age Differences in Pain Report, Psychological Impacts and Pain-Related Cognitive Aspects

15.2.1 Changes to Clinical Pain Report in Older Age

Uncontrolled studies of clinical pain report in older adults reveal that pain may be much less frequent and severe in a variety of somatic and visceral medical complaints, including myocardial ischemia, pneumonia, appendicitis, peptic ulcer, post-operative pain and cancer (Pickering 2005). For instance, the classic presentation of myocardial pain in the chest, left arm and jaw is much less common in older adults, with 35–42 % of adults over the age of 65 years experiencing apparently silent or painless heart attack (Hwang et al. 2009). The severity of chest pain is also less after controlling for severity of myocardial ischemia (Rittger et al. 2010). A retrospective review of more than 1,500 cases of various types of malignancy revealed a similar magnitude of age difference in the incidence of pain between younger adults and older adults (55 % vs. 26 % with pain) (Cherng et al. 1991) and a decline in reported pain severity (Caraceni and Portenoy 1999). In the post-operative recovery period, older adults have been shown to display a 10–20 % reduction in pain intensity for each additional decade of life after 60 years, even after controlling for the extent of operative tissue damage (Morrison et al. 1998; Thomas et al. 1998). The prevalence of radiographic osteoarthritis steadily increases until at least 90 years of age and undoubtedly contributes too much of the pain seen in older cohorts. However, the report of arthritic pain severity does not show the same ageing trend. After accounting for disease severity, the intensity of arthritic pain has been reported to decrease (Parker et al. 1998), increase (Chiou et al. 2009) or remain unchanged with advancing age (Gagliese and Melzack 1997). Given that the studies cited above are essentially uncontrolled clinical case reports, it is impossible to determine whether any observed decline in pain reflects actual age differences in the pain experience or differences in disease severity and/or the willingness to report pain as a symptom. Nonetheless, based on the available evidence, it does appear that advancing age is often associated with reduced severity of pain and a reduced frequency of pain as a presenting symptom, and this has important implications for clinical diagnosis and management. There are a variety of potential reasons as to why atypical pain presentations are more common in older persons, including the presence of comorbidity and altered beliefs about pain and age-related changes in physiological functions, including within the nociceptive system itself.

15.2.2 Pain-Related Mood Disturbance and Psychopathology

The comorbidity of chronic pain and depression has been well studied in the general adult population. Estimates of co-prevalence vary widely between different studies and depend on the method of assessment (clinical interview, psychometric assessment), the population studied (community, institutionalised, pain clinic samples) and the definition of depression used. For instance, depression can be used to denote

a symptom, a mood state or a psychiatric disorder. Further complicating the picture, several of symptoms of depression overlap with chronic pain (sleep disturbances, fatigue, changes in appetite), and this could potentially inflate the prevalence of depression in this population. Several studies show that up to 70 % of patients attending a pain clinic meet the cut-off score for mild depression when using psychometric assessment (Banks and Kerns 1996). Nonetheless, even when using strict clinical diagnostic criteria, between 32 and 54 % of patients with chronic pain meet the DSM-IV criteria for major depressive disorder (Banks and Kerns 1996). The occurrence of comorbid pain and depressive symptoms is known to be less common in community samples affecting between 19 and 35 % of persons with chronic pain (Miller and Cano 2009; Rosemann et al. 2007).

In terms of characterising any age differences in the relationship between mood disturbance and persistent pain, definitive research is currently lacking, although the majority of studies show no significant differences in the levels of self-reported depressive symptoms, anxiety or general mood disturbance (Gibson 2005). Most studies describe a 5–15 % reduction in the number of endorsed depressive symptoms in older adults, but this magnitude of difference fails to reach statistical significance unless the sample size is very large (Riley et al. 2000). Similarly, the rates of clinically diagnosed depression and anxiety in patients with chronic pain remain relatively constant age the adult lifespan (Gibson 2005; Wijeratne et al. 2001). The lack of ageing effect on comorbid mood disorders in persons with pain is perhaps surprising given the general literature demonstrating a decreased likelihood of depression, anxiety, anger and negative mood in older adults (see above, Gibson 1997). Given the disparate findings on ageing differences in mood disturbance between those with and without pain, one could postulate that persistent pain must have an increased negative influence on mood with advanced age in order to overwhelm the typically observed age-related reduction in self-rated mood symptoms seen in persons without pain. Further studies are required in order to clarify this apparent disparity and to identify the reasons why pain-related mood disturbance does not show the same pattern of attenuation seen in the general older population.

15.2.3 Pain-Related Cognitive Aspects

Cognitive beliefs, appraisals, attitudes and the meaning attributed to pain symptoms are known to be important mediators in shaping the experience of pain as well as the emotional and functional impacts. A growing body of evidence demonstrates that these cognitive attributes might differ as a function of age. It has been argued that older people see pain as a normal companion of older age and often misattribute pain symptoms to the normal ageing process (Gibson 2005; Molton and Terrill 2014). In a large epidemiological survey, more than 80 % of older adults agreed ‘somewhat’ or ‘strongly’ with the notion that ‘one has to expect more pain as you get older’ (Gibson 2005). The misattribution of pain symptoms to ageing instead of

disease or injury is likely to have profound implications for the response to mild aches and pain, with older persons being less threatened by pain, less distressed and less likely to seek treatment (Gibson 2005). This seems less obvious when pain is severe and older adults are just as likely to seek active medical treatment (Leventhal and Prohaska 1986). Others agree that pain is something to be expected and accepted in advanced age (Weiner and Rudy 2002; Molton and Terrill 2014), although there have also been some exceptions to this view (Gagliese and Melzack 1997) and the severity of pain may be an important consideration. It is also quite likely that older adults hold all of these different beliefs in varying degrees. They may believe that some pain is 'to be expected' in ageing but that pain is also worthy of medical treatment. This multifactorial basis of pain beliefs is supported by data from a study in which 40 % of older individuals said it was 'definitely true' that having more aches and pains was to be expected with ageing, but 94 % stated that it was also important that someone with aches and pains should always talk to a doctor about treating them (Sarkisian et al. 2002).

Clinical anecdote has long described older adults as being more stoic in their reports of pain and more recent studies using specialised questionnaires have confirmed this view (Yong et al. 2003). Pain-free community-dwelling older adults and older patients attending a multidisciplinary pain clinic report significantly higher levels of stoic reticence (no good complaining, just get on with it) when compared to younger adults and an increased reluctance to label sensations as being painful (Yong et al. 2003). Pain attitudes like stoicism are likely to lead to an underreporting of pain by older adults and a reduction in pain-related emotional disturbance (Yong 2006).

Catastrophising, an exaggerated negative appraisal of the pain experience, is known to be a maladaptive pain appraisal and is strongly related to increased depression, anxiety, disability and pain in young adult cohorts with chronic pain. Middle-aged (51–65 years) and older adults (66–85 years) with rheumatoid arthritis have been reported to use more catastrophising than younger adults when pain is mild but not if severe (Watkins et al. 1999). Other studies using pain clinic samples have failed to replicate this finding of an age difference in this negative pain appraisal (Gibson 2005). Moreover, the demonstrated relationship between higher levels of catastrophising and increased depressive symptoms appears to hold regardless of age (Wood et al. 2013). Self-efficacy, or the perceived ability to successfully take some action in order to control or reduce pain, also does not appear to change as a function of age (Gibson 2005). These findings highlight the relative stability of some cognitive appraisals and attitudes towards pain across the age spectrum and highlight the often enduring nature of the relationship between cognitive aspects of pain and the consequent emotional disabilities that may result.

The relationship between pain and cognitions appears to be bidirectional. The cognitive beliefs and attitudes discussed above emphasise their important role as mediators of pain and its impacts. However, unrelieved pain is also known to compromise cognitive functioning, and this might be of particular relevance when considering the older persons suffering from bothersome pain. A review of available

evidence on the relationship between chronic pain and cognitive functioning reveals deficits in attention, working memory, problems with mental flexibility, information processing, executive function, psychomotor speed and problem-solving abilities in both younger and older adults (Abeare et al. 2010; Weiner et al. 2006; Lee et al. 2010). Other cognitive domains such as IQ, calculation, planning ability, language and abstract thought remain relatively unaffected by the presence of pain (Hart et al. 2003; Oosterman et al. 2012). Both pain and its related psychosocial problems (depression, sleep disturbance, opioid use) may contribute to these observed deficits. The nature of these cognitive deficits has been interpreted to indicate a primary problem with attentional capacity and speed due to the fact that pain, by its very nature, competes for limited attentional resources. There have been relatively few studies to examine possible age differences in pain-related impacts on cognitive function, despite the fact that this may be one of the few potentially remedial contributors to cognitive impairment in older persons. In an early study, Brown et al. (2002) demonstrated that advancing age was independently associated with pain-related impairments in working memory, reasoning ability and information processing speed, although this finding was not replicated in a more recent study (Oosterman et al. 2011). Other studies have confirmed that cognitive performance is always worse in persons with chronic pain regardless of age (Söderfjell et al. 2006). However, Oosterman et al. (2013) recently showed that age may moderate the interaction between pain and cognitive function, with older adults showing a positive association between pain and executive functioning and no effect on memory or psychomotor speed, whereas in younger adults there was an inverse relationship between pain and all measured cognitive functions. An important implication of this work is that the often-seen negative impacts of pain on some aspects of cognitive performance may no longer be present in older adults and the direction of association is reversed such that higher self-reported levels of pain are seen in those with better executive function. Clearly, further work is needed to better characterise the exact nature of the relationship between pain and cognitive functions in older samples when compared to younger adult samples with pain. At present, there is growing evidence to show that unrelieved pain can have a strong impact on cognitive performance in both younger and older adults, particularly on aspects of attention, working memory and speed-related tasks. Advancing age may or may not moderate some of these effects. Further work is needed to resolve this issue.

15.3 The Special Case of Pain, Mood Disturbance and Cognition in People with Dementia

One area where the interaction between pain, emotion and cognition is of special relevance in older populations relates to persons with dementia. As noted earlier, age represents the most important risk factor for dementia, and the likely interplay between pain, psychological burdens and cognition is substantially more complex

in this group. There has been increased heuristic interest in this vulnerable population over recent years, and our understanding of the pain experience in persons with dementia is starting to grow.

15.3.1 Pain in Persons with Dementia

There is limited evidence to support the view that older persons with cognitive impairment or dementia have a lower prevalence of pain and make fewer spontaneous reports of pain than cognitively intact counterparts. A weak but significant negative relationship between pain report and cognitive impairment in nursing home residents has been found in early studies (Parmelee et al. 1993; Cohen-Mansfield and Marx 1993). Joint pain was reported by 45.2 % in cognitively intact adults versus 34.1 % in those with mild cognitive impairment and only 29.2 % in those with marked or severe cognitive impairment. Comparable figures for back pain were 46.0, 35.5 and 31.5 %, respectively, although pain at other sites including the neck, arms, legs, chest or gastrointestinal tract did not differ (Parmelee et al. 1993). More recent studies emphasise that the magnitude of difference is quite large. For instance, when using the minimum data set (a generalised proxy rating of pain), pain was detected in just 31.5 % of those with severe cognitive impairment, compared to 61 % of cognitively intact residents, despite both groups being equally afflicted with potentially painful disease (Proctor and Hirdes 2001). The apparent reduction in pain is not limited to mild aches and pain as the prevalence of substantial daily pain as rated by nursing staff (using the minimum data set) has also been reported at about half the rate in those with severe cognitive impairment (23.7 %) when compared to cognitively intact residents (40.4 %) (Wu et al. 2005). Subsequent work has confirmed this finding (Sawyer et al. 2007) even when using a different data set from the 2004 National Nursing Home Survey (Walid and Zaytseva 2009). The consistently lower prevalence of pain in those with cognitive impairment could suggest that pain is less of an issue in persons with dementia, but this conclusion may be premature and there are several notable limitations with the studies cited above.

Of fundamental importance is the impaired capacity for verbal communication in those with more severe cognitive impairment. This lack of verbal skills represents an obvious explanation to account for less frequently identified pain in those with dementia and physician-identified pain has been reported in 43 % of verbally communicative residents, but only 17 % of those who were verbally non-communicative (Sengstaken and King 1993). This suggests that verbal communication is still important for identifying pain even when making proxy-based ratings of pain. Some have also questioned whether the lack of staff training in non-verbal pain assessments, use of inappropriate assessment tools and the inability to identify salient pain-related behaviours is the actual reason why prevalence estimates of pain are reduced in those with dementia (Eritz and Hadjistavropoulos 2011; van Herk et al. 2009).

In support of this contention, studies examining pain prevalence using only self-report measures show a different picture. Pain assessment with a 5-point verbal

descriptor scale revealed that 35.8 % of community-dwelling cognitively impaired persons reported pain of moderate or greater intensity compared to 35.9 % of cognitively intact older adults (Shega et al. 2010a). Self-reported pain in verbally communicative nursing home residents did not differ significantly between those with intact cognition (48.7 %), mild impairment (46.5 %) or severe impairment (42.9 %) (Leong and Nuo 2007). Pain was more likely to be acute in those with cognitive impairment, and this pain was always present rather than episodic. In contrast, another population-based study of community-dwelling adults aged 75+ years revealed that 42.7 % of persons with a clinical diagnosis of dementia reported any pain in the past month compared to 68.8 % of persons without dementia (Mäntyselkä et al. 2004). Daily pain that interfered with activity was noted in 18.7 % versus 36.1 %, respectively. Finally, one population-based study even reports a 23 % *increase* in pain prevalence in those with a clinical diagnosis of dementia living in the community or residential care (Patel et al. 2013). Thus, the literature using predominately self-reported pain shows either increased, decreased or no change in pain frequency in persons with dementia. It is difficult to reconcile this literature, but the presence of cognitive impairment or dementia may have less impact on pain prevalence when examined among residents capable of self-reporting pain.

Another way to explore the issue of dementia-related changes in pain is to use non-verbal behavioural and physiological markers as an assessment methodology. Studies monitoring facial expressions of pain reveal either a significantly increased response in those with dementia (Kunz et al. 2007, 2009) or no change (Lints-Martindale et al. 2007). Facial expressions were also shown to be greater in persons with dementia immediately following a uniform painful clinical procedure, such as venipuncture, injection or movement-exacerbated pain (Porter et al. 1996; Hadjistavropoulos et al. 2000, 2008; Hsu et al. 2007). Persons with dementia have also been shown to display enhanced nociceptive flexion withdrawal reflexes (RIII) in response to experimental pain (Kunz et al. 2007, 2009; Lautenbacher et al. 2007). Facial responses and withdrawal represent a more reflexive, automatic response which may be disinhibited in persons with cognitive impairment. Irrespective of the exact reasons, the increased facial expressions and reflexes in response to pain seen in persons with dementia provides a complete contrast to the findings presented when using proxy-rated pain scales. Although these measures probably represent different aspects of the pain experience to self-report, they do challenge any argument regarding a so-called reduction in pain sensitivity in persons with dementia.

It is difficult to directly compare studies on putative dementia-related differences in pain frequency and intensity. Any person capable of self-report will not be in the most advanced stage of dementia, whereas proxy ratings can still be made in these individuals. Therefore, the findings have a major confounding between the method of pain assessment (self-report, informant proxy ratings, physiological indices) and the severity of dementia. Whether the apparent lesser prevalence of pain in persons with severe dementia reflects an actual reduction in pain or is simply due to the increased difficulty in communicating their pain to others remains unknown. Further studies are needed to address this issue.

15.3.2 Behavioural and Emotional Impacts of Persistent Pain in Those with Dementia

Cognitively intact older adults with pain typically display greater levels of mood disturbance, higher levels of disability, social isolation, poorer cognition, sleep and quality of life (Gibson and Lussier 2012). Whether similar psychological and behavioural impacts are seen in those with dementia has only just started to be investigated. It is possible that the types of pain-related impacts may differ in a dementia-specific way. For instance, the observed reduction in discretionary activities, such as social interaction, home maintenance, hobbies and recreations (Gibson and Lussier 2012), may be of less relevance in those with advanced dementia. Instead, behavioural and psychological symptoms of dementia (BPSD), such as wandering, resistance to care, agitation and aggression, depression and anxiety, may be of greater importance (Husebo et al. 2011b).

A large sample of nursing home residents in pain (78 % with cognitive impairment) was also shown to be 1.68–2.63 times more likely to have severe depression as based on psychometric assessment (Achterberg et al. 2010). A study of older adults with Alzheimer's disease (AD) revealed an increased number of depressive symptoms and a poorer quality of life in those with self-rated or proxy-rated pain, when compared to those without pain (Jensen-Dahm et al. 2012). Leong and Nuo (2007) report that the number of residents who were 'feeling depressed because of pain' was 32.4 % of cognitively intact persons and 53–55 % of those with mild or severe cognitive impairment. Another study has confirmed that those with more severe cognitive impairment have the strongest relationship between pain and depression (Kenefick 2004), and mood disturbance in those with dementia has been shown to be a very common accompaniment of persistent pain (Torvik et al. 2010). Other psychological impacts of pain in persons with dementia include increased levels of anxiety (Leong and Nuo 2007) and more frequent delusions and abnormal thought processes in those with comorbid pain (Tosato et al. 2012). These studies emphasise the importance of pain-related impacts on psychological functioning when attempting to characterise the multidimensional pain experience of persons with cognitive impairment or dementia (Gibson 2012). In aggregate, these studies consistently show that depression is a common impact of persistent pain in persons with cognitive impairment and that persons with both pain and dementia may actually increase the rates of comorbid depression in a synergistic fashion.

Self-reported disability has been found to be a very common sequela of persistent pain in those with severe cognitive impairment (60 %) when compared to cognitively intact older adults (47.4 %) (Leong and Nuo 2007). Older adults with cognitive impairment were also found to be 35 % more likely to have difficulty in performing basic daily self-care activities (eating, dressing, personal care), and this level of impact is comparable to those in pain but without cognitive impairment (Shega et al. 2010b). The levels of self-reported functional disability in instrumental activities of daily life (using telephone, cooking, shopping, travel, housework) was significantly greater in those with both pain and cognitive impairment (Shega et al.

2010b). Of interest, a path analysis of the relationship between pain and disability in persons with dementia revealed that increased depression entirely mediated this association (Cipher and Clifford 2004). Overall, it appears that the functional impacts of persistent pain commonly seen in older adults are as great, if not even greater, in persons with cognitive impairment in those that can self-report.

One potential area of impact unique to person with cognitive impairment relates to the occurrence of behavioural and psychological symptoms of dementia (BPSD). The presence of disruptive behaviours in persons with pain and dementia has long been noted (i.e. Cohen-Mansfield et al. 1990). Higher levels of agitation or aggression have consistently been shown to be associated with self-rated or proxy-rated pain (Husebo et al. 2011b; Pelletier and Landreville 2007), and this is most common in those with more severe cognitive impairment (Hodgson et al. 2014; Ahn and Horgas 2013). Pain is increasingly being recognised as an important potentially remedial causative factor for agitation and aggression (Husebo et al. 2011b), and a recent RCT of analgesics showed a significant reduction in the levels of agitation and aggression concomitant with reduced pain (Husebo et al. 2011a). With respect to other types of BPSD, pain was reported to be associated with a reduction in wandering (Ahn and Horgas 2013; Tosato et al. 2012), an increase in resistance to care (Tosato et al. 2012) and repetitive vocalisation (Cariaga et al. 1991). An overview of the current literature on the impacts of pain in persons with dementia emphasises some clear differences in the consequent behavioural and psychological impacts of pain in persons with dementia. It will be important to develop a more comprehensive understanding of these impacts and a better conceptual framework to guide future research into the likely sequela of pain in this highly dependent and vulnerable population.

15.4 Conclusion

The need to be fully informed about any age-related changes in pain and its impacts on mood and cognition is paramount, given the rapid ageing of the world's population, as this knowledge is required in order to select the most appropriate assessment and treatment approaches. Pain is very common in older adults, particularly in the joints, although there is also clear evidence for a greater proportion of atypical presentations in usually painful disease states, including a relative absence of pain symptoms. Evidence suggests that older persons are more accepting of mild aches and pains and have altered pain beliefs and attitudes, including increased stoicism. Pain itself can also have major effects on cognitive performance regardless of age, although unlike in younger adults, recent work suggests that the better executive functioning in older adults is related to greater self-reported pain. Mood disorders, such as depression and anxiety, decline in prevalence with advancing age except when comorbid with persistent pain. The differential effect in those with versus those without pain may suggest a greater impact of pain in older age. Older persons with dementia represent a special population of older adults with possible

alterations in the pain experience and with their own unique pain-related impacts on mood and behaviours. However, our current pool of knowledge in this area remains incomplete.

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