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Frontal brain functioning and pain

Possible underlying mechanisms of increased pain responses
in age- and dementia-related cognitive impairment

Steffie Bunk

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Possible underlying mechanisms of increased pain responses in
 age- and dementia-related cognitive impairment

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Contents

Chapter 1	General introduction	8
Chapter 2	Pain and executive functions: a systematic review	24
Chapter 3	Does EEG activity during painful stimulation mirror more closely the noxious stimulus intensity or the subjective pain sensation?	84
Chapter 4	Conditioned pain modulation (CPM) effects captured in facial expressions	104
Chapter 5	Pain processing in older adults and its association with prefrontal characteristics	124
Chapter 6	Pain processing in older adults with dementia-related cognitive impairment is associated with frontal neurodegeneration	152
Chapter 7	General discussion	188
	Summary	202
	Samenvatting	205
	Dankwoord	208
	Curriculum vitae	210

Chapter 1

General introduction

General introduction

The proportion of older individuals in our society is increasing.¹ One of the many implications of this demographic change is that the number of individuals with pain also increases. Pain is quite prevalent in older compared to younger individuals, with more than half of the people over the age of 60 experiencing pain.^{2,3} Pain is for example prevalent in older individuals with common chronic diseases such as cardiovascular, musculoskeletal and oncological diseases.⁴ In order to treat pain well, it is important to study why older individuals become more vulnerable to pain.

The present thesis studied the hypothesis that increased pain in older individuals might be due to decreased frontal brain functioning. We assessed frontal brain functioning by means of structural integrity of the frontal cortex and by neuropsychological performances that are linked to the function of the frontal cortex. The relation between pain and frontal functioning was not only studied in healthy older individuals but also in older individuals with dementia-related cognitive impairments, given that they might be even more vulnerable to pain due to more pronounced decreased frontal brain functioning.

The rationale behind the frontal brain functioning hypothesis will be described in this general introduction. In the first part, the topic pain will be introduced, with a focus on the neurobiological pathways that mediate pain processing and the methods used to study pain processing in humans. In the second part, the current knowledge about the effect of age- and dementia-related cognitive impairment on pain processing will be discussed. At the end of this chapter, an overview of the studies described in the upcoming chapters will be given.

Pain

Definition

The newest definition of pain, updated in 2020, according to the International Association for the Study of Pain is that pain is “an aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury.”⁵ This definition emphasizes that pain is an emotional and thus a subjective experience. Pain experience (especially acute pain) is often linked to nociceptive processes. Nociception refers to the physiological signal transduction and transmission in response to actual or potential tissue injury.⁶ The two routes for nociceptive information, called the “ascending pain pathway” and the “descending pain pathway”, will be discussed below.

Ascending pain pathway

Actual or potential tissue injury activates specialized receptors known as nociceptors

in tissue such as the skin. In response, nociceptors relay information to the dorsal horn of the spinal cord. From there, nociceptive information is transmitted via the thalamus, the major relay station of the brain, to the rest of the brain. This pathway, which transmits nociceptive information from the periphery to the brain, is known as the ascending pain pathway. Figure 1 illustrates some of the brain regions that receive nociceptive information from the thalamus. These brain regions can be divided into two networks, the lateral pain system and the medial pain system, which encode different dimensions of pain. The lateral pain system is involved in sensory-discriminative aspects, such as the location and intensity of pain, and consists of the primary and secondary somatosensory cortices. In contrast, the medial pain system is involved in motivational-affective aspects (i.e. unpleasantness of pain and the motivation to escape), cognitive-evaluative aspects (i.e. cognitive evaluation of the meaning of pain), memory for pain and autonomic responses to pain. This medial pain system includes, among other regions, the insula, anterior cingulate cortex, amygdala and prefrontal cortex.⁷⁻⁹

Figure 1. An overview of some of the brain regions and pathways involved in the processing of pain. ACC, anterior cingulate cortex; PAG, periaqueductal gray; PFC, prefrontal cortex; RVM, rostral ventromedial medulla; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; THAL, thalamus. Illustration adapted from Bushnell et al. (2013).¹⁵

Descending pain pathway

Nociceptive information is not only transmitted from the periphery to the brain, but information is also transmitted back to the spinal cord. This pathway is known as the descending pain pathway. The initiator of this descending transmission of nociceptive information is thought to be the frontal cortex. Other key areas of the descending pain pathway include the periaqueductal gray and rostral ventromedial medulla in the brain stem (Figure 1). The descending pain pathway can inhibit as well as facilitate ascending pain transmission at the level of the spinal cord and can thereby modulate pain. Modulation of pain can take place under the influence of cognitive and emotional factors such as anger, anxiety, attention and expectation.¹⁰ A clear example of pain modulation due to expectation is placebo analgesia, the phenomenon in which people experience pain relief following treatment with a placebo.¹¹ Another interesting form of pain inhibition is the concept of ‘pain inhibits pain’. It was found in rats that activity in the dorsal horn of the spinal cord in response to a noxious stimulus was inhibited when another noxious stimulus at a different location of the body was administered (this phenomenon has been called diffuse noxious inhibitory control).¹² This endogenous pain inhibition is sustained by a loop that involves spinal and brain stem structures and can function without involvement of higher cortical brain areas. In humans, similar effects have been observed. A noxious stimulus can inhibit the perceived pain of a second stimulus. This phenomenon has been named conditioned pain modulation (CPM).¹¹ Here, spinal and brain stem structures are also the critical structures, but higher cortical areas including the prefrontal cortex and the anterior cingulate cortex can have additional influences on CPM.^{13,14}

Studying pain processing in humans

Experimental pain protocols

In order to study the processing of pain in humans, one either needs participants that already have pain, for example due to a chronic pain condition, or one needs to induce pain experimentally. The most important advantage over clinical pain is that experimental pain allows to control and manipulate the duration and intensity of the noxious input, which can be related to the experience of pain.¹⁶ This makes it possible to assess static pain measures such as pain threshold (the lowest stimulus intensity that is perceived as painful), pain tolerance (the highest stimulus intensity that the participant can tolerate) and sensitivity to stimulus intensities above pain threshold. Dynamic protocols such as the CPM protocol can also be assessed. Figure 2 summarizes how endogenous pain inhibition is assessed using the CPM protocol and which pain induction methods can be used to do this. There exist a variety of different pain induction methods, such as heat, cold, mechanical pressure or electricity, which can be administered via brief stimuli (phasic stimulation) or via sustained stimulation (tonic stimulation).¹⁷ In the experimental pain studies described in this thesis, we

make use of phasic pressure stimuli and tonic heat stimulation, which both allow to induce pain in a standardized fashion.

Experimental pain responses give insight into how a person processes pain. Endogenous pain inhibitory capacity as assessed by CPM was for example found to be a predictor of pain after a surgical procedure. Patients that showed decreased pain inhibition before the surgery were more prone to develop chronic pain after the surgery.¹⁸ This suggests that increased nociceptive processing, indicated by decreased pain inhibition, is associated with a higher vulnerability to pain.

Figure 2. Pain induction methods used in the conditioned pain modulation (CPM) paradigm. During CPM, a test stimulus and a conditioning stimulus are simultaneously applied to different parts of the body to test the modulating effect of the conditioning stimulus on the pain experience of the test stimulus (pain inhibits pain).¹⁹ Test stimuli can be (1) thermal contact stimulation, (2) mechanical pressure, (3) electrical stimulation or (4) the nociceptive withdrawal reflex, which is a spinal reflex in response to stimulation of the sural nerve in the lower leg. Conditioning stimuli can be (5) thermal contact stimulation, (6) a cold water bath or (7) a hot water bath. Figure from Colloca et al. (2017).²⁰

Pain assessment

Since pain is a subjective experience, the gold standard to assess pain is to ask for a subjective pain rating. Numerous pain ratings scales exist, such as verbal and numerical rating scales.²¹ However, not every person is able to provide self-reports of pain, for example people with aphasia or a cognitive impairment.^{22–24} Effort has been made to find non-verbal indicators of pain for these people. Two types of non-verbal pain indicators that will be referred to regularly in this thesis are brain activation and facial expression.

Brain activity during pain can be measured using neuroimaging techniques such as electroencephalography (EEG), which measures voltage fluctuations at the scalp, and functional magnetic resonance imaging (MRI), which measures brain activity indirectly via changes in blood flow. Independent of the method, studies have found certain patterns of brain activation that increase during the experience of pain.²⁵

Facial expression can be assessed systematically using the Facial Action Coding System (FACS), a system that has separated all facial muscle movements into visually distinguishable Action Units (AUs).²⁶ A specific set of facial responses is consistently observed during pain in cognitively healthy individuals as well as in individuals with a cognitive impairment.²⁷ These pain-related facial responses are displayed in Figure 3. It was found that the facial expression of pain encodes both sensory and affective dimensions of pain.²⁸ Pain-related facial responses and self-report of pain increase in parallel with increasing stimulus intensity,²⁹ which suggests that facial expression is a useful indicator of pain.

Figure 3. Pain-related facial responses. Figure from Kunz et al. (2019).²⁷

Pain and cognitive decline

Age-related cognitive decline

Even when people age in good health, cognitive functions often decline over time. Memory performance, reasoning, spatial orientation and processing speed all decline during aging.³⁰ There is also a reduction in higher-level cognitive skills. This includes response inhibition, sustained attention and information updating, collectively known as executive functions.³¹ It is believed that these age-related changes in cognitive functioning are partly mediated by age-related structural changes in the brain.³²

Experimental pain studies show that pain responses in healthy older individuals differ from pain responses in healthy younger adults. A meta-analysis concluded that older individuals show decreased endogenous pain inhibition as assessed with the CPM protocol, which indicates increased nociceptive processing. It was hypothesized that this decrease in endogenous pain inhibition might make older individuals more vulnerable to pain.³³ Previous research suggests that decreased frontal brain functioning might be one of the mechanisms underlying increased nociceptive processing in older individuals. Especially decreased executive functioning as a measure of decreased frontal brain functioning was found to be associated with increased pain responses in older individuals. Executive functioning performance can be considered as an indirect measure of frontal functioning because these cognitive processes are linked to the function of the frontal cortex.^{34,35} Poorer executive functioning was found to be associated with reduced endogenous pain inhibition in healthy older individuals.^{36,37} We hypothesize that decreased pain inhibitory functioning will not only be associated with executive functioning but also with structural brain variations in the frontal cortex. As discussed above, the prefrontal cortex is thought to play a role in the processing of pain, especially in descending pain modulation.¹⁰ During aging, the structural integrity of the frontal cortex changes, as observed by gray matter atrophy³⁸ and alterations in white matter structure.³⁹ This might be associated with pain inhibitory functioning. Therefore, one of the research questions we studied in this thesis was whether structural integrity of the frontal cortex is associated with experimental pain responses in healthy older individuals.

Dementia-related cognitive impairment

One in six men and one in three women over the age of sixty-five will develop dementia.⁴⁰ Dementia is a syndrome characterized by deterioration of cognitive functions and commonly accompanied by changes in emotional control, behavior and motivation.⁴¹ Cognitive functions that are affected include memory, orientation, comprehension, language as well as executive functions.^{42,43} The symptoms of dementia can differ to some extent between the different subtypes of dementia.

The subtypes that will be discussed in this thesis are Alzheimer's disease (the most common subtype of dementia),⁴⁴ vascular dementia, frontotemporal dementia and mild cognitive impairment, a stage characterized by cognitive problems in between normal aging and dementia.

Dementia is associated with a loss of brain volume. For Alzheimer's disease and frontotemporal dementia, it is thought that this brain atrophy might be caused by abnormal intracellular and extracellular deposition of proteins.^{45,46} The exact locations in the brain where these pathological changes take place differ between dementia subtypes. For Alzheimer's disease, pathology predominantly starts in the medial temporal lobe, which include the hippocampus, a structure important for memory. As the disease progresses, brain atrophy is also observed in other brain areas, such as the parietal and frontal lobe of the brain. Similar but less severe changes are observed in mild cognitive impairment.^{47,48} A different pattern is observed in frontotemporal dementia, which is characterized by atrophy in the frontal lobe and to a lesser extent in the temporal and parietal lobe.⁴⁹ In contrast to Alzheimer's disease and frontotemporal dementia, vascular dementia is caused by reduced blood flow in the brain, for example due to a stroke. Due to the numerous types of vascular lesions that can occur, it is a highly heterogeneous disease.⁵⁰ More than other subtypes of dementia, vascular dementia is mainly characterized by changes in white matter of the brain, which are mainly observed in the frontal lobe of the brain and to a lesser extent in the parietal lobe.⁵¹ Vascular dementia often occurs together with Alzheimer's pathology, which sometimes only gets clear after autopsy.⁵² Thus, a considerable proportion of patients will likely have a combination of the pathologies described above.

Several brain regions affected by dementia overlap with brain regions involved in the processing of pain. It would therefore be expected that, depending on the exact location of the pathology, dementia-related changes in pain processing might be more severe than age-related changes in pain processing. It is important to study how people with dementia process, experience and respond to pain because they can have difficulties with reporting pain themselves. Most people with a mild stage of dementia are still able to communicate about their pain severity, but as the disease progresses, this can become difficult because dementia affects the ability to understand pain-related questions, use introspective knowledge to generate a pain rating and communicate about their pain.⁵³ This might explain why people with dementia receive significantly less pain medication than older individuals without dementia.⁵⁴ Pain in dementia might lead to behavioral and psychological symptoms, including depression, agitation and aggression.^{55,56}

Experimental pain studies that investigated how people with dementia respond to noxious stimulation mostly focused on Alzheimer's disease. When considering self-report ratings, dementia does not seem to affect pain responses in any clear

direction, with most studies reporting no significant changes.⁵⁷ In contrast, when considering non-verbal indicators of pain, the majority of studies suggest increased pain sensitivity in dementia. These studies found increased pain-related facial responses, increased pain reflexes and increased brain activity in response to experimental pain stimulation.^{58–61} So far, endogenous pain inhibition has not been studied in dementia. Based on the neuropathology of dementia and the results of studies in healthy older individuals, we hypothesize that decreased frontal brain functioning in dementia will result in a more severe decrease in endogenous pain inhibition compared to healthy older individuals, which might explain increased pain responses in dementia. We therefore studied the research question whether older individuals with a dementia-related cognitive impairment show decreased endogenous pain inhibition compared to cognitively healthy older individuals and whether this difference can be explained by dementia-related neurodegeneration in the frontal cortex.

Figure 4 summarizes how local changes in brain structure can be assessed using structural MRI scans.

Thesis aim and outline

The main aim of this thesis is to investigate whether age- and dementia-related changes in pain processing are indeed linked to frontal brain functioning. The studies investigating these questions are described in the last two empirical chapters. First, a systematic review and two methodological articles relevant for the final studies will be presented. Below, the chapters are discussed in more detail.

Chapter 2 presents a systematic review on the relation between pain and executive functioning. As outlined above, executive functioning declines during aging and dementia and has been suggested to be associated with pain responses, especially with pain inhibition. The review tries to give a comprehensive overview of the findings so far on the association between pain and executive functioning. It starts with an overview of the findings on the relation between executive functioning and chronic pain. Not only can age- and dementia-related cognitive impairment affect pain responses, the other way around some chronic pain patients also suffer from executive functioning deficits.^{65,66} We assessed the strength of this association between chronic pain and executive functioning deficits. The second part of the review gives an overview of the findings on the relation between executive functioning and experimental pain responses, with the aim to draw a conclusion about the direction of the relation between executive functioning and pain. The findings of this systematic review were reported separately for the different executive functioning domains inhibition, shifting and updating.

Figure 4. Techniques used to assess brain structure using structural MRI scans. MRI uses a magnetic field that changes the alignment of the protons in the body, which can be measured by the receiver of the scanner. For structural MRI, hydrogen protons are used because of its abundance in water and fat. Different tissue have different concentrations of hydrogen and will therefore give a different signal, which makes it possible to distinguish between gray matter (which mainly consists of cell bodies of neurons) and white matter (which mainly consists of axons of neurons, i.e. the nerve fibers).⁶² Top figure: Structural MRI scan of the brain (sagittal, coronal and axial view) used to investigate regional gray matter volume. A technique named voxel-based morphometry can be used to assess local concentrations of brain tissue voxel by voxel.⁶³ Bottom figure: A diffusion-weighted MRI scan of the brain. This is a variant of conventional magnetic resonance imaging that allows to measure the diffusivity of water molecules. Given that diffusivity of water is more restricted along an axon than perpendicular to an axon, it is possible to estimate orientation of the white matter tracts of the brain.⁶⁴ Measures of diffusivity are used to assess white matter integrity. The colors in the figure indicate the orientation (red: right-left; blue: superior-inferior; green: anterior-posterior).

Chapter 3 describes a study on the applicability of EEG as a nonverbal pain assessment tool. If EEG does indeed function as a potential indicator of pain, this could be used, for example, for people with a cognitive impairment who cannot report about pain. We therefore studied what information about pain is captured in the EEG signal. Does the signal mainly capture the intensity of the noxious stimulus or the subjective pain rating of the participant? We studied this in healthy individuals, given that we needed valid self-report ratings.

Chapter 4 describes a proof of concept study that determined whether the facial expression of pain could be used to assess pain inhibition measured using the CPM protocol. Most experimental pain studies in people with dementia only found increased pain responses when pain was assessed by nonverbal pain responses, for example using facial responses. Therefore, we first wanted to demonstrate that the facial expression of pain is sensitive enough to assess the CPM effect in healthy individuals, before we would use facial responses to assess CPM in people with dementia.

Chapter 5 describes an experimental pain study that investigated whether frontal brain functioning, defined by executive functioning and structural integrity of the frontal cortex, is associated with experimental pain responses in healthy older individuals. We assessed pressure pain sensitivity and endogenous pain inhibition as assessed using the CPM protocol. Pain was measured using self-report ratings as well as facial responses. MRI scans were used to assess gray and white matter structure of the prefrontal cortex. The aim of this study was to assess whether increased pain responses could be linked to specific executive functioning domains and structural brain variations.

Chapter 6 describes an experimental pain study that used the same protocol as described in chapter 5. Here, we also include individuals with a dementia-related cognitive impairment in order to investigate whether dementia-related neurodegeneration could explain differences in pain responses between individuals with a dementia-related cognitive impairment and healthy older individuals.

Chapter 7 provides a general discussion on the overall findings of this thesis and their implications.

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Chapter 2

Pain and executive functions: a systematic review

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Abstract

Background: A growing body of literature suggests that chronic pain patients suffer from problems in various neuropsychological domains, including executive functioning. The aim of this study was to better understand which components of executive functioning might be especially affected by pain and what mechanisms might underlie this association.

Methods: A systematic review was conducted, including both chronic pain studies (N=57) as well as experimental pain studies (N=28) that have investigated the relation between executive functioning and pain. The results were organized into the three domains of executive functioning: inhibition, shifting and updating.

Results and conclusion: Chronic pain studies show that pain is associated with poorer executive functioning. The findings of experimental pain studies suggest that this might be a bidirectional relationship: pain can disrupt executive functioning, but poorer executive functioning might also be a risk factor for higher vulnerability to pain.

Introduction

More than one-third of the people worldwide suffer from chronic pain.^{1,2} It is widely acknowledged that chronic pain does not only lead to emotional suffering, but can also have a negative impact on neuropsychological functioning.^{3,4} One domain of cognition that has been repeatedly found to be affected by pain is executive functioning.^{4,5} Executive functions are described as higher-order skills that enable an individual to regulate actions and thoughts during goal-directed behavior and can be seen as an umbrella term that encompasses a variety of quite heterogeneous cognitive processes.⁶ In an effort to break executive functions down into more homogenous components, Miyake and colleagues (2000) suggested three different components: information updating and monitoring (“Updating”), mental set shifting (“Shifting”), and inhibition of prepotent responses (“Inhibition”).⁷ Whereas updating refers to on-going task monitoring and online adjustments, shifting is the ability to switch attention between different task demands. Inhibition relates to an individual’s ability to exert control over prepotent responses, which are reflexive and automatic responses that need conscious, top-down control in order to be suppressed. Although additional executive functioning components have been postulated,⁸ these three components have been used most frequently.⁹

First evidence for a link between pain and executive functioning stems from clinical studies.^{10–12} Here, the relation between different components of executive functioning and pain is usually studied using two different study designs, namely by (i) group comparisons of executive functioning performance between pain patients and pain-free healthy controls and/or (ii) correlational approaches between executive functioning performance and self-reported pain intensity within a group of chronic pain patients. Using both designs, evidence in favor as well as evidence against a link between chronic pain and executive functions has been found. In order to draw conclusions, all empirical evidence has to be gathered in a systematic review or meta-analysis. So far, two meta-analyses by Berryman and colleagues have been conducted on this topic.^{5,13} However, these studies only focused on group comparisons between patients and controls. It was reported that people with chronic pain show a small to moderate impairment in executive functioning performance compared to pain-free individuals. The question remains whether executive functioning problems worsen with higher pain intensity.

Our systematic review serves to close this gap and include the empirical evidence on correlational analyses as well as group comparisons. Moreover, we want to gather evidence on the potential directions of this association. Is pain causing the executive functioning problems or might poor executive functioning precede the development of chronic pain and might even be a vulnerability factor for chronic pain? It is not possible to study the causal link using cross-sectional study designs in chronic pain

patients, but by experimentally induce pain (e.g. using heat or pressure), it might be possible to study the direction of the association between executive functions and pain. Therefore, we also include experimental pain studies in the current systematic review.

In experimental pain studies, pain responsiveness is often measured by asking the participants to rate the intensity of the experimental pain stimulus or by measuring when participants start to feel pain (pain threshold) or how much pain participants can tolerate (pain tolerance).¹⁴ One additional experimental pain model that is of interest in the context of executive functioning is the conditioned pain modulation paradigm, an experimental pain model to measure endogenous pain inhibition.^{15,16} The relation between these different responses to experimental pain and executive functions is mostly studied using three different designs: (i) an interference design in which participants perform an executive task twice, once with and once without painful stimulation, (ii) an interference design in which participants receive painful stimulation twice, once with and once without simultaneously performing an executive function task and/or (iii) a correlational approach in which executive functioning performance and pain responsiveness (e.g. pain threshold, pain tolerance or conditioned pain modulation) are assessed in two separate blocks. Whereas interference designs allow to draw more causational conclusions about interference effects of pain on executive functioning (or vice versa), correlational approaches help to better understand whether poor executive functioning might be linked to high pain responsiveness.

In sum, the purpose of this review is to give a comprehensive overview of the findings on the relation between executive functioning and pain by taking into consideration both chronic pain studies and experimental pain studies using various study designs. Regarding executive functions, we have attempted to organize the results into the three domains proposed by Miyake and colleagues: updating, shifting, and inhibition.⁷ Considering that pain is omnipresent in the clinical field, we hope to create a useful review not only for researchers, but also for people working in the clinic.

Methods

Search strategy

A systematic search of literature published until July 2018 has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines.¹⁷ The most appropriate electronic databases for this topic, namely PSYCINFO and MEDLINE, have been scrutinized via EBSCOhost with the following sensitive keywords relating to executive functioning: “executive function*” or “cognitive inhibition” or “prepotent inhibition” or “response inhibition” or “cognitive control” or “stroop” or “anti saccade” or “antisaccade” or “anti-saccade”

or “stop-signal task” or “stop signal task” or “set shifting” or “mental flexibility” or “attention switching” or “attention regulation” or “task switching” or “plus-minus task” or “plus minus task” or “number-letter task” or “number letter task” or “local-global task” or “local global task” or “updating” or “working memory” or “N-back” or “keep track task” or “letter memory task” or “tone monitoring task”. The above keywords were paired with the keyword “pain”. The search was further narrowed down to journal articles that were written in English and were making use of a human adult population. Access to the search log can be granted on inquiry.

Study selection

Articles were only considered to be part of this systematic review if all relevant methods and measures (i.e. executive functioning tests, measures of pain responses and/or pain induction methods) had previously been validated (e.g. tested for construct, criterion or content validity). Moreover, studies had to provide a clear description of statistics. For chronic pain studies, two types of study designs were considered relevant: (i) a group comparison of executive function performance between chronic pain patients and a healthy control group and (ii) a correlational approach that assesses the correlation between executive functioning performance and self-reported pain intensity within a group of chronic pain patients. For the experimental pain studies, three types of study designs were considered relevant: (i) an interference design in which participants perform an executive task twice, once with and once without receiving painful stimulation, (ii) an interference design in which participants receive painful stimulation twice, once with and once without simultaneously performing an executive function task and (iii) a correlational approach in which executive functioning performance and pain sensitivity are assessed in two separate blocks and are later correlated. The first interference design is conducted to investigate whether painful stimulation reduces executive function performance (pain → executive functioning), while the second interference design is conducted to investigate whether performing an executive functioning task reduces responsiveness to painful stimulation (executive functioning → pain).

Exclusion criteria

Studies that measured executive functioning solely based on subjective self-report or observer ratings were excluded. Studies were also excluded when the executive functioning task was confounded by other tasks that had to be performed simultaneously (e.g. a distraction task), with the exception of a simultaneous application of pain. If a neuropsychological test could not be assigned to one of the three domains proposed by Miyake (2000) or if test scores were compiled across different domains of executive functioning without reporting outcomes for the different domains separately, these studies were also excluded. For chronic pain studies, we only included studies where the patient group was suffering from diseases which symptoms are strongly pain-related (e.g. fibromyalgia, migraine). Whiplash

and chronic fatigue syndrome were excluded because these diseases have a weaker link to pain.

Study selection protocol

The results were exported to the citation management software Refworks (Proquest, Ann Arbor, Michigan, USA) and title-screened for eligibility by one author (LP). Following the title-screening the abstracts were independently investigated by two authors (LP, SB). In case there was disagreement, a group discussion was held (LP, SB, MK). After the selection procedure, two systematic reviews by Berryman and colleagues (2014) and Moriarty and colleagues (2011) as well as the literature summary by Buhle & Wager (2010) were searched for additional articles relevant for the present review.^{4,5,18} Figure 1 shows the selection procedure with a PRISMA flow chart.

Information extraction

From each included study we extracted the following information: type of pain (chronic pain and/or experimental pain), sample information (patients and/or healthy participants, mean age, number of participants), name of executive function test, cognitive domain reflected by the executive function test, type of study design (group comparison, correlational approach or interference design) and the outcome of the study (which executive tests showed significant associations with either chronic or experimental pain, the direction of this association and, if available, effect sizes [for group comparisons: mean values and standard deviation for the computation of the Glass' Δ effect size; for correlations: correlation coefficients]). For chronic pain studies, we also extracted mean pain intensity rating and disease duration of the patient group. For experimental pain studies, we also extracted the type of pain stimulus (e.g. heat, pressure) and the type of pain measure (e.g. intensity rating, threshold, tolerance, conditioned pain modulation, temporal summation). The information was extracted by one reviewer (LP) and independently counter-checked by a second reviewer (SB).

Risk of bias assessment

To assess the quality of the studies and the risk of bias, we graded the studies based on the following criteria (adopted from the Newcastle Ottawa criteria)¹⁹: (i) information about the gender distribution and age of the participants, (ii) a study population that represents the true population, (iii) a screening for psychiatric disorders, (iv) specification of executive function tests, (v) specification of type of pain stimulus in case of experimental pain and a diagnosis according to the accepted criteria in case of chronic pain, (vi) in case of chronic pain, control for age and education in the between-group comparison and (vii) in case of chronic pain, report of analgesic medication use. Each criterion was judged as either “successfully fulfilled” (1), “partially fulfilled (0.5) or “not fulfilled” (0). The maximum score for experimental

pain studies was 5. For chronic pain studies, the maximum score was 6 (correlational design) or 7 (group comparisons).

Figure 1. PRISMA (preferred reporting items for systematic review and meta-analysis) flow diagram.

Results

The initial literature search identified 807 studies with 15 additional studies found through manual searching of reference lists (Figure 1). After excluding duplicates and screening the remaining titles and abstracts, 98 studies remained. Seventeen articles were excluded after reviewing the full text articles (reasons for exclusion are listed in Figure 1). Altogether, 81 articles were retained for analyses, with 53 chronic pain studies, 24 experimental pain studies and 4 studies investigating both experimental and chronic pain. The average quality score, based on the risk of bias criteria, was 5.5 (out of 6 or 7, depending on the design) for the chronic pain studies and 4.4 (out of 5) for the experimental pain studies (see Table S1 and S2). Thus, we are confident that the reported outcomes are not biased by a lack of quality of the included studies.

Table 1 and 2 summarizes the number of significant findings for chronic pain and experimental pain, respectively. In Table 3 and 4, the findings of each study are presented in detail. In addition, Figure 2 displays the average effect sizes extracted from the studies. The results are discussed below separately for the chronic pain studies and the experimental pain studies and organized in terms of the three executive function domains proposed by Miyake and colleagues (2000).⁷

Chronic pain studies

Fifty-seven studies investigating the association between executive functioning and chronic pain were included in this review (see Table 3). The most commonly studied chronic pain condition was fibromyalgia, which was investigated in 21 studies. Other common studied pain conditions were migraine/headache (ten studies), rheumatoid arthritis/arthrosis (seven studies) and chronic back pain (five studies). Less commonly studied conditions include eosinophilia-myalgia, chronic pancreatitis, complex regional pain syndrome, temporomandibular disorder and chronic neuropathic/radicular pain. Sixteen studies did not investigate a specific pain condition, but studied a group of patients under the name “various chronic pain conditions”, “musculoskeletal pain” or “multiple functional somatic symptoms”.

The majority of studies (46 studies) compared executive functioning performance between chronic pain patients and pain-free individuals (group comparison design). Thirty studies correlated self-reported pain intensity of chronic pain patients with executive functioning performance (correlational approach). Three studies assessed executive functioning performance with and without an headache attack.^{23,32,49} We decided to label these three studies as group comparison designs, given that they follow a similar logic.

Inhibition - chronic pain studies

The most commonly used task to measure inhibition was the Stroop task (used in 29 studies). In total, 33.9% of all 59 tests confirmed that there is a significant

association between inhibition and chronic pain (Table 1). Most of these tests were group comparisons, of which 41.5% showed that the ability to inhibit is significantly reduced in chronic pain patients compared to pain-free individuals. In line with this, the computation of effect sizes for the group comparisons revealed medium effects. Interestingly, this reduced ability to inhibit (on a group-level) does not seem to be closely linked to the intensity of the chronic pain (correlational approach), given that only a small percentage of tests, 16.7%, showed that a high pain intensity is significantly correlated with reduced inhibition performance. These meager results were also reflected in a very small averaged effect size (correlation coefficients, see Figure 2).

Figure 2. Average effect sizes for the association between pain (chronic and experimental pain) and executive functioning (inhibition, shifting and updating).

The Glass' Δ effect size was computed for group comparisons (chronic pain patients vs. controls). The correlation coefficient indicates the strength of association between executive functioning performance and pain (intensity in chronic pain or responsiveness to experimental pain, respectively). The number of tests included in the calculation are shown in the figure because effect sizes were not available for every study. The effect sizes of the experimental pain studies using interference designs could not be calculated, given the lack of descriptive data reported in the original studies. The interpretation of the strength of the effect sizes is based on Cohen (1988)¹¹⁴ and Mukaka et al. (2012)¹¹⁵.

Table 1. Percentage of tests that show a significant association between chronic pain and executive functioning.

	Correlational approach Chronic pain is negatively correlated with executive functioning performance
Inhibition	16,7% (3 out of 18 tests)
Updating	19,4% (6 out of 31 tests)
Shifting	21,7% (5 out of 23 tests)
Total	19,4% (14 out of 72 tests)

Table 2. Percentage of tests that show a significant association between experimental pain responses and executive functioning.

	Correlational approach Executive functioning performance is negatively correlated with pain responsiveness.	Interference design Executive task demand reduces pain responsiveness (executive functioning → pain).
Inhibition	33,3% (16 out of 48 tests)	50,0% (3 out of 6 tests)
Updating	4,44% (2 out of 45 tests)	100% (3 out of 3 tests)
Shifting	15,4% (2 out of 13 tests)	-
Total	19,6% (21 out of 107 tests)	66,7% (6 out of 9 tests)

Updating - chronic pain studies

The most commonly used task to measure information updating and monitoring was the digit span backwards task (used in 15 studies). Other commonly reported tasks were verbal fluency tasks, the Operation Span Task and the Paced Auditory Serial Addition Test (see Table 3). In total, 28.2% of all 85 tests confirmed that there is a significant association between updating and pain (Table 1). Again, stronger findings were found for group comparisons. A third of these studies showed that updating performance is significantly reduced in chronic pain patients compared to pain-free individuals. In line with this, the effect size for group differences between patients and controls was medium to large. When looking at the correlations between pain intensity and updating performance, only 19.4% of the tests demonstrated that higher pain intensity in patients is significantly correlated with reduced updating performance. Only one study (3.2% of all tests that used a correlational approach) reported a significant correlation in the opposite direction, namely within a group of Alzheimer patients with arthrosis or arthritis.⁶¹ The averaged correlation coefficients point to very small effects (see Figure 2).

Shifting - chronic pain studies

The Trail Making Test B was used most often to assess shifting performance (used in 23 studies). The Wisconsin Card Sorting task was also frequently used (see Table 3). In total, 28.3% of all 60 tests confirmed that there is a significant association between pain and shifting performance (Table 1). Similar to updating, almost a third of the group comparisons showed that shifting ability is significantly reduced in chronic pain patients, which is also reflected in moderate to large effect sizes (see Figure 2). A smaller proportion, 21.7%, found that reduced shifting performance is significantly correlated to a higher pain intensity in patients. One study (4.3% of all tests that used a correlational approach) found that higher pain intensity was correlated with better shifting performance, in a group of elderly with various chronic pain conditions.⁵⁶ On average, correlation coefficients point to a very small association between pain intensity and shifting performance (see Figure 2).

Summary - chronic pain studies

There is medium to strong evidence that executive functioning performance is reduced in chronic pain patients compared to pain-free controls, with all three domains of executive functioning being similarly affected. In contrast, the evidence for a significant correlation between the intensity of chronic pain and executive functioning performance is much weaker.

Experimental pain studies

Twenty-eight studies investigated the association between executive functioning and experimental pain responses (see Table 4). The most commonly used methods of inducing pain were thermal heat pain and pressure pain, both used in eight studies.

Other methods were the cold pressor test, electrical stimulation and infrared laser stimulation.

Thirteen studies investigated whether responsiveness to painful stimulation is correlated with executive functioning performance (correlational approach). Twelve studies investigated whether painful stimulation reduces executive functioning performance (pain → executive functioning), by letting the participants perform an executive task twice, once while receiving painful stimulation and once without receiving painful stimulation (6 studies) or with non-painful stimulation (6 studies). In seven studies participants received painful stimulation twice, once while performing an executive function task and once while performing a neutral task, to investigate whether executive task demand reduces responsiveness to painful stimulation (executive functioning → pain).

Inhibition - experimental pain studies

Similar to the chronic pain studies, the most commonly used task to measure inhibition was the Stroop task (used in 15 studies). In total, one third of the 57 tests confirmed that there is a significant association between inhibition and responsiveness to painful stimulation (Table 2). Most of these tests used a correlational approach (48 tests), of which again one third showed that a reduced ability to inhibit is significantly correlated with a higher responsiveness to experimental pain (e.g. a higher pain intensity rating, a lower pain threshold or a lower pain tolerance). The effect size for this correlation was however only small (Figure 2). Three out of six studies showed that pain responsiveness was significantly reduced when performing an inhibition task (executive functioning → pain). None of the studies (3 out of 3) found evidence for a significant reduction in inhibition performance when simultaneously receiving painful stimulation (pain → executive functioning). For the interference design no effect sizes could be computed given the lack of reported data in the respective studies.

Updating - experimental pain studies

Several tests were frequently used to measure updating, including the N-back task, Digit Span backward and the OSPAN task (see Table 4). In total, 17.5% of all 57 tests confirmed that there is a significant association between updating and responsiveness to experimental pain (Table 2). Most of these tests used a correlational approach. However, only 4.4% of these correlational tests showed that higher responsiveness to painful stimulation is significantly correlated with reduced updating performance (2 out of 46 tests). The effect size for this correlation was negligible (Figure 2). In contrast, all interference studies conducted to investigate whether pain responsiveness changes when simultaneously performing an updating task (executive functioning → pain), showed that pain responsiveness is significantly reduced in this situation (3 out of 3 tests). Similarly, 4 out of 8 interference studies demonstrated that updating performance is significantly reduced when simultaneously receiving painful stimulation (pain →

executive functioning). Again, effect sizes for the interference designs could not be computed.

Shifting - experimental pain studies

Shifting was assessed using a variety of different tasks (e.g. Trail Making Task B, attentional switching task, Plus-minus) (see Table 4). In total, 4 of the 16 tests confirmed that there is a significant association between shifting and responsiveness to painful stimulation (Table 2). Only 15.4% of the tests that used a correlational approach could show that higher responsiveness to experimental pain is significantly correlated with reduced shifting performance (2 out of 13 tests). The effect size was also negligible (Figure 2). Two out of three tests showed that painful stimulation significantly reduces shifting performance in an interference design (pain → executive functioning). No study investigated whether performing a shifting task reduces responsiveness to painful stimulation (executive functioning → pain). Effect sizes for the interference designs could not be computed.

Pain inhibition – experimental pain studies

In the context of this review, there is one type of pain responsiveness that might be especially interesting, namely the ability to inhibit pain. It is possible that the ability to inhibit pain might be closely linked to a general ability to inhibit cognitive and behavioral responses (as assessed with neuropsychological tests). The ability to inhibit pain is most often measured using the conditioned pain modulation (CPM) paradigm. CPM refers to the process whereby one painful stimulus inhibits the perception of a second painful stimulus. Our results show that this endogenous pain inhibition seems to be especially associated with cognitive inhibitory functioning. In total, 45% of all tests performed showed that poor pain inhibition is significantly correlated with poor cognitive inhibition (5 out of 11 tests), with an average correlation coefficient of 0.36 (small effect size). In comparison, the correlation between pain inhibition and updating performance was less strong, only 10% of the tests performed showed significant associations. The correlation between shifting performance and pain inhibition has not been investigated.

Summary - experimental pain studies

The findings of studies using experimental pain stimulation partly confirm the findings of chronic pain studies. The results of studies using an interference design indicate that there is moderate evidence that painful stimulation reduces executive functioning performance and that responsiveness to experimental pain is reduced when performing an executive task. The results of studies using a correlational approach show that responsiveness to experimental pain can be negatively correlated with executive functioning performance, although evidence for this is very weak. Inhibition shows the strongest association with pain compared to updating and shifting, especially when looking at one specific type of pain responsiveness, namely the ability to inhibit pain.

Discussion

Executive functioning and chronic pain

With regard to the chronic pain studies, this review shows that there is ample evidence for a reduction in executive functioning in chronic pain, despite the heterogeneous patient groups being investigated and despite the various tests used to assess executive functioning. On average, one third of all group-comparisons being performed showed that executive functioning is significantly reduced in chronic pain patients, with medium to large effect sizes. No study reported an increase in executive functions in chronic pain patients compared to pain-free individuals, which corroborates the notion that the demonstrated decline in executive functioning is not simply a false positive finding. Our findings are in line with previous reviews,^{4,5,13} which also found small to moderate impairments in inhibition, updating and shifting ability in chronic pain patients.

In contrast to previous reviews/meta-analyses, we not only looked for differences between chronic pain patients and pain-free controls, but we also included studies investigating whether executive functioning performance is correlated with the severity of chronic pain. We found that executive functioning was negatively correlated with self-reported pain intensity across several studies, with stronger pain being associated with worse executive functioning. However, the evidence for this negative correlation is much weaker (average correlation coefficients were negligible) than the evidence for the reduction in executive functions in patients compared to controls. Nevertheless, almost all studies that found evidence for a significant correlation between pain intensity and executive functioning, report a negative correlation. Only two studies (2.8% of all tests) report a positive correlation, with one of these studies being conducted in patients suffering from dementia-related cognitive impairment.⁶¹ Given that the ability to validly report pain declines across the course of dementia,⁹⁵ the positive correlation between executive functioning and reported pain intensity could be due to the more severely impaired patients not being able to give a self-report of pain.

Together, the findings of chronic pain studies suggest that patients often have impairments in executive functions (moderate effect size), however, these impairments do not increase linearly when pain intensity increases.

Possible mechanisms mediating executive functioning impairment in chronic pain patients

One hypothesis that may explain the executive functioning problems occurring in chronic pain patients is the theory of limited cognitive resources.⁹⁶ It states that the processing of pain demands attention, similar to the fact that performing an executive task demands attention. Because of the attention demanded by pain, there are less

attentional resources available to perform executive functions.⁹⁷

Another possibility, but not excluding the theory of limited resources, is that chronic pain affects executive functioning via functional and anatomical changes in the brain that are caused by the chronic pain condition.⁴ Chronic pain has been found to be associated with several structural changes in the brain, with grey matter decline in the anterior cingulate cortex, insular cortex, orbitofrontal cortex and dorsolateral prefrontal cortex.⁹⁸ Two chronic pain studies included in this review demonstrated that these structural brain changes correlate with executive functioning performance. Gray matter volumes in the medial frontal cortex and the left middle frontal gyrus were positively correlated with updating performance in fibromyalgia patients.⁴³ Similarly, cortical thickness of the right dorsolateral prefrontal cortex was positively correlated with inhibition performance in patients with complex regional pain syndrome.⁴¹

These above mentioned theories act on the strong assumption that pain is the causal factor leading to a decline in executive functioning, either via limiting the cognitive recourses and/or via causing structural changes of the brain. These are, however, only assumptions given that cross-sectional chronic pain studies do not allow to investigate the causal direction between executive functions and pain. However, by manipulating pain using experimental pain stimuli, it might be possible to better determine the direction of the association between executive functions and pain. The findings of these experimental pain studies are discussed in the next section.

Executive functions and experimental pain, what disrupts what?

Interference design

In an experimental setting, it is possible to investigate the effect of simultaneously receiving painful stimulation while performing an executive functioning task. This condition is compared with a control condition in which participants only perform an executive functioning task and/or only receive painful stimulation. The results of the interference design studies included in this review suggest that pain does indeed interfere with executive functioning and vice versa. By letting the participants perform an executive task twice, once while receiving painful stimulation and once without receiving painful stimulation, roughly 40% of the studies could demonstrate that painful stimulation reduces executive functioning performance (especially for the domains “updating” and “shifting”). This is proving the causal direction of pain leading to a decline in executive functioning which is assumed by the studies on chronic pain. At the same time, the findings of the inference design studies also show that performing an executive task can reduce pain responsiveness. This is however not exclusively the case for executive tasks. Distraction in general reduces pain and therefore other cognitive tasks besides executive function tasks can also reduce pain responsiveness.^{99,100} Interestingly, pain-related brain activation also reduces

significantly when participants simultaneously perform an executive functioning task while receiving painful stimulation.^{73,76,90,91,93} Thus, in clinical practice, chronic patients should be encouraged to engage in cognitive stimulating and entertaining tasks or activities, since these have the capacity to distract from the pain.

Correlational design

In recent years, the association between executive functioning and pain has been suggested to be even more complex, because it has been suggested that worse executive functioning might be associated with a higher sensitivity to pain and a worse ability to cope with pain; and therefore be a risk factor for higher vulnerability to develop chronic pain. Evidence that worse executive functioning might be a risk factor for a higher pain sensitivity came from a recent longitudinal study investigating whether executive functioning performance before the start of a surgery can predict to what extent people will suffer from pain after the surgery.¹⁰¹ The study showed that poorer executive functioning performance can predict pain intensity up to a year after the surgery. Evidence supporting this assumption of a link between pain sensitivity and executive functioning stems from correlational analyses, usually conducted in pain-free individuals. This review shows that executive functioning can correlate negatively with responsiveness to experimental pain. However, the association is only weak, given very small effect sizes and the low number of studies that found a significant correlation (20%), but all significant findings were in the same direction of a negative correlation. Interestingly, the association becomes much stronger in those studies using a specific type of pain response, namely the pain inhibitory response (conditioned pain modulation) and correlating it with cognitive inhibition (e.g. Stroop task). Here, 45% of the correlations performed show that poor pain inhibition is correlated with poor cognitive inhibition. Thus, it might not be pain responsiveness in general that is linked to executive functioning, but certain aspects of the pain response system (e.g. the ability to inhibit pain).

Together, the different study designs used by experimental pain studies suggest that pain does not only disrupt executive functioning, but there might also be a shared underlying mechanism (see following paragraph) with poorer executive functioning being a risk factor for higher vulnerability to pain.

The frontal cortex as underlying mechanism

One candidate for the idea of a shared underlying mechanism might be the frontal cortex. As discussed above, chronic pain patients can have structural brain changes in the frontal cortex that correlate with executive functioning performance.^{41,43} The role of the frontal cortex in pain is supported by findings of animal studies showing that pain can lead to changes in neuronal morphology and a decrease in neuronal activation in the frontal cortex.^{102,103} Surely, the frontal cortex is a broad area that can be divided into multiple sub regions. With regard to the link between executive

functions and pain, there might be two regions that are of particular interest. These are the orbitofrontal cortex and the dorsolateral prefrontal cortex.

The orbitofrontal cortex is suggested to play a substantial role in the ability to inhibit pain. This notion is based on observations of increased activation of the orbitofrontal cortex during different pain inhibition tasks.^{73,93,104} Besides being involved in pain inhibition, the orbitofrontal cortex is also involved in executive functioning, especially in inhibitory functioning.¹⁰⁵ Thus, our finding of a significant positive correlation between cognitive inhibition and pain inhibition could be moderated by the orbitofrontal cortex.

The dorsolateral prefrontal cortex is involved in the ability to cope with pain.^{106–108} Pain coping skills are important because maladaptive coping can increase pain intensity and can be a risk factor for the development of chronic pain.¹⁰⁹ Beyond being involved in pain coping, the dorsolateral prefrontal cortex is also involved in various domains of executive functioning.⁹ Thus, dorsolateral prefrontal functioning can affect both the ability to cope with pain as well as executive performances.

In summary, poor functionality of the frontal cortex can result in poor executive performances as well as in high responsiveness to pain, possibly due to (i) limited pain inhibition as a consequence of reduced orbitofrontal functioning and/or (ii) due to limited pain coping skills as a consequence of reduced dorsolateral prefrontal functioning. A clinical implication of this assumption is that chronic pain patients might benefit from strengthening frontal capacities, for example by executive functioning training, to strengthen the system's ability to better inhibit pain as well as better cope with pain. It has to be tested in future research whether this would make individuals less vulnerable to pain.

The role of depression

Given that depressive symptoms are prevalent in chronic pain and have been shown to be associated with executive functioning deficits,¹¹⁰ it is possible that the link between pain and executive functioning might also be moderated by depressive symptoms. Being aware that depression is associated both with pain as well as with deficits in executive functioning, most chronic pain studies included in this review assessed the level of depressive symptoms (approximately 65%). When testing whether depressive symptoms might explain the relation between chronic pain and executive functioning, three studies found confirming evidence.^{31,36,67} However, even more studies failed to show that depressive symptoms can explain the executive functioning deficits in chronic pain patients.^{10–12,16,20,21,29,33,35,38,42,43,47,52,57,71} Therefore, depressive symptoms seems to play only a minor role in the association between chronic pain and executive functioning.

Limitations

An important limitation of this systematic review is the heterogeneous patient group that was being investigated. We decided to include many different pain conditions, in order to give a comprehensive overview of the findings on the relation between executive functioning and pain. When compiling the outcomes, we did not differentiate between different types of pain, although different types of pain can be expected to have a different impact on executive functions. However, the limited number of studies and the diversity of executive functioning tests being used did not allow for a more differentiated approach. Nevertheless a distinction between different pain types seems reasonable. An interesting example for the need for differentiation between different types of pain is the concept of cogniphobia. Patients with frequent (post-traumatic) headaches and with mild traumatic brain injury have been found to avoid cognitive tasks because of fear of developing or increasing pain.^{111,112} Thus, in a testing situation it should be taken into account that cogniphobia might exist in certain types of pain, which can decrease cognitive performance.

Another limitation is that many studies did not report in detail about the analgesic medication use in the chronic pain patient group, which was revealed by the risk of bias assessment. This would have been important, however, because opioid use can have an effect on cognition, including executive functions.¹¹³

Conclusion

In conclusion, this review shows that there is moderate to strong evidence that executive functions are decreased in chronic pain patients and that these executive dysfunctions do not linearly increase with the pain intensity. The findings of experimental pain studies suggest that there might be a bidirectional relation between pain and executive functioning: pain does not only disrupt executive functioning, but poorer executive functioning may be a (small) risk factor for higher vulnerability to pain. Changes in the frontal cortex of the brain, especially in orbitofrontal and dorsolateral regions, might moderate this association.

Table 3. Summary of papers investigating the association between chronic pain and executive functioning.

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Rheumatoid arthritis patients, 54 years, N=157	Self-report (0-100 VAS): 36.4	11.5 years	Stroop, Letter Number Sequencing	Inhibition, updating
Rheumatoid arthritis patients, 37.3 years, N=28; pain-free individuals, 33.7 years, N=30		7.3 years	Stroop	Inhibition
Fibromyalgia patients, 36.2 years, N=40; same control group	Self-report (0-10 VAS): 8	3.1 years		
Chronic back pain patients, 21-71 years, N=6; pain-free individuals, 25-64 years, N=10		8.6 years	Stroop, Digit Span Backward, WCST	Inhibition, updating, shifting
Eosinophilia-myalgia patients, 46.7 years, N=23; pain-free individuals, 47.6 years, N=18			PASAT, WCST	Updating, shifting
Frequent headache patients, 30.4 years, N=59	Self-report (0-100 VAS): 52.8 during headache		Flanker test, N-back, Cued Task Switching	Inhibition, Updating, shifting
Patients with chronic low back pain, 74.5 years, N=8; pain-free individuals, 69.9 years, N=8	MPQ-SF: 30.75	>3 months	Digit Span Backward, Letter Number Sequencing, TMT (B)	Updating, shifting
Fibromyalgia patients, 63.0 years, N=43; pain-free individuals, 64.8 years, N=44	Self-report: 6.3 (0-10 VAS)		Stroop, Digit Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting

Study design	Significance of findings and effect sizes	Reference
Correlation	Stroop/Letter Number Sequencing & pain intensity: $p < 0.05$ ($\Delta = 0.17/0.24$)	Abeare et al. (2010) ²⁰
Group comparison	Stroop performance patients < controls: $p < 0.05$	Akdoğan et al. (2013) ²¹
Group comparison, correlation	Stroop performance patients < controls: $p < 0.05$ Stroop & pain intensity: ns	
Group comparison	Stroop/Digit Span Backward/WCST performance patients < controls: ns ($\Delta = 1/0.5/-0.3$)	Apkarian et al. (2004) ²²
Group comparison, correlation	PASAT/WCST performance patients < controls: $p < 0.05$ ($\Delta = 1.57$) WCST/PASAT & pain intensity: ns	Armstrong et al. (1997) ¹⁰
Group comparison	Cued Task Switching performance during headache < during no headache: $p < 0.05$ ($\Delta = 0.4$) Flanker/N-back task performance during headache < during no headache: ns (only women: $p < 0.05$)	Attridge et al. (2017) ²³
Group comparison	Digit Span Backward/Letter Number Sequencing/TMT (B) performance patients < controls: ns ($\Delta = 1/0.5/0.91$)	Buckalew et al. (2008) ²⁴
Group comparison	Stroop performance patients < controls: $p < 0.05$ ($\Delta = 0.51$) Digit Span Backward/Verbal Fluency task TMT (B) performance patients < controls: ns ($\Delta = 0.45/-0.23/0.13$)	Cherry et al. (2012) ²⁵

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Fibromyalgia patients, 44.5 years, N=21; Pain-free individuals, 38.0 years, N=22		96.3 months	Stroop, OSPAN	Inhibition, updating
Fibromyalgia patients, 48.0 years, N=18; pain-free individuals, 42.0 years, N=19	MPQ: 7.61	4 years	Go-/No-go task	Inhibition
Fibromyalgia patients, 41.29 years, N=40; Pain-free individuals, 40.72 years, N=41	FIQ: 7 (0-10 NRS)	6.47 years	Tower of London, Digit-Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting
Fibromyalgia patients, 48.0 years, N=20; Pain-free individuals, 60.0 years, N=20	Self-report: 4.6 (0-10 VAS)	11.0 years	Test of Everyday Attention: updating and shifting	Updating, shifting
Rheumatoid arthritis patients, 62.9 years, N=20; same control group	Self-report: 4.5 (0-10 VAS)	18.9 years	Test of Everyday Attention: updating and shifting	Updating, shifting
Musculoskeletal disorder patients, 52.3 years, N=20; same control group	Self-report: 4.7 (0-10 VAS)	10.2 years		
Patients with migraine and obesity, 38.3 years, N=124	Self-report: 5.9 (0-10)		Stroop	Inhibition
Patients with various chronic pain conditions, 51.9 years, N=1399			Stroop	Inhibition
Migraine patients, 38.0 years, N=24	Self-report: 5.7 (0-10 VAS) during migraine attack	19.30 years	Stroop, Digit Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting

Study design	Significance of findings and effect sizes	Reference
Group comparison	Stroop/OSPAN performance patients < controls: $p < 0.05$	Coppieters et al. (2015) ²⁶
Group comparison	Go-/No-go task performance patients < controls: $p < 0.05$ ($\Delta = 0.29$)	Correa et al. (2011) ²⁷
Group comparison	Tower of London/Digit-Span Backward/Verbal Fluency task/TMT (B) performance patients < controls: $p < 0.05$ ($\Delta = 0.56/0.88/0.80/n/a$)	Di Tella et al. (2015) ²⁸
Group comparison, correlation	Updating performance patients < controls: $p < 0.05$ ($\Delta = 0.98$)	Dick et al. (2002) ²⁹
	Shifting performance patients < controls: ns ($\Delta = 0.10$)	
	Updating/shifting & pain intensity: ns	
	Updating performance patients < controls: $p < 0.05$ ($\Delta = 1.64$)	
	Shifting performance patients < controls: ns ($\Delta = 0.68$)	Dick et al. (2002) ²⁹
	Updating/shifting & pain intensity: ns	
	Updating/shifting performance patients < controls: ns ($\Delta = 0.84/0.61$)	
	Updating/shifting & pain intensity: ns	
Correlation	Stroop/Flanker test performance & pain intensity: ns (interictal assessment)	Galioto et al. (2018) ³⁰
Correlation	Stroop performance & pain intensity: $p < 0.05$ ($\Delta = 0.12$)	Gijssen et al. (2011) ³¹
Group comparison	Stroop/Digit Span Backward/Verbal Fluency task/TMT (B) performance during attack < during no headache: ns ($\Delta = 0.19/0.35/0.35/0.11$)	Gil-Gouveia et al. (2015) ³²

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Fibromyalgia patients, 43.6 years, N=18; pain-free individuals, 41.1 years, N=14	PED: 55.4 (0-100)		Go-/No-Go Task	Inhibition
Fibromyalgia patients, 48.9 years, N=32; pain-free individuals, 48.4 years, N=30	Self-report: 6.5 (0-10 VAS)		N-back	Updating
Fibromyalgia patients, 45.9 years, N=29 (+7 for correlation analysis); pain-free individuals, 44.7 years, N=29	Self-report: 4.2 (0-10 VAS)		PASAT	Updating
Patients with various chronic pain conditions, 45.0 years, N=33; pain-free individuals, 45.0 years, N=20	High-pain patients: 73.0 (0-100 VAS)	>1 year	Modified Stroop: inhibition and shifting	Inhibition, shifting
Multiple functional somatic symptoms patients, 36.6 years, N=22; pain-free individuals, 35.6 years, N=27	Self-report: 2.63 (0-10 VAS)	10.5 years	Digit Span Backward, COWAT, TMT (B)	Updating, shifting
Fibromyalgia with comorbid chronic fatigue syndrome patients, 40.2 year, N=30; pain-free individuals, 37.3 years, N=30	Self-report: 39.9 (0-100 SF-36)	11.3 years	Stroop, OSPAN	Inhibition, updating
Chronic pancreatitis patients, 49.5 years, N=16; pain-free individuals, 48.0 years, N=16		6.1 years	Verbal Interference, Go-/No-Go Task, Switching of Attention test	Inhibition, shifting

Study design	Significance of findings and effect sizes	Reference
Group comparison, correlation	Go-/No-Go Task performance patients < controls: ns ($\Delta=0.11$) Go-/No-Go Task performance & pain intensity: ns	Glass et al. (2011) ³³
Group comparison	N-back task performance patients < controls: ns ($\Delta=0.20$)	González-Villar et al. (2017) ³⁴
Group comparison, correlation	PASAT performance patients < controls: $p<0.05$ ($\Delta=0.61$) PASAT performance & pain intensity: $p<0.05$ ($r=0.36$)	Grace et al. (1999) ¹¹
Group comparison	Inhibition/shifting performance high-pain patients < controls: $p<0.05$	Grisart and Plaghki (1999) ¹²
Group comparison, correlation	Digit Span Backward/COWAT/TMT (B) performance patients < controls: $p<0.05$ ($\Delta=0.69/0.74/0.85$) Digit Span Backward/TMT (B) performance & pain intensity: $p<0.05$ ($r=0.71/0.49$) COWAT performance & pain intensity: ns ($r=0.34$)	Hall et al. (2011) ³⁵
Group comparison, correlation	Stroop performance patients < controls: $p<0.05$ ($\Delta=1.41$) OSPAN performance patients < controls: ns ($\Delta=0.44$) Stroop/OSPAN & pain intensity: ns	Ickmans et al. (2015) ¹⁶
Group comparison	Go-/No-Go Task/Verbal Interference Switching of Attention test performance patients < controls: $p<0.05$ ($\Delta=0.72/0.94/0.68$)	Jongsma et al. (2011) ³⁶

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Fibromyalgia patients, 42.2 years, N=50	Self-report: 5.8 (0-10 VAS)		Domain executive functioning: Go-/No-Go Task, Stroop	Inhibition
Patients with various chronic pain conditions, 76.1 years, N = 56	Self-report: 58.1 (0-100 VAS)		TMT (B)	Shifting
Migraine patients, 38.8 years, N=24; pain-free individuals, 43.1 years, N=24			Stroop	Inhibition
Tension-type headache patients, 42.8 years, N=18; same control group				
Chronic low back pain patients, 45.0 years, N=12; pain-free individuals, 44.0 years, N=14	Self-report: 25-48 (0-100 VAS)	7-15 years	Stroop	Inhibition
Complex regional pain syndrome patients, 36.1 years, N=25; pain-free individuals, 31.7 years, N=25		2.8 years	Stop-signal task, WCST	Inhibition, shifting
Patients with various chronic pain conditions, 37.7 years, N = 38	MPQ: 21.4	10.7 years	Stroop, COWAT, TMT (B)	Inhibition, updating, shifting
Fibromyalgia patients, 53.6 years, N = 20	MPQ: 63.5	14.4 years	Digit Span Backward, Corsi Block Span, TMT (B)	Updating, shifting
Migraine patients, 61.9 years, N=61; pain-free individuals, 66.8 years, N=367			Stroop, Digit Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting

Study design	Significance of findings and effect sizes	Reference
Group comparison (to normative data), correlation	Stroop/Go-/No-Go Task performance patients < controls: ns Executive functioning domain performance & pain intensity: $p < 0.05$ ($r = 0.32$)	Kalfon et al. (2016) ³⁷
Correlation	TMT (B) performance & pain intensity: $p < 0.05$ ($r = 0.42$)	Karp et al. (2006) ³⁸
Group comparison	Stroop performance patients < controls: ns ($\Delta = 0.11$) Stroop performance patients < controls: ns ($\Delta = 0.41$)	Kröner-Herwig et al. (2005) ³⁹
Group comparison	Stroop performance patients < controls: $p < 0.05$	Lamoth et al. (2008) ⁴⁰
Group comparison	Stop-signal task/WCST performance patients < controls: $p < 0.05$ ($\Delta = 1.36/0.97$)	Lee et al. (2015) ⁴¹
Correlation	Stroop/COWAT/TMT (B) performance & pain intensity: ns ($r = 0.02/0.10/0.02$)	Legaretta et al. (2016) ⁴²
Group comparison (to normative data), correlation	Corsi Block Span performance patients < controls: $p < 0.05$ Digit Span Backward/TMT (B) performance patients < controls: ns Digit Span Backward/Corsi Block Span/TMT (B) & pain intensity: ns	Luerding et al. (2008) ⁴³
Group comparison	Stroop/Digit Span Backward/Verbal Fluency task/TMT (B) performance patients < controls: ns (Interictal assessment)	Martins et al. (2012) ⁴⁴

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Non migraine headache patients, 69.3 years, N=50; same control group			Stroop, Digit Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting
Fibromyalgia patients, 49.8 years, N=29; pain-free individuals, 46.3 years, N=31	Self-report: 45.3 (0-100 VAS)	8.9 years	Stroop	Inhibition
Chronic lower back pain patients, 59.6 years, N=29; pain-free individuals, 60.7 years, N=30	Self-report: 56 (0-100 VAS)	7.58 years	Stroop, TMT (B)	Inhibition, shifting
Fibromyalgia patients, 46.6 years, N=33; pain-free individuals, 42.9 years, N=28	MPQ: 20.92	4.27 years	ANT-I (attentional network test-interactions)	Inhibition
Fibromyalgia patients, 45.9 years, N=77; pain-free individuals, 44.7 years, N=48			ANT-I (attentional network test-interactions)	Inhibition
Headache patients, 24.9, N=75			N-back task, Attentional Switching task	Updating, shifting
Patients with chronic neuropathic or radicular pain, 45.6 years, N=38; pain-free individuals, 44.2 years, N=38	CPG: 73.2	8.5 years	WCST	Shifting
Knee osteoarthritis patients, 70.0 years, N=79	MPQ-SF: 14.7	>3 months	Tracking test	Shifting
Chronic musculoskeletal pain patients, 74.6 years, N=44; pain-free individuals, 72.2 years, N=190	>4 (0-10 NRS)	>3 months	Letter and Category Verbal Fluency task, TMT (B)	Updating, shifting

Study design	Significance of findings and effect sizes	Reference
	Stroop/Digit Span Backward/Verbal Fluency task/TMT (B) performance patients < controls: ns	Martins et al. (2012) ⁴⁴
Group comparison	Stroop performance patients < controls: $p < 0.05$ ($\Delta = 0.89$)	Martinsen et al. (2014) ⁴⁵
Group comparison, correlation	Stroop/TMT (B) performance patients < controls: ns ($\Delta = 0.07/0.29$) Stroop/TMT (B) & pain intensity: ns	Masiliūnas et al. (2017) ⁴⁶
Group comparison, correlation	ANT-I performance patients < controls: $p < 0.05$ ($\Delta = 0.79$) ANT-I performance & pain intensity: ns ($r = 0.03$)	Miró et al. (2011) ⁴⁷
Group comparison, correlation	ANT-I performance patients < controls: $p < 0.05$ ANT-I performance & pain intensity: ns	Miró et al. (2015) ⁴⁸
Group comparison, correlation	N-back task/Attentional Switching task performance during headache < during no headache: $p < 0.05$ ($\Delta = 0.57/0.12$) N-back task/Attentional Switching task performance & pain intensity: ns	Moore et al. (2013A) ⁴⁹
Group comparison, correlation	WCST performance patients < controls: ns ($\Delta = 0.35$) WCST performance & pain intensity: ns	Moriarty et al. (2017) ⁵⁰
Correlation	Tracking test performance & pain intensity: ns	Morone et al. (2014) ⁵¹
Group comparison	Category Verbal Fluency task performance patients < controls: $p < 0.05$ ($\Delta = 0.42$) Letter Verbal Fluency task/TMT (B) performance patients < controls: ns ($\Delta = -0.12/0.17$)	Murata et al. (2017) ⁵²

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Patients with various chronic pain conditions, 39.9 years, N=40; pain-free individuals, 35.0 years, N=29	Self-report: 6.35 (0-10 VAS)		A Quick Test, Digit Span Backward, TMT (B)	Inhibition, updating, shifting
Patients with various chronic pain conditions, 51.5 years, N=34; pain-free individuals, 55.4 years, N=32	Self-report: 34.9 (0-100 VAS)	11.7 years	Digit Span Backward	Updating
Patients with various chronic pain conditions, 51.5 years, N=34; pain-free individuals, 55.4 years, N=32	Self-report: 34.9 (0-100 VAS)	11.7 years	Stroop, Zoo Map test, TMT (B),	Inhibition, updating, shifting
Patients with various chronic pain conditions, 28.8 years, N=22		9.8 years	Stroop, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting
Patients with various chronic pain conditions, 65.0 years, N=24		10.6 years		
Fibromyalgia patients, 47.83 years, N=23; pain-free individuals, 47.83 years, N=23	MPQ: 33.8		Reading and computational Span task (working memory domain), Verbal Fluency task	Updating
Migraine patients without aura, 36.7 years, N=32; pain-free individuals, 35.8 years, N=16		18.4 years	Stroop, COWAT, TMT (B),	Inhibition, updating, shifting
Migraine with aura, 42.1 years, N=12; same control group		16.3 years		

Study design	Significance of findings and effect sizes	Reference
Group comparison	A Quick Test performance patients < controls: $p < 0.05$ ($\Delta = 0.86$) Digit Span Backward/TMT (B) performance patients < controls: ns ($\Delta = 0.47/0.86$)	Nadar et al. (2016) ⁵³
Group comparison, correlation	Digit Span Backward performance patients < controls: $p < 0.05$ ($\Delta = 0.44$) Digit Span Backward performance & pain intensity: $p < 0.05$ ($r = 0.38$)	Oosterman et al. (2011) ⁵⁴
Group comparison, correlation	TMT (B) performance patients < controls: $p < 0.05$ ($\Delta = 0.76$) Stroop/Zoo Map test performance patients < controls: ns ($\Delta = 0.07/0.16$) Stroop/Zoo Map test/TMT (B) performance & pain intensity: ns	Oosterman et al. (2012) ⁵⁵
Correlation	TMT (B) performance & pain intensity: $p < 0.1$ Stroop/Verbal Fluency task performance & pain intensity: ns TMT (B) performance & pain intensity: $p < 0.05^*$ Stroop/Verbal Fluency task performance & pain intensity: ns	Oosterman et al. (2013) ⁵⁶
Group comparison, correlation	Working memory performance patients < controls: $p < 0.05$ ($\Delta = 2.44$) Verbal Fluency task performance patients < controls: ns ($\Delta = 0.40$) Working memory performance & pain intensity: $p < 0.05$ ($r = 0.61$) Verbal Fluency task performance & pain intensity: ns	Park et al. (2001) ⁵⁷
Group comparison	COWAT performance patients < controls: $p < 0.05$ ($\Delta = 1.11$) Stroop/TMT (B) performance patients < controls: ns ($\Delta = 0.47/0.87$) (Interictal assessment) Stroop/COWAT/TMT (B) performance patients < controls: ns ($\Delta = 0.33/1.03/0.55$) (Interictal assessment)	Le Pira et al. (2014) ⁵⁸

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Patients with various chronic pain conditions, 48.5 years, N=30	Self-report: 43 (0-100 VAS)	7 years	Stroop, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting
Fibromyalgia patients, 48.5 years, N=15; pain-free individuals, 44.3 years, N=15		1.1 years	Stroop, Digit Span Backward	Inhibition, updating
Rheumatoid arthritis patients, 41.9 years, N=15; same control group		1.6 years		
Patients with arthrosis/arthritis, 85.7 years, N=20	Self-report: 50.85 (0-100 CAS)		Executive functioning domain: Digit Span Backward, Category Fluency, Knox's Cube Imitation Test, Incomplete figures	Updating
Patients with arthrosis/arthritis and Alzheimer's disease, 86.4 years, N=19	Self-report: 21.55 (0-100 CAS), 0.56 (0-6 FPS)			
Patients with various chronic pain conditions, 44.4 years, N=91; pain-free individuals, 47.6 years, N=64		7 years	PASAT	Updating
Fibromyalgia patients, 48.1 years, N=23; pain-free individuals, 45.9 years, N=21	MPQ: 38.0		Stroop, Letter Number Sequencing, COWAT, PASAT, TMT (B), WCST	Inhibition, updating, shifting
Patients with various chronic pain conditions, 49.5 years, N=22; same control group	MPQ: 20.9			

Study design	Significance of findings and effect sizes	Reference
Correlation	Stroop/Verbal Fluency task/TMT (B) performance & pain intensity: ns ($r=0.08/0.12/0.21$)	Pulles and Oosterman (2011) ⁵⁹
Group comparison	Stroop/Digit Span Backward performance patients < Stroop/Digit Span Backward performance controls: ns Stroop/Digit Span Backward performance patients < Stroop/Digit Span Backward performance controls: ns	Roldán-Tapia et al. (2007) ⁶⁰
Correlation	Executive functioning performance & pain intensity: ns ($r=0.17$) Executive functioning performance & pain intensity: $p<0.05^*$ ($r=-0.675$)	Scherder et al. (2008) ⁶¹
Group comparison, correlation	PASAT performance patients < controls: ns ($\Delta=0.20$) PASAT performance & pain intensity: $p<0.05$	Sjørgen et al. (2005) ⁶²
Group comparison, correlation	Stroop/Letter Number /COWAT/PASAT/WCST/TMT (B) performance patients < controls: ns ($\Delta=0.51/0.70/0.33/0.62/-0.03/1.48$) Stroop/WCST/ Letter Number /COWAT/PASAT/TMT (B) performance & pain intensity: ns Stroop/Letter Number /COWAT/PASAT/WCST/TMT (B) performance patients < controls: ns ($\Delta=-0.02/0.67/0.25/0.20/0.49/1.76$) Stroop/WCST/ Letter Number /COWAT/PASAT/TMT (B) performance & pain intensity: ns	Suhr (2003) ⁶³

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Chronic musculoskeletal pain patients, 57.9 years, N=15; pain-free individuals, 25-83 years, N=14	Self-report median: 60 (0-100 NRS)		Emotional counting Stroop	Inhibition
Patients with migraine with aura, 30.1 years, N=20; pain-free individuals, 29.2 years, N=20	Attack self-report: 8.0 (0-10 VAS)	11.0 years	Verbal Fluency task, TMT (B), WCST	Updating, shifting
Patients with migraine without aura, 30.1 years, N=20; same control group	Attack self-report: 8.6 (0-10 VAS)	11.2 years	Verbal Fluency task, TMT (B), WCST	Updating, shifting
Episodic cluster headache patients, 40.8 years, N=11; pain-free individuals, 53.2 years, N=12		10.8 years	Stroop, Verbal Fluency task, Digit Span, Letter-number Sequencing, TMT (B)	Inhibition, Updating, shifting
Chronic cluster headache patients, 49.2 years, N=11; same control group		14.6 years		
Elderly with various chronic pain conditions, 78.1 years, N=765			Clock-in-the-box Test, Letter Fluency task, TMT (B)	Updating, shifting
Fibromyalgia patients, 30.4 years, N=35; Pain-free individuals, 29.3 years, N=35	Self-report: 49 (0-100 VAS)		Stroop, Multisource Interference Test	Inhibition
Fibromyalgia patients, 45.9 years, N=36; pain-free individuals, 45.0 years, N=36	WHYMPI: 4.62 (0-6 NRS)	11.5 years	WCST	Shifting

Study design	Significance of findings and effect sizes	Reference
Group comparison	Stroop performance patients < Stroop performance controls: $p < 0.05$	Taylor et al. (2016) ⁶⁴
Group comparison	Verbal Fluency task/TMT (B)/WCST performance patients < controls: ns ($\Delta = 0.87/0.60/0.14$) (Interictal assessment)	Tessitore et al. (2015) ⁶⁵
	Verbal Fluency task/TMT (B)/WCST performance patients < controls: ns ($\Delta = 0.38/0.68/-0.14$) (Interictal assessment)	Tessitore et al. (2015) ⁶⁵
Group comparison	Digit Span/TMT (B) performance patients < controls: $p < 0.05$ ($\Delta = 1.65/2.44$) Stroop/Letter-number Sequencing Verbal Fluency task performance patients < controls: ns ($\Delta = 1.10/1.31/0.47$) (Assessment during headache episode) Digit Span/Letter-number Sequencing performance patients < controls: $p < 0.05$ ($\Delta = 1.63/1.39$) Stroop/Verbal Fluency task/TMT (B) performance patients < controls: ns ($\Delta = 1.34/1.21/1.71$) (Interictal assessment)	Torkamani et al. (2015) ⁶⁶
Correlation	Clock-in-the-box Test/Letter Fluency task/TMT (B) performance & pain intensity: ns	van der Leeuw et al. (2016) ⁶⁷
Group comparison	Stroop/Multisource Interference Test performance patients < controls: ns ($\Delta = 0.51/-0.15$)	Veldhuijzen et al. (2012) ⁶⁸
Group comparison, correlation	WCST performance patients < controls: $p < 0.05$ ($\Delta = 0.75$) WCST performance & pain intensity: $p < 0.05$ ($r = 0.23$)	Verdejo-Garcia et al. (2009) ⁶⁹

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain
Fibromyalgia patients, 50.4 years, N=15; pain-free individuals, 49.0 years, N=15	Self-report: 4.5 (0-10 VAS)	>6 months	Stroop, Digit Span	Inhibition, updating
Chronic low back pain patients, 73.6 years, N=163; pain-free individuals, 73.5 years, N=160	MPQ: 12.2	14.2 years	TMT (B)	Shifting
Temporomandibular disorder patients, 35.2 years, N=17; pain-free individuals, 34.0 years, N=17	Self-report: 4.2 (0-10 NRS)	9.3 years	Counting Stroop	Inhibition

*Positive association

Abbreviations: VAS=Visual Analogue Scale; WCST=Wisconsin Card Sorting Test; PASAT=Paced Auditory Serial Addition Test; TMT=Trail Making Test; OSPAN=Operation Span Task; FIQ=Fibromyalgia Impact Questionnaire; CPG=Chronic Pain Grade; PED=Patient Experience Diary; NRS=Numerical Rating Scale; COWAT=Controlled Oral Word Association Test; MPI=Multidimensional Pain Inventory; WAIS-R=Wechsler Adult Intelligence Scale Revised; MPQ(-SF)=McGill Pain Questionnaire (Short Form); SF-36=Short Form (36) health survey (higher scores represent less pain); CAS=Colored Analogue Scale; FPS=Faces Pain Scale; WHYMPI=West Haven-Yale Multidimensional Pain Inventory; n/a=not available; r=correlation coefficient, Δ =Glass' Δ effect size

Study design	Significance of findings and effect sizes	Reference
Group comparison	Stroop/Digit Span performance patients < controls: ns ($\Delta=0.64/0.09$)	Walteros et al. (2011) ⁷⁰
Group comparison, correlation	TMT (B) performance patients < controls: $p<0.05$ ($\Delta=0.25$) TMT (B) performance & pain intensity: $p<0.05$	Weiner et al. (2006) ⁷¹
Group comparison	Stroop performance patients < controls: ns ($\Delta=0.63$)	Weissman-Fogel et al. (2011) ⁷²

Table 4. Summary of papers investigating the association between experimental pain and executive functioning.

Sample	Pain stimulus	Pain measure	Executive functioning tests	Cognitive domain
Pain-free individuals, 30.0 years, N=8	Heat	Intensity	Stroop	Inhibition
Pain-free individuals, 26.0 years, N=16	Infrared laser	Intensity	N-back	Updating
Pain-free individuals, 22.6 years, N=54	Cold pressor test	Threshold and tolerance	Stroop, Stop-signal, Left-right, Keep-track, Letter-memory, N-back, Plus-minus, Number-letter, Local-global	Inhibition, updating, shifting
Pain-free individuals, 21.5 years, N=61	Heat		Task-shifting	Shifting
Pain-free individuals, 25.0 years, N = 24	Heat	Intensity	N-Back task	Updating
Pain-free individuals, 26.0 years, N=12	Esophageal pressure	Intensity	N-back task	Updating
Pain-free individuals, 38.0 years, N=22	Pressure	Threshold cuff, CPM finger and shoulder, TS finger and shoulder	Stroop, OSPAN	Inhibition, updating

Study design	Significance of findings and effect sizes	Reference
Interference	Pain intensity during Stroop interference < during Stroop neutral: $p < 0.05$	Bantick et al. (2002) ⁷³
Interference	Pain intensity during 2-back task < during 1-back task: $p < 0.05$ 2-Back task performance during pain < during no pain: $p < 0.05$	Bingel et al. (2007) ⁷⁴
Correlation	Stroop & threshold/tolerance: $p < 0.05$ ($r = 0.28/0.40$) Stop-signal/Left-right/Keep-track/Letter-memory/N-back/Plus-minus/Number-letter/Local-global & threshold: ns ($r = -0.10/0.03-0.13/0.04/0.01/0.016/-0.01$) Stop-signal/Left-right/Keep-track/Letter-memory/N-back/Plus-minus/Number-letter/Local-global & tolerance: ns ($r = -0.16/0.08/-0.01/-0.02/-0.01/-0.06/-0.04$)	Bjekić et al. (2017) ¹⁴
Interference	Task-shifting performance during pain < during no pain: $p < 0.05$	Boselie et al. (2017) ⁷⁵
Interference	Pain intensity during 3-back task < during neutral task: $p < 0.05$ 3-back task performance during pain < 3-back task performance during no pain: $p < 0.05$	Buhle and Wager (2010) ¹⁸
Interference	Pain intensity during 1-back task < during neutral task: $p < 0.05$ 1-Back task performance during pain < during no pain: ns	Coen et al. (2008) ⁷⁶
Correlation	Stroop & CPM shoulder: $p < 0.05$ ($r = 0.45$) Stroop & threshold cuff/CPM finger/TS finger/TS shoulder: ns ($r = -0.01/0.30/0.33/0.08$) OSPAN & threshold cuff/CPM finger/CPM shoulder/TS finger/TS shoulder: ns ($r = 0.31/0.29/0.18/0.09/-0.16$)	Coppieters et al. (2015) ²⁶

Sample	Pain stimulus	Pain measure	Executive functioning tests	Cognitive domain
Fibromyalgia patients, 44.5 years, N=21				
Pain-free individuals, 37.3 years, N=30	Pressure	Threshold, CPM, TS; all on finger and shoulder	Stroop, OSPAN	Inhibition, updating
Chronic fatigue syndrome with comorbid fibromyalgia patients, 40.2 year, N=30				
Pain-free individuals, 22.2 year, N=49	Heat	Intensity measured by facial expression	Stroop, anti-saccade task	Inhibition
Pain-free individuals, 21.8 year, N=57	Cold pressor test	Tolerance	Stop-signal	Inhibition
Pain-free individuals, 20.6 years, N=70	Finger-pressing task	Tolerance	Stop-signal	Inhibition
Pain-free individuals, 25.0 years, N=62	Heat		Word Generation task	Updating
Pain-free individuals (dementia, mild cognitive impairments, 75.6 years, N=70	Electrical stimuli	Nociceptive flexion reflex threshold and facial expression	SIDAM (domain intellectual abilities/executive function)	Shifting
Pain-free individuals, 30.0 years, N=10	Infrared laser		N-back	Updating
Pain-free individuals, 25.0 year, N=16	Infrared laser		N-back	Updating
Pain-free individuals, ~45.9 years, N=44	Electrical stimulation	CPM	Stroop	Inhibition

Study design	Significance of findings and effect sizes	Reference
	<p>OSPAN & TS shoulder: $p < 0.05$ ($r = 0.53$)</p> <p>OSPAN & threshold cuff/CPM finger/CPM shoulder/TS finger: ns ($r = 0.19/-0.07/-0.19/0.43$)</p> <p>Stroop & threshold cuff/CPM finger/CPM shoulder/TS finger/TS shoulder: ns ($r = -0.09/-0.17/0.33/0.30/0.17$)</p>	
Correlation	<p>Stroop/OSPAN & threshold finger/threshold shoulder/CPM finger/CPM shoulder/TS finger/TS shoulder: ns</p> <p>Stroop/OSPAN & CPM finger: $p < 0.05$ ($r = 0.41/0.55$)</p> <p>Stroop/OSPAN & threshold finger/threshold shoulder/CPM shoulder/TS finger/TS shoulder: ns</p>	Ickmans et al. (2015) ¹⁶
Correlation	<p>Anti-saccade & facial expression: $p < 0.05$ ($r = 0.31$)</p> <p>Stroop & facial expression: ns ($r = -0.17$)</p>	Karmann et al. (2015) ⁷⁷
Correlation	Stop-signal & tolerance: $p < 0.05$	Karsdorp et al. (2014) ⁷⁸
Correlation	Stop-signal & tolerance: $p < 0.05$	Karsdorp et al. (2016) ⁷⁹
Interference	Word generation task performance during pain < during no pain: ns	Keogh et al. (2013) ⁸⁰
Correlation	SIDAM & nociceptive flexion reflex threshold/facial expression: $p < 0.05$	Kunz et al. (2015) ⁸¹
Interference	Performance 1-back task during pain < during no pain: ns	Legrain et al. (2011) ⁸²
Interference	Performance 1-back task during pain < during no pain: ns	Legrain et al. (2013) ⁸³
Correlation	Stroop & CPM: $p < 0.05$ ($r = 0.34$)	Marouf et al. (2014) ⁸⁴

Sample	Pain stimulus	Pain measure	Executive functioning tests	Cognitive domain
Pain-free women, 46.3 years, N=31	Pressure	Threshold	Stroop	Inhibition
Fibromyalgia patients, 49.8 years, N=29				
Pain-free individuals, 40.9 years, N=16	Pressure	Threshold, CPM; both on finger and shoulder	Stroop, OSPAN	Inhibition, updating
Pain-free individuals, 22.06 years, N=50	Heat		N-back task, Attentional Switching task	Updating, shifting
Pain-free individuals, 30.0 years, N=20	Heat		N-back task	Updating
Pain-free individuals, 31.0 years, N=20			Attentional Switching task	Shifting
Pain-free individuals, 59.1 years, N=31	Cold pressor test	Tolerance, intensity	Stroop, Letter fluency test, Digit Span Backward, Zoo Map Test, TMT (B)	Inhibition, updating, shifting
Pain-free individuals, 66.7 years, N=51	Pressure	Intensity measured by rating & facial expression	Stroop, Digit Span Backward, Zoo Map Test	Inhibition, updating
Pain-free individuals, 26.4 years, N=16	Electrical nerve stimulation		Counting Stroop	Inhibition
Pain-free individuals, 25.6 years, N=23	Electrical nerve stimulation	Intensity	Multisource interference task	Inhibition

Study design	Significance of findings and effect sizes	Reference
Interference	Threshold during Stroop interference > during control condition: ns Threshold during Stroop interference > during control condition: ns	Martinsen et al. (2014) ⁴⁵
Correlation	Stroop & CPM finger/CPM shoulder: $p < 0.05$ ($r = 0.61/0.60$) Stroop & threshold finger/threshold shoulder: ns ($r = -0.26/-0.29$) OSPAN & CPM finger/CPM shoulder/threshold finger/threshold shoulder: ns ($r = -0.33/-0.32/-0.4/0.03$)	Meeus et al. (2015) ⁸⁵
Interference	N-back/Attentional switching performance during pain < during no pain: $p < 0.05$	Moore et al. (2013B) ⁸⁶
Interference	N-back performance during pain < during no pain: $p < 0.05$ Attentional switching performance during pain < during no pain: ns	Moore et al. (2017) ⁸⁷
Correlation	Stroop & tolerance: $p < 0.05$ ($r = 0.42$) Letter fluency test/TMT (B)/Zoo Map Test/Digit Span Backward & tolerance: ns ($r = 0.04/-0.29/-0.26/-0.35$) Stroop/Letter fluency test/TMT (B)/Zoo Map Test/Digit Span Backward & pain intensity: ns ($r = 0.33/0.08/-0.04/-0.29/-0.11$)	Oosterman et al. (2010) ⁸⁸
Correlation	Stroop & pain intensity/facial expression: $p < 0.05$ Digit Span Backward/Zoo Map Test & pain intensity/facial expression: ns	Oosterman et al. (2016) ⁸⁹
Interference	Counting Stroop performance during pain < during no pain: ns	Seminowicz et al. (2004) ⁹⁰
Interference	Pain intensity during multisource inference test difficult < during multisource easy: ns Multisource interference test performance during pain < during pain: ns	Seminowicz and Davis (2007) ⁹¹

Sample	Pain stimulus	Pain measure	Executive functioning tests	Cognitive domain
Pain-free individuals, 24.0 years, N=36	Cold pressor test	Tolerance	Stroop	Inhibition
Pain-free individuals, 32.1 years, N=7	Heat	Intensity	Stroop	Inhibition
Pain-free women, 29.3 years, N=35	Pressure	Threshold	Stroop, Multisource Interference Test	Inhibition
Fibromyalgia patients, 30.4 years, N=35				
Pain-free individuals, 67.5 years, N=26	Cold pressor test	Threshold, tolerance, intensity	Stroop, Letter Fluency test, TMT (B)	Inhibition, updating, shifting

Abbreviations: CPM=Conditioned Pain Modulation; TS=Temporal Summation; OSPAN=Operation Span Task; SIDAM=Structured Interview for the Diagnosis of dementias of the Alzheimer type and Multi-infarct dementia and dementias of other aetiology; TMT=Trail Making Test; r =correlation coefficient.

Study design	Significance of findings and effect sizes	Reference
Interference	Stroop performance during pain < during no pain: ns Pain tolerance during Stroop > during Stroop neutral: $p < 0.05$	Terrighena et al. (2017) ⁹²
Interference	Pain intensity during Stroop task < during Stroop neutral: $p < 0.05$	Valet et al. (2004) ⁹³
Correlation	Stroop/multisource interference test & threshold: ns ($r = 0.2/0.34$)	Veldhuijzen et al. (2012) ⁶⁸
	Stroop/multisource interference test & threshold: $p < 0.05$ ($r = 0.41/0.37$)	
Correlation	Stroop & pain intensity: $p < 0.05$ ($r = 0.48$) Stroop & threshold/tolerance: ns ($r = -0.2/-0.2$) TMT (B) & threshold/tolerance/pain intensity: ns ($r = 0.09/0.09/-0.1$) Letter Fluency test & threshold/tolerance/pain intensity: ns ($r = 0.26/0.26/-0.31$)	Zhou et al. (2015) ⁹⁴

Table S1. Risk of bias assessment chronic pain studies.

Study	Are gender distribution and age reported?	Is the study population representative for the true population?	Were psychiatric disorders screened for?
Abeare et al. (2010) ²⁰	1	1	0.5
Akdoğan et al. (2013) ²¹	1	0.5	0
Apkarian et al. (2004) ²²	0.5	1	1
Armstrong et al. (1997) ¹⁰	1	1	1
Attridge et al. (2017) ²³	1	1	1
Buckalew et al. (2008) ²⁴	1	1	1
Cherry et al. (2012) ²⁵	1	0.5	0
Coppieters et al. (2015) ²⁶	1	1	0
Correa et al. (2011) ²⁷	1	1	1
Di Tella et al. (2015) ²⁸	1	0.5	1
Dick et al. (2002) ²⁹	1	1	1
Galioto et al. (2018) ³⁰	1	1	1
Gijzen et al. (2011) ³¹	1	1	1
Gil-Gouveia et al. (2015) ³²	1	1	1
Glass et al. (2011) ³³	1	1	1
González-Villar et al. (2017) ³⁴	1	1	1
Grace et al. (1999) ¹¹	1	1	0.5
Grisart and Plaghki (1999) ¹²	1	1	1
Hall et al. (2011) ³⁵	1	1	1
Ickmans et al. (2015) ¹⁶	1	1	0.5
Jongsma et al. (2011) ³⁶	1	1	0
Kalfon et al. (2016) ³⁷	1	1	0
Karp et al. (2006) ³⁸	1	1	0
Kröner-Herwig et al. (2005) ³⁹	1	1	1
Lamoth et al. (2008) ⁴⁰	1	1	0
Lee et al. (2015) ⁴¹	1	1	0.5
Legaretta et al. (2016) ⁴²	1	1	0.5
Luerding et al. (2008) ⁴³	1	1	0
Martins et al. (2012) ⁴⁴	1	1	0.5
Martinsen et al. (2014) ⁴⁵	1	0.5	1
Masiliūnas et al. (2017) ⁴⁶	1	1	1
Miró et al. (2011) ⁴⁷	1	1	1
Miró et al. (2015) ⁴⁸	1	1	1
Moore et al. (2013A) ⁴⁹	1	1	0
Moriarty et al. (2017) ⁵⁰	1	1	1
Morone et al. (2014) ⁵¹	1	1	0

Did they control for age and education in the group comparison?	Were patients diagnosed according to accepted criteria?	Are executive functioning tests specified well?	Is analgesic medication use reported?	Quality score
NA	1	1	0	4.5
1	1	1	0.5	5
1	1	1	0.5	6
1	1	0	0	5
NA	0	1	1	5
1	1	1	0.5	6.5
1	1	1	0.5	5
0.5	1	1	0.5	5
1	1	1	1	7
1	1	0.5	0	5
0.5	1	1	1	6.5
NA	1	1	0.5	5.5
1	0	1	0	5
NA	1	1	1	6
1	1	1	0	6
1	0.5	1	1	6.5
1	1	0.5	0.5	5.5
1	1	1	0	6
1	1	0.5	0.5	6
0.5	1	1	0.5	5.5
1	1	1	0.5	5.5
1	1	0.5	0.5	5
NA	0	1	0.5	3.5
NA	1	1	0.5	5.5
0.5	1	1	0	4.5
0.5	1	1	1	6
NA	0.5	1	0.5	4.5
NA	1	1	0.5	4.5
1	1	0.5	0	5
0.5	1	1	1	6
1	0.5	1	0.5	6
1	1	1	1	7
1	1	1	0.5	6.5
NA	1	1	1	5
1	0.5	1	1	6.5
NA	1	1	0	4

Study	Are gender distribution and age reported?	Is the study population representative for the true population?	Were psychiatric disorders screened for?
Murata et al. (2017) ⁵²	1	1	0
Nadar et al. (2016) ⁵³	1	1	1
Oosterman et al. (2011) ⁵⁴	1	1	0
Oosterman et al. (2012) ⁵⁵	1	1	0.5
Oosterman et al. (2013) ⁵⁶	1	1	0.5
Park et al. (2001) ⁵⁷	1	1	0.5
Le Pira et al. (2014) ⁵⁸	1	1	1
Pulles and Oosterman (2011) ⁵⁹	1	1	1
Roldán-Tapia et al. (2007) ⁶⁰	1	1	1
Scherder et al. (2008) ⁶¹	1	1	1
Sjörgen et al. (2005) ⁶²	1	1	0
Suhr (2003) ⁶³	1	1	0
Taylor et al. (2016) ⁶⁴	0.5	1	1
Tessitore et al. (2015) ⁶⁵	1	0.5	1
Torkamani et al. (2015) ⁶⁶	1	1	1
van der Leeuw et al. (2016) ⁶⁷	1	1	0
Veldhuijzen et al. (2012) ⁶⁸	1	0.5	0.5
Verdejo-Garcia et al. (2009) ⁶⁹	1	1	1
Walteros et al. (2011) ⁷⁰	1	1	0
Weiner et al. (2006) ⁷¹	1	1	0
Weissman-Fogel et al. (2011) ⁷²	1	1	1

NA = not applicable because these studies did not perform a group comparison.

Did they control for age and education in the group comparison?	Were patients diagnosed according to accepted criteria?	Are executive functioning tests specified well?	Is analgesic medication use reported?	Quality score
1	0.5	1	0.5	5
1	0	1	0.5	5.5
0.5	0	1	1	4.5
0.5	0	1	1	5
1	0	0.5	1	5
1	1	1	1	6.5
1	1	1	0	6
NA	0	1	1	5
1	1	1	1	7
NA	0.5	1	0	4.5
0.5	0	1	1	4.5
1	0	0.5	0	3.5
1	1	1	0.5	6
1	1	1	1	6.5
1	1	1	0	6
NA	0	1	0.5	3.5
1	1	1	1	6
1	1	1	0.5	6.5
1	0.5	1	0.5	5
1	1	1	0.5	5.5
0.5	1	1	1	6.5

Table S2. Risks of bias assessment experimental pain studies.

Study	Are gender distribution and age reported?	Is the study population representative for the true population?	Were psychiatric disorders screened for?
Bantick et al. (2002) ⁷³	1	0.5	1
Bingel et al. (2007) ⁷⁴	1	0	1
Bjekić et al. (2017) ¹⁴	1	0.5	1
Boselie et al. (2017) ⁷⁵	1	1	1
Buhle and Wager (2010) ¹⁸	1	0.5	1
Coen et al. (2008) ⁷⁶	1	0.5	0
Coppieters et al. (2015) ²⁶	1	1	0.5
Ickmans et al. (2015) ¹⁶	1	1	0.5
Karmann et al. (2015) ⁷⁷	1	0.5	0
Karsdorp et al. (2014) ⁷⁸	1	0.5	0
Karsdorp et al. (2016) ⁷⁹	1	0.5	0
Keogh et al. (2013) ⁸⁰	1	1	0
Kunz et al. (2015) ⁸¹	1	1	1
Legrain et al. (2011) ⁸²	1	1	1
Legrain et al. (2013) ⁸³	1	0.5	1
Marouf et al. (2014) ⁸⁴	1	1	1
Martinsen et al. (2014) ⁴⁵	1	0.5	1
Meeus et al. (2015) ⁸⁵	1	0.5	0
Moore et al. (2013B) ⁸⁶	1	0.5	0
Moore et al. (2017) ⁸⁷	1	1	0
Oosterman et al. (2010) ⁸⁸	1	1	1
Oosterman et al. (2016) ⁸⁹	1	1	0
Seminowicz et al. (2004) ⁹⁰	1	1	1
Seminowicz and Davis (2007) ⁹¹	1	1	0
Terrighena et al. (2017) ⁹²	1	0.5	0
Valet et al. (2004) ⁹³	1	1	1
Veldhuijzen et al. (2012) ⁶⁸	1	0.5	0.5
Zhou et al. (2015) ⁹⁴	1	1	1

Is the pain induction method well explained?	Are executive functioning tests specified well?	Quality score
1	1	4.5
1	1	4
1	1	4.5
1	1	5
1	1	4.5
1	1	3.5
1	1	6
1	1	6
1	1	3.5
1	1	3.5
1	1	3.5
1	1	4
1	0.5	4.5
1	1	5
1	1	4.5
1	1	5
1	1	5.5
1	1	3.5
1	1	3.5
1	1	4
0.5	0.5	4
1	1	4
1	1	5
1	1	4
1	1	3.5
1	1	5
1	1	6
1	0.5	4.5

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Chapter 3

Does EEG activity during painful stimulation mirror more closely the noxious stimulus intensity or the subjective pain sensation?

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Abstract

Background: Many researchers have tried to investigate pain by studying brain responses. One method used to investigate pain-related brain responses is continuous electroencephalography (EEG). The objective of the current study is to add on to our understanding of EEG responses during pain, by differentiation between EEG patterns indicative of (i) the noxious stimulus intensity and (ii) the subjective pain sensation.

Methods: EEG was recorded during the administration of tonic experimental pain, consisting of six minutes of contact heat applied to the leg via a thermode. Two stimuli above pain threshold, one at pain threshold and two non-painful stimuli were administered. Thirty-six healthy participants provided a subjective pain rating during thermal stimulation. Relative EEG power was calculated for the frequency bands alpha1, alpha2, beta1, beta2, delta and theta.

Results: Whereas EEG activity could not be predicted by stimulus intensity (except in one frequency band), subjective pain sensation could significantly predict differences in EEG activity in several frequency bands. An increase in subjective pain sensation was associated with a decrease in alpha2, beta1, beta2 as well as in theta activity across the midline electrodes.

Conclusion: The subjective experience of pain seems to capture unique variance in EEG activity above and beyond what is captured by noxious stimulus intensity.

Introduction

There is a growing interest in developing objective, non-verbal methods to measure pain in people who are not able to self-report pain; such as people with dementia or people in a minimally conscious state. One way to measure pain non-verbally is by measuring brain activity using electroencephalography (EEG). Continuous EEG has indeed been used to investigate which EEG pattern might be indicative of experimentally induced pain.¹⁻⁴

Although the findings of the EEG studies are quite promising, results are also contradictory. Reasons for these contradictory findings might be partly due to the various natures of pain being studied (experimental pain vs. clinical pain models). Using experimental pain, studies consistently found a decrease in alpha activity during pain,¹⁻⁴ whereas clinical studies reported an increase in alpha activity in chronic pain patients during rest.⁵ Another factor contributing to the contradictory EEG findings might be the definition of pain intensity. When investigating EEG patterns indicative of pain in an experimental setting, there are two ways of operationalizing EEG responses to painful stimulation: (i) by the objective noxious stimulus intensity or (ii) by the subjectively rated pain sensation. Noxious stimulus intensity can for example refer to the degree of Celsius of a heat stimulus. In contrast, subjective pain sensation is measured using rating scales, like Numerical Rating Scales where participants indicate their subjective pain sensation with a number from 0 - 10. Thus, these two different operationalizations are distinct with regard to that the first may highlight the noxious input side, whereas the second one may stress the psychological output side. In order to investigate whether these different operationalizations of pain intensity (noxious stimulus intensity vs. subjective pain intensity) can explain the contradictory results, studies are needed that include both definitions. So far, two experimental studies compared the effect of noxious stimulus intensity to the effect of subjective pain intensity on EEG signals and found that noxious stimulus intensity and subjective pain intensity might be differentially encoded in EEG activity.^{6,7} The decrease in alpha activity often observed in experimental pain studies was found to be associated with only noxious stimulus intensity, while subjective pain intensity was associated with an increase in gamma oscillations. However, these findings are contrary to another study that showed that alpha activity does correlate with subjective pain intensity.⁸

The objective of the current study was to add on to our understanding of EEG responses during painful stimulation by differentiation between EEG patterns indicative of (i) the noxious stimulus intensity and (ii) the subjective pain sensation. Five different stimulus intensities were used: two below pain threshold, one at pain threshold and two above pain threshold. In contrast to previous studies, which mostly selected intensities based on physical units (e.g. degree of Celsius), we favored a more

psychological approach by selecting intensities not only based on the individual pain threshold, but also based on just noticeable differences in temperature perception. By using just noticeable differences, we made sure that the five intensities would be perceived differently, while at the same time being as close as possible physically. This strict psychological stimulus definition biases our stimulation more towards the psychological side, whereas previous studies show a bias towards the physical side.

The predictive power of noxious stimulus intensity and subjective pain sensation to explain variance in EEG activity was tested using regression analyses. Since we chose a strict psychological stimulus definition, we aimed to account for this by entering the physical, noxious stimulus intensity first, followed by the subjective pain sensation. We hypothesize that subjective pain sensation can explain variance in EEG power beyond what can be explained by a change in noxious stimulus intensity.

Methods

Participants

Thirty-six participants (18 female, mean age=2.6 years, SD=3.2 years) were recruited using bulletins placed throughout the campus of the University of Bamberg. None of the participants was suffering from acute or chronic pain, a psychiatric disease or used analgesics. Participants were asked not to consume alcohol the evening before or on the day of the experiment itself. The study was approved by the ethics committee of the University of Bamberg and a written informed consent was obtained from all participants.

Experimental procedure

The experimental procedure was composed of several steps. The first step in the current study was to determine the customized stimulation temperatures. In order to determine these, we assessed the individual pain threshold. The individual pain threshold was used in combination with just noticeable difference scores (assessed in a preliminary study) to determine the target temperature of the tonic heat stimuli. Figure 1 shows a schematic overview of the stimulation procedure. Five different heat intensities were used, each lasting for six minutes (Figure 1A). Participants received heat stimulation applied to the left thigh while seated in a comfortable chair. EEG was recorded continuously and subjective pain sensation ratings were assessed at the end of each minute (Figure 1B). Participants were asked to look at a fixation cross at a computer screen during stimulation to prevent movements of the head that could affect the EEG signal. Just noticeable differences, the pain threshold and the tonic heat stimuli are explained in detail below.

A Five experimental blocks (5 intensities; 6 minutes each)

B

C

Thermal heat stimulation:
30 pulses per minute
amplitude of 1.3 °C

Figure 1. Schematic overview of the experimental procedure. A: The procedure consisted of five experimental blocks, in which participants received painful stimulation lasting for six minutes. During each block, a different heat intensity was used. B: Pain was rated during the last five seconds of each minute of stimulation. EEG was recorded continuously. C: The heat stimuli were oscillating with 30 pulses per minute and an amplitude of 1.3 °C, with the target temperature being reached at the peak.

Thermal stimulation

The heat stimuli were administered using a thermal sensory analyzer (Medoc TSA II, Ramat-Yishai, Israel), including a Peltier thermode with a 3 cm x 3 cm stimulation surface. The thermode was attached to the left thigh with an elastic band. The location of the thermode was changed after each of the five 6-minute episodes of stimulation. Therefore, the left dorsal thigh was divided into five equal-sized areas. Given that we decided to use temperature intensities tailored to the individual pain threshold and that we also took into account just noticeable differences (JNDs) in pain perception, pain threshold and JND had to be assessed beforehand.

Just noticeable differences

JNDs refer to the smallest difference in intensity between two stimuli that the participant is able to detect. We decided to assess JNDs in a preliminary study with 20 different participants. The reasons for this were that the JND assessment was time consuming and the results of the preliminary study showed good stability

(coefficient of variation, $CV=0.285$) so that we could use the values in the present study. To determine JNDs, we used the method of limits. The temperature of the thermal probe increased from a starting temperature of 32 °C at a rate of 0.3 °C/s and participants were instructed to press a stop button as soon as they noticed a difference in temperature. This difference is the JND. Pressing the stop button resulted in the temperature returning back to baseline. JNDs were assessed across a range of starting temperatures (32 °C – 45 °C, with 1°C difference between each starting temperature). The average JND values are shown in Figure 2. These values were then extrapolated to obtain a JND curve over the various starting temperatures. This curve is also shown in Figure 2.

Pain threshold

Individual pain thresholds were assessed directly above the knee using the method of adjustment in six trials. The method of adjustment is frequently used in studies applying tonic pain stimulation.^{4,9,10} Participants were asked to adjust a temperature starting from 36 °C, using heating and cooling buttons, until they obtained a level which was barely painful. A constant press of the buttons resulted in the heating or cooling of the probe at a rate of 0.7 °C/s. The first two trials served as an exercise. The average of the last four trials was considered as the pain threshold.

Tonic heat stimulation

JNDs and the individual pain threshold values were used to define the target temperatures of the tonic heat stimuli for each participant. The estimated JND curve was used to determine the participant's JND, based on the participant's pain threshold. The five stimulus intensities that we used were: pain threshold minus 2*JND (-2JND), pain threshold minus 1*JND (-1JND), pain threshold, pain threshold plus 1*JND (+1JND) and pain threshold plus 2*JND (+2JND). Using JNDs, we are assured that we use the smallest differences between intensities that participants are still able to detect. The stimuli were presented in a pseudo-randomized order.

For tonic heat stimulation we used the tonic heat pain model, which makes it possible to produce tonic pain perception over lengthy periods (6 minutes) without reaching pain tolerance level. This model has been described in detail before.¹¹ In short, the temperature started at a baseline of 36 °C and increased with a rate of 0.5 °C/s until the target temperature was reached. The stimuli of the tonic heat pain model consisted of small heat pulses with a constant frequency of 30 pulses/min (Figure 1C). The temperature was then oscillating with an amplitude of 1.3 °C (target temperature being reached at the peak) for six minutes.

Figure 2. Just noticeable difference (JND) curve. JND describes the objective change in temperature that is needed for a person to notice this change subjectively. It depends on the starting temperature, with higher starting temperatures leading to smaller JNDs. The average JND values are derived from a pilot study, where we assessed JND in a group of 20 participants. The results were extrapolated to obtain a JND curve.

Pain ratings

Pain sensation was rated during the last five seconds of each minute of stimulation (Figure 1B). This resulted in six ratings per tonic stimulus, which were averaged to obtain one subjective pain sensation for each stimulus intensity. A numerical rating scale (NRS) was used, which was displayed on a computer screen. This scale ranged from 0 to 10, in which 0 was defined as ‘no sensation’, 5 as ‘slightly painful’ and 10 as ‘extremely intense pain’. Accordingly, all painful stimuli should be rated with a 5 or higher and all non-painful stimuli should be rated by a number lower than 5.

EEG recording and analysis

EEG was recorded during the administration of the thermal stimuli. Eleven electrodes were affixed according to the 10/20 convention using the ECI Electro-Cap Electrode system (Electro-Cap International, USA), which was available in three sizes. Before attaching the electrodes, the scalp was prepared with alcohol to reduce resistance and participants were instructed to move as little as possible during recording. Our aim was to use an analysis approach that is more easy to apply and thus, has the potential to also be used in more clinical settings (e.g. to assess pain in non-verbal patients with dementia). To this aim, only three electrodes were used for further analyses. So far, there seems to be no specific electrodes that show a consistent association with pain across all studies. Since we wanted to cover at least anterior, middle and posterior regions of the brain, we decided to use the electrodes placed on the midline (Fz, Cz and Pz). Lateral electrodes would have increased the number of electrodes (given

right and left sites). The Cz electrode served as a reference during EEG recording, but this was then re-referenced to two electrodes attached to the mastoid bones. A ground electrode was connected to the forehead above the nasion. The electrooculography (EOG) was recorded for detection of eye movement artifacts with electrodes in the horizontal axis. Impedance was controlled to be lower than 5 k Ω . The EEG signals were recorded, amplified and analyzed using respectively BrainVision Recorder, BrainVision V-Amp and BrainVision Analyzer (Brain Products) software. Per minute of stimulation, three 2-second long artifact-free epochs were taken for analysis. This resulted in 18 epochs per stimulus intensity (6 minutes x 3 epochs). The criteria for the selection were no eye movements registered by the EOG and no apparent disturbances or irregularities in the EEG signal on visual inspection. Furthermore, no epoch was taken from the last 5 s of a recording minute, as the pain ratings were given during this time. Spectral analysis was performed using Fast Fourier Transform. Relative power spectra were calculated for each electrode for the frequency bands delta (0.5-3.5 Hz), theta (4-7 Hz), alpha1 (7.5-9.5 Hz), alpha2 (10-12 Hz), beta1 (13-23 Hz) and beta2 (24-34 Hz). The relative power of all 18 epochs per stimulus intensity were averaged to obtain a single power value for each stimulus intensity, separately for each frequency band and electrode.

Statistical analysis

Subjective pain sensation

Analyses of variance with repeated measures were conducted to examine whether the five stimulus intensities were rated significantly different as well as to confirm that the selected intensities elicited sensations in the expected range (non-painful as well as painful sensations).

Association between EEG power and stimulus intensity/subjective pain sensation

Multiple block wise linear regression analyses were conducted to examine whether stimulus intensity and/or subjective pain sensation could explain variance in EEG power. Regression analyses were performed for each frequency band separately using EEG power as the dependent variable. To control for electrode site (Fz, Cz, Pz), electrode site was entered as a dummy variable in the first step. In the second step (step 2), stimulus intensity was entered. In the last step (step 3), subjective pain sensation (ratings) was entered in the regression analyses to investigate whether subjective pain sensation can explain variance in EEG power beyond what can be explained by stimulus intensity.

Statistical analyses were performed using IBM SPSS Statistics 24. Alpha level was set to 0.05.

Results

Stimulus intensities

The mean pain threshold was 45.51 °C (SD=0.90). The five stimulus intensities, which were based on the individual pain threshold and JND, ranged from an average of 44.42 °C (-2JND; SD=0.92) to an average of 46.60 °C (+2JND; SD=0.88) (see Figure 3A).

Subjective pain sensation

As can be seen in Figure 3B, subjective pain ratings (NRS scale) increased significantly across the five stimulus intensities ($F(4,140)=108.5$, $p<0.001$). As intended, the two temperatures below pain threshold were on average rated as non-painful, whereas the two temperatures above pain threshold were on average rated as painful.

Figure 3. Mean values ($\pm$ SD) of (A) stimulus intensities applied during tonic stimulation and (B) of the subjective pain ratings. JND, just noticeable difference.

Stimulus intensities and subjective pain sensation predicting EEG responses

Multiple block wise linear regression analyses were conducted to examine whether stimulus intensity and/or subjective pain sensation could explain variance in EEG power during tonic heat stimulation for the frequency bands alpha1, alpha2, beta1, beta2, theta and delta. The results of each frequency band are reported below and in Table 1. The average EEG power values can be found in Figure 4-6.

Alpha1

After controlling for electrode site, stimulus intensity did not lead to a significant increase in explained variance of alpha1 power (Table 1). When entering subjective pain sensation to the model in the third step, we also did not find a significant increase in explained variance. Thus, we found no evidence that stimulus intensity or subjective pain sensation are related to alpha1 power during tonic heat stimulation.

Alpha2

After controlling for electrode site, stimulus intensity again did not lead to a significant increase in explained variance of alpha2 power (Table 1). However, when entering subjective pain sensation to the model in the third step, we did find a significant increase in explained variance of 2%, with increased pain sensation being related to a decrease in alpha2 power. Thus, our results indicate that subjective pain sensation is significantly related to alpha2 power during tonic heat stimulation but we found no evidence that stimulus intensity is related to alpha2 power.

Beta1

After controlling for electrode site, stimulus intensity again did not lead to a significant increase in explained variance of beta1 power (Table 1). As we found for alpha2 power, entering subjective pain sensation to the model in the third step led to a significant increase in explained variance (5%), with increased pain sensation being related to a decrease in beta1 power. Thus, our results indicate that subjective pain sensation is significantly related to beta1 power during tonic heat stimulation, but we found no evidence that stimulus intensity is related to beta1 power.

Beta2

Again, only subjective pain sensation led to a significant increase in explained variance of 2% (Table 1), with increased pain sensation being related to a decrease in beta2 power. Thus, our results indicate that subjective pain sensation is significantly related to beta2 power during tonic heat stimulation, but we found no evidence that stimulus intensity is related to beta2 power.

Table 1. Results of the multiple linear regression analyses. Analyses were performed for each frequency band ($\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, δ and θ) using EEG power as the criterion variable. In step 1, electrode site was entered as dummy variables. In step 2, stimulus intensity was entered as a predictor variable. In step 3, subjective pain sensation was entered as a predictor variable.

	Step	Predictor variable	β	t	Statistics – overall			Statistics – model change	
					R^2	F	p	ΔR^2	p
$\alpha 1$	1	Electrode site*			0.11	31.65	<0.001	0.11	<0.001
	2	Stimulus intensity	-0.01	-0.16	0.11	21.06	<0.001	<0.01	0.940
	3	Pain sensation	0.01	0.15	0.11	15.77	<0.001	<0.01	0.885
$\alpha 2$	1	Electrode site*			0.05	16.06	<0.001	0.06	<0.001
	2	Stimulus intensity	0.17	2.73	0.05	10.69	<0.001	<0.01	0.937
	3	Pain sensation	-0.22	-3.64	0.07	11.52	<0.001	0.02	<0.001
$\beta 1$	1	Electrode site*			0.02	4.20	0.015	0.02	0.015
	2	Stimulus intensity	0.25	4.07	0.02	2.83	0.038	<0.01	0.739
	3	Pain sensation	-0.32	-5.22	0.06	9.05	<0.001	0.05	<0.001
$\beta 2$	1	Electrode site*			0.01	1.61	0.201	0.01	0.201
	2	Stimulus intensity	0.18	2.91	0.01	1.55	0.200	<0.01	0.231
	3	Pain sensation	-0.18	-2.85	0.02	3.21	0.013	0.02	0.005
δ	1	Electrode site*			0.02	5.84	0.003	0.02	0.003
	2	Stimulus intensity	-0.14	-2.15	0.03	5.38	0.001	0.01	0.037
	3	Pain sensation	0.06	0.99	0.03	4.28	0.002	<0.01	0.319
θ	1	Electrode site*			0.02	4.87	0.008	0.02	0.008
	2	Stimulus intensity	0.14	2.20	0.02	3.24	0.022	<0.01	0.924
	3	Pain sensation	-0.19	-3.09	0.04	4.85	0.001	0.02	0.002

* β and t values cannot be reported for “electrode site” because the three electrode sites were entered as dummy variables.

Theta

Yet again, only subjective pain sensation significantly added explained variance of 2% to the model (Table 1), with increased pain sensation being related to a decrease in theta power. Thus, our results indicate that subjective pain sensation is significantly related to theta power during tonic heat stimulation, but we found no evidence that stimulus intensity is related to theta power.

Delta

In contrast to the other frequency bands, stimulus intensity did lead to a significant increase in explained variance of 1% in the delta band, with increased stimulus intensity being related to a decrease in delta power (Table 1). However, subjective pain sensation did not show a significant association with delta power. Thus, our results indicate that stimulus intensity is significantly related to delta power during tonic heat stimulation, but we found no evidence that subjective pain sensation is related to delta power.

Figure 4. Average EEG power for the frequency bands alpha1, alpha2, beta1, beta2, theta and delta for all five stimulus intensities, recorded at electrode sites Fz, Cz and Pz. Error bars represent standard deviation.

Summary

Overall, stimulus intensity could only explain variance in EEG power in one frequency band, namely the delta frequency band. In contrast, subjective pain sensation could significantly predict the power of several frequency bands during tonic heat stimulation, namely alpha2, beta1, beta2 and theta. The relation between subjective pain sensation and EEG power during tonic heat stimulation was negative for all these frequency bands, which means that an increase in subjective pain sensation was associated with a decrease in EEG activity in these frequency bands.

Discussion

The aim of this study was to add on to our understanding of EEG responses to painful stimulation by differentiation between EEG patterns indicative of (i) the noxious stimulus intensity and (ii) the subjective pain sensation. The unique part of our study is the approach that was used to select the stimulus intensities. Whereas previous studies mostly selected intensities based on physical units (e.g. degree of Celsius), thus showing a bias towards the physical characteristics of the stimuli (the input side of nociceptive processing); we selected intensities purely based on perception, thus biasing our approach towards the psychological side (the result of nociceptive processing). More precisely, individual pain thresholds and just noticeable differences (JNDs) units were used to obtain stimulus intensities that increased with subjective equal steps. This sets us apart from previous studies.

EEG patterns indicative of the subjective pain sensation

In line with our expectations, subjective pain sensation could explain parts of the variance in EEG power in several frequency bands, namely alpha2, beta1, beta2 and theta. In all of the frequency bands, EEG power was lower when the stimulus was rated more painful. In general, this is in agreement with studies which selected their pain intensities based on physical units. One experimental study used cold water to induce pain and found that subjective pain sensation was negatively correlated with EEG power in the same frequency bands as in our study.⁸ Moreover, negative correlations between alpha power and subjective pain sensation were also found in studies using experimental heat pain.^{3,12} Thus, regardless of whether one uses a stimulation approach that is more focused on the psychological side (our approach) or on the physical side, an increase in subjective pain sensation has been found to be associated with a decrease in EEG power. However, contradictory findings have also been reported. Two other studies found that pain sensation was associated with an increase (and not a decrease) in the EEG response, namely in the gamma frequency band.^{6,7}

EEG patterns indicative of the noxious stimulus intensity

When looking at the association between EEG power and stimulus intensity, we

observed that stimulus intensity could partly explain variance in EEG power in the delta frequency band. This is in accordance with previous findings.^{1,4,13,14} In other frequency bands, however, we did not find a significant association between stimulus intensity and changes in EEG power. This is in contrast to the majority of previous studies, which found significant associations between stimulus intensity and EEG power for several frequency bands. Besides delta, alpha power has continuously been found to be negatively associated with stimulus intensities.^{1-4,8,13-15} How can this contradiction between our and previous studies be explained? One possible explanation is that selecting stimulus intensities based on JNDs resulted in very small differences between stimulus intensities (approximately 0.5°C). Previous studies often used much larger differences between stimulus intensities, ranging between 1.3°C and 13.4°C for heat stimuli,^{1,3,4} up to 30°C for cold pain.^{2,8} Thus, using very small differences between stimulus intensities as we did in the present study, we could not confirm previous findings of strong associations between stimulus intensities and EEG power. On the other hand, the findings of previous studies are also not consistent. With regard to the delta frequency for example, some studies did find changes in EEG power during painful stimulation, while other studies could not demonstrate this.^{2,8} The stimulation protocol, stimulus intensity and electrode locations often differ between studies, and are likely a major factor leading to the different results between studies. This has made it challenging to find a common EEG pattern of pain.

Noxious stimulus intensity versus subjective pain sensation

Using block wise regression analyses, we could show that subjective pain sensation can explain variance in EEG power beyond what can be explained by stimulus intensity. In accordance with the present finding, previous studies have demonstrated that subjective pain sensation is differentially encoded in EEG activity compared to stimulus intensity.^{6,7} Whereas subjective pain sensation was associated with an increase in gamma oscillations in the medial prefrontal cortex, stimulus intensity was found to be associated with a decrease in alpha and beta oscillations in the sensorimotor cortex. In contrast to these two studies, gamma oscillations were not included in our study. Assessing gamma frequency is challenging because neuronal signals in this frequency band are highly contaminated by non-cerebral electrical sources (noise), which means that the signal-to-noise ratio is quite small,¹⁶ thus making it difficult to capture a good signal. With our study we decided to focus on the more robust frequency bands (alpha, beta, delta, theta) that are less sensitive to noise. Furthermore, the type of analysis (simple power analysis vs. time-frequency/source analysis) was different in our study. It is therefore difficult to directly compare our findings to these studies. Nevertheless, there seems to be enough evidence to support the notion that subjective pain sensation and physical stimulus intensity both capture unique variance in EEG activity.

It is difficult to directly translate the findings of the current study to relevant suggestions for future clinical practice. One implication surely is that when searching for EEG patterns that are indicative of pain, one should always assess the subjective report of the person in pain regardless of whether one uses experimental pain induction or clinical pain models; given that subjective pain sensation captures unique variance in EEG activity that is independent of the noxious input. With regard to an endeavor to use EEG signal in clinical practice to measure pain more objectively, our findings suggest that a simple recording with only a few electrodes and only looking at changes in EEG power might not be enough to capture pain specific changes in EEG activity. For example, we and others have found that a decrease in alpha activity is associated with an increase in pain perception.^{3,8,12} However, changes in alpha power are not only specific to pain but can be found in various affective and cognitive states (e.g. alpha power is related to memory performance¹⁷). Thus, more elaborated recordings (e.g. more recording sites) as well as more elaborated analyses (e.g. analysis of neuronal oscillations and synchrony) are necessary in order to come closer to a pain-specific EEG pattern that could be used to assess pain in clinical practice. However, such elaborated measures might hinder clinical usefulness because they are not easy to use.

Limitations

One important limitation is that we limited our analyses to three EEG electrodes, whereas other studies used a higher number of recording electrodes covering a broader surface of the brain. We wanted to reduce type II error (analyzing the EEG data for various recording sites would have substantially increased the number of analyses) and we aimed for an easy to use analysis approach (making it more useful for clinical practice). However, the disadvantage is that this small number might have limited the likelihood of finding effects. Indeed, the effects we found were rather small, with the highest explained variance being only 5%. The second limitation is that we used an averaged pain sensation over time for the statistical analyses instead of using the subjective pain sensation for each minute, which might have resulted in more precise findings. However, we decided to not analyze the data per minute because this would have increased the number of analyses by factor six. Moreover, the pain sensation across the six minutes was also quite stable. Although there were significant changes over time, these were rather small, with an average decrease of 0.9 on the NRS at the lowest tonic heat intensity and an average increase of 0.5 on the NRS for all remaining heat intensities.

Conclusion

In conclusion, we observed that EEG power during painful stimulation occurring across the midline of the brain mirrors more closely the subjective pain sensation than the stimulus intensity. Subjective pain sensation could explain variance in several frequency bands beyond what could be explained by stimulus intensity. This is likely

due to the way we selected stimulus intensities, biasing our stimulation towards the psychological compared to the physical side. Using this stimulation approach, we find that EEG activity mirrors more closely the psychological output side (ratings), than the physical input side (stimulus intensity) of nociceptive processing.

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Chapter 4

Conditioned pain modulation (CPM) effects captured in facial expressions

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Abstract

Background: Conditioned pain modulation (CPM) is most often assessed using self-report of pain. However, self-report of pain is not always available (e.g. in individuals with cognitive impairment) and is susceptible to report bias. In comparison, the facial expression of pain is more reflex-like and represents one of the most sensitive and specific non-verbal signals of pain. The aim of the present study was to investigate whether the facial expression of pain is sensitive enough to capture endogenous pain inhibition as elicited during CPM paradigms.

Methods: In total, 26 female participants took part in this study. Facial and verbal responses to phasic heat pain were assessed once while participants immersed their hand in a hot water bath and once without additional stimulation. Facial responses were analyzed using the Facial Action Coding System (FACS). Verbal responses were assessed using a Numerical Rating Scale (NRS).

Results: Pain-relevant facial responses as well as pain ratings to phasic heat pain were significantly reduced when participants simultaneously immersed their hand in a hot water bath compared to baseline. Thus, CPM effects could be demonstrated both on subjective as well as on facial responses. Moreover, CPM-induced changes in pain-relevant facial responses and in NRS ratings were significantly correlated.

Conclusion: The present study shows that facial expressions of pain are sensitive enough to capture CPM effects. Given the proven clinical usefulness of assessing CPM, the parallel assessment of verbal and facial CPM effects might be a promising approach with wider scope of applications. Further research in other demographic healthy participants and clinical cohorts is warranted.

Introduction

The study of pain inhibition by use of the so-called conditioned pain modulation (CPM) paradigm has become a major focus of interest in clinical pain research. The CPM paradigm refers to an experimental procedure that examines the extent to which pain responses to phasic stimuli (test stimuli) are reduced by the concurrent application of a tonic stimulus (conditioning stimulus) applied to a remote area of the body. There does not exist one gold-standard CPM protocol, but there is much variability with regard to the mode of application of the “test” as well as the “conditioning” stimuli. Despite the methodological variability, greater reductions in pain responses are interpreted as greater endogenous pain inhibition. There is clear evidence that CPM responses are reduced in many chronic pain syndromes^{1,2} such as chronic low back pain,³ irritable bowel syndrome,⁴ chronic orofacial pain,⁵ fibromyalgia,⁶ migraine^{7,8} and chronic tension-type headache,⁹ although it is still not definitely established whether the chronic pain is a consequence or cause of the changed CPM. Further studies addressed whether changes in CPM mediate or predict anti-nociceptive effects of certain forms of pain management^{1,10–12} while others targeted the analgesic effects of certain drugs and alcohol.^{13–16} Based on these findings, there is growing interest to use CPM paradigms in clinical practice for pain diagnostics and mechanism-based treatment (e.g. to predict analgesic responses or the risk for developing postoperative pain).^{17,18} Given its potential clinical relevance, it is not surprising that non-pathological variations of CPM due to age,¹⁹ sleep,^{8,20} personality²¹ and sex²² have also been found to affect CPM.

Most of the studies have applied psychophysical protocols, where changes in self-report ratings of the test stimulus are used as indicators of potential CPM effects. Relying solely on self-report ratings, however, limits the CPM assessment to vigilant and cognitively healthy individuals. There are methodological alternatives, which do not require self-report ratings, with the nociceptive flexion reflex (NFR) being the most frequently used alternative method to assess CPM inhibition.²³ Moreover, in a few recent studies, nociceptive brain potentials were also used as an alternative method for CPM inhibition.^{24–26} NFR and brain potentials can, however, only be elicited by very brief stimuli as produced by electrical current, short heat pulses and nasal gas puffs, that show little resemblance to clinical pain states.

To widen the methodological scope of CPM protocols, the aim of the present study was to test – for the first time – whether behavioral pain responses may also show CPM inhibition. In contrast to NFR and brain potentials, behavioral responses have the advantage that they can be elicited using a wider range of pain stimuli of various length; and thus, by stimuli that might show greater resemblance to clinical pain states. Facial responses to pain are the most prominent behavioral indicator of pain and they allow for fine-grained graduations both of clinical and experimental pain.²⁷ In case

of experimental pain, various modalities (heat, cold, pressure) and durations (phasic, tonic) can be used to reliably evoke facial activity.²⁷ The question under study was whether CPM effects can be inferred by using facial responses as outcome measures. We expected similar CPM effects for facial and for verbal responses, although facial and verbal responses to pain have rarely been shown to be strictly coupled.²⁸ Thus, the inhibitory effects on the facial responses were expected to be overlapping but yet independent from verbal responses. We created ideal conditions for this first test of a “facial CPM paradigm” by only studying women, which have been shown to facially express pain in a more fine-grained manner than men.²⁹

Methods

Participants

We recruited 27 female participants (age: mean=24.1; SD=4.4) by bulletins put up throughout the campus of the University of Jena. Sample size calculation (GPower 3.1) was based on previous studies^{14,30,31} and on our interest in “medium” effects that might be of clinical relevance (sample size calculation were conducted for 80% power and 0.05 level of significance; resulting in the above mentioned N of 27 subjects). All participants underwent a screening to test for any psychiatric disorders using the German version of the Mini-International Neuropsychiatric Interview (MINI)³² and a semi-structured interview for recording past and current neurological as well as psychiatric symptoms and disorders. Moreover, all participants were pain free and all participants were right-handed. The present experiment was part of a larger study on the effect of tryptophan depletion on cognitive performances, brain activation and pain.³³ Data of the present experiment were assessed during the pharmacological control condition. The study complied with the Declaration of Helsinki. Informed written consent was obtained in accordance with the protocols approved by the Ethics Committee of the University of Jena and all participants received monetary compensation. All participants were blind to the study hypothesis.

Design

The testing took place at the Department of Psychosomatic Medicine and Psychotherapy of the University Hospital Jena. The experimental procedure used to assess CPM effects was divided into three blocks (see Figure 1). In the first block, the individual heat pain threshold was assessed. In blocks 2 and 3, phasic heat pain (tailored to the pain threshold) was applied once without (baseline block) and once with concurrent tonic heat pain stimulation (CPM block). Facial and verbal responses to the phasic and tonic pain stimulation were assessed (see Figure 1).

Figure 1. Graphical overview of the study protocol.

Block 1: Heat pain thresholds

Thermal stimulation was applied on the tibia of the left leg (centrally in between knee and ankle) by a Peltier based contact stimulation device (Medoc, TSA-2001, Ramat Yishai, Israel) with a 30*30 mm contact thermode that was attached to the leg via an elastic bandage. Heat pain thresholds were determined using the method of limits. The temperature increased from 35°C at a rate of 1°C/s and participants were asked to press a mouse button as soon as the temperature reached a level that was barely painful. Each time they pressed the button, the temperature returned to 35°C (5°C/s) and the next trial started after an inter-stimulus interval of 9–11 seconds. Following two familiarization trials, there were four trials and the average of these trials was used to constitute the threshold estimate.

Block 2 and 3: Assessment of conditioned pain modulation (CPM)

CPM was assessed with thermal stimuli as conditioning (hot water immersion) as well as test (thermode) stimulus. This kind of parallel combination of hot water immersion for conditioning stimulation and thermode application for test stimulation has been well established in our laboratory and showed robust inhibitory effects in several studies for psychophysical data.^{4,30,31}

The test stimuli were applied on the tibia of the left leg by the above described Peltier-based contact stimulation device. The intensities were tailored to the individual threshold (+3°C above threshold) to ensure that the stimulation would be perceived as painful but tolerable. During each block, eight test stimuli were applied. The temperature increased from baseline (38°C) with a rate of 5°/s until it reached the target temperature, and remained at a plateau for 5s, before returning to baseline. A long and variable inter-stimulus interval (ISI) between 12 and 15s was used to prevent sensitization and to allow subjects to rate each stimulus. The eight test stimuli were first applied alone (block 2), and then in combination with the conditioning stimulus (block 3).

As a conditioning stimulus, we used tonic heat stimulation, which was realized by hand immersion in a circulation water bath (Witeg GmbH, WiseCircu WCB-22, Wertheim, Germany) containing water at a temperature of 46.5 °C. The participant immersed the right hand up to 2 cm above the wrist in this water bath. Water temperature was controlled with a thermostat, and the water was stirred with a force and suction pump to avoid layers of lower temperature around the hand. The immersion time of the hand into the water bath was as long as necessary to apply all eight test stimuli, which took around 4.5 minutes (test stimuli started after 30 seconds of hand immersion).

Pain responses

Self-report ratings

After the application of each test stimulus, participants were asked to verbally rate the perceived intensity using a numerical rating scale (NRS; 0–100). Participants were instructed that “0” corresponded to “no pain” and “100” to “extremely strong pain”, respectively. With regard to the conditioning stimulus, participants were asked at the beginning (after 10 seconds immersion time) as well as the end of hand immersion to verbally rate the pain intensity caused by water immersion on the same NRS (0–100).

Facial pain responses

The face of the participants was videotaped throughout blocks 2 and 3. The camera was located approximately 2.0 m from the participant. In order to mark the plateau phase of the stimuli, a LED visible to the camera, but not to the participant, was lit concurrently with the test stimuli, starting when the target temperature was reached. During stimulation, participants were instructed not to talk and to look at a cross on the wall behind the camera to ensure that the face would always be recorded in an upright and frontal view.

Facial expressions were coded from the video recordings using the Facial Action Coding System (FACS)³⁴, which is based on anatomical analysis of facial movements and distinguishes 44 different Action Units (AUs) produced by single muscles or combinations of muscles. A certified FACS coder (qualified by passing an examination given by the developers of the system), who was blind to the condition, identified the frequency and the intensity (5-point scale) of the different Action Units. In addition, 10% of the video data was also coded by a second certified observer and interrater reliability (using the Ekman–Friesen formula)³⁴ was 0.81, which compares favorably with other research in the FACS literature.^{35,36} A software designed for the analysis of observational data (the Observer Video-Pro; Noldus Information Technology) was used to segment the videos and to enter the FACS codes into a time-related database. Time segments of 7 s (5 s of plateau + 2 s return to baseline) were selected for scoring. In total, 16 segments of phasic pain stimulation (8 test stimuli x 2 blocks) were analyzed in each participant. For the purpose of necessary data reduction, we combined similar facial responses as has been done in preceding studies without any loss of information.^{36–39} Those combinations include AU1_2, AU6_7, AU9_10 and AU25_26_27. The percentage of occurrence of each AU was calculated across the 16 segments of phasic pain stimulation and are shown in Figure 2 (AUs that were never scored are not displayed).

For further analyses, we focused only on pain-relevant AUs, which are based on a recent review article on facial expressions of pain²⁷ and include AU4 (contraction of the eyebrows), AU6_7 (contraction of the muscles surrounding the eyes), AU9_10 (nose wrinkle/upper lip raise) and AU 26_26_27 (opening of the mouth). As can

be seen in Figure 2, these also were the most frequent AUs in the present study. AU-frequency and AU-intensity values for each of these pain-relevant AUs were combined (product terms) and then square root transformed, due to the fact that the values were not distributed normally (Kolmogorov–Smirnov p -values < 0.05).

Analyses

CPM effects on subjective and facial responses were analyzed using analyses of variance with repeated measurements (comparing responses to the test stimuli in the baseline block vs CPM block; ANOVA for verbal responses, MANOVA for facial responses). Moreover, we used correlation analysis to assess whether there is an association between subjective and facial CPM effects. Analyses were conducted using SPSS 26 and findings were considered to be statistically significant at $\alpha < 0.05$.

Figure 2. Percentage of occurrence of facial action units (AUs) across all painful stimuli (combining baseline and CPM blocks).

Results

The average heat pain threshold was 45.01°C (SD 1.07). Given that the test stimuli were tailored to the individual pain threshold (+3°C above threshold (there was one participant where the temperature could only be increased +2.9°C due to the upper temperature limit of 50°C)), the average temperature of the test stimuli correspondingly was 48.01 °C (SD 1.07°C) (intensities ranging from 45.6°C to 50.0°C).

The hot water immersion conditioning stimulus (stimulus intensity was set to 46.5°C) was rated as moderately painful (mean NRS rating of 61.6 (± 26.9) at the beginning and 65.4 (± 27.8) at the end ($p < 0.01$ between ratings)). In order to ensure that facial responses during the CPM paradigm (phasic heat) were not confounded by facial responses to the hot water immersion, we also inspected facial expressions occurring in response to the hot water immersion. Although facial expressions of pain were elicited by the hot water immersion, these facial responses were sparse and of low intensity and almost never (<3%) occurred right before the onset of the test stimulus (thermode) (3 seconds before start).

Conditioned pain modulation (CPM)

Self-report rating

As can be seen in Figure 3A, pain ratings of the phasic heat stimuli significantly decreased when participants simultaneously immersed their hand in a hot water bath compared to no concurrent pain stimulation ($F(1,25)=6.31$, $p=0.019$; effect size Cohen's d : 0.73). Thus, we found a significant CPM effect of moderate effect size on pain ratings. To determine whether this CPM effect might depend on the individual test stimulus temperature, we correlated the CPM effect (change in the NRS scores) with the test stimulus temperature and found no significant association ($r=0.287$, $p=0.155$).

Facial response

The MANOVA yielded a significant multivariate CPM effect ($F(4,22)=3.15$, $p=0.034$; effect size partial eta squared η^2 : 0.364). As can be seen in Figure 3B, facial responses to phasic heat pain significantly decreased when participants simultaneously immersed their hand in a hot water bath. As regards the univariate outcomes, we found significant CPM effects for contraction of the eyebrows (AU4; $p=0.014$; Cohen's d : 0.76), contraction of the muscles surrounding the eyes (AU6_7; $p=0.010$; Cohen's d : 0.79) and lifting of the upper lip (AU9_10; $p=0.018$; Cohen's d : 0.78), whereas no significant CPM effect was found for opening of the mouth (AU25_26_27; $p=0.125$; Cohen's d : 0.44). Thus, we found significant CPM effects of moderate to large sizes inferred by three out of the four pain-relevant facial responses. Figure 4 gives an individual example of the CPM effects inferred by facial responses.

To determine whether the significant CPM effects might depend on the individual test stimulus temperature, we correlated the CPM effect (change in the pain-relevant composite AU score) with the test stimulus temperature and found no significant association ($r=0.030$, $p=0.870$).

In an additional step, we wanted to investigate whether the CPM effects on self-report ratings and on facial responses, respectively, are independent enough, so that they prevail even when controlling for the other type of response.

Self-report (covariate facial response)

When entering the CPM effect on pain-relevant facial responses (change in the pain-relevant composite score) as a covariate into the analysis of variance, no significant CPM effects on self-report ratings could be found ($F(1,24)=0.635$, $p=0.433$; effect size η^2 : 0.026 (small effect)).

Pain-relevant facial response (covariate self-report)

When entering the CPM effect on self-report ratings (change in the NRS scores) as a covariate into the analysis of variance, the significant CPM effect on pain-relevant facial responses remained ($F(1,24)=5.859$, $p=0.023$; effect size η^2 : 0.202 (large effect)).

Figure 4. Examples of pain-relevant facial responses to the phasic heat pain (test stimuli) assessed during baseline block and the CPM block. The individual in the figure provided informed consent for her photos to be published.

A Self-report ratings

B Pain-relevant facial responses

Figure 3. CPM effect on self-report ratings (A) and on pain-relevant facial responses (B). Mean responses (and SD) are given for the baseline block and the CPM block. AU4, contraction of the eyebrows; AU6_7, contraction of the muscles surrounding the eyes; AU9_10, nose wrinkle/upper lip raise; AU 26_26_27, opening of the mouth. *Indicates $p < 0.05$; ns, not significant; NRS, numerical rating scale.

Correlation between self-report and facial CPM effect

In a last step, we wanted to investigate whether there is an association between CPM effects on self-report ratings and on facial responses. Correlation analysis showed a positive, moderate association between CPM effects on self-report ratings and on pain-relevant facial responses (composite score) ($r=0.449$, $p=0.021$). As can be seen in Figure 5, greater CPM effects on self-report ratings were associated with greater CPM effects on pain-relevant facial responses.

Figure 5. Correlation between CPM effects (change scores between baseline and CPM blocks) in the two pain response systems.

Discussion

In the present study, CPM effects were for the first time documented by assessing the reactions to the test stimuli through recording facial responses and not – as typically done – by means of self-report. What was the reason for looking for such behavioral alternatives? The motivation of this endeavor was to develop a protocol that does not depend on the individual being vigilant, cognitively healthy and/or linguistically competent. The presented methodological modification allows for widening the scope of CPM applications to cases with altered or limited consciousness and vigilance, cognitive impairment, aphasic problems and dementia. The available electrophysiological alternatives quantifying the modulatory CPM effect on the test stimulus by assessing nociceptive flexion reflexes²³ or nociceptive brain potentials^{24–26} are limited to very brief stimuli with a very immediate onset that do not mirror most clinical pain states. The use of facial responses allows application of clinically more relevant stimuli and responses.

The inhibitory effects determined through recording the facial responses were statistically significant and were of comparable size as the inhibitory effects assessed by means of psychophysical parameters (i.e. NRS ratings) in the present study. The facial responses also clearly show the peculiarity of CPM inhibition, which leads – in most cases – to a reduction of pain indication although a second pain stimulus was added and the total noxious load is increased. Thus, our CPM probe using facial responses appeared to be as sensitive as the typical CPM paradigms (demonstrating the variability in the CPM effect, ranging from inhibition (in most cases) to facilitation), at least under the ideal conditions, which we created for this first time testing by studying only women (women are known to grade pain intensities by different facial responses very well²⁹ and were for that reason sampled in the present study).

Interestingly, the CPM effect shown for facial response was not redundant to the one shown for self-report because the two modulatory effects were indeed significantly correlated but the correlation was only of moderate size allowing for the assumption of much unrelated variance. The relative independence of the “facial CPM” was also shown by the fact that statistically considering the variance of the “verbal CPM” effect did not abolish the large “facial CPM” effect. This finding relates well to the observation that although self-report ratings as well as facial responses to pain both reflect the intensity and the unpleasantness dimensions of pain,^{35,40} there are nevertheless some aspects of the multidimensional pain experiences that are not fully captured by each type of response (e.g.^{28,35,41,42}). Moreover, the self-report of pain is complex and is influenced as well as biased by higher mental processes. The facial response – in contrast – is a more automatic response that is less subject to voluntary control by higher mental processes.⁴³ Given the more reflex-like nature of facial responses, facial CPM probes might even give more direct insights into the basics of CPM mechanisms.

It has been shown over the last two decades that there is sizeable inter-individual variance in the facial expression of pain, which is due to varying combinations of Action Units (AUs).²⁷ The unifying backbone of these varying pain-relevant combinations seems to be AU 6_7 (contraction of the muscles surrounding the eyes; orbicularis oculi contraction).^{27,41} The orbicularis oculi contraction (AU 6_7) is the most frequent facial response to pain and may be combined with AU 4 (contraction of the eyebrows) or AU 9_10 (nose wrinkle/upper lip raise) or AU 25_26_27 (opened mouth) leading to the various pain faces known.⁴⁴ Given that we found significant CPM inhibition in 3 out of the 4 pain-relevant AUs and given that AU 6_7 (“unifying backbone” of the pain faces) showed a moderate to large CPM effect suggests that despite the variability in facial responses to pain, CPM effects can be found regardless of the individual pain face. Our finding also suggests, that it might be sufficient to just focus on the contraction of the muscles surrounding the eyes (AU 6_7) in order to assess the endogenous inhibitory CPM effects in the face. Just focusing on one facial movement could make it easier to apply this method in research (e.g. assessment via EMG recordings or FACS analysis) and in clinical context.

If future studies can replicate our findings and show that the facial CPM effect is a reliable and valid alternative of assessing endogenous pain inhibition in humans,^{2,45} the scope of study can be widened to patients, who are compromised in verbal communication due to impairments of cognitive and linguistic skills or by restriction of vigilance and consciousness.^{46–48} However, verbal and non-verbal assessment of pain inhibition must not be seen as mutually exclusive alternatives. Instead, both can strengthen the sensitivity of a diagnostic probe for testing CPM effects also in vigilant and cognitively intact humans when assessed in parallel, given the unique information that each type contributes.⁴³ Whereas the facial expression of pain can capture more bottom-up, automatic aspects of pain, the verbal report is easier to assess. Moreover, only relying on facial expression might hold the risk that mild pain is overlooked (given that the threshold of eliciting facial responses is often higher than the subjective pain threshold). The sample of the present study was deliberately biased to include only young women to create optimal conditions for this first time testing of CPM effects by recording the facial responses to the test stimulus. Since we were successful in verifying facial CPM effects in individuals who are particularly apt in facially expressing pain in a graded fashion,²⁹ replications in men and individuals with advanced ages⁴⁹ are now the necessary next step. Since FACS coding is still a manual task that requires a lot of time for execution, we could not manage the study of both genders and further age groups at once. Moreover, in future studies, different CPM protocols could be tried out;⁵⁰ e.g. applying the test stimuli after the end of the conditioning stimulus (sequential paradigm) to better separate the effect of distraction on facial and subjective pain responses from CPM effects.

Conclusion

We succeeded for the first to demonstrate modulatory CPM effects through recording of the facial response to the test stimuli instead of only using self-report ratings as a response measure. Given the clinical relevance of assessing CPM effects, the parallel assessment of verbal and facial CPM effects might be a promising approach with wider scope of applications and increased diagnostic robustness against biasing influences.

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Chapter 5

Pain processing in older adults and its association with prefrontal characteristics

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Abstract

Background: Aging is known to affect nociceptive processing, e.g. the ability to inhibit pain. This study aims to investigate whether pain responses in older individuals are associated with prefrontal characteristics, namely (i) executive functioning performance and (ii) structural brain variations in the prefrontal cortex.

Methods: Heat and pressure stimuli were applied to assess pressure pain sensitivity and endogenous pain inhibition in 46 healthy older individuals. Executive functioning performance was assessed in three domains (i.e. cognitive inhibition, shifting, and updating) and structural brain variations were assessed in both gray and white matter.

Results: Overall pain responses were significantly associated with the executive functioning domains cognitive inhibition and shifting. However, no specific type of pain response showed an especially strong association. Endogenous pain inhibition specifically showed a significant association with gray matter volume in the prefrontal cortex and with variations in white matter structure of tracts connecting the prefrontal cortex with the periaqueductal gray. Hierarchical regression analyses showed that these variations in the prefrontal cortex can explain variance in pain inhibition beyond what can be explained by executive functioning.

Conclusion: This results of this study might indicate that known deficits in pain inhibition in older individuals are associated with structural variations in prefrontal areas.

Introduction

Acute and chronic pain are more common in older than in younger individuals,^{1,2} and it has been suggested that this increased pain prevalence is partly due to age-related changes in nociceptive processing. Using experimental pain to study age-related changes in pain processing, the majority of evidence point to an increase in pain threshold (indicating decreased nociceptive processing) but also an increase in temporal summation of pain as well as a decrease in endogenous pain inhibition (both indicating increased nociceptive processing). Based on these findings, it has been suggested that both ascending excitatory and descending inhibitory pathways are altered during aging. However, inhibitory pathways might be more affected than excitatory pathways, thus leading to a higher pain prevalence in older individuals.³

Previous studies have tried to look for mechanisms that might underlie or accompany these age-related changes in pain processing. One of the mechanisms that has been studied is cognitive functioning, in particular, executive functioning. Executive functions are higher order skills that are linked to the function of the frontal cortex and that enable an individual to control behavior.⁴ Frontal functions are often subdivided into three domains: cognitive inhibition, shifting, and updating.⁵ Poorer functioning in these domains was found to be associated with reduced pain tolerance,⁶ increased pain responses⁷ and poorer endogenous pain inhibition^{8,9} in older individuals. Thus, frontal functioning might be one mechanism underlying increased pain processing in older individuals.

Executive functioning tests are considered to be an indirect measure of frontal functioning. Another indirect measure of frontal functioning is to assess the structure of the frontal cortex. It is known that the structure of the frontal cortex changes during aging, as observed by gray matter atrophy¹⁰ and alterations in white matter structure.¹¹ Given that the prefrontal cortex is thought to play a key role in the processing of pain, especially in descending pain modulation,¹² we hypothesize that pain responses in older individuals are not only associated with executive functions but also with structural variations within (gray matter) and between (white matter) the prefrontal cortex and other brain regions involved in pain processing.

To test this hypothesis, we assessed pain responses in a group of older individuals using two experimental pain paradigms, namely, sensitivity to phasic pressure pain and conditioned pain modulation (CPM) using heat and pressure pain to assess endogenous pain inhibition. Responses were assessed via verbal ratings as well as via facial expression to capture two output channels of pain. Assessing two output channels (self-report as the more controlled output where older adults have been found to be more reticent in reporting pain and facial expression as the more automated output with no age-related changes)^{13,14} might allow a more comprehensive assessment of pain. We investigated whether these pain responses in

older individuals are associated with prefrontal characteristics by relating them (i) to the different domains of executive functioning and (ii) to variations in gray and white matter structure of the prefrontal cortex.

Methods

Participants

Fifty-nine healthy older individuals were recruited through advertisements and among students of the local University of the Third Age. After exclusion of 13 participants of whom we could not obtain a structural brain scan (because of claustrophobia (N=2), metal implants (N=9), or image artifacts (N=2)), forty-six individuals participated in this study. None of the participants had a history of major neurological or psychological disorders and no participants had taken analgesic medication on the day of testing. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University Medical Center Groningen (code 2016/398). A written informed consent was obtained from all participants. Participants received monetary compensation for their participation.

Study procedure

The study consisted of three parts. Part one (experimental pain tests) and part two (executive functioning tests) were generally conducted between 10:00 a.m. and 3:00 p.m. On a separate day, participants underwent a structural magnetic resonance imaging (MRI) scan (part three). Figure 1 provides an overview of all variables used in the three parts of the study.

Experimental pain protocol

Apparatus

Pressure stimuli were applied to the midpoint of the upper border of the trapezius muscle (back shoulder area) using a pressure algometer with a probe area of 1 cm² (Algometer type II, Somedic Sales AB, Hörby, Sweden). Heat stimuli were administered to the right inner forearm using a thermal sensory analyzer (Medoc TSA II, Ramat-Yishai, Israel) with a Peltier thermode with a stimulation surface of 6 cm².

Pressure pain sensitivity

Four different pressure intensities (50, 200, 400, and 500 kPa) were applied to the shoulder in an ascending order. There were two trials, one to the right shoulder and one to the left shoulder. An ascending order was chosen to reduce anxiety in participants as well as to be able to immediately stop with the stimulation protocol if a participant found the stimulation to be too painful (this did not occur in the present sample). Pressure was increased steadily for 2 seconds until the desired intensity was reached and was then kept constant for 5 seconds.

Figure 1. An overview of all variables used in this study.

CPM

Endogenous pain inhibition was assessed using the CPM paradigm, in which a conditioning stimulus and a test stimulus are applied simultaneously to different parts of the body to test the modulating effect of the conditioning stimulus. The test stimuli used in this CPM paradigm were comparable to the stimuli used to assess pressure pain sensitivity, namely, four pressure intensities of 50, 200, 400, and 500 kPa applied to the right and left shoulder. Tonic heat stimulation served as the conditioning stimulus and consisted of a series of small heat pulses at a frequency of 30 pulses/min with an amplitude of 1.3 °C applied on the right inner forearm.^{15–19} Thus, the test stimuli were presented bilateral and the conditioning stimulus was presented on the right side. In the first block, the test stimuli on the shoulder were applied together with nonpainful tonic heat stimulation of 43 °C (baseline stimulus). In the second block, the test stimuli on the shoulder were applied together with painful tonic heat

stimulation of 45 °C (conditioning stimulus). The blocks lasted for around 2 min. Pain inhibition was indicated by a lower pain response to pressure stimuli paired with painful heat than to pressure stimuli paired with nonpainful heat (pressure pain during painful heat – pressure pain during nonpainful heat ≤ 0). Pain facilitation was indicated by a higher pain response to pressure stimuli paired with painful heat than to pressure stimuli paired with nonpainful heat (pressure pain during painful heat – pressure pain during nonpainful heat ≥ 0).

Pain responses

Ratings

Immediately after each stimulus (pressure and heat stimulation), participants were asked to rate the pain sensation using a five-category verbal rating scale (no pain, mild pain, moderate pain, strong pain, and very strong pain). For further analyses, the ratings of the pressure stimuli on the right and left shoulder were averaged to obtain one rating per intensity.

Facial responses

Facial responses were assessed during each pressure stimulus. The heat stimulation serving as the conditioning stimulus in the CPM protocol was only mildly painful and therefore did not elicit facial responses. A camera was placed approximately 2 m in front of the participants to videotape the faces of the participants. Participants were instructed to look into the camera and were asked not to talk when pain was induced. Facial responses were analyzed using the Facial Action Coding System (FACS).²⁰ This system describes 44 visually distinguishable action units (AUs). A FACS coder (qualified by passing the FACS examination) both identified the frequency and intensity of all AUs that occurred during stimulation. Another qualified FACS coder recoded a subset of 10% of the video segments. Inter-rater reliability, calculated using the Ekman–Friesen formula (number of AUs agreed upon $\times 2$ and divided by the overall amount of AUs coded), was 0.80, which compares favorably with other research in the FACS literature.^{21,22} The intensity of each AU was scored using a 5-point scale, which was entered into a time-related database from the onset of the stimuli till the end of the stimuli (5 s) using the Observer Video-Pro (Noldus Information Technology, Wageningen, The Netherlands). Some AUs represent facial movements of the same muscle and were, therefore, combined to reduce the number of variables (AU 1/2, AU 6/7, AU 9/10, and AU 25/26/27). For further analyses, we only used the AUs that occurred during at least 5% of the painful stimuli and that occurred more frequently during painful pressure stimulation (500 kPa) than during nonpainful pressure stimulation (50 kPa) (Cohen's d effect size $d \geq 0.5$).^{23,24} These were AU 1/2, AU 4, AU 6/7, AU 9/10, and AU 25/26/27 (listed in Table 1). To obtain a FACS composite score for each stimulus intensity, the frequency of each AU was multiplied by the AU intensity score and then averaged over all AUs.

Table 1. Facial action units (AUs) selected for further analysis.

Action Unit	Description	Percentage*
AU 1/2	Brow raiser	18.1
AU 4	Brow lower	14.1
AU 6/7	Orbit tightening	39.9
AU 9/10	Levator contraction	20.3
AU 25/26/27	Mouth opening	35.1

*Cumulative percentage of occurrence during all 500 kPa pressure stimuli.

Executive functioning tests

Three paper-and-pencil neuropsychological tests were used to assess executive functioning performance in the domains cognitive inhibition, updating, and shifting.⁵

Cognitive inhibition

The Stroop Interference score, measured using the Stroop Color and Word test,²⁵ was used to assess cognitive inhibition. This tests consists of three parts: (i) the Reading task, in which participants are asked to read aloud color names, (ii) the Color Naming task, in which participants are asked to name the color of printed colors, and (iii) the Color Word task, in which participants are asked to name the printed color of a color word that is printed in a different color than the meaning of the word. Thus, in this last task the participants must inhibit naming the written word. Every part of the test consisted of 100 items and lasted for 45 s. The Stroop Interference score was defined by the difference in number of correct responses between the Color Naming task and the Color Word task. A higher interference score indicated worse cognitive inhibition.

Shifting

Shifting was assessed using the Trail Making Test Part B, which measures the ability to alternate between cognitive categories.²⁶ Participants were asked to connect randomly placed numbers (1–13) and letters (A–L) in ascending order, alternating between numbers and letters. The score of the Trail Making Test Part B was the time to complete the task.

Updating

Updating was assessed using the Letter Fluency task,²⁷ in which participants are asked to produce as many words in Dutch starting with the letter D within 1 min. Thus, this task measures the ability to retrieve words and keep track of those words to avoid repetition. The score of this task was the total number of words produced.

MRI acquisition and analysis

MR images were acquired using a 3T MRI scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). A T1-weighted image was acquired using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (176 sagittal slices, repetition time=2300 ms, echo time=2.98 ms, inversion time=900 ms, flip angle=9°, voxel size=1×1×1 mm³, and field-of-view=256 mm²). Diffusion-weighted images were acquired along 64 directions using a b-value of 1000 s/mm² (60 slices, repetition time=6300 ms, echo time=66 ms, voxel size is 2.2×2.2×2.2 mm³, and field-of-view=220 mm²). Ten volumes with no diffusion weighting (b-value of 0 s/mm²) were acquired, one at the beginning and nine at the end of the acquisition. Despite of claustrophobia being an exclusion criterion, two participants experienced claustrophobia halfway during scanning time and, therefore, the acquisition of the diffusion-weighted data could not be completed.

Voxel-based morphometric analyses of gray matter

The T1-weighted images were used to identify significant correlations between pain responses and regional gray matter volume using voxel-based morphometry (VBM), a voxel-wise analysis of gray matter volume.²⁸ VBM analyses were performed using the Computational Anatomy Toolbox 12 (Jena University Hospital, Jena, Germany) within Statistical Parametric Mapping (SPM) 12 (Wellcome Department of Cognitive Neurology, London, United Kingdom), implemented in MATLAB (MathWorks, Natick, MA, USA). The VBM procedure involves spatial normalization of the MPRAGE images by registering the images to standard space (to correct for global differences in brain shape) and segmentation into gray matter images. After a data quality check, these gray matter images were smoothed using the default 8 mm full-width at half maximum Gaussian kernel.

First, exploratory whole brain VBM analyses were performed. Second, VBM analyses were restricted to areas in the frontal cortex that were associated with pain sensitivity and pain inhibition in previous structural and functional MRI studies^{29–34} using the small volume correction function implemented in SPM. The following regions of interest were used: the ventromedial prefrontal cortex (vmPFC; defined as the combination of Brodmann areas (BA) 10 and 11), the dorsolateral prefrontal cortex (dlPFC; BA 9 and 46), and the ventrolateral prefrontal cortex (vlPFC; BA 44, 45, and 47). The masks for these regions of interest were defined using the Talairach Daemon atlas in the WFU PickAtlas toolbox.^{35,36}

Probabilistic tractography of white matter

Probabilistic tractography can trace white matter tracts in the brain using diffusion-weighted MR data. This is possible because diffusion-weighted MRI allows to measure diffusivity of water molecules within axons.³⁷ Given that diffusivity of water is less restricted along an axon than perpendicular to an axon, it is possible to estimate fiber orientations. One measure to quantify this orientation is fractional anisotropy (FA).

An FA value of 0 indicates unrestricted diffusion (isotropic diffusion), while an FA value of 1 indicates diffusion in only one direction (anisotropic diffusion).

In this study, we aimed to investigate whether experimental pain responses in older individuals correlate with FA of the white matter tracts between the prefrontal cortex and the periaqueductal gray (PAG), located in the brainstem. The PAG has direct anatomical connections with the prefrontal cortex³⁸ and sends neuronal input to key components of the descending pain modulatory system, including the rostroventromedial medulla, caudal ventrolateral medulla, and dorsal reticular nucleus.³⁹ Stein et al. (2012) have demonstrated that FA of the white matter tracts connecting the prefrontal cortex with the PAG correlates with placebo analgesia.⁴⁰ We followed their method, aiming to investigate whether pressure pain sensitivity and CPM in older individuals also correlate with FA of the white matter tracts connecting the prefrontal cortex with the PAG. Stein et al. only studied the tracts between the PAG and the dlPFC, but we extended our analysis to the white matter tracts between the PAG and the vlPFC as well as the vmPFC, to mirror our analysis approach for gray matter.

All diffusion-weighted imaging analyses were performed using the FMRIB Software Library (FSL version 6.0.0, Oxford, UK). Preprocessing of the images consisted of visual inspection, motion correction, correction of eddy current distortions, and removal of non-brain tissue. The orientation of the fibers in each voxel was estimated using BEDPOSTX (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques with Crossing Fibers), which models the orientation of multiple crossing fibers within each voxel.^{41,42} PROBTRACKX (probabilistic tracking with crossing fibres) was used to generate 5000 pathways from every voxel within the PAG, each following a slightly different route based on the fiber orientations. We used the default options of BEDPOSTX and PROBTRACKX. Because there is no PAG mask available, the mask of the PAG was manually drawn based on Montreal Neurological Institute (MNI) coordinates of previous studies investigating the PAG.⁴³ Only the tracts that passed the prefrontal radiation of the thalamus⁴⁰ and either the dlPFC, vlPFC (left and right), or vmPFC were retained for further analysis. The generated pathways were terminated as soon as the pathways left the prefrontal cortex. The mask of the thalamus was created using the Oxford Thalamic Connectivity Probability Mask within FSL. The dlPFC, vlPFC, and vmPFC masks were defined by the middle and inferior frontal gyrus of the Harvard-Oxford Cortical Structural Atlas.³⁸ Using the Talairach Daemon atlas, we verified that the premotor cortex (BA 6) was not included in the masks. All masks were made in standard space. Therefore, registration from diffusion space to standard space was performed within the FSL diffusion toolbox, which results in transformation matrices needed for PROBTRACKX. By default, output files of PROBTRACKX are produced in the same space as the original masks, in this case, standard space. The original diffusion FA images were linearly registered to standard space and up-sampled to a voxel size

of 1 mm³ using trilinear interpolation to match the PROBTRACKX output files.⁴⁴

Probabilistic tractography results in a connection probability map in which the value of every voxel represents the number of generated pathways that pass through that voxel, i.e., the probability that a voxel is connected to the PAG and the prefrontal cortex. The results were normalized by dividing the number of generated pathways by the total number of generated pathways and then thresholded at 0.01%.^{45,46} As a last step, the mean FA from voxels within the thresholded pathways between the PAG and each of the five prefrontal regions (dlPFC left, dlPFC right, vlPFC left, vlPFC right, and vmPFC) was extracted for each participant.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 24, except for the VBM analyses, which were performed using SPM 12.

Pre-analyses/pain responses in older individuals

As a first step, we used analyses of variance to examine whether pain responses were affected by potential confounders, namely, age, sex, and level of education, which have been shown in previous studies to impact pain.⁴⁷ The second analysis step aimed at describing the pain responses in the present sample. We therefore used analyses of variance to test whether subjective and facial responses significantly increased across pressure intensities. Paired-samples *t*-tests were used to test whether participants showed a CPM effect, defined by the difference between the response to the test stimulus combined with the conditioning stimulus and the test stimulus combined with the baseline stimulus.

Hypotheses testing

Association between pain responses and executive functioning: Three multiple regression analyses were conducted to examine whether variance in pain responses could be explained by the executive functioning domains cognitive inhibition, shifting, and updating. The scores of the executive functioning tests were entered separately as predictor variables and the pain responses were entered as dependent variables. Univariate tests were used to examine which specific pain response could be predicted by the executive functioning tests.

Association between pain responses and gray matter volume: To examine whether pain responses are associated with regional gray matter volume in the brain, the smoothed normalized gray matter images resulting from VBM were entered in a general linear model. Pain responses were entered separately as covariates of interest. In addition, total intracranial volume was entered as a covariate in each general linear model to correct for differences in brain size. Exploratory whole brain analyses as well as region of interest analyses were performed. The threshold for significance was set at $p < 0.05$ family-wise error (FWE) corrected at peak level for both whole brain analyses as well as region of interest analyses.

Association between pain responses and white matter structure: To examine whether variance in pain responses could be explained by the structure of the white matter tracts between the PAG and the vlPFC, dlPFC (both left and right), and vmPFC, stepwise forward regression analyses were conducted. The mean FA values within these white matter tracts were entered as predictors and the pain responses were entered separately as dependent variables.

Results

Pain responses in older individuals

Experimental pain responses were not significantly affected by age (self-report: $F(1,44)=0.28$, $p=0.60$; facial expression: $F(33.01,54.37)=1.62$, $p=0.057$) nor by level of education (self-report: $F(4,40)=0.54$, $p=0.706$; facial expression: $F(1,44)=0.52$, $p=0.47$). However, pain responses differed significantly between men and women, with women having increased responses to the pressure stimulation compared to men. For this reason, demographic characteristics, executive functioning performance and pain responses are displayed separately for men and women in Table 2.

Pressure pain sensitivity

As can be seen in Figure 2A, pain ratings increased with increasing pressure intensity ($F(2.11,92.71)=283.25$, $p<0.001$). We also found a significant increase in facial responses across the different intensities of pressure stimuli ($F(2.07,91.11)=13.90$, $p<0.001$), as can be seen in Figure 2B. The pressure stimuli of 400 and 500 kPa were on average rated as painful (verbal rating scale ≥ 1 ; Figure 2A). Due to the low variability in pain ratings to these stimuli (ratings varying mostly between mild to moderate pain; see also Table 2), we decided to define pressure pain sensitivity as the average response of the 400 and 500 kPa stimuli. Given the found sex differences in Table 2, we also tested for sex difference for these combined scores and found significant differences (self-report: $t(44)=-2.61$, $p=0.012$; facial expression: $t(25.54)=-3.55$, $p=0.002$). Sex was, therefore, added as a covariate in further analyses on pressure pain sensitivity.

CPM

The pressure stimuli paired with painful heat were not rated significantly less painful (Figure 2A) or elicited significantly weaker facial responses (Figure 2B) than the pressure stimuli paired with non-painful heat. Thus, no significant CPM effects were observed. When looking at the descriptive data, less than half of the participants showed pain inhibition (15.2% for self-report and 45.7% for facial expression). Again, we tested for potential sex differences. CPM was not significantly different between men and women (self-report: $t(44)=1.66$, $p=0.10$; facial expression: $t(27.94)=1.11$, $p=0.28$), and we therefore refrained from entering sex as covariate in further CPM-related analyses.

Table 2. Demographic characteristics and executive functioning performance.

	Male (N = 25)	Female (N = 21)	Statistics
Demographic characteristics			
Age	67.8 ± 5.6 (mean ± SD)	67.5 ± 6.7 (mean ± SD)	$t(44) = 0.2$, $p = 0.88$
Education	N (%)	N (%)	
High school	4 (16)	7 (33)	
Secondary vocational education	4 (16)	2 (10)	$\chi^2(3) = 1.9$, $p = 0.60$
Higher professional education	12 (48)	9 (43)	
University education	4 (16)	3 (14)	
Executive functioning			
	mean ± SD	mean ± SD	
Stroop Interference score	30.3 ± 10.7	29.7 ± 10.2	$t(44) = 0.2$, $p = 0.84$
Trail Making Test Part B (time in seconds)	73.6 ± 20.0	84.9 ± 55.9	$t(43) = 0.4$, $p = 0.35$
Letter Fluency test (total number of words)	13.6 ± 4.6	16.3 ± 4.8	$t(44) = -2.0$, $p = 0.06$
Self-Report Rating			
	median [IQR]	median [IQR]	
50 kPa rating	0 [0 – 0]	0 [0 – 0]	
200 kPa rating	0 [0 – 1]	1 [0 – 1.5]	$F(1,44) = 6.5$, $p = 0.015$
400 kPa rating	1 [1 – 2]	2 [1 – 2.75]	
500 kPa rating	2 [2 – 2.75]	2.5 [2 – 3.5]	
Facial responses			
	mean ± SD	mean ± SD	
50 kPa facial response	0.20 ± 0.41	0.19 ± 0.33	
200 kPa facial response	0.15 ± 0.31	0.61 ± 1.23	$F(1,44) = 14.33$, $p < 0.001$
400 kPa facial response	0.26 ± 0.60	1.83 ± 2.07	
500 kPa facial response	0.59 ± 1.17	2.47 ± 2.57	

kPa, kilopascal; IQR, interquartile range; SD, standard deviation.

Figure 2. Average pain ratings (A) and the Facial Action Coding System (FACS) composite scores (B) of the different experimental pain stimuli. Subjective and facial responses to these stimuli significantly increased across intensities. No significant conditioned pain modulation (CPM) effect was found, neither when examining pain ratings nor when examining facial responses. CPM, conditioned pain modulation; kPa, kilopascal; FACS, facial action coding system; VRS, verbal rating scale (0=no pain, 1=mild pain, 2=moderate pain, 3=strong pain, and 4=very strong pain).

Predictors of pain responses in older individuals

Executive functions

Three different executive functioning tests, each representing one domain of executive functioning, were used to investigate whether executive functioning can explain pain responses in the group of older individuals. Sex was added as a covariate given the found sex differences for pressure pain sensitivity. The average scores of the executive functioning tests are displayed in Table 2. Table 3 shows the results of the regression analyses.

Cognitive inhibition: The Stroop Interference scores, used to measure cognitive inhibition, could significantly explain variance in pain responses (multivariate outcome). Univariate tests showed that cognitive inhibition performance was primarily associated with pressure pain sensitivity measured via facial expression, with worse performance on the Stroop test predicting stronger facial responses during painful pressure stimulation.

Shifting: Similar to the Stroop test, performance on the Trail Making Test B, used to measure shifting, could significantly explain variance in pain responses (multivariate outcome). Univariate tests showed that shifting performance was also primarily associated with pressure pain sensitivity. Worse performance on the Trail Making Test predicted stronger facial responses during painful pressure stimulation.

Updating: The number of words produced during the Letter Fluency test, used to measure updating, could not significantly explain variance in pain responses (multivariate outcome).

Table 3. Multiple regression analyses predicting pain responses by executive functioning performance.

	<i>R</i> ²	<i>p</i>	Standardized Beta Coefficients
Stroop Interference score			
Multivariate outcome	0.263	0.027*	
Univariate tests	Sex (covariate)	0.088	−0.295
	Pressure pain sensitivity: verbal	0.141	0.228
	Pressure pain sensitivity: facial	0.028*	0.374
	Pain inhibition: verbal	0.181	0.193
	Pain inhibition: facial	0.082	−0.250
Trail Making Test B			
Multivariate outcome	0.225	0.067	
Univariate tests	Sex (covariate)	0.827	−0.038
	Pressure pain sensitivity: verbal	0.225	−0.195
	Pressure pain sensitivity: facial	0.003*	0.530
	Pain inhibition: verbal	0.740	0.049
	Pain inhibition: facial	0.643	−0.068
Letter Fluency test			
Multivariate outcome	0.182	0.139	

Multivariate regression analyses were conducted to examine whether variance in overall pain responses could be explained by executive functioning performance. Univariate tests were used to examine which specific pain response could be predicted by the executive functioning tests. * $p < 0.05$.

Gray matter volume

VBM was used to identify significant correlations between pain responses and regional gray matter volume. In the case of subjective and facial pressure pain sensitivity, sex was added as a covariate. At the whole brain level, no significant correlations were observed for any of the pain responses. Region of interest analyses revealed that CPM measured via facial expression correlates with regional gray matter volume in two adjacent clusters in the right vLPFC (FWE corrected, $p < 0.05$), as illustrated by the highlighted area in Figure 3 and reported in Table 4. Better endogenous pain inhibition was related to larger gray matter volume in this area.

White matter structure

Probabilistic tractography was used to trace the white matter tracts connecting the PAG with the left and right dLPFC and vLPFC as well as the vmPFC. The mean FA from voxels within these tracts was extracted for each participant. Regression analyses including sex as a covariate revealed that pain sensitivity measured via facial expression could be explained by the mean FA within the pathway between the PAG and the vmPFC ($R^2 = 0.347$, $p < 0.01$, standardized beta coefficient = 0.340). For CPM, both subjective and facial measures could be explained by white matter structure. Mean FA within the pathway between the PAG and the right dLPFC could significantly explain variance in CPM measured via verbal rating ($R^2 = 0.131$, $p = 0.016$, and standardized beta coefficient = 0.362), while variance in CPM measured via facial expression could be explained by the mean FA between the PAG and left vLPFC ($R^2 = 0.095$, $p = 0.042$, and standardized beta coefficient = 0.308). For both pathways, increased FA was associated with decreased endogenous pain inhibition. Figure 4 shows the relationship between FA and CPM in scatterplots.

Hierarchical regression analyses explaining variance in pain inhibition

The previous sections demonstrate that structural brain variations can significantly explain variance in CPM in older individuals. In two additional analyses, we wanted to further investigate these significant associations between structural brain variations and CPM inhibition.

In the first analysis (I), we tested whether the association prevailed even when controlling for a potential moderator variable, namely, executive functioning (executive functioning correlated with CPM between $r = 0.33$ and 0.25). Hierarchical regression analyses were therefore conducted. Table 5 shows that structural brain variations could still significantly predict CPM inhibition even when controlling for executive functioning. More precisely, these findings confirm that gray matter volume within the vLPFC and the structure of the white matter tracts connecting the PAG with the vLPFC and dLPFC can significantly explain variance in CPM beyond what can be explained by executive functioning.

In the second analysis (II), we wanted to investigate whether gray matter and white matter FA could provide complementary information for explaining variability of CPM. Entering gray and white matter in a forward regression analysis showed that both gray and white matter provide complementary information for variability of CPM ($\Delta p=0.002$).

Figure 3. Better endogenous pain inhibition (CPM) was related to larger gray matter volume in the highlighted area in the right ventrolateral prefrontal cortex. See Table 4 for further details.

Table 4. Clusters of voxels that showed a significant correlation with pain inhibition (conditioned pain modulation, CPM) measured via facial expression in a region of interest VBM analysis (FWE-corrected, $p < 0.05$).

Anatomical Region	Side	Brodmann Area (BA)	MNI Peak Coordinate (x, y, z)	Peak T Value	Cluster Size (Number of voxels)
Ventrolateral Prefrontal Cortex	Right	BA45	38, 26, 2	4.24	30
	Right	BA47	36, 30, -2	4.21	4

Better inhibition was related to larger regional gray matter volume in two adjacent clusters in the right ventrolateral prefrontal cortex. Cluster size in voxels at an extent threshold of $p < 0.001$ uncorrected. FWE, family-wise error; MNI, Montreal Neurological Institute; VBM, voxel-based morphometry.

Figure 4. The level of pain inhibition (CPM) is significantly associated with the structure of the white matter tracts connecting the PAG with the right dorsolateral prefrontal cortex (orange) and the left ventrolateral prefrontal cortex (blue). An example of the pathways is shown for one participant overlaid on the MNI152 standard brain (coronal view; $y=15$). Mean FA within the pathway connecting the PAG with the right dorsolateral prefrontal cortex correlates with pain inhibition measured via verbal rating. Mean FA within the pathway connecting the PAG with the left ventrolateral prefrontal cortex correlates with pain inhibition measured via facial expression. For both pathways, increased FA was associated with decreased pain inhibition. CPM, conditioned pain modulation; FA, fractional anisotropy.

Table 5. Hierarchical regression analyses of predictors of pain inhibition (CPM).

	Model	R^2	p	ΔR^2	Δp
Pain inhibition facial expression	1 2a	0.065 0.366	0.444 0.004*	0.300	0.001*
Pain inhibition verbal rating	1 2b	0.109 0.223	0.207 0.044*	0.113	0.024*

Model 1: executive functioning (Stroop Interference score, Trail Making Test Part B, and Letter Fluency test) included. Model 2a: executive functioning, volume of Brodmann area 45 and mean FA between the PAG and left vIPFC included. Model 2b: executive functioning and mean FA between the PAG and right dlPFC included. * $p < 0.05$.

Discussion

This study aimed to investigate whether pain processing in older individuals can be related to executive functioning performance and structural variations in the prefrontal cortex. Our sample of older individuals did not show significant pain inhibition as measured using CPM, supporting evidence from previous studies in older individuals that showed decrease pain inhibition in older compared to younger individuals. This pattern of pain responses could partly be explained by executive functioning performance as well as by gray and white matter structure within and towards the prefrontal cortex. The predictive power of structural brain variations was limited to CPM effects and prevailed when controlling for executive functioning. Thus, structural variations in the prefrontal cortex could explain CPM responses in older adults beyond what could be explained by executive functioning. We will discuss these findings in detail below.

Executive functioning and pain responses in older individuals

A substantial amount of studies have reported a significant association between reduced executive functioning performance and increased pain responses. However, as we could show in a recently published systematic review, the overall strength of this association is only weak.⁴⁸ This might be due to the diversity regarding different types of experimental pain responses and executive functioning tests. The executive functioning domain cognitive inhibition was most frequently found to be associated with experimental pain responses but also the effect size of this association was only small. However, these findings are mostly based on studies investigating young adults. In contrast, findings of studies investigating older individuals suggest that the association between reduced executive functioning performance and increased pain responses might be more pronounced in older individuals.^{6–9}

The current study showed that reduced cognitive inhibition and shifting are associated with increased pain responses (mostly facial responses to pressure pain) in older individuals. Cognitive inhibition and shifting could explain approximately 20% of the variance in pain responses. Previous studies in older individuals mostly only investigated cognitive inhibition. These studies demonstrated that older individuals with lower performance on cognitive inhibition tasks show reduced endogenous pain inhibition,⁹ increased responses to pressure stimulation⁷ and reduced tolerance of cold pain.⁶ In the present study, we found that a reduction in cognitive inhibition in older individuals was especially associated with stronger facial responses to pressure stimulation. This finding is in line with previous findings in younger²² and older individuals.⁷ Here, individuals with a lower performance on cognitive inhibition also showed more facial responses during painful stimulation.

With regard to the executive functioning domain shifting, we found a similar relation with facial expressiveness, namely, older individuals with lower shifting performance showed more facial responses during pressure stimulation. Thus, worse shifting performance seems to be linked to a greater tendency for pain facilitation. This corroborates the findings of an association between cognitive inhibition and pain responses, given that the Trail Making Test B also involves some cognitive inhibitory functioning, i.e., the ability to stop responses to a number to be prepared to respond to a letter.

Several studies have pointed towards a specific association between cognitive inhibition and endogenous pain inhibition. However, as we could show in our review article, the overall effect size of an association between CPM and cognitive inhibition was only small.⁴⁸ The present study could also only demonstrate a small non-significant association between cognitive inhibition and CPM (r -values ≤ 0.21). It might be possible that cognitive inhibition is more strongly related to other forms of pain inhibition beyond CPM.

In sum, this study shows that poor executive functioning in older individuals can be linked to increased pain responses, but this association was not specific to one domain of executive functioning or one type of pain response.

Brain structure and pain responses in older individuals

To date, a small number of studies have used functional imaging to investigate the neural base of pain responses in older individuals,^{49–51} but no study has used structural imaging to investigate whether structural brain variations are associated with pain responses in older individuals. Studies in young adults showed that individual differences in pain sensitivity,^{32,33} pain inhibition,⁵² and temporal summation³⁰ can be linked to individual differences in regional gray matter structure. In contrast, in the present study, pain sensitivity in older individuals was not significantly linked to differences in gray matter structure nor to differences in white matter structure. Only

the variance in CPM could specifically be explained by structural brain variations in gray and white matter.

CPM was measured both via pain ratings as well as via facial expressions in response to the test stimuli. The conditioning stimulus was only mildly painful and therefore, no facial expression occurred in response to the conditioning stimulus. Since the responses to the bilaterally presented test stimuli were averaged, we had no prediction about the side of the brain that would be associated with CPM. We found that a loss in CPM measured via facial expression (meaning that the facial response to pressure stimulation did not decrease due to tonic heat counter stimulation) was related to reduced gray matter volume in the right vlPFC as well as to increased FA of the white matter tracts connecting the PAG with the left vlPFC. Moreover, CPM measured via verbal rating was related to increased FA of the white matter tracts connecting the PAG with the right dlPFC.

The importance of the prefrontal cortex in pain inhibition has been demonstrated by previous neuroimaging studies in younger healthy individuals. Several of these studies showed that the magnitude of the CPM effect is related to the level of activity in prefrontal areas during a CPM paradigm.^{29,34,53,54} Furthermore, the thickness of the orbitofrontal cortex has been found to correlate with CPM.⁵² In these young adults, a reduced response to a test stimulus presented on the right leg in the presence of a conditioning stimulus presented on the contralateral arm was correlated with a thicker right lateral orbitofrontal cortex. This is partly in line with our finding that CPM is associated with gray matter volume in the right vlPFC, because this area is close to the right lateral orbitofrontal cortex. We found that in older individuals, reduced CPM is associated with reduced gray matter volume in the right vlPFC. This is in line with the notion that age-related reduction in prefrontal volume might lead to reduced pain inhibition and thus, to higher prevalence of pain.

With regard to white matter, there is only one previous study that investigated the association between white matter structure and endogenous pain modulation.⁴⁰ They showed that stronger placebo analgesia responses are associated with increased FA in the white matter tracts between the PAG and the dlPFC. Although CPM is not directly related to the level of placebo analgesia in an individual,⁵⁵ we expected that similar white matter tracts might play a role in CPM. We indeed found significant associations, however, contrary to expectations, we found that increased FA of the white matter tracts between the PAG and the prefrontal cortex was not associated with better pain inhibition, but with worse pain inhibition. When interpreting the direction of FA, there is the difficulty that FA is influenced by several factors, including myelination, axon diameter, and the space between axons.⁵⁶ Nevertheless, in general, increased FA is thought to reflect better white matter structure. We can only speculate why increased FA was associated with poorer CPM. One possibility might be that loss in gray matter in older individuals might be compensated by an increase

in white matter connections. We also might have missed relevant white matter tracts by focusing solely on prefrontal connections. A recent study investigated the neural correlates of CPM beyond the prefrontal cortex using resting functional connectivity, which measures the temporal correlation between brain activity patterns of different regions.⁵⁷ Better pain inhibition was found to be associated with higher functional connectivity between the PAG and areas in the anterior cingulate cortex, insula, pons, and rostromedial medulla. Future studies might investigate whether structural variations in these white matter tracts beyond the prefrontal cortex might also explain variance in endogenous pain inhibition in older individuals.

In summary, we found that out of all pain measures, only CPM was related to structural brain variations in gray and white matter. This association prevailed even when controlling for executive functioning. Together, structural variations in the prefrontal cortex and executive functioning performance could explain 37% and 22% of the variance in CPM measured by facial expression and verbal rating, respectively.

Limitations

This study is a first explorative attempt to understand whether structural brain variations in the prefrontal cortex can explain pain responses in older individuals. The study should be replicated in another age group to examine whether our findings are unique to older individuals. In line with this, we cannot be certain that the deficits in pain inhibition measured with CPM protocol were indeed due to age, or might be due to the experimental design, given that we did not include a young control group. Furthermore, we used pain protocols that should be suitable for various groups of older individuals with various degrees of cognitive capacities. Therefore, we decided to use a cognitively less challenging rating scale and to use fixed stimulus intensities instead of intensities tailored to the individual pain threshold because assessment of pain threshold is not possible in all groups of older individuals (e.g. individuals with aphasia or dementia). Using less individualized pain intensities might have increased error variance in our sample. Finally, the small sample size limits the generalizability of the findings of this study.

Conclusions

The present study showed that pain responses observed in older individuals are associated with executive functioning performance and variations in gray and white matter within and towards the prefrontal cortex. Specifically, variance in CPM was associated with these structural brain variations. Speculatively, this association could be one of the underlying mechanisms explaining age-related changes in pain processing and therefore, increased clinical pain prevalence.

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Chapter 6

Pain processing in older adults with dementia-related cognitive impairment is associated with frontal neurodegeneration

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Abstract

Background: Experimental pain research has shown that pain processing seems to be heightened in dementia. It is unclear which neuropathological changes underlie these alterations.

Methods: This study examined whether differences in pressure pain sensitivity and endogenous pain inhibition (conditioned pain modulation (CPM)) between individuals with a dementia-related cognitive impairment (N=23) and healthy controls (N=35) are linked to dementia-related neurodegeneration. Pain was assessed via self-report ratings and by analyzing the facial expression of pain using the Facial Action Coding System.

Results: We found that cognitively impaired individuals show decreased CPM inhibition as assessed by facial responses compared to healthy controls, which was mediated by decreased gray matter volume in the medial orbitofrontal and anterior cingulate cortex in the patient group.

Conclusion: This study confirms previous findings of intensified pain processing in dementia when pain is assessed using non-verbal responses. Our findings suggest that a loss of pain inhibitory functioning caused by structural changes in prefrontal areas might be one of the underlying mechanisms responsible for amplified pain responses in individuals with a dementia-related cognitive impairment.

Introduction

In the last decade, the topic of pain and dementia has attracted considerable attention because of the notion that pain is underdetected and undertreated in dementia.^{1,2} Moreover, experimental pain research has shown that pain processing is not diminished but seems to be heightened in dementia. This conclusion is mostly based on studies that focused on non-verbal indicators of pain, given that the loss in verbal communication skills associated with dementia-related cognitive impairment makes the valid assessment of self-report challenging. Among these non-verbal pain indicators, facial responses in people with dementia were repeatedly found to be increased during experimental pain stimulation.³⁻⁶ In line with this, the nociceptive flexion reflex as well as brain activity in response to painful stimulation were also found to be amplified.^{4,7}

It is not yet known which neuropathological changes underlie these alterations in pain processing. Dementia is characterized by a widespread loss of brain tissue, with different subtypes showing different patterns of neurodegeneration.⁸ It has been hypothesized that neurodegeneration in brain structures involved in descending pain inhibition might contribute to altered pain responses.⁴ A brain area that plays a key role in descending pain inhibition is the prefrontal cortex.^{9,10} This is one of the brain regions that was found to show altered activity in response to noxious stimulation in Alzheimer patients.⁷ The assumption that dementia-related neurodegeneration in prefrontal areas might affect the processing of pain, especially the descending inhibitory system, is supported by findings of neuropsychological studies. Of all cognitive domains affected by healthy aging and dementia-related cognitive impairment, the increase in facial responses and the nociceptive flexion reflex could be best explained by deficits in executive functions,^{11,12} which are higher-order cognitive skills that are linked to the function of the frontal cortex.¹³ Moreover, in healthy older individuals, poorer executive functioning was found to be associated with poorer endogenous pain inhibition as assessed using the conditioned pain modulation (CPM) protocol.^{14,15} Thus, there are several indications that a loss in prefrontal functioning might be one mechanism underlying the increased pain responses in dementia-related cognitive impairment, possibly via a loss in endogenous pain inhibition. So far, this has not been tested.

The aim of the present study was to investigate whether increased pain responses in older individuals with dementia-related cognitive impairments can be linked to neurodegeneration especially in prefrontal areas. Given the decline in cognitive and verbal capacities, pain responses were not only based on self-report ratings but also on facial responses. As experimental pain protocols we used phasic pressure pain as well as the CPM protocol to assess pain inhibitory functioning. As for statistical analyses, we used mediation analyses to investigate whether structural brain changes

(especially in frontal areas) mediate the relation between cognitive decline and pain responsiveness, including CPM.

Methods

Participants

Individuals with dementia-related cognitive impairment over the age of 60 were recruited at the outpatient memory clinic of the University Medical Center Groningen, through the Dutch online registry Hersenonderzoek.nl that facilitates participant recruitment for neurosciences studies (www.hersenonderzoek.nl), via case managers for community-dwelling people with dementia and through advertisements. Age- and gender-matched controls were recruited among students of the local University of the Third Age and through advertisements.

Sample size calculation (Sample Power 2.0, SPSS Inc., Chicago, IL, USA) was based on previous findings of our group where we investigated pain responses (self-report, facial expression, heart rate) in patients with dementia (mostly Alzheimer disease).^{4,16} Given that we were interested in “medium” to “strong” effects between groups that might be of clinical relevance, sample size calculation was conducted for 80 % power and 0.05 level of significance. Based on these considerations, a sample size of 25 in each group should prove sufficient to reach adequate reliability for between-group comparisons. Previous neuroimaging studies investigating pain in dementia (mostly functional neuroimaging) used similar sample sizes.^{7,17–20} This sample size should also be sufficient for the structural neuroimaging analyses performed in the present study.²¹ Since recruitment of patients with dementia was challenging for this study, we chose a larger sample size for healthy individuals to increase statistical power. In total, 23 cognitively impaired individuals and 35 cognitively healthy older individuals participated in this study.

For the group of cognitively impaired individuals, inclusion criteria were either (a) a diagnosis of one of the most common subtypes of a major neurocognitive disorder according to criteria of the DSM-V (Alzheimer’s disease, vascular dementia or frontotemporal dementia) or (b) a mild neurocognitive disorder (also named mild cognitive impairment) based on subjective memory complaints and impairment in at least one cognitive domain (a score of one standard deviation below the mean score of the control group). Participants were excluded if they had a history of a major neurological or psychological disorder other than dementia or a contraindication to MRI. Participants did not take analgesic medication on the day of testing.

Table 1 provides demographic information, the number of participants per dementia subtype and the results of a neuropsychological test battery.

Table 1. Demographic and clinical characteristics of patients and controls.

	Patients (N=23) mean $\pm$ SD or N (%)	Controls (N=35) mean $\pm$ SD or N (%)	Group difference
Age	72.8 $\pm$ 7.6	69.2 $\pm$ 6.2	p=0.065
Female	7 (30%)	11 (31%)	p=0.936
Level of education			
Primary school	2 (9%)	0 (0%)	p=0.254
High school	4 (17%)	8 (23%)	
Secondary vocational education	6 (26%)	5 (14%)	
Higher professional education	7 (30%)	14 (40%)	
University education	3 (13%)	8 (23%)	
Dementia subtype	AD=14 (61%) FTD=4 (17%) MCI=4 (17%) VD=1 (4%)	-	
MMSE	23.7 $\pm$ 5.0	28.6 $\pm$ 1.4	p<0.001
15 word task immediate recall (number of words)	4.0 $\pm$ 2.3	8.2 $\pm$ 2.3	p<0.001
15 word task delayed recall (number of words)	1.7 $\pm$ 2.0	6.0 $\pm$ 2.5	p<0.001
Trail Making Test part A (time in seconds)	72.5 $\pm$ 43.6	36.5 $\pm$ 12.2	p<0.001
Trail Making Test part B (time in seconds)	169.6 $\pm$ 93.6	84.1 $\pm$ 41.8	p<0.001
Stroop difference score (number of correct responses)	31.2 $\pm$ 11.5	35.0 $\pm$ 9.5	p=0.174
Letter Fluency test (number of words)	11.0 $\pm$ 6.4	14.8 $\pm$ 5.4	p=0.018
Geriatric depression scale	2.6 $\pm$ 2.3	1.4 $\pm$ 1.7	p=0.022

Statistical significance was determined using independent samples t-tests (age, MMSE, depression) and chi-squared tests (gender, education). The neuropsychological test battery included the Mini-Mental State Examination (MMSE), the 15 word task (a Dutch adaption of the Rey Auditory Verbal Learning Test)⁴⁸ to assess episodic memory function (immediate recall after three trials; delayed recall after a distraction period of approximately 20 minutes), the Letter Fluency test to assess updating ability,⁴⁹ the Trail Making Test part A and B to assess processing speed and shifting ability respectively⁵⁰ and the Stroop Color and Word to assess inhibition (difference in number of correct responses between the color naming and the color word task).⁵¹ AD, Alzheimer's disease; FTD, frontotemporal dementia; MCI, mild cognitive impairment; SD, standard deviation; VD, vascular dementia.

The Mini Mental State Examination (MMSE) was used to assess global cognitive functioning. This score ranges between 0-30, with a higher score indicating better cognitive performance.²² The patient group scored on average 23.7, suggesting mild dementia-related impairment. Depressive symptoms were assessed using the short form of the Geriatric Depression Scale, consisting of 15 questions. A higher score indicates more depressive symptoms.²³ Although there was a significant difference in the number of depressive symptoms, both groups scored below the cut-off.²⁴

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University Medical Center Groningen. All participants still had legal capacity. After being informed about the study in a way adjusted to the individual intellectual capacities, a written informed consent was obtained from all participants. We monitored the patients continuously for any signs of disproportionate discomfort (verbally or non-verbally), in which case we stopped testing immediately. Participants received a minor monetary compensation.

Study procedure

The study consisted of three parts. Part one consisted of an experimental pain protocol of 30 minutes to assess pain responsiveness, part two consisted of a 30 minute neuropsychological examination to evaluate the cognitive status of the participants (MMSE, further neuropsychological tests applied are not part of the present article) and part three consisted of a structural MRI scanning session of 20 minutes. Part one and two were always conducted on the same day and took place in a laboratory room of the department of Elderly Care Medicine of the University Medical Center Groningen. Part three was most often conducted on a separate day, with time intervals between testing days on average being 19 days. The MRI scan was performed at the department of Radiology of the University Medical Center Groningen.

Experimental pain protocol

Apparatus

Pressure stimuli were applied to the midpoint of the upper border of the trapezius muscle (back shoulder area) using a pressure algometer with a probe area of 1 cm² (Algometer type II, Somadic Sales AB, Hörby, Sweden). Heat stimuli were administered to the right inner forearm using a thermal sensory analyzer (Medoc TSA II, Ramat-Yishai, Israel) with a Peltier thermode of 6 cm² stimulation surface.

Pressure pain sensitivity

In order to assess pressure pain sensitivity, four different pressure intensities (50, 200, 400 and 500 kilopascal (kPa)) were applied to the shoulder in an ascending order. An ascending order was chosen to reduce anxiety in participants as well as to be able to stop immediately with the stimulation protocol if a participant found the stimulation too painful. There were two trials, one to the right shoulder and one to

the left shoulder, applied in a fixed order. Pressure was increased steadily for 2 s until the desired intensity was reached and was then kept constant for 5 s.

CPM

Endogenous pain inhibition was assessed using the CPM paradigm, in which a conditioning stimulus and a test stimulus are applied simultaneously to different parts of the body to test the modulating effect of the conditioning stimulus. The test stimuli used in this CPM paradigm were similar to the stimuli used to assess pressure pain sensitivity, namely four pressure intensities of 50, 200, 400 and 500 kPa applied to the right and left shoulder. Tonic heat stimulation served as the conditioning stimulus and consisted of a series of small heat pulses at a frequency of 30 pulses/min with an amplitude of 1.3 °C applied on the right inner forearm.^{25–29} Thus, the test stimuli were presented bilateral and the conditioning stimulus was presented on the right side. We applied a conditioning stimulus twice, once painful and once non-painful. In the first block, the test stimuli (pressure) were applied together with non-painful tonic heat stimulation of 43 °C peak temperature (baseline stimulus). In the second block, the test stimuli on the shoulder were applied together with painful tonic heat stimulation of 45 °C peak temperature (conditioning stimulus). By using a non-painful and painful conditioning stimulus, we tried to avoid that CPM effects were mere due to distraction of attention by a second stimulus. The blocks lasted for around two minutes. Pain inhibition was indicated by a lower pain response to pressure stimuli paired with painful heat than to pressure stimuli paired with non-painful heat (pressure pain during painful heat – pressure pain during non-painful heat < 0). Pain amplification was indicated by a higher pain response to pressure stimuli paired with painful heat than to pressure stimuli paired with non-painful heat (pressure pain during painful heat – pressure pain during non-painful heat > 0).

Pain responses

Pressure pain sensitivity and CPM were assessed via self-report ratings as well as via facial responses. This resulted in four pain outcomes, namely pressure pain sensitivity measured by rating (Pain-rating), pressure pain sensitivity measured by facial expression (Pain-face), CPM measured by rating (CPM-rating) and CPM measured by facial expression (CPM-face).

Ratings

Immediately after each stimulus, participants were asked to rate the pain sensation, evoked by pressure stimulation, using a five-category verbal rating scale (no pain – mild pain – moderate pain – strong pain – very strong pain), which was printed on a large piece of paper and shown to the participant after each stimulus. This type of rating scale was found to be appropriate for older adults with and without mild to moderate cognitive impairment.^{30,31} For further analyses, the ratings of the pressure stimuli on the right and left shoulder were averaged to obtain one rating per intensity.

Facial responses

Facial responses were assessed during each pressure stimulus. A camera was placed approximately 2 m in front of the participants to videotape facial expression. Participants were instructed to look into the camera and were asked not to talk when pain was induced. Facial responses were analyzed using the Facial Action Coding System (FACS).³² This system describes 44 visually distinguishable action units (AUs). Two FACS coders (qualified by passing the FACS examination) both identified the frequency and intensity of the AUs that occurred during stimulation. One coder was completely blinded, both coders were aware of the study design and objectives. A sub-set of 10% of the video segments was randomly selected across the entire sample and was coded by both coders to calculate inter-rater reliability using the Ekman-Friesen formula (number of AUs agreed upon $\times 2$ and divided by the overall amount of AUs coded). This inter-rater reliability was found to be 0.80, which compares favorably with other research in the FACS literature.^{33,34} The intensity of each AU was scored using a 5-point scale, which was entered into a time-related database from the onset of the stimuli till the end of the stimuli (5 s) using The Observer Video-Pro (Noldus Information Technology, Wageningen, The Netherlands). Some AUs represent facial movements of the same muscle and were therefore combined to reduce the number of variables (AU 1/2, AU 6/7, AU 9/10 and AU 25/26/27). For further analyses, only pain-relevant AUs were included. We based this selection on a recent systematic review that showed that AU 4 (brow lower), AU 6/7 (cheek raise/lid tighten), AU 9/10 (nose wrinkle/upper lip raise) and AU 25/26/27 (mouth opening) are most consistently found to be associated with pain in both cognitively healthy and cognitively impaired individuals.³⁵ To obtain a FACS composite score for each stimulus intensity, the frequency of these AUs was multiplied by the AU intensity scores and then averaged over all four pain-relevant AUs. As for the ratings, the FACS scores of the pressure stimuli on the right and left shoulder were combined to obtain one FACS composite score per intensity. Previous research has demonstrated that facial expressions of pain are sensitive enough to capture CPM effects.³⁶

MRI acquisition and preprocessing

MR images of the brain were acquired using a 3T MRI scanner (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany). T1-weighted images were acquired using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (176 sagittal slices, repetition time=2300 ms, echo time=2.98 ms, inversion time=900 ms, flip angle=9°, voxel size=1x1x1 mm, field-of-view=256 mm). Diffusion-weighted images were acquired along 64 directions using a b-value of 1000 s/mm² (60 slices, repetition time=6300 ms, echo time=66 ms, voxel size is 2.2x2.2x2.2 mm, field-of-view=220 mm). Ten volumes with no diffusion weighting (b-value of 0 s/mm²) were acquired, one at the beginning and nine at the end of the acquisition.

Preprocessing of gray matter analyses

Differences in regional gray matter volume between cognitively impaired and cognitively healthy individuals were assessed using voxel-based morphometry (VBM), a voxel-wise statistical analysis.³⁷ Standard VBM was performed using the Computational Anatomy Toolbox (CAT) 12 (Jena University Hospital, Jena, Germany) within Statistical Parametric Mapping (SPM) 12 (Wellcome Department of Cognitive Neurology, London, United Kingdom), implemented in MATLAB 9.8 (MathWorks, Natick, MA, USA). We deliberately decided applying the standard VBM approach instead of the DARTEL VBM method as methodological studies showed either comparable or more restricted (i.e., in the sense of false negative) results with DARTEL based VBM analyses in dementia.^{38,39} The standard VBM procedure involves segmentation into gray matter images and spatial normalization by registering the images to standard space (to correct for global differences in brain shape). After performing quality control for inter-subject homogeneity and overall image quality as included in the CAT12 toolbox, the gray matter images were smoothed using the default 8 mm full-width at half maximum Gaussian kernel. The smoothed normalized gray matter images of cognitively healthy and cognitively impaired individuals were entered separately in a general linear model together with total intracranial volume as a covariate to correct for differences in brain size. Absolute threshold masking was set at 0.1.

Preprocessing of white matter analyses

Differences in white matter structure between the two groups were assessed using tract-based spatial statistics (TBSS), a voxel-wise statistical analysis part of the FMRIB Software Library (FSL version 6.0.0, Oxford, UK).⁴⁰ Diffusion-weighted MRI allows to measure diffusivity of water molecules within axons.⁴¹ Given that diffusivity of water is more restricted along an axon than perpendicular to an axon, it is possible to estimate fiber orientations. There exist multiple measures of diffusivity, including axial diffusivity (AD; diffusivity parallel to the fibers), radial diffusivity (RD; average diffusivity of the two directions perpendicular to the fibers), mean diffusivity (MD; average diffusivity of all three directions) and fractional anisotropy (FA; a measure of overall directionality of water diffusion).^{42,43} After a visual inspection of the data, FA images were created by fitting a tensor model to the raw diffusion data using the diffusion toolbox and then brain-extracted using the brain extraction tool.⁴⁴ All subjects' FA data were aligned into standard space using the nonlinear registration tool FNIRT. A mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. Each subject's aligned FA data was projected onto this skeleton. The nonlinear registration and skeletonisation stages were repeated for AD, MD and RD.

Statistical analyses

Group differences in pain responses

Repeated measures ANOVAs with one between-subject factor (group) and one within-subject factor (pressure intensity) were used to assess (I) whether facial and subjective responses increased across the four pressure intensities, (II) whether this increase differed depending on the cognitive status and (III) whether there was an interaction effect between group and pressure intensity. Moreover, independent-samples t-tests were used to compare facial and subjective pain responses (pressure pain sensitivity and CPM) to painful stimuli between patients and controls.

Group differences in gray and white matter

To assess group differences in gray matter volume, first, whole brain VBM analyses were performed. Second, VBM analyses were restricted to areas associated with descending pain modulation, given our hypothesis that endogenous pain inhibition might be affected in dementia. Based on previous MRI studies, Bogdanov et al. (2015) defined five descending pain modulation clusters,⁴⁵ listed in Table 2. We used these clusters for region-of-interest analyses using the small volume correction function implemented in SPM. The threshold for significance was set at $p < 0.05$ family-wise error (FWE) corrected at cluster level for both whole brain analyses as well as region of interest analyses.

Table 2. Description of regions of interest used for gray matter analyses.

Region of interest	MNI coordinate of center of gravity (x, y, z)
Medial orbitofrontal cortex	9, 41, -12 / -9, 41, -12
Lateral orbitofrontal cortex	34, 41, -15 / -34, 41, -15
Anterior cingulate cortex	9, 39, 18 / -9, 39, 18
Rostro-lateral prefrontal cortex	28, 53, 21 / -28, 53, 21
Caudo-lateral prefrontal cortex	44, 30, 27 / -44, 30, 27

Regions based on Bogdanov et al. 2015.⁴⁵ MNI; Montreal Neurological Institute.

Group differences in white matter structure were assessed by investigating differences in diffusivity (FA, AD, RD, MD) within the white matter skeleton. Voxel-wise statistical analyses were performed using FSL randomize with 5000 permutations. The threshold for significance was set at $p < 0.05$ corrected using threshold-free cluster enhancement (TFCE).

Brain areas that showed significant differences between the two groups were used for further analysis. Gray matter volume was extracted from significant gray matter clusters using a 6 mm sphere centered on the peak coordinate. Average values of the diffusivity measures were extracted from significant white matter clusters.

Mediation analyses: Is the effect of cognitive impairment on pain responses mediated by loss in gray and white matter?

Mediation analyses were performed to test whether observed differences in pain responses between the two groups can be explained by differences in brain structure. A mediation analysis consists of four steps: (1) confirm a significant relation between the potential mediators (extracted gray matter volume and white matter structure) and cognitive decline (MMSE score), (2) confirm a significant relation between the potential mediators and pain responses when controlling for cognitive decline, (3) assess the strength of the relation between cognitive decline and pain responses and (4) confirm that the effect of step 3 reduces when controlling for the potential mediator. Step 1 is described under 2.6.2 and step 3 is described under 2.6.1. However, since a continuous variable was needed for the mediation analyses, these analyses were repeated using MMSE score as a continuous measure for cognitive decline instead of using “group” as a dichotomous factor. All four steps of the mediation analyses were performed using PROCESS 3.4 implemented in SPSS 26.⁴⁶ PROCESS performs regression analyses for step 1-4. The mediation (or indirect) effect is equal to the product of the regression coefficients of step 1 and 2. PROCESS uses a non-parametric bootstrap approach (5000 samples), resulting in a 95% confidence interval used to assess the significance of the mediation effect. This method is suitable for small sample sizes.⁴⁷

Results

Influence of cognitive decline on pain responsiveness

The majority of participants was able to provide a self-report rating for each pressure stimulus. Only three individuals with cognitive impairments (13% of that group) were not able to provide a rating for every stimulus (this means no pain rating was given after being asked to rate the stimulus on the category scale). Figure 1A shows that pain ratings increased across the four pressure intensities (main effect of intensity: $F(3,162)=222.1$, $p<0.001$). There was no significant effect of group on pain ratings ($F(1, 54)=2.2$; $p=0.140$) and no significant interaction effect between group and intensity ($F(3,162)=0.7$, $p=0.584$), indicating that the pressure stimuli were rated similarly by cognitively impaired individuals and cognitively healthy individuals. As can be seen in Figure 1A, only the pressure intensities of 400 and 500 kPa were on average rated as being painful. Figure 1B shows the average pain-indicative FACS composite score for each pressure intensity. There was a significant main effect of intensity ($F(3, 168)=19.4$, $p<0.001$) as well as a significant effect of group ($F(1, 56)=9.0$, $p=0.004$) and a significant interaction effect between group and intensity ($F(3, 168)=6.5$, $p<0.001$). This indicates that cognitively impaired individuals showed more pain-indicative facial responses, which was most pronounced for higher pressure intensities.

Given our interest in pain responses, we decided to average subjective as well as facial responses to 400 and 500 kPa in order to gain responses that lie certainly in the painful range. The averaged pain responses (“subjective pain responses” and “facial pain responses”) were used for all further analyses.

Subjective pain responses

Pain-rating: As can be seen in Table 3, individuals with cognitive impairment did not rate the painful stimuli as more or less painful compared to healthy older individuals.

CPM-rating: Similarly, CPM measured by rating also did not differ significantly between the groups. As shown in Table 3, the average CPM effect for both groups was around zero, indicating no pain modulation due to the application of a noxious conditioning stimulus. This was confirmed by paired sample t-tests, which showed that there were no significant differences in pain rating between pressure stimuli paired with painful heat and pressure stimuli paired with non-painful heat for both cognitively healthy older individuals ($t(34)=1.1$, $p=0.246$) and individuals with a dementia-related cognitive impairment ($t(21)=-0.1$, $p=0.920$).

Facial pain responses

Table 4 presents the frequency of occurrence of the facial AUs used to compute the FACS composite score. It shows that all selected AUs are significantly more frequent during painful pressure stimulation than during non-painful pressure stimulation. Cognitively healthy individuals and cognitively impaired individuals showed the same AUs during painful pressure stimulation, corroborating earlier findings that the type of facial responses being displayed during pain is not affected by cognitive decline.³⁵

Pain-face: When considering the frequency as well as the intensity of the selected AUs, the average facial response to 400 and 500 kPa was significantly higher in cognitively impaired individuals compared to cognitively healthy individuals, as can be seen in Table 3.

CPM-face: The average CPM effect measured by facial expression for 400 and 500 kPa stimuli also differed significantly between the groups. As shown in Table 3, individuals with cognitive impairment showed pain amplification.

Summary

Together, these results show that the influence of cognitive decline on pain responsiveness in our sample is restricted to facial responses, with cognitively impaired individuals demonstrating increased facial responses to pressure stimuli and decreased pain inhibition when the CPM effect is assessed using facial expression.

Figure 1. Mean and standard deviation of pain ratings (A) and facial responses (B) to the four pressure intensities. KPa, kilopascal; FACS, facial action coding system; VRS, verbal rating scale (0=no pain, 1=mild pain, 2=moderate pain, 3=strong pain, and 4=very strong pain).

Table 3. Group difference in the pain responses: pressure pain sensitivity and conditioned pain modulation (CPM) measured by ratings and facial responses.

	Patients (Mean ± SD)	Controls (Mean ± SD)	Significance
Pain-rating	2.3 ± 1.0	1.9 ± 0.9	t(54)=-1.4, p=0.176
CPM-rating	-0.1 ± 0.5	0.06 ± 0.3	t(55)=0.6, p=0.532
Pain-face	3.4 ± 4.5	1.1 ± 1.8	t(56)=-2.7, p=0.008
CPM-face	0.9 ± 2.0	-0.3 ± 1.4	t(55)=-2.7, p=0.008

A CPM effect higher than zero indicates pain amplification, while a CPM effect lower than zero indicates pain inhibition. Facial response is a composite score of the frequency and intensity of selected facial action units as defined by the Facial Action Coding System. SD, standard deviation.

Table 4. Pain-relevant facial action units (AUs) used to compute the FACS composite score.

Action unit + Description	Patients		Controls	
	Occurrence¹	Significance²	Occurrence	Significance
AU 4: Brow lower	31.3%	t(21)=3.8, p=0.001	11.0%	t(34)=3.2, p=0.003
AU 6/7: Cheek raise, lid tighten	67.2%	t(21)=4.9, p<0.001	28.1%	t(34)=3.8, p=0.001
AU 9/10: Nose wrinkle, upper lip raise	47.0%	t(21)=3.7, p=0.001	13.8%	t(34)=3.5, p=0.001
AU 25/26/27: Mouth opening	49.3%	t(21)=2.9, p=0.008	28.6%	t(34)=2.6, p=0.015

¹Cumulative percentage of occurrence during all 400 and 500 kPa pressure stimuli.

²Paired-samples t-test between frequency of occurrence during all 50 kPa stimuli and during all 400 and 500 kPa stimuli (frequency of occurrence of 50 kPa was multiplied by two in order to calculate this). FACS, facial action coding system.

Influence of cognitive decline on gray matter volume

Figure 2 and Table 5 show the results of the VBM analysis comparing gray matter volume between the groups. At the whole brain level, cognitively impaired individuals showed significantly less gray matter volume in a large area of the temporal lobe and three smaller areas in the frontal cortex and the parietal cortex, specifically in the rostral prefrontal cortex, posterior cingulate cortex and supramarginal gyrus. Regions of interest analyses revealed additional significant clusters of reduced gray matter volume within the medial orbitofrontal cortex, lateral orbitofrontal cortex and anterior cingulate cortex. No areas showed increased gray matter volume in patients relative to controls.

Table 5. Clusters of voxels that showed significantly less gray matter volume in patients compared to controls in a VBM analysis (FWE-corrected, $p < 0.05$).

Anatomical Region	MNI Peak Coordinate (x, y, z)	Peak T Value	Cluster Size (Number of Voxels)
Whole brain analysis			
Temporal lobe	-30, -12, -14	9.85	78501
Rostral prefrontal cortex	18, 65, 2	4.99	944
Posterior cingulate cortex	-2, -56, 29	4.64	3921
Supramarginal gyrus	-44, -47, 44	4.45	1060
Region-of-interest analysis			
Medial orbitofrontal cortex	-11, 35, 21	5.95	1150
Lateral orbitofrontal cortex	-32, 33, -9	3.72	256
Anterior cingulate cortex	-11, 50, 11	3.81	115
	12, 47, 8	3.55	35

FWE, family-wise error; MNI, Montreal Neurological Institute; VBM, voxel-based morphometry.

Figure 2. Results of the voxel-based morphometry (VBM) analyses showing regions with gray matter volume loss in patients relative to controls. Results are presented at $p < 0.05$ FWE corrected. (A) Displays the results of the whole brain analysis, which shows a large significant area in the temporal lobe (sagittal view, $x = -24$). (B-D) Displays the results of the region-of-interest analyses, which shows the medial orbitofrontal cortex ($x = 8$), anterior cingulate cortex ($x = -11$) and the lateral orbitofrontal cortex ($x = -34$).

Mediation analyses: Are gray matter changes mediating the association between dementia-related cognitive decline and pain responsiveness?

Mediation analyses were conducted to examine whether the observed changes in pain responses associated with cognitive decline could be explained by the decrease in gray matter volume. Gray matter volume values were therefore extracted from the significant clusters resulting from the VBM analyses. The results of the mediation analyses are shown in Figure 3.

Cognitive decline, measured by MMSE score, could significantly predict CPM-face (Figure 3B and 3D, path c), which is in accordance with the results of the independent-samples t-test comparing CPM between the groups. This total effect was attenuated when controlling for gray matter volume specifically in the anterior cingulate cortex (ACC) and the medial orbitofrontal cortex (mOFC) (path c'). Gray matter volume in these areas could also significantly predict CPM-face when controlling for MMSE (path b). Together, this indicates that the observed decrease in CPM-face associated with cognitive decline was indeed mediated by reduced gray matter volume in the ACC and mOFC. This mediation effect was significant for both areas based on the confidence intervals. Other significant gray matter clusters resulting from the VBM analyses did not show a mediation effect for CPM-face.

In contrast to CPM-face, pain-face could not significantly be predicted by MMSE (Figure 3C, path c). However, because the independent-samples t-test did show a significant difference in pain-face between the groups, we still performed mediation analyses for this type of pain response. These analyses revealed that the (non-significant) effect of MMSE on pain-face was attenuated when controlling for gray matter volume specifically in the temporal cluster (path c'). Gray matter volume extracted from the temporal cluster could also significantly predict pain-face when controlling for MMSE (path b). This indicates that the increase in facial responses to pressure pain in cognitively impaired individuals was mediated by reduced gray matter volume in the temporal area. This mediation effect was significant based on the confidence interval. Other significant gray matter clusters resulting from the VBM analyses did not show a mediation effect for pain-face.

In Figure 3E-G, the relation between gray matter volume and pain are shown in scatterplots coded by subtype.

A **C**

Figure 3. Mediating effect of gray matter volume (GMV) on the relation between MMSE and pain responses measured by facial expression. (A) Schematic overview of the significant gray matter regions. (B-D) Diagrams showing the total effect of MMSE on pain (c), the direct effect of MMSE on pain when controlling for GMV (c'), the effect of MMSE on GMV (a) and the effect of GMV on pain when controlling for MMSE (b). The significance of the mediation effect (path $a*b$) is shown using a 95% confidence interval. (E-G) Scatterplots of the relation between gray matter volume and pain coded by dementia subtype. ACC, anterior cingulate cortex; CI, confidence interval; CPM, conditioned pain modulation; MMSE, mini-mental state examination; mOFC, medial orbitofrontal cortex. β ; standardized regression coefficient, * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

B

D

Influence of cognitive decline on white matter structure

The voxel-wise TBSS analysis revealed widespread differences in white matter structure between the groups. The group of cognitively impaired individuals showed a decrease in FA and an increase in MD and RD in white matter tracts throughout the entire brain, while no significant differences for AD were found. As can be seen in Figure 4, the most widespread differences between the groups were found for RD. No white matter tracts showed an increase in FA or a decrease in MD, RD or AD in cognitively impaired individuals relative to cognitively healthy individuals.

Mediation analyses: Are white matter changes mediating the association between dementia-related cognitive decline and pain responsiveness?

Our original aim was to extract diffusivity measures from the white matter tracts that differed significantly between patients and controls and investigate whether these could mediate the relation between MMSE and pain responses (similar as we have done for gray matter). However, since dementia did not affect specific white matter tracts but rather the whole brain, we decided to focus on the white matter tracts close to the gray matter areas that showed a significant mediation effect.

With regard to CPM-face, we focused on the forceps minor, a tract close to the mOFC and ACC. Given that RD showed the most widespread differences, we extracted average RD from this tract using the John Hopkins University (JHU) white matter tractography atlas implemented in FSL. The total effect of MMSE on CPM-face was attenuated when controlling for RD (Figure 5B, path c vs c'). RD of the forceps minor could also significantly predict CPM-face when controlling for MMSE (Figure 5B, path b). This suggests that the observed decrease in CPM-face in cognitively impaired individuals might be mediated by white matter structure of the forceps minor. However, this mediation effect was not significant based on the confidence intervals.

With regard to pain-face, we extracted mean RD of the cingulum of the hippocampal part using the JHU white matter tractography atlas. This white matter tract runs through the temporal gray matter cluster. However, RD of this tract could not significantly predict pain-face when controlling for MMSE (Figure 5C, path b). Thus, RD of the hippocampal part of the cingulum did not mediate the increased facial response to pressure pain in cognitively impaired individuals.

Figure 4. Results of the white matter analysis showing widespread differences in FA, MD and RD between cognitively impaired individuals patients and controls. The significant results (yellow) are overlaid on top of the mean skeleton (green), obtained using the TBSS analysis. Reduced FA in patients relative to controls was observed in one large cluster of 75355 voxels covering almost the entire brain and one smaller cluster of 66 voxels in the cingulum. An increase in MD and RD in patients was observed in two large clusters of 80728 and 89654 voxels respectively. Results are TFCE corrected at a threshold of $p < 0.05$. Sagittal view ($x = -14$), coronal view ($y = -4$), axial view ($z = 7$). FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; FWE, family-wise error; TBSS, tract-based spatial statistics; TFCE, threshold-free cluster enhancement.

A

Figure 5. Mediating effect of white matter structure (radial diffusivity (RD)) on the relation between MMSE and pain responses measured by facial expression. (A) Schematic overview of the white matter tracts. (B-C) Diagrams showing the total effect of MMSE on pain (c), the direct effect of MMSE on pain when controlling for RD (c'), the effect of MMSE on RD (a) and the effect of RD on pain when controlling for MMSE (b). The significance of the mediation effect (path $a*b$) is shown using a 95% confidence interval. CI, confidence interval; CPM, conditioned pain modulation; MMSE, mini-mental state examination. β ; standardized regression coefficient, * $p < 0.05$, ** $p < 0.01$.

Discussion

Association of cognitive decline and pain responsiveness

In line with previous studies investigating subjective responses to experimental pain in individuals with dementia,^{4,7,52} we could not demonstrate differences in subjective responses to pressure pain between cognitively healthy and cognitively impaired participants, despite using a cognitively less challenging rating scale. Similarly, we also could not demonstrate a significant group difference in CPM when pain responses were measured by self-report.

In contrast, facial responses to pain revealed significant group differences. Cognitively impaired individuals showed significantly increased pain-related facial responses to pressure pain stimuli compared to cognitively healthy individuals, which supports previous experimental studies investigating the facial expression of pain in dementia.^{3–5,53} Cognitively impaired individuals displayed the same types of facial movements during painful pressure stimuli as cognitively healthy individuals (Table 4) but the frequency and intensity of these facial movements were increased. This is in accordance with previous research that found that cognitive decline does not affect the type of facial response elicited during pain.³⁵

The use of facial responses as a measure of pain also revealed significant group differences in CPM in our study. Cognitively impaired individuals showed decreased endogenous pain inhibition compared to cognitively healthy individuals. Facial responses in cognitively impaired individuals were even increased due to the application of a noxious conditioning stimulus. Previous studies repeatedly found reduced endogenous pain inhibition in healthy older individuals compared with healthy young individuals.⁵⁴ The present study shows that endogenous pain inhibition measured via facial responses is even more reduced in older individuals with dementia-related cognitive impairments.

There might be several reasons why dementia-related cognitive impairment differentially affects subjective and facial responses to pain. Facial responses capture more autonomic behavior that is less subject to voluntary control⁵⁵ and it might therefore be a more valid response than self-report because it does not depend on cognitive resources. Moreover, facial responses to pain have been shown to be governed by a prefrontal network (especially the medial PFC) that regulates the intensity of facial expression of pain and thus, functions as an inhibitory gate for facial expression.^{56–58} Due to the neural loss in prefrontal structures in cognitively impaired individuals, the function of this inhibitory gate might be reduced, rendering individuals with a dementia-related cognitive impairment more facially responsive to pain.

Association of cognitive decline and brain structure

Whole brain group comparisons of brain structure revealed a large area in the temporal lobe and smaller clusters in the frontal and parietal lobe that showed reduced gray matter volume in cognitively impaired individuals. This is a typical finding for dementia, especially for Alzheimer's disease.^{59,60} Given our hypothesis that endogenous pain inhibition might be affected in cognitively impaired individuals, additional region-of-interest analyses were performed within regions known to be involved in descending pain modulation.¹⁰ These analyses revealed that cognitively impaired individuals also show reduced gray matter volume within several of these areas, namely the mOFC, IOFC and ACC. With regard to white matter, widespread differences throughout the brain were found between cognitively impaired individuals and cognitively healthy individuals, which corroborates earlier findings.^{61,62}

Mediating effect of structural brain changes on the relation between pain responses and cognitive decline***Increased facial responses to pressure pain***

Although the independent-samples t-test revealed a significant increase in pain-related facial responses to pressure pain stimuli in cognitively impaired compared to cognitively healthy individuals, this increase does not seem to be gradually linked to the magnitude of cognitive decline in our sample, given that we found no significant correlation with the MMSE score. Given the lack of significant correlation, results of the mediation analyses for facial responses to pressure pain (pain-face) must be interpreted with caution. With regard to gray volume, there was a significant mediation effect for the temporal lobe, indicating that the increase in facial responses to pressure pain in cognitively impaired individuals was mediated by reduced gray matter volume in the temporal area. Again, these results should be interpreted with caution although the role of temporal lobe in pain processing has been demonstrated before. A recent meta-analysis found that a specific area of the temporal lobe, the medial temporal lobe, shows altered brain activity during pain, with increased activity during experimental pain stimulation and decreased activity in chronic pain patients compared to healthy individuals.⁶³ The most reported subregion that showed abnormal activity was the hippocampus, which is known as a critical brain structure not only for memory formation⁶⁴ but also for emotion regulation together with the amygdala, another medial temporal structure.^{65,66} Although the temporal cluster of the present study covered more than only the medial temporal lobe, our observation may support the hypothesis that gray matter atrophy in the temporal lobe including the hippocampus might play some role in the elevated facial responses to pain in cognitively impaired individuals; possibly due to a lack of regulating the affective dimension of pain and its facial output.

Amplification of facial responses during the CPM paradigm

The observed decrease in CPM measured by facial expression in cognitively impaired individuals was found to be mediated by the reduction in gray matter volume in the frontal cortex, specifically in the mOFC and ACC. This was based on the findings that gray matter volume of these areas could significantly predict CPM measured by facial expression when controlling for MMSE and that the association between MMSE and CPM measured by facial expression was reduced when controlling for gray matter volume of these areas. This was not found for the other gray matter clusters. Continuing on this finding, we studied the mediating effect of white matter structure of the forceps minor, a tract close to the mOFC and ACC. Even though this mediation effect missed the set level of significance, the relation between MMSE and CPM measured by facial expression was reduced when controlling for the white matter structure of this tract, thus, pointing to a mediation effect and therefore corroborating the gray matter findings.

The mOFC and ACC clusters result from the VBM region-of-interest analyses based on areas known to be involved in descending pain modulation¹⁰ Thus, our finding that these structures indeed mediate the link between cognitive impairment and loss in endogenous pain inhibition (CPM facial expression) clearly suggests that a loss in frontal control seems to result in a loss in pain inhibitory functioning in cognitively impaired older individuals. Previous functional imaging studies repeatedly found that the ACC and mOFC are involved in pain modulation in cognitively healthy individuals. Changes in brain activity in these areas were observed during CPM,^{10,67–69} but also during placebo analgesia^{70,71} and cognitive-emotional pain modulation by distraction^{72–74} and reward.⁷⁵ Studies investigating the relation between brain structure and descending pain modulation are more scarce. One study found that a decrease in CPM was associated with a thicker cortex in the lateral orbitofrontal cortex in both healthy individuals as well as chronic pain patients, but no such association was reported for the mOFC.⁷⁶ Another study found that placebo analgesic responses in healthy individuals are associated with white matter structure of the ACC and the tracts connecting the ACC with the periaqueductal gray.⁷⁷

The findings of the present study indicate that a loss of gray matter in the mOFC and ACC as well as structural changes in the white matter tracts connecting these prefrontal areas are associated with deficits in endogenous pain inhibitory functioning in cognitively impaired individuals. This supports our hypothesis that neurodegeneration in brain structures involved in descending pain inhibition might contribute to altered pain responses in dementia-related cognitive impairments.

Limitations

The small sample size did not allow to investigate differences between dementia subtypes. The scatterplots coded by subtype in Figure 3 give a first indication of the variance between different dementia subtypes. However, larger sample sizes,

especially for patients with vascular dementia and frontotemporal dementia, are needed to really explore differences between dementia subtypes. Moreover, we only investigated individuals with mild cognitive impairment and mild forms of dementia, and thus, we cannot draw conclusions about more advanced forms of dementia. With regard to the facial expression of pain, an important question is whether this is a pain specific increase or just an unspecific increase in emotional arousal. Previous studies have shown that dementia patients mainly show an increase in pain-indicative facial responses in response to noxious stimuli and not an overall unspecific increase in pain-irrelevant facial responses, which suggest that indeed the pain experience is encoded in the elevated facial responses to noxious stimuli.^{3,5} Another limitation refers to the fact, that patients and controls were not rigorously matched for education. Although education did not differ significantly between groups, there were more highly educated individuals in the control group, which might have slightly influenced the outcomes. Finally, a disadvantage of using VBM to assess gray matter volume in dementia is that local neurodegeneration can impact the accuracy of registration. While smoothing may help to account for this, it may have an impact on the results.

Conclusions

This study confirms previous findings of intensified pain processing in dementia-related cognitive impairment when pain is assessed using non-verbal responses; especially facial responses. These increased pain responses were mediated by dementia-related neurodegeneration, with different brain areas mediating different aspects of pain responsiveness. The observed increase in pain-related facial responses to pressure pain was mediated by reduced gray matter volume within the temporal lobe, while the observed decrease in endogenous pain inhibition assessed by facial responses was mediated by reduced gray matter volume within the mOFC and ACC. This latter finding suggests that a loss of pain inhibitory functioning caused by structural changes in prefrontal areas might be one of the underlying mechanisms responsible for amplified pain responses in individuals with a dementia-related cognitive impairment.

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Chapter 7

General discussion

General discussion

The primary research objective of this thesis was to investigate age- and dementia-related changes in pain processing and their associations with frontal brain functioning. In this chapter, the main findings of each empirical chapter will first be summarized. Subsequently, I will discuss how our findings support the frontal functioning hypothesis. The chapter ends with a discussion on the strengths and limitations of the present studies, future directions for research and implications for clinical practice.

Summary of main findings

Pain and executive functioning

Chapter 2 presents a systematic review that provides a comprehensive overview of the findings so far on the relation between pain and executive functions. The review confirms that pain shows close linkage to executive functioning. This relation was most apparent for chronic pain patients, who show reduced executive functioning performance in all three domains of executive functioning. Moreover, it was found that executive functioning performance negatively correlates with experimental pain responses, suggesting that poorer executive functioning might be a risk factor for higher vulnerability to pain. Although the correlation coefficients were small for all three executive functioning domains, it is interesting that cognitive inhibition showed the strongest association with experimental pain responses compared to updating and shifting, suggesting that especially a lack of cognitive inhibitory functioning might render individuals more vulnerable to pain.

EEG activity during pain

Chapter 3 reports about a study aiming at better understanding whether electroencephalography (EEG) recordings might serve as an alternative way to assess pain, which might be used in individuals who lack the ability to report about pain verbally. We found that EEG activity mirrors more closely the subjective pain sensation than the stimulus intensity. An increase in subjective pain sensation was associated with a decrease in EEG activity in several frequency bands.

Pain responses in healthy older individuals and dementia-related cognitive impairment

Chapter 5 and 6 describe the findings of our experimental study investigating pain responses in healthy older individuals and older individuals with a dementia-related cognitive impairment, respectively. Given the decline in verbal communication skills in individuals with cognitive impairments, pain was not only measured using self-report ratings but also via facial responses. Moreover, given the reported linkage

between pain responses and cognitive inhibition (see Chapter 2), we were especially interested in assessing one experimental pain paradigm that allows to more precisely assess endogenous pain inhibition, namely the conditioned pain modulation paradigm (CPM). To test whether the CPM paradigm shows endogenous pain inhibition not only for self-report ratings but also for facial responses, the study described in Chapter 4 was conducted. Here, we found that facial responses can be used to assess endogenous pain inhibition by demonstrating that pain-relevant facial responses in healthy individuals decrease in the presence of a conditioning stimulus, similar to the decrease in self-report rating. Having validated this protocol, we used this CPM protocol in older individuals with and without cognitive impairments. In Chapter 5, we found that the majority of healthy older individuals did not show endogenous pain inhibition, neither in self-report ratings nor in facial responses. In Chapter 6, we found that endogenous pain inhibition was even more reduced in individuals with a dementia-related cognitive impairment. This significant difference between individuals with and without a dementia-related cognitive impairment was only present when endogenous pain inhibition was measured via facial responses and not when endogenous pain inhibition was measured via self-report. Similarly as for CPM, we found a significant difference in pressure pain sensitivity between the two groups when pain was assessed via facial responses. The next section discusses the associations we found between pain responses and frontal functioning.

Frontal brain functioning hypothesis

Executive functioning and pain responses in aging

Several studies have previously suggested that pain responses in healthy older individuals are associated with executive functioning performance. Poorer executive functioning in older individuals was found to be associated with reduced pain tolerance, increased facial responses to pain and poorer endogenous pain inhibition.¹⁻

⁵ The findings of the systematic review described in Chapter 2 support this frontal functioning hypothesis by demonstrating a general association between pain and executive functioning in both chronic pain studies and experimental pain studies. Given our interest in the association between frontal functioning and endogenous pain inhibition, we specifically examined the correlation between CPM and executive functioning performance in the systematic review. We indeed found higher (though still small) correlations between executive functioning performance and CPM than for overall experimental pain responses. This was found for the executive functioning domain inhibition. In Chapter 5, we aimed to replicate these findings in healthy older individuals. So far, previous studies in healthy older individuals did not study executive functioning performance separately in all three domains. We found that decreased executive functioning performance in the domains inhibition and shifting were associated with increased pain responses. In contrast to expectations, however,

these executive functioning domains were not associated with CPM. Thus, in contrast to our hypothesis, a reduction in endogenous pain inhibition in older individuals was not closely linked to frontal functioning as assessed by executive functioning.

Brain structure and pain responses in aging and dementia

In Chapter 2, we discuss specific sub regions of the frontal cortex that might serve as shared underlying mechanisms for poor executive functioning performance and increased pain responses. In Chapter 5 and 6, this hypothesis was tested by investigating whether increased pain responses in healthy older individuals and dementia-related cognitive impairment are indeed linked to the structural integrity of specific frontal brain regions.

Chapter 5 studied the association between individual differences in pain responses and structural brain variations in healthy older individuals. For these imaging analyses, we examined a large part of the prefrontal cortex to investigate whether pain responses are associated with regional gray matter and white matter integrity. For pressure pain sensitivity, only associations with white matter structure were found, namely between pressure pain sensitivity measured by facial expression and white matter structure between the ventromedial PFC and the PAG. In contrast, variance in endogenous pain inhibition was associated with structural brain variations in both gray and white matter. Endogenous pain inhibition measured by verbal rating was associated with white matter structure between the right dorsolateral PFC and the PAG. Endogenous pain measured by facial expression was associated with gray matter volume in the right ventrolateral PFC as well as with white matter structure between the left ventrolateral PFC and the PAG. These structural brain variations could significantly predict endogenous pain inhibition even when controlling for executive functioning.

Chapter 6 studied whether differences in pain responses between healthy older individuals and individuals with a dementia-related cognitive impairment are mediated by dementia-related neurodegeneration. We first assessed which brain areas showed structural differences in gray and white matter between healthy older individuals and individuals with a dementia-related cognitive impairment. Subsequently, we examined whether the structural integrity of these areas could mediate the relation between cognitive decline and pain responsiveness. We found that the increase in facial responses to pressure pain in cognitively impaired individuals was mediated by a reduction in gray matter volume in the temporal lobe. In contrast, the decrease in CPM measured by facial expression in cognitively impaired individuals was mediated by structural changes in prefrontal areas, namely by a reduction in gray matter volume in the mOFC and ACC and by changes in white matter structure of a tract close to these areas, namely the forceps minor.

Figure 1. Schematic model depicting brain areas affected by dementia that mediate the relation between decreased cognitive decline and decreased endogenous pain inhibition. In the right top corner, a copy of Figure 1 of Chapter 1 is displayed, showing brain regions involved in the processing of pain. The frontal cortex is enlarged, showing the brain areas that mediate decreased endogenous pain inhibition in dementia due to dementia-related neurodegeneration. These regions are the medial orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and the forceps minor, a white matter tract that runs through the frontal cortex.

Conclusion frontal functioning hypothesis in aging and dementia

Together, these findings indicate that age- and dementia-related changes in pain processing are linked to frontal brain functioning, especially to structural characteristics (gray and white matter) and to a lesser degree to executive functioning as an indirect measure of frontal functioning. Particularly endogenous pain inhibition as assessed using the CPM protocol seems to be associated with structural integrity of the frontal cortex. Our findings suggest that decreased endogenous pain inhibition in healthy older individuals might result from altered structural integrity of the ventrolateral PFC and the tracts connecting the ventro- and dorsolateral PFC with the PAG. Neurodegeneration in the mOFC, ACC and possibly the forceps minor might explain why individuals with a dementia-related cognitive impairment show even more reduced endogenous pain inhibition compared to healthy older individuals. This is summarized in Figure 1. Thus, increased pain responses in aging and dementia might partly be explained by the effect of aging and dementia on the descending pain inhibitory system, which results in intensified processing of noxious stimulation. Older individuals already have a higher likelihood to suffer more from conditions such as musculoskeletal and gastrointestinal disorders, cardiac diseases, genitourinary infections, wounds and poor oral health.^{6,7} It might be possible that the

presence of these painful conditions in combination with decreased pain inhibitory functioning makes healthy older individuals and individuals with a dementia-related cognitive impairment more vulnerable to pain.

Methodological considerations

Sample

The study described in Chapter 6 makes a significant contribution to research on pain in dementia by not focusing solely on Alzheimer's disease, as most previous studies did. We also included two other subtypes of dementia as well as mild cognitive impairment. However, we did not succeed in our aim to recruit enough participants to be able to draw conclusions on differences in pain responses between subtypes. We could for example not replicate the only experimental pain study in frontotemporal dementia that found reduced pain sensitivity in these patients.⁸ This is in contrast to most findings in Alzheimer's disease and it would therefore be interesting to replicate this study. Future experimental pain studies should therefore investigate differences in pain responses between dementia subtypes and how these differences are related to neurodegeneration. Such a study should probably be performed in a multicenter setting to facilitate the recruitment process. Furthermore, it would be helpful to include participants with a more severe stage of dementia, since the average MMSE score of the participants in the current sample indicated only mild dementia-related impairment. Patients with a more severe stage of dementia will probably also show more pronounced decreased frontal brain functioning. It would be interesting to assess how this would affect pain inhibitory functioning. Recruitment of this fragile group will be difficult, but feasible, since a few studies have successfully recruited patients with severe dementia for experimental pain research, of which one also included an MRI scanning session.^{9–11}

Study design

The last two empirical chapters were cross-sectional studies performed in pain-free individuals, i.e. participants that did not use analgesic medication. Therefore, our study design did not allow to investigate whether decreased pain inhibitory functioning due to decreased structural integrity also relates to clinical pain. It would be useful to conduct the same study protocol in older individuals with clinical pain and compare the findings to see whether these individuals have worse reduced endogenous pain inhibition and decreased frontal functioning. A longitudinal design would give even more insight on the relation between pain inhibitory functioning, altered frontal functioning and vulnerability to pain, especially on the temporal order of these events. Recently, three longitudinal studies in the field of pain and cognition investigated whether the presence of chronic pain could predict the risk of developing cognitive decline and dementia.^{12–14} These studies showed that (severe) pain increase

the risk of developing cognitive decline. Based on the results of the present thesis, future longitudinal studies should also investigate whether frontal dysfunctions as assessed by impaired executive functioning and decreased structural integrity of the frontal cortex increase the risk of developing pain. This would support the hypothesis that decreased frontal brain functioning makes older individuals more vulnerable to pain.

Pain assessment

In Chapter 3, we conducted a preliminary study on the question whether EEG could be used as a non-verbal pain assessment tool. EEG activity in healthy individuals was found to capture mainly subjective pain sensation and not the noxious input, which is a prerequisite for using EEG as a pain assessment tool in clinical practice. However, the effect we found was rather small and probably not pain specific, since a decrease in EEG activity was found in various affective and cognitive states by other studies, as discussed in the article. The low spatial resolution of EEG probably asks for more elaborated recordings and analyses to come closer to a pain-specific EEG pattern. This would however hinder clinical usefulness. Moreover, dementia itself is also associated with changes in EEG activity and thus, a pain-specific EEG pattern in healthy individuals might be different in patients with dementia.^{15–17} Therefore, EEG was not used in further studies of this thesis. Instead, we used facial expression assessed via FACS as a non-verbal indicator of pain, which is widely used in experimental pain research and is assumed to be a valid pain assessment tool in dementia.¹⁸ Nevertheless, it is important to realize that facial responses to pain do not reflect the exact same aspects of the multidimensional pain experience as captured by self-report. In Chapter 4, we found that the correlation coefficient between CPM measured by rating and CPM measured by facial expression was only of moderate size, suggesting much unrelated variance. Facial responses capture more autonomic behavior¹⁹ and it might therefore be an even more valid response than self-report because it does not depend on cognitive resources.

Experimental pain protocols

Endogenous pain inhibition was in this thesis assessed via the CPM protocol. There are, however, also other paradigms to test inhibitory pain mechanisms. In Chapter 1, placebo analgesia has been introduced. This paradigm has already been studied in dementia. It was found that placebo analgesia is reduced in Alzheimer patients, which is not unexpected because people with (severe) dementia will probably not have expectations about the benefit of an analgesic treatment.²⁰ What is interesting is that reduced placebo analgesia was associated with reduced frontal connectivity between the prefrontal cortex and the rest of the brain. This finding is in line with our finding that reduced CPM is associated with neurodegeneration in frontal brain areas. It should be further elucidated how the underlying mechanisms of CPM and placebo analgesia relate to each other.²¹ Next to CPM and placebo analgesia, a third

method for measuring endogenous pain inhibition is offset analgesia. This refers to a large decrease in pain when the intensity of a noxious stimulus is only slightly reduced. Similar to CPM, offset analgesia was found to be reduced in cognitively healthy older individuals.²² A functional MRI study revealed different patterns of brain activity during CPM and offset analgesia.²³ Future fundamental pain studies might assess how neurodegeneration differentially affects CPM, offset analgesia and placebo analgesia.

Future directions for research

Frontal functioning hypothesis in other patient groups

In addition to age- and dementia-related cognitive impairment, cognitive impairment can be found in various other patient groups. Some of these patient groups also show altered pain responses. This combination of cognitive impairment and altered pain responses has for example been observed in Parkinson disease, Huntington disease, multiple sclerosis, autism, stroke and traumatic brain injury.²⁴ To support the frontal functioning hypothesis studied in this thesis, it would be interesting to explore whether altered pain responses in these conditions also relate to executive functioning performance and/or to structural integrity of the frontal cortex. In the light of the results of the present thesis, the association between endogenous pain inhibition and frontal brain functioning might especially be interesting. A few studies already examined the CPM effect in the above-mentioned patient groups. It was found that patients with Parkinson disease and autism spectrum disorders do not show altered CPM compared to healthy controls, however, these studies did not take the degree of cognitive impairment or structural brain changes into account.^{25–27}

Can pain inhibitory functioning be improved?

If healthy older individuals and individuals with a dementia-related cognitive impairment are indeed more vulnerable to pain due to decreased endogenous pain inhibition, the question remains whether pain inhibitory functioning can be improved again. For a non-pharmacological intervention, it might be interesting to explore groups of people that show enhanced pain inhibition. Extreme athletes, for example, have been found to show increased endogenous pain inhibition compared to healthy adults who perform regular physical exercise.^{28,29} A recent cross-sectional study investigated whether this association between physical activity and pain inhibitory functioning is also present in older individuals, who are on average much less physically active than younger adults. It was found that individuals who show less sedentary behavior and more light physical activity have increased endogenous pain inhibition.³⁰ It remains unclear whether the relation between exercise and endogenous pain inhibition is a causal relation. So far, it is known that despite the physical and cognitive status of individuals with dementia, exercise interventions are feasible in moderate to severe dementia.³¹ More studies are needed to investigate whether exercise interventions

might increase endogenous pain inhibition in older individuals and thereby decrease pain vulnerability. This also applies to psychological interventions, since there are for example indications that mindfulness might increase endogenous pain inhibition.³²

With regard to pharmacological pain treatment, it is interesting to point out that several studies in chronic pain patients found that pain inhibitory functioning as assessed via CPM might predict the effectiveness of certain analgesic treatments, including opioids, serotonin–norepinephrine reuptake inhibitors and nonsteroidal anti-inflammatory drugs.^{33–36} Recently, it has been argued that more studies are needed to investigate efficacy of pharmacological pain treatment in dementia, since no evidence-based guidelines exist for treating pain in people with dementia.⁶ Based on our findings of decreased endogenous pain inhibition in dementia, it might be specifically worthwhile to investigate whether pain inhibitory functioning might predict efficacy of analgesics in dementia, aiming at personalized pain treatment.

Implications for practice

This thesis resulted in important lessons for clinical practice. It again highlights the importance of non-verbal pain assessment in dementia, given that the differences in pain responses between healthy older individuals and individuals with a dementia-related cognitive impairment were only observed when pain was measured via facial responses but not when pain was measured via self-report. Observing the facial expression of pain might help to recognize pain in this fragile patient group. Observational scales for pain assessment in dementia already exist for several years. Recently, an improved observational scale was developed based on the best items of existing scales.³⁷ This resulted in fifteen items on facial expression, body movements and vocalization, together named the PAIC15. The items on facial expression include three items that are similar to the action units that we used to calculate the facial expression composite score in our experimental studies, namely “frowning” (brow lowering), “raising upper lip” (upper lip raise, wrinkled nose) and “mouth opening”. In addition, the PAIC15 also scores the intensity of “narrowing the eyes” and the more subjective item “looking tense”.

As described in Chapter 6, most participants with a dementia-related cognitive impairment in our experimental study had a mild stage of dementia and were able to provide a self-report rating for the painful stimuli. Despite this, differences in facial responses were found between healthy older individuals and individuals with a dementia-related cognitive impairment. Thus, the results of the present thesis indicate that observational pain assessment tools such as the PAIC15 might not only be used for assessing pain in people with dementia who can clearly not communicate about pain anymore but also for assessing pain in people with mild dementia who are still able to give a pain rating.

Conclusion

The key message of this thesis is that one should not forget about pain in dementia. For clinical practice, it is important to keep in mind that as opposed to the general functional decline in dementia, pain processing is not diminished but seems to be increased. This might be due to a loss of pain inhibitory functioning caused by structural changes in prefrontal areas, which especially affects the descending pain inhibitory system. For research, this finding might help future studies to discover new pain management options.

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Appendix

Summary

Samenvatting

Dankwoord

Curriculum vitae

Summary

Pain is more prevalent in older individuals compared to younger individuals. In order to treat pain well, it is important to study why older individuals become more vulnerable to pain. This holds for cognitively healthy older individuals but even more for cognitively impaired older individuals because they can have difficulties reporting pain themselves. The present thesis studied the hypothesis that increased pain in older individuals might be due to decreased frontal brain functioning. Frontal brain functioning was assessed by means of structural integrity of the frontal cortex and by neuropsychological performances that are linked to the function of the frontal cortex, namely executive functions. The relation between pain and frontal functioning was studied in healthy older individuals as well as in older individuals with dementia-related cognitive impairments.

We first conducted a systematic review, described in **Chapter 2**, in order to get a comprehensive overview of the findings so far on the association between executive functioning and pain. The literature search resulted in a large number of chronic pain studies and experimental pain studies that used a variety of different executive functioning tests. We organized our findings based on the three executive functioning domains inhibition, shifting and updating. The review confirms previous findings that chronic pain patients show reduced executive functioning performance in all three domains, but this reduction was not highly correlated with pain severity. The findings of experimental pain studies that let participants perform executive functioning tasks while receiving painful stimulation show that painful stimulation can reduce executive functioning performance and, the other way around, performing an executive task can reduce pain responsiveness. Moreover, it was found that executive functioning performance negatively correlates with experimental pain responses, suggesting that poorer executive functioning may be a risk factor for higher vulnerability to pain. The correlation coefficient was small for all three executive functioning domains, but cognitive inhibition showed the strongest association with experimental pain responses compared to updating and shifting, especially with endogenous pain inhibition.

Chapter 3 reports about a study investigating electroencephalography (EEG) responses during pain. In theory, EEG could be an interesting method to assess pain in people with dementia who can no longer report about pain. With this aim in mind, we investigated what aspect of pain is reflected by EEG activity in healthy individuals. The use of experimental pain stimulation allowed us to investigate whether EEG activity mirrors more closely the intensity of the stimulus (the noxious input, in this case heat) or the subjectively rated pain sensation (the psychological output). We assessed the smallest change in temperature that is needed for a person to notice this change subjectively and we used this ‘just noticeable difference’ as interval between

stimulus intensities. Using these small differences between stimulus intensities, we found that EEG activity mirrors more closely the subjective pain sensation than the stimulus intensity. An increase in subjective pain sensation was associated with a decrease in EEG activity in several frequency bands. It is promising that EEG activity mainly captures subjective pain sensation and not the noxious input, however, the effect we found was rather small and probably not pain specific.

In Chapter 5 and 6, we studied experimental pain responses in cognitively healthy individuals and individuals with dementia-related cognitive impairments, and their associations with frontal brain functioning. We assessed pain sensitivity to pressure stimulation and endogenous pain inhibition using the conditioned pain modulation (CPM) paradigm. We were especially interested in this paradigm because the findings of the systematic review together with previous studies suggest that reduced endogenous pain inhibition might be associated with reduced executive functioning and might be one of the mechanisms underlying increased nociceptive processing in older individuals. Given the loss in verbal communication skills over the course of dementia, pain was measured using self-report ratings as well as via facial responses. Since facial responses had not been used before to assess endogenous pain inhibition, we first performed a study in healthy adults to investigate whether the facial expression of pain is sensitive enough to assess endogenous pain inhibition as elicited during a CPM paradigm. This study is described in **Chapter 4**. It was found that pain-relevant facial responses decrease in the presence of a conditioning stimulus, which was comparable to the decrease in self-report rating. Thus, this study indicates that facial responses can be used to assess endogenous pain inhibition. In Chapter 5 and 6, this method was used.

Chapter 5 focuses on pain responses in the group of healthy older individuals. We found that the majority of healthy older individuals did not show endogenous pain inhibition. In contrast to expectations, decreased executive functioning performance was not associated with endogenous pain inhibition but with facial responses to pressure pain. This was specifically the case for the executive domains inhibition and shifting. With regard to the structural integrity of the frontal cortex, associations with white matter structure between the prefrontal cortex and the periaqueductal gray were found for pressure pain sensitivity measured by facial expression as well as for endogenous pain inhibition. Endogenous pain inhibition measured by facial expression was also associated with gray matter volume within the prefrontal cortex. These structural brain variations could significantly predict endogenous pain inhibition even when controlling for executive functioning.

Chapter 6 focuses on the differences in pain responses between healthy older individuals and individuals with a dementia-related cognitive impairment. A comparison between the two groups revealed reduced endogenous pain inhibition and increased pressure pain sensitivity in individuals with a dementia-related

cognitive impairment. These significant differences were only present when these pain responses were assessed via facial responses and not when assessed via self-report. The increase in facial responses to pressure pain was mediated by a reduction in gray matter volume in the temporal lobe. In contrast, the decrease in endogenous pain inhibition measured by facial expression was mediated by structural changes in prefrontal areas, namely by a reduction in gray matter volume in the medial orbitofrontal cortex and anterior cingulate cortex and by changes in white matter structure of the forceps minor. This latter finding suggests that a loss of pain inhibitory functioning caused by structural changes in prefrontal areas might be one of the underlying mechanisms responsible for amplified pain responses in individuals with a dementia-related cognitive impairment.

In **Chapter 7**, the findings of this thesis were discussed. The main conclusion is that increased pain responses in cognitively healthy older individuals and older individuals with a dementia-related cognitive impairment can be linked to frontal brain functioning. Particularly endogenous pain inhibition as assessed using the CPM protocol seems to be associated with structural integrity of the frontal cortex. Thus, increased pain responses in aging and dementia might partly be explained by the effect of aging and dementia on the descending pain inhibitory system, which results in intensified processing of noxious stimulation. Further research is needed to determine whether this also leads to a higher vulnerability to clinical pain. For clinical practice, this thesis again highlights the importance of non-verbal pain assessment in dementia, given that the differences in pain responses between healthy older individuals and individuals with a dementia-related cognitive impairment were only observed when pain was measured via facial responses.

Samenvatting

Pijn komt vaker voor bij oudere personen dan bij jongere personen. Om pijn goed te kunnen behandelen, is het belangrijk om te onderzoeken waarom ouderen kwetsbaarder worden voor pijn. Dit geldt voor cognitief gezonde ouderen, maar nog meer voor ouderen met cognitieve problemen, omdat zij moeite kunnen hebben om zelf aan te geven dat zij pijn hebben. In dit proefschrift is onderzocht of pijn bij ouderen het gevolg kan zijn van een verminderde frontale hersenfunctie. Frontale hersenfunctie werd gemeten aan de hand van de structuur van de frontale cortex en aan de hand van executief functioneren, wat is gelinkt aan het functioneren van de frontale cortex. De relatie tussen pijn en frontale hersenfunctie werd onderzocht bij zowel cognitief gezonde ouderen als bij ouderen met een aan dementie gerelateerde cognitieve stoornis.

We hebben eerst een systematische review uitgevoerd, beschreven in **Hoofdstuk 2**, om een uitgebreid overzicht te krijgen van eerdere wetenschappelijke onderzoeken naar het verband tussen executief functioneren en pijn. Het literatuuronderzoek resulteerde in een groot aantal wetenschappelijke onderzoeken naar chronische pijn en experimentele pijn. Deze studies maakten gebruik van verschillende testen om executieve functies te meten. Wij hebben de resultaten van deze studies ingedeeld op basis van de drie domeinen van executief functioneren, namelijk inhibitie, cognitieve flexibiliteit en werkgeheugen. Onze review bevestigt eerdere bevindingen dat patiënten met chronische pijn problemen hebben met executief functioneren in alle domeinen. De mate waarin executief functioneren was verminderd correleerde echter niet sterk met de ernst van de pijn. De resultaten van de experimentele pijnstudies die deelnemers executieve testen lieten uitvoeren terwijl zij pijnprikkels toegediend kregen, laten zien dat executief functioneren afneemt in de aanwezigheid van pijnprikkels, en omgekeerd, dat het uitvoeren van een executieve test de pijnreactie kan verminderen. Bovendien vonden we dat verminderd executief functioneren gecorreleerd was met een verhoogde reactie op experimentele pijnprikkels, wat suggereert dat verminderd executief functioneren een risicofactor is voor een grotere kwetsbaarheid voor pijn. De correlatiecoëfficiënt was klein voor alle drie de domeinen van executief functioneren, maar inhibitie liet de sterkste associatie zien in vergelijking cognitieve flexibiliteit en werkgeheugen. Inhibitie was met name geassocieerd met endogene pijninhibitie.

Hoofdstuk 3 beschrijft een studie waarin de elektrische activiteit van de hersenen tijdens pijn werd onderzocht. Elektrische activiteit werd gemeten met behulp van elektro-encefalografie (EEG). In theorie zou EEG een interessante methode kunnen zijn om pijn te beoordelen bij mensen met dementie die zelf niet meer aan kunnen geven dat zij pijn hebben. Met dit doel voor ogen hebben we onderzocht welk aspect van pijn wordt weerspiegeld in het EEG signaal bij gezonde individuen. Omdat

we gebruik maakten van experimentele pijnprikkels, konden we onderzoeken of de EEG activiteit beter overeenkomt met de intensiteit van de pijnprikkel of juist met de subjectieve beoordeling van de pijnprikkel. We hebben eerst gezocht naar de kleinste verandering in temperatuur die nodig is voor een persoon om deze verandering subjectief op te merken. Dit nog net merkbare verschil gebruikten we als interval tussen de verschillende pijnprikkels. Door gebruik te maken van deze kleine verschillen in intensiteit tussen de verschillende pijnprikkels ontdekten we dat EEG activiteit meer overeenkomt met de subjectieve pijnsensatie dan met de intensiteit van de pijnprikkel. Een toename in subjectieve pijnsensatie was geassocieerd met een afname van de EEG activiteit in verschillende frequentiebanden. Het is veelbelovend dat EEG activiteit voornamelijk de subjectieve pijnsensatie weerspiegelt en niet de intensiteit van de pijnprikkel, maar het effect dat we vonden was vrij klein en waarschijnlijk niet pijn specifiek.

In Hoofdstuk 5 en 6 hebben we reacties op experimentele pijnprikkels onderzocht bij cognitiefgezonde ouderen en bij ouderen met een aan dementie gerelateerde cognitieve stoornis. Vervolgens onderzochten we de relatie tussen deze reacties en de frontale hersenfunctie. Als pijnprikkels gebruikten we drukprikkels om pijngevoeligheid te meten en de geconditioneerde pijnmodulatie (CPM) test om endogene pijninhibitie te meten. We waren vooral geïnteresseerd in deze CPM test, omdat de bevindingen van de systematische review (Hoofdstuk 2) samen met eerdere studies suggereren dat verminderde endogene pijninhibitie geassocieerd zou kunnen zijn met verminderd executief functioneren en mogelijk één van de mechanismen zou kunnen zijn van een verhoogde pijnverwerking bij ouderen. Omdat mensen met dementie moeite kunnen hebben met het aangeven van pijn, werd pijn niet alleen gemeten met behulp van zelfrapportage, maar ook aan de hand van gezichtsexpressie. Gezichtsexpressie was nog niet eerder door andere studies gebruikt om endogene pijninhibitie te meten en daarom hebben we eerst een onderzoek uitgevoerd bij gezonde volwassenen om te onderzoeken of de gezichtsuitdrukking van pijn gevoelig genoeg is om endogene pijninhibitie vast te kunnen stellen. Deze studie is beschreven in **Hoofdstuk 4**. Het bleek dat de afname in pijnrelevante gezichtsreacties in aanwezigheid van een conditionele stimulus vergelijkbaar is met de afname in zelfrapportage. Deze studie laat dus zien dat gezichtsexpressie kan worden gebruikt om endogene pijninhibitie te bepalen. In Hoofdstuk 5 en 6 is deze methode gebruikt.

Hoofdstuk 5 richt zich op pijnreacties in de groep gezonde ouderen. We zagen dat de meerderheid van de gezonde ouderen geen endogene pijninhibitie vertoonde. In tegenstelling tot wat we verwachtten, was verminderd executief functioneren niet geassocieerd met endogene pijninhibitie, maar met gezichtsreacties op de drukprikkels. Dit was met name het geval voor de executieve functie domeinen inhibitie en cognitieve flexibiliteit. Wat betreft de hersenstructuur vonden we dat de structuur van de witte stof tussen de prefrontale cortex en het periaqueductale grijs was geassocieerd met zowel gezichtsreacties op de drukprikkels als endogene

pijninhibitie. Endogene pijninhibitie gemeten aan de hand van gezichtsexpressie was daarnaast ook geassocieerd met grijze stof volume in de prefrontale cortex. Ook als er gecontroleerd werd voor executief functioneren konden deze variaties in hersenstructuur endogene pijninhibitie voorspellen.

Hoofdstuk 6 richt zich op de verschillen in pijnrespons tussen gezonde ouderen en personen met een aan dementie gerelateerde cognitieve stoornis. Een vergelijking tussen de twee groepen liet zien dat endogene pijninhibitie is verminderd en pijngevoeligheid voor drukprikkelers is verhoogd bij personen met een aan dementie gerelateerde cognitieve stoornis. Deze significante verschillen waren alleen aanwezig wanneer deze pijnreacties werden gemeten aan de hand van gezichtsexpressie en niet wanneer pijnreacties werden gemeten via zelfrapportage. De toename in pijnrelevante gezichtsreacties in reactie op drukprikkelers werd gemedieerd door een afname in grijze stof volume in de temporale kwab. De afname in endogene pijninhibitie gemeten via gezichtsexpressie werd daarentegen gemedieerd door structurele veranderingen in prefrontale gebieden, namelijk door verminderd grijze stof volume in de mediale orbitofrontale cortex en de cortex cingularis anterior en door veranderingen in de structuur van de witte stof van de forceps minor. Dit suggereert dat verminderde pijninhibitie veroorzaakt door structurele veranderingen in prefrontale gebieden één van de onderliggende mechanismen zou kunnen zijn van een verhoogde pijnverwerking bij personen met een aan dementie gerelateerde cognitieve stoornis.

In **Hoofdstuk 7** zijn alle resultaten van dit proefschrift samen bediscussieerd. De belangrijkste conclusie is dat verhoogde pijnreacties bij cognitief gezonde ouderen en oudere personen met een aan dementie gerelateerde cognitieve stoornis in verband kunnen worden gebracht met het functioneren van de frontale hersenen. Met name endogene pijninhibitie lijkt verband te houden met de structuur van de frontale cortex. De toegenomen pijnrespons bij veroudering en dementie zou dus gedeeltelijk verklaard kunnen worden door het effect van veroudering en dementie op het pijninhibitie systeem, wat zou kunnen resulteren in een verhoogde pijnverwerking. Verder onderzoek is nodig om te bepalen of dit ook leidt tot een verhoogde kwetsbaarheid voor klinische pijn. Voor de klinische praktijk benadrukt dit proefschrift opnieuw het belang van non-verbale pijnbeoordeling bij dementie, aangezien de verschillen in pijnreactie tussen gezonde ouderen en ouderen met een aan dementie gerelateerde cognitieve stoornis alleen werden waargenomen wanneer pijn werd gemeten via gezichtsexpressie.

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Steffie

Curriculum vitae

Steffie Bunk werd geboren op 24 april 1991 in Blaricum. Na het gymnasium aan het Goois Lyceum in Bussum begon ze in 2009 aan de bachelor Gezondheid en Leven aan de Vrije Universiteit Amsterdam. Aansluitend volgde ze de Engelstalige onderzoeksmaster Neurosciences aan dezelfde universiteit. Ze heeft wetenschappelijke stages gelopen bij achtereenvolgens het Nederlands Herseninstituut in Amsterdam, de afdeling Biologische Psychologie van de Vrije Universiteit Amsterdam en het onderzoeksinstituut Neuroscience Research Australia in Sydney. Tijdens deze laatste stage in Australië deed ze onderzoek naar dementie met behulp van structurele MRI. Ze zette haar werk op het gebied van onderzoek naar dementie voort op de afdeling Huisartsgeneeskunde en Ouderengeneeskunde van het Universitair Medisch Centrum Groningen, waar ze in 2016 begon met een promotieonderzoek naar pijn bij dementie, waarvan u de resultaten in dit proefschrift kunt lezen. Tijdens haar promotieonderzoek heeft ze onder andere deelgenomen aan de European Pain School aan de Universiteit van Siena in Italië en was ze penningmeester van GOPHER, de promovendivereniging van de Rijksuniversiteit Groningen. Sinds januari 2021 is ze werkzaam als epidemioloog bij GGD Fryslân.