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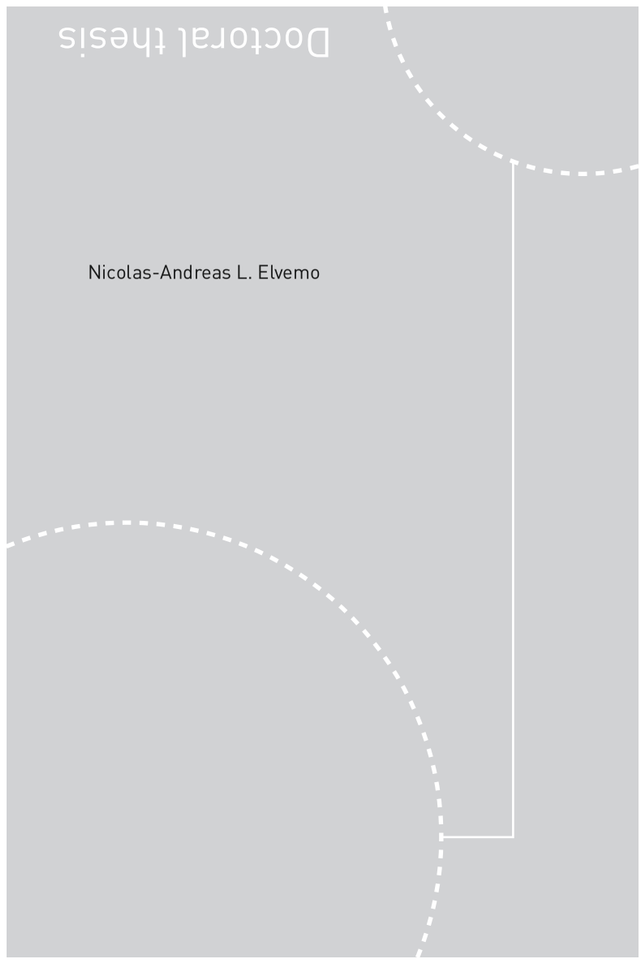
Nicolas-Andreas L. Elvemo

Cognitive and neurophysiological correlates of chronic pain



ISBN 978-82-326-1428-8 (printed ver.)
ISBN 978-82-326-1429-5 (electronic ver.)
ISSN 1503-8181

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Department of Neuroscience
Faculty of Medicine
Degree of Philosophiae Doctor
Technology Thesis for the
Norwegian University of Science and
NTNU

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Cognitive and neurophysiological correlates of chronic pain

Thesis for the Degree of Philosophiae Doctor

Trondheim, februar 2016

Norwegian University of Science and Technology
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Department of Neuroscience

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Printed by NTNU Grafisk senter

Norsk sammendrag

Bakgrunn: Kroniske smerter er utbredt i befolkningen, og pasientgruppen rapporterer hyppig kognitive svekkelser i tillegg til smertene. Kognitive svekkelser er avdekket i flere ulike domener, som arbeidshukommelse og beslutningstagning. Depresjon og søvnproblemer er også svært utbredt blant disse pasientene, og disse kan i seg selv gi kognitive svekkelser i de samme domenene som smerter.

Formål: Målet med denne avhandlingen var å øke vår forståelse for kognitive svekkelser hos pasienter med kroniske smerter, og hvordan disse svekkelsenes henger sammen med sentralnervesystemet.

Metode: Vi undersøkte 20 pasienter med kroniske smerter og 20 kontrollpersoner, med tilsvarende alder og utdanningsnivå. Pasientene ble undersøkt med nevropsykologiske tester, fysiologiske målinger (funksjonell MRI og målinger av autonome funksjoner som puls, hudkonduktans og blodtrykk) og ulike spørreskjema.

Hovedfunn: Vi avdekket at søvnproblemer er viktigere for endring av hjerneaktivitet undersøkt med funksjonell MR enn smerter og depresjon når smertepasientene gjør oppgaver som belaster arbeidshukommelsen. Vi avdekket at smertepasientene hadde mindre autonomrespons enn kontroller før dårlige beslutninger, som er en mulig forklaringsmekanisme på dårligere emosjonell beslutningstagning hos smertepasienter. Videre avdekket vi at pasientene hadde redusert responsivitet på belønning sammenlignet med kontrollene, og at endringen kunne knyttes til hjerneforandringer i hjernens belønningskretser.

Konklusjon: Kognitive svekkelser hos smertepasienter kan kobles til endringer i flere ulike fysiologiske systemer. De fysiologiske mekanismene og følgene av kroniske smerter er trolig

sammensatte og mangfoldige. Det er et behov for økt forståelse for hvordan kronisk smerte påvirker disse systemene, for på lang sikt å kunne gi pasientgruppen behandling eller lindring for de i dag utbredte kognitive svekkelsene, og kanskje også den kroniske smerten i seg selv.

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Veiledere: Asta Håberg (hovedveileder), Nils Inge Landrø (biveileder), Petter Borchgrevink (biveileder)

Finansieringskilder: Samarbeidsorganet for NTNU og St. Olavs Hospital.

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i klinisk medisin. Disputas finner sted i auditorium MTA, Medisinsk-Teknisk Forskningssenter, NTNU, torsdag 18. februar.

Acknowledgements

This thesis was carried out at the Competence Center for Functional Magnetic Resonance Imaging, Department of Circulation and Medical Imaging at the Norwegian University of Science and Technology (NTNU) and Department of Medical imaging St. Olav's Hospital. Data collection was done in connection with a research project as part of the Faculty of Medicine's Student Research Program.

The work was funded by the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology.

I would like to thank a number of people whose help has been necessary for this thesis. The seemingly never-ending supply of Dr. Asta Håberg's in-depth criticism and patience has not only been important, her unwavering support since my first peek into medical research in 2005 was undoubtedly necessary for my completion of this project. In combination with Dr. Håberg's efforts, I have been blessed with two other dynamic and motivating supervisors in Dr. Nils Inge Landrø and Dr. Petter Borchgrevink. I have also been lucky enough to work with Dr. Kristian Bernhard Nilsen, whose motivational advice was as invaluable as his scientific input. I am also grateful for the amount of support from all the members of the fMRI Group through the years for support and in all technical and scientific matters, and for creating a motivational and positive work environment.

Finally, I would also like to thank my parents for their support and for trying so hard to hide their worry that I would never finish this thesis. And not least my girlfriend Siri for motivating me to work hard every day, but also sharing in my enthusiasm for my research.

List of papers

Paper 1: Elvemo, N. A., Landrø, N. I., Borchgrevink, P. C., & Håberg, A. K. (2015). A particular effect of sleep, but not pain or depression, on the blood-oxygen-level dependent response during working memory tasks in patients with chronic pain. *Journal of pain research*, *8*, 335.

Paper 2: Elvemo, N. A., Nilsen, K. B., Landrø, N. I., Borchgrevink, P. C., & Håberg, A. K. (2014). Patients with chronic pain lack somatic markers during decision-making. *Journal of pain research*, *7*, 425.

Paper 3: Elvemo, N. A., Landrø, N. I., Borchgrevink, P. C., & Håberg, A. K. (2015). Reward responsiveness in patients with chronic pain. *European Journal of Pain*.

Abbreviations

BOLD: Blood oxygen level dependent

COMT: Catechol-O-methyl transferase

fMRI: Functional magnetic resonance imaging

IGT: Iowa Gambling Task

MRI: Magnetic resonance imaging

NRS: Numerical Rating Scale

PVSAT: paced visual serial addition task

SCR: Skin conductance response

SMH: Somatic marker hypothesis

Summary

Cognitive complaints are common among patients with chronic pain. This thesis presents three investigations into the neurophysiological, neuropsychiatric and neuroanatomical aspects of cognitive impairments.

The first paper describes a functional magnetic resonance imaging (fMRI) study of brain activation of chronic pain patients and their controls during working memory tasks. The study determined that activation and deactivation was reduced for pain patients compared to controls, and that sleep problems in the patients was important for the difference. The second paper describes a test of autonomic function during a decision-making task. Patients had less autonomic activation prior to decisions, which suggests a mechanism for impaired emotional decision making in these patients. The third paper describes an investigation into reward responsiveness in chronic pain patients and its link to cerebral anatomy. Patients proved to be significantly less responsive to rewards than controls, and patients had a different relationship between reward responsiveness and anatomy of a cerebral reward center.

In total, our results suggest that some cognitive processes in chronic pain patients are different from those of controls, and that these differences involve anatomy, physiology and function of the brain in a complex interplay with each other.

Introduction

Chronic pain is in itself a complex phenomenon, and so are the cognitive impairments that are seen in patients suffering from it. In this thesis aspects of neuroanatomy, neurophysiology and neuropsychiatry of chronic pain patients are investigated.

Pain

The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bogduk, 1994). Pain is thus subjective, and only truly appreciated by the subject that experienced the pain.

It is important to distinguish between pain and nociception. Nociception is the nervous system's encoding and processing of harmful stimuli, engendered by peripheral nerve endings, or "pain receptors" called nociceptors. These receptors only respond to tissue damage from chemical, mechanical or thermal exposure. Nociception does not necessarily lead to pain and vice versa; severe pain may persist on the basis of only negligible or absent nociception. The latter may be the case in a number of chronic pain conditions. Pain that is non-nociceptive can be caused by pathology in the somatosensory nervous system (neuropathic pain) or have an unknown cause (idiopathic pain) (Treede et al., 2015).

Acute pain, which is usually nociceptive, is pain that starts quickly in connection with cell damage and has limited duration. It decreases gradually and terminates when tissue damage has healed, usually within three months.

Chronic pain

Pain of sufficient intensity that does not subside is labeled chronic (Merskey & Bogduk, 1994). The time needed to label a pain chronic varies depending on condition and expected

healing time, but an often used criteria is pain lasting for three or six months (Merskey & Bogduk, 1994). In research and in the clinic, the pain intensity can be considered sufficient for labeling it chronic pain if the subject rates it as 4 or higher on a scale of 0-10 where 0 is no pain and 10 is the worst imaginable pain (Hjermstad et al., 2011). Chronic pain may have started in connection with a specific event, but is often also described without an identifiable injury or disease. If the pain condition has started with an injury, it can be defined as chronic if it lasts beyond the time expected for healing following tissue damage.

Chronic pain is a relatively common complaint in the population, at any given time affecting 20 to 30% of people in Europe or the United States (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Johannes, Le, Zhou, Johnston, & Dworkin, 2010). Chronic pain has a strong negative impact on quality of life (Liedberg, Burckhardt, & Henriksson, 2005) and approximately one of five sufferers reported that they have lost their job because of their pain condition (Breivik et al., 2006).

Chronic pain is often classified after the site of pain (e.g. back, neck, viscera) or the etiology of pain (e.g. neuropathic, arthritic, cancer). In academic research this large number of chronic pain conditions is often sorted into somewhat smaller, but still broad, groups based on etiology or symptoms (e.g. arthritis, back pain, fibromyalgia, headache and neuropathic pain, or primary pain) (Treede et al., 2015).

To some extent different chronic pain types have different neuropsychological impairments (Landrø et al., 2013) and different morphological and physiological changes in the brain (Baliki, Schnitzer, Bauer, & Apkarian, 2011), although some are also common across pain types (Smallwood et al., 2013).

An important aspect of many chronic pain conditions is pain hypersensitivity, i.e. a “lowered threshold” for what stimuli is experienced as painful or not. Pain hypersensitivity can be

induced in healthy subjects, but is seen in several chronic pain states and there is evidence that this sensitization to pain is caused by processes in the central nervous system (Woolf, 2011).

Development of chronic pain

An important mechanism for the chronification of pain is connected to the descending modulatory system. The descending pain modulatory system is responsible for controlling what nociceptive signals can pass through the spinal cord dorsal horn to reach the brain. There is some evidence that this network can become dysfunctional in its inhibition of ascending nociceptive signals leading to development of chronic pain through mechanisms such as serotonin dysfunction (Denk, McMahon, & Tracey, 2014). Only a minority of patients with acute pain will develop chronic pain, 5-40% of surgical patients and about 35% of patients with low back pain (Denk et al., 2014), but why one patient's pain condition becomes chronic and another resolves is poorly understood.

In the clinic, presence of psychosocial risk factors referred to as "yellow flags" are assessed to predict risk of conversion of acute to chronic pain and take appropriate steps to prevent such conversion (Reese & Mittag, 2013). The risk factors include psychiatric symptoms, poor job satisfaction or financial incentives, unhelpful beliefs or expectations about pain and treatment, strong emotional response to the pain and pain avoidance, as well as demographic factors like female sex and older age (Nicholas, Linton, Watson, & Main, 2011; Waddell, Burton, & Main, 2003).

While many of the yellow flags for chronic pain are social, an important somatic risk factor is sleep problems. A large number of prospective studies have shown that sleep disturbances increase the risk for developing chronic pain in subjects who are pain-free, and worsen the prognosis for existing pain conditions such as headache or chronic musculoskeletal pain

(Finan, Goodin, & Smith, 2013). For instance, a longitudinal population study of 12 350 pain-free women found that those with sleep problems had three times the risk of having diagnosis of fibromyalgia on follow up 10 years later, and that sleep problems explained two-thirds of the incidence of fibromyalgia (Mork & Nilsen, 2012; Sivertsen et al., 2014; Siv S. Ødegård et al., 2011).

Changes in the reward system of the brain also precede chronification of lower back pain, as changes in grey matter density and white matter integrity, together with an increase in connectivity between nucleus accumbens and the prefrontal cortex, predicts chronification of acute pain by over 80% (Baliki et al., 2012; Mansour et al., 2013). While dopamine, an important neurotransmitter in the reward system, has been suggested as central to the dysfunction (Finan & Smith, 2013), our understanding of this is still evolving. Nevertheless, that Baliki et al was able to predict who would recover and who would develop chronic pain at such an early stage is striking. These longitudinal studies lend important support to the hypothesis that some, but not all, people have an underlying vulnerability to chronic pain in the reward system, where an event can trigger this vulnerability to turn acute pain to chronic pain (Denk et al., 2014).

The tendency to magnify the threat value of pain and to feel helpless in the context of pain – called pain catastrophizing – is also considered an important contributor for chronification of pain (Quartana, Campbell, & Edwards, 2009). Indeed, a meta-analysis showed that pre-surgical pain catastrophizing significantly increased the odds ratio of chronic post-surgical pain (Theunissen, Peters, Bruce, Gramke, & Marcus, 2012). Although anxiety shares many traits with pain catastrophizing and is common in patients with chronic pain (Asmundson & Katz, 2009), recent research suggests that pain catastrophizing is an independent construct from anxiety (Tran et al., 2015).

Genetic studies lend some support to the importance of reward processes. Chronic pain is known to have a component of heritability based on a study on the UK twin registries (Vehof, Zavos, Lachance, Hammond, & Williams, 2014). Catechol-O-methyl transferase (COMT) is an enzyme involved in degradation of catecholamine neurotransmitters, including dopamine. Some genetic studies have linked polymorphisms in the COMT-encoding gene to pain sensitivity in healthy subjects (Zubieta et al., 2003) and fibromyalgia or chronic widespread pain, but not migraine or musculoskeletal pain conditions (Tammimäki & Männistö, 2012). There is also some evidence that chronic pain induces epigenetic changes in the central nervous system, for instance by silencing genes for peripheral morphine receptors (Descalzi et al., 2015).

Interdependency between pain, sleep and depression

As evident from the above, several of the factors shown to affect pain sensitivity and risk of chronification of pain appear together in the clinical picture. Not only does a large body of research show that pain, sleep problems and depression independently impair cognition; pain, sleep problems and depression reinforce each other as well. Thus any investigation into cognitive impairment of chronic pain must also take into account the effects of sleep problems and depression.

Sleep problems

Sleep problems is a very common complaint among chronic pain sufferers, found to be severe among more than 50% (Pilowsky, Crettenden, & Townley, 1985). Patients with chronic pain report taking longer to fall asleep, waking up more frequently and for longer periods of time during the night, and having less sleep in total (Morin, Gibson, & Wade, 1998; Smith & Haythornthwaite, 2004). The interaction between sleep deprivation and pain is bidirectional (Lautenbacher, Kundermann, & Krieg, 2006). However, polysomnography studies have not

shown a consistent pattern of objective sleep disturbances across studies on non-malignant chronic pain patients. The most common objective findings are sleep fragmentation and alterations of sleep architecture, although the findings are so far inconsistent and a number of studies have failed to find significant differences also on these measures (Bjurstrom & Irwin, 2015).

Studies of experimental sleep restriction have showed that healthy subjects report more pain after two nights of sleep restriction (Haack & Mullington, 2005; Siv Steinsmo Ødegård et al., 2014) or after one night of disrupted sleep continuity (Smith, Edwards, McCann, & Haythornthwaite, 2007). The results are of clinical interest because patients with chronic pain seem to be more sensitive than healthy controls. In one study, one night of sleep restriction (4 hours) led to increased pain, fatigue, depression and anxiety in a group of rheumatic arthritis patients, compared to no change in sleep deprived controls (Irwin et al., 2012). Experimental studies have shown that interruption of a specific sleep phase, slow wave sleep, induces a hyperalgesic state (Lentz, Landis, Rothermel, & Shaver, 1999), although this has not been found consistently in studies of patients with chronic pain (Bjurstrom & Irwin, 2015). A recent meta-analysis of randomized controlled trials show a small but significant reduction in pain after non-pharmacological sleep treatment in chronic pain patients, but the number of studies is still small and methodologies seem to have varying effectiveness (Tang et al., 2015).

Depression

Pain is the second most common somatic symptom among those with a depressive disorder, occurring in over 50% of patients and sometimes even masking the underlying depressive disorder for years (Wörz, 2003). Depression is also very common in patients with chronic pain; studies on patients in pain clinics have reported that a majority of subjects suffer from depression (Fishbain, Goldberg, Meagher, Steele, & Rosomoff, 1986; Poole, White, Blake,

Murphy, & Bramwell, 2009). However, one larger self-report population study found that a lower number, 21% of pain sufferers, said they had been diagnosed with depression (Breivik et al., 2006). Experimentally inducing sad mood in patients with major depression increases pain and reduces their pain threshold (Tang et al., 2008; Terhaar et al., 2010), and conversely negative mood prior to surgery predicts postoperative pain (Ip, Abrishami, Peng, Wong, & Chung, 2009; Papaioannou et al., 2009).

Interdependencies between pain, sleep and depression

While sleep problems, depression and anxiety are described independently above and it is evident that they frequently appear together in clinical practice, studies have also shown that they affect each other.

The amount of sleep interruption and total amount of sleep correlate with mood (Durmer & Dinges, 2005), and sleep quality significantly predicts not only pain but also depression ratings (Naughton, Ashworth, & Skevington, 2007). Simultaneous studies of pain, sleep problems and depression are equivocal on which parameter mediates the others (Boardman, Thomas, Millson, & Croft, 2005; Chung & Tso, 2010; Miró et al., 2011; O'Brien et al., 2010; Smith et al., 2008; A. Vgontzas, Cui, & Merikangas, 2008; Wilson, Eriksson, D'Eon, Mikail, & Emery, 2002), although the majority show a relationship between pain and sleep problems above that of depression. Prospective studies have shown both that pain and sleep problems predict depression (Nicassio & Wallston, 1992) and that sleep problems predict pain, which in turn predicts depression (Bigatti, Hernandez, Cronan, & Rand, 2008).

A recent meta-analysis of 11 randomized controlled trials on non-pharmacological treatments to improve sleep in chronic pain patients led to a reduction in pain and depression, although the effect sizes were small (pain 0.18, depression 0.24) (Tang et al., 2015). Unfortunately, the trials that have been done so far are relatively small, totaling 965 patients, and use very

different methodologies (face to face treatments work significantly better than telephone or internet) and include many different pain groups (including malignant and non-malignant pain). Although the research shows that non-pharmacological sleep treatments are effective improving sleep, and to some degree reducing pain and depression, it is still too early to say that non-pharmacological treatment of sleep problems is a clinically proven treatment for chronic pain and depression.

While the interdependencies between pain, sleep and depression are still not clearly understood, dopamine dysregulation has been proposed as a mechanism behind the comorbidity of chronic pain, sleep problems and depression (Finan & Smith, 2013). For a discussion on this, see the "Neurophysiology and pain" subchapter.

Cognition in chronic pain

Cognitive complaints in chronic pain patients

Patients with chronic pain frequently complain about cognitive impairment, and this type of self-reported impairment correlates with objective impairments on neuropsychological tests (Landrø et al., 2013). Three hypotheses have been frequently used to explain the cognitive deficits in chronic pain; the limited resource hypothesis posits that cognitive tasks have to compete with pain for limited attentional resources (Eccleston & Crombez, 1999), the neuroplasticity hypothesis suggests that neural reorganization in the brain caused by chronic pain impairs normal cognitive function (Hart, Martelli, & Zasler, 2000) while the neuromediator hypothesis, partially overlapping with the neuroplasticity hypothesis, argues that chronic pain induces changes in neurochemical mediators which in turn affects cognition (Hart et al., 2000).

Working memory

Working memory is a system that stores information short-term and processes the information with capacity limits on both storage and processing (A. Baddeley, 2012; Alan D. Baddeley & Hitch, 1974). Baddeley's model for working memory consists of a central executive responsible for information processing and control of information flow, and slave systems responsible for storing the information (A D Baddeley, 2000). Working memory capacity depends on attention resources in the central executive, which decides the ability to keep relevant information available for retrieval and manipulation, in part by maintaining or suppressing the relevant information (Engle, 2002).

A simple test of short-term memory from the Wechsler Adult Intelligence Scale is the Digit Span Forward test where subjects must repeat a series of digits that gradually increase in length. The subject is scored by the longest sequence of digits they can repeat, testing merely phonological maintenance. This short-term memory is modified into a working memory test by requiring use of the ordering process; the task is done again with new strings of digits, but the subject is now asked to repeat the digit strings in backward order (Digit Span Backward) (Wechsler, 1997).

One frequently used working memory test that requires use of the updating process is the n-back task, in which subjects are presented sequential objects (letters, numbers, words or pictures) and respond (e.g. by pressing a button) when the presented object matches a previous object (Cohen et al., 1997; Wager & Smith, 2003). In a 1-back test the presented object would match the previous one, in a 2-back it would match the one before a previous one, etc. In this way, the task requires continuously removing one object and adding another object to working memory storage.

A working memory test that also requires manipulation is the Paced Visual Serial Addition Test. It is similar to the n-back, but subjects are required to add the number shown with the previously shown number (not to the previously calculated *sum*). This test is considered more challenging than the n-back, and is considered frustrating and stressful, so much that it has even been used to provoke psychological stress in an experimental setting (Tombaugh, 2006).

Pain and working memory

Two selection methods exist for prioritizing access to working memory and conscious processing: bottom-up and top-down. Bottom-up selection relies on attention-capture by a signal's salience relative to the competing signals, wherein nociception is prioritized by the pre-attention systems, likely from an evolutionary standpoint because of its function as an alarm for risk of impending bodily harm. Top-down selection depends on cognitive goals, where the more goal-relevant signals are prioritized above other goals. The neurocognitive model of attention to pain suggests that pain disrupts cognitive tasks by bottom-up selection to working memory, but that in chronic pain patients it can also disrupt by affecting top-down selection, e.g. by pain catastrophizing (Legrain et al., 2009). A large number of studies have investigated these impairments, and a meta-analysis confirmed that although the effect is moderate, working memory is indeed significantly impaired in chronic pain patients (Berryman et al., 2013).

Healthy subjects exposed to experimental pain while performing working memory tasks show no impairment of tasks that only depend on phonological maintenance (e.g. Digit Span Forward), but do so on tasks that require some executive function (e.g. Digit Span Backward, n-back, paced visual serial addition task (PVSAT)) (Attridge, Noonan, Eccleston, & Keogh, 2015; Moore, Keogh, & Eccleston, 2012; Schoofs, Wolf, & Smeets, 2009). If the load is sufficient in an n-back test, healthy subjects exposed to experimental pain showed a reciprocal relationship between pain intensity and working memory capacity in one study (Buhle &

Wager, 2010). This suggests that pain and working memory share capacity-limited cognitive resources, so that pain affects working memory by reducing the resources available for working memory processes.

Working memory tests of patients with chronic pain have found that both central executive functions are impaired in these patients (Berryman et al., 2013; B. D. Dick & Rashiq, 2007; B. Dick, Eccleston, & Crombez, 2002). The working memory impairment is reduced independently of the pain level in one study (B. D. Dick & Rashiq, 2007), suggesting that the mechanism for impairment in chronic pain is more complex than simply ongoing continuous pain competing for resources.

Confounding effects on working memory

Sleep problems and depression independently impair working memory, and both are common among pain patients which makes it very challenging to pin point the exact mechanisms underlying the impairments of working memory in this patient group.

There are three major theories to how sleep deprivation affect working memory in otherwise healthy subjects. One theory posits that sleep deprivation affects working memory by specifically impairing the executive component of working memory (K. Jones & Harrison, 2001). State instability theory instead postulates that sleep deprivation impairs working memory by impairing attention, a crucial component of executive working memory (Doran, Van Dongen, & Dinges, 2001). A third theory posits that sleep is regulated on the level of neuron groups, so that sleep deprivation leads neuronal groups to go offline. Variation in performance would then increase with increasing load, as the lack of neuronal capacity becomes more apparent (Krueger et al., 2008). One study in 23 healthy subjects specifically investigating these mechanisms found impairments of sleep deprivation but no support for the two first hypotheses (Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010), while a

separate study in sleep-deprived rats found evidence for the hypothesized neuronal "local sleep" (Vyazovskiy, Olcese, Hanlon, & Nir, 2011). The local sleep hypothesis suggests that while sleep is a global phenomenon, sleep deprivation leads to increasing cognitive deficits by small groups of neurons "turning off" for brief periods independent of other areas when the subject has been without sleep for sufficiently long. Such an unspecific and widespread reduction in neuronal function would lead to unspecific negative consequences for performance.

Depression impairs cognitive performance, especially executive functions, where a meta-analysis found that depressed patients are impaired on tests related to neuropsychological constructs of working memory, in addition to inhibition, shifting, planning and verbal fluency (Snyder, 2012). A number of explanations have been offered to why depression impairs cognitive performance. One framework proposes that negative automatic thoughts divert attention and take up cognitive capacity, leading to reduced performance on metrics like working memory (Christopher & MacDonald, 2005; N. P. Jones, Siegle, Muelly, Haggerty, & Ghinassi, 2010), while another framework suggests reduced motivation in depressed subjects is the cause of impaired cognitive performance (Scheurich et al., 2008). A third framework suggests that increased cortisol levels is the cause of cognitive impairments, not only on hippocampus-dependent processes like memory, but also on working memory (Hinkelmann et al., 2009), and is supported by studies showing impaired and improved working memory in healthy subjects by respectively blocking (Cornelisse, Joëls, & Smeets, 2011) or stimulating (Hinkelmann et al., 2015) mineralocorticoid receptors in the brain.

Emotional decision-making

A framework for real-world decision-making that has received much attention in the last decades is the Somatic Marker Hypothesis (SMH) (A Bechara, Damasio, Damasio, & Anderson, 1994). The SMH states that when faced with an ambiguous decision, cognitive

processes are guided by emotions, which are engendered by the somatic state sensed by autonomic physiological reactions in the body. The framework was based on patients studied by Damasio et al. that had lesions in the ventromedial prefrontal cortex and were impaired in real-world decision-making but relatively non-impaired in other regards, (Damasio, Tranel, & Damasio, 1990) an impairment first described in the tragic story of Phineas Gage (Harlow, 1848, 1868). Empiric support for the SMH comes from studies using the Iowa Gambling Task (IGT), where test subjects must make choices with limited information. In healthy subjects somatic markers are measured in the seconds preceding choices, and the markers are more pronounced before disadvantageous choices. Crucially, patients with ventromedial prefrontal lesions have no somatic markers preceding disadvantageous choices, and they fail to develop advantageous decision-making during the test. Chronic pain patients have shown impaired decision-making in a number of studies (Apkarian, Sosa, Krauss, et al., 2004; Tamburin et al., 2014; Verdejo-García, López-Torrecillas, Calandre, Delgado-Rodríguez, & Bechara, 2009; Walteros et al., 2011), but it has not been assessed whether somatic markers are present or not.

One recent study in patients with chronic pain found that low back pain patients in a gambling task were more sensitive to rewards than controls, preferring high-risk high-reward cards (Berger et al., 2014). Patients also had increased nucleus accumbens connectivity with subcortical areas like amygdala, versus prefrontal areas for the controls. The authors hypothesized that the disconnection between prefrontal and striatal areas led to a blunting of emotional decision-making.

Reward and pain

Reward processing is an inherent component of decision-making. It has previously been suggested that reward processing is disrupted in patients with chronic pain based on clinical observation and animal studies (Becker, Gandhi, & Schweinhardt, 2012). A recent study

found that patients with low back pain had increased gain sensitivity, i.e. they were less loss averse because an increased preference for higher rewards, and that this gain sensitivity correlated with connectivity between the prefrontal cortex and the nucleus accumbens connectivity, which is central to reward processing (Berger et al., 2014). In two animal models for chronic pain, synaptic modification in the nucleus accumbens was necessary for changes in motivation to take place (Schwartz et al., 2014).

Gray's reinforcement sensitivity theory is a framework for reward related behavior that proposes two major opposing systems in the brain contribute to behavior and personality, the behavioral activation system and the behavioral inhibition system (J. a Gray & Mcnaughton, 2000). High behavioral activation system increases the likelihood of experiencing positive feelings and of engaging in goal-directed behavior, and is correlated with dopamine activity, dopamine receptor density and (negatively) to dopamine metabolism (Reuter, Schmitz, Corr, & Hennig, 2006). The behavioral inhibition system inhibits behavior that may lead to negative outcomes like punishment or non-reward and is comprised of cholinergic projections that inhibit the behavioral activation system-related activity in the nucleus accumbens. A construct used to measure behavioral activation system is Reward Responsiveness (Carver & White, 1994), defined as the "ability to experience pleasure in the anticipation of reward-related stimuli" (Taubitz, Pedersen, & Larson, 2015). Behaviorally, subjects with high Reward Responsiveness perform better on reward omission tasks than those with low Reward Responsiveness, and the pattern is opposite for punishment omission tasks (Boksem, Tops, Kostermans, & De Cremer, 2008). Reward Responsiveness also correlates with likelihood of reward maximization behavior (Scheres & Sanfey, 2006) and with reactivity in areas of the endogenous opioid system (Wanigasekera et al., 2012).

Reward can be divided into three major components; the hedonic pleasure or "Liking" of the reward, the motivational drive to get the reward again ("Wanting") and the reward-related

learning (Berridge & Kringelbach, 2013). In everyday life Liking and Wanting are correlated, but the two can be dissociated both anatomically and behaviorally (Baliki et al., 2013; Berridge, Robinson, & Aldridge, 2009). While orbitofrontal cortex and endogenous opioids are primarily involved in Liking, the nucleus accumbens and dopamine are necessary for motivational drive or Wanting. The nucleus accumbens is also an important target for opioid projections, contributing to the coupling of Liking with later Wanting, reinforcing behavior that create rewards (Schultz, 2007). Dopaminergic activity is subdivided in phasic (short term) or tonic (long term) activity, and the two are inversely related so that higher tonic activity decreases the amplitudes of phasic activity. Phasic activity is the brief bursts of dopamine caused by rewards, while tonic activity is the level of dopamine in the extracellular space (Schultz, 2007). Thus, while phasic increase of dopamine in the nucleus accumbens increases Wanting, long term tonic increase of dopamine in the same area will reduce Wanting (Schultz, 2007). An experimental study where postsynaptic dopamine D2/3 receptors were blocked, equivalent to chronic increased dopamine, found that the healthy subjects had impaired choice performance in reward tasks, but not punishment tasks (Eisenegger et al., 2014). The effect was more marked in subjects with higher serum levels of the dopamine antagonist, and in subjects with genetically reduced receptor density. See "Neurophysiology in pain" for a more in-depth introduction to reward-related neurophysiological changes in chronic pain.

Pain and the brain

The literature on brain abnormalities in chronic pain is very comprehensive, and only a very brief review of findings in humans relevant to the current thesis is presented below. For a more complete review, see Schmidt-Wilcke (Schmidt-Wilcke, 2015).

Brain morphology in pain

Morphological changes in the brain of chronic pain patients have been known for over a decade (Apkarian, Sosa, Sonty, et al., 2004), although studies diverge with regard to the differences reported, possibly because of differences in study samples, design and analysis methods. In one study patients with chronic back pain or osteoarthritis had a 90% overlap in the areas of decreased grey matter volume, while there was a 9% overlap between the back pain or osteoarthritis groups and findings in complex regional pain syndrome patients. Based on a subgroup of 10 subjects per group it was possible to classify remaining patients and controls into groups with a specificity above 90% and a sensitivity of 69-82% (Baliki et al., 2011). The changes in grey matter volumes did not correlate with depression, anxiety or medication, but changes in some areas such as the insula had larger reductions in grey matter volume for patients with longer pain duration. These results support the notion that brain changes are affected by the etiology and duration of chronic pain. Nevertheless, while individual studies diverge, a consistent pattern of grey matter changes was shown in a meta-analysis of 23 studies in chronic pain patients (Smallwood et al., 2013). Decrease in grey matter volume was demonstrated in clusters that included the middle and inferior frontal gyrus, cingulate cortex, insula, superior temporal gyrus and putamen, while an increase in grey matter volume was found in the temporal lobe. Some but not all of these areas, are seen as part of the pain neuromatrix of nociception (Legrain, Iannetti, Plaghki, & Mouraux, 2011), which could suggest that chronic pain also affects areas of the brain not involved directly in nociception.

Unfortunately, the cause of the changes in grey matter from imaging data has yet to be decided: Grey matter changes could be caused by a reduction in number of neurons, or glia, or a reduction in cell size, or in the extracellular matrix (Moriarty, McGuire, & Finn, 2011). While neuronal loss has been suggested as a mechanism (Grachev, Fredrickson, & Apkarian,

2000), changes in grey matter volume are reversible after surgical intervention to reduce peripheral pain (Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2013). The exact mechanism for the identified grey matter changes remains unresolved.

Diffusion tensor imaging has also been examine changes in white matter in chronic pain patients, showing decrease in white matter fractional anisotropy (Geha et al., 2008; Mansour et al., 2013). Relative to morphometry there are few studies of white matter in chronic pain and more research is needed before a consistent picture of white matter changes in chronic pain patients can be formed.

Brain physiology in pain

The pain hypersensitivity seen in chronic pain patients is a distinguishing characteristic of chronic pain and has been described as an augmentation of sensory input to the central nervous system (Latremoliere & Woolf, 2009). Several mechanisms of such "central sensitization" are known, where neuronal changes on the cellular level increases the duration and magnitude of nociceptive input, and allow non-harmful input to be misinterpreted as nociceptive (Latremoliere & Woolf, 2009).

Chronic pain patients have been shown to have changes in fundamental aspects of neurophysiology, for instance by increased cerebral blood flow (Wasan et al., 2011), altered functional connectivity (Cauda et al., 2009; Harris et al., 2013; Napadow et al., 2010) and metabolite concentrations (Harris & Clauw, 2012). While the literature as a whole is far from equivocal on the exact nature of the changes, some studies have shown remarkable specificity. For instance, the functional connectivity between nucleus accumbens and cortical regions in patients before the pain has become chronic can predict with >80% accuracy which patients will transition to chronic pain a year later (Apkarian, Baliki, & Farmer, 2013; Baliki et al., 2012).

Dysregulation of neurotransmitters have been implicated in chronic pain (Harris & Clauw, 2012). Serotonin, for instance, is important for the top-down modulation of nociception, and a down-regulation of serotonin thus leads to both reduced inhibition of nociceptive signals and depression (Boakye et al., 2015). For this thesis, however, dopamine and endogenous opioids are somewhat more relevant and therefore described in more detail below.

A proposed mechanism is that chronic pain leads to increased tonic dopamine level (Gandhi, Becker, & Schweinhardt, 2014). No direct evidence of this tonic increase in dopamine exists, but some results in animals and patients support this notion. Reduced levels of dopamine release is seen in patients with chronic pain (Wood et al., 2007) and in chronically stressed rats (Gambarana et al., 1999; Puglisi-Allegra, Imperato, Angelucci, & Cabib, 1991). In healthy animals and humans, such reduced phasic dopamine leads to an increase in tonic dopamine opposite of what observed in chronic pain (Wood, 2006). Pain hypersensitivity is also seen in individuals with dopamine deficits (Jarcho, Mayer, Jiang, Feier, & London, 2012), and dopamine levels in healthy subjects correspond to the intensity of experimental pain (Tiemann, Heitmann, Schulz, Baumkoïtter, & Ploner, 2014). Dopamine positron emission tomography of chronic pain patients found reduced available dopamine (D2/3) receptors in the striatum, suggesting either reduced dopamine receptor density or increased synaptic dopamine (Martikainen et al., 2015; Wood et al., 2007). D2/3 receptor availability was associated with positive, but not negative, affect scores among the pain patients, and μ-opioid receptor availability in the amygdala, indicating that reduced dopamine receptor availability is linked with reduced positive affect in chronic pain patients (Martikainen et al., 2015). Our understanding of dopamine's role in chronic pain is still evolving rapidly, and will in all likelihood improve in the future.

Dopamine dysregulation has been proposed as a mechanism behind the comorbidity of chronic pain, sleep problems and depression, as elevated tonic dopamine also increases

arousal which could contribute to sleep problems and contribute to depressive symptoms through reduction of motivational drive (Finan & Smith, 2013). Sleep deprivation studies have found increased amounts of dopamine precursors in urine (A. N. Vgontzas et al., 1998) and reduced D2/3 receptor availability in the nucleus accumbens (Volkow et al., 2009). The dopamine hypothesis is further supported by studies showing that COMT, the gene involved in pain sensitivity and a number of chronic pain conditions, is also involved in dopamine metabolism and changes in background activity in rapid eye movement and non-rapid eye movement sleep (Bodenmann et al., 2009).While the evidence linking dopamine and depression is not as convincing, the hypothesis does not depend on it since research suggests that depression follows pain and sleep instead of the other way around.

The opioid system is also disrupted in patients with chronic pain. Patients with fibromyalgia or neuropathic pain have decreased binding potentials for opioids, caused by increased endogenous opioid levels, decreased receptor density or both (Harris et al., 2007; Maarrawi et al., 2007). A mechanism for the down-regulation in μ-opioid receptors is suspected from endogenous μ-opioids – β-endorphins – released in the chronic pain state or prolonged exposure to exogenous opioids, leading to desensitization (Narita et al., 2014). Chronic pain models in animals lead to a down-regulation of dopamine synthesis and μ-opioid receptors in the ventral tegmental area, which has important dopamine projections to the nucleus accumbens. A recent study found an association between reduced receptor availability for dopamine in the ventral striatum and μ-opioids in the amygdala (Martikainen et al., 2015). As such, opioid dysfunction might be linked to the abovementioned dopamine dysfunction (Narita et al., 2014). A recent animal study found that dopamine dependent reward behavior could be recovered in an animal model of chronic pain by treatment targeting the cellular mechanisms of the dysfunction, giving hope for future therapies (Taylor et al., 2015).

In summary, chronic pain patients are different from controls on a neuronal level, with changes in activation, coupling and several neurotransmitter systems.

Therapies for chronic pain

While opioids were prevalent in chronic pain therapies in the past, current trends in pharmacotherapy reserve opioids to patients that cannot be treated adequately with other means (Kroenke, Krebs, & Bair, 2009). Paracetamol and Non-Steroidal Anti-Inflammatory Drugs are used for most pain etiologies, but different groups of pharmaceuticals are preferred for different types of pain (for a review see (Kroenke et al., 2009)). In general tricyclic antidepressants or tramadol are preferred before anticonvulsants or serotonin-norepinephrine reuptake inhibitors (Kroenke et al., 2009).

Cognitive behavioral therapy is also used to treat chronic pain, although critics claim the theoretical foundation for this is unclear and the treatment lacks effect on pain level compared with an active control, according to a large meta-analysis (Williams, Eccleston, & Morley, 2013). A large number of other treatments, including acupuncture, ultrasound, patient education, exercise and chiropractic, have been studied (Deare et al., 2013; Ebadi, Henschke, N, Fallah, & Mw, 2014; Gross et al., 2012; Hayden, van Tulder, Malmivaara, & Koes, 2005; Veehof, Oskam, Schreurs, & Bohlmeijer, 2011; Walker, French, Grant, & Green, 2010). Although some of these treatments are better than no treatment or waiting list, there is a lack of therapies that work better than active control. One possible explanation is that treatments that have therapeutic effect in some patients fail to reach significance even in very large randomized controlled trials because the treatments are used on many patients that could never benefit from it, watering out any clinically relevant, but highly specific effects. Improved understanding of the mechanisms underlying chronic pain could improve patient

selection and therapy targeting, as treatments may be targeted according to objective criteria and the effects proven in robust studies.

Aims of the thesis

The overarching aim of this thesis was to improve our understanding of the cognitive impairments of patients with chronic pain and their neural correlates. Chronic pain is a widespread problem and among those with chronic pain, cognitive impairment is a frequent complaint. Increased understanding of this problem might eventually lead to treatments or relief for this patient group. The current thesis includes three separate papers in the same patient population and their matched controls.

Pain and depression affect blood oxygen level dependent (BOLD) signal during working memory tasks, but in spite of interdependencies with sleep problems the effects of sleep problems on the same BOLD signal remained unexplored. The aim of the first paper was to investigate working memory in patients with chronic pain using fMRI, specifically assessing the effects of pain, sleep problems and depression on the BOLD activations.

Decision-making has been shown impaired in chronic pain patients, but the morphologic and physiologic correlates of decision-making abilities have not been explored. The aim of the second paper was to investigate decision making in patients with chronic pain, assessing whether previously described impairments were linked to autonomic nervous system reactivity and brain morphology in the chronic pain group compared to the matched controls.

Reward processing has been proposed involved in pain pathophysiology, but reward drive and reward responsiveness have not been tested in patients with chronic pain. Nucleus accumbens is central to reward processing and affected by chronification of pain. The aim of the third paper was to investigate reward sensitivity in chronic pain patients compared to matched controls, and subsequently whether these measures were linked to nucleus accumbens volume.

Materials and methods

Participants

We recruited a total of 20 subjects (16 females) with chronic pain, and 20 age- and education matched healthy controls. One subject was excluded from all analyses, as a history of neurological disease was discovered after inclusion. Other subjects were excluded from the different papers due to issues specific to each paper, such as missing data or technical issues regarding electrophysiological measures or MRI.

Paper 1 was based on 15 patients and 17 controls. Four patients and three controls were excluded due to unexpected loss of data after collection. Paper 2 was based on 18 patients and 19 controls. One was excluded from each group due to technical issues during autonomic data collection. Paper 3 contained all 19 patients and 20 controls. Subjects were excluded on an analysis-by-analysis basis in cases where data was missing.

Data collection

The experimental layout was as follows; day one: depression and pain ratings, neuropsychological tests during fMRI scanning; day two: questionnaires covering sleep, fatigue, reward sensitivity and pain ratings and neuropsychological tests, including the IGT. During the IGT, measures of autonomic nervous system reactivity such as skin conductance was recorded. All procedures are described in detail in the relevant papers (See Table 1).

TABLE 1: Data collection methods and analysis methods detailed in papers

Method	**Paper**
Questionnaires	
Pain (Brief Pain Inventory)	Paper 1
Depression (Beck Depression Inventory II)	Paper 1
Sleep problems (Pittsburgh Sleep Quality Index)	Paper 1
Reward responsiveness (Behavioral Activation Scale)	Paper 3
Reward drive (Behavioral Activation Scale)	Paper 3
Anhedonia	Paper 3
Neuropsychological tests	
Working memory tests (WAIS-III Digit Span and Letter Number Sequencing)	Paper1
Working memory tests during fMRI scanning (0-back, 2-back, Paced Visual Serial Addition Test)	Paper 1
Decision making (Iowa Gambling Task)	Paper 2
Neuronal measurement methods	
Skin conductance response (SCR)	Paper 2
Cardiac autonomic regulation, including heart rate variability	Paper 2
Blood pressure	Paper 2
BOLD fMRI	Paper 1
Morphological MRI and volumetric assessment	Paper 3

Statistical analysis

Analyses were done in Chart (ADInstruments, Dunedin, New Zealand), Microsoft Excel (Microsoft Corporation, USA) and SPSS (IBM Corporation, NY, USA). For details on statistical methods, se the respective papers (Table X).

Additional analyses specific to the D summary

In the writing of this thesis summary, some additional analyses were performed on the whole patient sample, excluding subjects with missing data on an analysis-by-analysis basis to maximize the number of subjects in the analyses.

To investigate whether decision-making might also be affected by sleep problems, Spearman correlational analyses were done of IGT score versus sleep problem score, versus SCR or versus Reward Responsiveness score.

Synopsis of results

Paper 1

Background

A frequently reported cognitive impairment in patients with chronic pain is impaired working memory, although effect sizes are generally small to moderate. Working memory is affected by pain, depression and sleep problems – all commonly seen in chronic pain – but the unique contributions for each of these factors to BOLD activation during working memory performance has remained unexplored.

Methods

Subjects were given three working memory tasks during the T2* scans; two n-back tasks (0-back and 2-back) and a PVSAT, while information was presented on a screen and responses from subjects were collected using response buttons. Questionnaires were used to assess levels of pain, depression and sleep problems.

Results

We found significantly less BOLD activation and deactivation in the parietal and frontal lobes of the patients with chronic pain compared to the controls. Further investigation revealed that pain, depression and sleep problems all independently contributed to this decrease in BOLD activation, even when performance was not significantly different between the chronic pain and the control group. However, in a common general linear model with all three parameters only sleep problems contributed to the decrease in activation observed in the chronic pain patients. There were comparably small differences in activation between the 2-back and PVSAT, even though only the latter had a significant component of manipulation.

Conclusions

Patients with chronic pain had less BOLD activation and deactivation than controls during two different working memory tasks. Sleep problems had a stronger impact than pain or depression scores on the difference in BOLD activation. This suggests that sleep problems had a significant impact on the BOLD response and that the effect of sleep problems on neuropsychological functioning could have been underestimated in earlier studies.

Paper 2

Background

Studies have shown decision-making deficits in patients with chronic pain, and ascribed these to neurophysiological deficits predicted by the SMH. However, whether chronic pain patients lack somatic markers during decision-making remained untested.

Methods

Subjects performed the IGT while skin conductance, heart rate and blood pressure was monitored. Normalized brain volumes were obtained from the subjects' T1 weighted 3d MRI scans.

Results

Patients with chronic pain failed to generate anticipatory SCR before disadvantageous choices, and that they switched more between disadvantageous and advantageous card decks compared to the matched controls. The other autonomic measures investigated were similar during IGT performance in the chronic pain and control group, and groups did not react differently to rewards and punishments measured with SCR. In controls, IGT score correlated with the amount of anticipatory SCR, while in chronic pain patients IGT score and total cortical grey matter volume correlated.

Conclusions

Chronic pain patients were for the first time shown to lack anticipatory SCR before disadvantageous choices. This indicates impaired somatic marker generation in chronic pain patients, although the precise localization or nature of the impairment was not possible to identify. The finding in patients was in contrast to the finding in controls, where SCR correlated with IGT score. In the patients, IGT score instead correlated with total grey cortical volume. Lack of somatic markers to guide decision-making could lead to impaired decision-making in chronic pain patients.

Paper 3

Background

Involvement of reward processing in chronic pain pathophysiology has been proposed. Still, reward drive and Reward Responsiveness have not been tested in patients with chronic pain. Nucleus accumbens is central in reward processing and has been shown to reduce in volume in patients as pain becomes chronic, but it has not been investigated if it is linked to reward processing impairments in chronic pain patients.

Methods

Normalized brain volumes were obtained from the subjects' T1 weighted 3d MRI scans. Questionnaires were used to assess Reward Responsiveness and Reward Drive

Results

The patients had significantly lower scores on a measure of Reward Responsiveness than controls, but not for Reward Drive. Reward Responsiveness scores were correlated with nucleus accumbens volume in the pain group after adjusting for anhedonia. This correlation

was significantly different from that found in the control group. There was no relationship between duration of chronic pain and Reward Responsiveness or nucleus accumbens volume.

Conclusions

Reward Responsiveness was significantly reduced in the patients with chronic pain. The lack of relationship between measures and duration of chronic pain suggests they could be indicators of vulnerability to chronic pain or markers of the presence of chronic pain.

Additional results specific to the D summary

In an additional investigation on whether sleep problems (paper 1) and decision-making (papers 2 and 3) were related, the correlation of IGT score versus sleep problem score was investigated using Spearman correlation. There was a significant positive correlation in the patient group (rho = 0.542, p = 0.02, n = 18), but not in the control group (rho = -0.356, p = 0.147, n = 18). The other Spearman correlations performed (IGT score versus SCR; IGT score versus Reward Responsiveness score) were not significant in either group.

Discussion

The overarching aim of this thesis was to improve our understanding of the cognitive impairments of patients with chronic pain and their neural correlates, to help create the groundwork for future treatment or relief of the cognitive impairments.

In paper 1 we showed that sleep problems are more important for working memory brain activity measured with BOLD fMRI than pain or depression. That sleep-correlated changes in brain activation during working memory tasks suggest that sleep is important for the cognitive impairments seen in chronic pain patients.

In paper 2 we showed for the first time that chronic pain patients lack somatic markers that are linked to decision-making. The somatic markers are, according to the SMH, important for emotional decision-making, suggesting a mechanism for impaired decision-making in chronic pain patients.

In paper 3 we showed that Reward Responsiveness is reduced in pain patients and that the measure is associated with Nucleus accumbens volume. Pain patients thus have similar wanting, but reduced liking after reward and this change is associated with Nucleus accumbens volume.

Main findings

Sleep and working memory

We performed several cognitive tests, but found limited differences between patient and control groups. This is in line with previous studies, as shown in a meta-analysis of working memory performance studies (Berryman et al., 2013). In paper 1 we did however find a significant group difference in BOLD activation during working memory tasks when

correlating with sleep problems, as patients exhibited both reduced activation and reduced deactivation. BOLD activation during a working memory task in chronic pain patients was more affected by sleep problems than pain or depression. The areas where activation was reduced in the chronic pain group included areas that are part of the pain neuromatrix (e.g. insula, thalamus and the anterior cingulate cortex). These results could suggest that lower task related activation in chronic pain patients in areas already recruited for pain processing in the pain patients, which is in line with the limited resource hypothesis where fewer resources are available when the subject is faced with a cognitive task. It is possible that the lack of behavioral impairment was caused by low task difficulty. This could mean that future studies investigating cognitive deficits in chronic pain patients should not only consider differences in behavior, but also differences on physiological measures. A clinical implication is that sleep might be more important for cognitive impairments in pain patients than believed to date.

As chronic sleep restriction is known to lead to impairment of working memory (Killgore & Weber, 2014; Van Dongen, Maislin, Mullington, & Dinges, 2003) and the changes in BOLD activation resembled those of sleep deprivation, we suggested in paper 1 that the role of sleep deprivation in BOLD activity during working memory has been underestimated. There was a significant difference in BOLD activation between tasks that taxed executive working memory or merely short-term memory (0-back vs. 2-back or PVSAT), but not between two tasks that required use of updating versus updating and manipulation (2-back vs. PVSAT). This suggests that updating, but not manipulation, is sensitive to chronic pain and sleep deprivation. The difference between groups on the presence or absence of the central executive function updating (2back>0back) suggests that the effect was linked to executive function. However, since the two tasks were not equally difficult the effect could also be

linked to cognitive load, and without a sufficiently difficult control task we cannot settle this question.

Sleep problems were significantly more important for activation differences compared to depression or pain. Of the abovementioned theories for effect of sleep deprivation on working memory, the BOLD activation results and their correlation to sleep problems lend some support to the neuronal local sleep-hypothesis, as task activation showed widespread reduction and the difference in activation was when high load tasks (2back and PVSAT) were contrasted with the low load task (0back). A neuronal local sleep effect is interesting as the difference between pain patients and controls correlated more with sleep problems than pain, which ought to be expected by the limited resource hypothesis where pain competes with task for resources. Further research is needed to ascertain if neuronal local sleep is indeed responsible for cognitive deficits seen in pain patients. If confirmed, this could indicate that sleep problems might be a treatment target to improve lives of chronic pain patients.

A previous study found that daytime sleepiness did not correlate with performance or BOLD activation (Glass et al., 2011). While daytime sleepiness is a symptom of depression, it is not a symptom of chronic pain per se (Menefee et al., 2000), possibly because sleepiness is a poor correlate of long term sleep restriction (Van Dongen et al., 2003) or because the sleep problems are caused by increased arousal (Finan & Smith, 2013). As chronic pain sleep problem behavior is not equivalent to somnolence, future studies investigating the sleep-related BOLD activation in chronic pain patients should take care to measure sleep problems directly, as done in paper 1.

Furthermore, while long-acting analgesics are necessary for some pain patients to fall asleep, opioid use in healthy subjects disrupt sleep quality and central sleep apnea is significantly more common among patients on chronic opioids (Okifuji & Hare, 2014). Non-

pharmacological therapies for improved sleep have been tested in chronic pain groups with some success on significantly reducing sleep problems, pain and mode, although the effects are moderate. The non-pharmacological avenue seems promising, and although a limited number of studies have been performed so far, face-to-face therapies have significantly better results than therapies using Internet or telephone (Tang et al., 2015). Further research should focus on developing and testing therapies using face-to-face therapy methods.

Brain morphology

In paper 2 we found significant differences in brain morphometrics, as the pain group had a significantly smaller nucleus accumbens. There was no difference in total cortical gray matter, hippocampus, amygdala or brain stem volumes. The changes in nucleus accumbens volume were further investigated in paper 3, and linked to Reward Responsiveness, which is discussed more in-depth below under "Reward processing in chronic pain."

A lack of difference in total cortical gray matter is perhaps not surprising as it is a very unspecific measure in light of the findings that etiology-specific changes found in gray matter volume (Baliki et al., 2011). That we found a correlation between total gray matter volume and IGT score in the pain group was all the more surprising, and is discussed further below under "Chronic pain and somatic markers". We found no difference in amygdala volume, which is in line with earlier studies (Cauda et al., 2014; Smallwood et al., 2013). As the amygdala is important for somatic marker generation, this finding is also discussed under "Chronic pain and somatic markers".

We found no difference in hippocampus volume, which is in line with a recent meta-analysis (Cauda et al., 2014). Another meta-analysis found a systematic increase in hippocampus volume (Smallwood et al., 2013). This is peculiar as hippocampus volume is reduced in patients with major depression (Cole, Costafreda, McGuffin, & Fu, 2011), which is common

in pain patients. While we can not rule out that a type 2 error hid any pain-correlated increases in hippocampus volume as many patients had increased depression scores, the equivocal results in the literature makes conclusions difficult on this issue.

Chronic pain and somatic markers

In paper 2 we found a marked difference in the SCR before advantageous and disadvantageous choices in pain patients compared to their controls. This is the first study to link previously shown impairments in decision-making in chronic pain patients to the somatic marker deficits hypothesized to underlie that deficit.

There was a significant difference in SCR before disadvantageous choices between groups, which is in line with the SMH explanation of how decision-making happens on the IGT. This finding offers an explanation to earlier studies that showed significant impairments in decision-making behavior for patients with chronic pain, and showed how the impairment was possible to explain within the SMH framework as faulty detection or interpretation of somatic information.

While paper 2 confirms that chronic pain patients have reduced somatic markers compared to controls when pondering decisions, the study cannot fully elucidate the causes of this impairment. The finding does, however, narrow down the list of possible structures underlying the observed dysfunction. The controls and patients did not differ on SCR after rewards, nor did the patients exhibit signs of autonomic dysfunction on autonomic measures of heart rate or blood pressure, suggesting that general autonomic function was not impaired. Since somatic marker generation did not differ between advantageous and disadvantageous decks within patients unlike controls, patients were able to generate impulses after reward and punishment, suggesting that engagement of amygdala and primary sensory cortices were intact in the patient group. Amygdala volume was also investigated and we found no

between-groups difference, in line with previous research (Cauda et al., 2014; Smallwood et al., 2013). Unfortunately, the SMH is somewhat vague on how the various neuronal subsystems work together to affect decision-making, which makes it hard to be more precise with regard to the neurological basis for the impairment in SCR when pondering before drawing from disadvantageous decks.

In paper 2 we offered two possible mechanisms that equally well explain the lack of SCR before disadvantageous choices. First, the physiological somatic state, which serves as a basis for the somatic marker, is changed by chronic pain. In this sense chronic pain creates a backdrop of noise that decreases the signal to noise ratio for detecting a somatic marker signal, possibly increasing the time needed to detect a marker. Second, structures in the brain that interpret the somatic state or create the somatic marker are impaired by a chronic pain signal. There is some support to the first mechanism based on trend for a correlation between IGT score and pain before the experiment in the patient group. For the second mechanisms the primary suspects with regard to anatomical brain structures according to the SMH would be the insula, the striatum (including the nucleus accumbens), the anterior cingulate cortex and the ventromedial prefrontal cortex. The nucleus accumbens and the anterior cingulate cortex's roles are to bias decision in other parts of the cortex, the ventromedial prefrontal cortex triggers somatic markers, while the insula's role is to use the somatic state to create "a substrate for feeling the emotional state" and to stimulate the ventromedial prefrontal cortex (Verdejo-García & Bechara, 2009). Since all the abovementioned structures have reduced volume in chronic pain patients (Smallwood et al., 2013), any relationship between volumetrics and somatic marker impairment may be obscured.

We found in paper 2 a significant correlation between IGT score and total cortical gray matter volume in the pain group, unlike in the control group. This suggests that the IGT is sensitive to cortical volume in chronic pain patients. While cortical gray matter volume is unspecific

and correlates with broad measures like general intelligence (Narr et al., 2007), it might be a broad measure of how affected patients are by chronic pain. Several of the cortical areas that are generally thinned in chronic pain patients are involved in emotional regulation (Smallwood et al., 2013), and a reduction in cortical gray matter could be expected to involve these regions. If the IGT assesses emotional decision-making and chronic pain patients lack somatic markers, it is also possible that the patients rely on a more rational and less emotional decision-making process compared to healthy subjects. Further research is needed to understand this link better, as different decision-making in patients might impact treatments that rely on patient compliance and joint clinician-patient decisions.

IGT performance could possibly be influenced by sensitivity to reward and punishment. In paper 3 we showed that chronic pain patients have reduced Reward Responsiveness. A recent study found that chronic pain patients had increased gain sensitivity (Berger et al., 2014) and this could be an alternative explanation for why patients prefer cards that are disadvantageous over the longer term, but more rewarding over the short term. In paper 2 we showed that there was no difference between groups in SCR after rewards or punishments, and that both differentiated between rewards and punishment in terms of amount of SCR. An investigation into the IGT performance from paper 2 and Reward Responsiveness or Reward Drive in paper 3 does not show any associations between SCR and the reward measures. If the increased gain sensitivity found in lower back pain patients by Berger et al. is present in more mixed pain populations like ours, we did not manage to find any signs of it in our data. As our studies were not designed to test this specific hypothesis, it would be beneficial if a direct investigation into any relationship between gain sensitivity, IGT performance and Reward Responsiveness in chronic pain patients was done. Should indeed gain sensitivity be increased in pain patients and affect IGT performance, it would be challenging to reconcile with the

SMH foundation of the IGT and potentially invalidate some of the assumptions linking somatic markers to decision-making impairments in chronic pain patients.

Earlier studies in healthy subjects have found mixed results when assessing reward processing and IGT. In healthy subjects scoring lower on the IGT has been associated with either higher (Franken & Muris, 2005) or lower (Suhr & Tsanadis, 2007) Reward Responsiveness score, or no association has been found (Brand & Altstötter-Gleich, 2008). Additional analyses of correlation between total IGT score versus Reward Responsiveness, or of SCR versus Reward Responsiveness, showed no significant correlations in either group when combining the data in paper 2 and paper 3. While changes in the reward systems could affect IGT performance, the lack of correlation between Reward Responsiveness and IGT performance suggests that any decision-making impairments are influenced by more factors. Further research is needed to assess these questions.

Reward processing in chronic pain

In paper 3 we showed that chronic pain patients have reduced Reward Responsiveness, which has not been described before among patients with chronic pain. The difference in Reward Responsiveness was also linked to morphological differences in the reward system between chronic pain patients and their controls.

While several previous studies have suggested impairments of the reward system in chronic pain (Becker et al., 2012; Finan & Smith, 2013) and changes in nucleus accumbens volume have been shown to be a potential early marker of chronic pain (Baliki et al., 2012), this study is the first to show reduced Reward Responsiveness in a chronic pain patient group and link this to changes in nucleus accumbens within the same study sample. Since decrease in nucleus accumbens volume as well as connectivity have been shown as an early marker of chronification of pain (Baliki et al., 2012; Hashmi et al., 2013; Mansour et al., 2013), a

decrease in Reward Responsiveness could turn out to be an early neuropsychological marker of chronification of pain, although more research is needed to test this speculation.

Increased tonic dopamine levels in the nucleus accumbens would impair phasic dopamine release which is necessary for normal reward processing (Eisenegger et al., 2014). It is important to clarify that dopamine and its involvement in reward processing is not an alternative to the SMH, but seen as a link or subsystem under the SMH (Reimann & Bechara, 2010). However, if somatic markers merely bias decisions under ambiguity, any dysfunction in the underlying decision-making systems could create an apparent impairment unrelated to somatic marker processing. We did not identify any relationships between somatic marker-related changes and changes in dopamine-related systems, but recent studies have emerged that indicate dopamine regulation is dysfunctional in chronic pain patients. Further research should investigate if a dopamine dysfunction is underlying the changes we found in SCR. Other methods for detecting changes in dopamine-related systems such as positron emission tomography are available that might detect changes that were not visible with the methods used in Paper 3.

Reward Responsiveness as a construct is not designed to specifically measure Liking or Wanting ability, and as such it is not possible to further dissect the reduced Reward Responsiveness without resorting to speculation. The same is true for the IGT, as it was not designed to separate Liking from Wanting. However, while the SCR results in paper 2 was interpreted within the SMH context, it is possible to interpret SCR prior to choices as a marker of Wanting, while the SCR after choices is a marker of Liking. In this light, the SCR results at the very least suggest that chronic pain patients have altered processes in the decision-making phase where Wanting is most relevant, but that their response in the Liking phase is no different from their controls. Reduced Wanting could be a result of increased tonic dopamine levels in the nucleus accumbens (Eisenegger et al., 2014). Another explanation is

that the changes in Reward Responsiveness are indicative of changes in the opioid system, as Reward Responsiveness correlated with μ-opioid sensitivity in healthy subjects (Wanigasekera et al., 2012). Such an opioid dysfunction could manifest itself as reduced Liking after rewards. As dysfunction in the opioid system is known to affect the dopamine system (Narita et al., 2014), the two explanations are not exclusive.

A hypothesis of reduced Wanting is challenged by a recent study that found increased sensitivity to gains in patients with chronic back pain (Berger et al., 2014), as sensitivity to gain is correlated with Reward Responsiveness in healthy subjects (Penolazzi, Gremigni, & Russo, 2012). A selective impairment in the gain domain has also been seen in subjects during selective dopamine D2/3 receptor blocking similar to the effect of increased tonic dopamine, but such receptor blocking led the healthy subjects to pick fewer high-probability choices (Eisenegger et al., 2014). In light of the evidence of dopamine dysfunction in chronic pain patients, it is possible that relationships between reward-related measures in healthy subjects do not necessarily hold for chronic pain subjects. Should however the results of Berger et al. be confirmed, they would contradict a reduced Wanting-interpretation of our results.

Decision-making and sleep problems

Based on our findings, sleep problems are more important for BOLD activity during working memory than previously believed, leading to the question of whether sleep problems also play a role in decision-making or reward processing. An analysis performed specifically for this thesis found that sleep problem scores in patients with chronic pain correlated significantly with IGT scores, but in the positive direction, i.e. that worse sleep quality was correlated with better IGT scores among the pain patients. This was unexpected, as IGT performance would be expected to be worse in patients with more sleep problems. While little research has been done on the effects of sleep restriction on IGT performance (Khazaie et al., 2010), IGT

performance in controls is, like many other cognitive domains, impaired by total sleep deprivation (Killgore, Balkin, & Wesensten, 2006; Killgore, Grugle, & Balkin, 2012). Patients with chronic sleep disorders such as sleep apnea (Daurat, Ricarrère, & Tiberge, 2013) and restless legs syndrome (Bayard, Yu, Langenier, Carlander, & Dauvilliers, 2010; Galbiati et al., 2015) are impaired on the IGT, but their IGT scores do not correlate with or see a significant contribution from sleep problems. These studies would not lead us to expect a negative correlation between IGT score and sleep problems in our group, but it does not help explain the apparent positive correlation in our results. Based on the SMH, we can speculate that higher sensitivity to somatic states might improve IGT performance while the same increased sensitivity would introduce more interruption of sleep, i.e. worse quality of sleep. It is also possible that some dysfunction in chronic pain patients has a negative effect on sleep problems but a paradoxical relative improvement on IGT scores. We can speculate that dopamine dysfunction in chronic pain patients might serve as such a common mechanism as it would affect both sleep and decision making (Finan & Smith, 2013). Because of the relatively strong correlation, it seems reasonable to investigate this paradoxical result in further studies.

While sleep deprivation has detrimental effects on general decision-making in healthy subjects, more interesting tasks are generally more resistant to be affected by sleep deprivation than less interesting tasks (Harrison & Horne, 2000). However, in our paper 2 there was no difference between groups on SCR after wins or losses, a reduction in SCR upon feedback is seen in a non-IGT gambling task in healthy sleep deprived subjects, indicative of blunted affective response due to sleep deprivation (Whitney, Hinson, Jackson, & Van Dongen, 2015). This suggests that the decision-making impairments in patients with chronic pain do not have a linear relationship with sleep problems, although it is not possible to rule out that sleep problems have a detrimental effect. A detrimental effect could be mediated

through dopamine, since sleep deprivation leads to a reduction in dopamine D2/3 receptor availability (Volkow et al., 2009) which in healthy subjects affect reward processing (Eisenegger et al., 2014).

Consequences for treatment

While several randomized controlled trials have tested the effects of non-pharmacological improvements in sleep on pain and mood (Tang et al., 2015), our paper 1 suggests that sleep problems could be more important for cognitive impairments than previously believed. While paper 1 did not find a significant difference in cognitive function, it suggests that objective or subjective cognitive function assessment could be a relevant end-point of improved sleep trials in pain patients. While the evidence is not yet available to prefer one treatment method over another, some clinics already use the Pittsburgh Sleep Quality Index used in paper 1 to enable clinicians to get a quick and overview of the patient's quality of sleep (Valenza, Rodenstein, & Fernández-de-las-Peñas, 2011).

Changes in Reward Responsiveness and decision-making could have impact for treatments that depend on patient compliance or where patient effort is crucial for the treatment to work. While some treatments offer quick pain relief (e.g. opioids), others are only effective and sustainable after a substantial investment of time and effort (e.g. exercise therapy or physiotherapy). Clinicians must tailor therapies to each individual patient, but the results of paper 2 and 3 suggest that clinicians should be on the lookout for reward impairments that lead patients to approach decisions and reward in a different manner than healthy subjects would.

While it is not possible to say currently if Reward Responsiveness is a measure predating to the chronic pain or a consequence of the pain, the finding is interesting in light of the studies by Baliki et al that used nucleus accumbens function and volume to predict chronification of

pain at an early stage (Baliki et al., 2011), because it suggests that Reward Responsiveness or a similar measure might be used as a prognostic factor for patients with acute pain.

Should further research prove that the reduction in Reward Responsiveness is linked to opioid receptor function, dopamine activity or both, the measure might be used to tailor pharmaceutical treatment. This could include avoiding exogenous opioids or using pharmaceuticals that treat the dopamine dysfunction directly as shown in recent animal studies (Taylor et al., 2015), or indirectly via stress reduction and sleep improvement. Further, an understanding of the process of pain chronification on a neuronal level might help create new non-pharmacological treatments, possibly attacking the abovementioned factors that contribute to dopamine dysfunction.

Finally, the results might serve as educational tools that help patients with chronic pain and their surroundings to externalize the impairments instead of seeing them as a result of the patient's poor will. While this is obvious from the perspective of neuroscience, laypeople in western culture still have a dualist perspective like Descartes, where the brain is something distinct and separate from the self (Pinker, 2002). In this framework at least some patients can find consolation in the idea that poor concentration or poor decision-making is not caused by "me", but by my pain condition and abnormalities in "my brain."

Methodological issues

Measuring pain

While the definition of chronic pain offered in the introduction - an average pain level above 4 for 6 months or more - is simple to understand, there are methodological issues with measuring pain in chronic pain patients. In the present thesis, current and recalled 24-hour averaged Numerical Rating Scale (NRS) were used to estimate pain, while 6 month recalled

pain was only as an inclusion criterion. While this is common for pain studies, it is not without its limitations.

The 11-point NRS can be used to measure current pain level, pain assessment over longer time lengths are problematic. While 24-hour retrospective recalled averages are relatively accurate, 7-day retrospective recalled averages tend to overestimate the NRS with increasing pain level (Giske, Sandvik, & Røe, 2010). The inaccuracies in using recalled pain becomes problematic when assessing the effects of past pain on working memory, decision-making or Reward Responsiveness. Past pain is often pooled into one measure of recalled average pain, disregarding aspects of past pain that might have had an effect (e.g. peak pain level, peak frequency, the actual average pain level, et cetera). We did not try to measure past pain beyond 24 hours in the current study, partly because of the significant additional resources needed to do several rounds of data collection per subject.

While past pain measurement has its problems, real-time measurement has its own. We elected to measure pain before neuropsychological tests, but not during tests. However, pain level in patients with chronic pain changes spontaneously with a relatively high frequency, and can significantly affect the real-time pain level during MRI scanning (Apkarian, Krauss, Fredrickson, & Szeverenyi, 2001). This real-time pain reporting requires cognitive resources, and thus changes the total cognitive load on a subject during neuropsychological testing. This might warrant validating the test anew and limit comparability of results. While not knowing pain levels during a neuropsychological test might lead to increased variation in the patient sample and a type II error, we prioritized using accepted paradigms.

Subjective measures

In addition to pain discussed above, subjective measures of sleep problems and Reward Responsiveness were central to the results in paper 1 and paper 3.

A significant amount of research has gone into objective measurements of sleep behavior, and while the Pittsburgh Sleep Quality Index is useful in many ways – not least that it is significantly less resource intensive – it is not valid at the same level as polysomnography. While future studies should use objective measures like polysomnography and actinography to confirm our findings, the former procedure is resource intensive and the latter was not available at the time of the study, which is why they were not used in a first study of the phenomenon.

We used subjective reports on Reward Responsiveness, as this correlates with reward behavior and physiological reward responses in healthy subjects (Boksem et al., 2008; Bress & Hajcak, 2013; Lange, Leue, & Beauducel, 2012; Van den Berg, Franken, & Muris, 2010). A general problem with self-report assessment of Reward Responsiveness is that it assesses emotional and motivational consequences of remembered reward experiences. Recent studies have instead used objective measures that correlate with Reward Responsiveness in pain patients (Berger et al., 2014; Tamburin et al., 2014). This makes interpretation of impairments possible as dysregulation in the reward systems makes comparability to studies on healthy subjects, but runs the risk of being less ecologically valid than behavioral testing.

The Iowa Gambling Task and the Somatic Marker Hypothesis

IGT has remained popular since the original publication on the SMH in 1994 (A Bechara et al., 1994). Indeed, IGT has been used in a significant amount of medical research on topics such as substance abuse and pathological gambling, as well as conditions like depression and obsessive-compulsive disorder (Buelow & Suhr, 2009). The IGT has however received criticism on a number of issues (Buelow & Suhr, 2009). An issue that has received little attention in the literature is the fundamental test design where the decks are organized with the cards in a specific order which influences the timing of the first major disadvantageous

card. The advantageous (C and D) and disadvantageous (A and B) decks are supposed to have similar types of punishment frequencies (A and C have a high frequency of punishment cards, B and D low frequency). However, the frequencies are not identical. The first punishment card comes late for both deck B (card 9) and deck D (card 10), but the next two punishment cards then come faster for deck B (12 cards; card 14 and 21) than for deck D (19 cards; card 20 and 29) (A Bechara et al., 1994). Since frequency of punishment factors into decision-making and this measure is updated based on the information available to the subject, we could not rule out that differences in punishment frequency might affect decision-making.

Bechara et al has to our knowledge not published how they arrived at their specific order of cards and why it is superior to randomize between subjects but keeping the same reward-punishment frequency within each sequence of 10 cards. In our paper 2 we chose to randomize within sub-deck of 10 cards to avoid any effect on behavior from card order. While we did not get a significant difference between groups on the autonomic data, overall IGT scores did not differ. Although our study was not designed to test the effect of card order, we speculate that the order of cards designed by Bechara et al. might have been optimized to accentuate behavioral differences between groups, while the differences in physiological responses to advantageous and disadvantageous choices are less dependent on card order. More research is needed on the effects of card order on behavior and decision-making physiology.

The SMH, on which the IGT is built, has been strongly criticized (Dunn, Dalgleish, & Lawrence, 2006). The SMH was weakened with the finding that six patients with pure autonomic failure – a degenerated peripheral autonomic nervous system – actually performed significantly better than age-matched controls (Heims, Critchley, Dolan, Mathias, & Cipolotti, 2004). Unfortunately for interpretation of the SMH, the autonomic failure study – like many other studies that employed the IGT – did not actually measure autonomic function during the

IGT, making interpretation of the results difficult. Nevertheless, those results certainly casts doubt over the assumption that the autonomous nervous system is a critical component of decision-making of the type that IGT aims to measure (Antoine Bechara, 2011).

Study sample

The study sample is of relatively small size and mixed etiology due to recruiting difficulties. While the small size reduces generalizability of the results, the mixed etiology increases the ecological validity of the results as any significant group difference is less likely to be caused by an underlying cause of chronic pain and more likely to be generalizable across clinical pain populations and caused by the chronic pain per se. Reproduction of results in subgroups of chronic pain patients is needed for generalization of the results.

While it is not possible to say with certainty how our results differ if our sample had not been mixed, it is possible to speculate. A well-studied chronic pain group is patients with chronic back pain, and in this patient group early changes in nucleus accumbens has been found (Baliki et al., 2012), and recently also changes in reward processing (Berger et al., 2014). While we would expect to find similar results in that patient group, subjects in our papers were not back pain, but more generalized. The BOLD fMRI results of paper 1 and paper 2 resemble those found in fibromyalgia patients (Seo et al., 2012; Verdejo-García et al., 2009; Walteros et al., 2011), and the frequently seen sleep problems in this group suggests the results of paper 1 could be reproduced there (Menefee et al., 2000). The current study had no patients with neuropathic pain, and as this patient group has a somewhat different profile on cognitive impairments (Landrø et al., 2013), it is possible that the results would be different had more patients with neuropathic pain been included.

An unintended result of the exclusion and inclusion criteria and serial recruitment among general pain clinic patients was that there were significantly more women than men among the participants. While the control group was matched for sex, since the results were not corrected for sex differences any effects that are affected by sex might limit the comparability of the results to other similar studies.

Conclusion

Sleep problems are important for the reduced BOLD activation and deactivation found in patients with chronic pain. Chronic pain patients lack autonomic markers before disadvantageous choices, possibly showing a mechanism for impaired emotional decision-making in this patient group. They also have reduced Reward Responsiveness, which could be related to reward circuitry changes in patients with chronic pain.

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Journal of Pain Research

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ORIGINAL RESEARCH

A particular effect of sleep, but not pain or depression, on the blood-oxygen-level dependent response during working memory tasks in patients with chronic pain

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Background: Patients with chronic pain (CP) are often reported to have deficits in working memory. Pain impairs working memory, but so do depression and sleep problems, which are also common in CP. Depression has been linked to changes in brain activity in CP during working memory tasks, but the effect of sleep problems on working memory performance and brain activity remains to be investigated.

Methods: Fifteen CP patients and 17 age-, sex-, and education-matched controls underwent blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging at 3T while performing block design 0-back, 2-back, and paced visual serial addition test paradigms. Subjects also reported their level of pain (Brief Pain Inventory), depression (Beck Depression Inventory II), and sleep problems (Pittsburgh Sleep Quality Index) and were tested outside the scanner with neuropsychological tests of working memory.

Results: The CP group reported significantly higher levels of pain, depression, and sleep problems. No significant performance difference was found on the neuropsychological tests in or outside the scanner between the two groups. There were no correlations between level of pain, depression, and sleep problems or between these and the neuropsychological test scores. CP patients exhibited significantly less brain activation and deactivation than controls in parietal and frontal lobes, which are the brain areas that normally show activation and deactivation during working memory tasks. Sleep problems independently and significantly modulated the BOLD response to the complex working memory tasks and were associated with decreased brain activation in task-positive regions and decreased deactivation in the default mode network in the CP group compared to the control group. The pain and depression scores covaried with working memory activation.

Discussion: Sleep problems in CP patients had a significant impact on the BOLD response during working memory tasks, independent of pain level and depression, even when performance was shown not to be significantly affected.

Keywords: magnetic resonance imaging, 2-back, serial addition test, deactivation, activation

Introduction

Cognitive complaints are common in patients with chronic pain (CP),[1] as well as objectively measured cognitive deficits.[2,3] Working memory is often reduced in CP, and the reduction is independent of local analgesia.[4] The effect of CP on working memory is moderate and there is considerable discrepancy between studies.[5] Furthermore, working memory is affected by depression[6] and sleep problems,[7] both of which are common in CP patients. Approximately 70% of CP patients are reported to be moderately or severely depressed,[8] and/or experience sleep problems.[9,10] It has been shown that pain

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submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/JPR.S83486

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sensitivity is increased by the induction of sad mood in CP[11] and by sleep deprivation.[12,13] Moreover, sleep deprivation has negative effects on mood,[14] and sleep problems are present in the majority of depressed subjects.[15] Several prospective studies have also found that sleep problems increase the risk of later CP,[16–20] and that restorative sleep is independently associated with later resolution of widespread pain.[21] Thus, CP, depression, and sleep problems are closely entwined, and all may affect working memory.

A number of studies have investigated the effect of experimental pain on brain activity during working memory tasks with T2* weighted, blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI),[22,23] but only one fMRI study has investigated working memory in a group of CP patients.[24] In the latter study, patients with chronic fibromyalgia exhibited reduced brain activation relative to controls, and a significant effect of level of depression on brain activity was reported. Since sleep deprivation is also known to reduce BOLD activation in brain regions during working memory tasks in healthy controls (HC),[25–31] sleep problems may impact working memory related brain activity in CP patients, but this remains to be studied. Indeed, fMRI studies on working memory in CP patients that simultaneously take into account level of pain, depression, and sleep problems are lacking.

The aim of the current study was to investigate BOLD activation in CP patients compared with HC during different working memory tasks, and to study the relationship between BOLD activation and level of pain, depression, and sleep problems to verify the contribution of each of these to BOLD signal differences.

Methods

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Sciences Data Service. Written informed consent was obtained from all participants. In addition, all participants were informed personally and in writing that they could withdraw their consent at any time without any consequences. All participants were offered a monetary compensation of 400 NOK and pictures from their morphological brain scan.

Subjects

A total of 20 CP patients (16 females) were recruited from a local university hospital pain clinic. Inclusion criteria for the CP group were ≥6 months with average pain intensity of ≥4 on the Verbal Rating Scale.[32,33] An experienced clinician performed the clinical assessment. To minimize external effects on cognition or brain activity, subjects with high consumption of analgesics were excluded (>180 mg codeine or equivalent per 24 hours, 24 hours continuous benzodiazepine treatment, or using carisoprodol). The included subjects were instructed not to consume caffeine and/or nicotine in the hours prior to testing and scanning. No morphological abnormalities were detected in the MRIs of any of the participants.

In addition, a control group of 20 age-, sex-, and education-matched HC (18 females) were recruited from the local community. Exclusion criteria for both CP patients and HC were severe psychiatric disorder and any neurological disorders, including traumatic brain injury (<13 Glasgow Coma Scale at the time of injury) and MRI contraindications. A diagnosis of mild or moderate depression did not warrant exclusion in any of the groups, neither did use of antidepressants. All participants reported being right-handed, and were assessed with the Edinburgh Handedness Inventory[34] (CP: 0.82±0.21, range: 0.43–1; HC: 0.91±0.16, range: 0.45–1).

One subject was excluded after previous neurological disease was discovered in the clinical interview. A series of technical problems caused data loss that resulted in the final groups consisting of 15 CP subjects (13 females) and 17 HC subjects (16 females). Of the 15 included patients, ten were classified as having musculoskeletal pain, four idiopathic pain, and one as having visceral pain. None had neuropathic pain.

Pain

Pain intensity was assessed using the validated Norwegian translation[35] of the Brief Pain Inventory (BPI).[36] Total BPI score was calculated. In BPI, the intensity of pain during the last 24 hours is rated using a numerical rating scale (NRS), where 0 is no pain and 10 is worst imaginable pain. The NRS measure was used as an estimate of individual level of pain at time of the experiment and applied in the fMRI analysis.

Depression

The level of depression was assessed with the validated Norwegian translation[37] of the Beck Depression Inventory (BDI) II.[38] BDI has been validated in a CP population with BDI Negative Thoughts and BDI Behavior,[39] and recommended for use in clinical studies of CP.[40] Score on the BDI was used as the level of depression in analyses, and not for diagnosing the presence or absence of clinical depression.

Quality of sleep

The Norwegian validated version[41] of the Pittsburgh Sleep Quality Index (PSQI)[42] was used to measure the quality

of sleep. PSQI is related to the subjective sleep experience rather than objective measures of sleep quality and sleep problems.[43] It has been used in a number of studies in patients with CP.[44–46] The cut-off value of five was used to differentiate good sleepers from bad sleepers (sensitivity 89.6%, specificity 86.5%).[42]

Working memory and fMRI task design

The Wechsler Adult Intelligence Scale (WAIS)-III subtests Digit Span and Letter Number Sequencing[47] were administered to all subjects. Age-adjusted scores for the groups are reported. While the Digit Span Forward requires basic attention, phonological loop, and short-term memory, the Digit Span Backward, and to a larger extent the Letter Number Sequencing, requires maintaining and updating the information. WAIS-III subtests were performed according to the instructions described by Wechsler.[47]

For the fMRI experiments, 0- and 2-back (collectively referred to as n-back) plus paced visual serial addition test (PVSAT) paradigms were implemented. The n-back task is one of the more popular paradigms for studying working memory with functional neuroimaging[48] and is frequently used.[49] The PVSAT is an adapted version of a working memory, attention, and processing speed test used in CP and other patient groups.[50] The n-back and PVSAT paradigms test different attention and executive processes: basic attention and the phonological loop (0- and 2-back and PVSAT), updating and maintaining information (2-back and PVSAT), and manipulation of information (PVSAT). The 0-back probes sustained attention and other processes that underlie working memory. The design of the 0/n-back paradigm resembles a Go/No Go-task[51] as subjects respond if the current element is identical to a predefined element, and in 66% of the trials the subject has to withhold the response. Reaction time (RT) variability on Go-elements of a Go/No Go-task has been used as a measure of inhibitory efficiency and is sensitive to sleep deprivation.[52,53]

The n-back and PVSAT paradigms were all block designs. There were six 30 seconds "off" blocks and five 30 seconds "on" blocks for the n-back paradigms. For the PVSAT paradigms, there were eight 30 seconds "off" blocks and seven 30 seconds "on" blocks. In the "off" blocks, participants were instructed to fixate on a white cross in the center of a black screen. In each "on" block in the n-back tasks, 12 numbers were shown for 500 ms with a fixation asterisk lasting for 2,000 ms between the numbers. In the "on" blocks in the PVSAT, 15 numbers were shown for 500 ms with a fixation asterisk lasting for 2,000 ms between the start of each numbers. The n-back and PVSAT tasks were balanced in such a way that the number of correct responses per block was similar for all three paradigms. This was done to ensure that data from the different conditions would later be comparable. The n-back and the PVSAT tasks were programmed, presented, and the subjects' performance recorded in E-Prime 1.1 (Psychology Software Tools, Inc., Sharpsburg, PA, USA). The paradigm presentation order was randomized and the stimuli presentation order was pseudorandomized. During fMRI scanning, the tasks were displayed on an LCD screen mounted behind the bore opening, and viewed through a mirror mounted on the head coil. All responses were recorded using response buttons from NordicNeuroLab (NNL) (Bergen, Norway). The participants were familiarized with the fMRI paradigms outside the scanner and performed computer-based test versions of each paradigm until full compliance was obtained.

n-back paradigm

The subject was instructed to press a response button every time the number shown was identical to the number preceding it by n steps.[54] Subjects were tested with n=0 and n=2, referred to as 0-back and 2-back, respectively. The numbers shown were between 1 and 13. For the 0-back, subjects were instructed to respond by pressing the button whenever the number shown was 7 or 13. Thus, no manipulation of information in working memory was required. For the 2-back condition, the subjects were instructed to press the button whenever they saw a number identical to the one before the previous. Both n-back trials induced button presses 33% of the time if performed correctly.[54] n-back tasks are usually performed with letters. Since there is a small, but significant difference between using numbers and letters in an n-back paradigm,[55] we used numbers in our n-back task in order to ensure comparability with the PVSAT paradigm.

PVSAT

All participants completed one PVSAT paradigm. In the PVSAT, subjects were shown a series of numbers between 1 and 12 and asked to add every number to the number before it. When the sum was either 7 or 13, the subject was instructed to press the response button. This was done in order to keep the PVSAT comparable to the n-back paradigms with regard to both the response method and the interstimulus intervals, ie, nonverbal button press responses. To ensure that all subjects did indeed add the numbers as instructed, the approach of Mainero et al[56] was modified by asking subjects to press the response button every time the sum equaled 7 or 13. Previous research shows that training has a significant effect on

Paced Auditory Serial Addition Test (PASAT) scores, partly because experience with the test alleviates frustration and anxiety, which have negative effects on scores.[57] With this in mind, all participants received a standardized and thorough explanation of the task adapted from the Gronwall version of PASAT instructions,[58] including an out-of-scanner 8-minute PVSAT training session, a set up identical to the fMRI run, but with 12 blocks of 15 numbers, and resting blocks only lasting 10 seconds. The training session paused at 33% and 66% completion, and started again when subjects decided they were ready to continue. The subjects also trained in the scanner before fMRI scanning commenced.

fMRI

Scanning was performed on a 3T Siemens Trio scanner with a 12-channel head matrix coil (Siemens AG, Erlangen, Germany). Foam pads were used to minimize head motion. T2* weighted, BOLD sensitive images were acquired using an echo-planar imaging pulse sequence (repetition time 3,000 ms, echo time 35 ms, field of view 220 mm, slice thickness =2.8 mm, slice number =41, in-plane resolution 2.8×2.8 mm). Each functional run contained either 111 (n-back) or 152 volumes (PVSAT), with slices positioned parallel to the plane through the anterior and posterior commissures. For anatomical reference, one T1 weighted 3D volume was acquired (2,300 ms repetition time, 2.88 ms echo time, 900 ms inversion time, 9° flip angle, 526 mm field of view, 160 slices, 1.2 mm slice thickness, 1.0×1.0 mm in-plane resolution).

Functional image analysis

Imaging data preprocessing and analysis were performed with FSL 4 (FMRIB Software Library; Analysis Group, FMRIB, Oxford, UK). Preprocessing involved brain extraction, motion correction (MCFLIRT), interleaved slice time correction, spatial smoothing (FWHM 6.0 mm), intensity normalization, and high-pass temporal filtering (cut-off 90 seconds). Nonlinear coregistration was performed to the 1 mm Montreal Neurological Institute (MNI) template with a warp resolution of 10 mm. For each paradigm, absolute and relative displacements were calculated for all participants.

Individual runs were analyzed with an uncorrected statistical threshold of $P<0.05$ in the first level. Intra-individual contrasts in the second level (2-back > 0-back, PVSAT > 0-back, PVSAT > 2-back) were analyzed with fixed effects analysis and an uncorrected statistical threshold of $P<0.05$. Between-subject differences were first investigated with a threshold of $P<0.005$ uncorrected and cluster size >20 voxels, which is equivalent to a false discovery rate (FDR) of $q<0.05$ and suggested for use in fMRI studies with smaller samples.[59] Group differences were subsequently assessed with a mixed effects analysis (FLAME1) with pain, depression, and sleep scores as regressors (see Group differences on BOLD activations and impact of level of pain, depression, and sleep). These analyses were also subsequently thresholded with a cluster-corrected Z threshold of $Z>3.0$ and $P<0.05$. Stricter statistical thresholds were employed to enable better specification of the locations of activation differences between groups for the different contrasts.

It has been shown that CP,[60,61] BDI depression score,[62] and sleep deprivation[25,29,63,64] can affect cerebral blood flow and/or the BOLD response. BOLD activity in the CP group could thus be significantly affected by level of pain, depression, and/or sleep problems, which could mask or increase group differences in brain activation between the CP and HC groups. To unpack the possible independent contributions of pain, depression, and sleep on brain activity during working memory tasks between the CP and HC group, we combined the three self-report measures (NRS rating, BDI score, and PSQI score), which were uncorrelated ("Results" section), as regressors in a common general linear model. Analyses were run one time for each regressor separately, each time with the two other regressors orthogonalized on the regressor of interest. This was done to establish the presence of a unique contribution to BOLD activity for pain, depression, and sleep scores in the CP and HC groups.

Study protocol

The experimental layout was as follows: day one: BDI and BPI, n-back and PVSAT; day two: PSQI and Wechsler Adult Intelligence Test-III. The testing was separated over 2 days to avoid exhausting the participants.

Statistical analysis

Questionnaires and fMRI behavioral data were analyzed using Excel 2004 (Microsoft Corporation, Redmond, WA, USA) and PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Results are given as mean ± standard deviation and range where normal distribution applied in both groups. Where results from one or both group were not normally distributed, median and range are reported. Normality was assessed with the Shapiro–Wilk test.

For each fMRI paradigm, correct responses and nonresponses were registered as total scores. Likewise, the total number of errors of commissions, ie, a response when a nonresponse was correct, and the total number of errors of omission, ie, a nonresponse when a response was correct,

were calculated. RT was measured from the presentation of new stimulus to the time of first subsequent button press.

Sleep deprivation has been found to increase variability in RT.[52,53] Since pain is associated with sleep problems we calculated, for each paradigm, the individual variability in RT over all trials where responses were given. RT variability was assessed with Intra-Individual Coefficient of Variation, which is defined as the standard deviation of individual RT divided by the mean individual RT, after removing all trials where subjects did not respond correctly.[27] The RT variability was calculated for each fMRI paradigm and compared between the CP and HC groups.

Two-tailed, unpaired Student's *t*-tests with $P \leq 0.05$ as a statistical threshold for significance were used on the behavioral data with normal distribution to statically evaluate the differences between the CP and HC groups. For measures that were not normally distributed (NRS, BDI, and PSQI among HC, and the majority of n-back and PVSAT behavioral measures), Independent Mann–Whitney *U* tests were used. To compare proportions in each group, chi-square test was used. Cohen's *d* was calculated and classified as small (d=0.15–0.40), medium (d=0.40–0.75), or large (d>0.75). To evaluate potential relationships between the three self-report measures (NRS, BDI, and PSQI) and also with behavior, a correlation matrix with bivariate Spearman correlation was set up in the CP group. The behavioral data obtained from the three fMRI paradigms (total scores) and the scores of pain, depression, and sleep problem questionnaires were entered into the analysis. Similar correlations were not performed in the HC group due to the limited range in scores. Correlations with a $P<0.05$, two-tailed, were considered significant.

Results

Demographics

Age, sex distribution, and years of education were not significantly different between the groups (Table 1).

Subjects reported pain in a nonspecific pattern, both with regard to the localization of the painful areas and areas of maximal pain (Figure 1). Total BPI score was significantly higher in the CP group (45.0, range: 28–81) compared to that in the HC group (2.7, range: 0–16) ($P<0.001$), as was the average level of pain during the last 24 hours, in the CP group (6.0, range: 3–8) compared to that in the HC group (0.0, range: 0–2) ($P<0.0001$) (Table 1).

The CP group scored significantly higher on BDI with 12.0 (range: 0–33), compared to the HC group scoring 1.0 (range: 0–8) ($P<0.0001$) (Table 1). According to a CP-specific BDI cut-off, only two patients had a BDI

Table 1 Demographics, level of pain, depression, and sleep quality and working memory performance in 15 chronic pain patients and matched healthy controls

Measure	CP (n=15)	HC (n=17)	*P*-value	Cohen's *d*
Age, years	38.6±7.2 (22–49)	37.6±7.0 (23–48)	0.69	0.14
Education	4.5±2.4 (0–10)	5.1±2.5 (1–11)	0.51	0.24
NRS	6.0 (3–8)	0.0 (0–2)	0.00*	3.64[a]
BDI	12.0 (0–33)	1.0 (0–8)	0.00*	1.69[a]
PSQI	11.0 (2–16)	2.0 (0–6)	0.00*	2.39[a]
Letter number sequencing	8.0±2.1 (5–12)	9.4±2.4 (6–14)	0.11	0.61
Digit span forward	8.3±2.0 (6–12)	9.3±2.3 (6–14)	0.23	0.45
Digit span backward	5.4±1.3 (4–8)	6.0±1.9 (3–9)	0.32	0.37

Notes: Numbers are average scores ± standard deviation and (range) in CP patients with pain self-rating of ≥4/10 for ≥6 months and in HC. Numbers are mean ± standard deviation where both groups had a normal distribution. Only where one or more group was not normally distributed, the median is reported. Range is given in parenthesis. Statistical differences were estimated/calculated with a two-tailed two-sample *t*-test where equal variance was assumed if Levene's test for equality of variances was significant with a $P<0.05$. For measures that were not normally distributed in both groups (NRS, BDI, and PSQI among HC), an independent Mann–Whitney *U* test was used. *Significance on *t*-test for $P \leq 0.001$; [a]large effect sizes. Education: Years of education after high school. Handedness recorded with Edinburgh Handedness Inventory.
Abbreviations: CP, chronic pain; HC, healthy controls; NRS, average pain last 24 hours, rated on a numerical rating scale before scanning; BDI, Beck Depression Inventory II score; PSQI, Pittsburgh Sleep Quality Index score.

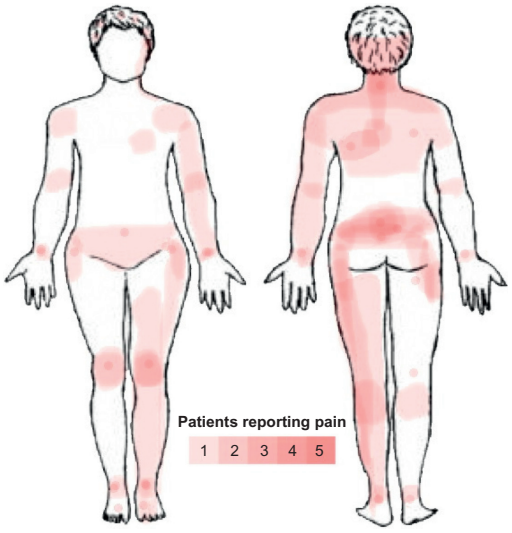

Figure 1 Body map over pain location in CP group.
Notes: Colored areas correspond to the areas where patients reported pain on the human figure from the Brief Pain Inventory questionnaire. Color intensity corresponds with number of patients that report pain in the given area, the colored box indicates color intensity corresponding to one patient (lightest pink) to five patients (darkest pink).
Abbreviation: CP, chronic pain.

score that indicated they were likely clinically depressed.[8] Three CP patients were on selective serotonin reuptake inhibitors.

The CP group had a significantly higher PSQI score of 11.0 (range: 2–16) compared to 2.0 (range: 0–6) in the HC group ($P<0.0001$). Indeed, the CP group differed significantly from the HC group on all the sleep problem subscales (P-values between $P<0.02$ and $P<0.001$) (Table 1). Furthermore, 86.7% in the CP group were poor sleepers, compared to 5.9% in the HC group ($\chi^2[1]=21.13$, $P<0.001$).

Working memory testing and fMRI task behavior

Analysis of motion correction data showed that there were no significant group differences in maximum absolute or relative displacement during scanning between the CP and HC groups, and also no large effect sizes.

There were no significant group differences on the neuropsychological working memory tests Letter Number Sequencing, Digit Forward or Digit Backward, but there was a medium effect size (Cohen's d=0.61) for Letter Number Sequencing with lower scores in the CP group (Table 1).

Working memory performance during fMRI did not differ with regard to number of correct responses, errors of commission, errors of omission, average RT or RT variability on any of the fMRI paradigms between the CP and HC groups, although a large effect size was evident for RT variability on the 0-back (Table 2).

There were no significant correlations between pain, depression, sleep, PVSAT-, and n-back scores in either group (CP group results shown in Table 3).

Group differences on BOLD activations and impact of level of pain, depression, and sleep

With FDR $q<0.05$, significant group differences were present for the 2-back > 0-back, PVSAT > 0-back, PVSAT > 2-back contrast without the three self-report measures as regressors. Differences in activations were found in all brain lobes for both HC > CP and HC < CP. In general, the HC groups had higher Z values and more extensive activations compared with the CP group for the 2-back and PVSAT versus 0-back (Table 4). When including pain, depression, and sleep problem scores as regressors, the number of significantly different voxels was reduced for pain and depression, but markedly increased for sleep problems. Since the areas of increased activation were quite extensive, a stricter statistical threshold ($Z>3.0$, cluster $P\leq0.05$) was applied to

Table 2 Performance on the fMRI paradigms for chronic pain patients and healthy controls

Test	CP (n=15)	HC (n=17)	*P*-value	Cohen's *d*
0-back				
Score	60.0 (39.0–60.0)	60.0 (55–60)	0.60	0.63
RT	521 (404–1,146)	555 (437–856)	0.71	0.40
ICV	0.18 (0.05–0.73)	0.15 (0.09–0.26)	0.15	0.76[a]
EC	0.0 (0.0–7.0)	0.0 (0.0–2.0)	0.35	0.63
EO	0.0 (0.0–17.0)	0.0 (0.0–5.0)	0.58	0.54
2-back				
Score	54.5±3.6 (47.0–59.0)	56.4±3.0 (51.0–60.0)	0.12[n]	0.55
RT	598 (478–1,311)	630 (461–1,261)	0.85	0.08
ICV	0.26±0.12 (0.11–0.51)	0.27±0.09 (0.16–0.43)	0.88[n]	0.06
EC	2.0 (0.0–5.0)	1.0 (0.0–4.0)	0.58	0.26
EO	3.5±2.5 (0.0–8.0)	2.1±1.5 (0.0–6.0)	0.08[n]	0.65
PVSAT				
Score	99.9±3.7 (94.0–105.0)	100.1±3.9 (91.0–105.0)	0.89[n]	0.05
RT	848 (634–1,224)	876 (615–1,377)	0.63	0.23
ICV	0.30±0.08 (0.18–0.49)	0.27±0.07 (0.12–0.35)	0.20[n]	0.47
EC	2.0 (0.0–5.0)	1.0 (0.0–5.0)	0.55	0.13
EO	2.0 (0.0–10.0)	2.0 (0.0–9.0)	0.85	0.00

Notes: Numbers are medians and ranges in CP patients with pain self-rating of ≥4/10 for ≥6 months and their matched HC. Numbers are mean ± standard deviation where both groups had a normal distribution. Only where one or more group was not normally distributed, the median is reported. Range is given in parentheses. There were no statistical significant group differences found with the two-tailed independent sample Student's t-test (where both variables were normally distributed, marked with [n]) or the Mann–Whitney U test (where one or more variables were not normally distributed) with significance level set to $P<0.05$; [a]large effect sizes. Score: Subjects get 1 point when they correctly push or correctly refrain from pushing the response button.

Abbreviations: fMRI, functional magnetic resonance imaging; CP, chronic pain; HC, healthy controls; PVSAT, paced visual serial addition test; RT, reaction time in milliseconds; ICV, individual coefficient of variation for RT variability; EC, errors of commission, responding when nonresponse was correct; EO, errors of omission, nonresponse when response was correct.

Table 3 Correlations between working memory test, pain (NRS), depression (BDI), and sleep problems (PSQI) scores in chronic pain patients

Self-report and test scores	NRS	BDI	PSQI
NRS	1	–	–
BDI	–0.041	1	–
PSQI	–0.230	0.157	1
0-back score	–0.346	–0.235	0.124
2-back score	–0.277	0.012	0.240
PVSAT score	–0.021	–0.390	0.126

Notes: All numbers are Spearman's *r* between factors in a bivariate correlation analysis in a group of 15 CP patients with pain self-rating of ≥4/10 for ≥6 months. There were no significant correlations using a two-tailed analysis and a statistical threshold of r $P<0.05$.

Abbreviations: CP, chronic pain; NRS, average pain last 24 hours, rated on a numerical rating scale before scanning; BDI, Beck Depression Inventory II score; PSQI, Pittsburgh Sleep Quality Index score; PVSAT, paced visual serial addition test.

enable better differentiation of the activations resulting from the different analyses. Again, significant group differences were demonstrated for all three contrasts (2-back > 0-back, PVSAT > 0-back, PVSAT > 2-back) for HC > CP and to a limited extent in CP > HC. As expected, the regions with activation differences were similar, but the activations were more confined. Moreover, only sleep scores remained a significant contributor to working memory related differences in brain activity between the CP and HC groups with the stricter statistical threshold. With sleep scores as the main regressor, the HC group had significantly increased activation compared with the CP group, both for the 2-back > 0-back (bilateral lateral occipital cortex, bilateral middle frontal gyrus, right superior frontal gyrus, bilateral paracingulate gyrus, frontal pole, inferior temporal gyrus, and the thalamus) and the PVSAT > 0-back (bilateral lateral occipital cortex, right middle frontal gyrus, bilateral paracingulate gyrus, left precentral gyrus, left supramarginal gyrus, and right inferior frontal gyrus). The HC group also had increased activation in the frontal poles, bilaterally, in the 2-back > PVSAT condition. In addition, PVSAT > 0-back elicited higher activation bilaterally in the medial frontal lobe, in the CP group compared to the HC group. Detailed information on activation differences between the groups for the different contrasts is given in Table 5 and Figure 2. The sleep score related reductions in brain activation in the CP group compared with that in the HC group were found in all regions of the dorsal attention and the frontoparietal control networks for the 2-back > 0-back contrast.[65] Several areas in the dorsal attention and frontoparietal control networks also showed reduced activation in the PVSAT > 0-back contrast in the CP group. The regions with decreased activity in the CP compared with the HC group, resulted from less activation, not lack of activation. The increased activation in the CP > HC group for PVSAT > 0-back in the bilateral medial prefrontal gyrus, part of the default mode network,[66,67] had a different origin. It stemmed from less deactivation in the CP group compared to the HC group (Figure 3). The CP group thus showed both significantly reduced activation in the dorsal attention and frontoparietal control networks and significantly reduced deactivation in the default mode network compared to controls during more complex working memory tasks that were performed similarly at the behavioral level in the two groups.

Table 4 Clusters of significantly increased or decreased activity in the CP versus HC groups during working memory fMRI

Contrast	HC > CP		HC < CP	
	Clusters	Total no of voxels	Clusters	Total no of voxels
2-back > 0-back	70	21,486	7	941
PVSAT > 0-back	39	13,755	20	5,138
PVSAT > 2-back	3	294	33	6,661

Notes: Numbers are numbers of clusters above threshold equivalent to $q<0.05$ false discovery rate between a group of 15 patients with pain self-rating of ≥4/10 for ≥6 months and 17 HC.

Abbreviations: CP, chronic pain; HC, healthy controls; fMRI, functional magnetic resonance imaging; PVSAT, paced visual serial addition test.

Discussion

The current study demonstrated that working memory performance was similar in the CP group and the matched HC group both for the traditional working memory tests and during fMRI. However, this similar performance was accompanied by areas of both reduced brain activation in the dorsal attention and frontoparietal control networks and deactivation in the default mode network in the CP group. Importantly, the difference in brain activity was explained by sleep problems in the CP group.

The CP and HC groups performed similarly on the working memory tests from WAIS-III and on the fMRI tasks. A lack of significant group differences on cognitive measures is not uncommon in CP studies.[5] There was a large effect size for RT variability for the simplest task, 0-back, but not for the 2-back and PVSAT in the CP group. Increased RT variability is often seen in sleep deprivation, and simple rather than more complex tasks are most affected at the behavioral level.[68] It should be noted that the CP group was not comparable to controls with total sleep deprivation. The CPs most likely suffered from partial sleep deprivation. In partial sleep deprivation in HC, the behavioral effects increase with time and the degree of deprivation, and significant performance effects are not observed before sleep deprivation reaches 50%

Table 5 Localization of maxima of increased and decreased BOLD signal in patients with CP versus HC for working memory tasks with sleep problems as main regressor and pain and depression scores orthogonalized

Cluster number	Cluster peak	Lateralization	Cluster voxel size	Cluster *Z* max	Coordinates (MNI) for cluster peak			Symmetry w/cluster number
					X (mm)	Y (mm)	Z (mm)	
2-back > 0-back; HC > CP								
1	Lateral occipital cortex, superior division	L and R	33,282	5.08	28	−68	37	5, 1*
2	Middle frontal gyrus	L	15,682	4.60	−52	30	22	3, 9
3	Middle frontal gyrus	R	14,706	5.04	40	34	14	2, 7
4	Superior frontal gyrus	R	10,028	4.97	25	10	55	–
5	Lateral occipital cortex, superior division	L	7,512	4.38	−46	−40	39	1
6	Paracingulate gyrus	L and R	5,522	4.59	8	19	35	5*
7	Frontal pole	L	4,793	4.19	−32	51	14	3
8	Inferior temporal gyrus, temporooccipital part	R	2,929	4.35	54	−46	−12	–
9	Inferior frontal gyrus, pars opercularis	R	2,536	4.34	54	14	9	2
10	Thalamus	L	1,735	4.13	−13	−13	−4	–
PVSAT > 0-back; HC > CP								
11	Lateral occipital cortex, superior division	R	12,196	4.66	28	−67	36	14, 16
12	Middle frontal gyrus	R	6,304	4.76	30	11	58	13
13	Paracingulate gyrus	L and R	2,998	4.52	−9	2	60	12, 13*
14	Lateral occipital cortex, superior division	L	2,717	4.00	−16	−65	47	11
15	Precentral gyrus	L	2,039	4.25	−47	−2	37	–
16	Supramarginal gyrus, posterior division	L	2,031	4.20	−40	−46	39	11
17	Inferior frontal gyrus	R	1,767	4.29	38	33	15	–
0-back > PVSAT; HC > CP								
18	Medial frontal lobe	L and R	9,313	−4.33	−4	62	19	18*
2-back > PVSAT; HC > CP								
19	Frontal pole	L	3,454	4.03	−34	51	12	20
20	Frontal pole	R	2,114	4.02	37	50	3	19

Notes: Statistical threshold was set to $Z \geq 3.0$ and cluster $P < 0.05$ in all analyses. Activation was judged as symmetrical if similar activation was found above threshold in the contralateral hemisphere. Symmetrical activation is marked with an * if the bilateral activation is in the same cluster. The cluster peak coordinates are given in mm in an MNI 152 coordinate space. Lateralization: R, right side; L, left side. The Harvard-Oxford cortical and subcortical structural atlases were used in deciding which anatomical region each maximum belonged to.

Abbreviations: BOLD, blood-oxygen-level dependent; CP, chronic pain; HC, healthy controls; PVSAT, paced visual serial addition test; MNI, Montreal Neurological Institute.

of recommended sleep duration.[69] The lack of significant effects or correlations between sleep scores and test scores are therefore not unexpected.

Importantly, despite similar performance, there were significant group differences in brain activation during the more complex working memory tests. The between-group differences in the current study are quite similar to those reported in the only other fMRI study of working memory in chronic fibromyalgia patients using an n-back task.[24] Furthermore, the increased activity in the HC compared with that in the CP group during the 2-back and PVSAT tasks was located to areas where healthy subjects generally activate on the two tasks.[48,70–72]

The main finding in this study is that sleep problems contribute independently to the differences in brain activation between the CP and HC group. When using pain or depression scores as primary regressors, the difference in BOLD activations between the CP and HC groups during performance of working memory tasks became smaller (significant impact seen only using the less strict statistical threshold) and not present (with the stricter threshold). This is in line with the Seo et al[24] study that reported a negative correlation between pain and depression scores and BOLD activity in frontoparietal regions in chronic fibromyalgia patients. Seo et al[24] specifically noted that pain and depression could not fully explain the differences in brain activity between the CP patients and controls. The current study adds to their findings by demonstrating the importance of sleep for differences in brain activity between the CP and HC groups. Sleep problems are as frequent in CP groups

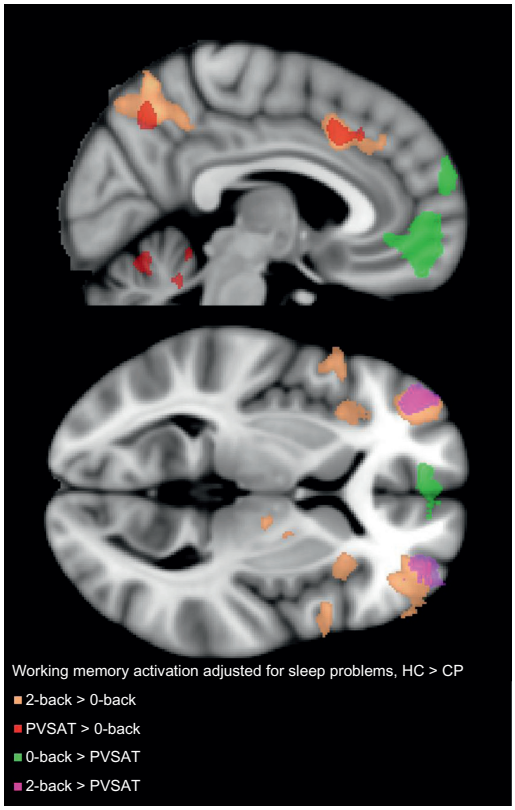

Figure 2 Between-group differences in working memory activation.
Notes: Brown corresponds to HC > CP activation in the 2-back > 0-back condition, red to the PVSAT > 0-back condition, green to the 0-back > PVSAT condition, and magenta to the 2-back > PVSAT condition. All images are thresholded at $Z>3.0$, cluster level $P<0.05$. There was no activation above threshold for the HC < CP contrast in the 2-back > 0-back condition. Coordinates are given in MNI 152 coordinate space.
Abbreviations: HC, healthy controls; CP, chronic pain; PVSAT, paced visual serial addition test; MNI, Montreal Neurological Institute.

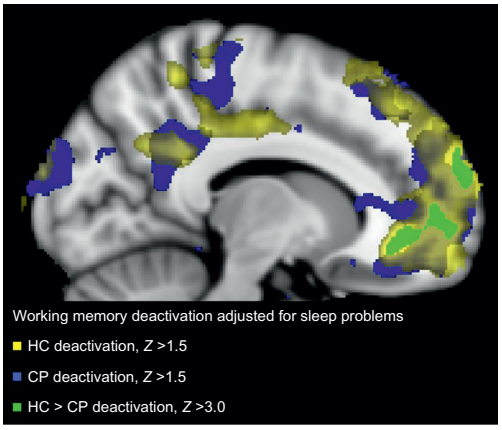

Figure 3 Brain regions with decreased activation at the whole brain level for contrast 0-back > 2-back with sleep problem score (PSQI), and scores for depression (BDI) and pain (NRS) as orthogonalized covariates in the CP group alone (blue), HC group alone (yellow), and the significant difference between them (HC > CP; green).
Notes: The areas where there is a significant difference in activation overlaps closely with the regions where HC have higher deactivation than CP. Thus the areas where the CP group seems to have higher activation than HC are in fact areas where HC has higher deactivation than CP. Coordinates are given in MNI 152 coordinate space.
Abbreviations: HC, healthy controls; CP, chronic pain; PSQI, Pittsburgh Sleep Quality Index score; BDI, Beck Depression Inventory II score; NRS, average pain last 24 hours, rated on a numerical rating scale before scanning; MNI, Montreal Neurological Institute.

referred to specialist pain services as depression, and are found in ~70%.[8,9] Still, controlling for sleep in studies in CP is not common. In a meta-analysis of 23 behavioral working memory studies in CP, most of the studies did not control for sleep, which was described as a risk of bias.[5] Specifically, the present results demonstrated that sleep problems had an effect on brain activity in the CP group during complex working memory tasks since brain activity differences were increased for 2-back > 0-back and PVSAT > 0-back with sleep scores included in the model and pain and depression scores orthogonalized. Depression and pain scores, on the other hand, covaried similarly with brain activity for 2-back, PVSAT, and 0-back conditions, and with these as main regressors, the differences in brain activity between the HC and CP groups were reduced (for the sensitive statistical threshold) or had no additional impact (with the stricter statistical threshold). Increasing sleep problems were associated primarily with decreased BOLD response in the CP group in the same areas that the HC group activated. Sleep deprivation has previously been demonstrated to reduce working memory related BOLD signal in parietal[25–31] and frontal[26,27,31] regions in HC, the same regions in which the CP group had lower activation compared with the HC group in the current study. Reduced activation in the frontoparietal areas in the CP group could be explained by reduced cerebral blood flow and glucose metabolism described in previous studies on sleep deprivation in HC.[73,74] It is suggested that sleep deprivation causes local populations of neurons to collectively enter a nonrapid eye movement-sleep-like state and stop firing in wake subjects.[75] Such "local sleep" could explain reduced cerebral blood flow, glucose metabolism, and BOLD signal. The lower activation implies a reduced ability in the CP group to recruit more neural resources within the task-positive networks with increasing sleep problems. The CP group also displayed lack of deactivation during working memory task performance in medial frontal lobe, part of the default mode network. With increasing sleep problems, an increasing impairment in de-engaging the default mode

activity was detected in the CP group. This is in line with previous reports in HC,[28,29,76–78] and in chronic back pain patients during a simple attention task.[79] Taken together, sleep problems were shown to be connected to both reduced activation of task-positive networks and reduced deactivation of the default mode network during more complex working memory tasks in the CP group.

The areas involved in pain processing, sometimes referred to as the pain neuromatrix, include the primary and secondary somatosensory cortex, insula, anterior cingulate cortex, prefrontal cortex, and thalamus.[80] One hypothesis for cognitive impairments in CP is the limited resource hypothesis.[3,81] Here, brain activity caused by pain interferes with concurrent cognitive processing relying on the same brain regions. There was overlap between the regions where differences in working memory activations where detected between the CP and HC groups and areas in the pain neuromatrix. Both prefrontal cortex and thalamus had significantly lower activity levels in the CP compared with the HC groups both in the analysis with sleep as main regressor and in the between-group analysis without regressors. However, current pain did not increase activation differences between the CP and HC groups in this study. This may be due to spontaneous pain fluctuations occurring during fMRI scanning in the CP group being more important for brain activity than average pain reported prior to scanning.[82] Nevertheless, these results indicated that CP per se affected brain activation rather than the current level of pain. Furthermore, CP may induce changes in the pain neuromatrix, which in turn influences cognitive processing capabilities. However, since the brain activity differences between the CP and HC groups without and with regressors were mostly outside the neuromatrix, other mechanisms appear to be more important for the altered BOLD response in CP than the limited resource hypothesis.

This study has several limitations. First, the CP group had CP of mixed etiology, which reduces the study's sensitivity to any etiology-specific effects. This design does, however, increase the ecological validity and generalizability of the study's results to CP patients in general. Moreover, most participants in the CP group were on analgesics and some on opioids, although high-dose users were excluded to avoid strong confounding effects, as opioids increase cerebral blood flow in HC.[83] Opioids are known to affect sleep patterns in both healthy subjects and CP[84,85] and could therefore influence the results. Similarly, three patients were on antidepressants, which might be a confounder. Exclusion of all patients on opioids or antidepressants would have made it impossible to study the effect of depression, pain, and sleep in the same group of patients, and reduced the ecological validity of the results, while stopping medication would have introduced confounding withdrawal effects and be ethically questionable. Moreover, the small sample size makes it sensitive to type I and type II errors. Relatively strict statistical thresholds were used in the fMRI analysis, while all other statistical analyses were uncorrected for multiple testing. This limits the generalizability of the results before more research is done. Another issue is PSQI as a measure of sleep. PSQI measures subjective sleep quality and habitual patterns of sleep over time, ie, aspects of the sleep–wake experience distinct from objective measures like actigraphy or polysomnography.[43] The use of nonobjective measure of sleep problems makes it difficult to pinpoint the exact aspect(s) of the CPs' sleep cycle, which is disturbed and possibly linked to the observed changes in brain activation. An objective measurement of habitual sleep behavior is very resource-intensive. For a first study of the impact of sleep on working memory performance and brain activity, PSQI is a reasonable compromise.

In conclusion, the current study demonstrated that sleep problems independently and significantly contributed to differences in BOLD activity in the CP group compared with the HC group during complex working memory tasks. The degree of sleep problems was associated with both decreased activation and deactivation in the CP group. These results suggest that working memory problems in CP stem from impaired recruitment of task-positive networks, which normally override the effects of lack of sleep as task complexity increases. This could have implications for future treatment of CP.

Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL RESEARCH

Patients with chronic pain lack somatic markers during decision-making

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Abstract: Patients with chronic pain have impaired cognitive functions, including decision making, as shown with the Iowa gambling task (IGT). The main aim of this study was to elucidate whether patients' decision making is associated with a lack of the anticipatory skin conductance response (SCR). An increase in anticipatory SCR before making unfavorable choices is known to guide decisions in healthy controls during the IGT. Since several brain regions involved in decision making are reported to have altered morphology in patients with chronic pain, the second aim was to explore the associations between IGT performance and brain structure volumes. Eighteen patients with chronic pain of mixed etiology and 19 healthy controls matched in terms of age, sex, and education were investigated with a computerized IGT during the recording of SCR, heart rate, and blood pressure. The participants also underwent neuropsychological testing, and three-dimensional T1-weighted cerebral magnetic resonance images were obtained. Contrary to controls, patients did not generate anticipatory SCRs before making unfavorable choices, and they switched between decks of cards during the late phase of the IGT significantly more often, and this was still observed after adjusting for depression scores. None of the other autonomic measures differed during IGT performance in either group or between groups. In patients, IGT scores correlated positively with total cortical grey matter volume. In controls, there was no such association, but their IGT scores correlated with the anticipatory SCR. It may be speculated that the reduction in anticipatory SCRs makes the chronic pain patients rely more on cortical resources during decision making.

Keywords: Iowa gambling task, skin conductance response, autonomic measures, magnetic resonance imaging, cortex

Introduction

Patients with chronic pain have impaired cognitive functions;[1] among those are impaired decision making,[2–4] as demonstrated in the Iowa gambling task (IGT), a test that simulates real-life decision making.[5] In this test, the goal is to win as much as possible by discerning which of the two decks of cards are advantageous and which two are disadvantageous. Previous research on the IGT has shown that patients with chronic pain score lower and/or switch more frequently between decks compared to healthy controls (HCs).[2–4]

The IGT was introduced as a test of the somatic marker hypothesis.[5] This hypothesis states that when facing ambiguous decisions, cognitive processes are insufficient in guiding choices.[6,7] Instead, autonomic physiological reactions, such as skin conductance responses (SCRs) that are learned to be associated with a specific outcome, are engendered in the body and are relayed to the brain where they give rise to an

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submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/JPR.S62492

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emotion-guided decision.[7] This is called a somatic marker. In healthy subjects, increased anticipatory SCRs are present before choosing cards from the disadvantageous decks of cards in the IGT (see Figures 1 and 2 for an illustration of the model).[8] This is not found in subjects with lesions in the ventromedial prefrontal cortex, who have impaired decision-making skills, but who are otherwise spared intellect.[8,9] Similarly, the reduced decision-making ability in patients with chronic pain may arise from a lack of anticipatory SCR generation, but this has not yet been investigated.

As far as we know, there is also a lack of knowledge as to whether impaired performance on the IGT correlates with changes in the cerebral morphology of patients with chronic pain. This may be expected, since several brain regions involved in decision making are reported to have altered morphology in chronic pain patients.[10] Decision making relies on many brain regions for generating, relaying, and interpreting SCR and/or other somatic signals. The winner of any competing signals influences the final choice.[7] This process is dependent on trigger structures (the amygdala and ventromedial prefrontal cortex), effector structures (such as the hypothalamus, periaqueductal gray area, nucleus accumbens, and neurotransmitter brainstem nuclei), sensory structures (sensory brain stem nuclei), and processing structures (such as the insula and somatosensory cortices), as well as memory structures (for instance, the hippocampus and dorsolateral prefrontal cortex).[7] In patients with chronic pain, gray matter volume reductions have been reported in all these mentioned structure groups, most consistently in the trigger (ventromedial prefrontal cortex), processing (insula), and memory (dorsolateral prefrontal cortex) structures.[10–12]

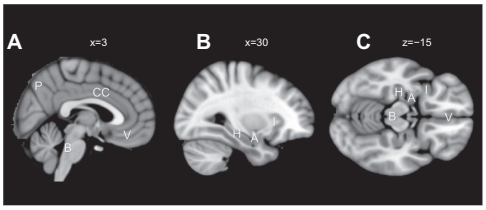

Figure 1 Decision-making structures important during the Iowa gambling task.
Notes: Trigger structures are the (**A** and **C**) V, and (**B** and **C**) A. The A mainly works as a trigger structure for the impulsive system, while the V is a trigger structure for the reflective system. Important supporting structures for the V are the dorsolateral prefrontal cortex (not shown) and (**B** and **C**) H. Effector structures include the hypothalamus, nucleus accumbens, and periaqueductal gray area, while sensory structures include the sensory brain stem nuclei such as the parabrachial nucleus and neurotransmitter nuclei. For effector structures and sensory structures, the figure only displays the (**A** and **C**) B. Important structures for processing information from the sensory structures are the (**B** and **C**) I, the (**A**) CC, (**A**) the P, as well as the somatosensory cortices (not shown). X and Z give the location of the two saggital and one transverse planes in the illustration.
Abbreviations: P, precuneus; B, brainstem; CC, cingulated cortex; V, ventromedial prefrontal cortex; H, hippocampus; A, amygdala; I, insula.

The overall intention of this study was to explore and compare differences and associations between IGT behavior, autonomic signals, and brain structure volumes in patients with chronic pain and matched HCs. The main aim was to examine whether patients' impaired decision making is associated with a lack of anticipatory autonomic physiological reactions. We predicted, based on the previously reported deficits in performance on the IGT in chronic pain patients,[2–4] and on the somatic marker hypothesis, that the patient group would lack the anticipatory SCR before picking cards from the disadvantageous decks. To elucidate possible contributions of other autonomic physiological reactions on IGT performance in the patient group, heart rate (HR) and blood pressure were also measured. The secondary aim was to explore the associations between IGT performance and brain structure volumes. We anticipated that reduced brain structure volumes would be related to impaired IGT performance in patients with chronic pain.

Methods

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Sciences Data Service, and was performed in accordance with their requirements and the Declaration of Helsinki. Written informed consent was obtained from all participants.

Materials

Twenty subjects (16 females) with chronic pain were recruited during consultations in a university pain clinic, and 20 (18 females) age- and education-matched HCs were recruited from the local community. Prior to inclusion, the patients had to report a 6-month average pain intensity of ≥4 on the Verbal Rating Scale, with scores ranging from 0–10.[13] The included patients also had to be in a chronic pain state, which corresponds to Verbal Rating Scale scores ≥4 for at least 6 months.[14]

All participants were offered a monetary compensation of 400 Norwegian Kroner (NOK) (approximately USD $65) and pictures from their morphological brain scan. Psychiatric and neurological disorders, known traumatic brain injuries (13 Glasgow coma scale score at the time of injury), or magnetic resonance imaging (MRI) contraindications were used as exclusion criteria. A diagnosis of mild or moderate depression did not warrant exclusion in any of the groups. Furthermore, patients with a high consumption of analgesics were excluded (>180 mg of codeine or its equivalent per 24 hours, 24-hour continuous benzodiazepine treatment, or use of carisoprodol). All participants

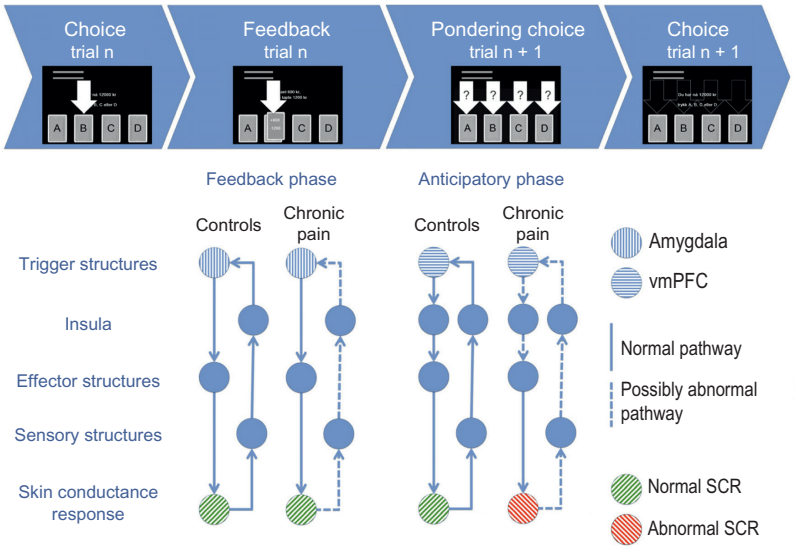

Figure 2 The generation of SCR during the IGT in the PCP and HC groups in the present study in light of the somatic marker hypothesis.
Notes: The schematic representation of the neuronal structures involved in generating and utilizing SCR during the IGT is from the somatic marker hypothesis.[7] The top row shows the phases of the IGT. After choice n, the subject is presented with a reward and possibly a punishment (feedback phase). This visual feedback generates a feedback SCR. The subject ponders choice n + 1, which generates an anticipatory SCR (anticipatory phase). Anticipatory SCRs are interpreted by the brain and influence choice n + 1. The flow charts show the structures involved in generating SCRs and interpreting them during the IGT in HCs and in PCP. The arrows indicate the direction of information flow in a continuous process, initiated by the two trigger structures. The amygdala is more important as a trigger structure in the feedback phase due to its role in the impulsive system. The ventromedial prefrontal cortex is more important as a trigger structure in the anticipatory phase, and it triggers effector structures via the insula. The dotted lines indicate pathways that the current study suggests are abnormal in PCP, since they managed to generate normal feedback SCRs, but not normal anticipatory SCRs during pondering.
Abbreviations: SCR, skin conductance response; IGT, Iowa gambling task; PCP, patients with chronic pain; HC, healthy control; n, choice number; vmPFC, ventromedial prefrontal cortex.

reported being right-handed, and they were assessed with the Edinburgh Handedness Inventory[15] (patients: 0.82±0.21 [mean±standard deviation]; controls: 0.91±0.16).

One patient was excluded due to a neurological disease that was discovered after inclusion, and one patient and one control were excluded due to technical problems during the IGT presentation. Thus, the groups included in the final analysis consisted of 18 patients with chronic pain (15 females) and 19 HCs (17 females).

Of the 18 included chronic pain patients, eleven were classified as having pain of musculoskeletal etiology, five of idiopathic etiology, two with visceral etiology, and none with neuropathic pain.

Data collection

Procedure

On day 1, the participants underwent MRI scanning. On day 2, the participants filled out questionnaires measuring pain and completed neuropsychological tests to assess their general intelligence, depression level, working memory and effort, and finally performance on the IGT during neurophysiological monitoring.

The IGT testing began with the subjects visiting the lavatory and washing their hands to ensure good SCR readings. Following that, various autonomic measuring equipment were attached (see below). Instructions for the computerized version of the IGT[16] were read to the subjects by the researcher (NAE) while the game was demonstrated. The subjects were then left alone in the room and monitored by closed-circuit camera and microphone by the researcher. They were instructed to relax while an on-screen clock counted down from five minutes, and they were then instructed to commence with the task. They began to choose cards by pressing keyboard keys labeled A, B, C, and D, which corresponded to the labeling of the card decks on the screen.

Room temperature was consistently maintained between 22°C–26°C, and this was confirmed before testing with an electronic thermometer (Digitron 2088T, Elektron Technology, Cambridge, UK).

Iowa gambling task (IGT)

We used a modified computerized version of the original IGT, which is similar to the version described by Bechara et al.[16] To avoid confusion about the value of foreign currencies,

all USD values from the original IGT were converted to local currency (NOK). Subjects chose cards from four decks (A, B, C, and D) with the goal of winning as much as possible. In each deck, there are varying amounts of rewards and punishments, with decks A and B offering a fixed gain of $100, and decks C and D offering a fixed gain of $50. The losses vary in frequency, with a 10% loss in decks B and D, and a 50% loss in decks A and C. This results in an average gain or loss after ten cards, with a $250 loss for cards from decks A and B, and a $250 gain for decks C and D. Decks C and D were thus the advantageous decks, and A and B were the disadvantageous decks. On the computer display of the four card decks, a red bar indicating the amount of debt and a green bar indicating the amount of winnings were presented.On the same screen, updated instructions were presented to the subjects in Norwegian ("You now have X NOK", "Press A, B, C, or D", "You won Y NOK", and on some trials "but you lost Z NOK", where X, Y and Z were currency amounts) (Figure 3). The IGT has been described in more detail elsewhere.[16]

We randomized the on-screen position and naming of the different decks to avoid bias from naming or placement on the screen (see Figure 3).[17] Furthermore, we shuffled the decks of cards between subjects. Randomization of the card order increases the robustness of averaging the autonomic signal, and it also rules out the effect of a specific card order on somatic marker generation. Randomization was obtained by block randomization in blocks of ten cards, keeping the original punishment and reward frequencies as described by Bechara et al.[5]

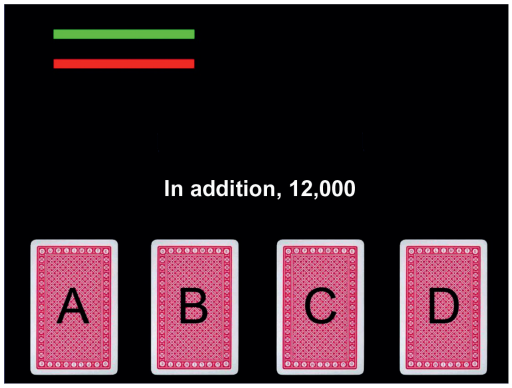

Figure 3 The Iowa gambling task.
Notes: The Iowa gambling task is designed to test decision making. The figure illustrates the starting screen on a computerized version developed by the first author. The four decks from which subjects can choose have different and fixed rewards, while punishment frequencies vary between the decks, and punishment size also varies within the decks. From these characteristics, two decks are disadvantageous over time, while two decks are advantageous over time. Decision-making ability is scored by the number of cards the subject draws from the advantageous decks minus the cards drawn from the disadvantageous decks. The white text provides instructions to the subject in Norwegian ("You now have $2,000/press A, B, C, or D"). The green bar displays the amount of money the subject has, while the red bar displays the total sum of money the subject has borrowed to play. In this version, the placement of the four decks was randomized on the screen for each subject, and renamed A–D from left to right. In this article A–D refers to the decks by the classic nomenclature of the Iowa gambling task, not the letters displayed to the subjects.

The interval from one choice to the next was set to a minimum of 6.5 seconds, and it ended when the subject chose a card. The IGT has been criticized for allowing certain decks to run out of cards,[18] thus reducing its sensitivity to detecting impairment in decision making. Because of this, we set all decks to contain 100 cards, which is equal to the total amount of cards that the subject was allowed to draw.

Autonomic measures

As a measure of the state and balance of the autonomic nervous system, several autonomic measurements were made. Skin sweat gland activity (ie, SCR), HR (ie, R wave to R wave intervals [RR]) from electrocardiogram (ECG) (PowerLab unit, ADInstruments, Dunedin, New Zealand) recordings, and blood pressure from the finger manometer were recorded during IGT performance. The ECG data was used to calculate both HR and HR variability. HR variability was calculated based on the HR, according to current recommendations.[19] SCR, RR intervals, and blood pressure were used in event-related analyses (autonomic activity directly preceding or following choices). The average HR, HR variability, and blood pressure were calculated separately for the 5-minute baseline period before the IGT ("Baseline") and for the entire IGT period ("Activity"). In addition the individual's change (Δ) in these measurements from Baseline to Activity was calculated, for example:

$$\text{Baseline HR} - \text{Activity HR} = \Delta\text{HR}. \quad (1)$$

Sample characteristics

Pain

Pain intensity was assessed using the validated Norwegian translation of the Brief Pain Inventory (BPI).[20,21] The BPI assesses the intensity of pain during the last 24 hours using a 0–10 numerical rating scale.

Depression level

Since major depressive disorder is known to affect decision making,[22] depression levels were scored with the Beck Depression Inventory-II to enable the correction of IGT scores.[23]

Working memory

Working memory function is necessary for normal IGT performance,[24] and reduced working memory performance

has been reported in chronic pain samples.[25] Thus, all subjects completed the Letter–Number Sequencing subtest of the Wechsler Adult Intelligence Scale III, a standard two-back test, and a visual version of the Paced Auditory Serial Addition Test.[26] These three tasks cover various aspects of working memory, ranging from simple storage of information in working memory, to manipulation of the stored information.

Hardware

For the autonomic measurements, all data were collected using Chart (version 5.5; ADInstruments, Dunedin, New Zealand) and sampled at 1 kHz. The computer was fed data from PowerLab 16/30 (ADInstruments), which got user input data and card information data via a serial output/parallel input cable (Leteng AS, Oslo, Norway). The SCR was measured with finger electrodes with a dedicated preamplifier (MLT116F and ML135; ADInstruments). Respiration (Thermistor; Sleepmate® Technologies, Glen Burnie, MD, USA) and one-lead ECG (lead II) were also measured. Continuous finger blood pressure was measured (Finometer® PRO, internal sampling at 200 Hz; Finapres Medical Systems BV, Amsterdam, the Netherlands). Recordings of blood pressure and SCR were done on the left (nonmoving) hand to reduce motion artifacts.

Image acquisition

Scanning was performed on a 3T Siemens Trio scanner with a 12-channel Head Matrix Coil (Siemens AG, Munich, Bavaria, Germany). Foam pads were used to minimize head motion. One T1-weighted three-dimensional volume measurement was acquired (repetition time [TR] =2,300 ms; echo time [TE] =2.88 ms; inversion time [TI] =900 ms; flip angle =9°; field of view [FOV] =526; slices =160; slice thickness =1.2 mm; in-plane resolution of 1.0 mm × 1.0 mm). No morphological abnormalities were revealed in any of the participants.

Analysis

IGT measurements

The IGT score was calculated as the number of advantageous (cards chosen from decks C and D) minus disadvantageous choices (cards chosen from decks A and B).

Patients with chronic pain have been shown to have reduced persistence during IGT performance (ie, they switch more often between the four decks of cards) than controls.[2,4] IGT switching was calculated as the frequency at which a subject switched from drawing from an advantageous or disadvantageous deck choice, to drawing from the other type of deck choice. For example, "A, A" and "A, B" were not counted as a switch, but "A, C" and "A, D" were counted as a switch.

For IGT score and switching, total score and total switching was calculated for the whole test (cards 1 to 100). Additionally, score and switching was calculated for the learning phase of the test (cards 1 to 40) and the performance phase of the test (cards 41 to 100), as the processes underlying decision making have been shown to differ in the first 40 versus the last 60 cards in controls[27] and in patients with chronic pain.[2]

Event-related autonomic analysis

Previous research on anticipatory SCR during the IGT has used a variety of methods for calculating the SCR.[28–31] We measured both anticipatory responses (5–0 seconds prior to making a choice) and feedback responses (0–5 seconds after making a choice) for SCR. SCRs were calculated in a manner similar to that reported by Bechara et al[32] (ie, the integral of the detrended skin conductance level curve, or the area under the curve, was obtained, with the skin conductance level recorded at the beginning of the integral serving as the baseline).

We used the same method to calculate the integral of systolic blood pressure and heart RR intervals in the 5 seconds prior to making a choice and after making a choice.

For the analysis of blood pressure levels, the delay from true aortic blood pressure to the pulse signals measured in the hand was assumed at a fixed 250 ms delay. Automatic calibration of the blood pressure monitoring equipment and ectopic heart beats were identified by manual inspection of the data, and any RR or blood pressure intervals that included such events were excluded from the analysis.

Postchoice SCRs were analyzed to assess whether SCR generation following punishment or reward was similar in the control and patient groups. For this analysis, SCRs after making a choice were grouped based on whether the card actually punished the subject or not (50% of cards in decks A and C and 10% of cards in decks B and D punished the subject). The integral was analyzed in the 5-second period after making a choice; otherwise, they were similar to anticipatory SCR calculations.

Analyses at the event level (ie, integrals for a period prior to making a card selection for a given subject) and HR variability analyses were done in Chart 7.0 (ADInstruments).

Cardiac autonomic regulation

Analysis of normalized low frequency (LF) power (0.04–0.15 Hz ms^2), normalized high frequency (HF) power (0.15–0.4 Hz ms^2), and the LF to HF ratio (LF/HF) were performed in the frequency domain (LabChart 7.0; ADInstruments)

(Welch window, 1,024 data points, and segment overlap, 50%). The maximal frequency was set to 0.5 Hz.

Artifacts were excluded from the analyses, and RR intervals were estimated from the intervals noted before and after the ectopic heartbeats occurred. The recordings were inspected manually and corrected when necessary.

HR, HR variability, and blood pressure were calculated as the average for the 5-minute resting period before the start of the IGT (for example, "Baseline HR"), for the duration of the IGT (for example, "Activity HR"), and for each group's mean absolute change from Baseline to Activity across all cardiac autonomic measures (for example, "ΔHR").

MRI analysis

The volumetric assessment of subjects' T1-weighted brain MRI volumes was performed using NeuroQuant software (CorTechs Labs, Inc., La Jolla, CA, USA). This software enables automated analysis of T1-weighted brain volumes and provides a morphology report on the volume of the total cortical gray matter, as well as of the ventricles, brainstem, cerebellum, and some subcortical structures (hippocampus, amygdala, caudate, putamen, pallidum, thalamus, nucleus accumbens, and brainstem), which was corrected for intracranial volume.[33] For each structure, the volumes of the structures in the right and left hemisphere were combined. The volumes of the structures of interest (total cortical gray matter, amygdala, hippocampus, brainstem, and nucleus accumbens) were compared between groups and correlated with total IGT scores, pain, and autonomic data.

Statistical analysis

PASW Statistics 18.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

Two-tailed, unpaired Student's *t*-tests were used to identify the differences between groups on demographic, depression level, pain, and neuropsychological measures, as well as on IGT scores, brain structure volumes, and autonomic activity. Cohen's *d* was calculated and classified as small (d=0.15–0.40), medium (d=0.40–0.75), and large (d>0.75).

Paired Student's *t*-tests were used for all within-groups analyses of event-related or cardiac autonomic measures. Spearman's rank–order correlation was performed to assess the relationships between the IGT total score, the IGT total switching, pain level (evaluated using the BPI) before the IGT, and event-related autonomic data, as well as between the IGT total score and brain structure volumes. Possible confounding effects of depression levels on the IGT score were investigated with Spearman's partial correlation. The significance threshold was set to $P \leq 0.05$ (two-tailed) for both Student's *t*-tests and Spearman's correlations.

A mixed-design analysis of variance (ANOVA) ("split-plot ANOVA") was used to investigate the interactions between the three autonomic measures related to choosing from the advantageous versus disadvantageous decks and subject group (chronic pain patients versus HCs). Outliers were identified as studentized residuals ≥±3 standard deviations. Simple main effects were investigated where significant interactions were found. Effect sizes were calculated as partial eta squared (ηp^2), and they were classified as small (>0.01), medium (>0.06), or large (>0.14).

All data are given as the mean ± standard deviation.

Results

Participants

As shown in Table 1, there were no differences in age, length of education, or the sex distribution between the patients and control groups. The patient group scored significantly higher on both the average pain for the last 24 hours and average pain at the time of testing than did the controls. (Table 1).

There were no significant differences on the working memory tests (Table 1).

Iowa gambling task behavior

As shown in Table 2, the IGT total score was not different between the patients and controls. There were also no differences in the IGT score for the learning or performance phases of the IGT between the groups (Table 2).

During the entire IGT period, there was a trend toward increased switching in the patient group compared to the

Table 1 Demographic, clinical, and working memory measures in patients with chronic pain and matched healthy controls

	PCP	HCs	*P*	*d*
Education	4.67±2.4	5.26±2.7	0.484	0.23
Sex	18 (3 male)	19 (2 male)	0.597	0.18
Age	38.5±7.1	38.4±7.0	0.955	0.02
Pain NRS (prior 24 hour average)	6±1.64	1±1.29	0.000*	3.39
Pain NRS (at testing)	4.11±1.49	0.05±0.23	0.000*	3.86
Depression level	14.2±8.6	1.9±2.4	0.000*	1.96
Working memory measures				
Letter–number sequencing	9.2±2.2	9.9±2.0	0.313	0.34
2-back score	47.9±3.8	50±2.9	0.059	0.64
PVSAT score	99.1±4.9	100.1±3.8	0.492	0.23

Notes: Depression level was determined with the Beck Depression Inventory II. Numbers are the numbers are the mean values ± standard deviation within groups of PCP with a pain self-rating of ≥4/10 for ≥6 months and in their healthy controls. Statistical differences between groups were explored with a two-tailed, two-sample Student's *t*-test. Significance on the Student's *t*-test is marked with * for $P \leq 0.05$. Effect size is calculated as Cohen's *d*.

Abbreviations: PCP, patients with chronic pain; HCs, healthy controls; NRS, Numerical Rating Scale; PVSAT; Paced Visual Serial Addition Test.

Table 2 IGT total scores and switching in the learning phase (1–40 cards) and performance phase (41–100 cards), and brain volumes in PCP and matched HCs

	PCP	HCs	*P*	*d*
IGT score	5.2±28.6	5.7±31.0	0.959	0.02
IGT score, learning phase	−7.4±10.7	−9.2±13.3	0.665	0.14
IGT score, performance phase	−0.3±26.9	1.6±27.4	0.830	0.07
Switch total	0.35±0.15	0.26±0.15	0.080	0.59
Switch, learning phase	−6.13±0.16	−6.17±0.17	0.472	0.24
Switch, performance phase	−6.17±0.18	−6.29±0.16	0.031*	0.74
Brain volume, % of ICV				
Total cortical gray matter	32.75±2.81	33.93±2.47	0.209	0.44
Hippocampus	0.53±0.04	0.54±0.05	0.872	0.06
Amygdala	0.25±0.02	0.25±0.02	0.556	0.20
Nucleus accumbens	0.07±0.01	0.08±0.01	0.034*	0.75
Brainstem	1.62±0.15	1.57±0.11	0.293	0.36

Notes: Numbers are the mean values ± standard deviation within groups of PCP with a pain self-rating of ≥4/10 for ≥6 months and in their healthy controls Cerebral volume is the combined volume of the two hemispheres in the % of ICV. Statistical differences between groups were explored with a two-tailed, two-sample Student's *t*-test. Significance of the Student's *t*-test is marked with * for $P \leq 0.05$. Effect size is calculated as Cohen's *d*.
Abbreviations: IGT, Iowa gambling task; PCP, patients with chronic pain; HCs, healthy controls; ICV, intracranial volume.

control group. In the performance phase of the IGT, the chronic pain patients switched significantly more often than did the HCs (Table 2).

There were no significant correlations between the different IGT scores and pain level before the test in any of the groups (Table 3). These correlations remained nonsignificant after adjusting for depression scores (results not shown).

Autonomic activation during decision making

SCR

A mixed-design ANOVA (group [chronic pain patient or control] × deck [advantageous or disadvantageous]) on the SCR before choices showed a weak, nonsignificant main effect for group, no main effect for deck, but a significant group × deck interaction with a large effect size (Table 4 and Figure 4). There was one outlier in the patient group, but the group × deck interaction remained when excluding the outlier (F[1, 33]=5.227, P=0.029, η_p^2=0.137).

The SCRs before choosing from advantageous and disadvantageous decks were significantly different, with a large effect size observed within the control group (Table 4 and Figure 5). In the patient group, there was no difference in SCRs before choosing from advantageous and disadvantageous decks (Table 5 and Figure 4). For disadvantageous decks, the SCR was significantly higher in controls than in patients with a large effect size (F[1, 34]=6.581, P=0.015, η_p^2=0.162). There was no such group difference in SCR before the advantageous deck choices (Figure 2).

For HCs, there was a significant correlation between the SCR before the disadvantageous deck choices and the IGT total score (Spearman's rho =0.568, P=0.011). This was not found in the patient group. Rather, the SCRs before the disadvantageous and advantageous deck choices were made were correlated with each other in the chronic pain group (Spearman's rho =0.539, P=0.026). Except for the aforementioned results, no correlations were found in the chronic pain group between SCR and IGT behavior, or between SCR and pain level (Table 3). None of these correlations changed in significance after adjusting for depression level (results not shown).

There were no differences in the postchoice SCRs between receiving a punishment and a no-punishment card within the patient or control groups, or between the groups (Table 5).

Table 3 Correlations between pain level, the different IGT scores, and SCR before and during the IGT in PCP and matched HCs

	PCP					HCs				
	Pain level	IGT score	IGT switching	SCR Before advantageous choices	SCR Before disadvantageous choices	Pain level	IGT score	IGT switching	SCR Before advantageous choices	SCR Before disadvantageous choices
Pain level	1*					1*				
IGT score	−0.388	1*				−0.151	1*			
IGT switching	0.262	−0.009	1*			0.172	−0.277	1*		
SCR before advantageous choices	−0.02	0.103	0.091	1*		0.172	0.184	−0.119	1*	
SCR before disadvantageous choices	0.044	0.063	0.203	0.539*	1*	0.215	0.568*	0.151	0.253	1*

Notes: Numbers are Spearman's rho in PCP with a pain self-rating of ≥4/10 for ≥6 months and in their healthy controls. Statistical differences within groups were explored with a two-tailed Spearman's rank–order correlation. Significance of the Student's *t*-test is marked with * for $P \leq 0.05$.
Abbreviations: IGT, Iowa gambling task; SCR, skin conductance response; PCP, patients with chronic pain; HCs, healthy controls.

Table 4 Results of the mixed ANOVA (group × choice type) analyses of the autonomic SCR, heart rate (RR), and BP before choosing from the disadvantageous or the advantageous decks in PCP and matched HCs

	F	*P*	η_p^2
SCR			
Group	*F*(1,34)=2.869	0.099	0.078
Deck	*F*(1,34)=1.005	0.323	0.029
Group × deck	*F*(1,34)=6.195	0.018*	0.154
RR			
Group	*F*(1,32)=1.917	0.176	0.057
Deck	*F*(1,32)=2.755	0.107	0.079
Group × deck	*F*(1,32)=0.542	0.467	0.017
BP			
Group	*F*(1,32)=1.753	0.802	0.002
Deck	*F*(1,32)=1.916	0.176	0.056
Group × deck	*F*(1,32)=1.382	0.249	0.041
Simple main effects			
SCR			
HC group	*F*(1,18)=5.349	0.033*	0.229
PCP group	*F*(1,16)=1.363	0.260	0.079
Disadvantageous decks	*F*(1,34)=6.581	0.015*	0.162
Advantageous decks	*F*(1,34)=0.374	0.545	0.011

Notes: Relationship between group status and anticipatory autonomic activation among PCP with a pain self-rating of ≥4/10 for ≥6 months and in their healthy controls. The mixed ANOVA is by group (PCP or HCs) × deck type (advantageous or disadvantageous) for each of the three autonomic measures used in the study (SCR, RR, and BP). One patient was excluded from all SCR analyses due to technical problems with the recordings. Two controls were excluded from all BP and heart rate analyses because of excessive amount of extrasystoles. Measures are integrals of autonomic measures in the 5 seconds preceding the subject's choice of card, which were either classified as advantageous or disadvantageous. Significance of the Student's *t*-test is marked with * for $P \geq 0.05$.
Abbreviations: ANOVA, analysis of variance; SCR, skin conductance response; RR, R wave to R wave interval; BP, systolic blood pressure; PCP, patients with chronic pain; HCs, healthy controls.

RR intervals

A mixed-design ANOVA on the RR integral before choices (group [chronic pain patient or control] × deck [advantageous or disadvantageous]) showed no main effect for group, deck, or the group × deck interaction (Table 4). There were no outliers in any group.

Blood pressure

The mixed-design ANOVA on the blood pressure integral before choices (group [chronic pain patient or control] × deck [advantageous or disadvantageous]) showed no main effect for group, deck, or the group × deck interaction (Table 4). There was one outlier in the control group, but removing this did not alter the results.

Cardiac autonomic regulation

The Student's *t*-tests showed no significant group differences for the Baseline HR or Baseline HR variability measures (LF/HF, LF, or HF), or the Baseline blood pressure between the patient and the control groups, and all of the effect sizes were small. There was also no significant group difference for the change from Baseline to Activity on any of the cardiac autonomic measures. However, there were medium effect sizes for the group differences on ΔHR, ΔLF/HF, and ΔHF (Table 6).

Brain structure volumes

As shown in Table 2, the nucleus accumbens volume was significantly reduced in the chronic pain group. For the other

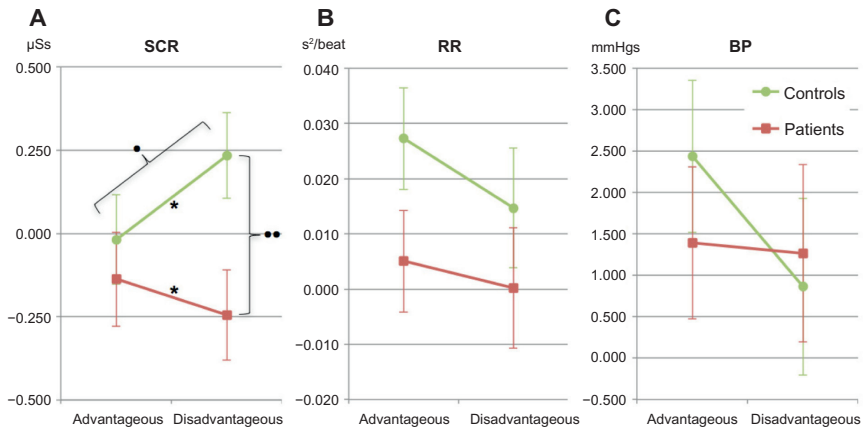

Figure 4 Autonomic measures from the anticipatory phase of the Iowa gambling task before drawing from either the advantageous or disadvantageous decks.
Notes: The autonomic measures were SCR (**A**), heart RR (**B**), and BP (**C**). The Y-axes denote the area under the respective measurement curves from 5.0 seconds before a card was picked from a deck. Points are split into PCP (red lines and squares) and their HCs (green lines and circles). The bars mark standard errors. •Significant within-group difference, $P<0.05$; ••significant between-group difference, $P<0.05$; *significant interactions between groups and card deck type, $P<0.05$.
Abbreviations: SCR, skin conductance response; RR, R wave to R wave intervals; BP, systolic blood pressure; PCP, patients with chronic pain; HCs, healthy controls.

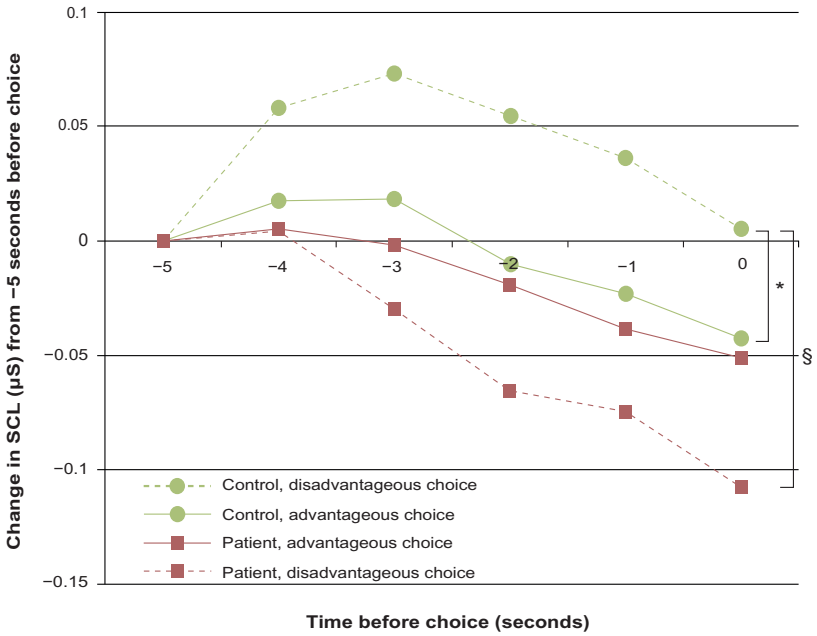

Figure 5 SCR during the Iowa gambling task for pain patients and controls.
Notes: The relative changes in SCL for the 5 seconds prior to making advantageous choices (continuous line) or disadvantageous choices (dashed line) for PCP (red line) and HCs (green line), for illustrative purposes. Curves of significantly different SCRs are marked with * or §. The SCR was calculated as the area under a continuous SCL curve, with baseline as the SCL 5 seconds prior to making a choice. Simple main effects in a mixed design ANOVA showed that the SCR was significantly higher in HCs than in PCP for disadvantageous (§), but not advantageous choices. Only within the HC group was there a significant difference between the SCRs prior to making advantageous and disadvantageous choices (*).
Abbreviations: SCL, skin conductance level; SCR, skin conductance response; PCP, patients with chronic pain; HCs, healthy controls; ANOVA, analysis of variance.

Table 5 SCR before disadvantageous and advantageous choices, and after receiving reward and punishment cards in the IGT in PCP and matched HCs

	PCP	HCs	Between groups	
			P	*d*
SCR before choice				
Advantageous	−0.14±0.67	−0.02±0.49	0.545	0.2
Disadvantageous	−0.24±0.68	0.23±0.42	0.015*	0.86
Within groups				
P	0.260	0.033*		
d	0.16	0.55		
SCR after choice				
No punishment	0.24±0.79	0.08±0.50	0.467	0.25
Punishment	0.39±0.78	0.03±0.73	0.166	0.47
Within groups				
P	0.224	0.742		
d	0.19	0.08		

Notes: Numbers are mean values within groups ± standard deviation in PCP with a pain self-rating of ≥4/10 for ≥6 months and in their healthy controls. Statistical differences between and within groups were explored with a two-tailed, two-sample Student's *t*-test. Significance of the Student's *t*-test is marked with * for $P \leq 0.05$. Effect size is calculated as Cohen's *d*.
Abbreviations: SCR, skin conductance response; IGT, Iowa gambling task; PCP, patients with chronic pain; HCs, healthy controls.

four brain structures, no significant group differences were found, but a medium effect size was present for the reduced total cortical gray matter volume in the chronic pain patients (Table 2).

The chronic pain group had a significantly positive correlation between total cortical gray matter volume and IGT total score (Table 7). Moreover, there was a negative correlation between IGT total switching and amygdala volume in the chronic pain patients (Table 7). No such correlations with IGT behavior were found in the control group. All correlations remained significant after adjusting for depression levels (results not shown).

Discussion

To our knowledge, this is the first study to show that patients with chronic pain lack SCR before making disadvantageous decisions. In line with our hypothesis, the patient group was impaired at generating SCRs before choosing from disadvantageous card decks in the IGT. The other main finding in this study was that the decision-making ability in the chronic

Table 6 Cardiac autonomic regulation during the IGT and rest in PCP and matched HCs

	PCP		HCs		Between-groups tests			
	Baseline	IGT	Baseline	IGT	Baseline		ΔIGT	
					P	*d*	*P*	*d*
Blood pressure	126±18.6	123±13.8	125±17.1	123±12.7	0.617	0.17	0.892	0.05
Heart rate	73.5±8.4	75.1±13.6	72.4±8.1	75.2±13.6	0.466	0.25	0.161	0.48
Low-to-high frequency power ratio	2.41±1.51	2.66±3.49	1.65±1.16	2.55±3.39	0.310	0.35	0.135	0.52
Normalized low frequency power	62.1±16.1	61±13.8	54.8±14.6	57.8±17.1	0.583	0.19	0.294	0.36
Normalized high frequency power	33.2±13.99	35.22±12.9	41.86±14.18	38.46±16.4	0.516	0.22	0.145	0.50

Notes: Numbers are mean values within groups ± standard deviation in PCP with a pain self-rating of ≥4/10 for ≥6 months and in their healthy controls. Measures are calculated for the baseline period (resting period prior to task) and during the IGT. Between-groups tests were performed on the baseline data and on the group-averaged ΔIGT. Statistical differences between baseline and IGT within groups were explored with a two-tailed, two-sample Student's *t*-test. Significance on the Student's *t*-test is marked with * for $P \leq 0.05$. The effect size is calculated as Cohen's *d*.

Abbreviations: IGT, Iowa gambling task; PCP, patients with chronic pain; HCs, healthy controls; ΔIGT, increase from baseline to IGT.

pain patient group correlated positively with total cortical gray matter volume.

As predicted by the somatic marker hypothesis, a specific and significant increase in anticipatory SCR appeared when controls chose from the disadvantageous decks, and this correlated positively with the total IGT scores. This finding is in line with those from previous studies that showed a positive relationship between IGT performance and strength of the anticipatory SCR in healthy subjects.[34–36] Similar findings were not present in the patient group.

The lack of the anticipatory SCRs in the patients with pain was not caused by a general impairment in SCR generation. There were no group differences in terms of the autonomic measures that indicated the presence of autonomic dysfunction in the patient group. For instance, despite abnormal anticipatory SCRs before the choices were made, the patient group exhibited similar SCRs after the choices were made as the controls when receiving punishment or reward. These results suggest that the chronic pain group was able to trigger somatic responses due to innate or learned stimuli, but they were impaired in the somatic marker structures necessary for sensing (sensory brain stem nuclei), processing (insula, somatosensory cortices, posterior cingulate cortex, and precuneus), or triggering (ventromedial prefrontal cortex, hippocampus, and dorsolateral prefrontal cortex) the somatic states during the pondering of choices (Figure 2).[37] Figure 2 illustrates the possible abnormal pathways, shown as dotted lines, in the chronic pain group that could lead to the observed lack of SCR generation before making disadvantageous choices. The figure is based on the model by Bechara,[7] as described in the Introduction.

Patients and controls also displayed different behavior during the IGT. The patient group switched significantly more between advantageous and disadvantageous decks compared to the controls in the performance phase of the

Table 7 Correlations between IGT behavior and autonomic measures and brain volumes in PCP and matched HCs

	PCP		HCs	
	IGT score	Switching	IGT score	Switching
Autonomic activity before IGT choices				
SCR advantageous	0.103	0.091	0.184	–0.119
SCR disadvantageous	0.063	0.203	0.568*	0.151
RR advantageous	0.06	0.289	0.083	–0.044
RR disadvantageous	–0.027	0.483	0.298	0.132
BP advantageous	–0.370	0.250	0.280	–0.402
BP disadvantageous	–0.194	0.417	–0.184	–0.338
Combined cerebral volume in % ICV				
Total cortical gray matter	0.691*	–0.182	0.03	–0.042
Hippocampus	0.436	–0.319	0.129	–0.426
Amygdala	0.156	–0.701*	0.011	0.061
Nucleus accumbens	0.315	–0.152	0.108	–0.068
Brainstem	0.068	0.130	0.099	–0.355

Notes: Numbers are Spearman's rho in PCP with a pain self-rating of ≥4/10 for ≥6 months and in their healthy controls. Cerebral volume is the combined volume of the two hemispheres in % of ICV. Statistical differences within groups were explored with a two-tailed Spearman's rank–order correlation. Significance on Student's *t*-test is marked with * for $P \leq 0.05$.

Abbreviations: IGT, Iowa gambling task; PCP, patients with chronic pain; HCs, healthy controls; SCR, skin conductance response; RR, R wave to R wave interval; BP, systolic blood pressure; ICV, intracranial volume.

test. This is in line with results from previous studies that reported a difference in switching measures among patients.[2,4] The current study did not find a significant group difference in the IGT total score between patients and controls. While this is in line with the findings from the largest study conducted thus far on the IGT in chronic pain patients,[3] the opposite has been reported in two other studies.[2,4] Compared with the reports on the IGT studies that exhibited group differences,[2,4] our control group appears to have performed subpar, but based on a review of previous IGT studies, the HCs scored within the range of the control groups.[38] Furthermore, the mean score of the current study's chronic pain group lies between the two chronic pain subgroups of the only past chronic pain study that reported mean scores of the IGT, albeit graphically.[4] The current study thus suggests that increased switching and SCR deficits are more sensitive to chronic pain-induced impairments in decision making than in the total IGT score. The lack of standardized scores for the IGT and the general lack of mean score reporting complicate the interpretation and comparison between publications.

Moreover, normal IGT-scores have been seen in subjects without SCRs,[39] as other body signals can help construct somatic markers in the brain.[7] Thus, it is possible that other bodily signals guided the patient group's decisions. However, we failed to find any signs of increased reliance on other somatic states (ie, cardiac autonomic measures) in the patient group. Still, decision making in chronic pain patients can be supported by signaling pathways that were not monitored (for example, proprioceptive, vagal, or humoral pathways),[7] or by the as–if loop between the effector structures and sensory structures that bypass the body altogether (Figure 2). Another possibility is that the chronic pain group draws on cognitive resources for decision making, as suggested by the association between cortical volumes and IGT scores in the chronic pain patients.

To our knowledge, this is the first study to show that performance on the IGT correlates with changes in the cerebral morphology of chronic pain patients. The present study demonstrated a strong positive correlation between the IGT total score and cortical gray matter volume in the patient group. Such a correlation was not found for the subcortical structures or the brain stem. Previous clinical studies have showed a relationship between IGT performance and cortical thickness of the ventromedial prefrontal cortex in patient groups with Parkinson's disease and alcoholism,[40,41] but not in controls.[42] The current results could suggest that the IGT is sensitive to cortical thinning in chronic pain patients. The location of such thinning cannot be derived from the current results, but all the cortical areas involved in decision making are known to be affected in chronic pain patients.[10]

The present findings indicate that decision-making deficits in chronic pain patients are dependent on cortical volume rather than on reductions in subcortical structures, including the nucleus accumbens. The latter structure is suggested in the somatic marker hypothesis to be involved both in registering the somatic states and as an effector structure (Figure 2).[37,43] Although this study demonstrated a reduction in nucleus accumbens volume in the patient group, which was in line with previous research,[44] no correlation between the size of the nucleus accumbens and the IGT total score in the patient group was found. Furthermore, the amygdala, brainstem, and hippocampus are important for the generation of anticipatory SCRs and decision making (Figure 2). Although size alone does not determine function, their normal volume in the patient group suggests the observed anticipatory SCR impairment in this group has its neurophysiological correlates elsewhere.

Different mechanisms within the framework of the somatic marker hypothesis could explain the neurophysiology behind the altered decision making in chronic pain patients (see Figures 1 and 2). One possibility is that the processing structures (for example, the insula, cingulate cortex, or somatosensory cortices) interpret pain as part of the somatic state. Chronic pain may create a backdrop of noise that increases the time necessary for a somatic marker to form. There is some support for this speculation in the current data, as there is a weak, nonsignificant correlation between IGT score and pain rating immediately before testing (Table 2). A not mutually exclusive possibility is that the sensory structures or the aforementioned processing structures are affected by the abnormal amount of pain signals in chronic pain patients, making them less sensitive to normal interoceptive signals that contribute to the formation of the somatic markers. This explanation draws some support from the correlation between the IGT total score and cortical gray matter volume, assuming reduced cortical volume is indicative of reduced sensory functions.

Limitations

Unlike other decision-making tests such as the Cambridge Gambling Task, the IGT is reliant on working memory.[45] Differences in cognitive abilities did not seem to contribute to the observed difference in IGT behavior between the chronic pain patients and controls since there were no correlations (data not shown) between the working memory and the different IGT scores in any of the groups.

The IGT procedure in the current study closely resembles that of the original computerized IGT,[16] with a few exceptions previously described. Notably, the positions of

all four decks were randomized on screen from subject to subject, as opposed to the original computerized IGT, where placements of the advantageous and disadvantageous decks are standardized.[16] Studies have shown that decision making is affected by the placement of the options.[17,46,47] Randomization of placement is a simple tool that can be used to eliminate any possible confounding effect of placement in the original IGT.[18]

The number of participants was relatively low, but still higher than in the other studies conducted assessing the IGT in chronic pain groups.[2,4] Another limitation is the lack of a common pain etiology in the patient group. In general, the use of heterogeneous groups makes a study more vulnerable to type 2 errors, and there is indication that patients with different pain etiologies may have different changes in brain morphology.[48] A recent meta-analysis of studies of changes in brain morphology in chronic pain patients did, however, find significant changes compared to controls.[10] This indicates that, although pain etiology-specific differences may be found in brain morphology, different etiologies do have important common findings. The effect sizes of the reported significant findings in the current study do not indicate a type 2 error. Findings in a heterogeneous pain group have stronger external validity than do more homogeneous studies, as chronic pain patients are a mixed-etiology group in real-life settings. A finding in a mixed-etiology pain group is also less likely to be dependent on a cause underlying the pain per se, and increases the probability that the findings are related to chronic pain.

Two-tailed statistical tests were chosen due to the low number of participants in the current study to avoid a type 1 error. While this method increases the chance of a type 2 error, it ensures that any results from the current study are worth further investigation. To avoid too high a risk of a type 2 error, correction for multiple comparisons was not applied.

Conclusion

The current study shows that chronic pain patients have impaired generation of anticipatory SCRs before making disadvantageous decisions, possibly caused by the interpretation of pain as part of the somatic state, or by a reduced ability to process the somatic state due to chronic pain. It can be hypothesized that the patient group compensated for the reduction in anticipatory signals by becoming more dependent on cortical resources in their decision making, and they demonstrated increased switching between advantageous and disadvantageous decks during the IGT.

In summary, the presence of chronic pain was found to affect fundamental aspects of decision making, which may have significant implications for everyday functioning and choices in this patient group.

Acknowledgment

We would like to thank Professor Trond Sand, Department of Neurophysiology, St Olav's University Hospital, for letting us use his facilities.

Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL ARTICLE

Reward responsiveness in patients with chronic pain

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Funding sources
Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU).

Conflicts of interest
None declared.

Accepted for publication
19 January 2015

doi:10.1002/ejp.687

Abstract

Background: It is proposed that changes in reward processing in the brain are involved in the pathophysiology of pain based on experimental studies. The first aim of the present study was to investigate if reward drive and/or reward responsiveness was altered in patients with chronic pain (PCP) compared to controls matched for education, age and sex. The second aim was to investigate the relationship between reward processing and nucleus accumbens volume in PCP and controls. Nucleus accumbens is central in reward processing and its structure has been shown to be affected by chronic pain conditions in previous studies.
Methods: Reward drive and responsiveness were assessed with the Behavioral Inhibition Scale/Behavioral Activation Scale, and nucleus accumbens volumes obtained from T1-weighted brain MRIs obtained at 3T in 19 PCP of heterogeneous aetiologies and 20 age-, sex- and education-matched healthy controls. Anhedonia was assessed with Beck's Depression Inventory II.
Results: The PCP group had significantly reduced scores on the reward responsiveness, but not reward drive. There was a trend towards smaller nucleus accumbens volume in the PCP compared to control group. There was a significant positive partial correlation between reward responsiveness and nucleus accumbens volume in the PCP group adjusted for anhedonia, which was significantly different from the same relationship in the control group.
Conclusions: Reward responsiveness is reduced in chronic pain patients of heterogeneous aetiology, and this reduction was associated with nucleus accumbens volume. Reduced reward responsiveness could be a marker of chronic pain vulnerability, and may indicate reduced opioid function.

1. Introduction

Pain and reward processing interact in the brain, and it is proposed that changes in the function and structure of the brain's reward network are involved in the pathophysiology of chronic pain (Becker et al., 2012; Denk et al., 2014). In animal models, chronic pain alters the motivation to obtain reward (Cahill et al., 2013; Wade et al., 2013) and leads to preference of larger infrequent rewards (Pais-Vieira et al., 2009). In experimental acute pain in humans, motivation to obtain reward was shown to be increased without affecting the self-reported hedonic response to reward (Gandhi et al., 2013). Furthermore, an individual's responsiveness to reward has been demonstrated to correlate with magnitude of analgesia during acute experimental pain in healthy controls (Wanigasekera

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What's already known about this topic?
- Nucleus accumbens is involved in reward processing.
- Reward drive and responsiveness is altered in experimental pain.
- Chronic pain influences nucleus accumbens volume.

What does this study add?
- Reward responsiveness is reduced in chronic pain patients.
- Nucleus accumbens volume is positively associated with reward responsiveness in chronic pain patients.

et al., 2012). Taken together, these results suggest a role of altered motivation or drive to obtain reward and reward responsiveness in pain, which may also be present in patients with chronic pain (PCP). Whether PCP have altered reward drive and/or responsiveness remains to be ascertained. An individual's drive to obtain reward and hedonic response to the presence or anticipation of reward can be measured with Reward Drive and Reward Responsiveness, respectively (Gray, 1981; Carver and White, 1994). Both scales correlate with reward-maximizing behaviour in healthy controls, although more strongly reward responsiveness (Scheres and Sanfey, 2006).

In the brain, reward processing is closely linked to the nucleus accumbens (Becerra et al., 2001; Salamone and Correa, 2012). Ventral striatum grey matter density has been shown to correlate with both a combination score of personality traits that included reward drive and reward responsiveness and degree of placebo analgesia in healthy controls (Schweinhardt et al., 2009). Furthermore, a systematic meta-analysis of brain structure in PCP demonstrated reduced volume in the area of the nucleus accumbens (Smallwood et al., 2013), and nucleus accumbens grey matter density has been shown to decrease after the onset of chronic back pain (Baliki et al., 2012). The biological mechanisms underlying the observed volume change are unknown, but chronic pain induced changes in several neurotransmitter systems (D'Angio et al., 1987; Li et al., 2001; Chang et al., 2014; Schwartz et al., 2014), and connectivity with other basal ganglia as well as cortical regions (Mansour et al., 2013; Chang et al., 2014) may play a role. The observed structural changes in the nucleus accumbens may in turn be linked to the proposed changes in reward processing in pain conditions.

To our knowledge, reward drive, reward responsiveness and the relationship between them and nucleus accumbens volume have not been investigated in PCP. The first aim of the present study was to investigate if reward drive and/or reward responsiveness are reduced in PCP compared to controls matched for education, age and sex. The second aim was to investigate the relationship between reward processing and nucleus accumbens volume in PCP and controls. Since anhedonia is common in PCP and interacts with both reward responsiveness (Beevers and Meyer, 2002) and nucleus accumbens volume (Harvey et al., 2007; Wacker et al., 2010), correlation analyses were corrected for anhedonia.

2. Methods

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Sciences Data Service, and performed in accordance with their requirements and the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.1 Materials

Twenty patients (16 females) were recruited from a university hospital pain clinic, and 20 age-, education- and sex-matched healthy controls (HC) (18 females) from the local community. Exclusion criteria were left handedness, neurological disease, psychiatric disease (not including mild or moderate depression), known traumatic brain injury and high analgesics consumption (>180 mg codeine or equivalent per 24 h, 24 h continuous benzodiazepine treatment, or using carisoprodol). One PCP was excluded during the study due to neurological disease discovered after inclusion. The final sample encompassed 19 PCP (16 females) and 20 HC (18 females).

2.2 Pain

Pain was assessed with a Norwegian translation of the Brief Pain Inventory (Cleeland, 1991). The questionnaire assesses pain intensity at present and the average pain intensity over the last 24 h using a numerical rating scale from 1 to 10, as well as present analgesics use. Aetiology of pain and duration of pain was calculated based on data from patient journals and classified to 1–2 years, 2–4 years, 4–6 years, 6–10 years or 10+ years by one of the authors, an experienced clinician (P.C.B.).

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2.3. Reward responsiveness

The Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS) was used to assess different aspects of reward (Carver and White, 1994) based on Gray's reinforcement theory (Gray, 1981). Reward drive was assessed with the Drive subscale, which measures the self-reported tendency to pursue reward. Reward responsiveness was assessed with the Reward Responsiveness subscale, which measures the emotional response to the presence or anticipation of rewards. The third BAS subscale Fun Seeking, a measure of impulsivity and desire for excitement linked to obtaining rewards, was not included, as this measure has not been suggested to be involved in pain pathology.

2.4 Anhedonia

Anhedonia was assessed with the Beck Depression Inventory II (BDI) (Beck et al., 1996). A subscale for anhedonia, BDI-Anhedonic, was calculated from BDI (Leventhal et al., 2006).

2.5 Magnetic resonance imaging

Scanning was performed on a 3T Siemens Trio scanner with a 12-channel Head Matrix Coil (Siemens AG, Erlangen, Germany). Foam pads were used to minimize head motion. One T1-weighted 3D volume was acquired (TR = 2300 ms, TE = 2.88 ms, TI = 900 ms, flip angle = 9°, FOV = 526, slices 160, slice thickness = 1.2 mm, in-plane resolution of 1.0 × 1.0 mm). No morphological abnormalities were revealed by inspection in any of the included participants.

The T1-weighted 3D images were analysed in NeuroQuant (CorTechs Labs, Inc., CA, USA) to quantify the volume of nucleus accumbens corrected for ICV (Brewer et al., 2009). NeuroQuant is an FDA 510k-approved fully automated morphometric method for clinical use where segmentation of subcortical structures is atlas-based using both intensity and location for determining structure.

2.6 Statistical analyses

Normality was tested for all variables. For variables with a normal distribution within the group, statistical differences between the group means were tested with two-tailed independent group Student's *t*-test (nucleus accumbens volume). For variables with a non-normal distribution in both groups, statistical differences between groups were tested with two-tailed Mann–Whitney *U*-tests (pain measures, reward responsiveness, drive and anhedonia). Only BAS measures with significant group differences were used in further analyses.

Within-group partial correlations were tested with two-tailed Spearman's Rho, adjusted for anhedonia. A non-parametric test for correlation was used, since the variables except nucleus accumbens volumes, were not normally distributed in at least one group. Statistical differences between the within-group correlation coefficients obtained in the PCP and HC groups, respectively, were tested with Fisher's *r*-to-*z* transformation (Myers and Sirois, 2006). Exact *p*-values are reported, and $p \leq 0.05$ was considered statistical significant. Effect sizes were calculated as $r = Z/\sqrt{N}$. Due to incomplete questionnaire responses, reward responsiveness data were excluded for two controls and anhedonia for one control. MRI data from four PCP were lost due to technical problems. These subjects were excluded on an analysis by analysis basis.

3. Results

The PCP group had significantly higher Brief Pain Inventory scores at the time of investigation ($U = 380.0$, $p < 0.001$, $r = 0.90$) and during the 24 h prior to testing ($U = 375.5$, $p < 0.001$, $r = 0.84$) (Table 1). Pain duration was from 1 to >10 years in the PCP group (number of years of chronic pain: number of patients; 1–2: 1, 2–4: 4, 4–6: 2, 6–10: 4, >10: 8). Pain was widely distributed to a number of body areas (see Fig. 1).

The majority of subjects in the PCP group reported using analgesics (regular users of paracetamol: 11;

Table 1 Pain, Behavioral Activation Scale reward responsiveness and drive scores in patients with chronic pain and healthy control groups.

	Median				
	Patients with chronic pain	Healthy controls	*U*	*p*	*r*
Pain level last 24 h	6.00	0.50	375.5	<0.0005*	0.84
BAS-Reward Responsiveness	15.00	18.00	80.0	0.005*	−0.46
BAS-Reward Drive	10.00	9.50	174.5	0.916	0.02

Numbers are medians within groups in chronic pain patients with pain self-rating of ≥4 out of 10 for ≥6 months and in their matched healthy controls. Statistical differences between groups were explored with a two-tailed Mann–Whitney *U*-test. Effect size *r* is calculated as $r = Z/\sqrt{N}$. BAS, Behavioral Activation Scale.
*$p < 0.05$.

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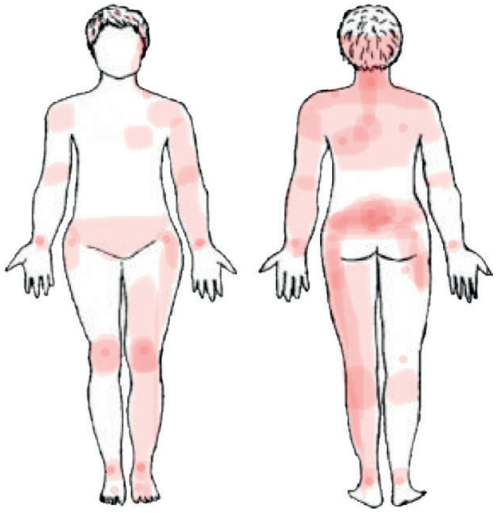

Figure 1 Subjective location of pain reported by patients, in the Brief Pain Inventory questionnaire. Red areas indicate areas where patients felt pain, and dots indicate areas where patients felt highest levels of pain. The colouring was made translucent to show increased intensity in areas where more than one patient reported pain.

Table 2 Number of chronic pain patients according to pain aetiology, pain duration and types of medication used.

Pain aetiology	
Musculoskeletal	12
Visceral	5
Idiopathic	2
Neuropathic	0
Pain duration (years)	
<2	1
2–4	4
4–6	2
6–10	4
>10	8
Analgesic users	
Paracetamol	11
Codeine	9
NSAID	8
Pregabalin	4
Amitriptyline	2
SSRI	2

Numbers are number of patients in each class. Each patient was classified according to one aetiology. Classification was performed by an experienced clinician (P.C.B.) based on patient records. SSRI, selective serotonin receptor inhibitors; NSAID, non-steroidal anti-inflammatory drugs.

codeine: 9, NSAID: 8; pregabaline: 4; amitriptyline: 2; SSRI: 2) (Table 2). Twelve in the PCP group reported using more than two types of medications.

As expected, the PCP group exhibited significantly higher anhedonia scores than controls ($U = 288.0$, $p < 0.01$, $r = 0.56$). Pain types, duration, medication and distribution in the PCP group are described in Table 2 and Fig. 1.

The PCP group had significantly lower reward responsiveness scores ($U = 80$, $p = 0.005$, $r = 0.46$) (Table 1). There was no difference between the PCP and HC groups on the reward drive scores (Table 1). A Student's *t*-test revealed a trend towards smaller nucleus accumbens volume in the PCP group compared to the HC group (PCP: 0.076 ± 0.012, controls: 0.082 ± 0.009; $p = 0.062$).

There was a significant positive partial correlation between nucleus accumbens volume and reward responsiveness scores in the PCP group when adjusting for anhedonia (rho = 0.534, $p = 0.049$) (Table 3 and Fig. 2). There were no significant correlations between nucleus accumbens volume, 24-h pain rating or duration of pain condition in the PCP group (Table 3). There was no significant correlation between nucleus accumbens volume and reward responsiveness scores in the HC group (Table 3 and Fig. 2). Statistical comparisons of the correlation coefficients for reward responsiveness scores and nucleus accumbens volumes in the PCP and HC groups demonstrated a significantly different relationship between reward responsiveness and nucleus accumbens volume in the two groups (Fisher *r*-to-*z* transformation, $z = 2.12$ or $p = 0.034$).

4. Discussion and conclusion

In the present study, we showed that the PCP group had a specific reduction in reward responsiveness demonstrating a lower sensitivity to the occurrence or anticipation of reward. This is the first direct evidence for reduced reward responsiveness in PCP. There was no difference in reward drive between the PCP and HC groups.

The current finding of a specific reduction in reward responsiveness while reward drive was at control levels was unexpected. To our knowledge, this has not been investigated before in chronic pain patients, but experiments in healthy subjects have shown that acute pain increases motivation, but does not affect the hedonic reward response (Gandhi et al., 2013). The present finding of normal reward drive does not support the suggestion that chronic pain would reduce motivation (Gandhi et al., 2013). Rather, our finding of a significant reduction in reward responsiveness in the PCP group demonstrates reduced hedonic response to rewards in PCP.

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Table 3 Partial correlations in patients with chronic pain and healthy controls.

	Patients with chronic pain			Healthy controls		
	Pain level 24 h	BAS-Reward Responsiveness	Nucleus accumbens volume	Pain level 24 h	BAS-Reward Responsiveness	Nucleus accumbens volume
Pain level 24 h	–			–		
BAS-Reward Responsiveness	$r = -0.006$ $p = 0.980$	–		$r = -0.065$ $p = 0.812$	–	
Nucleus accumbens volume	$r = 0.171$ $p = 0.559$	$r = 0.534$* $p = 0.049$	–	$r = 0.238$ $p = 0.341$	$r = -0.341$ $p = 0.197$	–
Pain duration	$r = -0.057$ $p = 0.821$	$r = 0.254$ $p = 0.309$	$r = 0.382$ $p = 0.178$	–	–	–

Numbers are Spearman's rho from partial correlation in patients with chronic pain and their matched healthy controls, adjusted for anhedonia scores. Statistical differences within groups were explored with a two-tailed Spearman's rank order correlation.
Anhedonia was measured with a subscale of the Beck Depression Inventory II that measures anhedonic state. Nucleus accumbens volume is the combined volume of the left and right nucleus accumbens in % of intracranial volume. Duration of chronic pain was only recorded for patients with chronic pain, not in the matched healthy controls.
*$p < 0.05$.

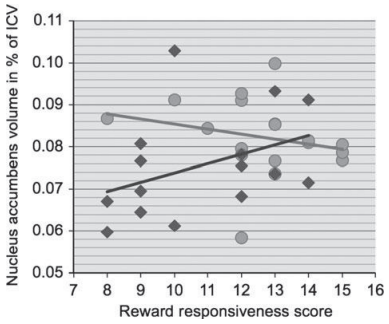

Figure 2 Nucleus accumbens volume by reward responsiveness for patients with chronic pain (dark grey boxes) and their matched healthy controls (light grey circles).

If acute pain does not affect the hedonic experience of rewards (Gandhi et al., 2013), reduced reward responsiveness in PCPs could be a consequence of the long-term effects of pain or a marker of chronic pain vulnerability (Denk et al., 2014).

The trend towards reduction in nucleus accumbens volume concurs with a previous study that showed reduction in its size as pain became chronic and in a meta-analyses of morphometric studies on PCPs (Baliki et al., 2012; Smallwood et al., 2013). However, one study on rheumatoid arthritis patients found increased nucleus accumbens volume (Wartolowska et al., 2012). Many of the patients in the current study were included in a previous study on decision making where significantly smaller nucleus accumbens volume was demonstrated in the PCP group (Elvemo et al., 2014). This, combined with the large effect size for nucleus accumbens volume differences between the PCP and HC in the current study, indicates that the current study is underpowered and sensitive to type II errors. The lack of correlation between nucleus accumbens volume and pain duration could be explained by the much longer duration of the pain conditions in the present study than in the study by Baliki et al. (2012).

The reduction in reward responsiveness was significantly correlated with reduced nucleus accumbens volume in PCPs, and this relationship was significantly different from that found in the controls. Using voxel-based morphometry, it has previously been shown in healthy men that ventral striatum grey matter density correlated positively with both placebo analgesia and a combination score of personality traits which included reward drive and reward responsiveness as well as other measures (Schweinhardt et al., 2009). This finding differs from the result in the healthy controls (predominantly women) in the present study where no significant association between reward responsiveness scores and nucleus accumbens volumes was detected. These contrasting results could be due to differences in 'reward' measures, including anhedonia scores, as well as different image analysis approaches and sex and age distributions. There is no straightforward relationship between behaviour or function and brain structure volume, but it is well known that nucleus accumbens is important for reward processing (Salamone and Correa, 2012). The significant correlation between nucleus accumbens volume and reward responsiveness, combined with the significantly reduced reward responsiveness in PCP group provide experimental support to the hypothesis that

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PCP have altered reward processing and that nucleus accumbens is involved in this.

It has been suggested that reward processing in PCP might be disrupted due to changes in the dopamine and/or opioid systems (Comings and Blum, 2000; Becker et al., 2012). Both increased tonic levels of dopamine in the nucleus accumbens causing reduced phasic dopamine levels thereby affect motivational 'wanting', and reduced opioid receptor density in the nucleus accumbens disrupting hedonic 'liking' are possible mechanisms of altered reward processing in PCP (Leknes and Tracey, 2008; Berridge et al., 2009). A potential interpretation of the current results in the light of Becker and colleagues' hypothesis is that the reduced reward responsiveness stems from opioid system dysfunction. In support of this interpretation are findings in healthy subjects demonstrating that reward responsiveness is correlated with magnitude of opioid analgesia and predicts neural activity in the nucleus accumbens (Wanigasekera et al., 2012). Previous studies have shown that PCP have abnormal opioid systems (Harris et al., 2007) and in the clinic, these patients frequently show reduced response to opioids (Manchikanti et al., 2011). During chronification of pain, changes in the opioid and dopamine systems are accompanied by changes in neuronal activity and connectivity in an animal models of neuropathic pain (Chang et al., 2014), consistent with cross-sectional and longitudinal studies in humans with chronic pain (Baliki et al., 2012). These changes may be linked to both changes in nucleus accumbens volume and reward processing. One may speculate that the correlation between nucleus accumbens volume and reward responsiveness is associated with reduced opioid response in PCP, which in turn points to reduced reward responsiveness as a possible predictor of opioid response. Since reward is linked to the dopaminergic neurotransmitter system, dopamine is necessarily also a part of this.

There was no significant correlation between reward responsiveness and pain duration. As the current study was not designed to investigate causality, it is not possible to conclude on the causal relationship of chronic pain and reduced reward responsiveness. Grey's BAS is considered to measure a stable personality trait, and reduced reward responsiveness may hence be present before a chronic pain condition is established. If this is the case, reward responsiveness assessment may be an important factor to take into consideration in individuals at risk of developing chronic pain conditions, such as in acute back pain. However, it would be surprising if the neurochemical and/or neuropsychological changes present in PCPs (Apkarian et al., 2011) does not also affect brain activity related to BAS.

While the PCP group had heterogeneous pain aetiologies that reduce the current study's ability to find aetiology-specific differences, the heterogeneity increases the ecological validity and makes significant findings more applicable to chronic pain in general. Moreover, right and left nucleus accumbens volumes were combined to reduce number of statistical tests, and because the small PCP group had varying degrees of lateralization of pain (see Fig. 1). Thus, lateralization effects and specificity of nucleus accumbens changes with regard to localization of the chronic pain could not be investigated. Inclusion of patients on different types of analgesics could also have affected the results, at the benefit of increased ecological validity. At the risk of type I errors, the current study did not correct for multiple comparisons since the number of tests and subjects was low and this would increase the risk a of type II errors.

In summary, chronic pain patients exhibited significantly reduced reward responsiveness which was positively associated with nucleus accumbens volume. There was no difference in reward drive between the PCP and HC groups. Future research should investigate if reduced reward responsiveness is a premorbid trait of chronic pain, and if so a marker of susceptibility to chronic pain and/or an indicator for treatment type and/or response.

Author contributions

N.A.E. participated in the design of the experiment, recruited subjects, collected neuropsychological and MRI data, analysed data, participated in manuscript writing and revision, and approved the final version of this manuscript. N.I.L. and P.C.B. participated in the design of experiment, in manuscript writing and revision and approved the final version of this manuscript. A.K.H. was responsible for the design of experiments, data analysis, manuscript writing and revision, and approved the final version of this manuscript.

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