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Reward responsiveness in patients with chronic pain

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Conflicts of interest
None declared.

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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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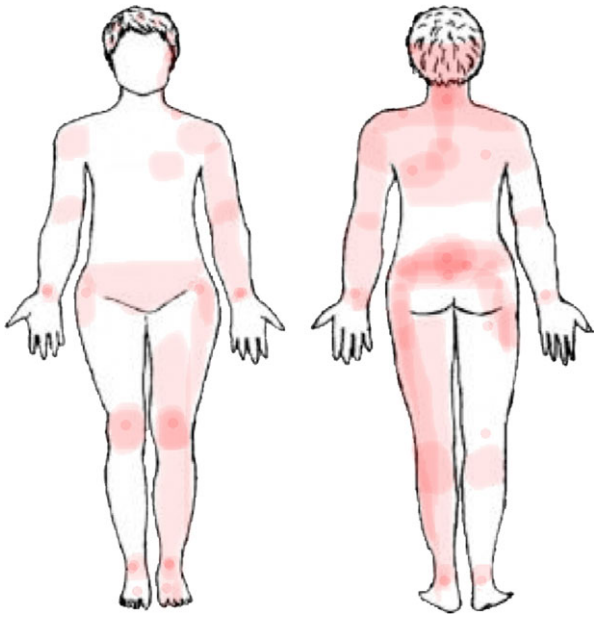

Figure 1 Subjective location of pain reported by patients, in the Brief Pain Inventory questionnaire. Red areas indicate areas where patients felt pain, and dots indicate areas where patients felt highest levels of pain. The colouring was made translucent to show increased intensity in areas where more 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.
*$p < 0.05$.

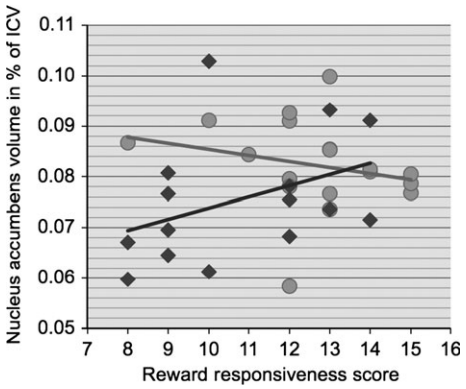

Figure 2 Nucleus accumbens volume by reward responsiveness for patients with chronic pain (dark grey boxes) and their matched healthy controls (light grey circles).

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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