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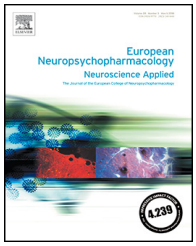

Effects of social exclusion and physical pain in chronic opioid maintenance treatment: fMRI correlates

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Abstract
Opioids interact with systems processing pain and social stimuli. Both systems are crucial for responding to strains of everyday life and both are linked to relapse risk in opioid-dependent patients. The investigation of those systems seems essential to better understand opioid addiction as a whole. 17 patients on opioid maintenance treatment (OMT) and 21 healthy individuals underwent a functional magnetic resonance imaging (fMRI) social ball-tossing (Cyberball) paradigm simulating social inclusion and exclusion. In addition, painful and non-painful temperature stimuli were applied, in order to test pain sensitivity. Patients on OMT showed reduced pain sensitivity. Subjective pain was higher after social exclusion compared to social inclusion trials. In comparison to healthy controls, OMT patients felt less included and more excluded during inclusion and control conditions, and equally excluded during the social exclusion condition. Feelings of exclusion during the inclusion trials were associated with higher scores on the childhood trauma questionnaire. Across all conditions, OMT patients demonstrated decreased fMRI activation in the bilateral superior and middle occipital and bilateral cunei, the lingual gyri, as well as in the left fusiform gyrus (whole brain FWE-corrected). Comparing social exclusion and inclusion conditions, healthy individuals showed significant activation in brain areas

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related to social feedback and emotion processing, such as the anterior cingulate cortex, the insula and fusiform gyrus, whereas OMT patients showed no difference across conditions. As negative social affect is a potential trigger for relapse, patients might benefit from therapeutic strategies that enhance social integration.

1. Introduction

Opioid dependence is a chronic disease with high relapse and low abstinence rates (Shalev et al., 2002). Negative social interaction and poor social support were associated with negative treatment outcome in opioid addiction, whereas patients in a relationship had better outcomes (Termorshuizen et al., 2005). Therefore, the investigation of behavioral and neural response of opioid dependent patients to positive and negative social interaction seems important to better understand mechanisms that drive relapse behavior. Social exclusion plays a multifaceted role in addictive disorders. Evidence points towards a bidirectional relationship between drug consumption and social exclusion, i.e. social exclusion increases the risk for using drugs (Morgan et al., 2002), while increased drug use can also increase social exclusion of addicted patients (Ahern et al., 2007), leading to a vicious circle (Frischknecht et al., 2011).

According to the "shared representation theory" (MacDonald and Leary, 2005) both, social stimuli and pain stimuli are processed in a neural network that shares some common structures, such as the insula, the anterior cingulate cortex (ACC) and the somatosensory cortex (Kross et al., 2011). Indeed, physical pain and social rejection involve similar biological regulatory systems, such as the endogenous opioid system (Hsu et al., 2013) and functional imaging studies showed that physical and social pain activated common brain areas (Kross et al., 2011). However, this does not imply shared representations at all levels (e.g. neuronal level) and recent functional imaging studies have shown that separate representations may underlie the experience of physical pain and social rejection despite common fMRI activity at the gross anatomical level (Woo et al., 2014). Still, modulation of physical and social pain is associated with opioidergic neurotransmission. It has been shown that opioids reduce social pain, such as separation distress behaviors in non-human mammals (Panksepp et al., 1978). Moreover, application of buprenorphine decreased perceived social rejection in human volunteers (Bershad et al., 2016). In contrary, other research demonstrated that administration of oxycodon resulted in a decreased functional brain response to positive social stimuli, e.g. happy faces in healthy participants (Wardle et al., 2014). Currently, there is a lack of research on the effect of chronic opioid exposure on social interaction.

While acute administration of opioids has been associated with reduced physical pain, previous work reported mixed results regarding long-term effects of opioids on pain sensitivity. While studies that incorporated a cold pressor test to probe pain sensitivity found decreased pain tolerance in patients on OMT, studies that used electric pain stimulation or heat stimuli did not find opioid-induced hyperalgesia (Compton et al., 2001; Hay et al., 2009). Recent work suggested that pain modulation by long-term opioid-treatment might be modality specific. Investigating heat pain stimuli, studies reported lower supra-threshold pain ratings in patients on OMT, reflecting opioid analgesia. In addition, patients on OMT with chronic pain reported increased pain thresholds for heat stimuli (Peles et al., 2011). As acute pain has been associated with poorer retention in OMT, it is of great interest, how pain stimuli are processed in patients on OMT (Rosenblum et al., 2003; Trafton et al., 2004).

To our knowledge, no study to date has investigated behavioral and neural response to social exclusion, social inclusion and pain stimuli in patients on OMT.

1.1. Hypotheses

Firstly, based on previous findings that the administration of opioids reduces perceived social rejection (Bershad et al., 2016), while also reducing functional brain response to positive social stimuli (Kornreich et al., 2003), we hypothesize that patients on OMT will feel less excluded during experimental induction of social exclusion and also less included during social inclusion. Further, we expected to detect altered neural response in brain areas associated with social cognition and emotion processing, such as the ACC, insula, somatosensory cortex, caudate and cuneus (Adolfi et al., 2017; Cacioppo et al., 2013).

Secondly, we hypothesized that patients on OMT have a reduced sensitivity for heat pain stimuli. As neural correlate of the analgesic effect of opioids, we expect lower fMRI brain activation in the pain network: e.g. primary and secondary somatosensory cortices, insula and dorsal anterior cingulate cortex (dACC) (Wager et al., 2013).

Thirdly, we expected that social rejection increases subjective pain while social inclusion reduces subjective pain.

Fourthly, we explored factors modulating responses to social exclusion and inclusion. We hypothesized that those living in a constant partnership feel less excluded during, while participants that experienced childhood traumata in the past feel more excluded (van Harmelen et al., 2014).

2. Experimental procedures

2.1. Participants

Opioid dependent patients, identified according to the ICD-10 criteria (16 males, 1 females, mean age $\pm$ SD 38.5 $\pm$ 6.5 years), were recruited in an outpatient opioid maintenance program of the Central Institute of Mental Health in Mannheim, Germany. Patients were on OMT for several years (mean $\pm$ SD) 6.9 $\pm$ 7.2 years. Patients did not

undergo a formal screening for comorbid psychiatric disorders prior to being included in the current study, however all patients were interviewed by two independent separate professional psychiatrists at the institute, in order to rule out relevant comorbid psychiatric diseases. In addition, patients were treated at the department's opioid maintenance unit for an average of 6.9 years with regular appointments with a specialized psychiatrist once a week and no clinical evidence for a comorbid psychiatric disorder could be determined during this time for any of the participants. None of the patients had a history of chronic pain or was treated for pain symptoms at the time of the experiment. None of them was HIV positive, but $n = 5$ were tested positive for hepatitis C antibodies. Twelve of the patients were treated with methadone and five with buprenorphine. The mean methadone equivalence dose (mean $\pm$ SD) was 70 ± 40 mg/d. The methadone equivalence dose was calculated with 100 mg methadone = 16 mg buprenorphine (Strain et al., 2000). Eleven patients had a concurrent harmful use of other substances, such as benzodiazepines, cocaine, alcohol and cannabis (see Table 1). None of the substances were medically prescribed. At the time of scanning, urine sampling was conducted to detect other (non-prescribed) psychoactive substances (see Table 1). In order to control for effects of psychoactive substances in neuroimaging studies, the computation of a composite medication score was used as described by (Sackeim, 2001). According to previous studies (Phillips et al., 2008; Sackeim, 2001), the dose of each substance (e.g. benzodiazepine) was coded as absent (0), low (1) or high (2). For benzodiazepines, the lorazepam equivalent dose was computed and coded as absent, low or high with reference to the midpoint of the recommended daily dose range (Almeida et al., 2009). For other substances (e.g. cocaine) no similar reference was available. Therefore, doses were coded as absent, low or high based on urine drug screening results (e.g. negative vs. positive vs. highly positive screening results). The methadone equivalence dose was categorized into low or high based on the recommended daily dose range (i.e. less or more than 120 mg per day)(Benkert and Hippius, 2016). The resulting composite medication load (M = 2.47, SD = 1.23, range = 1.0-5.0) was included as a covariate in the statistical analyses of neuroimaging data. Further clinical and social characteristics are displayed in Table 1. The study was approved by the local ethics committee of the University of Heidelberg and performed in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants. The healthy control group consisted of volunteers that were recruited from newspaper or clinic homepage advertisement ($n = 21$, 19 males, 2 females). Participants of this group were not formally screened for mental disorders, however there were interviewed by experienced clinical psychiatrists that found no indications for a substance abuse disorder or other mental illnesses. All participants were compensated for their time with.

2.2. Study design

Eligible participants were asked to complete several questionnaires before performing magnetic resonance imaging (MRI). These questionnaires included the Beck Depression Inventory (BDI, (Beck et al., 1961) and the Childhood Trauma Questionnaire (CTQ, (Karos et al., 2014; Klinitzke et al., 2012). All participants underwent a fMRI Cyberball task that simulates social inclusion and social exclusion while applying painful and neutral reference temperature stimuli that was used in previous studies (Domsalla et al., 2014).

The previously validated fMRI Cyberball task (Williams and Jarvis, 2006) consisted of 18 blocks of alternating social inclusion, exclusion and neutral motor response conditions in combination with a painful heat stimulus or neutral reference temperature stimulus that was used in previous studies (Domsalla et al., 2014). Before the actual experiment started, participants were told that two other persons lying in other MR scanners were teammates and simultaneously controlling the other two stickmen that were presented on the screen during the Cyberball task (i.e. patients were deceived). To enhance the feeling of playing with other humans, pictures of two human players were constantly displayed on the same screen as the Cyberball task above the two stickmen displaying the other player's actions. After each Cyberball block, participants were asked to rate their feelings of both exclusion and inclusion (e.g. "how intense is your feeling of exclusion / inclusion"). The ratings for subjective exclusion and inclusion intensity were assessed on an 11-point-visual scale ranging from "not at all" (0) to "very strong" (10).

The Cyberball blocks were divided into three conditions, social exclusion, social inclusion and neutral motor response trials. During social exclusion trials, the stickmen representing the participant received the ball only once at the beginning of each block and was excluded for the rest of the Cyberball block (i.e. did not receive any ball toss). During social inclusion trials, there was an equal number of ball tosses to every of the three stickmen representing the different players. In order to control motor response without decision making i.e. choosing to which teammate to toss the ball next, a control condition was included with the instruction to always toss the ball in a predefined direction (i.e. always to the right during one block and always to the left in the next block). Following these predefined game rules, each participant received an equal number of ball tosses. Each subject underwent 6 blocks (mean duration 30 s) per condition (exclusion, inclusion, motor response), which resulted in a total of 18 blocks. This modified Cyberball task has been used and validated by previous studies (Domsalla et al., 2014). All participants were debriefed after completing the experiment and completed a short questionnaire to assess how much participants believed in playing with two other players. Participants were asked if they had any doubts playing with two other human players at the start of the experiment on an eleven-point scale (0 - "not doubts at all" to 10 - "much doubts"). Participants of both groups reported on having no doubts on playing with real partners (mean score 1.83, SD 2.9).

Each Cyberball block was directly followed by the administration of either a painful (subjective pain intensity = 60%) or non-painful neutral reference temperature stimulus (32 °C). Temperature stimuli (duration 30 s) were delivered to the inner side of the left forearm by using a thermode (3×3 cm^2) controlled by a quantitative sensory tester (TSA-II; Medoc Advanced Medical Systems, Ra-

Table 1 Clinical characteristics of study participants.

	Opioid-dependent patients ($N = 17$) M (SD)	Healthy controls ($N = 21$) M (SD)	Statistics	p
Sex (male:female)	16:1	19:2	$Chi^2_{(1)} = 0.171$	0.581
Age (years)	38.53 (6.5)	38.19 (8.1)	$t_{(36)} = 0.140$	0.889
Housing situation (alone/with partner/with relative)	8/5/4	6/11/4	$Chi^2_{(2)} = 2.56$	0.465
Relationship status (single/partner - separate apartment/partner - shared apartment)	11/5/1	5/11/5	$Chi^2_{(2)} = 6.821$	0.033*
Education (no post secondary educ./apprenticeship only/attended college or higher)	12/5/0	2/10/9	$Chi^2_{(2)} = 17.583$	0.001*
Duration of heroin abuse (years)	6.9 (7.2)	-	-	-
Medication (methadone:buprenorphine)	12:5	-	-	-
Methadone equivalence dose (mg)	70.2 (40.3)	-	-	-
Current use of drugs other than methadone (yes:no)	11:6	-	-	-
Drugs used other than methadone (absolute numbers)	BZD = 9, OPT = 9, ALC = 1, THC = 2, COC = 2	-	-	-
Composite medication load	2.4 (1.2)	-	-	-
Pain threshold (°C)	44.9 (0.8)	43.5 (2.1)	$t_{(36)} = 2.607$	0.014*
CTQ - subscale emotional abuse	11.0 (7.1)	6.3 (2.1)	$t_{(36)} = 2.635$	0.017*
CTQ - subscale physical abuse	11.8 (7.4)	5.1 (0.4)	$t_{(36)} = 3.672$	0.002*
CTQ - subscale sexual abuse	7.0 (5.7)	5.3 (0.9)	$t_{(36)} = 1.218$	0.240
CTQ - subscale emotional neglect	13.8 (7.0)	9.8 (4.2)	$t_{(36)} = 2.049$	0.050*
CTQ - subscale physical neglect	9.7 (4.1)	7.0 (2.5)	$t_{(36)} = 2.400$	0.024*
BDI (sum score)	15.1 (15.6)	1.9 (2.8)	$t_{(36)} = 3.830$	0.001*
Relationship status (single:partnership)	11:6	5:16	$Chi^2_{(1)} = 6.446$	0.011*

BDI = Beck Depression Inventory, CTQ = Childhood Trauma Questionnaire, BZD = benzodiazepine, OPT = opiates other than methadone/buprenorphine, LAC = alcohol, THC = tetrahydrocannabinol, COC = cocaine; Methadone equivalence dose was calculated with 100 mg methadone = 16 mg buprenorphine (Strain et al., 2000).

mat Yishai, Israel). For pain stimuli, the temperature was chosen individually to correspond to a pain intensity of 6 on a scale from 0 ("no pain") to 10 ("maximum pain"), i.e. 60% of subjective maximal pain. Pain and neutral reference stimuli were presented equally often after the Cyberball blocks in a pseudo-randomized order. The pain intensity of 60% was determined by following a standard procedure prior to the experiment. The stimulation temperature started at 37 °C in time blocks of 30 s, oscillating + /- 1 °C, and was increased in 1 °C steps (above 41 °C, in 0.5 °C steps) until a subjective pain intensity of 60% was reached. This setup was used in previous studies (Bungert et al., 2015).

Presentation® software (Version 16.0, Neurobehavioral Systems Inc., Albany, CA, USA) and MRI-compatible goggles (MRI Audio/Video Systems, Resonance Technology Inc., Los Angeles, CA, USA) were used to present task data and record participants responses. A LumiTouch fMRI Optical Response Keypad (Photon Control Inc.; Burnaby, BC, Canada) was used as a patient response system.

2.3. Functional MRI acquisition and pre-processing

Functional and anatomical brain images were acquired using a 3T whole-body tomograph (MAGNETOM Trio, Siemens Medical Systems, Erlangen, Germany). Task-related blood oxygen level-dependent (BOLD) response was measured using T2*-weighted echo planar imaging (EPI) sequences (TR = 2 s, TE = 30 ms, 36 slices, slice thickness = 3 mm, voxel dimensions $3 \times 3 \times 3$ mm^3, FOV = 192×192 mm^2, 64×64 in-plane resolution). In addition, high resolution anatomi-

cal scans using a T1-weighted 3-D magnetization-prepared-rapid-acquisition-gradient-echo (MPRAGE) sequences were acquired for each participant ($1 \times 1 \times 1$ mm^3 voxel size).

Brain imaging data were pre-processed and analyzed using SPM5 (preprocessing and individual statistics) and SPM8 (second-level group analyses; Wellcome Department of Cognitive Neurology, London, UK). In accordance to standard procedures implemented in the SPM software package, spatial realignment and smoothing procedures using an isotropic Gaussian kernel for group analyses (full width at half maximum: 8 mm) were applied to the imaging data and images were normalized to a standardized MNI (Montreal Neurological Institute, Quebec, Canada) EPI template. Individual first level contrast images were computed by modelling the following factors in a multiple regression model: 3 regressors for the Cyberball task conditions (i.e. exclusion, inclusion, and motor control), 3 regressors for the heat pain temperature stimuli after the different Cyberball conditions, 3 regressors for the non-painful reference temperature blocks after the different Cyberball condition; and 1 regressor for key press (for details refer to Domsalla et al., 2014). In a next step, the relevant first-level-contrast images were entered into a second level analysis full-factorial-model.

2.4. Statistical analyses

Demographical data, rating data, pain thresholds and questionnaire data were analyzed using two-sample *t*-tests and chi-square tests as implemented in the Statistical Package for the Social Sciences (SPSS, IBM Corp., Somers, NY, USA) version 24.0. Following the analyses of group differences, multiple linear regression analysis using a stepwise approach was conducted to further assess the influence of subject status (patient vs. healthy control), childhood trauma (measured by the CTQ), partnership status (constant relationship vs. single) and depressive symptoms (measured by the BDI questionnaire) on participants' feelings of social exclusion and inclusion during experimental induction of social inclusion. fMRI Group-level differences were analyzed by implementing the first level contrast images in a ($2 \times 3 \times 2$) full-factorial model with group (patients, controls) x task condition (inclusion, exclusion, motor response) x temperature stimulus properties (neutral reference temperature, pain). In order to further characterize intra-group condition-dependent differences, separate analyses were conducted for patients and healthy controls in a 3×2 full-factorial model with task condition x temperature stimulus properties. The statistical threshold was set to a family-wise error (FWE) corrected whole brain threshold of $p_{FWE} < 0.05$. For exploratory analyses and multiple regression analyses (covariates: methadone equivalence dose, pain ratings), the threshold was set to $p < 0.001$ uncorrected with a cluster size threshold of 20 voxels. In order to control for differences in BDI and CTQ scores, variables were implemented as covariates in the statistical models. In addition, the composite medication load was included a covariate in all within-group statistical models. To illustrate the findings of exploratory regression analyses, parameter estimates were extracted from the main activation clusters of both regression analyses using functionally defined region of interest masks that were built from the main activation clusters of both significant analyses, i.e. (i) negative correlation with methadone equivalence dose - peak voxel [x = 6 y = −1 z = 31], (ii) positive correlation with subjective pain ratings - peak voxel [x = −27 y = −13 z = −14]. Individual mean beta values were then extracted from both masks using MarsBar software (http://marsbar.sourceforge.net/) and imported in SPSS for further analyses.

3. Results

3.1. Group characteristics

Analyses of demographical and clinical variables indicated significant differences between patients and healthy controls regarding partnership status and education level (see Table 1). Patients reported more often living without a partner and having fewer years of education. In addition, patients more frequently reported childhood trauma and more depressive symptoms (all *p*-values < 0.05) (see Table 1). None of the patients received prescriptions for any psychoactive medication. Still, analyses of clinical and drug screening data indicated intake of illegal psychoactive substances (see Table 1).

The mean absolute temperature corresponding to the subjective individual pain threshold of 60% (rating 6 on a VAS from 0–10) was significantly higher in opioid dependent patients on OMT (44.9 °C ± 0.8) in comparison to healthy controls (43.5 °C ± 2.1; t = 2.723 $p = 0.012$, see Table 1).

3.2. Effect of stimulus temperature and task condition on subjective pain

Across both groups and all conditions, neutral reference temperature stimuli were consistently rated as less painful compared to painful stimuli ($M_{neutral} = 0.9$, SD = 0.3, $M_{pain} = 5.8$, SD = 0.2; $t_{(36)} = 13.920$, $p < 0.001$, see Table 2). Comparing the effect of task condition (inclusion, exclusion, motor response), pain ratings of the painful stimuli after the exclusion condition (M = 6.1, SD = 2) were significantly higher compared to the inclusion condition (M = 5.5, SD = 1.6) and motor response condition (M = 5.8, SD = 1.9, $F_{(2,36)} = 3.819$, $p = 0.027$, see Table 2). There was no significant difference between the subjective pain ratings of the non-painful stimulus across the three task conditions ($p > 0.05$, see Table 2). In addition, there was no significant task condition-related difference between patients and controls with regards to subjective ratings of the painful and non-painful stimulus ($p > 0.05$, see Table 2).

3.3. Effect of task condition on subjective feeling of inclusion and exclusion

During the exclusion condition, both groups reported increased feelings of exclusion (M = 6.5, SD = 2.7) compared to the inclusion (M = 2.0, SD = 1.6) and motor response condition (M = 1.4, SD = 1.7, $F_{(2,36)} = 90.467$ $p = 0.001$, see Table 2).

Table 2 Ratings of feeling included or excluded following Cyberball and pain ratings after pain stimulation.

	Opioid-dependent patients ($N = 17$) M (SD)	Healthy controls ($N = 21$) M (SD)	Statistics	p
Feeling of being excluded after				
… Cyberball exclusion trials	6.6 (2.2)	6.4 (3.1)	$t_{(36)} = 0.246$	0.784
… Cyberball inclusion trials	2.6 (1.6)	1.6 (1.4)	$t_{(36)} = 1.062$	0.036*
… Cyberball motor response trials	1.9 (1.7)	0.9 (1.6)	$t_{(36)} = 1.042$	0.060
Feeling of being included after				
… Cyberball exclusion trials	2.4 (1.3)	2.9 (2.7)	$t_{(36)} = 0.552$	0.444
… Cyberball inclusion trials	6.4 (1.5)	7.7 (1.4)	$t_{(36)} = 1.272$	0.011*
… Cyberball motor response trials	6.9 (1.9)	8.6 (1.6)	$t_{(36)} = 1.679$	0.006*
Subjective pain ratings for the painful stimulus after				
… Cyberball exclusion trials	6.2 (1.7)	5.9 (2.3)	$t_{(36)} = 0.583$	0.733
… Cyberball inclusion trials	5.6 (1.6)	5.5 (1.6)	$t_{(36)} = 0.102$	0.909
… Cyberball motor response trials	5.8 (1.9)	5.8 (2.0)	$t_{(36)} = 0.053$	0.978
Subjective pain ratings for the neutral reference temperature stimulus after				
… Cyberball exclusion trials	1.5 (2.2)	0.4 (0.9)	$t_{(36)} = 3.137$	0.084
… Cyberball inclusion trials	1.0 (1.7)	0.7 (1.0)	$t_{(36)} = 1.022$	0.443
… Cyberball motor response trials	1.1 (1.8)	0.5 (0.8)	$t_{(36)} = 1.887$	0.162

	Patients living single ($N = 11$)	Patients in a partnership ($N = 5$)	Statistics	p	HC living single ($N = 5$)	HC in a partnership ($N = 16$)	Statistics	p
Feeling of being included after								
… Cyberball exclusion trials	2.4 (1.4)	2.4 (1.4)	$t_{(14)} = 0.042$	0.955	1.9 (0.7)	3.2 (3.0)	$t_{(19)} = 0.922$	0.368
… Cyberball inclusion trials	5.8 (1.4)	7.8 (0.9)	$t_{(14)} = 1.948$	0.013*	7.9 (1.5)	7.6 (1.4)	$t_{(19)} = 0.462$	0.649
… Cyberball motor response trials	6.8 (1.9)	7.2 (2.1)	$t_{(14)} = 0.306$	0.781	8.5 (2.3)	8.6 (1.5)	$t_{(19)} = 0.169$	0.868
Feeling of being excluded after								
… Cyberball exclusion trials	6.9 (1.8)	5.6 (2.9)	$t_{(14)} = 1.352$	0.270	7.2 (1.7)	6.1 (3.5)	$t_{(19)} = 0.706$	0.489
… Cyberball inclusion trials	3.1 (1.6)	1.3 (0.8)	$t_{(14)} = 1.772$	0.041*	0.9 (0.6)	1.75 (1.5)	$t_{(19)} = 1.158$	0.261
… Cyberball motor response trials	2.4 (1.7)	0.7 (0.9)	$t_{(14)} = 1.630$	0.070	0.3 (0.6)	1.1 (1.8)	$t_{(19)} = 0.973$	0.343

HC = healthy control participants.

During the inclusion ($M = 7.1$, $SD = 1.6$) and motor response condition ($M = 7.9$, $SD = 1.9$), healthy controls and patients felt more included compared to the exclusion condition ($M = 2.7$, $SD = 2.2$, $F_{(2,36)} = 135.910$ $p < 0.001$). Patients felt less included during the inclusion ($M = 6.4$, $SD = 1.5$; $t_{(36)} = 2.694$, $p = 0.011$, see Table 2) and motor response condition ($M = 6.9$, $SD = 1.9$; $t_{(36)} = 2.923$, $p = 0.006$, see Table 2) compared to the group of healthy controls ($M_{incl} = 7.7$, $SD_{incl} = 1.4$; $M_{motor} = 8.6$, $SD_{motor} = 1.6$). In addition, patients displayed increased feelings of exclusion compared to healthy controls during the inclusion condition ($M_{pat} = 2.6$, $SD_{pat} = 1.6$, $M_{ctrl} = 1.6$, $SD_{ctrl} = 1.4$; $t = 2.177$, $p = 0.036$, see Table 2).

3.4. Interpersonal relationship

Patients that reported to be in a partnership rated that they felt more included during the inclusion trials and less excluded during the exclusion trials, compared to patients that were single (see Table 2). In the group of healthy control participants there was no effect of partnership status on social exclusion or inclusion.

3.5. Childhood trauma

There was a significant positive association between the childhood trauma questionnaire (CTQ) emotional neglect subscale scores and subjective reports of feeling excluded during the inclusion trials ($r = 0.307$, $p = 0.030$). In addition, higher scores on the CTQ emotional neglect subscale negatively correlated with the feeling of inclusion during the Cyberball inclusion conditions ($r = -0.367$, $p = 0.012$). There was no significant association between CTQ scores and feelings of inclusion and exclusion during social exclusion trials (p's > 0.05).

3.6. Within-group analyses of fMRI data in healthy participants

Whole-brain within-group analyses in healthy participants, corrected for multiple testing ($p_{FWE} < 0.05$ whole brain corrected), showed increased functional brain response to painful stimuli relative to non-painful stimuli (main effect of stimulus) in a large network of brain regions, including the insula, inferior and middle frontal gyri, somatosensory cortex, inferior parietal gyrus, supramarginal gyrus and superior temporal gyrus (see Table 3(a) and Fig. 1(d)), while non-painful stimuli did not evoke higher brain activation in any brain area (see Table 3(b)).

During social exclusion relative to motor control trials, healthy controls displayed higher activation in the ventral anterior cingulate cortex (vACC) and also small parts of the anterior cingulate cortex (dACC), the middle cingulate cortex, insula, caudate, and parts of the superior, middle and inferior frontal gyri, as well as parts of the superior, middle and inferior temporal gyri and fusiform gyri (see Table 3(c) and Fig. 1(a)). Social inclusion relative to motor control trials elicited increased BOLD response in healthy controls in two clusters that included the bilateral middle and posterior cingulum and the right precuneus (see Table 3(d) and

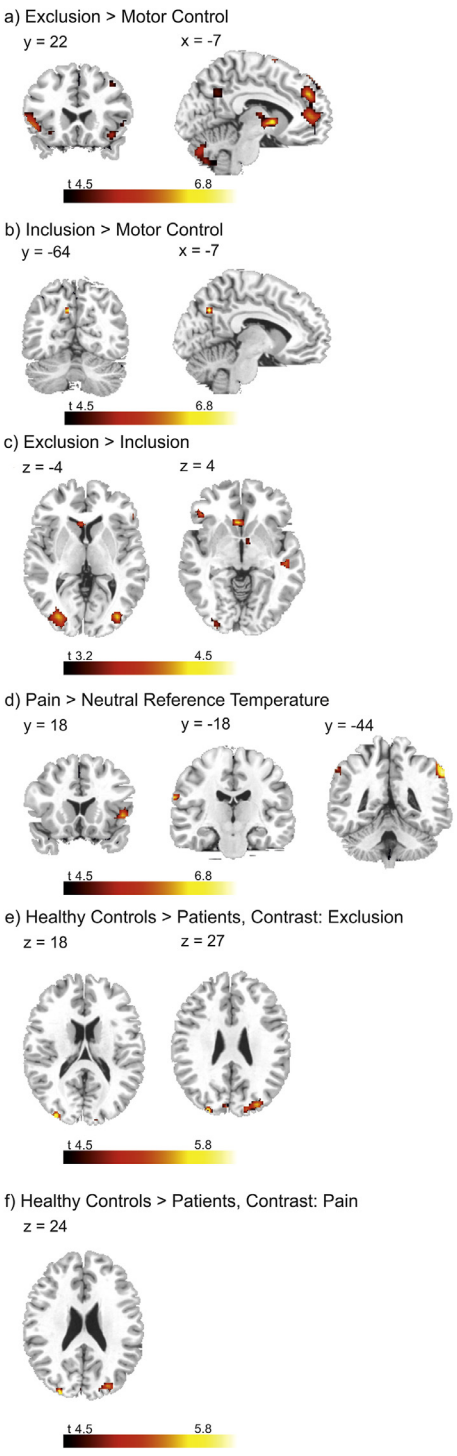

Fig. 1 Within-group significant whole brain corrected [$p_{FWE} < 0.05$, cluster size > 10] BOLD response differences in the healthy control group: (a) exclusion > motor response, (b) inclusion > motor response, (c) exclusion > inclusion [$p < 0.001$ uncorrected, cluster size > 20 voxels], (d) pain > warm, and significant between-group differences between healthy controls and patients: (e) healthy participants > patients [contrast: social exclusion], (f) healthy participants > patients [contrast: painful stimulation].

Table 3 Significant within- group brain activation differences in the healthy control group and significant group differences between opioid dependent patients ($n = 17$) and healthy control participants ($n = 21$), corrected for depressive symptom scores (BDI) and childhood trauma scores (CTQ). Correlations between methadone dose, subjective pain ratings and functional brain activation ($N = 38$, $p_{FWE} < 0.05$ whole brain corrected, cluster size > 20 voxels).

Side	Lobe	Brain areas	Cluster size (voxel)	MNI coordinates (x, y, z)			t_{max}
Within group effects Healthy control group ($n = 21$)							
(a) Contrast: Pain > Neutral reference temperature							
R	Frontal, Temporal	Middle and Inferior Frontal Gyrus, **Insula**, Superior Temporal Gyrus	137	42	41	−8	5.74
R	Parietal	Inferior Parietal Gyrus, Supramarginal Gyrus	102	60	−46	40	5.67
L	Parietal	Supramarginal Gyrus, **Somatosensory Cortex**	28	−66	−19	22	5.52
L	Parietal	Inferior Parietal Gyrus, Supramarginal Gyrus	53	−63	−49	34	5.45
R		Caudate	10	15	5	10	4.78
(b) Contrast: Neutral reference temperature > Pain							
-	-	-	-	-	-	-	-
(c) Contrast: Exclusion > Motor response							
L	Frontal, Temporal	**Insula**, Superior, Middle and Inferior Frontal Gyri, Superior Temporal Gyrus	127	−39	26	−14	6.76
R	Frontal	**Insula**, Middle and Inferior Frontal Gyrus	240	54	29	1	6.55
L & R	Temporal	Cerebellum, Inferior Temporal Gyrus, Fusiform Gyrus	1463	−39	−64	−17	6.46
L	Temporal	Middle Temporal Gyrus	111	−57	−34	−8	6.46
L & R		Caudate, Thalamus, Pallidum	192	12	−7	−2	6.43
R	Temporal	Superior and Middle Temporal Gyrus	277	57	−25	−14	6.15
L & R	Frontal	Superior Medial Frontal Gyrus, **Anterior and Middle Cingulate Cortex**, Superior and Middle Frontal Gyrus	790	9	44	31	6.08
L & R		Precuneus, Posterior Cingulate Cortex	75	3	−49	22	5.47
L	Frontal	Middle Frontal Gyrus	30	−39	17	43	5.30
L	Temporal	Superior, Middle and Inferior Temporal Gyri	76	−51	−58	25	5.25
R		Putamen, Insula	24	30	17	−11	5.06
R	Temporal	Superior Temporal Gyrus, Supramarginal Gyrus	26	57	−49	25	4.78
(d) Contrast: Inclusion > Motor Response							
R		Precuneus	15	9	−67	34	5.10
L & R		Posterior Cingulum,	8	3	−49	22	4.78
L & R		Middle Cingulum	9	3	−28	37	4.78
(e) Contrast: Exclusion > Inclusion°							
L	Frontal	Lateral and Posterior Orbitofrontal Cortex, Inferior Frontal Gyrus	64	−45	35	−14	4.36
L & R		Putamen, **Anterior Cingulate Cortex**, Caudate	90	−3	20	−5	4.30
R	Temporal	Superior and Middle Temporal Gyrus	65	54	−25	−11	4.14

(*continued on next page*)

Table 3 (*continued*)

Side	Lobe	Brain areas	Cluster size (voxel)	MNI coordinates (x, y, z)			t_{max}
Within group effects Healthy control group ($n = 21$)							
R	Frontal	Superior, Middle and Inferior Frontal Gyrus	143	36	−82	4	4.04
L	Frontal	Superior, Middle and Inferior Frontal Gyrus	247	−33	−82	7	4.02
L		Fusiform Gyrus, Cerebellum	36	−39	−61	−17	3.91
R		Cerebellum	162	24	−73	−41	3.90
L	Parietal	Superior Parietal Gyrus	30	−24	−64	61	3.83
R		Caudate	22	12	−4	−5	3.78
		Patient group (n = 17)					
-	-	-	-	-	-	-	-
Group differences							
(f) Contrast: Pain; Healthy Controls > Patients							
L	Occipital	Superior and Middle Occipital Gyrus, Cuneus, Fusiform Gyrus	48	−33	−94	13	5.82
R	Occipital	Superior and Middle Occipital Gyrus, Cuneus	41	30	−85	25	5.51
(g) Contrast: Exclusion; Healthy Controls > Patients							
L	Occipital	Superior and Middle Occipital Gyrus	56	−33	−94	13	5.91
R	Occipital	Superior and Middle Occipital Gyrus, Cuneus, Lingual Gyrus, Calcarine	65	27	−85	22	5.39
R	Occipital	Cuneus	11	−6	−88	25	4.88
(h) Contrast: Inclusion; Healthy Controls > Patients,							
R	Occipital	Cuneus, Superior and Middle Occipital Gyrus	70	30	−85	25	5.46
R	Occipital	Superior and Middle Occipital Gyrus	35	−27	−91	22	5.22
Multiple Regression Analyses (n = 38)							
(i) Negative correlation between Methadone equivalent dose and neural activation during social exclusion°							
L & R		Middle Cingulum	22	6	−1	31	5.93
L	Parietal	Superior Parietal Gyrus	20	−18	−52	43	5.52
R		Cerebellum	81	6	−76	−11	4.99
(j) Positive correlation between subjective pain ratings and neural activation during social exclusion°							
L		Amygdala, Insula, Hippocampus, Superior Temporal Gyrus	183	−27	−19	−14	4.83
R		Amygdala, Insula, Putamen, Hippocampus, Superior Temporal Gyrus	135	12	−16	−17	4.46

CTQ = childhood trauma questionnaire, BDI = Beck Depression Inventory, ° exploratory analyses with $p < 0.001$ uncorrected, cluster size > 20 voxels

Fig. 1(b)). Analyzing differences between neural activation during social exclusion and inclusion conditions in the healthy sample revealed no significant differences when applying a conservative threshold ($p_{FWE} < 0.05$ whole brain corrected). However, analyses with a combined voxel- ($p < 0.001$ uncorrected) and cluster-size (cluster > 20 voxel) threshold showed increased brain response in the lateral and posterior orbitofrontal cortex, the anterior cingulate cortex, putamen, caudate, superior and middle temporal and frontal gyri, and superior parietal gyri (see Table 3(e) and Fig. 1(c)).

3.7. Within-group analyses of fMRI data in patients

Patients on OMT did not display differential brain activation patterns across experimental conditions when a stringent statistical threshold was applied (see Table 3). The consideration of methadone dose equivalent and composite medication load score as covariates did not change the significance of within-group analyses in the patient sample.

3.8. Between-group analyses of fMRI data

Factorial analyses showed a significant main effect of group The between-group analyses revealed reduced brain activation in the patient group, compared to healthy participants during painful stimulation in the bilateral superior and middle occipital and bilateral cunei (see Table 3(f) and Fig. 1(f)). While performing social exclusion trials, patients showed lower BOLD response in the bilateral superior and middle occipital and lingual gyri, bilateral cunei, as well as in the left fusiform gyrus (see Table 3(g) and Fig. 1(e)). During social inclusion, patients showed diminished brain response in the bilateral cunei, superior occipital gyri, right middle occipital gyrus and left lingual gyrus (see Table 3(h)). Additional analyses of the interaction between group x temperature and the three-way interaction between group x temperature x condition on brain activation did not show any effect that survived stringent FWE-correction.

3.9. Association of methadone dose and neural brain response

Exploratory correlation analysis in the patient sample indicated an inverse correlation of daily methadone dose and brain activation during social exclusion after painful stimulation in the middle cingulum, left parietal cortex and cerebellum (see Table 3(i)). Correlation between parameters estimates extracted from the cluster of main activation and methadone equivalence dose are displayed in supplementary Fig. S1.

3.10. Association of subjective pain ratings and neural brain response

Subjective pain ratings correlated with neuronal brain response during social exclusion when this trial was preceded by a painful stimulus in a cluster that comprised the bilateral hippocampus, amygdala, insula, and superior temporal cortex ($p < 0.001$ uncorrected, cluster size of > 20 voxels) (see Table 3(j)). The association between subjective pain magnitude and parameters estimates extracted from the cluster of main activation is illustrated in supplementary Fig. S1.

3.11. Multiple regression analysis

Two separate multiple regression analyses were calculated to predict (i) subjective inclusion during inclusion trials and (ii) subjective exclusion during inclusion trials. Regarding both multiple linear regression analyses, only one independent variable (patient status) met the predefined stepwise inclusion criteria. Consequently, all other variables were excluded from the regression models. A significant regression equation was found ($F_{(1,34)} = 11.593$, $p = 0.002$), with an adjusted R^2 of 0.232 predicting subjective inclusion based on group status (0 = control, 1 = patient). In addition, a significant regression equation, predicting subjective exclusion during inclusion trials, was found ($F_{(1,34)} = 4.739$, $p = 0.036$), with an adjusted R^2 of 0.092.

4. Discussion

The current study is the first to show that opioid-dependent patients experience more social exclusion and less social inclusion during social inclusion trials and reduced activation in brain areas associated with social cognition and emotion processing.

Opioid dependent patients felt more excluded and less included in comparison to the healthy control sample during the social *inclusion* condition. This finding might be explained by a reduced flexibility to adapt to social inclusion, i.e. positive social stimuli. This assumption is supported by the finding that oxycodone administration dampened functional brain response to positive social stimuli, e.g. happy faces (Wardle et al., 2014). Another reason might be that social rejection is a common reaction drug addicts encounter every day (Frischknecht et al., 2011). As a consequence, patients may be more suspicious regarding pro-social interaction.

The finding of similar subjective exclusion ratings in patients and controls during social *exclusion* trials seem to contradict previous research that indicated alleviation of social rejection by opioids. However, those studies investigated the effect of acute opioid exposure in healthy participants. It is conceivable that chronic opioid exposure reduces the alleviating effect of opioids on social rejection. Positron emission tomography (PET) studies indicated that chronic OMT treatment leads to a reduced availability of opioid receptors in the thalamus, amygdala, caudate, anterior cingulate cortex and putamen. Receptor availability was 19–32% lower in patients, suggesting that not all opioid receptors are available to function in their normal physiological roles (Kling et al., 2000). Therefore, similar release of endogenous opioids might yield lower effects, resulting in less reduction of feeling socially rejected in chronic versus acute opioid exposure.

While no significant differences between experimental conditions were found in the patient sample, healthy individuals displayed a differential activation pattern across social inclusion and exclusion trials. The experimental simulation of social exclusion in the current study induced brain activation in the heathy control group in clusters of mesolimbic and frontal brain areas, including the insula and parts of the anterior, middle and posterior cingulate cortex. The insula and the ventral anterior cingulate cortex (vACC) have been identified as brain areas that are essential for processing social stimuli. Increased activation of both structures has been linked to the affective value of social exclusion (Bolling et al., 2011; Eisenberger et al., 2003; Kross et

al., 2011). It has been suggested that insula activation reflects negative emotional reaction to ostracism and distress (Moor et al., 2012).

The simulation of social inclusion during the experiment resulted in brain activation in a thalamo-cingular cluster. Studies indicated that neural activation in the middle cingulum is associated with the magnitude of stimulus value during fMRI reward learning tasks (Lin et al., 2012). Additional work has demonstrated that positive social feedback elicits increased activation in thalamic regions (Guyer et al., 2012). Exploratory analyses with a liberal threshold indicated that social exclusion compared to social inclusion induced higher neural activation in the orbitofrontal cortex (OFC), inferior frontal gyrus (IFG), putamen, ACC, caudate, temporal gyri and cerebellum and in fusiform gyri. A recent meta-analytic study evaluated the results of more than 200 studies on social cognition, emotion and interoception (Adolfi et al., 2017). Results indicate that the ACC, putamen and IFG are frequently associated with social cognition, with the putamen and IFG also being involved in emotion processing. The OFC and fusiform gyrus have been implicated in emotion perception. The caudate and cerebellum play a role in processing interoceptive information, whereas the temporal gyri are also associated with social cognition.

Within group- analyses in the patient sample could not show significant differences in brain activation across task conditions. Multiple factors might have contributed to this finding. Firstly, analyses indicated a negative association between the extent of brain activation and methadone equivalent dose. This suggests that neural activation in patients might be attenuated and levelled across conditions partly due to medication effects. However, the consideration of methadone equivalent doses and composite medication load in the analyses still yielded no significant difference between conditions in the patient group. This suggest that factors, other than medication and intake of psychoactive substances, may contribute to these findings. Animal studies demonstrated that opioid exposure decreases mu-opioid receptor sensitivity and availability (Maher et al., 2005), modulates $GABA_A$ receptor functioning (Zarrindast et al., 2004), and modifies glutamate receptor targeting (Glass et al., 2005), thereby modifying and shaping neural responses. Subsequent studies in prescription opioid-dependent patients demonstrated altered functional connectivity compared to healthy controls in brain areas that are involved in social cognition (e.g. amygdala) (Upadhyay et al., 2010). Further studies suggested that chronic morphine exposure is also associated with gray matter volume changes (Younger et al., 2011). While the exact mechanism underlying the missing differences across task conditions in the patient group could not be determined in the current study, it is conceivable that adaptive changes on multiple levels (e.g. receptors) that result from prolonged opioid exposure might contribute to the finding. Still, the exact mechanisms await further investigation.

Comparing the neural responses to social feedback of patients and healthy individuals showed that healthy controls displayed higher neural brain response compared to patients on OMT during social exclusion in the superior and middle occipital gyri and lingual cunei. It was suggested that the occipital cortices play a role in processing interoceptive information and emotions and that the cuneus and the lingual gyrus are involved in social cognition (Adolfi et al., 2017). Further analyses showed higher brain activation during the inclusion condition in right cuneus and occipital gyri of healthy participants versus patients on OMT. A recent study found that the cuneus displayed increased activation in response to positive social feedback (Dalgleish et al., 2017). In addition, response in this area was more pronounced during positive feedback than negative feedback. In the light of previous work, current results indicate that healthy participants modulate their neural response to social feedback more than patients on OMT. In other words, patients receiving OMT may have reduced neural and behavioral flexibility, possibly resulting in habitual, negative social expectations.

In accordance to our second hypothesis, our data suggest that opioid-dependent patients have increased heat pain-thresholds relative to healthy controls. This finding is supported by earlier work that found heat hypoalgesia in patients on OMT (Peles et al., 2011).

Results show that painful stimuli induce neural activation in the insula, caudate, temporal gyrus and cortical regions (e.g. the somatosensory cortex, IFG) that have been associated with pain perception and emotion processing before (Adolfi et al., 2017; Wager et al., 2013). Regression analyses indicated that activation in many of those areas (e.g. insula and temporal gyri) also demonstrated a positive association with subjective pain ratings during the scanning session, supporting the association between functional activation in those areas and pain perception. Findings corroborate results of studies using a similar version of the Cyberball task (Bungert et al., 2015). Authors reported increased pain-induced brain response in the insula, amygdala and right thalamus. Contrary to current findings, authors also reported bilateral activation in the anterior cingulate cortex. A possible explanation for different findings could be that samples of both studies differ with regards to age, sex and comorbidities. Supporting that notion, multiple studies indicated that all of those factors influence pain perception (Fillingim et al., 2009; Lautenbacher et al., 2005). Partially overlapping neural activation patterns of patients on OMT and patients with borderline personality disorder in the study by Bungert et al. 2015 might result from shared disease processes. It is conceivable that both patient groups show patterns of unstable and intense interpersonal relationships and repeated, potentially self-damaging, impulsivity (e.g. substance abuse) that might underlie the observed behavioral and neural patterns. Future studies are needed to determine similarities and differences between both patient groups.

In line with the second hypothesis, results of our study demonstrated reduced brain response in opioid-dependent patients during pain trials in superior and middle occipital, fusiform gyrus and cuneus. Studies have found that the fusiform gyrus is active during painful electrical stimulation (Roy et al., 2009; Schwedt et al., 2014). Other research reported increased heat pain stimulus-induced activation in the lateral occipital gyrus and cuneus (Maleki et al., 2013). It has been suggested that those areas are active when expectations regarding pain intensity are violated, e.g. a preceding cue does not correctly predict pain intensity (Roy et al., 2009). This might indicate that neuro-adaptation and

learning processes contribute to an altered pain perception in opioid-dependent patients on OMT.

In line with the third hypothesis, social exclusion was associated with increased subjective pain. This result corroborates previous findings that social interaction and social support modulate pain perception (Campbell et al., 2011; Master et al., 2009).

In accordance to earlier work and our fourth hypothesis, our results indicated that social integration modulates the magnitude of perceived exclusion in opioid dependent patients (Karremans et al., 2011). Patients in a relationship reported to feel more included during social inclusion and exclusion trials. In addition, a positive association between childhood trauma and feelings of exclusion during social *inclusion* trials was found, while no relation between childhood trauma and feelings of exclusion or inclusion during social *exclusion* trials was found. These findings parallel the finding that patients on OMT reported to feel more excluded and less included during social inclusion, while reporting same values as healthy individuals during social exclusion trials. Previous work has established a relation between rejection sensitivity and childhood trauma experience (Downey et al., 1998; Feldman and Downey, 1994). One can speculate that higher rates of childhood trauma in OMT patients might contribute to a predisposition to react with suspicion to positive social feedback, thereby contributing to higher feeling of exclusion during inclusion trials. This proposition harmonizes with findings by Chamberland and colleagues that found that emotional neglect is a predictor of lack of self-esteem and interpersonal difficulties (Chamberland et al., 2012). The missing association between childhood trauma and feelings of inclusion and exclusion during social exclusion trials was unexpected. One can speculate that this might be due to a restricted variability of measurement scores, small sample size or a non-linear association between trauma and reaction to social exclusion or a combination of all of the aforementioned. Results of multiple regression analyses indicated that group affiliation (patient vs. healthy control) best predicted subjective experience of social exclusion and inclusion. While this suggests that patient status is most relevant, current findings do also support the notion that partnership status and past learning history contribute to differences in social interaction patients and healthy individuals.

A possible limitation of the current study is the rather small sample size. Therefore, small effects might have been lost. The current study intended to address this issue by implementing more liberal statistical thresholds for a selected number of analyses of interest. Further, the study sample was too small to allow for subgroup analyses based on age. However, we intended to reduce bias risk by matching control group to the patient sample with regards to age and sex. Moreover, patients that were included in the current study took substances other than methadone (or buprenorphine), such as benzodiazepines. This might limit internal validity, but a naturalistic sample of opioid-dependent patients – as included in the current sample – might enhance external validity and therefore represent a reasonable trade-off between both entities. In addition, we intended to control for the effects of psychotropic substances by considering a composite medication load in our statistical analyses. While psychotropic substances undoubtedly have the potential to induce changes in brain activation, the significance of reported results did not change when medication load was controlled for. While the pharmacokinetics of buprenorphine and methadone are different, there is a lack of research on differential effects of both pharmaceuticals on neural response. Some studies investigating effects of methadone and buprenorphine on heroin cue-induced brain response found that acute administration of buprenorphine and methadone both reduced neural activation in the amygdala and in the hippocampal complex, while activation in the ventral tegmental area (VTA) and thalamus was only reduced by buprenorphine and insular activation only by methadone (Langleben et al., 2008; Mei et al., 2010). However, those effects were observed after acute administration of both substances and patients in the current study were scanned hours after last administration of either buprenorphine or methadone. In addition, less than one third of patients in the current sample were treated with buprenorphine. Therefore, combining both groups in the current study most likely didn't bias results substantially. Additionally, group sizes for analyzing the effect of social support (i.e. relationship status) were limited and results need further validation.

According to previous neuroimaging studies on pain perception, the current study determined pain thresholds at an individual level (Wilcox et al., 2015). Neuroimaging studies that compared percept-related (i.e. subjective experience of pain) and stimulus-related (i.e. nociceptive properties) models to identify brain networks associated with pain concluded that percept-related models capture more extensive activation than stimulus-related models, suggesting that physical properties of the stimuli do not correspond directly to the experience of pain, neither to the extent of fMRI activation (Wilcox et al., 2015). While this seems to favor analytical approaches using percept-related models, there still might be a contribution or risk of bias resulting from differences in absolute stimulus properties. Therefore, we performed additional analyses of the imaging data using the absolute temperature of the individual pain threshold as covariate. Results showed that significance of the results remained unchanged and the peak activation voxels could be replicated.

While social exclusion might be a predisposing factor for addictive disorders and the current study cannot draw conclusions about causal relations, much evidence supports the notion that social exclusion persists even when drug use is reduced or ended, and remains strongly associated with mental health symptoms (Link et al., 1997). Therefore, the investigation of social exclusion in the current study might contribute to a better understanding of the effects of social cognition during the course of dependence as well as treatment success in stimulant abusers.

To sum up, current results indicate that opioid-dependent patients experience more social exclusion and less social inclusion during experimental induction of social inclusion which is accompanied by a reduced variability of neural brain response in brain areas associated with social cognition and emotion processing. In addition, response to social inclusion and exclusion was modulated by social integration, i.e. partnership status. This indicates that nega-

tive social affect, which is a potential trigger for a relapse to heroin, can be attenuated by social integration. Therefore, therapeutic strategies enhancing social integration of opioid-dependent patients might be an important therapeutic element for reducing relapse risk.

Authors contribution

Authors Derik Hermann, Falk Kiefer, Christian Vollmert and Sabine Vollstädt-Klein designed the study and wrote the protocol. Authors Patrick Bach, Ulrich Frischknecht, Melanie Bungert and Damian Karl managed the literature searches and analyses. Authors Patrick Bach, Damian Karl, Sabine Vollstädt-Klein and Ulrich Frischknecht undertook the statistical analysis, and authors Patrick Bach, Stefanie Lis, Derik Hermann and Christian Vollmert wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None of the authors reported any financial interests or any potential conflicts of interest.

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Supplementary materials

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