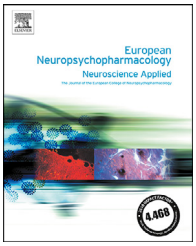
European Neuropsychopharmacology (2019) 29, 1442–1452



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The effects of nalmefene on emotion processing in alcohol use disorder – A randomized, controlled fMRI study

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Received 27 June 2018; received in revised form 13 September 2019; accepted 29 October 2019

KEYWORDS
Addiction;
Attentional bias;
Emotion processing;
Dot-probe;
Emotional faces task;
Opioid system

Abstract
Nalmefene is a μ- and δ-opioid receptor antagonist and a partial κ-opioid receptor agonist. The drug is suggested to reduce the craving for, and the consumption of alcohol effectively, also alleviating anxiety and anhedonia. The present fMRI study is the first to investigate the processing of emotions as a possible mechanism of action of nalmefene in humans. Fifteen non-treatment-seeking participants suffering from alcohol use disorder (AUD) (24–66 years; 5 females) finished this randomized, placebo controlled, double blind study. Following a cross over design, participants received either a single dose nalmefene or a placebo, with an interval of one week between sessions. Using fMRI, we investigated neural reactivity during the presentation of emotional faces picture sets. Additionally, we performed a visual dot-probe task to detect nalmefene's effects on attentional bias. We detected an increase in the response to emotional faces in the supramarginal gyrus, the angular gyrus as well as the putamen in the nalmefene vs. placebo condition. However, contradictory to our initial hypotheses, amygdala activation was not altered significantly in the placebo condition – a limitation, which might be associated with a lack of activation in the placebo condition maybe due to the small sample size. Attentional bias analyses revealed an interaction effect by trend, which was driven by a significant effect in a sub-analysis showing increased attentional shift towards happy compared to fearful facial expressions under nalmefene. Nalmefene increased brain activation in

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https://doi.org/10.1016/j.euroneuro.2019.10.014

areas responsible for empathy, social cognition and behavior, which might help alleviating the reinforcing properties of alcohol.

1. Introduction

Alcohol use disorder (AUD) is very prevalent and its associated individual and societal burden is high (Rehm et al., 2013). Current data indicate that the level of alcohol consumption in Europe is double the global average (Rehm et al., 2012). Approximately 12% of the European population drinks in a harmful way and 5.4% of all men, and 1.5% of all women suffer from an AUD (Rehm et al., 2012). This situation is aggravated by the fact that, amongst those suffering from an AUD, treatment outcomes are unsatisfying and relapse rates are very high.

During the course of an AUD, adaptations in endogenous opioid pathways, e.g. changes in transmitter levels, such as up- and downregulation of dynorphin A and alterations of opioid receptor availability and binding (μ-, δ-opioid and κ-opioid receptor (KOR)) may lead to aversive emotions and depressive-like emotional states and behaviors (Koob and Le Moal, 2008; Koob and Volkow, 2016). Relapse has been attributed to and often is triggered by negative and aversive emotions, stress and interpersonal conflicts as well as withdrawal symptoms and substance craving (Chung and Maisto, 2006). Against this backdrop, higher amygdala activation following an emotional faces task was revealed in depressed patients if compared to healthy participants – a finding that could be resolved by an antidepressant (Sheline et al., 2001). With respect to AUD, a recent fMRI study (Gowin et al., 2016) highlighted that heavy drinkers show increased amygdala activation to fearful faces. Moreover, an attentional bias, i.e. the phenomenon of hyper-attention towards alcohol related visual triggers, has also been associated to increased relapse risk in AUD (Vollstädt-Klein et al., 2009). Therefore, alcohol might be exploited as a 'self-treatment', due to its anxiolytic effects, negatively reinforcing drinking. Despite all this, it is well known that the majority of AUD patients do not receive adequate and disorder-specific treatment (Kraus et al., 2015). The resulting treatment gap also arises out of, at least from patients' perspective, the choice of unattractive treatment goals, e.g. the 'gold standard' of AUD treatment – lifelong abstinence. Picking up on this conflict, the European Medicines Agency recommended a reduction of alcohol consumption as an alternative treatment goal and the US Food and Drug Administration highlighted a reduction in heavy drinking as an alternative clinical outcome for AUD treatment studies (European Medicines Agency (EMA), 2010; Food and Drug Administration, 2015). Taking this into account, pharmacological agents developed to reduce alcohol consumption, such as naltrexone and nalmefene, both modifying endogenous opioid signaling, are becoming increasingly important.

Naltrexone is a μ-, δ-opioid and κ-opioid receptor antagonist. Intriguingly, whereas selective blockade of μ- and δ-opioid receptors reduces alcohol self-administration in non-dependent rodents, selective blockade of κ-opioid receptor (KOR) does not (Lutz and Kieffer, 2013). In humans, oral naltrexone is effective in preventing 'any drinking' (Number needed to treat (NNT) = 20) and 'return to heavy drinking' (NNT = 12) (Jonas et al., 2014) as well as self-reported craving (Hendershot et al., 2017). On a neurobiological basis, neural cue-reactivity as the brain's response to alcohol-associated cues and contexts has been established as an objective measure to assess the anticipation of the rewarding effects of alcohol (Yalachkov et al., 2012). It has been demonstrated that naltrexone decreases fMRI cue-reactivity in the ventral striatum of non-treatment-seeking alcoholics, and has been found to be efficacious in patients with increased neural cue-reactivity especially (Miranda et al., 2014; Myrick et al., 2008). In 2013, nalmefene was introduced and approved in the European Union for the reduction of alcohol consumption (Mann et al., 2016). Nalmefene is a μ- and δ-opioid receptor antagonist and a partial KOR agonist, distinguishing it from naltrexone. It has been hypothesized that nalmefene counteracts endogenous opioid signaling if the KOR network is activated, but is also able to enhance downregulated opioid signaling (Lutz and Kieffer, 2013). As mentioned above, increased endogenous opioid signaling might cause anxiety, anhedonia and negative emotions (Mann et al., 2016), all of which has been linked to craving and relapse. In line with this, nalmefene's tone dependent antagonism of the KOR pathway might therefore reverse anxiety and negative affect but compulsive and habitual alcohol consumption, as a result of an increased dynorphin tone in the dorsal striatum in severe AUD, as well (Quelch et al., 2017). This might facilitate the correct decoding and identification of emotional facial expressions and might prevent or attenuate social conflicts, again reducing relapse risk and alcohol intake subsequently (Mann et al., 2016). Regarding alternative treatment goals and harm reduction strategies, a recent meta-analysis (Jonas et al., 2014) found that nalmefene is more efficacious in reducing alcohol consumption than in maintaining abstinence. Nevertheless, up to now there is no data on the neural effects of a single oral dose of nalmefene on emotion processing in non-treatment seeking AUD subjects, using fMRI.

To address these issues, the present study investigates whether nalmefene (i) decreases neural activation of brain structures involved in emotion processing, e.g. the amygdala, and (ii) increases the activation of brain structures responsible for empathy and the facilitation of social interaction, e.g. the angular as well as supramarginal gyrus, if compared to neural activation of the same structures following the administration of placebo. Finally, we expected nalmefene to alleviate the attentional bias towards fearful faces, using a visual dot-probe paradigm. The above-mentioned aspects might be associated with improved emotional control and social skills, which again might reduce risk of relapse or the amount of alcohol consumed.

2. Experimental procedures

The study was approved by the Ethics Committee of the Medical Faculty Mannheim at the University of Heidelberg, Germany (registration at: clinicaltrials.gov; NCT02372318). Non-treatment seeking participants suffering from AUD were enrolled in this study, and all individuals gave their written informed consent. All clinical investigations were conducted considering the Declaration of Helsinki.

2.1. Sample and study plan

Participants were recruited between 2015 and 2016 by newspaper advertisements, flyers in bars and via the internet. They received a financial compensation of 100 Euro upon successful completion of the study procedures. Only non-treatment seeking participants were enrolled in the study. Initially, 115 participants were prescreened via telephone. Inclusion criteria were: right-handedness, normal or corrected to normal vision, age between 18 and 70 years, diagnosis of an AUD (following DSM-5, American Psychiatric Organisation, 2013), which corresponds to former nomenclature "dependence" (Dawson et al., 2013) as well as ICD-10 criteria (in order to allow for the fact that nalmefene is approved in Europe only) and consumption of more than 60 g alcohol per day (male participants) and more than 40 g per day (female participants) on at least five days per week. Exclusion criteria were: intoxication (breath alcohol concentration $>$ 0.3 ‰), diagnosis of any other Axis-I disorder according to DSM-IV-TR, except from nicotine dependence in the last 12 months (as assessed using a standardized psychiatric interview, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), First et al., 2001), previous severe withdrawal or withdrawal complications, previous inpatient detoxification treatment, intake of any psychoactive substances, anti-craving or anticonvulsive medication within the last 14 days, comorbid severe internal or neurological condition (including liver cirrhosis, viral hepatitis and clinically relevant liver function deficits, i.e. altered clotting), positive drug-screening and/or relevant withdrawal symptoms (CIWA-Ar, Sullivan et al., 1989 score $>$ 4) at the investigation day, any contraindications for receiving a MRI-scan (e.g. metal implants, pregnancy, lactation), contraindications for the administration of nalmefene. Of the initial 115 subjects, 29 were included and 86 were excluded because they did not meet all the inclusion criteria. After the baseline investigation, further six subjects opted to withdraw from the study (for the CONSORT flow diagram, please see Supplementary Fig. 1).

At the beginning of the first investigation session, the remaining participants were randomized to two groups ('the nalmefene/placebo group', receiving 18 mg of nalmefene as one single administration at time T1 or 'the placebo/nalmefene group') and following a double-blind, cross-over design they either received nalmefene at time T1 and placebo at time T2 (one week later) or vice versa (for the CONSORT flow diagram, please see Supplementary Fig. 1). A randomization schedule was created for 40 subjects choosing a block length of four, which resulted in ten blocks.

Two hours after the ingestion of the study medication, fMRI measurements followed by the visual dot-probe task were performed. As demonstrated by Kyhl et al. (2016), after oral administration of nalmefene, plasma concentrations reach their peak around 1 to 1.5 h. Further, after a single oral administration of nalmefene μ-opioid receptor occupancy remains between 60% and 90% for up to 22–24 h.

2.2. Procedures

2.2.1. Baseline

Subjects were informed about the aim of the study, study procedures and potential risks associated with their participation. After giving their written informed consent, participants provided sociodemographic data. Participants underwent the Structured Clinical Interviews for DSM-IV, SCID-I, (Wittchen et al., 1997) to rule out psychiatric comorbidities. Moreover, the Revised Clinical Institute Withdrawal Assessment Scale (CIWA-Ar, Sullivan et al., 1989) was applied to rule out withdrawal symptoms at the investigation day and we conducted the Alcohol Dependence Scale (ADS, Skinner and Allen, 1982). All of these were recorded via an electronic platform (Social Science Survey, https://www.soscisurvey.de/).

Moreover, information on somatic and both internal and neurological disorders were collected and a physician performed a medical examination. Furthermore, a blood draw, urine drug screening, measurement of breath alcohol concentration, and in females a pregnancy test was performed.

2.2.2. Cross over sessions T1 and T2

At both time points, participants were examined medically, current withdrawal symptoms were recorded, urine drug screenings, measurement of breath alcohol concentration, and in females a pregnancy test was performed. Moreover, possible changes in medication were documented. After assuring the absence of any exclusion criteria valid at MRI investigation, study medication was handed out to the participant and intake was supervised. Alcohol consumption since baseline measurement or investigation day 1 respectively was recorded using the Form 90 interview (Scheurich et al., 2005). Before actual fMRI measurement, the participants' craving status was captured via paper-pencil assessment applying the Alcohol Urge Questionnaire (AUQ, Bohn et al., 1995), the Alcohol Craving Questionnaire (ACQ, Raabe et al., 2005), Mannheim Reward-Relief Drinking Scale (Nakovics and Mann) and visual analogue scales. Subsequently, participants underwent fMRI measurement comprising an emotional faces processing task ('emotional faces task', Hariri et al., 2002). After the fMRI, the AUQ and ACQ were applied again and participants completed two computer-based tasks as well. They worked on a short memory test to verify task attendance and an emotional dot-probe task to capture attentional bias in emotional information processing (adapted from Vollstädt-Klein et al., 2009). After a quick medical check-up, participants were dismissed. On T2, the Mannheimer Craving Scale (MaCS), i.e. a questionnaire for quantitative measurements of craving and obsessive-compulsive symptoms in the context of substance abuse and dependence (Nakovics et al., 2009) and the ADS were administered additionally after the fMRI session.

2.3. fMRI

Scanning was conducted using a Siemens MAGNETOM 3 Tesla whole-body-tomograph (MAGNETOM Trio, TIM technology, Siemens, Erlangen, Germany), collecting 135 T2*-weighted echo-planar images (EPI) for each participant. All participants underwent the same emotional faces task (angry/fearful faces vs. forms; for more details please see (Hariri et al., 2002) and Supplementary Fig. 2). During the emotional faces task, the standardized imaging parameters were as follows: TR = 2 s, TE = 30 ms, flip angle = 80°, 28 slices, slice thickness = 4 mm, 1-mm gap, voxel dimensions 3 × 3 × 3 mm^3, *field of view* (FOV) = 192 × 192 mm^2, 64 × 64 in-plane resolution). To rule out structural alterations of the brain, a T1-weighted 3D Magnetization prepared rapid gradient-echo dataset consisting of 192 sagittal slices (slice thickness 1 mm, 1 × 1 × 1 mm^3 voxel size, FOV 256 × 256 mm^2, TR = 2300 ms, TE = 3.03 ms, flip angle = 9°) was acquired.

The visual stimuli were presented via goggles using MRI Audio/Video Systems (Resonance Technology Inc., Los Angeles, CA, USA) and picture presentation as well as behavioral data were performed using the Presentation® software (Version 17.0,

Neurobehavioral Systems Inc., Albany, CA, USA) (for more details please see Vollstädt-Klein et al., 2012).

2.3.1. *The visual dot-probe task* (adapted from Vollstädt-Klein et al., 2009)

By using the visual dot-probe task, we measured the attentional bias towards emotional faces. Pictures were derived from the standard set of emotional pictures (Ekman and Friesen, 1976), showing either, happy, fearful or neutral facial expressions. Participants were seated in front of a 13-inch display laptop with a display resolution of 600 × 800 pixels. Picture pairs were presented for 50 ms. Pairs comprised either an emotional facial expression (happy vs. fearful) or a neutral facial expression. Participants were instructed to concentrate highly on the picture pairs. Immediately after the presentation of the picture pairs, a dot-probe appeared in either the location of the left or the right picture. Participants had to respond as quickly as possible and were instructed to state whether the dot appeared on the right or the left side.

If the subjects made any errors or if the subjects' reaction time exceeded 1000 ms, trials were not included in the analyses. An attentional bias score (Lubman et al., 2000) to happy faces was calculated for each participant by subtracting the mean response time in milliseconds in congruent trials (the dot replaced a picture showing a happy facial expression) from the mean response time in incongruent trials (the dot replaced a neutral picture) so that values greater than zero indicated an attentional bias to happy facial expressions. For fearful faces, an attentional bias score was calculated similarly.

2.3.2. Pre-processing and statistical analyses

Individual and group brain imaging data were analyzed using the statistical parametric mapping software for Matlab version 8 (SPM, Wellcome Department of Cognitive Neurology, London, UK). We eliminated the first five MRI images to minimize the risk of artefacts due to magnetic saturation effects. The remaining MRI scans were temporally realigned to minimize temporal differences in slice acquisition, corrected for residual geometric distortion on the basis of the acquired magnetic field map, spatially realigned to correct for movement, as well as normalized to a standard MNI [Montreal Neurological Institute, Quebec, Canada] EPI template before smoothing using an isotropic Gaussian kernel for group analysis (8 mm Full Width at Half Maximum).

2.4. Statistics

We used the Statistical Package for the Social Sciences (SPSS) version 24.0 for Windows to perform the analyses of psychometric and dot-probe data. A two-factorial analysis of variance (ANOVA) with the factors: medication (nalmefene vs. placebo) and facial expression (happy vs. fearful) was conducted. Descriptive results are reported as means and standard deviations (SD). Statistical analyses of the pre-processed fMRI data on the first (individual) level were performed by modeling the different conditions (boxcar functions convolved with the hemodynamic response function) as explanatory variables within the context of the general linear model (GLM) on a voxel-by-voxel basis with SPM8. Realignment parameters were included as regressors of no interest.

Individual images (contrast: "faces > forms", according to the procedure in previous studies since the emotional faces task is not designed to discriminate between diverse emotions) of the participants were included in second-level analyses to identify main effects (one sample *t*-test), differences between the nalmefene and the placebo condition (paired *t*-test) as well as the association between brain activation and ADS (linear regression). To control for multiple statistical testing the probability of a family wise error (FWE) was set to 0.05. For this purpose, we used a voxel-wise threshold of $p < .01$ combined with a cluster extent threshold, determined the program 3dClustSim implemented in the software Analysis of Functional NeuroImages (AFNI, https://afni.nimh.nih.gov/), using 25,000 Monte Carlo simulations. The cluster extent threshold was 439 voxels for the one sample *t*-test, 462 voxels for the paired *t*-test and 438 voxels for the linear regression. Estimation of smoothness based on the residual images was conducted using SPM by taking the maximum of the 3 estimated parameters in *x*, *y* and *z* direction.

3. Results

3.1. Sample description

The final sample consisted of 15 participants (5 females; with a mean age of 54 ± 11 years, range from 24 to 66 years), who finished all investigational examinations. Of those, eight were smokers (53%). Participants fulfilled 6.3 ± 1.4 of the DSM-5 as well as 4.2 ± 1.0 of the ICD-10 criteria of an AUD and consumed 7.0 (±4.5) standard drinks of alcohol (à 12 g) per day, adding up to an average of 84 ± 54 g pure alcohol per day (for details on drop-outs see Table 1, Supplementary Fig. 1 as well as CONSORT flow diagram).

3.1.1. Nalmefene side effects

23 participants were exposed to study medication on at least one investigational day. 10 (44%) experienced medication side effects. These comprised between two and eleven symptoms, with a mean of 5.8 (SD = 2.7) symptoms (see Table 1). The symptoms lasted between 11 and 84.5 h with a mean duration of 37.5 (SD = 22.3) h. Of the 15 participants included in the final analysis (emotional faces task), 7 participants (47%) reported medication side effects. They experienced on average 6 (SD = 2.8) symptoms, lasting 35.4 (SD = 26.2) h (range: 11–84.5 h, see Table 1). Of the 11 participants included in the final analysis (dot-probe paradigm), 5 participants (45%) reported medication side effects. They experienced on average 5.4 (SD = 2.4) symptoms which lasted 35.2 (SD = 28.9) h (range: 11–84.5 h, see Table 1).

3.1.2. The emotional faces task

The final sample comprised 15 participants (for details on drop-outs see Supplementary Fig. 1, CONSORT flow diagram). Processing of emotional faces (angry, fearful) and neutral geometric forms were captured to detect alterations of activation in brain regions responsible for emotional processing and empathy after administration of placebo or nalmefene.

Brain regions with increased BOLD-signal during the "emotional faces task" (contrast "faces>forms") in the placebo condition included bilateral inferior, middle and superior occipital gyrus, the cuneus as well as the left inferior temporal and fusiform gyrus. Following the administration of nalmefene, an increased BOLD-signal in the bilateral inferior and middle occipital and fusiform gyrus, as well as the left hippocampus, parahippocampus and thalamus was revealed.

Neural response to faces vs. forms was significantly higher in the nalmefene vs. placebo condition in the bilateral

Table 1 Reported side effects of nalmefene of $N = 23$; $N = 15$ (included in the final analyses) and $N = 11$ (included in the final analyses + dot-probe task) participants.

Symptom	$N = 23$	$N = 15$	$N = 11$
Insomnia	5	4	4
Vertigo	5	3	2
Nausea	4	2	2
Faintness/drowsiness/tiredness	4	4	3
Appetite loss	3	3	1
Headache	2	1	0
Tunnel vision	2	2	0
Tenseness	2	2	2
Restlessness	2	1	0
Irritability/aggressiveness	2	1	0
Perceptional disturbance	2	1	1
Attention deficit/lack of concentration	2	2	1
Depersonalization	2	0	2
Derealization	1	0	0
Skin tingle	1	1	1
Numbness (of body parts)	1	1	0
Body perceptional disturbances	1	1	0
Arrest of thought	1	0	1
Stimulus satiation	1	1	0
Prolonged reaction time	1	0	1
Panic/anxiety	1	1	0
Diarrhea	1	1	1
Dry throat	1	0	1
Increased salivation	1	1	1
Tremor	1	1	1
Palpitation	1	1	0
Hot and cold feeling	1	1	0
Cold sweat	1	1	1
Hyperhidrosis	1	1	1
Nervousness/uneasiness	1	1	1
Impairment in daily life	1	1	1

inferior parietal lobule (i.e. contrast "faces - forms", comparison nalmefene vs. placebo), including the right angular gyrus and the supramarginal gyrus (Fig. 1(A)), and the left middle as well as posterior cingulate gyrus as well as the left putamen (Fig. 1(B)) (see also Table 2). There was no significant decrease in brain activation in any brain region by nalmefene.

In the placebo condition, we were only able to detect statistically significant amygdala activation (i.e. contrast "faces - forms" in the placebo condition) at an uncorrected threshold [left amygdala: $T = 3{,}95$; $(x,y,z) = (-22, -8, -12)$; 25 voxel; right amygdala: $T = 2{,}92$; $(x,y,z) = (26, -8, -14)$; 14 voxel; $T = 1{,}88$; $(x,y,z) = (28, -2, -28)$; 5 voxel]. This limitation might be associated with the small sample size. The linear regression on analyses did not reveal any statistically significant associations between the ADS, AUQ, ACQ as well as the MaCS and the neural activation (i.e. contrast "faces - forms") in the emotional faces task.

3.1.3. The visual dot-probe task

The two-factorial ANOVA (medication/facial expression) did not reveal a statistically significant interaction effect, most probably due to the small sample size ($N = 11$). However, an interaction effect by trend was revealed [$F(1,10) = 4.28$; $P = .066$], which was driven by an increased attentional shift towards happy compared to fearful facial expressions under nalmefene ($t = 2{,}00$; $P = .037$) (see Table 3 and Fig. 2). The linear regression analyses did not reveal any statistically significant associations between the ADS, AUQ, ACQ as well as the MaCS and the visual dot-probe task.

4. Discussion

Here, we present data on the first randomized, placebo-controlled, double blind study to investigate nalmefene's effects on emotion processing in non-treatment seeking humans suffering from AUD.

In line with our hypotheses, nalmefene increased neural activation of brain structures mediating social interaction and empathy (i.e. contrast "faces - forms", comparison nalmefene vs. placebo). Specifically, nalmefene significantly heightened neural response to faces in the bilateral inferior parietal lobule, including the right angular and supramarginal gyrus, and also in the left middle and posterior cingulate gyrus as well as in the putamen. This is in line with the limited literature in this field. It has been shown that the supramarginal gyrus is important for empathy (Lawrence et al., 2006) and especially the right supramarginal gyrus seems to be important to overcome emotional egocentricity bias in social judgments, strengthening the self as a reference point to perceive the world and gain information about other people's mental states (Silani et al., 2013). Moreover, it has been reported that the inferior parietal lobule promotes decoding of dynamic facial expressions (Sarkheil et al., 2013), while the angular gyrus, as part of the inferior parietal lobule has been associated with attention and spatial, as well as social cognition in healthy participants (Seghier, 2013). The angular gyrus has also been associated to the concept of theory of mind, i.e. the ability to understand others' mental states, in humans (Kandylaki et al., 2015; Seghier, 2013). With respect to AUD, one further study (Uekermann and Daum, 2008) found that patients suffer from severe impairments of social cognition, including problems of emotional face perception, as well as theory of mind and humor processing deficits, if compared to healthy controls. In line with this, Salloum et al. (2007) reported on reduced activation of the cingular gyrus in AUD patients vs. healthy controls following the presentation of facial expressions, such as fear and disgust. Furthermore, a meta-analysis (Fusar-Poli et al., 2009), investigating fMRI studies showed that healthy participants experience increased activation of the putamen following the processing of emotional facial expressions. Taking this a step further, the present study adds evidence to the hypothesis that nalmefene might enhance, i.e. normalize, activation in brain regions responsible for social skills and empathy. This might therefore be interpreted as a beneficial effect, caused by the drug, on the individuals' ability to interact socially, which again might decrease the amount of alcohol consumed and might also decrease the risk of relapse in AUD patients.

Up to now only one clinical trial investigated nalmefene's influence on fMRI activation in humans suffering from

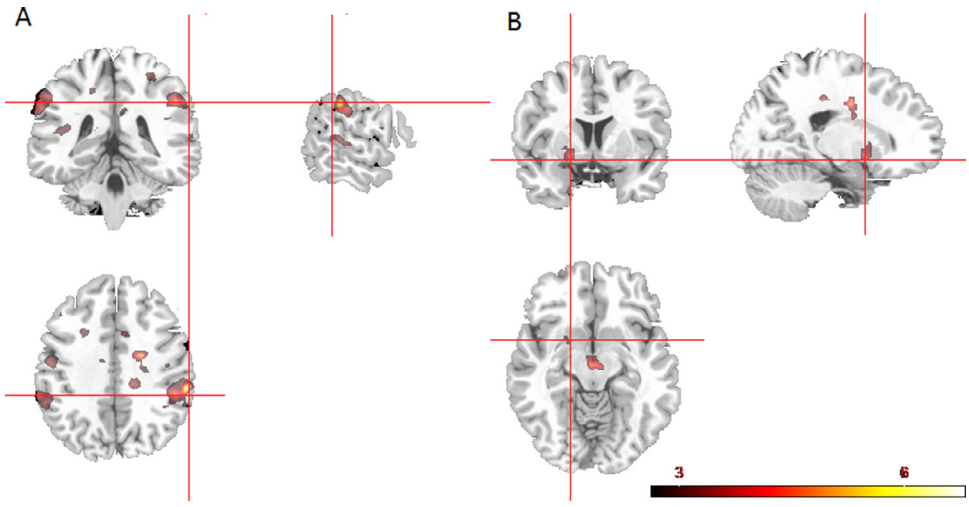

Fig. 1 Brain regions with increased BOLD-Signal during the "emotional faces task" (contrast "faces > forms") after 18 mg nalmefene compared to placebo; $p < .05$ FWE-corrected (corresponding to cluster extent threshold $p < .01$, 462 voxels), A: left putamen, $(x,y,z) = (-20,6,-10)$, B: bilateral inferior parietal lobule, $(x,y,z) = (62,-38,38)$.

Table 2 Brain regions with increased BOLD-Signal during the "emotional faces task" (contrast "faces > forms") after 18 mg nalmefene compared to placebo; $p < .05$ FWE-corrected (corresponding to cluster extent threshold $p < .01$, 462 voxels).

Hemisphere/lobe	Brain region	Brodmann area	Cluster size	MNI coordinate			*T* value
				x	*y*	*z*	
L parietal lobe	Inferior parietal lobe (postcentral gyrus, supramarginal gyrus)	40, 2	822	−58	−34	38	6.79
L limbic lobe	Middle and posterior cingulate gyrus	31, 23	478	−22	−6	34	5.97
L	Putamen, red nucleus, left palli-dum		644	6	−18	−8	5.19
R parietal lobe	Inferior parietal lobe (angular gyrus, supramarginal gyrus)	39, 40	643	62	−38	38	4.37

Table 3 Mean (M) and standard deviations of reaction times (RT) and attentional bias scores (RT incongruent - RT congruent) to fearful (a) and happy (b) faces, $N = 11$; *p* and *t* values corresponding to paired *t*-tests.

Medication						
Trial type	Nalmefene		Placebo			
	M	SD	*M*	SD	*t(10)*	*p*
(a)						
RT incongruent (fearful) [ms]	496,32	102,12	497,76	69,65	0.062	.952
RT congruent (fearful) [ms]	498,27	93,00	485,87	69,91	−0.603	.560
Attentional bias [ms]	−1,96	21,54	11,89	25,99	1.224	.249
(b)						
RT incongruent (happy) [ms]	493,61	97,81	491,62	72,76	−0.119	.908
RT congruent (happy) [ms]	480,73	85,62	489,19	64,99	0.628	.544
Attentional bias [ms]	12,87	23,60	2,42	16,10	−1.191	.261

AUD - using a monetary incentive delay task during an i.v. alcohol challenge (Quelch et al., 2017). The researchers showed that in the presence of the alcohol infusion, nalmefene significantly reduced the BOLD response in the striatal region of interest, including parts of the putamen, globus pallidus, nucleus accumbens as well as caudate, compared with placebo (Quelch et al., 2017). This finding contrasts with the present finding, since we did not detect decreased but increased neural response following the administration of nalmefene. However, the paradigm used in the reported study (Quelch et al., 2017) is significantly different from that we used, focusing on emotional processing rather than on reward anticipation.

Not in line with our hypotheses, nalmefene did not decrease amygdala activation following the presentation of emotional faces (i.e. contrast "faces - forms", comparison nalmefene vs. placebo). This is counterintuitive since it has been stated that low reactivity of the amygdala and high

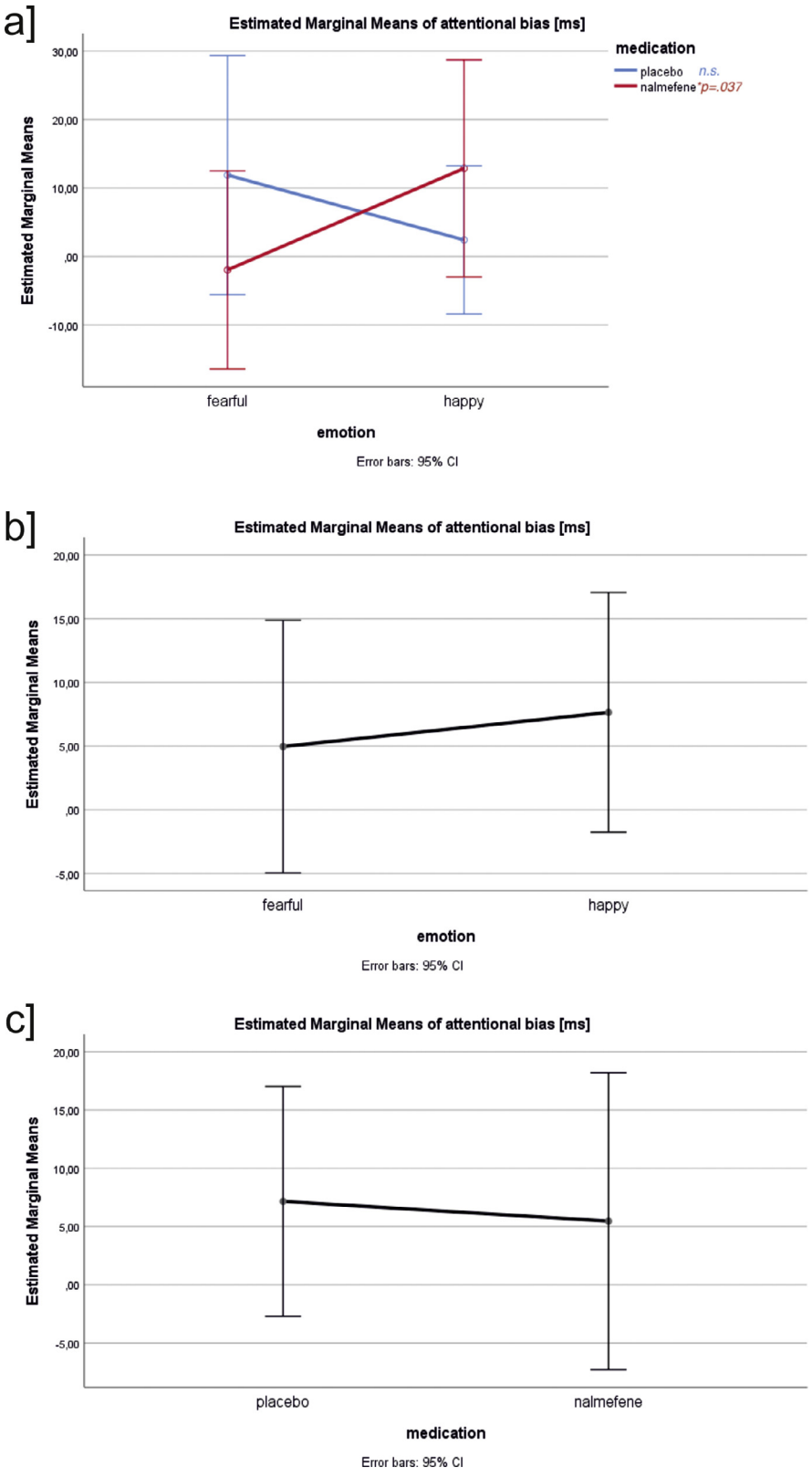

Fig. 2 Attentional bias scores (RT incongruent – RT congruent) to (a) fearful and happy faces under placebo and nalmefene; (b) fearful and happy faces (main effect of emotion); (c) under placebo and nalmefene (main effect of medication); $N = 11$.

activity of the prefrontal cortex are necessary to enable successful emotional regulation (Hariri et al., 2002). Moreover, both depressed (Sheline et al., 2001) as well as alcohol dependent patients (Gowin et al., 2016) showed higher amygdala activation following an emotional faces task. Interestingly, the higher amygdala activation could be resolved by an antidepressant in the first (Sheline et al., 2001) and varenicline in the second study (Gowin et al., 2016). Additionally, a recent study (Gilman et al., 2012) demonstrated that social but not heavy drinkers, receiving an i.v. alcohol challenge, experience a significant amygdala activation following the presentation of fearful faces. Jorde et al. (2014) highlighted that an increased cue-reactivity of the amygdala of AUD patients, who are G-allele carriers of the GATA4 gene, that encodes a transcription factor of atrial natriuretic peptide, might predict lower relapse risk. Additionally, amygdala activation to fearful faces correlated with both the number of drinks consumed in the previous 90 days and obsessive-compulsive drinking scale scores. Therefore, the authors concluded that amygdala response to fearful faces may be developed as a biomarker of the effectiveness of medications for the treatment of AUD (Gowin et al., 2016). In a very recent study, Savulich et al. (2017) compared effects of naltrexone to those of placebo on neural response of alcohol dependent as well as poly-drug dependent individuals, while viewing aversive and neutral images. With respect to emotional processing, a group-by-treatment-by-condition interaction in the right amygdala was revealed, which was mainly driven by a normalization of response for aversive relative to neutral images under naltrexone in the alcohol/drugs group. The authors suggested that naltrexone might influence on negative emotional processing in combined alcohol and drug dependence, but not alcohol dependence alone, possibly due to alterations in endogenous opioid transmission or due to naltrexone's antagonistic action at the KOR. Finally, in another study (Wardle et al., 2016), naltrexone increased attention to emotional expressions, slowed identification of sadness and fear, and decreased ratings of arousal for social and nonsocial emotional scenes. The authors stated that their findings contribute to naltrexone's antagonistic activity at the KOR more than to its effects at μ-opioid receptors (Wardle et al., 2016).

With regard to the reported studies, in animal models of AUD, brain region dependent increased (for review please see Mann et al., 2016) as well as decreased (Quelch et al., 2017) dynorphin A and/or altered KOR signaling have been associated with increased negative affect and dysphoric states, which again might promote relapse. Therefore, both naltrexone as well as nalmefene would antagonize alcohol-induced opioid release in mesolimbic pathways, via blockade of μ- and δ-opioid receptors. In addition, nalmefene could also have differential, tone dependent effects on dynorphin A and KOR signaling (Quelch et al., 2017). On the one hand, nalmefene might alleviate the up-regulated dynorphin A and KOR tone in ventral striatal and orbitofrontal as well as dorsolateral pre-frontal areas (Walker et al., 2012), which would result in a decrease of the rewarding effects of alcohol. On the other hand, a down-regulation of the KOR has been reported in the caudate and putamen, i.e. parts of the dorsal striatum, of patients suffering from AUD (Sarkisyan et al., 2015). Intriguingly, a low KOR activity would lead to increased dopamine signaling (Quelch et al., 2017), again increasing the risk for substance intake and relapse, since it has been shown that 'the ventral to dorsal shift' is associated to compulsive and habitual alcohol consumption (Vollstädt-Klein et al., 2010). In such a condition, nalmefene could have the ability to increase KOR (re-)activity, preventing compulsive and habitual alcohol consumption (Quelch et al., 2017). It is of note, that in the present study, neural cue-reactivity in the putamen was indeed higher following the administration of nalmefene if compared to placebo.

Taking up on these aspects, it would have also been 'plausible' if nalmefene, in analogy to the antidepressant, varenicline and naltrexone, had decreased amygdala activation in patients – approaching to the findings in healthy participants. However, in the present study, neither the placebo nor the nalmefene condition revealed statistically significant amygdala deactivation. Therefore, we point out that the reported results are preliminary given the small sample size of 15 participants (emotional faces task). Against this backdrop, the small sample size might be the reason of a significant bilateral activation only at an uncorrected threshold in the placebo condition. In addition, it remains speculative whether nalmefene's partial agonistic actions at the KOR are necessary for the alleviation of emotional processing in AUD at all. It also would be possible that μ- and δ-receptors might be more relevant. In order to answer this as well as the question whether nalmefene exerts differential effects on emotional processing, further investigation is needed. Finally, it has to be emphasized that there are also several studies demonstrating lower (Glahn et al., 2007; Salloum et al., 2007) or failed to detect any (Charlet et al., 2014) amygdala activity in patients compared to healthy participants following the presentation of visual emotional stimuli. With respect to the heterogeneous results, it might only be speculated whether an increase or decrease of the amygdala activation is associated to an impaired emotion processing in AUD patients. The contradictory results might be due to differences in the paradigms used, different disease stages, differences in general study design, medication effects etc. This inconsistency of study findings may also reflect the presence of 'biologically' different subgroups or different stages of the illness (non-treatment seeking vs. alcohol dependent participants or patients suffering from multiple substance use disorders), differences in methodology, timing and frequency of the MRI analyses as well as investigation of small sample sizes.

With regard to the visual dot-probe paradigm, the present study showed a trend towards an attentional shift from fearful to happy facial expression, following the administration of nalmefene. The present study lacks a control group and is not able to directly answer the question whether AUD patients are generally characterized by an attentional bias towards fearful facial expressions. However, according to clinical experience, it seems reasonable that AUD patients might suffer from an attentional bias towards fearful faces/emotions, which again might increase craving and the risk of relapse consequently. In another study, buprenorphine, a partial agonist at the μ-opioid and antagonist at the κ-opioid receptor decreased perceived social rejection during the ball-toss game and reduced initial attention to fearful facial expressions without influencing the atten-

tion to angry, happy, or sad faces. In addition, during the picture-viewing task, buprenorphine increased ratings of positivity of images with social content without affecting ratings of nonsocial images (Bershad et al., 2016). It has to be emphasized, that the results of the dot-probe task might be influenced by both the small sample size ($N = 11$), only detecting a nalmefene interaction effect by trend and a sequence effect since the fact that despite this was a randomized trial, most of the participants, undergoing all investigational time points received nalmefene at T2.

Almost half of the participants experienced side effects of nalmefene. Due to the small sample size, it was not possible to answer the question whether the group differences might be explained by side-effects of nalmefene, since subgroup analyses of participants with vs. without side effects would not have been appropriate. It has to be highlighted that the present study was not aimed to investigate whether low visual neural activity during face processing in brain regions responsible for social interaction and empathy and/or high visual neural activity in areas responsible for emotion processing might predict response to nalmefene. In the last years, nalmefene has been proven to be most effective in patients with high/very high drinking risk levels at the start of treatment (van den Brink et al., 2014, 2015). Up to now, it remains unclear, whether a positive family history of an AUD or other factors, including high baseline craving (Monterosso et al., 2001), early onset of alcohol problems (Rubio et al., 2005) or genetic polymorphisms (Schacht et al., 2013, 2017) might predict better treatment outcome – as it has been shown for naltrexone (Garbutt et al., 2014). In addition, it has been stated that negative emotions and affect, also during early withdrawal in both animal models of AUD as well as in humans (for review please see Mann et al., 2016), might increase the risk of consuming alcohol again, i.e. increasing the risk of relapse in patients suffering from AUD (Anand et al., 2017), nalmefene is not approved to be administrated during early physical withdrawal. Therefore, the present study, just like all clinical nalmefene studies, is not able to assess potential nalmefene effects during and on early withdrawal. Finally, the present study cannot resolve the degree to which smoking or fasting status might have influenced the results, since smoking was not prohibited and participants' meals were not standardized before scanning. However, all scans were performed at the same time of the day.

5. Conclusion

The present study was aimed at investigating the effects of a single dose nalmefene on neural response to angry and fearful faces as well as to examine the influences on attentional bias regarding happy and fearful faces in subjects suffering from AUD. Summing up, it was demonstrated that nalmefene increased neural cue-reactivity in brain regions responsible for social cognition and empathy, which might indicate that nalmefene acts on emotion processing, enabling the patient to decode emotions in facial stimuli better. Specific therapeutic interventions, such as combining nalmefene to the 'training' of special brain areas by real-time functional magnetic resonance imaging neurofeedback (Kirsch et al., 2016) or cue-exposure therapy (Vollstadt-Klein et al., 2011) may help patients to better evaluate situations in social interactions, which again might facilitate the reduction of alcohol consumption or to even maintain abstinence.

Role of the funding source

The study was supported by Lundbeck A/S, Denmark, and by a grant from the Deutsche Forschungsgemeinschaft (grant ID TRR 265/1 2019 SP C01 and SP A03).

Contributors

SVK, KM and FK were responsible for the study design. AO, CD and DK contributed to the acquisition of fMRI and psychometric data. SVK and AO performed the data analysis. SVK, JMB, AO and DH interpreted the data. SVK and JMB drafted the manuscript. AK and DH contributed to the recruitment of patients and conducted physical examinations. All authors revised the manuscript critically for important intellectual content and approved the final version.

Conflict of interest

We do not have further commercial or financial involvements that might present an appearance of a conflict of interest.

Acknowledgments

We would like to thank Ms. Schmid for editing this article, Michael Riess for his assistance in data collection and Sabine Hoffmann for her assistance in data management. Further we would like to thank Prof. Dr. Georg W. Alpers for the review of AO's master thesis on this topic.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.10.014.

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