Psychopharmacology
DOI 10.1007/s00213-014-3573-7

ORIGINAL INVESTIGATION

Opposing neural effects of naltrexone on food reward and aversion: implications for the treatment of obesity

Elizabeth Murray · Sietske Brouwer · Rob McCutcheon · Catherine J. Harmer · Philip J. Cowen · Ciara McCabe

Received: 21 August 2013 / Accepted: 6 April 2014

Abstract
Rationale Opioid antagonism reduces the consumption of palatable foods in humans but the neural substrates implicated in these effects are less well understood.
Objectives The aim of the present study was to examine the effects of the opioid antagonist, naltrexone, on neural response to rewarding and aversive sight and taste stimuli.
Methods We used functional magnetic resonance imaging (fMRI) to examine the neural responses to the sight and taste of pleasant (chocolate) and aversive (mouldy strawberry) stimuli in 20 healthy volunteers who received a single oral dose of naltrexone (50 mg) and placebo in a double-blind, repeated-measures cross-over, design.
Results Relative to placebo, naltrexone *decreased* reward activation to chocolate in the dorsal anterior cingulate cortex and caudate, and *increased* aversive-related activation to unpleasant strawberry in the amygdala and anterior insula.
Conclusions These findings suggest that modulation of key brain areas involved in reward processing, cognitive control and habit formation such as the dorsal anterior cingulate cortex (dACC) and caudate might underlie reduction in food intake with opioid antagonism. Furthermore we show for the first time that naltrexone can increase activations related to aversive food stimuli. These results support further investigation of opioid treatments in obesity.

Electronic supplementary material The online version of this article (doi:10.1007/s00213-014-3573-7) contains supplementary material, which is available to authorized users.

E. Murray · S. Brouwer · R. McCutcheon · C. J. Harmer · P. J. Cowen
Department of Psychiatry, Warneford Hospital, University of Oxford, Neuroscience Building, Oxford OX3 7JX, UK

C. McCabe (✉)
School of Psychology and Clinical Language Sciences, University of Reading, Reading RG6 6AL, UK
e-mail: c.mccabe@reading.ac.uk

Keywords Reward · Aversion · fMRI · Naltrexone · Food · Obesity · Neuroimaging · Opioid antagonism

Introduction

"The worldwide prevalence of obesity has doubled since 1980, with overweight and obesity as the fifth leading risk for global deaths" (http://www.who.int/mediacentre/factsheets/fs311/en/ 2012). Despite the pervasive adverse health consequences of excessive food consumption, the neurobiological mechanisms underpinning disordered eating in humans remain unclear.

Due to its increasing prevalence, there is a clear need to find treatments for obesity but to date this has been complicated by the adverse psychiatric side effects of anti-obesity drug treatments (Nathan et al. 2011). The opioid system with its involvement in ingestion (Nogueiras et al. 2012) is a target for anti-obesity drug development, with antagonists such as naltrexone currently being trialled in combination therapies as potential anti-obesity treatments (Billes and Greenway 2011; Hollander et al. 2013; Katsiki et al. 2011; Lee and Fujioka 2009; Makowski et al. 2011; McElroy et al. 2013).

Studies examining the effect of opioid antagonists on food reward have demonstrated decreased consumption in animals and humans (Fantino et al. 1986; Yeomans and Gray 1996; Yeomans and Wright 1991) and suggest decreased intake might be related, among many other processes, to a modest reduction in the hedonic properties of food (Yeomans and Gray 2002). Whether this is the case, however, remains unclear. For example, not all studies in humans found that the pleasantness of food was affected by opioid antagonism (Hetherington et al. 1991) or that side effects of drug treatments such as nausea and fatigue could be ruled out as contributing factors to reduced food intake. Furthermore, it has been demonstrated in both animal and human studies that

Published online: 25 April 2014

changes in the sensory qualities of the food are unlikely to be responsible for the effect of opioid antagonism on food intake (Scinska et al. 2000; Yeomans and Gray 2002). In particular, μ-opioid receptors have been shown in animal studies to have a fundamental role in mediating hedonic responses to palatable foods with μ-opioid receptor "hotspots" having been identified in regions such as the pallidum and nucleus accumbens (Kelley et al. 2002; Migliori et al. 1999). Therefore, the aim of this experiment was to examine the neurobiological effects of naltrexone which attenuates the activity of endogenous opioids by blocking μ-, κ- and δ-opioid receptors, to test the hypothesis that opioid antagonism may modify appetitive stimuli in humans (Drewnowski et al. 1992, 1995).

Despite work investigating the effects of opioids on the neural response to food in animals there is little research examining the effect of opioid antagonism on neural responses to food reward in humans. Employing both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), Rabiner et al. (2011) compared the effects of a single dose of naltrexone, to a newer opioid compound GSK1521498 which has a higher degree of selectivity than naltrexone for the μ-opioid receptor sub-type. They found food reward-related activation attenuated by GSK1521498 only in the amygdala region of interest, a region reported to be involved in both appetitive and aversive processing and salience detection (Morrison and Salzman 2010; Sander et al. 2003). However further examination of whole brain data revealed modulation of palatable food by the opioid compounds in the nucleus accumbens, thalamus and insula (Rabiner et al. 2011).

Whilst a great deal of research has implicated opioidergic pathways in the hedonic properties of rewarding food stimuli, how opioids affect the neural processing of *aversive* food stimuli has not, to our knowledge, previously been studied. Opioid antagonists such as naloxone have however been shown to *increase* the subjective perception of tonic pain and hyperalgesia (Gracely et al. 1983; Koppert et al. 2003, 2005) with naltrexone also being reported to increase feelings of anxiety in already anxious patients (Colasanti et al. 2011). Although not examining food stimuli but rather responses to monetary rewards and losses, Petrovic et al. (2008) found that the ACC activity to reward outcomes vs. zero outcomes was attenuated with naloxone yet also showed that anterior insula and caudal ACC activity during monetary loss outcomes vs. zero outcomes was *increased* under opioid antagonism with naloxone (Petrovic et al. 2008).

The aim of the present study was to examine the effects of a single dose of the antagonist naltrexone on the neural response to both rewarding and aversive food stimuli in healthy volunteers. We hypothesised an overall negative shift in processing, i.e., that naltrexone would decrease reward responses in regions such as the ventral and dorsal striatum, orbitofrontal cortex and ACC that we have shown previously, using the same task, to be involved in the processing of rewarding stimuli including food (Knutson et al. 2001; McCabe et al. 2009; O'Doherty et al. 2001; Rolls and McCabe 2007) while increasing the processing of aversive food stimuli in regions such as the lateral orbitofrontal cortices, the insula and the amygdala (McCabe et al. 2010, 2011, 2012; Petrovic et al. 2008; Rolls et al. 2003; Zald et al. 2002). As there are few data on the effects of opioid antagonism on food reward and aversion in humans, we also explored the effects of naltrexone with whole brain analysis.

Methods

Participants

Twenty participants (Female $n=10$) aged 19–37 years were included in a repeated-measures within-subjects, double-blind, placebo controlled, cross over design. Participants were recruited from the university volunteer register and via internet adverts. Volunteers were assessed with the Structured Clinical Interview for DSM IV Axis I Disorders Schedule (SCID-I) (First et al. 1997) to exclude a current or previous history of major depression or any other Axis 1 disorder. Participants also had no history of drug or alcohol misuse and did not smoke more than five cigarettes a day. Participants were right handed, according to the Edinburgh Handedness Inventory (Oldfield 1971) and had normal/corrected to normal vision and were not on medications apart from the contraceptive pill. Participants filled out a chocolate craving questionnaire to make sure they liked chocolate as a reward (Rolls and McCabe 2007). Participants had no contraindications for MRI examination or neurological disorders. Ethical approval was obtained from the Oxford Research Ethics Committee and after complete description of the study to the subjects, written informed consent was obtained.

Baseline ratings of mood and anhedonia were collected using the Beck Depression Inventory (BDI) (Beck et al. 1961), the Fawcett–Clarke Pleasure Scale (FCPS) (Fawcett et al. 1983), and the Snaith–Hamilton Pleasure Scale (SHAPS) (Snaith et al. 1995). Participants reported liking and craving chocolate as measured by a previously designed questionnaire (Rolls and McCabe 2007). Body mass index (BMI) and an Eating Attitudes questionnaire were used to rule out eating disorders (EAT; Garner et al. 1982) (Table 1). Participants were scanned twice, once with drug (50 mg naltrexone 1 h before scan to allow for peak blood plasma levels to occur) or placebo and then again 1 week later with either the drug/placebo. The order of treatment was counterbalanced

Table 1 Descriptive statistics of demographic variables

	Mean	SD
Age (years)	22.80	4.60
BMI	23.09	1.80
SHAPS	18.25	3.84
FCPS	142.30	15.16
BDI	1.25	2.49
EAT	4.60	8.27
Chocolate craving	8.05	1.28
Chocolate liking	8.85	1.09
Chocolate frequency of consumption	1.95	0.22

BDI Beck Depression Inventory, *FCPS* Fawcett Clarke Pleasure Scale, *SHAPS* Snaith–Hamilton Pleasure Scale, *BMI* body mass index, *EAT* Eating Attitudes questionnaire

and both participant and experimenter were blind to the condition.

Experimental design

We compared brain responses to rewarding and aversive stimuli food tastes and sights. Each of the following conditions were applied nine times in a randomised order (see Table S1): chocolate in the mouth, chocolate picture, chocolate in the mouth with chocolate picture, medicinal-flavoured strawberry in the mouth, unpleasant strawberry picture (strawberries with mold on them), strawberry in the mouth with strawberry picture. The participants were instructed not to eat chocolate for 24 h before the scan, and to eat only a small breakfast on the day of scanning. Scanning took place between 9 am and 12 noon. Mood state and side effects were recorded on the study day with the Befindlichkeits scale (BFS) of mood and energy (von Zerssen et al. 1974) and on visual analogue scales (alertness, disgust, drowsiness, anxiety, happiness, nausea and sadness).

Rewarding and aversive stimuli

Stimuli were delivered to the subject's mouth through three Teflon tubes (one for the tasteless rinse control, one for chocolate taste and one for strawberry taste); the tubes were held between the lips. Each tube was connected to a separate reservoir via a syringe and a one-way syringe activated check valve (Model 14044-5; World Precision Instruments, Inc.), which allowed 0.5 ml of any stimulus to be delivered manually at the time indicated by the computer. The chocolate was formulated to be liquid at room temperature. The aversive stimulus was a medicinal-flavoured strawberry flavoured placebo solution (Rosemount Pharmaceuticals Ltd) which was rated equal in intensity to the chocolate but unpleasant in valence (McCabe et al. 2009). A control tasteless solution (0.5 ml) (25×10^{-3} mol/l KCl and 2.5×10^{-3} mol/l $NaHCO_3$ in distilled H_2O) was used after every trial that had a taste component (tl in Table S1), and a control grey image was used after every trial that had a sight component. This allowed the subtraction on every trial of the appropriate control condition. This allows the taste, texture, and olfactory areas to be shown independently of any somatosensory effects produced by introducing a fluid into the mouth (de Araujo et al. 2003a; de Araujo et al. 2003b; O'Doherty et al. 2001). Both the liquid chocolate and strawberry had approximately the same texture which enabled them to pass freely through the Teflon delivery tubes.

Experimental procedure

At the beginning of each trial, one of the six conditions chosen by random permutation was presented. If the trial involved an oral stimulus, this was delivered in a 0.5-ml aliquot to the subject's mouth. At the same time, a visual stimulus was presented, which was either the picture of chocolate, of mouldy strawberries or a grey control image of approximately the same intensity. The image was turned off after 7 s at which time a small green cross appeared on a visual display to indicate to the subject to swallow what was in the mouth. After a delay of 2 s, the subject was asked to rate each of the stimuli for "pleasantness" on that trial (with +2 being very pleasant and −2 very unpleasant), for "intensity" on that trial (0 to +4), and for "wanting" (+2 for wanting very much, 0 for neutral, and −2 for very much not wanting). The ratings were made with a VAS in which the subject moved the bar to the appropriate point on the scale using a button box. After the last rating, the grey visual stimulus indicated the delivery of the tasteless control solution which was also used as a rinse between stimuli; this was administered in exactly the same way as a test stimulus and the subject was cued to swallow after 7 s by the green cross. The tasteless control was always accompanied by the grey visual stimulus. On trials on which only the picture of chocolate or picture of strawberries was shown, there was no rinse but the grey visual stimulus was shown in order to allow an appropriate contrast as described above.

Functional MRI data acquisition

The experimental protocol consisted of an event-related interleaved design using in random permuted sequence the six stimuli described above and shown in Table S1. Images were acquired with a 3.0-T Varian/Siemens whole-body scanner at the Oxford Centre for Functional Magnetic Resonance Imaging (FMRIB), where T2* weighted EPI slices were acquired every 2 s (TR=2). Imaging parameters were selected to minimise susceptibility and distortion artefact in the orbitofrontal cortex (Wilson et al. 2002). Coronal slices with in-plane

resolution of 3×3 mm and between plane spacing of 3 mm were obtained. The matrix size was 64×64 and the field of view was 192×192 mm. Acquisition was carried out during the task performance yielding 972 volumes in total. A whole brain T2* weighted EPI volume of the above dimensions, and an anatomical T1 volume with coronal plane slice thickness 3 mm and in-plane resolution of 1.0×1.0 mm was also acquired.

Data analysis

fMRI analysis

Imaging data was pre-processed and analysed using statistical parametric mapping software SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Data pre-processing included realignment, normalisation to the Montreal Neurological Institute (MNI) coordinate system, reslicing with sinc interpolation, and 6 mm half-maximum, and spatial smoothing with a full-width isotropic Gaussian kernel and global scaling (Collins et al. 1994). For each voxel, time-series non-sphericity was accounted and corrected for (Friston et al. 2002), a low-pass filter was applied (with a haemodynamic response kernel), as was a high pass filter, with a cut off period of 128 s. In the single event design, a general linear model was then applied to the time course of activation where stimulus onsets were modelled as single impulse response functions and then convolved with the canonical haemodynamic response function (HRF) (Friston et al. 1994). Linear contrasts were defined to test specific effects. Time derivatives were included in the basis functions set. Following smoothness estimation, linear contrasts of parameter estimates were defined to test the specific effects of each condition with each individual dataset. Voxel values for each contrast resulted in a statistical parametric map of the corresponding t statistic, which was then transformed into the unit normal distribution (SPM Z). Movement parameters for each person were added as additional regressors in the first level analyses. Second-level fMRI analyses firstly examined simple main effects of task with one-sample *t*-tests, in the placebo test session only (Tables S4 and S5). To examine the effect of naltrexone, we utilised the one-way ANOVA-within subjects design recently implemented by SPM8 (repeated measures) for each condition separately and report all data thresholded at $p=0.05$. Regions of interest in which we had a priori hypotheses, based on our previous studies using this task were as follows: orbitofrontal cortex [26 32−10] (McCabe et al. 2010) and anterior cingulate cortex [−2 26 20][10 16 30] (McCabe et al. 2011, 2012), ventral striatum [−12 6 4] (Rolls and McCabe 2007) insula [−34 16 0] [−32 18 6] [42 20−10], and amygdala [20−2−22] (Horder et al. 2010; McCabe et al. 2009, 2011, 2012). Peaks within 15 mm of these a priori regions and within the functional regions of interest identified by our one sample main effects t tests (task-related activations; Tables S4 and S5), which also had a cluster threshold of at least thirty contiguous voxels ($k=30$), had small volume corrections (SVC) for multiple comparisons applied (family wise error [FWE], $p<0.05$). Thresholding at $p=0.05$ with a cluster threshold of $k=30$ was our attempt at reducing both Type I and Type II errors in our results. Given that we have ran this particular design in previous studies with other kinds of medication we believe we are less likely to attribute real activation to noise (Type I errors are not likely to replicate across multiple studies) and more likely instead to miss effects by increasing the p threshold. Therefore we increase the cluster threshold to 30 in an attempt to rebalance the Type I and Type II error rate. We also think this is appropriate given that a single dose drug study in healthy human volunteers might have relatively subtle effects (Lieberman and Cunningham 2009).

Gender and order were also added as covariates of no interest in the SPM8 model. For the exploratory whole brain analysis clusters were corrected ($p<0.05$ FWE for multiple comparisons). Plots of peak contrast estimates were extracted using the plots tool in SPM8, and WFU Pick Atlas; http://www.fmri.wfubmc.edu/cms/software) was used to display neural activation. Activation co-ordinates are listed in the stereotactic space of the MNI's ICBM 152 brain (Table 2).

Results

Demographic data

Demographic data analysis (Table 1) revealed participants had low depression scores, as well as normal EAT scores and were in the healthy weight range. Participants demonstrated a high level of chocolate craving and liking as demonstrated by their responses on the chocolate eating questionnaire. One-way ANOVAs revealed no significant effects ($p>0.05$) of gender on any of the demographic measures.

Mood, energy and affect scores

Repeated-measures ANOVAs were employed to examine the effect of drug (placebo/naltrexone) and time (pre-scan/post-scan) on scores of mood, energy and affect, as measured by the BFS and VAS. Results revealed there was no main effect of drug on mood, energy or affect ($p>0.05$). In order to assess any potential confounding effects of gender or order in which the scans were completed (i.e., placebo scan first or naltrexone scan first) on mood, energy and affect scores, gender and order were included in the analyses as independent variables. No main effects of gender or order, and no gender×drug or order×drug interactions were revealed, suggesting that the order of drug condition and gender of the participant did not have an effect on mood, energy and affect ratings (Table S2).

Table 2 Blood oxygenation level dependent (BOLD) changes induced by naltrexone

	Montreal Neurological Institute (MNI) coordinates				
Neural Area *p* values	*x*	*y*	*z*	Z score	
Placebo vs. naltrexone					
Chocolate picture and taste					
dACC	8	8	26	3.22	0.004
adACC/MFG	12	30	36	2.75	0.05*
Chocolate Picture	10	28	28	3.03	0.024*
adACC					
Caudate	16	−10	24	3.45	0.008
Naltrexone vs. placebo					
Strawberry Picture and Taste					
Amygdala	32	−2	−24	2.69	0.028*
Strawberry Picture					
Insula	−46	22	6	2.79	0.035*

Threshold was set at $p<0.05$

adACC anterior dorsal anterior cingulate cortex, *MFG* medial frontal gyrus; *p* values whole brain corrected ($p<0.05$, family wise error [FWE]-corrected for multiple comparisons)

[a] Small volume corrected (SVC; $p<0.05$, FWE-corrected for multiple comparisons). Gender and order were added as covariates of no interest

Subjective ratings of stimuli

Repeated-measures ANOVAs were used to examine the effect of drug (placebo/naltrexone) on subjective ratings of pleasantness, wanting and intensity across the six conditions (chocolate taste, chocolate picture, chocolate taste and picture, strawberry taste, strawberry picture, strawberry taste and picture). There was a main effect of condition as expected, as the pleasant chocolate stimuli and the unpleasant strawberry stimuli were rated differently, but there were no main effects of drug or drug × condition interactions (Fig. S1, Table S3).

Main effects of stimuli on BOLD responses

Tables S4 and S5 provide a summary of the main effects for the rewarding chocolate stimuli vs. the control stimuli and the aversive strawberry stimuli vs. the control stimuli. As expected, the pleasant chocolate taste and picture stimuli activated reward relevant circuitry including the ventral striatum the ACC and the medial frontal gyrus. Similar but slightly weaker activations were produced by the sight alone and the taste alone (Table S4). As expected, the unpleasant strawberry taste and picture stimuli activated circuitry including the amygdala, insula and occipital cortex. Similar but slightly weaker activations were produced by the strawberry sight alone and the taste alone (Table S5). Notably, the ventral striatum was not activated by the aversive stimuli (Table S5).

Effect of naltrexone on BOLD responses to food stimuli

Table 2 provides a summary of the results of the effects of naltrexone. Region of interest analyses revealed that naltrexone, compared to placebo, reduced BOLD activations in response to the chocolate taste and picture in the anterior dorsal ACC [10 28 28] (Fig. 1), and *increased* BOLD activations in response to the aversive strawberry taste and picture in the amygdala [32−2−24] (Fig. 2), and to the strawberry picture in the anterior insula [−46 22 6] (Fig. 3).

We also found in our whole brain analysis that naltrexone, compared to placebo, reduced BOLD activations in response to the chocolate, in the dorsal ACC [8 8 24] the adACC/medial frontal gyrus [12 30 36], and the caudate [16−10 24]. Figures display the significant between group differences and the inset in each figure allows the visualisation of the direction of effects in the other conditions for the same region. Although not significant there was a trend for reduced activation in the ACC at [8 8 20] under naltrexone for the chocolate taste alone. This is likely due to the weaker response to taste alone condition when compared to the sight and the taste combined condition. This is plausibly due to the combination condition being a more effective stimulus as indicated by the pleasantness ratings, whereby the combination of the taste and sight produces larger responses.

Discussion

The aim of the current study was to examine the effects of a single dose of the opioid antagonist, naltrexone, on the neural

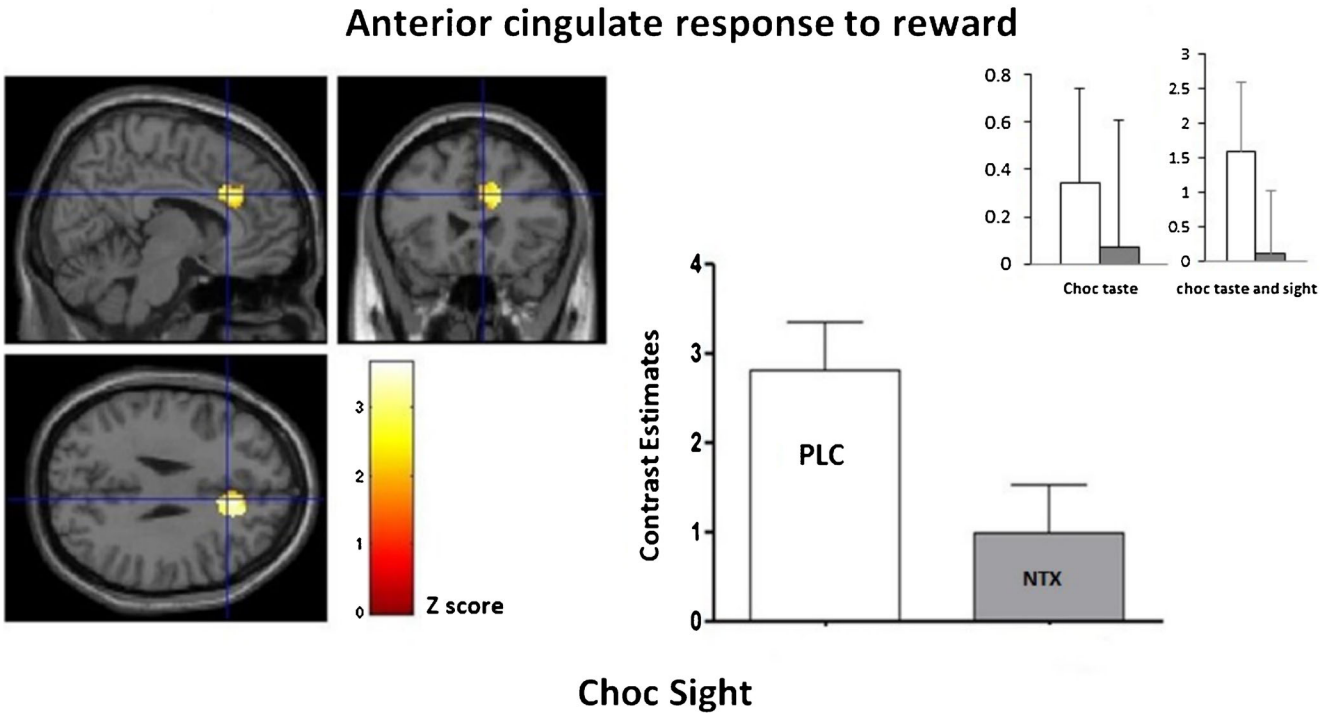

Fig. 1 **a** Chocolate sight: axial, sagittal and coronal image of decreased adACC in the naltrexone compared to placebo, small volume corrected (Z=3.03, p=0.024 SVC FWE-corrected for multiple comparisons). **b** Contrast estimates for adACC centered at 10, 28, 28 for chocolate sight. *Inset*: contrast estimates for ACC centered at 10, 28, 28 for chocolate taste

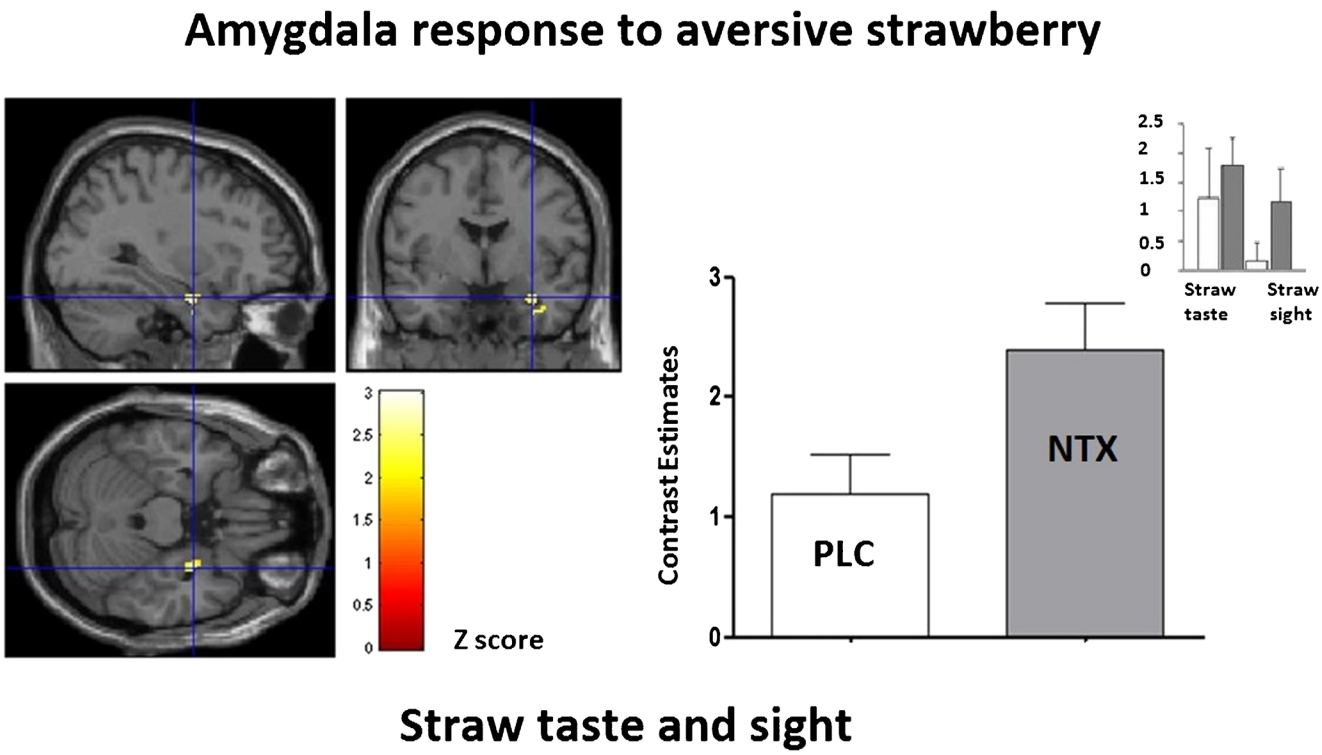

Fig 2 **a** Strawberry sight and taste combined: axial, sagittal and coronal image of increased amygdala in naltrexone compared to placebo, small volume corrected (Z=2.69, p=0.028 SVC FWE-corrected for multiple comparisons). **b** Contrast estimates for amygdala centered at 32−2−24 for strawberry sight and taste combined. *Inset*: contrast estimates for amygdala centered at 32−2−24 for strawberry sight and taste separately

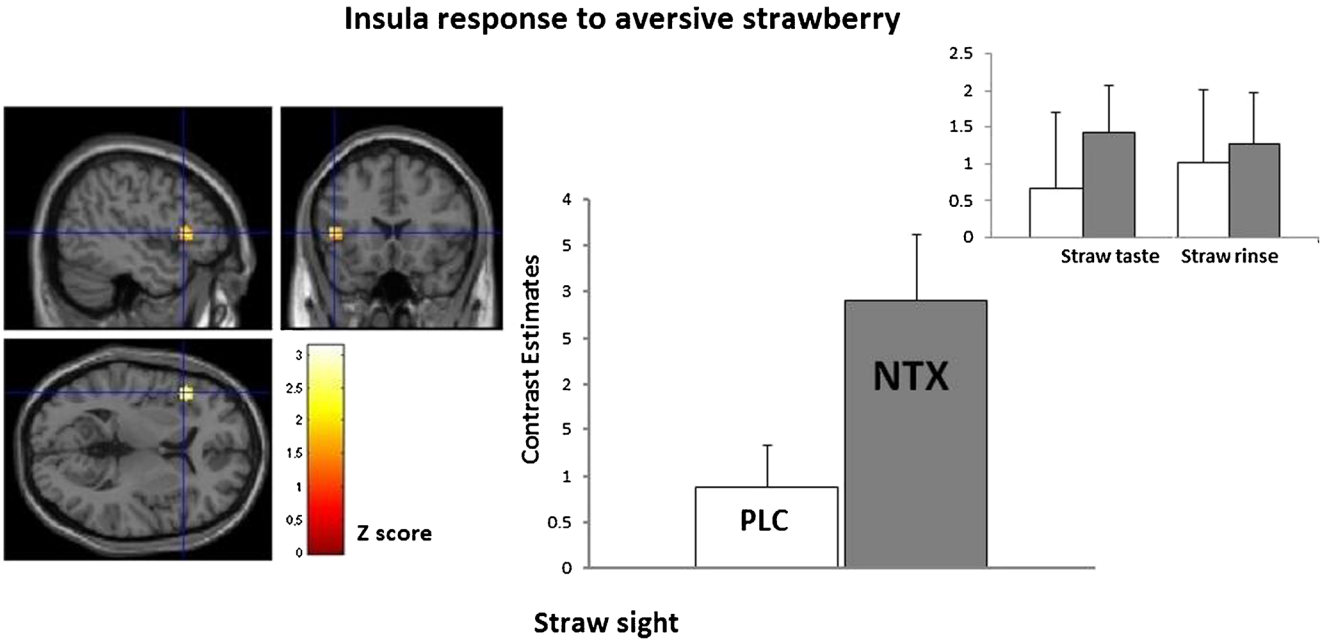

Fig. 3 **a** Strawberry sight: axial, sagittal and coronal image of increased insula in naltrexone compared to placebo, small volume corrected (Z=2.79, p=0.035 SVC FWE-corrected for multiple comparisons). **b** Contrast estimates for insula centered at −46 22 6 for strawberry sight. *Inset*: contrast estimates for insula centered at −46 22 6 for strawberry taste

processing of rewarding and aversive food stimuli in the healthy human brain. We found that naltrexone *decreased* reward-related activation and *increased* aversive-related activations supporting our hypothesis of an overall negative shift in rewarding and aversive-stimuli processing after naltrexone treatment.

Consistent with the literature showing opioid antagonism does not affect the subjective sensory quality of foods (Scinska et al. 2000; Yeomans and Gray 2002) we did not find an effect of naltrexone on the intensity ratings of the pleasant and unpleasant conditions. Furthermore we found no effects of naltrexone on the ratings of pleasantness/wanting, which might be explained by the differences in the experimental design compared to previous studies. The current study had a very small amount of actual food tasted, i.e., only 0.5 ml of chocolate liquid on a taste trial in an fMRI scanner in healthy volunteers, as opposed to previous studies where some subjects were obese and allowed to free feed meals and drinks over many days (Yeomans and Gray 2002). Our results are consistent however with Petrovic et al. (2008) and Rabiner et al. (2011) who also found no effect of opioid antagonism on subjective pleasantness. However Petrovic et al. reported attenuation of subjective pleasure ratings for larger reward outcomes, and for losses found that under naloxone all levels of negative outcome were rated as more unpleasant. Also studies by Drewnowski et al. and Nathan et al. (2012) with naloxone and the μ-opioid receptor antagonist GSK1521498, respectively, did show a reduction in subjective hedonic rating with dairy products of varying levels of fat and sugar (Drewnowski et al. 1995; Nathan et al. 2012). Although we found no changes in subjective assessment of the pleasantness or aversive qualities of our tastes and pictures, it is possible that, similar to the way in which acute doses of antidepressants can modulate the neural response to emotions *before* a change in subjective mood takes place (Harmer and Cowen 2013), the neural changes we have observed with naltrexone may, with repeated treatment over time, become translated into alterations in subjective liking and wanting of food. It is possible therefore that the effects of naltrexone on subjective experience in our study would have been more apparent with larger food rewards, a larger sample size, a more detailed subjective experience questionnaire and repeated treatment.

In our study, we found that naltrexone decreased the response in the anterior and dorsal ACC to the rewarding sight and taste of chocolate combined. Petrovic et al. (2008) also showed a trend toward decreased activity in a similar ACC region under naloxone to monetary reward outcomes vs. zero outcomes. The ACC has been identified as a μ-opioid receptor-dense region (Mansour et al. 1987), involved in the hedonics of consumption (Goldstein and Volkow 2002) and the subjective experience of craving (Volkow et al. 1999). Neuroimaging evidence previously identified that cocaine intoxication resulted in an *increased* BOLD response in the ACC, which was strongly correlated with the reward-related properties of the drug (Breiter et al. 1997), and more recent neuroimaging data have revealed the relationship between the ACC opioid receptor density and cocaine craving (Gorelick et al. 2005) and treatment outcome (Ghitza et al. 2010). Therefore, the ACC might be implicated in the ability of

naltrexone to reduce the euphoria and the "crash" produced by intravenous cocaine injection (Kosten et al. 1992).

The ACC has also been specifically implicated in food related processing, with increased taste-induced activation in this region demonstrated to predict subsequent decreased intake of sweet and savory juice (Spetter et al. 2012) and in the saliency of food pictures in the dorsal ACC and the reward value of food pictures in the rostral ACC (Garcia-Garcia et al. 2013). The current study further provides evidence in humans that naltrexone specifically decreases dACC activity in response to food reward, which is interesting given the recent work showing that this region is critical for predicting expected cognitive demand and optimizing future behavioural responses (Sheth et al. 2012). Therefore, it would be of interest in future studies to investigate if naltrexone might be able to modulate decision making processes regarding food stimuli and if the change in ACC activity is related to less attention towards or salience of foods.

Naltrexone also decreased activation to the sight of chocolate in the μ-opioid receptor-rich, dorsal striatum, caudate nucleus. The dorsal striatum has been shown to be involved in the conditioning to rewards and is reported as being mostly involved in the habitual process of drug taking (Belin and Everitt 2008; Porrino et al. 2004; Volkow et al. 2006). Cues for drugs of abuse increase dopamine release in addicts in these areas which are then directly correlated with the strength of the addiction (Volkow et al. 2011). Consistent with this, studies using fMRI have shown that cocaine users show increased activation in the caudate, in response to cocaine-related images (Garavan et al. 2000). Interestingly, a recent study reports that naltrindole, an opioid antagonist, blocks ethanol consumption and opioid receptor activity specifically in the dorsal striatum of rats (Nielsen et al. 2012). Further a recent study in humans has shown that high doses of amphetamine induces opioid release in the brain but specifically in regions such as the dorsal striatum and ACC (Colasanti et al. 2012) which is consistent with the regions we find in this study to be modulated by opioid antagonism. Therefore, our results suggest that naltrexone might aid reduction in food intake blocking the caudate-dependent habit and craving-inducing qualities of certain foods.

Although, as expected, we did see ventral striatal responses to the chocolate in the placebo condition, we did not find any effects of opioid blockade on ventral striatal activity in this study. Interestingly, in our previous study, using this same model, on the effects of the cannabis (CB1) antagonist rimonabant (the CB1 receptor is highly expressed in reward areas such as the basal ganglia; Herkenham et al. 1991), we did find decreased ventral striatal activity in the chocolate sight condition and the sight of the aversive strawberry condition. We also found that rimonabant increased the activation related to strawberry taste and sight in the lateral orbitofrontal cortex even outside of any effects on the subjective experience of wanting and liking. However, as rimonabant was launched as an anti-obesity drug and then removed from the market due to adverse depression like side effects (Christensen et al. 2007; Horder et al. 2010), we suggested that the reduction in reward response in regions such as the ventral striatum might not only explain the reduction in food intake produced by rimonabant but might also explain the *depression* like side effects associated with this drug. Consistent with this, imaging studies have found decreased ventral striatal neural responses in depressed patients, with decreasing activation correlating with increased anhedonia, a key criterion in the diagnosis of depression (Keedwell et al. 2005; McCabe et al. 2009; Wacker et al. 2009). Naltrexone, however, is described as well tolerated and apparently without depression like side effects (Dean et al. 2006; Miotto et al. 2002), and it is tempting to speculate that this may be because it modulates different aspects/regions of the reward system compared to rimonabant. Furthermore, naltrexone is by itself a weak anti-obesity agent and this may be because it has limited effects on the ventral striatal response to reward. However, to test this fully, longer-term treatment with naltrexone would be of interest.

Rabiner et al. (2011) examining the more specific μ-opioid receptor antagonist GSK1521498 did show attenuation in the ventral striatum after whole brain analyses, supporting the idea that different μ-opioid receptor antagonists may have differing effects on specific aspects of reward circuitry. The lack of effect of naltrexone on ventral striatum in this study may be also due to variability in the peak plasma concentration of naltrexone across participants. The time to maximum blood levels (TMAX) ranges from 0.5 to 3 h for naltrexone; this could mean that at 1 to 1.5 h, when we carried out our testing, not all participants would necessarily have reached the same levels of μ-receptor occupancy; this may have reduced our ability to detect effects (Mason et al. 2002). Furthermore a recent PET imaging study has indicated that the occupancy of opiate receptors by naltrexone is not dependent purely on plasma naltrexone levels and is prolonged in time relative to the plasma half-life of naltrexone itself (Rabiner et al. 2011). Hence, it is possible that in our study when subjects came for their second placebo session there may have been some residual μ-opioid receptor occupancy by naltrexone which could have led to an underestimate of its effects relative to placebo.

Our results also show that a single dose of naltrexone *increases* the neural activity to aversive food stimuli in the amygdala compared to placebo. The amygdala has been shown to play a role in aversive taste processes (Nitschke et al. 2006), and studies have identified distinct amygdala neuronal populations responsible for processing aversive information (Paton et al. 2006). Although no studies to date have directly examined the effect of opioid antagonism on the neural basis of aversive food processing, studies have examined the role of opioid modulation in other aversive conditions. For example, baseline opioid binding in the amygdala

has been suggested to play an anxiolytic role, modifying the negative effects associated with aversive environments (Liberzon et al. 2002). Furthermore, injection of the opioid agonist, morphine, into the amygdala *decreases* the fear response in rats (Good and Westbrook 1995), and naltrexone has been shown to reverse morphine-induced analgesia through amygdaloid modulation (Pavlovic et al. 1996). Therefore it is possible that opioid antagonism may reduce food intake by both reducing rewarding aspects of feeding and increasing aversive aspects. The details of the latter have yet to be investigated in humans; however a recent study by Liang et al. (2013) report that the combination of naltrexone with exendin-4 (a peptide that clears blood glucose for the treatment of type 2 diabetes and has appetite reducing properties) has an additive effect on reducing food intake in rats but also an additive effect on the speed with which conditioned taste aversion is learnt (Liang et al. 2013). This suggests that naltrexone may reduce food intake by converting pleasant tastes to unpleasant. Furthermore a study examining food preferences in rats found that naltrexone reduced food intake by potentiating the sensory specific satiety effect (Woolley et al. 2007), the phenomenon whereby foods being repeatedly consumed reduce in hedonic value from pleasant to unpleasant, until the cessation of consumption (Rolls et al. 1981). Therefore our results of increased neural activation to the unpleasant stimuli during naltrexone treatment might be another mechanism by which food becomes rated as less pleasant during opiate receptor blockade. It would be of interest to examine the effects of naltrexone on satiety signals and see if it increases the speed with which satiety is reached in humans.

Our results also show that naltrexone increases the neural activity in the anterior insula during the aversive food sight condition compared to the grey image control condition. The anterior insula is known to be part of the gustatory system (Bencherif et al. 2005; Faurion et al. 1998) but is also involved in the processing of aversive stimuli and disgust (Anders et al. 2004; Fitzgerald et al. 2004; Liu et al. 2011; Wager et al. 2004; Wicker et al. 2003). This is consistent with previous research whereby naloxone increased insular activation in response to pain (Borras et al. 2004). As stated above, it is possible that this finding might be a mechanism by which opioid antagonism aids food reduction by enhancing aversive sensitivity to, and even disgust of, less pleasant foods.

It is important to note however that enhancing the processing of aversive information might also be related to the negative side effects witnessed in previous anti-obesity treatments. In fact in our previous study examining the anti-obesity treatment, rimonabant, we also found enhanced processing of aversive tastes in some brain regions (Horder et al. 2010) and also negative emotional information (Horder et al. 2012). This highlights the need for careful research into the effects of drug treatments not only on the human reward response but also on how the processing of aversive stimuli will be modulated and how affective state might therefore be modified. Therefore, it will be important to know if the effects from this study with naltrexone are specific to aversive taste processing or are also seen under the processing of negative emotional information. Although we did get different effects of naltrexone depending on the valence of the stimuli, i.e., decreased activation to reward and increased activation to aversive stimuli, it is possible that the effects seen in this study are related to effects of naltrexone on baseline perfusion; therefore, in future studies it would be helpful to control for this effect by adding a perfusion scan to examine any baseline and global effects of the drug.

Taken together, our findings suggest that opioid antagonism can both reduce reward responses and enhance the processing of aversive food stimuli in the brain, which supports the interest in naltrexone as a possible treatment for obesity. Currently, naltrexone is used therapeutically for the treatment of opioid and alcohol dependence, and has been shown to be effective in reducing relapse in opiate- and alcohol-addicted individuals (Hillemacher et al. 2011; Streeton and Whelan 2001). It has been suggested that the mechanism by which naltrexone reduces relapse is through decreasing the hedonic properties associated with consuming rewarding substances (Littleton and Zieglgansberger 2003); however, our data also adds the possibility that naltrexone might also work by enhancing the processing of aversive stimuli related to alcohol-related negative consequences.

Although the combination of the dopamine and noradrenaline re-uptake blocker bupropion together with naltrexone shows promise as anti-obesity treatment (Greenway et al. 2010) other studies examining the efficacy of naltrexone alone in obesity have had mixed results (Lee and Fujioka 2009), potentially due to the wide range of factors contributing to the development and maintenance of obesity, including, for example, cognitive control and satiety signals (Kelley and Berridge 2002). Perhaps another explanation is related to the work from Stice and colleagues who show that those with obesity have hypofunctioning reward systems; at the neural level, this might explain why further reducing the reward system as a treatment is not effective (Stice et al. 2008, 2010). In contrast, those "at risk" of obesity have an increased neural response to reward (Stice et al. 2011) as do binge eaters (Filbey et al. 2012; Schienle et al. 2009). We therefore suggest that treatments such as naltrexone that can reduce the neural reward response might be more valuable as preventative treatments in those "at risk" of obesity or binge eating.

In fact, naltrexone has received some attention as a potential therapy for the treatment of binge eating (Nathan and Bullmore 2009) and has so far proved promising, with demonstrated improvements in bulimic patients in binge-related indices, including number (Marrazzi et al. 1995) and duration (Alger et al. 1991) of binge episodes. Furthermore, recent studies examining the effects of the μ-opioid receptor

antagonist, GSK1521498, on moderate binge eating found evidence of reduced motivation for food, alongside reduced striatal activation, after GSK1521498 treatment (Cambridge et al. 2013; Ziauddeen et al. 2013). However, it is important to note though that these last two studies were in obese patients. We suggest the need to characterise the effects of opioid antagonism on both rewarding and aversive food stimuli in those "at risk," with perhaps familial obesity, but not a personal history of obesity.

In conclusion, this study found that a single dose of naltrexone reduced food reward-related brain activations and enhanced food aversion related activations in healthy human volunteers. These results provide further evidence of opioid antagonism modulating reward responses and for the first time the effects of opioid antagonism on the neural responses to aversive food stimuli in healthy human volunteers. These results might improve understanding of how opiate antagonism may be of benefit in the treatment of compulsive disorders such as alcoholism and also suggest potential uses in certain eating disorders such as binge eating and obesity.

Conflicts of interest Dr. McCabe has acted as a consultant to P1Vital, Givaudan, GWpharma, the British Broadcasting Company (BBC) and Channel 4. Professor Harmer is a company director of Oxford Psychologists and has acted as a consultant to Servier, GlaxoSmithKline, Astra Zeneca, Johnson & Johnson, Roche, Lundbeck and P1Vital. Professor Cowen is a member of an advisory board for Lundbeck. Elizabeth Murray, Sietske Brouwer and Rob McCutcheon report no biomedical financial interests or potential conflicts of interest.

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