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Original article

## Behavioural activation system sensitivity is associated with cerebral $\mu$ -opioid receptor availability

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### Abstract

The reinforcement-sensitivity theory proposes that behavioural activation and inhibition systems (BAS and BIS, respectively) guide approach and avoidance behaviour in potentially rewarding and punishing situations. Their baseline activity presumably explains individual differences in behavioural dispositions when a person encounters signals of reward and harm. Yet, neurochemical bases of BAS and BIS have remained poorly understood. Here we used *in vivo* positron emission tomography with a  $\mu$ -opioid receptor (MOR) specific ligand [<sup>11</sup>C]carfentanil to test whether individual differences in MOR availability would be associated with BAS or BIS. We scanned 49 healthy subjects and measured their BAS and BIS sensitivities using the BIS/BAS scales. BAS but not BIS sensitivity was positively associated with MOR availability in frontal cortex, amygdala, ventral striatum, brainstem, cingulate cortex and insula. Strongest associations were observed for the BAS subscale 'Fun Seeking'. Our results suggest that endogenous opioid system underlies BAS, and that differences in MOR availability could explain inter-individual differences in reward seeking behaviour.

**Key words:** BAS; BIS; carfentanil; opioid; PET

### 25 Introduction

The reinforcement-sensitivity theory (RST) proposes that two neurophysiologically separable systems guide human behaviour during potentially beneficial and harmful encounters (Gray, 1970; Gray, 1987). The behavioural-activation/approach system (BAS) is an appetitive-motivational system that is activated by reward consumption and conditioned signals of reward or non-punishment, triggering approach behaviour. The behavioural inhibition system (BIS), on the other hand, is an aversive motivational system activated by signals of punishment, loss of reward, novelty or uncertainty and inhibits behaviour that might lead to negative outcomes. (Pickering and Gray, 1999) Relative activities of these systems presumably

explain whether individuals approach potentially rewarding targets or whether they inhibit or withdraw the behaviour because of the associated risks (Gray, 1970). Previous studies have shown that the sensitivity (i.e. baseline activity) of these systems broadly influences individuals' behavioural tendencies: People with high BAS sensitivity eagerly seek reward, are socially outgoing and open to new experiences, while low BAS sensitivity is associated with introversion and depression (Carver and White, 1994; Heubeck *et al.*, 1998; Kasch *et al.*, 2002; Caseras *et al.*, 2003). On the other hand, high BIS sensitivity is associated with anxiousness and avoidance behaviour, and individuals with high BIS sensitivity frequently avoid anxiety-provoking situations (Carver and White, 1994).

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RST postulates separable yet interacting neuroanatomical systems underlying BAS and BIS (Gray, 1987; Pickering and Gray, 1999). The brain's dopaminergic reward circuits, including the ventral tegmental area, ventral striatum and their projections to the prefrontal cortex, have been suggested to subserve BAS (Gray, 1987; Pickering and Gray, 1999; Depue and Collins, 1999). A bulk of fMRI studies support this proposition by showing that BAS sensitivity—as measured with self-reports—is positively associated with reward-cue-triggered haemodynamic responses in reward circuits (Beaver et al., 2006; Hahn et al., 2009; Simon et al., 2010; Costumero et al., 2013). The most important anatomical substrate of BIS is the septo-hippocampal system, consisting of the hippocampus proper, the dentate gyrus, the entorhinal cortex, the subicular area and the posterior cingulate cortex (Gray and McNaughton, 2000). Moreover, amygdala and prefrontal and cingulate cortices have been also implicated in BIS function (Gray, 1987; Gray and McNaughton, 2000).

Despite these advances in understanding the functional brain mechanisms associated with BAS and BIS, the neurochemical mechanisms serving them are still unclear. While dopaminergic neurotransmission is often linked to BAS (Gray, 1987; Pickering and Gray, 1999), findings from both animal research and human molecular neuroimaging studies suggest that the endogenous opioid system, and particularly  $\mu$ -opioid receptors (MORs), might be another important neurochemical pathway for it. In animals, the opioidergic system has been shown to modulate approach behaviour and reward functions (Van Ree et al., 2000; Papaleo et al., 2007), both of which are essential features of BAS. Human positron emission tomography (PET) studies have also suggested that individual differences in BAS-driven behaviour are linked with the MOR system, as MOR availability is associated with the trait impulsivity (Love et al., 2009). Further, high BAS sensitivity may predispose individuals for developing addictions (Johnson et al., 2003) and, in turn, both alcohol (Heinz et al., 2005; Weerts et al., 2011) and cocaine (Zubieta et al., 1996; Gorelick et al., 2005) dependencies are associated with increased MOR availability in reward circuits. Finally, MOR availability is also associated with the closeness of interpersonal relationships (Nummenmaa et al., 2015), which fits with the previously established association between BAS and prosociality (Carver and White, 1994; Heubeck et al., 1998; Caseras et al., 2003).

Limited evidence links MORs also with BIS. First, anxiolytic effects of opiates (Colasanti et al., 2011) suggest that activation of opioidergic circuits may attenuate baseline BIS activity. Second, people who typically avoid harmful situations have elevated MOR availability in frontal cortex (Tuominen et al., 2012). Such behaviour is also common in high-BIS individuals (Carver and White, 1994), suggesting that BIS could be associated with tonic MOR upregulation.

Altogether, previous studies show that BAS affects drive for reward and sociality—both of which are associated with MORs—while limited evidence also suggest a link between BIS and MORs. However, the exact link between MORs and BAS (and potentially BIS) remains elusive. To investigate whether baseline MOR availability is associated with BAS and BIS sensitivities, we used *in vivo* PET with highly selective MOR agonist ligand [ $^{11}\text{C}$ ]carfentanil coupled with behavioural BAS and BIS scales (Carver and White, 1994). Based on their mutual involvement in reward, we specifically hypothesized that BAS would be positively associated with cerebral MOR availability in the brain's reward circuits.

## Materials and methods

### Participants

The study protocol was approved by the ethics board of the hospital district of Southwest Finland, and the study was conducted in accordance with the Declaration of Helsinki. *A priori* power analysis based on effect sizes in previous PET studies on associations between personality trait variables and MOR availability (Tuominen et al., 2012) suggested that sample sizes exceeding  $N = 45$  would have power higher than 0.90 for detecting statistically significant effects at  $r = 0.44$ . Consequently, we studied altogether 50 healthy adults (20 females, mean  $\pm$  SD age  $32 \pm 6.4$  years, range 19–58). One subject was removed from the sample because a previously non-diagnosed neurological disease was revealed from the MRI scan. Exclusion criteria were lack of compliance, smoking, alcohol consumption exceeding eight weekly doses, substance abuse determined by interview and blood tests, a history of or current psychiatric or neurological disease, current medication affecting the central nervous system, as well as standard PET and MRI exclusion criteria. Subjects signed ethics-committee-approved, informed consent forms and they were compensated for their time and travel costs. These data have originally been collected in clinical trials SleevePET2, (NCT01373892), EXEBRAIN (NCT02615756) as well as the PLEASUREPET project. Portions of the PET data unrelated to the present study have been published previously (Karlsson et al., 2015a,b; Nummenmaa et al., 2015; Tuominen et al., 2015).

### Questionnaires

The participants completed the BIS/BAS scales (Carver and White, 1994) that measure individual differences in the sensitivities of BIS and BAS, reflecting affective responses to impending reward and punishment. The questionnaire consists of 20 Likert-scale questions and has been psychometrically validated to yield stable and reliable results (Carver and White, 1994) across different cultures (Leone et al., 2001). The questionnaire consists of one BIS scale and three BAS subscales: Drive, Reward Responsiveness, and Fun Seeking. All the subscales of the questionnaire have good internal consistency reliabilities (0.66–0.76) (Carver and White, 1994). As the BIS and BAS total scores were not correlated ( $r = -0.05$ ), they were both used as covariates in the full-volume regression analyses (see below). Because the MOR system is associated with both mood- and anxiety-related processes (Colasanti et al., 2011; Lutz and Kieffer, 2013) participants also completed Beck Depression Inventory (BDI) II (Beck et al., 1988) and State-Trait-Anxiety Inventory (STAI) (Spielberger et al., 1983) questionnaires to rule out that anxious or depressive symptoms could explain the results.

### PET imaging and analysis

Data were acquired with the Philips Ingenuity PET-MR and GE Healthcare Discovery TM 690 PET/CT scanners in Turku PET Centre. Radiotracer production has been described previously (Karlsson et al., 2015a). After a bolus of intravenous radioligand injection (targeted dose 250 MBq; mean 251 MBq,  $SD = 11$  MBq), radioactivity in the brain was measured with the PET camera for 51 min (with increasing frame length:  $1 \times 3, 3 \times 4, 6 \times 6$  min) with in-plane resolution of 3.75 mm. The subjects were lying in a supine position throughout the studies. Data were corrected for dead-time, decay and measured photon-attenuation and dynamic PET scans were reconstructed with vendor-provided

standard MRAC and MRP methods (Alenius and Ruotsalainen, 1997).

To correct for head motion, dynamic PET images were first realigned frame-to-frame. High-resolution anatomical MR images (1mm<sup>3</sup> resolution) were acquired with the Philips Ingenuity PET-MR or Philips Gyroscan Intera scanners using T1-weighted sequences. The individual MR images were coregistered to the summation images calculated from the realigned frames. Occipital cortex was delineated manually on MR images with PMOD 3.4 software (PMOD Technologies Ltd., Zürich, Switzerland) and used as a reference region. Receptor binding was expressed in terms of  $BP_{ND}$ , which is the ratio of specific to non-displaceable binding in the brain using the occipital cortex as the reference region.  $BP_{ND}$  was calculated for each voxel using the simplified reference tissue model with reference tissue time-activity curves as input data (Gunn et al., 1997). Subject-wise parametric  $BP_{ND}$  images were normalized to the MNI space using the T1-weighted MR images, and smoothed with a Gaussian kernel of 12 mm full width at half maximum.

The effects of BAS and BIS scores on MOR availability were assessed in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>) using linear regression model with PET camera as a covariate. Statistical threshold was set at  $P < 0.05$ , FDR-corrected at cluster level. We also conducted a complementary region of interest (ROI) analysis for eleven a priori anatomical ROIs involved in reward and emotion processing (anterior cingulate cortex, amygdala, dorsolateral prefrontal cortex, hippocampus, insula, nucleus accumbens, occipital cortex, orbitofrontal cortex, pallidum, putamen and thalamus) FreeSurfer 5.3 (<http://surfer.nmr.mgh.harvard.edu/>) was used to segment an MNI template brain, and the FreeSurfer-generated segments were then combined to generate ROI masks. Subsequently, the masks were used to extract the voxels within each ROI in the normalized  $BP_{ND}$  images. Mean ROI-wise  $BP_{ND}$  were calculated and then predicted with BAS and BIS scores using linear regression and stepwise linear regression analyses.

## Results

Full-volume analysis revealed a positive association between BAS sensitivity and [<sup>11</sup>C]carfentanil  $BP_{ND}$  in a large cluster extending in both hemispheres from the frontal lobe to the parieto-occipital sulcus, as illustrated in Figure 1. Significant associations were also observed in insula, thalamus, amygdala, brainstem and temporal cortices. Additional analysis revealed that the BAS subscale Fun Seeking was mainly driving the effect, with statistically significant associations in largely overlapping regions with those observed in the analysis of total BAS scores. The other subscales and BIS did not correlate statistically significantly with MOR availability in full-volume analysis. The results remained essentially unchanged when subject age, total intracranial volume (derived from DARTEL-segmented T1 images), STAI or BDI scores were included as nuisance covariates. Because morbid obesity is associated with lowered BMI (Karlsson et al., 2015a,b) we also tested whether BMI would be predictive of MOR availability in the present sample of non-obese subjects (mean BMI = 22.9). However this analysis revealed no significant clusters. Similarly including BMI as a covariate to the main analysis did not alter the results.

Table 1 shows the ROI-level-associations between the BIS/BAS scales and MOR binding potentials. [<sup>11</sup>C]carfentanil  $BP_{ND}$  was significantly correlated with the BAS total scale in anterior cingulate cortex, amygdala, insula and orbitofrontal cortex (Figure 2), and with the BAS subscale Fun Seeking in the amygdala (Pearson correlation  $r = 0.29$ ,  $P = 0.04$ ) and nucleus accumbens ( $r = 0.29$ ,

$P = 0.04$ ). No significant negative correlations were found between  $BP_{ND}$  and BIS scores. Stepwise regression analyses revealed that  $BP_{ND}$  in the amygdala emerged as the sole predictor for BAS scores ( $\beta = 4.36$ ;  $R^2 = 0.09$ ;  $P < 0.05$ ).

## Discussion

We demonstrated that individual differences in BAS sensitivity are positively associated with MOR availability in multiple brain regions involved in reward and pain, including ventral striatum, orbitofrontal cortex, brainstem, cingulate cortex, insular cortex and thalamus. However, no associations were observed between MOR availability and BIS, trait anxiety or BMI, suggesting that MOR availability is independent of more general mood processes and eating habits. Together with results of previous human and animal studies on the role of the endogenous opioid system in both incentive motivation and hedonic functions (Berridge et al., 2010), these data suggest that individual variation in MOR availability is associated with sensitivity to reward cues. Furthermore, the present results suggest that BIS does not depend on the MOR system.

### Opioidergic basis of BAS

BAS sensitivity was positively associated with MOR availability widely within the brain. Such extensive association is not surprising, because MOR expression, as quantified with [<sup>11</sup>C]carfentanil  $BP_{ND}$ , is consistent across different cortical and subcortical sites (Tuominen et al., 2014). The present results thus imply that BAS sensitivity is associated globally with MOR tone in the brain, instead of regionally specific alterations. Even though the Fun Seeking subscale had most consistent associations with MOR availability, it must be noted that in general all the subscales showed a similar, yet slightly less consistent associations with MOR availability (See Table 1). These effects thus likely reflect the general association between overall BAS sensitivity and the MOR system.

Regional associations between BAS and MOR availability were observed in prefrontal, cingulate and insular cortices, as well as subcortical regions, such as ventral striatum, amygdala and brainstem. These regions process both hedonic and nociceptive signals (Leknes and Tracey, 2008). Our data accord with a previous human PET study showing that baseline MOR availability in these regions is associated with impulsiveness (Love et al., 2009), a personality trait closely related to BAS (Caseras et al., 2003). Animal studies have also established that the MOR system drives motivated behaviour and reward functions (Van Ree et al., 2000; Berridge and Robinson, 2003). Specifically, the opioid system mediates liking responses to rewarding stimuli (Berridge and Kringelbach, 2008). Microinjections of morphine to MOR-dense nucleus accumbens increases liking reactions in rats (Peciña and Berridge, 2000), suggesting that MORs mediate hedonic sensations resulting from reward consumption. Accordingly, our results show that an individual's MOR availability may alter their capacity for experiencing hedonic sensations, and, consequently influence their sensitivity to reward signals.

In addition to reward circuits, BAS sensitivity was also associated with MOR availability in brainstem, insula and anterior cingulate cortex. All these regions are involved in processing nociceptive signals, and MOR mediates analgesic effects of several exogenous opiates (Fields, 2004). MOR density in striatum is also positively associated with pain threshold (Hagelberg et al., 2012). This dual role of MORs in both reward and pain-relief

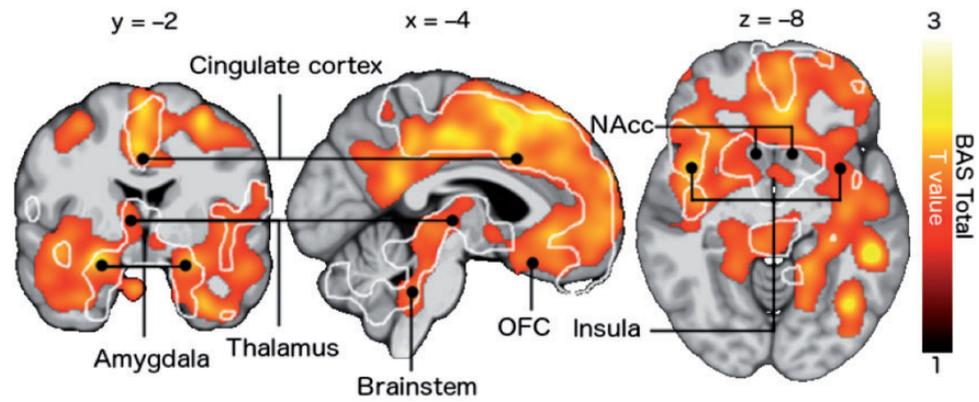


Fig. 1. Association between BAS total scores and  $[^{11}\text{C}]$ carfentanil  $BP_{ND}$ . The data are thresholded at  $P < 0.05$ , FDR-corrected at the cluster level. The white outlines show regions where the BAS subscale Fun Seeking was associated with  $BP_{ND}$ . OFC = orbitofrontal cortex, NAcc = nucleus accumbens.

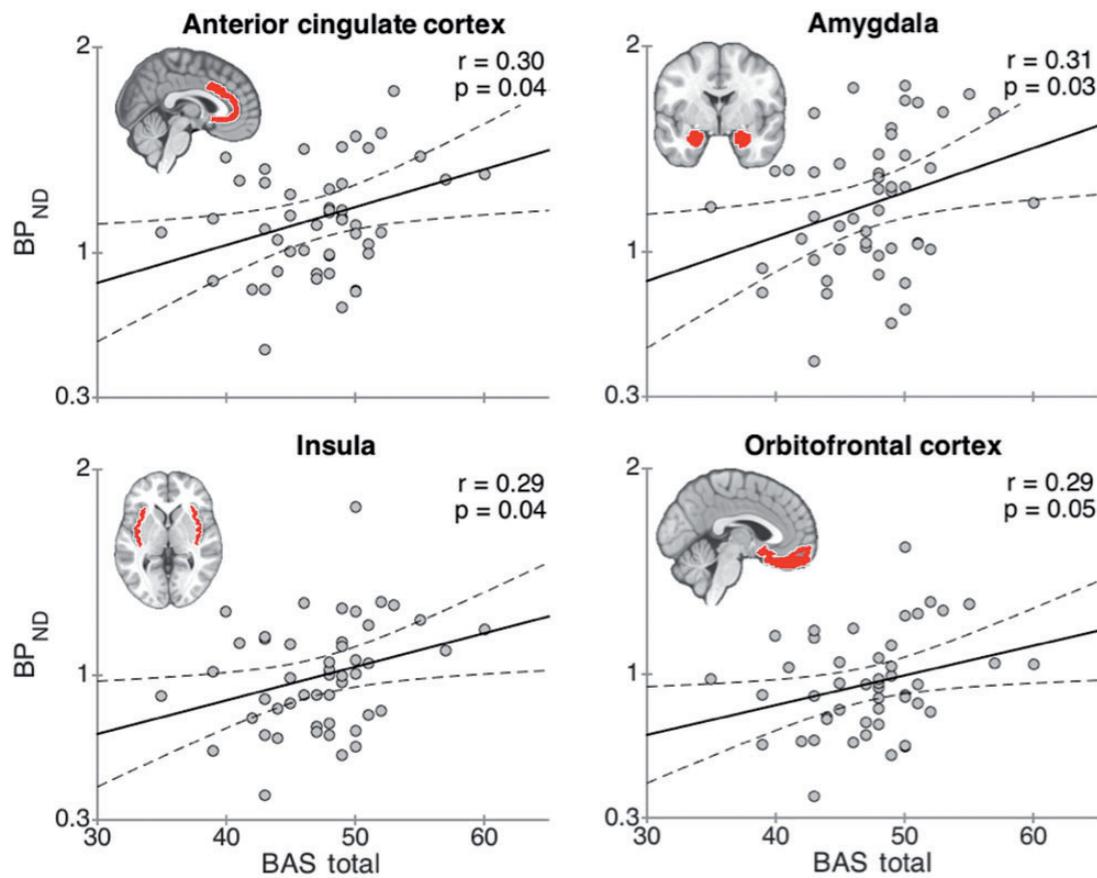


Fig. 2. Least-squares (LS) regression lines for  $[^{11}\text{C}]$ carfentanil  $BP_{ND}$  as a function of BAS total score in anatomically determined regions of interest in anterior cingulate cortex, amygdala, insula and orbitofrontal cortex. The dashed lines represent 95% confidence intervals for the LS lines.

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could explain why individuals with high baseline MOR availability are motivated to approach high-incentive targets possibly leading to physical or social pain.

5 First, high baseline MOR availability may intensify pleasure responses upon reward reception. In line with this, mice with lowered MOR density consume more opiates than their controls (Zhang et al., 2015), suggesting that they need a larger opiate dose for achieving the desired pleasure response. Similarly, human studies have proposed that low MOR availability might promote overeating and obesity, as it yields individuals unresponsive to the pleasure triggered by palatable food consumption (Karlsson

et al., 2015a,b). Second, high MOR density also provides enhanced capacity for relieving the possible physical (Zubieta et al., 2001) or social (Hsu et al., 2013) harm experienced while trying to obtain the rewards (Peciña et al., 2015). This combination of MOR-dependent elevated euphoric capacity and high pain tolerance may make high-BAS individuals well-equipped to impulsively approach rewards (Love et al., 2009).

15 It is however clear that the MOR system alone does not determine human reward-seeking tendencies. In addition to the MOR system, dopamine and endocannabinoid systems contribute significantly to motivational and reward functions (Mahler

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**Table 1.** Pearson correlations between BIS/BAS scores and regional BP<sub>ND</sub>

Region of interest	BAS Total	BAS fun seeking	BAS drive	BAS reward responsiveness	BIS
ACC	<b>0.30*</b>	0.18	0.24	0.21	0.12
Amygdala	<b>0.31*</b>	<b>0.29*</b>	0.18	0.15	0.10
DLPFC	0.27	0.16	0.21	0.22	0.17
Hippocampus	0.26	0.19	0.18	0.19	0.13
Insula	<b>0.29*</b>	0.21	0.22	0.18	0.09
NAcc	0.23	<b>0.29*</b>	0.10	0.07	0.06
OC	0.26	0.15	0.21	0.22	0.05
OFC	<b>0.29*</b>	0.22	0.20	0.16	0.14
Pallidum	0.19	0.09	0.14	0.17	0.10
Putamen	0.23	0.14	0.18	0.16	0.15
Thalamus	0.25	0.25	0.11	0.15	0.14

Statistically significant ( $P < 0.05$ ) correlations are marked with boldface and an asterisk.

\*ACC = anterior cingulate cortex, DLPFC = dorsolateral prefrontal cortex, NAcc = nucleus accumbens, OC = occipital cortex, OFC = orbitofrontal cortex.

et al., 2007; Fields and Margolis, 2015). Indeed, already the early formulations of the RST suggested that dopaminergic circuits would contribute to BAS function (Gray, 1987; Pickering and Gray, 1999). The present data thus suggest that human reward-sensitivity may be determined by interactions between multiple neurotransmitter systems; this idea is also supported by prior work highlighting how dopamine-opioid interactions are critical for reward and motivation system related conditions such as addiction (Mick et al., 2015) and obesity (Tuominen et al., 2015).

Previous studies have shown that high BAS sensitivity may predispose individuals to addiction disorders (Johnson et al., 2003; Franken et al., 2006), and functional neuroimaging studies suggest that this association might be mediated by increased neural sensitivity to reward signals in high-BAS individuals (Beaver et al., 2006; Hahn et al., 2009; Simon et al., 2010; Costumero et al., 2013). Our data suggest that high MOR availability may increase an individual's sensitivity to reward, thus promoting behaviours that more frequently activate the MOR system and possibly making the individual more vulnerable to addiction. Supporting this explanation, people with genetically determined lowered MOR availability (Peciña et al., 2015) have reduced likelihood to develop a drug addiction (Schwantes-An et al., 2015). Furthermore, MOR availability is elevated during early stages of abstinence in cocaine and alcohol abusers (Zubieta et al., 1996; Gorelick et al., 2005; Heinz et al., 2005; Weerts et al., 2011), suggesting that upregulation of MORs explains craving for these substances. In line with these clinical observations, MOR availability in healthy individuals is also associated with personality factor trait impulsivity (Love et al., 2009), suggesting that the clinical examples may be simply extreme forms of the same phenomenon. Together, these data suggest that MOR availability may partially explain human reward-sensitivity in both healthy individuals and in patient populations.

MOR availability has been previously linked with obesity, which is also associated with altered BAS sensitivity (Dietrich et al., 2014). Specifically, obese individuals have significantly lower global MOR availability than normally weighted controls (Karlsson et al., 2015a,b). However we found no linear association between MOR availability and BMI in the present sample of normal-weight individuals. This result suggests that obesity may alter MOR function and BAS sensitivity only above certain weight threshold, whereas these processes remain uncoupled in the normal-weight population.

Our experimental design does not allow distinguishing the direction of causality. It is indeed possible that our results

reflect the genetically determined role of endogenous MOR system in regulating appetitive behaviour, or alternatively the neuroplastic changes resulting from such behaviour. Other lines of evidence, however, suggest the effect may be bidirectional. First, the OPRM1 gene is known to affect MOR expression (Zhang et al., 2005; Maguet et al., 2009) and [<sup>11</sup>C]carfentanil binding (Peciña et al., 2015). Second, both BAS sensitivity (Salavert et al., 2007) and MOR availability (Karlsson et al., 2015b) of an individual may fluctuate depending on their internal state and environment. Consequently, changes in behaviour may override the genetic tendencies and modify the baseline tone of both MORs and BAS.

Our results suggest that individual differences in MOR system do not explain BIS-dependent behaviour. This accords with our previous study that found no association between attachment anxiety and MOR availability (Nummenmaa et al., 2015). Indeed, both human and animal studies suggest that instead of MOR, the serotonergic system is a plausible neuromolecular candidate subserving BIS-dependent avoidance functions. Activation of the serotonergic system is critical for avoidance behaviour in rodents (Deakin and Graeff, 1991), and genetic variations in expression of serotonin transporter influence fear circuit's responsiveness to acute threat signals in humans (Hariri et al., 2002). Finally, acute lowering of serotonin levels by tryptophan depletion abolishes punishment-dependent inhibition (Crockett et al., 2009), suggesting that individual differences in the serotonin system could underlie BIS. This however needs to be tested in future studies.

### Limitations

The most obvious limitation of our study is that instead of direct measures, we used self-reports to assess sensitivity to reward and punishment signals. However, prior studies have established that these self-reports accurately reflect the tendencies to engage in approach/avoidance behaviour (Johnson et al., 2003; Coplan et al., 2006; Kimbrel et al., 2010) and they are also associated with functioning of the corresponding neural circuits, as revealed by neuroimaging experiments (Beaver et al., 2006; Barrós-Loscertales et al., 2006a,b; Hahn et al., 2009; Simon et al., 2010; Costumero et al., 2013). Finally, it must be stressed that our outcome measure (BP<sub>ND</sub>) does not distinguish between receptor density, affinity and the amount of endogenous neurotransmitter occupancy. However, MOR density itself is largely determined by long-term endogenous neurotransmitter tone: low opioid tone leads to high receptor density and visa versa

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(McConalogue et al., 1999; Lesscher et al., 2003; Rajashekara et al., 2003). Thus, it is can be assumed that baseline MOR availability is associated with long-term endogenous MOR tone.

## Conclusions

5 We show that opioidergic system mediates BAS but not BIS function in human healthy adults. High BAS sensitivity was manifested as elevated cerebral MOR availability in brain regions involved in processing reward and pain information. BAS and BIS thus appear to have independent neuromolecular basis.  
10 Altogether these data suggest that individual differences in baseline cerebral MOR availability may explain why some people more actively seek reward than others, and thus provide a possible neurobiological explanation for our behavioural dispositions when encountering signals of reward.

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