Garcia-Garcia I, Horstmann A, Jurado MA, Garolea M, Chaudhry SJ, Margulies DS, Villringer A, Neumann J. **Reward processing in obesity, substance addiction and non-substance addiction.** Obes Rev. 2014;11:853-69.

Summary

Similarities and differences between obesity and addiction are a prominent topic of ongoing research. We conducted an activation likelihood estimation meta-analysis on 87 studies in order to map the functional magnetic resonance imaging (fMRI) response to reward in participants with obesity, substance addiction and non-substance (or behavioural) addiction, and to identify commonalities and differences between them. Our study confirms the existence of alterations during reward processing in obesity, non-substance addiction and substance addiction. Specifically, participants with obesity or with addictions differed from controls in several brain regions including prefrontal areas, subcortical structures and sensory areas. Additionally, participants with obesity and substance addictions exhibited similar blood-oxygen-level-dependent fMRI hyperactivity in the amygdala and striatum when processing either general rewarding stimuli or the problematic stimuli (food and drug-related stimuli, respectively). We propose that these similarities may be associated with an enhanced focus on reward – especially with regard to food or drug-related stimuli – in obesity and substance addiction. Ultimately, this enhancement of reward processes may facilitate the presence of compulsive-like behaviour in some individuals or under some specific circumstances. We hope that increasing knowledge about the neurobehavioural correlates of obesity and addictions will lead to practical strategies that target the high prevalence of these central public health challenges.

Introduction

Does obesity present similarities to addiction? The conceptualization of obesity as mere food addiction disorder is over simplistic, and its construct validity has been questioned [1, 2]. However, neurobehavioural studies point at the existence of some parallels between obesity and addiction [3-5], including similarities in the brain's dopaminergic system [6, 7]. In this regard, one important parallel might be the existence of similar functional brain alterations in the processing of reward.

Substance dependence can be defined by compulsive use of a drug at the expense of other activities, which intensifies with repeated access [8, 9]. Likewise, people who are addicted to non-drug entities (e.g. gambling or video games) describe similar experiences of compulsive behaviour and interference with life functioning [10, 11]. Neuroimaging studies have provided initial evidence that the neural response to gambling or playing video games in those individuals resembles the response observed in addicted individuals after the administration of substances of abuse [12]. The use of a unified approach to study substance and non-substance addictions is particularly interesting for understanding addictive processes, given that some of the phenotypic characteristics associated with substance abuse might be caused by the neurotoxic effects of drugs.

With respect to obesity, growing research suggests that obesity and addiction may present some parallels in the neural response to rewarding stimuli [3, 4]. This possibility is one of the arguments that have led to the construction of a theoretical framework known as the food addiction concept (e.g. [3, 13]). In recent years, seminal papers have outlined weaknesses and inconsistencies of this model (e.g. [2]) and as a result, instead of food addiction, today the addictive or compulsive dimensions of some types of obesity are more often referred to [5, 14].

There are different perspectives on whether obesity might be more closely associated with substance or with non-substance addictions. Theoretical works have compared obesity with non-substance addictions [12]. However, the observation that intermittent access to sugar can lead to behavioural and neurochemical changes that resemble the effects of a substance of abuse might constitute a similar biological mechanism operating in obesity and in substance abuse disorders [8]. A major shortcoming of the existing reviews comparing obesity and addictions is that they subjectively summarize published reports and, therefore, do not allow quantitative conclusions about the similarities between these disorders. Neuroimaging research on functional similarities between obesity and addictions remains scarce. To date, two studies have attempted to address this issue. They found that participants scoring higher on questionnaires reflecting an 'addictive' or 'compulsive' pattern of eating behaviour (such as the Yale Food Addiction Scale or the Binge Eating Scale) exhibited higher activity in the amygdala, anterior cingulate and orbitofrontal cortex [14, 15].

An interesting approach to examine parallels between different disorders is to conduct a meta-analysis. Meta-analyses are essential techniques to determine the convergence of results across independently performed studies. Activation likelihood estimation (ALE) is a coordinate-based meta-analysis technique for neuroimaging data that uses spatial coordinates and numbers of participants from studies to model the voxel-wise convergence of functional activation in a whole-brain approach. In its recently published version, ALE is among the state-of-the-art methods for structural and functional neuroimaging meta-analyses [16, 17]. ALE has been successfully used to map the neural response to primary and secondary rewards in healthy participants [18], and to assess general brain alterations in obesity and substance addiction [19], brain responses to alcohol [20], food and tobacco [21], and drug cues [22, 23], as well as neural activation to food stimuli in obesity [24]. However, to date, no study has integrated data on the processing of reward in obesity, non-substance addiction and substance addiction.

The aims of the present study were threefold: (i) to investigate the neural correlates of reward processing in obesity; (ii) to investigate the neural correlates of reward processing in non-substance addiction and substance addiction and (iii) to identify possible commonalities and differences in the processing of reward between these disorders. Although obesity cannot simply be characterized as either a substance or non-substance addiction, sometimes it presents some similar behavioural components with both types of addiction. Thus, we hypothesized functional similarities between obesity and addictions in brain areas implicated in reward and salience processing as well as in behavioural control.

Methods

Study selection

We searched for studies that focused on the neural response to rewarding stimuli in obesity and addiction using PubMed. Search terms included combinations of the following: (i) neuroimaging terms: MRI, fMRI, brain, magnetic resonance; (ii) disorder-related terms: obesity, overweight, BMI, body mass index, addiction, drug abuse, substance abuse and (iii) stimuli-related terms: reward, pleasant, food, monetary reward, drug cue, cocaine, cannabis, marijuana, heroin, alcohol, tobacco. Additional articles were collected by manual searches of the bibliographies of the articles retrieved.

Studies had to fulfill the following inclusion criteria: (i) peer-reviewed original research articles in English language journals; (ii) studies in humans; (iii) studies reporting contrasts as (participants with obesity/addiction > controls) or (controls > participants with obesity/addiction) and (iv) studies reporting group differences in Talairach or Montreal Neurological Institute (MNI) space. Region-of-interest studies were excluded to enable a data-driven whole-brain approach for the meta-analysis. Further exclusion criteria were the lack of a control group, the inclusion of participants with medical or psychiatric disorders other than obesity or addictions, and studies that examined the effect of a particular drug in non-addicted subjects or the impact of a particular hormone. In case of studies assessing the effect of a particular treatment [25, 26], we only entered in the meta-analysis results obtained in the baseline condition or in the placebo condition. We included in the meta-analysis 87 papers: 16 studies assessed functional brain alterations in obesity, 22 in non-substance addictions (Internet/gaming addiction and pathological gambling) and 53 in substance addictions (nicotine addiction, alcohol addiction and other substance-dependent disorders) (Fig. 1 presents a flow chart of the selection process; consult supporting information Tables S1–S6 for an overview of the studies included).

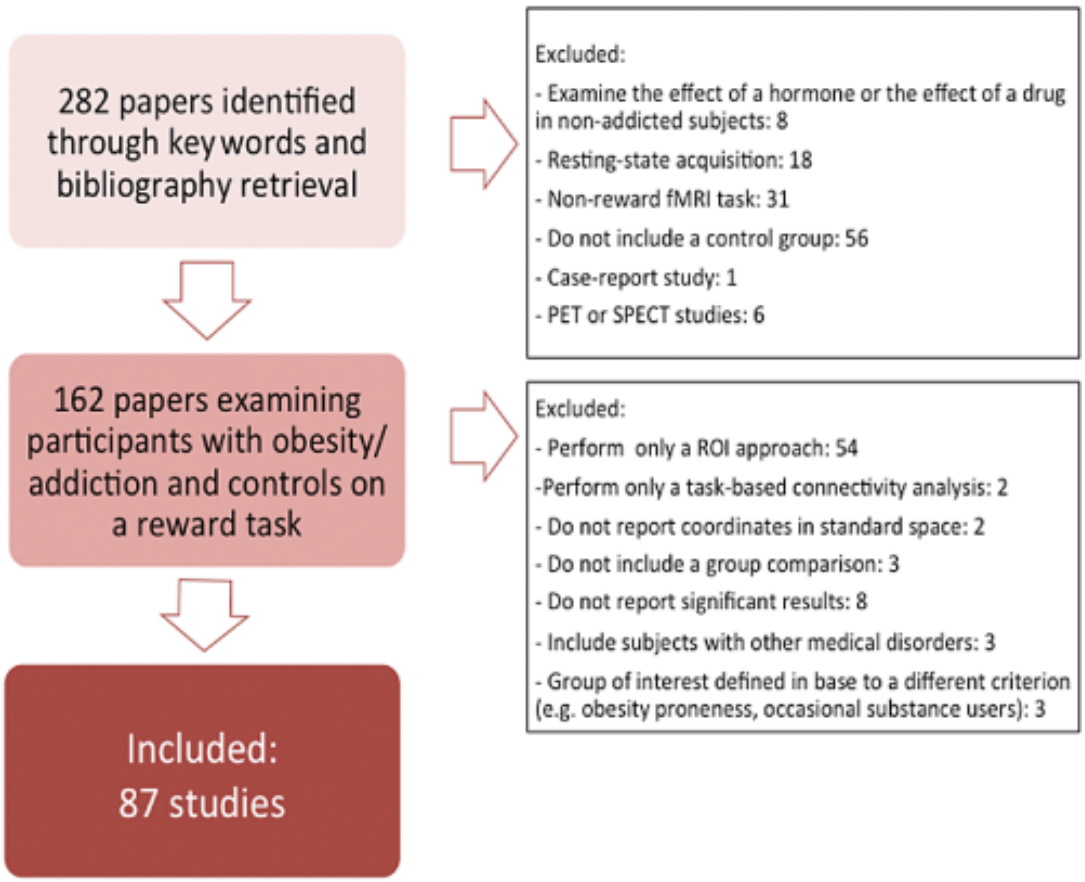

Figure 1. Flow chart illustrating the study selection procedure that was used for this meta-analysis.

Note that, unlike gambling disorder, Internet gaming disorder is a new disorder not included in the diagnostic category of behavioural addictions in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), so far. However, emerging evidence points at commonalities between Internet gaming disorder and other types of addiction [11]. Therefore, we included it in our current analysis.

Activation likelihood estimation

ALE is a method for conducting meta-analyses of neuroimaging data that focuses on identifying common regions of activation across studies (for a thorough description, see [16, 17]). This type of meta-analysis identifies prototypical networks of activation related to the investigated phenomena. In the current study, we were interested in the location of regions that differ in functional activation between a group of interest (obese, non-substance-addicted and substance-

addicted participants) and a control group. Our analyses were performed using GingerALE 2.3 (www.brainmap.org).

In ALE, spatial coordinates are modelled as three-dimensional Gaussian probability distributions rather than single points. From the probability distributions of each coordinate or focus, ALE calculates for each voxel the probability that a given focus lies within it. The probabilities are then combined within and across experiments to produce a whole-brain map of ALE values for each voxel. This empirical ALE map is compared to a null hypothesis map representing the noise distribution which is generated by combining the results of several thousand permutations of randomly selected foci. The null hypothesis is rejected voxel by voxel based on whether the probability of obtaining a given ALE value under the null hypothesis meets the significance criteria. Significance tests are corrected for multiple comparisons using a false discovery rate of .05.

We investigated reward processes in (i) overweight and obesity; (ii) non-substance addictions (Internet/gaming addiction and pathological gambling) and (iii) substance addictions (nicotine addiction, alcohol addiction and other substance addictions). For each disorder, we assessed two conditions: (i) general reward processing and (ii) the processing of the problematic stimuli (e.g. food in obesity, gaming in non-substance addictions, substance-related stimuli in substance addictions).

In the cases where the number of studies was large enough (e.g. substance addictions), additional analyses were performed (e.g. examination of monetary reward).

Finally, by using conjunction and subtraction analyses, we addressed commonalities and differences between obesity, non-substance addictions and substance addictions both during the processing of general rewarding stimuli and during the processing of the problematic stimuli.

We verified the anatomical location of clusters by using the Harvard–Oxford cortical and subcortical atlases (http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html) as well as matching coordinates with areas indicated in the studies that contributed the coordinates.

Results

Obesity

The literature search retrieved 16 studies on the neural response to reward processing in obesity [26-41]. These studies were published between 2007 and 2013 and represent 556 participants (228 with overweight or obesity and 328 with normal weight) with an age range between 9.57 and 64 years. The percentage of female participants was 87.59% (Supporting Information Table S1). With regard to the reward paradigm used, 14 studies examined food reward (nine utilized visual stimuli, four used gustatory cues and one applied olfactory stimuli) and two

studies employed monetary reward. All studies reported body mass index (BMI) (kg m−2) in order to characterize participants.

During the examination of general reward processing, in the contrast obese/overweight > controls we found differences in the putamen, postcentral gyrus, lingual gyrus, superior frontal gyrus and amygdala. In the contrast obese/overweight < controls we obtained clusters located in the central operculum/middle insula, lateral occipital cortex, postcentral gyrus and in the temporo-occipital lobe (Table 1 and Fig. 2). The postcentral gyrus was found both hyper and hypoactivated in association with obesity. In order to explain this contradictory result, we examined the characteristics of the studies located within the boundaries of the ALE cluster. An obesity-related enhanced activation of the postcentral gyrus was reported both in studies on visual and on gustatory food stimuli, while an obesity-related decreased activity was reported only in papers on visual food stimuli.

Table 1. Results of the meta-analysis. Significant differences in activation elicited during the processing of rewarding stimuli

Cluster	Size (mm^3)	MNI coordinates X	Y	Z	ALE value	Anatomical location
Obese/overweight > Controls (eight contributing experiments; sample size = 206; foci = 124)						
1	504	−16	4	−8	.0141	Left putamen/pallidum/accumbens
2	360	56	−14	32	.0132	Right postcentral gyrus
3	336	20	−48	0	.0013	Right lingual gyrus
4	336	−2	12	66	.0157	Superior frontal gyrus
5	216	22	4	−18	.0111	Right parahippocampal gyrus/amygdala
Obese/overweight < Controls (14 contributing experiments; sample size = 543; foci = 66)						
1	664	−42	2	12	.0152	Left central operculum/middle insula
2	440	−16	−76	46	.0113	Left lateral occipital cortex
3	304	−56	−18	22	.0121	Left postcentral gyrus

Non-substance addictions > Controls (18 contributing experiments; sample size = 497; foci = 162)

1	1,192	−52	14	26	.0223	Left inferior frontal gyrus
2	536	−10	−56	12	.0139	Left posterior cingulate cortex
3	392	14	2	−16	.0123	Right amygdala/parahippocampal gyrus
4	376	−10	30	30	.0160	Left paracingulate cortex
5	304	−46	−28	−10	.0144	Left temporal horn
6	288	−24	0	58	.0110	Left precentral cortex
7	256	8	4	26	.0118	Right middle cingulate
8	248	26	56	12	.0128	Right superior frontal gyrus
9	240	50	26	8	.0123	Right inferior frontal gyrus
10	216	10	32	30	.0116	Right paracingulate cortex

Non-substance addictions < Controls (nine contributing experiments; sample size = 266; foci = 76)

1	280	40	−20	−16	.0106	Right hippocampus
2	264	46	−28	40	.0111	Right inferior parietal gyrus
3	256	−48	−22	32	.0104	Left postcentral gyrus
4	208	−14	−80	−12	.010	Left occipital lobe/declive

Substance addictions > Controls (43 contributing experiments; sample size =1774; foci = 395)

1	994	−2	−10	4	.0256	Thalamus
2	928	38	16	0	.0238	Right anterior insula
3	864	−2	42	40	.0188	Left superior frontal gyrus
4	776	−10	10	−6	.0241	Left caudate/accumbens
5	640	40	38	28	.0215	Right middle frontal gyrus

6	624	−24	8	2	.0170	Left putamen/pallidum
7	624	−6	−34	28	.0155	Posterior cingulate cortex
8	616	24	0	−20	.0238	Right amygdala/parahippocampal gyrus
9	528	2	30	14	.0202	Anterior cingulate cortex
10	432	36	24	−8	.0154	Right anterior insula/inferior frontal gyrus
11	416	−20	28	54	.0212	Left superior frontal gyrus
12	400	26	4	−2	.0204	Right putamen/pallidum
13	368	16	6	6	.0147	Right caudate
14	320	−10	8	10	.0163	Left caudate
15	264	−58	−26	22	.0180	Left postcentral gyrus
16	264	−2	−2	34	.0174	Middle cingulate cortex
17	232	−36	−86	20	.0162	Left lateral occipital cortex
18	232	30	−68	44	.0165	Right precuneus
19	224	−16	−2	−22	.0155	Left amygdala
20	224	8	48	22	.0176	Right paracingulate gyrus

Substance addictions < Controls (30 contributing experiments; sample size =1152; foci = 250)

1	1,744	10	30	32	.0209	Right paracingulate gyrus/anterior cingulate cortex
2	1,016	−16	14	−16	.0167	Left caudate/putamen/pallidum/accumbens
3	784	8	−90	8	.0186	Right lingual gyrus
4	704	16	14	54	.0151	Right medial frontal gyrus
5	592	36	−24	−2	.0155	Right posterior insula/sub-lobar
6	376	14	24	2	.0153	Right caudate/accumbens
7	368	−36	−62	12	.0154	Left lateral occipital cortex

8	352	70	−26	6	.0173	Right superior temporal cortex
9	304	−2	36	44	.0182	Superior frontal cortex
10	248	42	16	8	.0150	Right anterior insula
11	224	22	−64	50	.0153	Right precuneus

Notes: Results corrected at FDR <.05. Minimum cluster size 200 mm^3.
ALE, activation likelihood estimation; MNI, Montreal Neurological Institute.

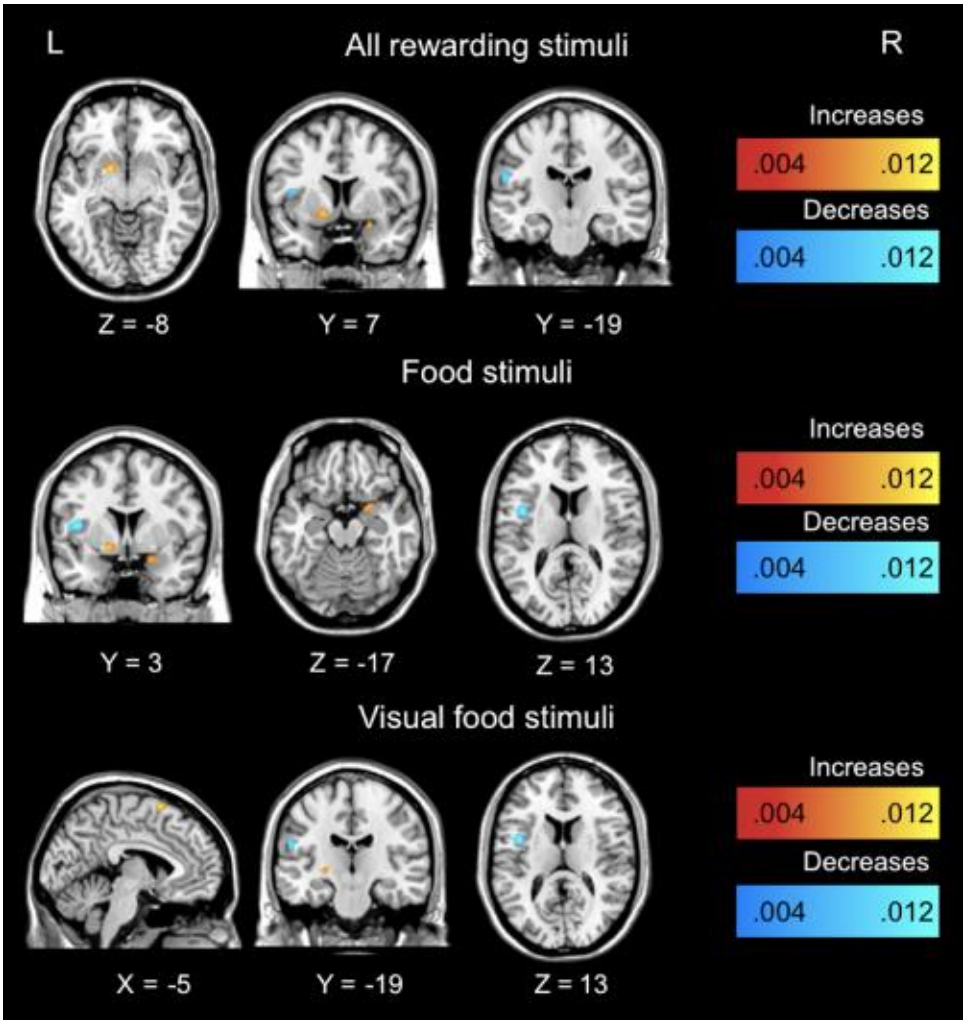

Figure 2. Results of the meta-analysis in overweight and obesity. Increases and decreases in BOLD fMRI activity in participants with overweight and obesity relative to controls during the processing of all rewarding stimuli, food stimuli and visual food stimuli (P < .05 FDR whole brain corrected). Color bars represent ALE values.

The clusters obtained during the examination of food reward in obesity were highly similar to the ones obtained in general reward processing (Table 2 and Fig. 2).

Table 2. Results of the meta-analysis. Significant differences in activation elicited during the processing of the problematic stimuli

Cluster	Size (mm^3)	MNI coordinates X	Y	Z	ALE value	Anatomical location
Obese/overweight > Controls (seven contributing experiments; sample size = 168; foci = 115)						
1	560	−16	4	−8	.0141	Left putamen/pallidum/accumbens
2	392	20	−48	0	.0013	Right lingual gyrus
3	384	56	−14	32	.0132	Right postcentral gyrus
4	336	−2	12	66	.0157	Superior frontal gyrus
5	280	22	4	−18	.0111	Right parahippocampal gyrus/amygdala
6	208	−24	−20	−2	.0105	Left pallidum/thalamus
7	200	−4	18	−14	.0104	Left ventromedial prefrontal cortex
Obese/overweight < Controls (11 contributing experiments; sample size = 430; foci = 56)						
1	672	−42	2	12	.0152	Left central operculum/middle insula
2	472	−16	−76	46	.0113	Left lateral occipital cortex
3	312	−56	−18	22	.0121	Left postcentral gyrus
Non-substance addictions > Controls (10 contributing experiments; sample size = 247; foci = 114)						
1	984	−50	14	28	.0166	Left inferior frontal gyus
2	736	−10	−56	12	.0140	Left posterior cingulate cortex
3	408	−46	−28	−10	.0144	Left temporal horn
4	328	50	26	8	.0123	Right inferior frontal gyrus

5	312	8	4	26	.0116	Middle cingulate cortex
6	288	14	2	−16	.0112	Right amygdala/parahippocampal gyrus
7	248	16	−48	−38	.0109	Right cerebellum

Non-substance addictions < Controls (three contributing experiments; sample size = 74; foci = 27)

Meta-analysis not performed

Substance addictions > Controls (27 contributing experiments; sample size = 958; foci = 239)

1	1,152	−2	−10	4	.0253	Thalamus
2	1,104	−2	−44	26	.0148	Posterior cingulate cortex
3	648	−20	28	54	.0212	Left superior frontal gyrus
4	584	−26	4	2	.0174	Left putamen
6	480	−10	6	10	.0160	Left caudate
7	432	38	18	0	.0160	Right anterior insula
8	384	−10	12	−6	.0170	Left accumbens/putamen
9	352	2	30	14	.0167	Anterior cingulate cortex
10	336	12	10	12	.0144	Right caudate
11	312	0	32	48	.0175	Superior frontal gyrus
12	304	24	2	−20	.0185	Right amygdala/parahippocampal gyrus
13	296	54	22	−12	.0138	Right inferior frontal gyrus
14	296	−2	50	0	.0142	Anterior cingulate cortex
15	288	34	34	−14	.0142	Right lateral orbitofrontal cortex
16	264	−38	−64	26	.0165	Left middle temporal gyrus
17	208	−4	−16	−16	.0124	Brainstem

Substance addictions < Controls (10 contributing experiments; sample size = 364; foci = 51)

1	600	12	−88	8	.0130	Right intracalcarine cortex
2	254	8	22	48	.011	Right superior frontal gyrus

Notes: Results corrected at FDR <.05. Minimum cluster size 200 mm3.
ALE, activation likelihood estimation; MNI, Montreal Neurological Institute.

Finally, we focused on the response to visual food stimuli in obesity. We found that participants with overweight/obesity exhibited an enhanced blood-oxygen-level-dependent (BOLD) activity in the superior frontal lobe and pallidum, and a decreased BOLD activity in the middle insula and in the postcentral gyrus (Fig. 2 and Supporting Information Table S7).

Non-substance addiction

We identified 22 studies on the processing of reward in non-substance addictions. Eleven studies compared participants with Internet/gaming addiction and control participants [42-52] and 11 studies evaluated differences between participants with pathological gambling and control subjects [53-63]. They were published between 2003 and 2014.

Overall, these studies comprised 604 participants (302 with non-substance addiction disorders and 302 control participants) aged between 13 and 65 years old. The percentage of female participants was 4.5%.

Regarding the reward paradigms used, 12 studies examined the processing of primary problematic stimuli (Internet and gaming stimuli or a gambling scenario) and 10 papers examined the response to monetary reward.

The meta-analysis on the processing of reward (Table 1 and Fig. 3) revealed that participants with non-substance addictions exhibited increased activation in areas including the inferior frontal gyrus, posterior cingulate cortex, paracingulate cortex and amygdala, as well as decreased activation in the hippocampus, inferior parietal gyrus and postcentral gyrus. Supporting Information Table S8 presents these results for the different patient groups (Internet/gaming addiction and pathological gambling).

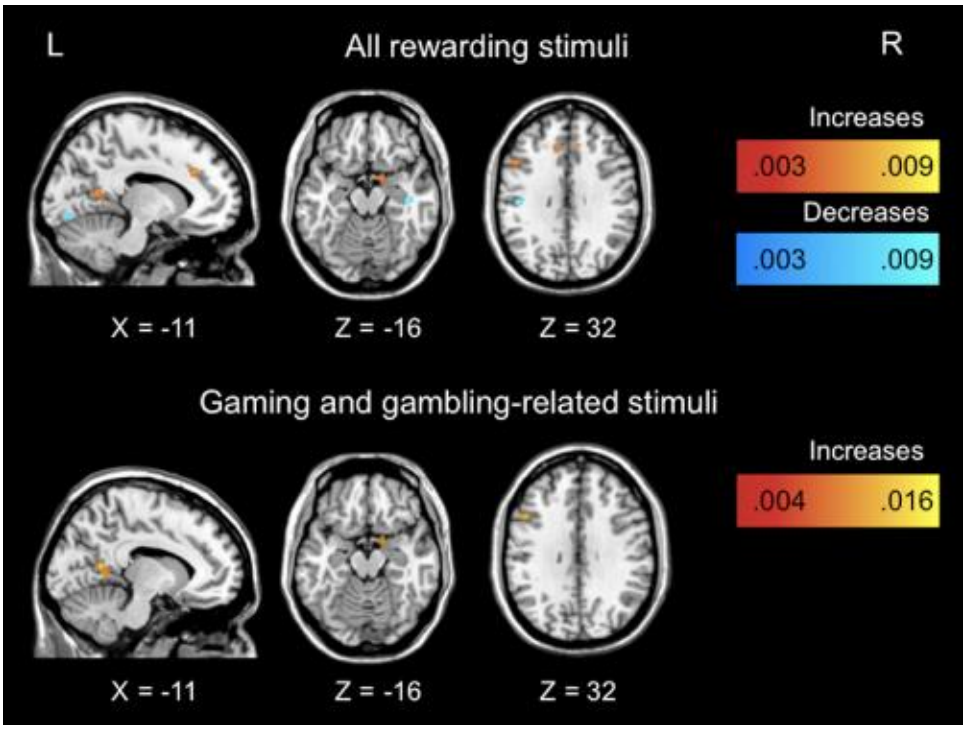

Figure 3. Results of the meta-analysis in non-substance addictions. Increases and decreases in BOLD fMRI activity in participants with non-substance addictions relative to controls during the processing of all rewarding stimuli and gambling or gaming-related stimuli ($P < .05$ FDR whole brain corrected). Color bars represent ALE values.

We then focused on the processing of the problematic stimuli in non-substance addictions (e.g. visualization of gaming images). Here, we obtained comparable results (Table 2 and Fig. 3).

An additional analysis on the processing of monetary reward did not yield any significant results, possibly due to the low number of studies available.

Substance addiction

We identified 53 studies on the processing of reward in substance addictions: 10 addressed nicotine addiction [56, 64-72], 16 evaluated alcohol dependence [61, 73-87] and 27 focused on participants addicted to other substances [25, 88-113] (nine studies on cocaine or psychostimulants abuse, eight on cannabis dependence, six on opioid dependence, three on methamphetamine dependence and one on ecstasy abuse). They were published between 2001 and 2014.

The total sample size was 2,139 participants (1,112 with substance abuse problems and 1,027 controls aged between 13 and 60 years). The proportion of women was 28.00%. Regarding the paradigms employed, 29 studies focused on the problematic stimuli (e.g. drug images), 19 included an examination of monetary reward, six included an assessment of the response to pleasant pictures/happy faces, two were conducted on pleasant interoceptive stimulation (soft touch) and one focused on food reward. Finally, one study conducted a reward learning paradigm that used a gift voucher instead of monetary reward.

The processing of general reward (Table 1 and Fig. 4) elicited a greater activation in drug-addicted individuals in several regions including the thalamus, anterior insula, superior and middle frontal gyri, basal ganglia (caudate/accumbens and putamen/pallidum), amygdala, posterior cingulate cortex and anterior cingulate/paracingulate cortex. The ALE meta-analysis also yielded clusters for the contrast substance dependence < controls in areas including the anterior cingulate cortex, superior frontal gyrus, caudate, putamen and anterior insula. Some brain areas, like the striatum, anterior insula and superior frontal gyrus, showed both hyper- and hypoactivation associated with substance addictions. Studies reporting an addiction-related hyperactivation in these areas were conducted on either drug-related stimuli or monetary reward, and in the latter case, they were mainly associated with the outcome phase of the paradigm. By contrast, studies reporting a blunted BOLD activity in these structures in participants with substance addictions were conducted on either monetary reward or on other rewarding paradigms (e.g. food reward or pleasant soft touch). Supporting Information Table S9 presents these analyses separated by groups of interest (nicotine addiction, alcohol addiction and other substance addictions).

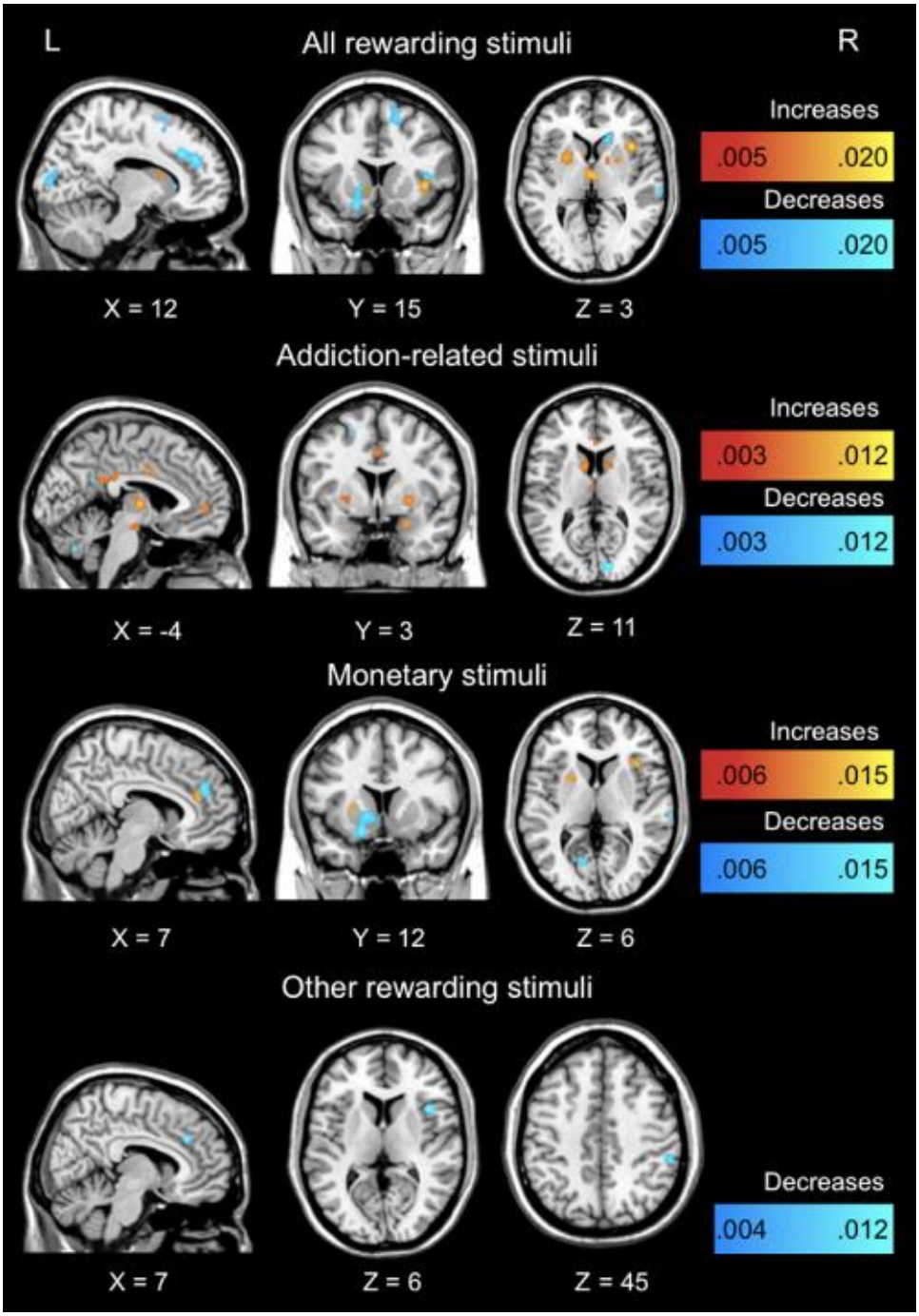

Figure 4. Results of the meta-analysis in substance addictions. Increases and decreases in BOLD fMRI activity in participants with substance addictions relative to control participants during the processing of all rewarding stimuli, drug-related stimuli, monetary stimuli and other rewarding stimuli ($P < .05$ FDR whole brain corrected). Color bars represent ALE values.

When examining the processing of substance-related stimuli, we observed that relative to controls, participants with substance addictions exhibited higher BOLD activity in a widespread set of frontal regions (e.g. superior frontal gyrus, anterior cingulate cortex, orbitofrontal cortex and inferior frontal gyrus), in subcortical structures (e.g. putamen, caudate, amygdala and accumbens) and in the brainstem. Participants with substance addictions exhibited lower BOLD activity in the intracalcarine cortex and in a superior cluster within the superior frontal gyrus (Table 2 and Fig. 4).

Monetary reward (Fig. 4 and Supporting Information Table S10) was associated with an enhanced activation in participants with substance addictions relative to controls in several anterior regions (e.g. the anterior cingulate cortex, medial frontal gyrus, middle and inferior frontal gyri, anterior insula) in the parahippocampal gyrus, in posterior regions (e.g. the precuneus, cuneus and lateral occipital cortex), and also in the putamen and pallidum. Relative to controls, participants with substance addictions exhibited decreased BOLD activity in extended regions within the striatum (e.g. accumbens, putamen, pallidum and caudate), in the medial frontal gyrus and in the superior temporal gyrus. Both the lenticular nuclei (putamen and pallidum) and the medial frontal gyrus were found hyper- and hypoactivated in participants with substance addictions. The studies reporting an addiction-related enhanced activity in the striatum and in the medial prefrontal cortex contained a higher percentage of female participants (ranging from 7 to 54%) than the studies reporting an addiction-related decreased BOLD activity in the same areas (in this last case, it ranged from 0 to 7%). Moreover, in the majority of cases, studies reporting an addiction-related hyperactivity in the lenticular nuclei were associated with an outcome phase of the monetary task. A sub-analysis focusing on anticipation of monetary reward is presented in the Supporting Information Table S10.

Finally, the processing of other rewarding stimuli (e.g. positive faces, pleasant soft touch) elicited a diminished BOLD activity in substance-dependent participants relative to controls in the anterior insula, paracingulate gyrus, inferior parietal lobe and medial frontal gyrus (Fig. 4 and Supporting Information Table S11).

An additional analysis on the processing of reward separated for active substance-dependent population and for treatment-seeking population can be consulted in Supporting Information Table S12.

Commonalities in obesity, non-substance addiction and substance addiction

The conjunction analyses for the processing of general reward showed that participants with obesity and participants with substance addictions exhibited an overlapping cluster of increased BOLD signal in the right amygdala (128 mm3; MNI coordinates: 22 4 −18; ALE value: .0111) and in the left accumbens extending to the putamen and pallidum (120 mm3; MNI coordinates: −14 6 −8; ALE value: .0123) (Fig. 5). This last result was formed by the overlap between a

cluster obtained in obesity – with a peak of maximal ALE value located in the putamen – and a cluster obtained in substance addictions with a peak of maximal ALE value in the caudate. Participants with non-substance addictions also exhibited increased BOLD activation in the right parahippocampal gyrus extending to the amygdala (MNI coordinates: 14 2 −16); however, the cluster found here did not overlap with the ones found for obesity and substance addiction, but was located more extending to superior layers (Fig. 5).

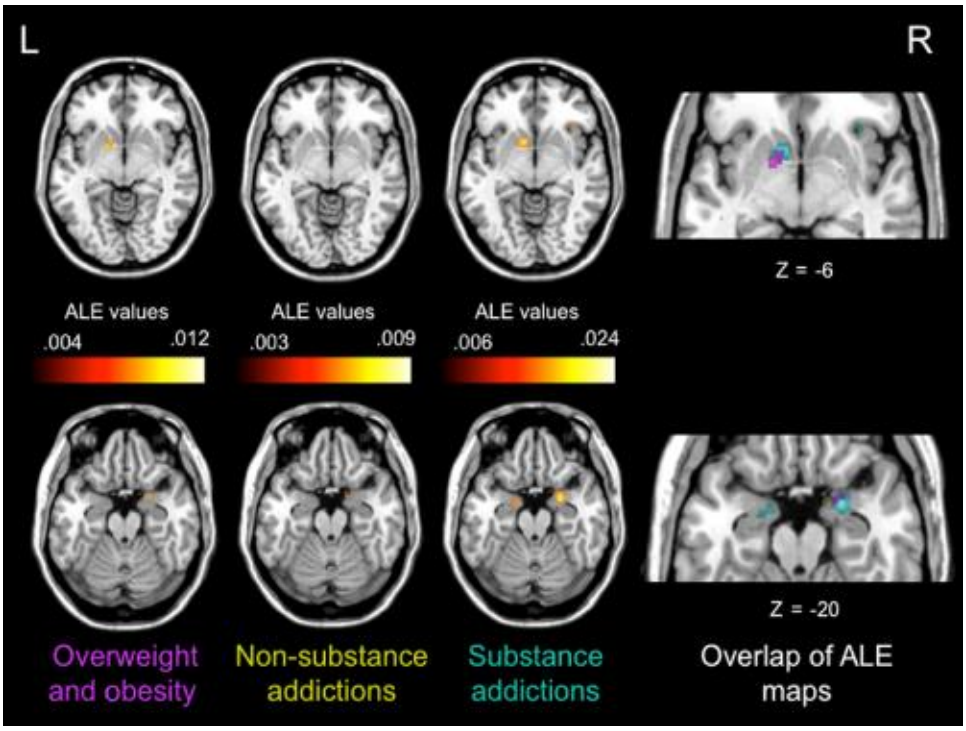

Figure 5. Alterations in obesity and in substance addictions in the amygdala and striatum during reward processing. The first three columns show the ALE maps ($P < .05$ FDR whole brain corrected) for obesity, non-substance addictions and substance addictions in the striatum (upper part) and the amygdala (lower part). The rightmost column represents the overlapping maps in the striatum and in the amygdala (obesity = violet; substance addictions = cyan; non-substance addictions = yellow).

The conjunction analyses were also performed on the processing of the problematic stimuli. Again, obesity and substance addictions exhibited an overlapping cluster of increased BOLD activity in the right amygdala (88 mm3; MNI coordinates: 24 4 −18; ALE value: .0110) and in the left putamen extending to the accumbens (72 mm3; MNI coordinates: −12 8 −6; ALE value: .0102) (Fig. 6). As in the previous analysis, non-substance addictions exhibited alterations in the

right amygdala, but again, this cluster did not overlap with the ones found for obesity and substance addictions.

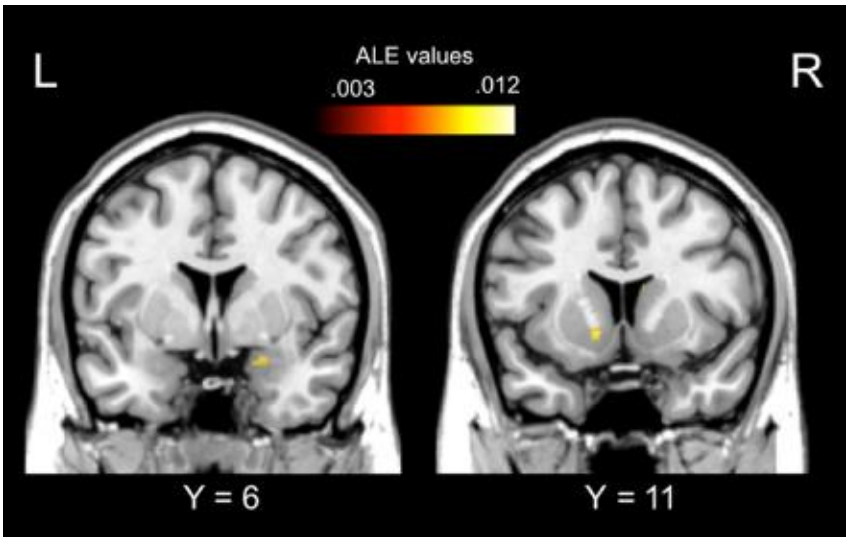

Figure 6. Overlapping cluster of BOLD fMRI signal increase for obesity and substance addiction during the processing of the problematic stimuli. Convergent alteration between participants with obesity and participants with substance addictions during the processing of the problematic stimuli (food in obesity; drug-related stimuli in substance addictions) in the amygdala and in the striatum (ALE maps: $P < .05$ FDR whole brain corrected).

No common areas were found when examining maps of increased BOLD activation in controls relative to the groups of interest.

Differences between obesity, non-substance addiction and substance addiction

Despite divergent patterns of functional alterations obtained in the individual analyses for obesity, non-substance addictions and substance addictions, the subtraction analysis directly comparing these maps did not yield any clusters representing statistically significant differences between the disorders. This can most likely be attributed to the low statistical power of the subtraction analysis, due to the relatively low number of studies in each category.

Discussion

Our study adds three findings to the current body of research. First, we confirmed the presence of obesity-related functional alterations in a core set of brain regions in response to (ranging from more general to more specific) rewarding stimuli, food stimuli and visual food stimuli. Second, we characterized differences between participants with addictions and control participants in response to general rewarding stimuli and also restricted to the processing of the addictive stimuli. In substance addictions, we expanded this information and presented differences associated with the processing of monetary reward and other rewarding stimuli. Third, obesity and substance addictions exhibited a similar increased activation in the amygdala and striatum, which was detected in response to general rewarding stimuli and, also more specifically, in response to the problematic stimuli (food in obesity, drug stimuli in substance addictions).

Obese and overweight participants presented some functional differences to normal-weight subjects in response to rewarding stimuli. Specifically, relative to controls, participants with overweight or obesity exhibited higher activation in several regions including the putamen, pallidum and amygdala/parahippocampal gyrus and superior frontal gyrus, as well as a decreased activation in regions including the central operculum/middle insula and visual areas. Of note, the exclusion of studies on monetary reward produced a very similar map of functional differences between participants with overweight or obesity and controls, which may indicate either that the aforementioned alterations were mostly driven by studies on food reward or that, in obese participants, monetary reward yielded a similar pattern of activity than food reward. When regarding visual food stimuli only, we found an obesity-related enhanced activation in the superior frontal lobe and pallidum and an obesity-related decreased activation in the insula and postcentral gyrus. These results are in coherence with a previous meta-analysis on food reward in obesity [24].

An important consideration when interpreting these results is the definition of overweight and obesity. BMI (kg m−2) is typically used as a surrogate for adiposity. According to the World Health Organization, individuals with a BMI equal to or higher than 25 kg m−2 are classified as overweight, while individuals with a BMI equal to or above 30 kg m−2 are defined as obese [114]. The BMI has been criticized for neglecting other factors like muscular mass or insulin resistance (e.g. [115]) and for not being associated with addictive-like eating behaviour in obesity [15]. Nonetheless, the BMI is still conveniently used in the characterization of obesity, and all studies included in the meta-analysis on obesity provided this measure in order to define their groups of participants. Binge eating disorder (BED) is a condition presented together with overweight or obesity (in the majority of individuals with this disorder) and characterized by recurrent episodes of uncontrolled consumption of large amounts of food without compensatory (e.g. vomiting or purgative use) weight-control behaviours. It has been suggested that individuals with BED – specifically those with a more severe and compulsive symptomatology – may display a clinical profile akin to individuals with substance use disorders [116]. Some caveats for this conceptualization have been pointed out: the BMIs of some individuals with BED fall in the

normal-weight range, while on the other hand, the majority of overweight or obese individuals are not classified as binge eaters [2]. Despite these considerations, it has been proposed that food addiction may reflect the end of a continuum in pathological eating in the obese population, ranging from a 'passive' form of eating behaviour to a severe and compulsive subtype of BED [116]. This end of the continuum seems to share clinical similarities with substance use disorders [116]. Studies on the BOLD functional magnetic resonance imaging (fMRI) response to visual food stimuli have found that participants with BED exhibited higher activity in the orbitofrontal cortex relative to controls ([117]; reviewed in [118]). Additionally, compulsive eating scores have been associated with the activation of mesocorticolimbic areas including the amygdala, putamen and thalamus [14]. In general, these results in food reward processing are in coherence to the ones found in overweight and obesity in the current study.

The ALE meta-analysis revealed functional alterations in substance and non-substance addictions in a widespread network of brain regions. These patients exhibited enhanced BOLD activity in areas including the inferior frontal gyrus, posterior cingulate cortex and parahippocampal cortex/amygdala. These differences were detected for both general reward processing and the processing of the problematic stimuli. In substance addictions, in response to drug-related stimuli, patients also exhibited an increased BOLD activity in the ventral and dorsal striata (caudate, putamen and accumbens) and in the brainstem. This enhanced activation in addictive disorders is in coherence with the observation that these patients may manifest an unusual focus on the addictive incentive stimuli [119] and may account for feelings of loss of control towards drug consumption that are present in addiction. Similar to what we previously describe in obesity, compulsive drug consumption may also be presented in a dimensional continuum and addiction may represent its pathologic end. Nonetheless, also in participants with addictive disorders, compulsive behaviours may be dynamic and flexible. As such, an individual may exhibit a particularly prominent compulsive behaviour under determined circumstances (e.g. stressful life events) while being able to exert impulse control under other circumstances [4].

It has been hypothesized that drugs of abuse 'hijack' brain reward systems such that drug-related stimuli become overvalued while non-drug-related stimuli become undervalued [119]. In line with this idea, the examination of other positive reinforcements yielded a somewhat different pattern of activation than the one observed during the processing of the problematic stimuli. Monetary reward was associated with decreased striatal activity (although an increased activity in the putamen was also found) and increased activity in several frontal regions like the middle and inferior frontal gyri and anterior insula. Despite being a non-drug reward, it is possible that monetary stimuli may still be associated with drug availability. However, this association is unlikely in the case of other rewarding stimuli such as positive faces, food stimuli or pleasant soft touch stimulation. In response to these last types of stimuli, substance-addicted participants exhibited a diminished BOLD activity in areas including the anterior insula and the medial frontal gyrus in relative to controls. However, caution should be taken when interpreting the

findings obtained in this 'other rewarding stimuli' category, given the low number of studies and the high heterogeneity of the paradigms included.

Our conjunction analyses revealed a similar increased activation in the right amygdala for obesity and substance addiction. The amygdala is a convergence zone for highly salient information [120] and it has been widely studied for its involvement in emotional processing, fear and anxiety (e.g. [121]). Growing evidence suggests an important role of the amygdala in the escalation of drug use and in the development of compulsive drug seeking [122]. With regard to eating behaviour processes, different studies in healthy participants have found activation of the bilateral amygdala in response to salient attributes of food stimuli, such as palatability or caloric content, and also when participants are in a food deprivation condition (reviewed in [118]). Obesity and substance addiction disorders also exhibited an overlap in the left striatum, specifically in the nucleus accumbens. This overlapping cluster resulted from two clusters in obesity and in substance addictions with peaks of maximal ALE value located in the putamen and the caudate, respectively. Putamen and caudate are part of the dorsal striatum and receive dopaminergic inputs from the substantia nigra pars compacta [123]. The dorsal striatum has been traditionally considered to be closely associated with movement [124], and today it is thought to be involved in the initiation, production and sequencing of motor behaviour [125]. Additionally, strong evidence links the dorsal striatum to food motivation [126] and it is considered to be recruited in the development of compulsive drug-seeking behaviour [127]. The nucleus accumbens, on the other hand, is part of the ventral striatum and is recognized as a key structure in mediating the rewarding effects of drugs of abuse, food and sexual behaviour [128]. All together, the similarities found between obesity and substance addictions are notably small. Nonetheless, they are located in areas that seem to be crucial for reward and salience processing. Although this result may be in line with the food addiction model, it has to be noted that this overlap does not necessarily indicate the existence of common biological mechanisms in obesity and addition. A more plausible explanation is that it may be associated with an enhanced focus on rewarding stimuli – especially with regard to food or drug-related stimuli – in both obesity and substance addiction. We hypothesize that in some individuals with obesity or addiction, as well as under some specific circumstances (e.g. stressful life events), this enhanced focus on rewarding stimuli may be associated with the presence of some compulsive-like behaviour or with some degree of difficulties in impulse control.

Methodological issues

The present meta-analysis has some limitations that need to be acknowledged. First, a great number of studies focus on one type of addiction but include participants with some degree of use of other substances. We would like to indicate the need for reporting toxic habits, which is not always done. Thus, we cannot exclude the possibility that at least some results are influenced by the interaction between different substances or addictive behaviour. Second, studies on the

problematic stimuli were examined together, encompassing different reward processes (e.g. anticipatory or consummatory reward) and types of stimuli (studies on sight, smell, taste and touch). Unfortunately, the number of studies available so far does not allow disentangling patterns resulting from different tasks employed. It is only in the case of obesity that we could present the results focusing on visual food stimuli. Third, studies on processing monetary reward encompass heterogeneous experiments (e.g. monetary cue presentation, monetary incentive delay tasks or delay discounting tasks) and processes (e.g. anticipatory reward, outcome evaluation, outcome in the context of a decision-making task). While in the context of substance addictions a sub-analysis for the anticipation of monetary reward could be performed, further sub-analyses were not possible due to the small number of available studies. Thus, caution should be taken when interpreting our results for the processing of monetary reward as a whole, given the relatively low number of studies contributing to this contrast and the high heterogeneity among them.

Fourth, demographic characteristics such as age and gender vary depending on the group of interest analysed. For example, in studies on obesity, the percentage of female participants was high, which stands in contrast with the low proportion of female participants in studies on non-substance addictions. The current implementation of ALE takes into account the number of subjects included in each individual study and prevents multiple foci from a single experiment to cumulatively influence ALE values [16], which constitutes an advantage over previous versions [129]. However, current meta-analysis methodology does not facilitate the inclusion of additional covariates into the analysis in order to correct for their potential impact on the results. Thus, a possible influence of confounding factors like sociodemographic variables cannot be ruled out when interpreting our results. Fifth, obesity per se does not necessarily implicate the presence of compulsive (addictive-like) overeating behaviour, and as such, the participants included in the studies in obesity may not be characterized by a lack of control over ingestive behaviour. In this sense, it is important to note that food addiction scores are not related to BMI [15] and that, as discussed above, overeating may be better conceptualized as a continuum with an increasing degree of compulsive eating behaviour [117]. Sixth, the studies in obesity defined the groups based on BMI. The inclusion of other adiposity-related measures (e.g. abdominal adiposity, leptin levels or insulin resistance) may produce differences in the results. Seventh, following previous approaches [24], we did not exclude studies comparing the group of interest and a control group under placebo conditions. While this maintained a high statistical power for our analysis, we cannot rule out that the placebo effect may have differed across groups. Eighth, the age range of the participants was broad. Of note, we additionally performed the analyses excluding studies conducted in adolescent participants. These analyses showed the same pattern of results than the ones obtained with the whole pool of data. Nevertheless, because the majority of the studies included were performed by participants in young-to-middle adulthood, our results may not directly generalize to other stages of the lifespan (e.g. in adolescence or older adulthood).

Finally, it should be noted that because this is a coordinate-based meta-analysis, we are not comparing the amplitude of brain activity between different disorders, but the spatial consistency of reported peaks of activity between different groups of studies. As such, this consistency is not influenced by the intensity of the neural activation in response to reward, but rather by the number of studies that have reported the existence of alterations in these areas.

Conclusion

So, in conclusion, does obesity present similarities in brain function with addictions? The current study has addressed this question with respect to the processing of reward and has provided the first objective integration of fMRI results on studies in obesity, substance addiction and non-substance addiction. The results suggest the existence of some similar abnormalities between obesity and substance addictions during the processing of food and the problematic stimuli in the amygdala and striatum, which are brain structures implicated in reward and salience processing. An important next step will be to specifically address the comparison between substance and non-substance addictive behaviours and addictive-like patterns of eating behaviour in the obese population. It is hoped that increasing knowledge about the neurobehavioural correlates of obesity and addictions will lead to practical strategies that target the high prevalence of obesity and addictive disorders. In line with the findings presented here, therapeutic approaches should attempt to reduce the salient and reinforcing properties of food and addiction-related stimuli and apply cognitive control strategies that can lead to a more efficient impulse control behaviour.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

IGG was funded by the Max Planck International Research Network on Aging (MaxNetAging) and the Catalan Government (FI-DGR 2012 and BE-DGR 2012). AH, AV and JN were supported by the German Federal Ministry of Education and Research (FKZ: 01EO1001) and the German Research Foundation (SFB 1052 Obesity mechanisms).

References

1 Ziauddeen H, Fletcher PC. Is food addiction a valid and useful concept? Obes Rev 2013; 14: 19–28.

2 Ziauddeen H, Farooqi IS, Fletcher PC. Obesity and the brain: how convincing is the addiction model? Nat Rev Neurosci 2012; 13: 279–286.

3 Smith DG, Robbins TW. The neurobiological underpinnings of obesity and binge eating: a rationale for adopting the food addiction model. Biol Psychiatry 2013; 73: 804–810.

4 Volkow ND, Wang GJ, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. Obes Rev 2012; 14: 2–18.

5 Volkow ND, Wang GJ, Tomasi D, Baler RD. The addictive dimensionality of obesity. Biol Psychiatry 2013; 73: 811–818.

6 Wang GJ, Volkow ND, Logan J et al. Brain dopamine and obesity. Lancet 2001; 357: 354–357.

7 Volkow ND, Chang L, Wang GJ et al. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the prefrontal cortex. Am J Psychiatry 2001; 158: 2015–2021.

8 Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 2008; 32: 20–39.

9 Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science 1997; 278: 52–58.

10 Potenza MN. Review. The neurobiology of pathological gambling and drug addiction: an overview and new findings. Philos Trans R Soc Lond B Biol Sci 2008; 363: 3181–3189.

11 Kuss DJ, Griffiths MD, Karila L, Billieux J. Internet addiction: a systematic review of epidemiological research for the last decade. Curr Pharm Des 2014; 20: 4026–4052.

12 Olsen CM. Natural rewards, neuroplasticity, and non-drug addictions. Neuropharmacology 2011; 61: 1109–1122.

13 Kelley AE, Berridge KC. The neuroscience of natural rewards : relevance to addictive drugs. J Neurosci 2002; 22: 3306–3311.

14 Filbey FM, Myers US, Dewitt S. Reward circuit function in high BMI individuals with compulsive overeating: similarities with addiction. Neuroimage 2012; 63: 1800–1806.

15 Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. Arch Gen Psychiatry 2011; 68: 808–816.

16 Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P. Minimizing within-experiment and within-group effects in Activation Likelihood Estimation meta-analyses. Hum Brain Mapp 2012; 33: 1–13.

17 Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation meta-analysis revisited. Neuroimage 2012; 59: 2349–2361.

18 Sescousse G, Caldu X, Segura B, Dreher JC. Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. Neurosci Biobehav Rev 2013; 37: 681–696.

19 Tomasi D, Volkow ND. Striatocortical pathway dysfunction in addiction and obesity: differences and similarities. Crit Rev Biochem Mol Biol 2013; 48: 1–19.

20 Schacht JP, Anton RF, Myrick H. Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. Addict Biol 2013; 18: 121–133.

21 Tang DW, Fellows LK, Small DM, Dagher A. Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. Physiol Behav 2012; 106: 317–324.

22 Chase HW, Eickhoff SB, Laird AR, Hogarth L. The neural basis of drug stimulus processing and craving: an activation likelihood estimation meta-analysis. Biol Psychiatry 2011; 70: 785–793.

23 Kuhn S, Gallinat J. Common biology of craving across legal and illegal drugs – a quantitative meta-analysis of cue-reactivity brain response. Eur J Neurosci 2011; 33: 1318–1326.

24 Brooks SJ, Cedernaes J, Schioth HB. Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: a meta-analysis of FMRI studies. PLoS ONE 2013; 8: e60393.

25 Goudriaan AE, Veltman DJ, van den Brink W, Dom G, Schmaal L. Neurophysiological effects of modafinil on cue-exposure in cocaine dependence: a randomized placebo-controlled cross-over study using pharmacological fMRI. Addict Behav 2013; 38: 1509–1517.

26 Oltmanns KM, Heldmann M, Daul S et al. Sibutramine promotes amygdala activity under fasting conditions in obese women. Psychopharmacology (Berl) 2012; 221: 693–700.

27 Balodis IM, Kober H, Worhunsky PD et al. Monetary reward processing in obese individuals with and without binge eating disorder. Biol Psychiatry 2013; 73: 877–886.

28 Bragulat V, Dzemidzic M, Bruno C et al. Food-related odor probes of brain reward circuits during hunger: a pilot fMRI study. Obesity 2010; 18: 1566–1571.

29 Bruce AS, Lepping RJ, Bruce JM et al. Brain responses to food logos in obese and healthy weight children. J Pediatr 2013; 162: 759–764.

30 Davids S, Lauffer H, Thoms K et al. Increased dorsolateral prefrontal cortex activation in obese children during observation of food stimuli. Int J Obes 2010; 34: 94–104.

31 Delgado-Rico E, Soriano-Mas C, Verdejo-Roman J, Rio-Valle JS, Verdejo-Garcia A. Decreased insular and increased midbrain activations during decision-making under risk in adolescents with excess weight. Obesity 2013; 21: 1662–1668.

32 Dimitropoulos A, Tkach J, Ho A, Kennedy J. Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults. Appetite 2012; 58: 303–312.

33 Frank GK, Reynolds JR, Shott ME et al. Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacology 2012; 37: 2013–2046.

34 Frank S, Wilms B, Veit R et al. Altered brain activity in severely obese women may recover after Roux-en Y gastric bypass surgery. Int J Obes 2014; 38: 341–348.

35 Gearhardt AN, Yokum S, Stice E, Harris JL, Brownell KD. Relation of obesity to neural activation in response to food commercials. Soc Cogn Affect Neurosci 2014; 9: 932–938.

36 Heni M, Kullmann S, Ketterer C et al. Differential effect of glucose ingestion on the neural processing of food stimuli in lean and overweight adults. Hum Brain Mapp 2014; 35: 918–938.

37 Nummenmaa L, Hirvonen J, Hannukainen JC et al. Dorsal striatum and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. PLoS ONE 2012; 7: e31089.

38 Rothemund Y, Preuschhof C, Bohner G et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage 2007; 37: 410–421.

39 Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. J Abnorm Psychol 2008; 117: 924–935.

40 Stice E, Yokum S, Burger KS. Elevated reward region responsivity predicts future substance use onset but not overweight/obesity onset. Biol Psychiatry 2013; 73: 869–876.

41 Szalay C, Aradi M, Schwarcz A et al. Gustatory perception alterations in obesity: an fMRI study. Brain Res 2012; 1473: 131–140.

42 Dong G, Hu Y, Lin X, Lu Q. What makes Internet addicts continue playing online even when faced by severe negative consequences? Possible explanations from an fMRI study. Biol Psychol 2013; 94: 282–289.

43 Dong G, Hu Y, Lin X. Reward/punishment sensitivities among internet addicts: implications for their addictive behaviors. Prog Neuropsychopharmacol Biol Psychiatry 2013; 46: 139–154.

44 Dong G, Huang J, Du X. Enhanced reward sensitivity and decreased loss sensitivity in Internet addicts: an fMRI study during a guessing task. J Psychiatr Res 2011; 45: 1525–1529.

45 Han DH, Hwang JW, Renshaw PF. Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with Internet video game addiction. Exp Clin Psychopharmacol 2010; 18: 297–304.

46 Han DH, Kim SM, Lee YS, Renshaw PF. The effect of family therapy on the changes in the severity of on-line game play and brain activity in adolescents with on-line game addiction. Psychiatry Res 2012; 202: 126–131.

47 Ko CH, Liu GC, Hsiao S et al. Brain activities associated with gaming urge of online gaming addiction. J Psychiatr Res 2009; 43: 739–747.

48 Ko CH, Liu GC, Yen JY, Chen CY, Yen CF, Chen CS. Brain correlates of craving for online gaming under cue exposure in subjects with Internet gaming addiction and in remitted subjects. Addict Biol 2013; 18: 559–569.

49 Ko CH, Liu GC, Yen JY, Yen CF, Chen CS, Lin WC. The brain activations for both cue-induced gaming urge and smoking craving among subjects comorbid with Internet gaming addiction and nicotine dependence. J Psychiatr Res 2013; 47: 486–493.

50 Liu G-C, Yen J-Y, Chen C-Y et al. Brain activation for response inhibition under gaming cue distraction in internet gaming disorder. Kaohsiung J Med Sci 2014; 30: 43–51.

51 Lorenz RC, Krüger J-K, Neumann B et al. Cue reactivity and its inhibition in pathological computer game players. Addict Biol 2013; 18: 134–146.

52 Sun Y, Ying H, Seetohul RM et al. Brain fMRI study of crave induced by cue pictures in online game addicts (male adolescents). Behav Brain Res 2012; 233: 563–576.

53 Balodis IM, Kober H, Worhunsky PD, Stevens MC, Pearlson GD, Potenza MN. Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. Biol Psychiatry 2012; 71: 749–757.

54 Choi JS, Shin YC, Jung WH et al. Altered brain activity during reward anticipation in pathological gambling and obsessive-compulsive disorder. PLoS ONE 2012; 7: e45938.

55 Crockford DN, Goodyear B, Edwards J, Quickfall J, el-Guebaly N. Cue-induced brain activity in pathological gamblers. Biol Psychiatry 2005; 58: 787–795.

56 de Ruiter MB, Veltman DJ, Goudriaan AE, Oosterlaand J, Sjoerds Z, van den Brink W. Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. Neuropsychopharmacology 2009; 34: 1027–1038.

57 Goudriaan AE, de Ruiter MB, van den Brink W, Oosterland J, Veltman DJ. Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: an fMRI study. Addict Biol 2010; 15: 491–503.

58 Miedl SF, Fehr T, Meyer G, Herrmann M. Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI. Psychiatry Res 2010; 181: 165–173.

59 Potenza MN, Steinberg MA, Skudlarski P et al. Gambling urges in pathological gambling: a functional magnetic resonance imaging study. Arch Gen Psychiatry 2003; 60: 828–836.

60 Power Y, Goodyear B, Crockford D. Neural correlates of pathological gamblers preference for immediate rewards during the Iowa gambling task: an fMRI study. J Gambl Stud 2012; 28: 623–636.

61 Romanczuk-Seiferth N, Koehler S, Dreesen C, Wüstenberg T, Heinz A. Pathological gambling and alcohol dependence: neural disturbances in reward and loss avoidance processing. Addict Biol 2014; [Epub ahead of print].

62 Sescousse G, Barbalat G, Domenech P, Dreher JC. Imbalance in the sensitivity to different types of rewards in pathological gambling. Brain 2013; 136: 2527–2538.

63 Tanabe J, Thompson L, Claus E, Dalwani M, Hutchison K, Banich MT. Prefrontal cortex activity is reduced in gambling and nongambling substance users during decision-making. Hum Brain Mapp 2007; 28: 1276–1286.

64 Bühler M, Vollstädt-Klein S, Kobiella A et al. Nicotine dependence is characterized by disordered reward processing in a network driving motivation. Biol Psychiatry 2009; 67: 745–752.

65 Kobiella A, Ripke S, Kroemer NB et al. Acute and chronic nicotine effects on behaviour and brain activation during intertemporal decision making. Addict Biol 2014; [Epub ahead of print].

66 Luijten M, Veltman DJ, Hester R, Smits M, Pepplinkhuizen L, Franken IH. Brain activation associated with attentional bias in smokers is modulated by a dopamine antagonist. Neuropsychopharmacology 2012; 37: 2772–2779.

67 Luijten M, Veltman DJ, van den Brink W et al. Neurobiological substrate of smoking-related attentional bias. Neuroimage 2011; 54: 2374–2381.

68 Luo S, Ainslie G, Giragosian L, Monterosso JR. Striatal hyposensitivity to delayed rewards among cigarette smokers. Drug Alcohol Depend 2011; 116: 18–23.

69 Rose EJ, Ross TJ, Salmeron BJ et al. Acute nicotine differentially impacts anticipatory valence- and magnitude-related striatal activity. Biol Psychiatry 2013; 73: 280–288.

70 Rubinstein ML, Luks TL, Dryden W, Rait MA, Simpson GV. Adolescent smokers show decreased brain responses to pleasurable food images compared with nonsmokers. Nicotine Tob Res 2011; 13: 751–755.

71 Yalachkov Y, Kaiser J, Gorres A, Seehaus A, Naumer MJ. Sensory modality of smoking cues modulates neural cue reactivity. Psychopharmacology (Berl) 2013; 225: 461–471.

72 Zhang X, Salmeron BJ, Ross TJ et al. Anatomical differences and network characteristics underlying smoking cue reactivity. Neuroimage 2011; 54: 131–141.

73 Ames SL, Grenard JL, He Q et al. Functional imaging of an alcohol-Implicit Association Test (IAT). Addict Biol 2013; 19: 467–481.

74 Beck A, Schlagenhauf F, Wustenberg T et al. Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. Biol Psychiatry 2009; 66: 734–742.

75 Beck A, Wustenberg T, Genauck A et al. Effect of brain structure, brain function, and brain connectivity on relapse in alcohol-dependent patients. Arch Gen Psychiatry 2012; 69: 842–852.

76 Fryer SL, Jorgensen KW, Yetter EJ et al. Differential brain response to alcohol cue distractors across stages of alcohol dependence. Biol Psychol 2013; 92: 282–291.

77 Gilman JM, Smith AR, Bjork JM, Ramchandani VA, Momenan R, Hommer DW. Cumulative gains enhance striatal response to reward opportunities in alcohol-dependent patients. Addict Biol 2014; [Epub ahead of print].

78 Heinz A, Wrase J, Kahnt T et al. Brain activation elicited by affectively positive stimuli is associated with a lower risk of relapse in detoxified alcoholic subjects. Alcohol Clin Exp Res 2007; 31: 1138–1147.

79 Hermann D, Smolka MN, Wrase J et al. Blockade of cue-induced brain activation of abstinent alcoholics by a single administration of amisulpride as measured with fMRI. Alcohol Clin Exp Res 2006; 30: 1349–1354.

80 Ihssen N, Cox WM, Wiggett A, Fadardi JS, Linden DE. Differentiating heavy from light drinkers by neural responses to visual alcohol cues and other motivational stimuli. Cereb Cortex 2011; 21: 1408–1415.

81 Lee E, Ku J, Jung YC et al. Neural evidence for emotional involvement in pathological alcohol craving. Alcohol Alcohol 2013; 48: 288–294.

82 Schneider F, Habel U, Wagner M et al. Subcortical correlates of craving in recently abstinent alcoholic patients. Am J Psychiatry 2001; 158: 1075–1083.

83 Seo D, Lacadie CM, Tuit K, Hong K-I, Constable RT, Sinha R. Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. JAMA Psychiatry 2013; 70: 727–739.

84 Tapert SF, Brown GG, Baratta MV, Brown SA. fMRI BOLD response to alcohol stimuli in alcohol dependent young women. Addict Behav 2004; 29: 33–50.

85 Tapert SF, Cheung EH, Brown GG et al. Neural response to alcohol stimuli in adolescents with alcohol use disorder. Arch Gen Psychiatry 2003; 60: 727–735.

86 Vollstadt-Klein S, Wichert S, Rabinstein J et al. Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. Addiction 2010; 105: 1741–1749.

87 Wrase J, Schlagenhauf F, Kienast T et al. Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. Neuroimage 2007; 35: 787–794.

88 Ames S, Grenard JL, Stacy AW et al. Functional imaging of implicit marijuana associations during performance on an Implicit Association Test (IAT). Behav Brain Res 2013; 256: 494–502.

89 Asensio S, Romero MJ, Palau C et al. Altered neural response of the appetitive emotional system in cocaine addiction: an fMRI Study. Addict Biol 2010; 15: 504–516.

90 Cousijn J, Wiers RW, Ridderinkhof KR et al. Individual differences in decision making and reward processing predict changes in cannabis use: a prospective functional magnetic resonance imaging study. Addict Biol 2012; 18: 1013–1023.

91 Filbey FM, Dunlop J, Myers US. Neural effects of positive and negative incentives during marijuana withdrawal. PLoS ONE 2013; 8: e61470.

92 Goldstein RZ, Alia-Klein N, Tomasi D et al. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. Proc Natl Acad Sci USA 2009; 106: 9453–9458.

93 Goldstein RZ, Tomasi D, Alia-Klein N et al. Dopaminergic response to drug words in cocaine addiction. J Neurosci 2009; 29: 6001–6006.

94 Goldstein RZ, Woicik PA, Maloney T et al. Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. Proc Natl Acad Sci USA 2010; 107: 16667–16672.

95 Gowin JL, Stewart JL, May AC et al. Altered cingulate and insular cortex activation during risk-taking in methamphetamine dependence: losses lose impact. Addiction 2014; 109: 237–247.

96 Gradin VB, Baldacchino A, Balfour D, Matthews K, Steele JD. Abnormal brain activity during a reward and loss task in opiate-dependent patients receiving methadone maintenance therapy. Neuropsychopharmacology 2014; 39: 885–894.

97 Gruber SA, Rogowska J, Yurgelun-Todd DA. Altered affective response in marijuana smokers: an FMRI study. Drug Alcohol Depend 2009; 105: 139–153.

98 Jia Z, Worhunsky PD, Carroll KM et al. An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. Biol Psychiatry 2011; 70: 553–560.

99 Li Q, Wang Y, Zhang Y et al. Craving correlates with mesolimbic responses to heroin-related cues in short-term abstinence from heroin: an event-related fMRI study. Brain Res 2012; 1469: 63–72.

100 Li Q, Yang WC, Wang YR et al. Abnormal function of the posterior cingulate cortex in heroin addicted users during resting-state and drug-cue stimulation task. Chin Med J 2013; 126: 734–739.

101 May AC, Stewart JL, Migliorini R, Tapert SF, Paulus MP. Methamphetamine dependent individuals show attenuated brain response to pleasant interoceptive stimuli. Drug Alcohol Depend 2013; 131: 238–246.

102 Migliorini R, Stewart JL, May AC, Tapert SF, Paulus MP. What do you feel? Adolescent drug and alcohol users show altered brain response to pleasant interoceptive stimuli. Drug Alcohol Depend 2013; 133: 661–668.

103 Monterosso JR, Ainslie G, Xu J, Cordova X, Domier CP, London ED. Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. Hum Brain Mapp 2007; 28: 383–393.

104 Nestor L, Hester R, Garavan H. Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. Neuroimage 2010; 49: 1133–1143.

105 Potenza MN, Hong KI, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. Am J Psychiatry 2012; 169: 406–414.

106 Roberts GM, Garavan H. Neural mechanisms underlying ecstasy-related attentional bias. Psychiatry Res 2013; 213: 122–132.

107 Tabatabaei-Jafari H, Ekhtiari H, Ganjgahi H et al. Patterns of brain activation during craving in heroin dependents successfully treated by methadone maintenance and abstinence-based treatments. J Addict Med 2014; 8: 123–129.

108 Tau GZ, Marsh R, Wang Z et al. Neural Correlates of Reward-Based Spatial Learning in Persons with Cocaine Dependence. Neuropsychopharmacology 2014; 39: 545–555.

109 van Hell HH, Vink M, Ossewaarde L, Jager G, Kahn RS, Ramsey NF. Chronic effects of cannabis use on the human reward system: an fMRI study. Eur Neuropsychopharmacol 2010; 20: 153–163.

110 Wesley MJ, Hanlon CA, Porrino LJ. Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences. Psychiatry Res 2011; 191: 51–59.

111 Yamamoto DJ, Reynolds J, Krmpotich T, Banich MT, Thompson L, Tanabe J. Temporal profile of fronto-striatal-limbic activity during implicit decisions in drug dependence. Drug Alcohol Depend 2014; 136: 108–114.

112 Yang Z, Xie J, Shao YC et al. Dynamic neural responses to cue-reactivity paradigms in heroin-dependent users: an fMRI study. Hum Brain Mapp 2009; 30: 766–775.

113 Zijlstra F, Veltman DJ, Booij J, van den Brink W, Franken IH. Neurobiological substrates of cue-elicited craving and anhedonia in recently abstinent opioid-dependent males. Drug Alcohol Depend 2009; 99: 183–192.

114 World Health Organization. Obesity and overweight. 2012. URL http://www.who.int/mediacentre/factsheets/fs311/en/index.html (accessed January 2014).

115 Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. Prog Cardiovasc Dis 2014; 56: 426–433.

116 Davis C. From passive overeating to '"Food Addiction"': a spectrum of compulsion and severity. ISRN Obes 2013; 2013: 1–20.

117 Schienle A, Schäfer A, Hermann A, Vaitl D. Binge-eating disorder: reward sensitivity and brain activation to images of food. Biol Psychiatry 2009; 65: 654–661.

118 Garcia-Garcia I, Narberhaus A, Marques-Iturria I et al. Neural responses to visual food cues: insights from functional magnetic resonance imaging. Eur Eat Disord Rev 2013; 21: 89–98.

119 Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology 2010; 35: 217–238.

120 Pessoa L, Adolphs R. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. Nat Rev Neurosci 2010; 11: 773–783.

121 Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 2005; 48: 175–187.

122 Lesscher HM, Vanderschuren LJ. Compulsive drug use and its neural substrates. Rev Neurosci 2012; 23: 731–745.

123 Nauta WJ, Mehler WR. Projections of the lentiform nucleus in the monkey. Brain Res 1966; 1: 3–42.

124 Threlfell S, Cragg SJ. Dopamine signaling in dorsal versus ventral striatum: the dynamic role of cholinergic interneurons. Front Syst Neurosci 2011; 5: 1–11.

125 David HN, Ansseau M, Abraini JH. Dopamine-glutamate reciprocal modulation of release and motor responses in the rat caudate-putamen and nucleus accumbens of 'intact' animals. Brain Res Brain Res Rev 2005; 50: 336–360.

126 Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci 2011; 15: 37–46.

127 Everitt BJ, Robbins TW. From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. Neurosci Biobehav Rev 2013; 37: 1946–1954.

128 Carlezon WA Jr, Thomas MJ. Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. Neuropharmacology 2009; 56: 122–132.

129 Laird AR, Fox PM, Price CJ et al. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 2005; 25: 155–164.