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BEHAVIORAL NEUROSCIENCE

Common biology of craving across legal and illegal drugs – a quantitative meta-analysis of cue-reactivity brain response

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Abstract

The present quantitative meta-analysis set out to test whether cue-reactivity responses in humans differ across drugs of abuse and whether these responses constitute the biological basis of drug craving as a core psychopathology of addiction. By means of activation likelihood estimation, we investigated the concurrence of brain regions activated by cue-induced craving paradigms across studies on nicotine, alcohol and cocaine addicts. Furthermore, we analysed the concurrence of brain regions positively correlated with self-reported craving in nicotine and alcohol studies. We found direct overlap between nicotine, alcohol and cocaine cue reactivity in the ventral striatum. In addition, regions of close proximity were observed in the anterior cingulate cortex (ACC; nicotine and cocaine) and amygdala (alcohol, nicotine and cocaine). Brain regions of concurrence in drug cue-reactivity paradigms that overlapped with brain regions of concurrence in self-reported craving correlations were found in the ACC, ventral striatum and right pallidum (for alcohol). This first quantitative meta-analysis on drug cue reactivity identifies brain regions underlying nicotine, alcohol and cocaine dependency, i.e. the ventral striatum. The ACC, right pallidum and ventral striatum were related to drug cue reactivity as well as self-reported craving, suggesting that this set of brain regions constitutes the core circuit of drug craving in nicotine and alcohol addiction.

Introduction

It is commonly assumed that addicts are particularly vulnerable to drug use when being exposed to stimuli related to previous episodes of use. This assumption goes in line with the notion of simple Pavlovian conditioning (Pavlov, 1927). During the history of drug use, environmental contexts and stimuli such as drug paraphernalia become associated with the positive effects of drug intake. These stimuli become conditioned stimuli by virtue of being paired with the drug (the unconditioned stimulus), which elicits desirable effects (the unconditioned response). By means of association, drug-related stimuli can elicit conditioned responses that are similar to the unconditioned response (Robinson & Berridge, 2008).

Based on this reasoning, cue-reactivity paradigms have been widely used in the past decades to monitor the neural response of addicts to drug-related stimuli (Drummond *et al.*, 1995; Tapert *et al.*, 2004; Brody *et al.*, 2007; Franklin *et al.*, 2007; Wrase *et al.*, 2007; Myrick *et al.*, 2008; McClernon *et al.*, 2009; Volkow *et al.*, 2010). In these paradigms, smokers, alcoholics or cocaine addicts are exposed to drug-specific cues, e.g. pictures depicting drug paraphernalia or typical drug-use situations. A growing number of studies have applied functional neuroimaging techniques to the study of drug cue reactivity. However, to date it is unknown whether there is a consistent pattern of cue-reactivity responses across different drugs of abuse. A qualitative meta-analysis by Wilson *et al.* (2004) pointed to the involvement of the amygdala, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC). A review by Yalachkov *et al.* (2010) stressed the importance of sensory and motor aspects of addiction. To our knowledge, a quantitative assessment of the brain regions involved in cue-reactivity responses is still lacking. Therefore, the aim of the present study was to perform a quantitative meta-analysis to assess the correspondence of neural activations across multiple neuroimaging studies of drug cue reactivity using the activation likelihood estimation (ALE) approach (Turkeltaub *et al.*, 2002; Laird *et al.*, 2005; Eickhoff *et al.*, 2009). This approach reveals statistically significant concordance of activated voxels across numerous studies and controls for chance clustering. By seeking concordance at the voxel level, ALE tests for statistically reliable clustering of activations in standardized locations, avoiding spatial distinction errors and problematic incongruence of labelling across studies that can befall narrative-based reviews and tabular meta-analytic approaches. With a subsequent

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conjunction analysis we then assess correspondence across drugs by identifying where clusters from different drugs either directly overlap or converge within the same brain structures.

Most of the studies using cue-reactivity paradigms implicitly assume that the experimental setup elicits craving. This is acknowledged by the fact that the experimental setup is most often referred to as a so-called 'cue-induced craving' paradigm. Different types of craving, such as drug but also food or sexual desires, have been assumed to share common neural pathways (Garavan *et al.*, 2000; Orford, 2001; Childress *et al.*, 2008). Although there is little consensus on the concept of craving (Koslowski & Wilkinson, 1987), it has frequently been understood as a conditioned appetitive motivational state; hence as the accompanying emotional state elicited by conditioned stimuli that have been associated with the rewarding effects of drug use (Franken, 2003).

In line with the assumption that drug-associated stimuli elicit craving, an early meta-analysis on cue-reactivity paradigms has indeed demonstrated this increase in self-reported craving (Carter & Tiffany, 1999). However, these self-reports of craving have been criticized as possibly reflecting participants' compliance with experimental demands (Orne, 1962). Therefore, we aimed at testing whether brain areas that show consistently increased activity in response to drug cues overlap with brain areas that consistently correlate with self-reported craving. Hence this overlap could provide scientific evidence for the implicit assumption that the cue-reactivity paradigm can elicit craving.

Materials and methods

Selection of studies

Studies were selected using a systematic search process. Peer-reviewed articles published in English until March 2010 were selected from the search results of two separate databases (Pubmed and ISI Web of Knowledge). Keyword searches were conducted using the following terms: (i) 'neuroimaging' or 'functional magnetic resonance imaging' or 'positron emission tomography' and (ii) 'cue' or 'craving', and (iii) the drug-specific terms 'smoking' or 'tobacco' or 'nicotine', 'alcohol', 'cocaine' and 'drugs'. From the resulting papers we selected those that presented drug-related cues to addicted populations and compared these drug cues with a neutral cue. The reference lists of these selected papers were searched for additional studies that fit these criteria. Whenever we found studies that employed this type of paradigm but did not report the contrast of interest or did not report activation foci as three-dimensional coordinates in stereotaxic space we contacted the authors and asked for this information. Finally, we included all studies for which we were able to obtain Montreal Neurological Institute (MNI) or Talairach (Talairach & Tournoux, 1988) coordinates of the whole-brain contrast drug cue vs. neutral cue of addicted subjects. We included coordinates resulting from analyses computed across the whole brain and not restricted using partial coverage, regions of interest or small volume correction. From studies containing multiple independent samples, all appropriate coordinates were included as separate studies (e.g. Franklin *et al.*, 2009, subjects were divided into nine repeats or 10/10 repeats of dopamine active transporter (DAT) genotype). We included data from functional magnetic resonance imaging and positron emission tomography studies despite the fact that they have a different physiological basis because both methods have been used to identify the neural correlates of cue-induced craving. Our rationale was to provide an all-embracing overview over the attempts to identify the neural correlates of cue reactivity. In total, 13 nicotine studies with 135 foci of 251 participants (Table 1a), 10 alcohol studies with 102 foci of 112 participants (Table 1b) and 6 cocaine studies with 39 foci of 83 participants were included (Table 2).

Furthermore, we aimed at assessing brain regions that reveal a correlation between craving judgements and brain activation during cue exposure. We included coordinates resulting from either whole-brain correlations or region of interest-based correlations whenever the regions of interest were based on our contrast of primary interest (drug cue vs. neutral cue contrast in addicts). We included six nicotine and six alcohol studies, but no cocaine studies, because only two of them reported correlations with craving.

Creation of activation likelihood estimation maps

The ALE method provides a voxel-based meta-analytic technique for neuroimaging data (Turkeltaub *et al.*, 2002; Eickhoff *et al.*, 2009). By means of the software Brainmap GingerALE (http://brainmap.org/ale/), statistically significant concordance in the pattern of brain activity among several independent experiments was computed. ALE maps display regions in the brain that comprise statistically significant peak activation locations from multiple studies. Coordinates reported in Talairach were converted to MNI using Lancaster *et al.* (2007) (icbm2tal). In the approach taken by ALE, localization probability distributions for the foci are modelled at the centre of three-dimensional Gaussian functions, where the Gaussian distributions are summed across the experiments to generate a map of inter-study consistencies that estimate the likelihood of activation for each voxel, the ALE statistic, as determined by the entire set of studies. The false discovery rate method was employed to correct for multiple comparisons at a significance threshold of $P < 0.01$ and a cluster threshold of 100. For the ALE maps of cocaine and for the craving correlations in nicotine and alcohol studies, we used a more lenient threshold, false discovery rate at a significance threshold of $P < 0.05$ and a cluster threshold of 100, because we only found six studies to include. For the meta-ALE analysis, we used a stronger significance threshold of false discovery rate at $P < 0.001$ and a cluster threshold of 100.

Conjunction analysis

The ALE maps were then imported into SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) in order to undertake a conjunction analysis that examines the correspondence of consistently activated regions during drug cue reactivity in nicotine, alcohol and cocaine studies. The conjunction was determined by overlaying the resulting ALE maps for nicotine, alcohol and cocaine onto an anatomical template in Montreal Neurological Institute space. This conjunction does not constitute a statistical test but depicts regions of overlap.

Results

Activation likelihood estimation maps of drug cue-reactivity concurrence

The results of the drug-specific ALE analyses on nicotine, alcohol and cocaine cue-reactivity studies are presented in Fig. 1. The coordinates of concurrence can be found in Table 3.

Conjunction of activation likelihood estimation maps of drug cue-reactivity concurrence

The conjunction analysis of nicotine, alcohol and cocaine cue-reactivity ALE maps revealed direct overlap in the left ventral striatum

TABLE 1. List of included studies on (a) nicotine and (b) alcohol cue-induced craving

Study	Stimuli	Modality	*N*	Foci	Drug status	Age (years); sex (F/M)	Average consumption (cigarettes/day)	Craving correlation*
(a)								
Brody *et al.* (2002)	Cigarette videos & holding cigarette in hand vs. nature videos & holding a pen in hands	PET (F-18)	20	7	24 h abstinent	42.5; 6/14	32.6	X
Brody *et al.* (2007)	Cigarette cue video & holding cigarette in hand vs. nature video & holding a pen in hands	fMRI (1.5 T)	42	17	Exhaled CO > 8 ppm	38; 12/30	23.3	X
Dagher *et al.* (2009)	Cigarette videos (young men and women smoking in typical social settings such as bars vs. control videos (young people getting their hair cut)	fMRI (3 T)	15	3	Not abstinent	18–40; 7/8	12	
David *et al.* (2005)	Smoking pictures vs. neutral pictures (matched for gender)	fMRI (3 T)	9	3	No information	34.4; 5/4	18.3	
Franklin *et al.* (2007)	Audio-videos & holding cigarette in hand vs. neutral audio-video & holding a pen in hands	Perfusion fMRI (3 T)	21	9	Not abstinent	34.3; 12/9	19.6	X
Franklin *et al.* (2009)	Audio-videos & holding cigarette in hand vs. neutral audio-video & holding a pen in hands	Perfusion fMRI (3 T)	10 + 9	9 + 13	No information	35.8; 9/10	21.4	X
Lee *et al.* (2005)	2D and 3D smoking and alcohol pictures vs. control stimuli of seascapes	fMRI (1.5 T)	8	14	7 h abstinent	17.13; 0/8	15.3	
McBride *et al.* (2006)	Smoking videos vs. control videos (e.g. people getting hair cut)	fMRI (1.5 T)	20	10	12 h abstinent	27; 10/10	22	
McClernon *et al.* (2009)	Smoking pictures vs. control cues (people engaged in everyday activities)	fMRI (4 T)	18	19	24 h abstinent	28.6; 11/7	17.8	X
Van Rensburg *et al.* (2009)†	Smoking pictures vs. control cues (people engaged in everyday activities)	fMRI (1.5 T)	10	5	15 h abstinent	18–50; 4/6	13.7	
Wilson *et al.* (2005)	Looking at & holding cigarette in hand vs. looking at & holding neutral objects in hand	fMRI (1.5 T)	22	9	8 h abstinent	24.4; 0/22	21.6	
Yalachkov *et al.* (2009)†	Smoking pictures vs. control cues (people engaged in everyday activities)	fMRI (3 T)	15	10	Not abstinent	27.1; 6/9		
Yasuno *et al.* (2007)	Smoking videos vs. control videos	PET (O-15)	12	7	24 h abstinent	28.5; 0/12	25.4	X
(b)								
Braus *et al.* (2001)	Alcohol pictures vs. matched abstract pictures	fMRI (1.5 T)	4	3	> 1 week abstinent	39; 2/2	Average consumption Lifetime alcohol consumption 1026 kg	
George *et al.* (2001)	Alcoholic beverage pictures vs. non-alcoholic beverage pictures	fMRI (1.5 T)	10	2	> 24 h abstinent	29.9; 2/8	7 drinks/drinking day	
Myrick *et al.* (2004)	Alcoholic beverage pictures vs. non-alcoholic beverage pictures	fMRI (1.5 T)	10	6	> 24 h abstinent	33.6; 2/8	8.2 drinks/day	X
Myrick *et al.* (2008)	Alcoholic beverage pictures vs. non-alcoholic beverage pictures	fMRI (1.5 T)	24	11	> 24 h abstinent	24.8; 6/18	9.2 drinks/drinking day	X

TABLE 1. Continued.

Study	Stimuli	Modality	*N*	Foci	Drug status	Age (years); sex (F/M)	Average consumption	Craving correlation*
Park *et al.* (2007)	Alcohol pictures vs. matched abstract pictures	fMRI (3 T)	9	9	5 ml alcohol before study	23.2; 1/8	9.8 drinks/drinking day	X
Schneider *et al.* (2001)	Exposure to ethanol odour vs. room air	fMRI (1.5 T)	10	11	< 3 weeks abstinent	41.4; 0/10	11.9 drinks/day	
Tapert *et al.* (2003)†	Alcoholic beverage pictures vs. non-alcoholic beverage pictures	fMRI (1.5 T)	15	21	> 48 h abstinent	17; 6/9	49.8 drinks/month	X
Tapert *et al.* (2004)†	Alcohol words vs. neutral words	fMRI (1.5 T)	8	17	> 48 h abstinent	19.5; 8/0	105.9 drinks/month	X
Wrase *et al.* (2002)	Alcohol pictures vs. matched abstract pictures	fMRI (1.5 T)	6	16	> 1 week abstinent	42.5		
Wrase *et al.* (2007)	Alcohol pictures vs. matched abstract pictures	fMRI (1.5 T)	16	6	5–37 days abstinent	42.4; 0/16		X

*The authors kindly provided coordinates not reported in their original publication †Studies analysing the association between cerebral activity and self-reported craving.

(−10, 11, −8) for nicotine and alcohol as well as in the right ventral striatum (10, 10, −6) for cocaine and alcohol as well as nicotine and alcohol (7, 5, −7; Fig. 2). Moreover, we explored the convergence of ALE maps where clusters did not exactly overlap but were in close proximity within the same brain structure. Clusters are said to converge if they fall within the same Brodmann's area or anatomical region (e.g. amygdala). Although considerably apart, nicotine and cocaine studies revealed concurrence in the ACC. Moreover, the amygdala revealed convergence with significant concurrence for alcohol in the right hemisphere and nicotine as well as cocaine in the left hemisphere.

In order to test the regions common to nicotine, alcohol and cocaine statistically, we computed a meta-ALE map comprising coordinates of all three drug types. We found significant concurrence in the left ventral striatum (−16, 14, −16) and ACC (−6, 30, 24; Fig. 2).

Activation likelihood estimation maps of correlations with self-reported craving

In order to validate the assumption that the contrast drug cue vs. neutral cue indeed captures cue-induced craving, we aimed at relating these findings to subjective reports of experienced craving. We computed ALE maps based on studies that report positive correlations between reported craving judgements with either the whole-brain activation or brain activity in ROIs of the contrast drug cue vs. neutral cue (included studies are marked with an X in Table 1a,b). The results of the craving correlation ALE analyses for nicotine and alcohol are depicted in Fig. 3 and the coordinates of concurrence can be found in Table 4.

Conjunction of activation likelihood estimation maps of positive correlations with self-reported craving

A conjunction revealed that there is neither overlap between the nicotine and alcohol ALE maps of correlations with self-reported craving nor close proximity. Furthermore, we compared the ALE maps resulting from the contrast drug cue vs. neutral cue with the ALE maps resulting from positive correlations with reported cravings for nicotine and alcohol separately. For nicotine we found close proximity (but no direct overlap) in the ACC between the concurrence in the contrast smoking cue vs. neutral cue and the correlation with nicotine craving. For alcohol, however, we found overlap in the bilateral ventral striatum and close proximity in the right pallidum.

Discussion

The present study presents quantitative meta-analyses on cue-induced craving studies. It assesses the strength of evidence for a core set of brain regions that are activated in response to drug cue exposure and likewise related to self-reported craving.

Neural correlates of drug cue reactivity

First we determined brain regions of high concurrence separately for nicotine-, alcohol- and cocaine-related cue reactivity. Concurrence of cue reactivity in smokers was found in the bilateral ventral striatum, ACC, left amygdala and left temporo-parietal junction. Regions of reliable cross-study activity in cue reactivity of alcohol-dependent subjects was found in the bilateral ventral striatum, left pallidum, right amygdala, left thalamus, right inferior frontal gyrus and left middle

TABLE 2. List of included studies on cocaine cue-induced craving

Study	Stimuli	Modality	*N*	Foci	Age (years); sex (F/M)	Average consumption	Drug status
Garavan *et al.* (2000)	Cocaine videos (drug dialog and consumption) vs. nature videos (vs. sex videos)	fMRI (1.5 T)	17	19	34; 3/14	Average monthly cocaine expenditure of $1,025	No information
Goldstein *et al.* (2009)	Cocaine related words vs. neutral words	fMRI (4 T)	15	2	43.6; 3/12	3.6 days/week cocaine use during last month	Consumed during last 30 days
Kilts *et al.* (2001)	Individual scripts describing personal experiences of cocaine use and of an anger-related event were audiotaped and replayed	PET (O-15)	8	7	36; 0/8	19 days/week cocaine use during last month	7–17 days abstinent
Kilts *et al.* (2004)	Individual scripts describing personal experiences of cocaine use and of an anger-related event were audiotaped and replayed	PET (O-15)	8	9	35.9; 8/0		1–14 days abstinent
Volkow *et al.* (2010)	Cocaine videos vs. fixation	PET (F-18)	24	1	46; 3/21	16 days/week cocaine use during last month (2.2 g/day)	2.5 days abstinent
Wexler *et al.* (2001)*	Video with an actress talking about happy or sad content vs. happy or sad cocaine experimence	fMRI (1.5 T)	11	1	34; 3/8		15 days abstinent

*The authors kindly provided coordinates not reported in their original publication.

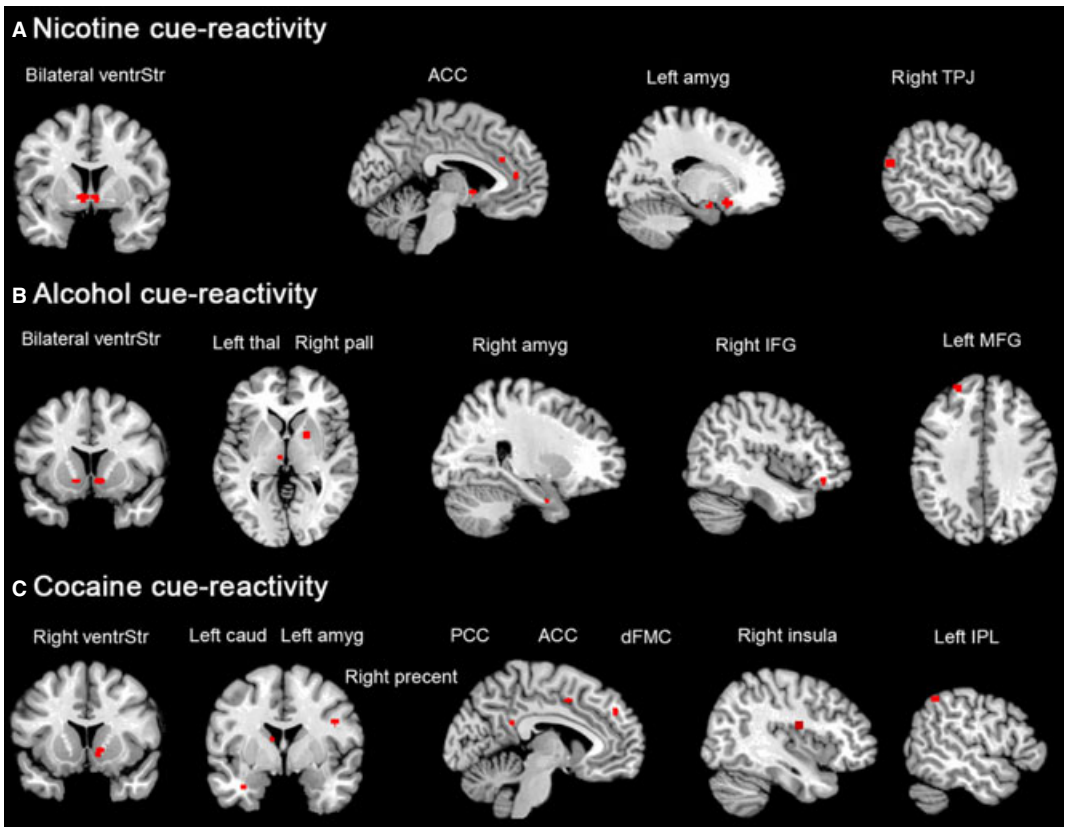

FIG. 1. ALE meta-analysis maps for correlates of (A) nicotine, (B) alcohol and (C) cocaine cue reactivity demonstrating significant concordance across studies ($P < 0.01$ for nicotine and alcohol, $P < 0.05$ for cocaine, corrected for multiple comparisons). ventrStr, ventral striatum; IFG, inferior frontal gyrus; TPJ, temporo-parietal junction; Thal, thalamus; Pall, pallidum; Amyg, amygdala; MFG, middle frontal gyrus; Caud, caudate; Precent, precentral gyrus; PCC, posterior cingulate cortex; dFMC, dorsofrontomedian cortex; IPL, inferior parietal lobe.

TABLE 3. (a) Nicotine, (b) alcohol and (c) cocaine cue-reactivity results

Anatomical region	Broadmann's area	Coordinates (MNI)			Volume (mm^3)
		x	*y*	*z*	
(a)					
Left ventral striatum		−6	4	−5	904
Left temporo-parietal junction	39	55	−67	18	224
Right ventral striatum		5	5	−6	160
Anterior cingulate cortex	32/24	−5	30	24	160
Left amygdala		−19	−4	−18	152
Anterior cingulate cortex	32	−4	42	10	144
(b)					
Left middle frontal gyrus	8	−20	46	37	496
Right ventral striatum		9	7	−8	472
Left pallidum		20	4	0	200
Left ventral striatum		−13	12	−9	144
Left cerebellum		−12	−78	−30	120
Right amygdala		23	−1	−31	112
Right inferior frontal gyrus (orbitalis)	47	45	34	−13	112
Left thalamus		−5	−19	0	112
(c)					
Right ventral striatum		11	13	−7	304
Left amygdala		−32	0	−27	176
Right mid-posterior insula	13	40	−8	18	160
Lingual gyrus	17	4	−82	−10	152
Anterior cingulate cortex	24	−6	4	44	152
Left inferior parietal lobe	40	−52	−52	48	152
Posterior cingulate cortex	30	−6	−45	24	144
Left caudate		−9	−4	12	128
Dorso-frontomedian cortex	9	−5	46	34	120
Right precentral gyrus	6	44	−1	27	112
Left caudate		−13	−13	20	104

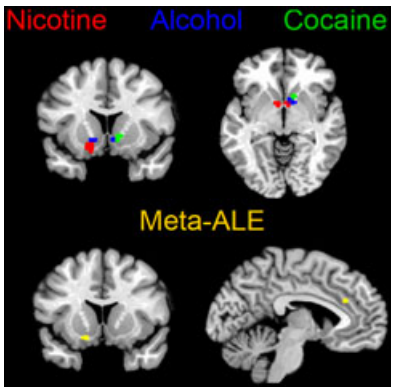

FIG. 2. Top – overlap of ALE meta-analysis maps for correlates of nicotine, alcohol and cocaine cue reactivity in ventral striatum. Bottom – meta-ALE meta-analysis including nicotine, alcohol and cocaine cue-reactivity coordinates.

frontal gyrus. Cocaine-related cue reactivity was associated with the right ventral striatum, left amygdala, left caudate, ACC, right mid-posterior insula, left inferior parietal lobe, posterior cingulate cortex, dorsofrontomedian cortex, right precentral gyrus and lingual gyrus.

By exploring the conjunction between the drug-specific ALE maps, we found direct overlap between nicotine, alcohol and cocaine cue reactivity only in the ventral striatum. Based on this, we propose that the ventral striatum is the core brain region involved in neural responses to drug cue exposure. When also taking brain regions of concurrence into account that are in close proximity to one another or in the same brain structure only in the opposite hemisphere, one could also consider the amygdala (present in nicotine, alcohol and cocaine cue reactivity) and ACC (present in nicotine and cocaine cue reactivity) as part of the brain regions involved in drug cue reactivity.

These brain regions are considerably different to the core regions proposed in the qualitative meta-analysis by Wilson *et al.* (2004). The results converge concerning the importance of the amygdala and ACC in drug cue reactivity but the authors do not mention the importance of the ventral striatum and instead put emphasis on the OFC and DLPFC. Our quantitative meta-analysis reveals concurrence in neither the OFC nor the DLPFC. Wilson *et al.* (2004) have suggested that treatment status is a crucial factor that affects the findings of studies on drug cue reactivity. They demonstrate that DLPFC and OFC activation is reliably found in individuals who are still actively using the drug but not in individuals seeking treatment. Unfortunately, treatment status is scarcely reported unequivocally. When participants are explicitly recruited from a treatment-seeking population their status is clear, whereas it is not when they are recruited via newspaper advertisements. One might speculate that subjects participating in studies on addiction are aware of possible health risks and might consider the option to quit. In the sample of studies included in our meta-analysis, treatment status was roughly counterbalanced for alcohol (5 of 10 studies recruited from a treatment-seeking population) and cocaine (3 of 6 studies) addicts. The nicotine studies seemed to contain less treatment-seeking subjects (4 of 13 studies explicitly mention that they recruited treatment seekers). However, even though the nicotine sample contained considerably fewer subjects seeking treatment, we did not find concurrence in the OFC or DLPFC. This contradiction could be due to methodological differences between tabular qualitative and quantitative meta-analyses as well as due to imprecision in nomenclature. Authors might, for example, refer to activations as being localized in the OFC although the z-coordinate is considerable higher (and would be labelled ventromedial prefrontal cortex by other groups) solely because previous studies stressed the importance of the OFC in drug cue reactivity. These inaccuracies of nomenclature do affect qualitative but not quantitative meta-analyses because the latter are based on the coordinates themselves and not on the labels used by different authors. In order to exclude that the lack of OFC convergence in our results is due to higher field strengths in more recent fMRI studies that are accompanied by increased signal dropout in the OFC, we computed a meta ALE map excluding studies measured with field strengths above 1.5 T (Tables 1 and 2). The results were very similar to those reported in the Results (right ventral striatum and ACC) but no concurrence was found in the OFC.

Neural correlates of self-reported craving

Furthermore, we aimed at exploring the neural overlap between brain correlates of self-reported craving and brain regions identified in the context of drug cue reactivity. The ALE maps of correlations with subjective craving in smokers revealed concurrence in the ACC, posterior cingulate cortex, right anterior insula, left inferior frontal gyrus, right angular gyrus and right cerebellum. Regions of reliable cross-study activity for alcohol addicts were found in the bilateral ventral striatum, right pallidum, perigenual ACC, left superior parietal lobe, right precentral gyrus, paracentral lobule and bilateral lingual gyrus. Our conjunction analysis revealed no direct overlap or close proximity between both ALE analyses. Nevertheless, the concurrence in the ACC found for correlations with self-reported craving in smokers was proximal to brain regions that also revealed concurrence in smoking cue reactivity. Similarly, concurrence in the bilateral

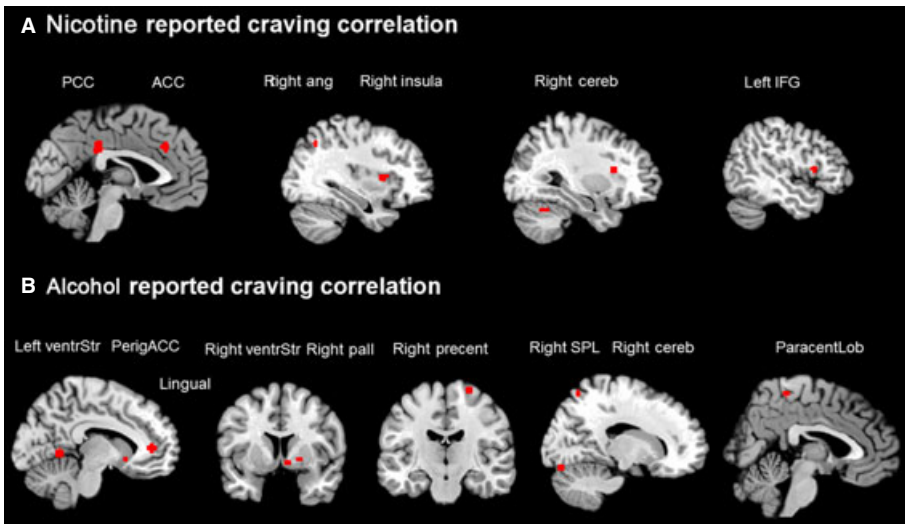

FIG. 3. ALE meta-analysis maps for (A) nicotine and (B) alcohol positive correlations with self-reported craving demonstrating significant concordance across studies ($P < 0.05$, corrected for multiple comparisons). PCC, posterior cingulate cortex; Ang, angular gyrus; Cereb, cerebellum; IFG, inferior frontal gyrus; ventrStr, ventral striatum; perigACC, perigenual anterior cingulate cortex; Lingual, lingual gyrus; Pall, pallidum; Precent, precentral gyrus; SPL, superior parietal lobe; ParacentLob, paracentral lobule.

TABLE 4. Positive correlations with self-reported craving in (a) nicotine and (b) alcohol addiction

Anatomical region	Broadmann's area	Coordinates (MNI)			Volume (mm^3)
		x	*y*	*z*	
(a)					
Right anterior insula	13	38	10	6	824
Posterior cingulate cortex	31	−2	−35	32	712
Anterior cingulate gyrus	32	−2	28	23	536
Left inferior frontal gyrus	44	−47	13	7	256
Right cerebellum		30	−57	−29	184
Right angular gyrus	39	46	−62	43	184
(b)					
Perigenual anterior cingulate cortex	32	−8	42	4	656
Left lingual gyrus	19	−11	−54	−2	576
Right precentral gyrus	4	25	−16	70	312
Right ventral striatum		8	7	−6	224
Right pallidum		20	4	−5	160
Paracentral lobule	5	2	−40	59	160
Left superior parietal lobe	7	16	−66	61	160
Right lingual gyrus	18	16	−82	−16	152
Left ventral striatum		−10	15	−8	128

ventral striatum and right pallidum associated with self-reported craving overlapped (directly for the ventral striatum and proximal for the right pallidum) with concurrence in alcohol cue reactivity.

The core brain regions of drug craving

It is remarkable that the brain regions in which we identified overlap between craving correlations and cue reactivity (ventral striatum and ACC) were similar to those regions in which we found overlap or close proximity in cue reactivity between different drug types (ventral striatum, ACC and left pallidum). Based on this observed convergence, we propose that the ventral striatum, pallidum and ACC constitute the core brain areas involved in drug-related craving.

Ventral striatum

The ventral striatum contains the nucleus accumbens and receives extensive projections from the orbitofrontal, ventromedial and ventrolateral cortex, and dopaminergic input from the ventral tegmental area (Groenewegen *et al.*, 1999). Moreover, the ventral striatum has connections with limbic areas implicated in emotional processing, such as the amygdala. A vast array of research implicates the importance of the striatum in reward-related processing (Delgado, 2007; Heinz *et al.*, 2009). Neurons in the nonhuman primate striatum have been shown to respond to the delivery (Apicella *et al.*, 1991) but also to the anticipation (Apicella *et al.*, 1992; Kawagoe *et al.*, 1998) of reward. Striatal neurons code reward magnitude, incentive salience and fire more vigorously for preferred rewards (Hassani *et al.*, 2001; Heinz & Schlagenhauf, 2010).

Pallidum

The ventral pallidum has been recognized as receiving input from the ventral striatum (Heimer & Wilson, 1975). Furthermore, it receives projections from a host of other reward-related brain areas such as the amygdala, ACC and OFC (Zahm, 2000; Kalivas & Volkow, 2005). A growing body of research has demonstrated a major role of the ventral pallidum in the processing of food reward (Berridge, 1996), sex (Rauch *et al.*, 1999), social affiliation (Bales *et al.*, 2007) and other rewards. In rats, the ventral pallidum as well as the ventral striatum have been entitled 'hedonic hot spots' because drug microinjections of opioids in both areas amplify the 'liking' of sweet taste rewards (Pecina *et al.*, 2006; Smith *et al.*, 2010).

Anterior cingulate cortex

The ACC has been associated with processes of conflict avoidance and attentional control (Barch *et al.*, 2001; Braver *et al.*, 2001; Liu *et al.*, 2004). Moreover, engagement of the ACC has repeatedly been associated with cognitive reappraisal and cognitive modulation of emotion (Ochsner *et al.*, 2004; Kalisch *et al.*, 2006). This may reflect the active direction of attention away from the salient drug-related stimuli as an effortful process that works against the automatic patterns of attention. Its relation to craving self-reports may be

explained by the fact that the urge to consume the drug in the scanner environment, where it is obviously impossible, affords regulation.

The critical circuit for craving has previously been described as the so-called 'final common pathway' involving projections from prefrontal cortex (ACC and OFC) to the nucleus accumbens core and ventral pallidum (Kalivas & Volkow, 2005). This pathway is supported by the fact that the ACC (as well as the OFC) has been anatomically associated with the core of the nucleus accumbens and appears to be a primary site mediating the expression of learned behaviour in response to stimuli predicting motivationally relevant events (Di Ciano & Everitt, 2001; Kelley, 2004). The accumbens, however, has dense projections carrying GABA and neuropeptides to the ventral pallidum that have been shown to be critical for the expression of motivated behaviour (Mogenson *et al.*, 1993). Taken together, our results are in line with the assumption of a final common pathway that has been suggested to mediate craving.

Limitations

The number of studies included is rather modest, limiting the power to perform more detailed analyses (e.g. treatment-seeking vs. nontreatment-seeking addicts). Nevertheless, a striking degree of convergence was obtained across the heterogeneous literature. Moreover, meta-analyses are susceptible to biases present in the literature, e.g. the heterogeneity of how the drug user population is defined, as well as a lack of suitable studies exploring certain drugs, e.g. heroin. Future research might focus on the comparison between cue reactivity in response to drug stimuli and to natural reinforcers such as sexual and food stimuli.

Conclusion

The present study identified brain regions of concurrence between studies of drug cue reactivity in nicotine-, alcohol- and cocaine-dependent participants by means of ALE. We found consistency between nicotine, alcohol and cocaine cue-reactivity concurrence in the ventral striatum. Brain regions of concurrence within close proximity of one another were found in the amygdala (nicotine, alcohol and cocaine) and ACC (nicotine and cocaine). Furthermore, we demonstrated that brain regions of concurrence in drug cue-reactivity paradigms overlap with brain regions of concurrence in self-reported craving correlations in the ACC (for nicotine) and ventral striatum and right pallidum (for alcohol). From this we conclude that the ventral striatum, pallidum and ACC constitute the core set of brain regions involved in drug-related craving.

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Conflict of interest

The authors report no conflict of interest.

Abbreviations

ACC, anterior cingulate cortex; ALE, activation likelihood estimation; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex.

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