Neuroscience and Biobehavioral Reviews 37 (2013) 2806–2817

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Common and distinct neural targets of treatment: Changing brain function in substance addiction

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ARTICLE INFO

Article history:
Received 23 May 2013
Received in revised form
17 September 2013
Accepted 8 October 2013

Keywords:
Addiction
Therapeutic intervention
Pharmacotherapy
Pharmacological challenge
Cognitive-behavioral therapy
Craving regulation
Functional neuroimaging
Functional magnetic resonance imaging (fMRI)
Positron emission tomography (PET)
Activation likelihood estimation (ALE) meta-analysis

ABSTRACT

Neuroimaging offers an opportunity to examine the neurobiological effects of therapeutic interventions for human drug addiction. Using activation likelihood estimation, the aim of the current meta-analysis was to quantitatively summarize functional neuroimaging studies of pharmacological and cognitive-based interventions for drug addiction, with an emphasis on their common and distinct neural targets. More exploratory analyses also contrasted subgroups of studies based on specific study and sample characteristics. The ventral striatum, a region implicated in reward, motivation, and craving, and the inferior frontal gyrus and orbitofrontal cortex, regions involved in inhibitory control and goal-directed behavior, were identified as common targets of pharmacological and cognitive-based interventions; these regions were observed when the analysis was limited to only studies that used established or efficacious interventions, and across imaging paradigms and types of addictions. Consistent with theoretical models, cognitive-based interventions were additionally more likely to activate the anterior cingulate cortex, middle frontal gyrus, and precuneus, implicated in self-referential processing, cognitive control, and attention. These results suggest that therapeutic interventions for addiction may target the brain structures that are altered across addictions and identify potential neurobiological mechanisms by which the tandem use of pharmacological and cognitive-based interventions may yield synergistic or complementary effects. These findings could inform the selection of novel functional targets in future treatment development for this difficult-to-treat disorder.

Contents

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0149-7634/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neubiorev.2013.10.002

1. Introduction

Addiction is characterized by continued drug-seeking and drug use despite reduced pleasure derived from the drug and often in the face of catastrophic social, emotional, and legal consequences. The recurrent nature of the disease poses a large economic burden to society and significant personal distress to the individual and their family (Volkow et al., 2011). Limited treatment options are available, and many are only effective in a subset of individuals. Thus, a critical step toward improving treatments for addiction is to clarify the neurobiological mechanisms of therapeutic interventions that are currently used or under investigation.

Addiction affects a distributed set of brain regions and neurotransmitter systems. Although different drugs of abuse have different mechanisms of action, they all increase dopamine release in what has traditionally been labeled as the brain's reward circuit to exert their reinforcing effects (Chen et al., 2010; Sulzer, 2011). Regions comprising this circuit include midbrain (ventral tegmental area and substantia nigra) and basal ganglia structures including the ventral (nucleus accumbens) and dorsal striatum. Chronic drug use modifies dopamine signaling in these regions, facilitating the transition from recreational to habitual use that characterizes addiction (Everitt and Robbins, 2005). These changes result in a state of impaired motivational drive and difficulty with inhibiting conditioned responses to drug-related cues, undermining more goal-directed behavior (Kalivas and Volkow, 2005). Following protracted use, exposure to drug-related cues activates the ventral striatum (among other regions like the cingulate cortices and amygdala) across substance addictions (Chase et al., 2011; Kuhn and Gallinat, 2011) in ways that may facilitate relapse to drug use (Grusser et al., 2004; Kosten et al., 2006). In addition to craving, the negative emotional state of withdrawal during periods of abstinence may also involve the reward circuit (Treadway and Zald, 2011), as well as the amygdala and autonomic structures (Koob and Volkow, 2010).

However, brain regions (and their corresponding functions) outside the reward system also appear affected by chronic drug use. In particular, drug addicted individuals exhibit alterations in the anterior cingulate, orbitofrontal, and dorsolateral prefrontal cortices, where abnormalities are linked to impaired emotion regulation and inhibitory control (Goldstein and Volkow, 2011). Thus, the ability of addicted individuals to achieve abstinence may be diminished both by pathologically strengthened drug-seeking behavior and impairments in the capacity to regulate such behavior (Everitt and Robbins, 2005; Kalivas, 2009). The effectiveness of therapeutic interventions may consequently depend on the ability of these interventions to target and normalize addiction-related deficits in reward regions to decrease motivation for drugs (e.g., craving and withdrawal) and in control regions to increase inhibitory control, respectively. Furthermore, while different drugs of abuse share common neurobiological substrates (e.g., in reward and cognitive control regions), differences also exist and these differences may have implications for addiction treatment. For example, the influence of contextual triggers on relapse to drug use, supported by the medial prefrontal cortex, appears to be more profoundly impacted by stimulant use than by opiate use (Badiani et al., 2011); similarly, visuospatial attention, supported by occipital, parietal, and medial temporal lobe regions, appears to be more profoundly impacted by alcohol use; impulsivity and cognitive flexibility, supported by the orbitofrontal cortex, striatum, and thalamus, by alcohol and stimulant use; and fluency and working memory, supported by inferior frontal and parietal regions, by opiate use than by use of other substances, respectively [for review, see (Crunelle et al., 2012; Fernandez-Serrano et al., 2011; van Holst and Schilt, 2011)]. Thus, therapeutic interventions for addiction may share a common neural mechanism across addictions, and/or a unique mechanism by specific addiction type.

A number of therapeutic interventions for addiction have been put forth and some have been tested in clinical trials with the goal of reducing the amount or frequency of drug use, or extending time to relapse. These interventions can be broadly divided into pharmacological and cognitive-based (psychosocial) strategies [for review, see (Potenza et al., 2011)]. Briefly, pharmacological interventions are proposed to primarily target the reward circuit and influence neural processes that mediate negative mood and craving. Most pharmacological interventions for addiction block or mimic the reinforcing effects of drugs (Potenza et al., 2011). For example, among others, studies have tested the efficacy of nicotinic receptor agonists (e.g., varenicline, nicotine patch) and antagonists (e.g., bupropion) for nicotine addiction (Cahill et al., 2010; Eisenberg et al., 2008), opioid receptor agonists (e.g., methadone, buprenorphine) and antagonists (e.g., naltrexone) for opioid (Johansson et al., 2006) and alcohol (Srisurapanont and Jarusuraisin, 2005) addiction, and dopamine and norepinephrine agonists (e.g., psychostimulants including modafinil and methylphenidate) for stimulant addictions (Anderson et al., 2009; Castells et al., 2010; Dackis et al., 2005, 2012; Longo et al., 2010). Cognitive-based interventions are proposed to primarily target executive control processes dependent on the prefrontal cortex. These interventions aim to help addicted individuals recognize and implement strategies to change cognitions and behaviors associated with drug use, and to increase motivation for change (Carroll and Onken, 2005). Interventions that have been tested in their efficacy for motivating change include motivational interventions (e.g., smoking cessation messages), psychoeducation (e.g., health-related information), and contingency management (e.g., receiving monetary incentives) (Burke et al., 2003; Dutra et al., 2008). Interventions that provide strategies for change include cognitive behavioral therapy (CBT) and its active components (e.g., self-regulation strategies, exposure therapy) (Dutra et al., 2008; Magill and Ray, 2009). Interventions that motivate individuals to quit and remain abstinent after quitting may involve the reward circuit and regions such as the ventromedial prefrontal cortex, anterior and posterior cingulate cortex, and insula that are involved in delay discounting (Luhmann, 2009), or the drive for immediate at the expense of delayed yet larger rewards, and effort (Prevost et al., 2010; Treadway et al., 2012). Taken together, pharmacological interventions may primarily target brain reward regions, while cognitive-based interventions may target *both* reward and control regions.

Neuroimaging offers an opportunity to examine the neurobiological mechanisms through which treatments for addictions might exert their effects, which is of fundamental interest to both basic and clinical neuroscience. A focus on studies using functional neuroimaging is important because, given what is known about the brain changes accompanying addiction in humans, it provides an appropriate context for evaluating changes with treatment beyond what can be gleaned from self-report or behavior alone. Indeed, neural activity has been shown to be a good predictor of relapse following treatment [e.g., (Brewer et al., 2008; Grusser et al., 2004; Janes et al., 2010; Jia et al., 2011; Paulus et al., 2005)]. Here, we quantitatively summarize studies that evaluated the neural correlates of therapeutic interventions for addiction using activation likelihood estimation (ALE) meta-analysis (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002). Meta-analysis offers the chance to aggregate data across studies to identify the most reliable patterns. Such an analysis can provide a synthesized and unbiased account of the neural mechanisms of therapeutic interventions, further revealing novel information about specific coordinates (not just anatomical boundaries) of localization of effects and statistical significance (not just a qualitative evaluation of presence/absence) in the convergence across studies of these effects. Meta-analysis can also be used for comparisons which were not or could not be feasibly performed in a single study, such as a direct comparison between pharmacological and cognitive-based interventions, or of their effects in specific populations and experimental paradigms. We therefore first examined the neural correlates of all interventions versus a non-intervention comparison condition. Conjunction and difference contrasts were then used to identify the common and distinct neural correlates of pharmacological and cognitive-based interventions, respectively. Lastly, more exploratory analyses contrasted subgroups of studies based on study (single-dose versus repeated administration interventions and use of a drug-related versus non-drug related task) and sample (primary drug of use) characteristics.

2. Methods

2.1. Study selection

We searched Medline/Pubmed to identify relevant studies published between January 1, 2000 and July 31, 2013. In addition, several recently published reviews (Addolorato et al., 2012; Goldstein and Volkow, 2011; Newhouse et al., 2011; Potenza et al., 2011; Sharma and Brody, 2009; Sofuoglu, 2010; Spanagel and Vengeliene, 2012) and book chapters (Adinoff and Stein, 2011) were identified that specifically discussed the use of neuroimaging to evaluate therapeutic interventions for drug addiction. Importantly, however, these review papers or chapters did not perform meta-analysis. All studies identified in the database search and those cited by one of the reviews underwent the study selection process. Further details of the search strategy and a complete description of the study selection process are presented in the Supplemental Material.

Studies were included if they (1) used functional magnetic resonance imaging (fMRI) or 2-deoxy-2[^{18}F]fluoro-D-glucose positron emission tomography (FDG-PET); (2) involved $\geq$10 participants between the ages of 18–65 years; (3) used diagnostic criteria for substance use disorder as specified by DSM or ICD; (4) reported peak activation coordinates in Talairach or Montreal Neurological Institute (MNI) space from the condition of interest (e.g., pharmacological agent) contrasted with an appropriate control condition (e.g., placebo); (5) used a cognitive or drug cue-reactivity task or measured activity at rest (i.e., resting scan); and (6) provided information about inclusion criteria, clinical characteristics, and basic demographics of the study sample.

Fifty-one studies met the inclusion criteria representing a total of 1052 substance users and 380 foci (Table 1 & S1-S2). These studies were conducted using generally accepted methods that focused on pharmacological or components of cognitive-based interventions that are established clinically for the treatment of specific addictions or that are in the investigational phase but that have shown promise in controlled clinical trials. Twenty-three of these studies (143 foci) used established interventions for an indicated population of substance users (the rest using more investigational approaches), and 15 studies (103 foci) used a randomized, controlled study design and observed a therapeutic clinical effect (reduction in craving, withdrawal, or amount of use; these studies used either established or more investigational interventions). Thirty-five studies (229 foci) used pharmacological interventions and 16 studies (151 foci) used cognitive-based interventions. Of the 35 pharmacological studies, 26 studies (169 foci) were placebo-controlled. Of the 16 cognitive-based studies, 8 studies (92 foci) used cognitive inhibition or self-regulation strategies, 3 studies (17 foci) used standardized psychotherapy/CBT, and 5 studies (42 foci) used motivational interventions or psychoeducation. Twenty-six studies (171 foci) used a drug cue-related task and 25 studies (203 foci) used a non-drug related task or measured activity at rest. Ten studies (35 foci) investigated therapeutic interventions in alcohol users, 27 studies (253 foci) in nicotine users, 5 studies (23 foci) in opioid users, 8 studies (62 foci) in stimulant users, and 1 study (7 foci) in mixed drug users.

Table 1
Study and sample characteristics of the included studies.

Intervention	Num. of studies	Num. of participants	Num. of foci	Age[a]	Sex[a]	% Participants/substance (num. of foci)	Illness duration[a]	Task/stimulus
All	51	1052	380	36.7 y	65% Male 35% Female	17% Alcohol (35) 62% Nicotine (253) 8% Opioids (23) 13% Stimulants (62) 1% Mixed (7)	16.7 y	49% Drug-related 51% Non-drug related
Pharmacological	35	604	229	36.1 y	67% Male 33% Female	25% Alcohol (20) 44% Nicotine (129) 13% Opioids (23) 18% Stimulants (61) 0% Mixed (0)	15.8 y	46% Drug-related 54% Non-drug related
Cognitive-based	16	448	151	38.1 y	63% Male 37% Female	6% Alcohol (15) 86% Nicotine (128) 0% Opioids (0) 5% Stimulants (1) 3% Mixed (7)	18.6 y	63% Drug-related 37% Non-drug related

[a] Note that this number is an estimate and only includes studies that reported the specified information.

2.2. Activation likelihood estimation (ALE) maps

The ALE method (Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002), which is a voxel-wise meta-analytic technique for aggregating data across neuroimaging studies, was used to investigate the neural correlates of therapeutic interventions as implemented in GingerALE 2.1 (http://brainmap.org/ale/). In contrast to conventional meta-analyses that provide estimates of effect size, ALE provides information about convergence in the spatial location of effects across studies. Coordinates reported in Talairach space were converted to MNI space using the icbm2tal transformation (Lancaster et al., 2007). These coordinates (i.e., foci) were then used to generate "activation likelihoods" for each voxel in the brain. For each reported focus, ALE scores each voxel as a function of its distance from that focus using a three-dimensional Gaussian probability density function (estimated with respect to the number of subjects in each study) centered at the coordinates of the focus. The Gaussian distributions are then summed across studies to generate a map of inter-study consistencies that estimate the likelihood of activation for each voxel, the ALE statistic. Thus, the ALE statistic represents the probability of a given voxel to belong to any of the included foci.

2.3. Statistical analyses

We performed several ALE meta-analyses on the studies listed in Tables S1 & S2. The first meta-analysis included all reported foci. We also calculated separate meta-analyses for pharmacological and cognitive-based interventions. To answer the question of common neural targets of these interventions, we performed a conjunction analysis of the two separately calculated ALE meta-analyses. The ALE meta-analysis can also be used to contrast two independent meta-analyses. Thus, this latter approach allowed us to directly contrast the pharmacological and cognitive-based ALE meta-analyses and inspect for brain regions that were selectively or preferentially more likely to be activated by one type of intervention versus the other.

Three exploratory analyses examined the influence of study and sample characteristics of the included studies. Here, we divided all foci based on whether a study used a single-dose or repeated (e.g., occurring over two or more sessions) intervention administration and whether the intervention was used in the context of a drug-related or non-drug related task (the latter including resting activity). We also divided all foci based on the primary drug of use. Again, these separate meta-analyses were contrasted to identify regions that were selectively or preferentially more likely to be activated in one context than in another context.

To test for significance, a permutation procedure is used where the ALE statistic in each voxel is compared with a null distribution generated via repeatedly calculating ALE statistics from randomly placed activation foci. This null distribution is then used to estimate the threshold resulting for a given false discovery rate (FDR). For the difference contrast, the null distribution is determined similarly, with the exception that the null distribution comes from the differences between the ALE statistics of randomly generated foci. Finally, a cluster size threshold (minimum spatial extent of significant clusters) can be applied. Here, we used a $p < 0.05$ FDR-corrected threshold with a minimum cluster size of 100 mm^3 to test the main meta-effects and for differences between meta-analyses. We used a more lenient threshold of $p < 0.005$ uncorrected and a minimum cluster size of 100 mm^3 to test for the conjunction of the meta-analyses. This conjunction does not constitute a statistical test but rather depicts overlap between two meta-analyses at the specified threshold. The resulting maps were exported to Mango (http://ric.uthscsa.edu/mango/) and overlaid on an anatomical template spatially normalized to MNI space.

3. Results

3.1. Primary analyses: Common and distinct neural targets of therapeutic interventions

3.1.1. Effects of any therapeutic intervention (all foci together)

Several networks of brain regions were identified in the analysis across all studies (Fig. 1, Table 2), that included regions involved in reward processing and associative learning [ventral striatum (caudate head), parahippocampal gyrus/amygdala, midbrain], executive functions (anterior cingulate cortex, superior and middle frontal gyrus), and sensory integration and attention (precuneus, cuneus/occipital lobe, cerebellum, thalamus). These results mostly held when the analysis was limited to either (1) studies that used established interventions for an indicated population of substance users, or (2) studies that used a randomized, controlled study design and that observed a therapeutic clinical effect (i.e., interventions that showed efficacy within each study). Regions that appeared in these sub-analyses and the analysis across all studies are indicated in Table 2, with additional convergence observed in the right thalamus (medial dorsal nucleus), anterior cingulate cortex/medial frontal gyrus (BA 32 and 9), right precentral gyrus (BA 4), and right occipital lobe/cuneus (BA 17) in the sub-analysis of established interventions.

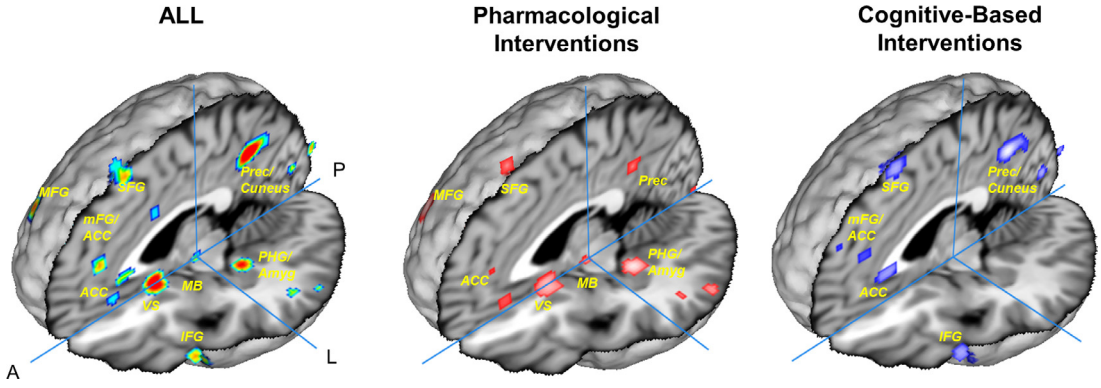

Fig. 1. Any (all foci together) and individual effects of therapeutic interventions (effects by intervention strategy). Threshold: $p < 0.05$ FDR-corrected and a minimum cluster size of 100 mm^3. ACC, anterior cingulate cortex; Amyg, amygdala; IFG, inferior frontal gyrus; MB, midbrain; mFG, medial frontal gyrus; MFG, middle frontal gyrus; PHG, parahipppocampal gyrus; Prec, precuneus; SFG, superior frontal gyrus; VS, ventral striatum.

Table 2
Brain areas activated by therapeutic interventions for addiction from the ALE meta and subtraction analyses.

	BA	Side	Volume (mm^3)	*X*	*Y*	*Z*
All interventions combined						
Caudate head[a,b]		R,L	2040	10	6	−8
				−4	12	−8
Precuneus[a]	31	L	1976	−6	−50	36
Inferior frontal gyrus	47	L	624	−46	24	−18
				−48	26	−10
Inferior frontal gyrus	47	R	560	50	24	−6
Middle frontal gyrus[b]	9	L	560	−46	14	32
Middle frontal gyrus[a]	9,6	R	536	52	12	36
				42	12	44
Middle frontal gyrus[a]	6	L	488	−46	10	44
Inferior frontal gyrus	47	R	448	26	22	−20
Thalamus[a]		L	416	−12	−14	12
Parahippocampal gyrus	28	L	400	−22	−28	−10
Anterior cingulate cortex	24	R,L	400	6	34	8
				−2	28	6
Anterior cingulate cortex[b]	32	L	400	−6	40	22
Superior temporal gyrus[b]	39	L	392	−58	−62	24
				−54	−56	16
Inferior parietal lobule	40	R	360	42	−46	62
Superior frontal gyrus	6	L	352	0	26	66
				−4	22	58
Superior frontal gyrus[a]	8	R	320	30	48	38
Posterior cingulate cortex	31	R	304	4	−30	32
Cerebellum: Vermis		L	232	2	−82	−24
Cuneus/Occipital lobe	18	L	232	−4	−100	18
Cerebellum[a,b]		L	208	−14	−78	−28
Claustrum/Insula[a,b]		L	208	−36	16	0
Anterior cingulate cortex[a]	11	R	192	0	36	−4
Anterior cingulate cortex[a]	32	R	184	10	46	−12
Inferior frontal gyrus[a,b]	46	L	184	−46	40	8
Cuneus/Occipital lobe	17	L	160	−6	−84	10
Amygdala		R	152	24	−8	−26
Middle temporal gyrus[a,b]	21	L	152	−70	−40	0
Middle occipital gyrus[b]	19	R	152	40	−76	12
Putamen		L	144	−28	−8	4
Superior frontal gyrus	8	L	144	−8	54	34
Midbrain: mammillary body		L	136	−2	−12	−12
Inferior parietal lobe	40	L	128	−60	−28	40
Pharmacological interventions						
Caudate head[c]		R,L	2208	10	6	−8
				−4	12	−8
Thalamus[c]		L	752	−12	−14	12
Parahippocampal gyrus[c]	28	L	640	−22	−28	−10
Anterior cingulate cortex[c]	32	R	576	10	46	−12
Cerebellum: Vermis[c]		L	456	2	−82	−24
Superior frontal gyrus[c]	8	R	440	30	48	38
Inferior frontal gyrus[c]	46	L	432	−46	40	8
Putamen[c]		L	296	−28	−8	4
Anterior cingulate cortex[c]	11	R	248	0	36	−4
Thalamus		R	240	6	−18	8
Midbrain: mammillary body		L	232	−2	−12	−12
Inferior frontal gyrus	47	R	232	50	24	−8
Middle temporal gyrus[c]	20	L	200	−58	−44	−8
Paracentral lobule	31	R	200	12	−28	46
Posterior cingulate cortex[c]	31	L	184	0	−44	32
Superior frontal gyrus[c]	6	L	184	0	26	66
Putamen[c]		R	176	26	12	16
Middle frontal gyrus[c]	9	L	168	−46	14	32
Inferior frontal gyrus	47	R	152	26	22	−20
Parahippocampal gyrus/Amygdala[c]		L	144	−20	−10	−16
Posterior cingulate cortex	31	R	144	6	−28	32
Cognitive-based interventions						
Precuneus	31	L	1840	−8	−50	36
Superior temporal gyrus	39	L	712	−58	−62	24
				−54	−56	16
Inferior parietal lobe	40	R	640	42	−46	62
Middle frontal gyrus	6	R	624	50	10	40
				42	12	44
Inferior frontal gyrus	47	L	400	−48	26	−12
				−48	22	−20
Anterior cingulate cortex	24	L	392	−2	28	6
Cerebellum		L	360	−14	−78	−28
Middle frontal gyrus	6	L	344	−46	10	44
Anterior cingulate cortex	32	L	320	−8	40	22

Table 2 (*Continued*)

	BA	Side	Volume (mm^3)	*X*	*Y*	*Z*
Middle temporal gyrus	21	L	312	−70	−40	0
Anterior cingulate cortex	32	R	312	8	36	22
Cuneus/Occipital lobe	17	L	296	−6	−84	10
Superior frontal gyrus	8	L	288	−8	54	34
Superior frontal gyrus	6	L	272	−4	22	58
Cuneus/Occipital lobe	18	L	240	−6	−100	18
Claustrum/Insula		L	152	−34	16	2
Precuneus	7	R	120	26	−62	56
Pharmacological > cognitive-based						
None						
Cognitive-based > Pharmacological						
Precuneus/Posterior cingulate cortex	31	L	736	−8	−52	37
Middle frontal gyrus	6	R	336	43	12	45
				45	8	40
Anterior cingulate cortex	32	R	216	8	38	26
				8	34	22

False discovery rate (FDR) $p < 0.05$ corrected and a minimum cluster size of 100 mm^3.
Regions are listed in hierarchical order based on cluster size.
[a] Regions that also appear in the sub-analysis of studies that used approved or established interventions for an indicated population of substance users.
[b] Regions that also appear in the sub-analysis of studies that used a randomized, controlled study design and that observed a therapeutic clinical effect (reduction in craving, withdrawal, or use).
[c] Regions that also appear in the sub-analysis of placebo-controlled pharmacological studies.
R, right; L, left.

3.1.2. Individual effects of therapeutic strategy (foci split by intervention type)

To isolate the individual effects of therapeutic interventions, we conducted separate meta-analyses on the foci reported for the two types of intervention strategies. The results of the therapeutic intervention-specific ALE analyses are summarized in Fig. 1 and Table 2. In general, results within pharmacological studies closely paralleled those of all studies together. These results also largely held when the analysis was limited to placebo-controlled studies (regions appearing in both analyses are indicated in Table 2) with additional convergence observed in the left dorsal striatum (caudate body) and right cuneus/occipital lobe (BA 17). Brain regions activated by the combined group of cognitive-based strategies included the anterior cingulate cortex, precuneus/posterior cingulate cortex, superior and middle frontal gyrus, and regions involved in sensory integration and perception including the cuneus/occipital lobe, superior and middle temporal gyrus, and the inferior parietal lobule.

3.1.3. Common effects of pharmacological and cognitive-based interventions (conjunction analysis)

The conjunction analysis of the thresholded ALE maps of pharmacological interventions and all cognitive-based interventions revealed direct overlap in the left precuneus/posterior cingulate cortex and left middle frontal gyrus (Fig. 2A; $p < 0.05$ FDR-corrected and 100 mm^3). When the threshold was reduced to $p < 0.005$ uncorrected and 100 mm^3, additional overlap was observed in the left ventral striatum, right inferior frontal gyrus, right orbitofrontal cortex, and right middle frontal gyrus.

3.1.4. Differential effects of pharmacological and cognitive-based interventions (direct contrast)

A direct comparison of the ALE analyses of pharmacological and cognitive-based interventions indicated that the left precuneus/posterior cingulate cortex, right anterior cingulate cortex, and right middle frontal gyrus were more likely to be activated by cognitive-based than pharmacological interventions (Fig. 2B, Table 2). No regions were observed in the reverse contrast of pharmacological > cognitive-based at the specified threshold. Thus, with the exception of the anterior cingulate cortex, while the effects of specific interventions directly overlapped in the left precuneus/posterior cingulate cortex and right middle frontal gyrus, activations in these regions were more likely to be observed in studies employing cognitive-based than pharmacological strategies.

Differences in analytic procedures of the included studies such as the use of small volume correction or partial volume coverage did not differentially influence results in any of the identified regions of overlap or difference (Supplemental Material).

3.2. Exploratory analyses based on duration of therapeutic intervention (single-dose versus repeated administration studies)

The effects of therapeutic interventions in studies of single-dose and repeated administration interventions are summarized in Table S3. The conjunction analysis revealed overlap in the left ventral striatum (Fig. S1A; $p < 0.05$ FDR-corrected and 100 mm^3) and in the left and right middle frontal gyrus at the reduced $p < 0.005$ uncorrected threshold and 100 mm^3. A direct contrast of single-dose studies versus repeated administration studies indicated that the right thalamus/globus pallidus and right ventral striatum were significantly more likely to be activated in repeated administration studies than single-dose studies (Fig. S1B, Table S4). No regions appeared in the reverse contrast of single-dose studies > repeated administration studies, which suggests that false positives (that could have occurred during a single-dose) are not a substantial problem in the reviewed studies.

3.3. Exploratory analyses based on task characteristics (drug cue-related versus non-drug related tasks)

The effects of therapeutic interventions in studies using drug cue-related and non-drug related tasks are summarized in Table S5. The conjunction analysis revealed overlap in the left middle frontal gyrus, left precuneus/posterior cingulate cortex, and the left and right ventral striatum, suggesting that therapeutic interventions targeted the reward system irrespective of the type of task that was used (Fig. S2A; $p < 0.05$ FDR-corrected and 100 mm^3); the right orbitofrontal cortex was additionally observed when the threshold was reduced to $p < 0.005$ uncorrected and 100 mm^3. A direct contrast of studies using drug cue-related versus non-drug related tasks revealed significantly more activation in the left ventral anterior cingulate cortex for drug cue-related tasks and in the left thalamus for non-drug related tasks (Fig. S2B, Table S6).

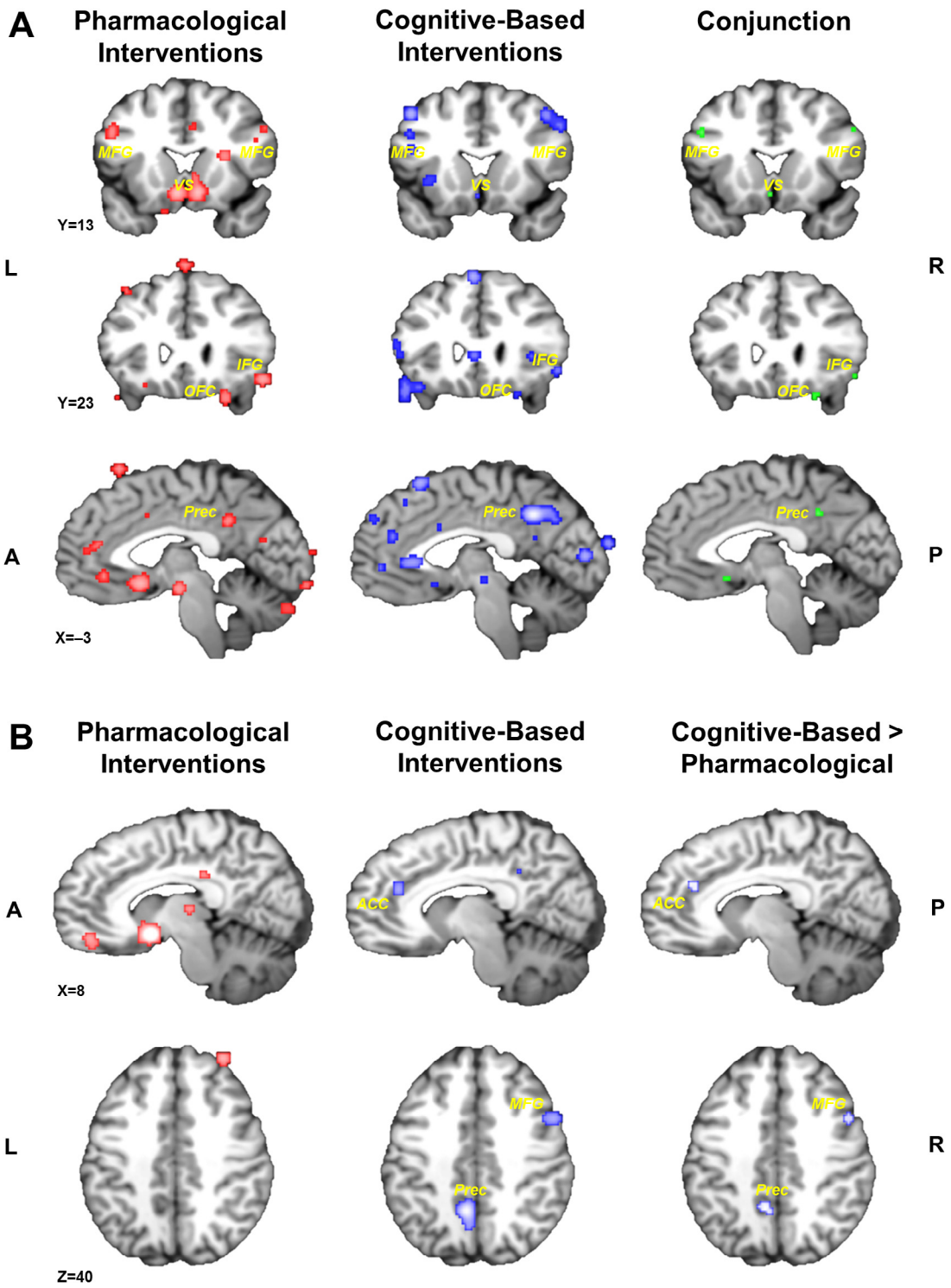

Fig. 2. Common (A) and distinct (B) neural targets of pharmacological and cognitive-based therapeutic interventions. Threshold for conjunction: $p < 0.005$ uncorrected and a minimum cluster size of 100 mm^3. Threshold for difference contrast: $p < 0.05$ FDR-corrected and a minimum cluster size of 100 mm^3. ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; OFC, orbitofrontal cortex; Prec, precuneus; VS, ventral striatum.

3.4. Exploratory analyses based on sample characteristics (primary drug of use)

The effects of therapeutic interventions in studies of alcohol, nicotine, and stimulant users, excluding opioid and mixed drug users due to small sample sizes of these substances, are summarized in Table S7. The conjunction analysis of studies in nicotine users and studies in alcohol and stimulant users (the latter two were combined due to small sample size) revealed overlap in the left ventral striatum ($p < 0.05$ FDR-corrected and 100 mm^3; Fig. S3A) (consistent with the main effects described above); the right inferior frontal gyrus, left middle frontal gyrus, and left anterior cingulate cortex were additionally observed when the threshold was reduced to $p < 0.005$ uncorrected and 100 mm^3. Differences were also noted however (Fig. S3B, Table S8): therapeutic interventions in alcohol and stimulant users were more likely to

activate the right ventral striatum (here, on the opposite side to the region of overlap) than in nicotine users, while therapeutic interventions in nicotine users were more likely to activate the left precuneus/posterior cingulate cortex than in alcohol and stimulant users.

Thus, although some differences were noted (i.e., in the left precuneus/posterior cingulate cortex), in general, the duration of intervention administration, the type of task, and the type of addiction also did not differentially influence results in the regions of overlap or difference as described above.

4. Discussion

Functional neuroimaging has informed much of what is known about neural abnormalities associated with human drug addiction. More recently, this tool has also allowed researchers to investigate whether and how these abnormalities can be targeted and potentially normalized by therapeutic interventions. Here, we used ALE meta-analysis to aggregate data across functional neuroimaging studies to examine the common and distinct neural targets of pharmacological and cognitive-based interventions for addiction in individuals with clinically-relevant substance use disorders.

4.1. Common neural targets of pharmacological and cognitive-based interventions

Although distinct neural patterns were observed in studies of pharmacological and cognitive-based strategies (Fig. 1), the conjunction of these intervention-specific ALE maps revealed direct overlap in the left ventral striatum, right inferior frontal gyrus, and right orbitofrontal cortex (Fig. 2A). Further analyses showed that neither the administration paradigm (i.e., single-dose versus repeated) nor the type of addiction (i.e., stimulant and alcohol versus nicotine) or type of task used (i.e., drug-related versus non-drug related) significantly influenced results in these regions of overlap. The ventral striatum contains the nucleus accumbens which receives dense dopaminergic projections from the midbrain and is targeted by all drugs of abuse (Di Chiara and Imperato, 1988; Volkow et al., 2004). This region plays an important role in associative learning (Belin et al., 2009) and response to drug-related cues across substance addictions (Chase et al., 2011; Kuhn and Gallinat, 2011). Although the precise mechanism of action of therapeutic interventions in this region cannot be determined by the current meta-analytic approach, we speculate that the effects of interventions in this region could serve to reduce drug-seeking (Kosten et al., 2006) and impulsive (Dalley et al., 2011, 2007, 2008) behavior or normalize disturbances associated with withdrawal and negative mood (Treadway and Zald, 2011). The orbitofrontal cortex plays an important role in the evaluation of salient, motivationally significant, information and goal-directed behavior (Balleine et al., 2011; Morrison and Salzman, 2011), while the right inferior frontal gyrus is consistently implicated in response inhibition (Robbins, 2007). As chronic drug use reduces gray matter and impairs functioning of these regions across substance addictions (Goldstein and Volkow, 2011), both therapeutic approaches may additionally help improve higher-order cognition including decision-making and inhibitory control. An interesting possibility is that neural changes due to therapeutic interventions depend more on the regions of dysfunction than the specific nature of the intervention, a notion that is supported by similarities in the neural correlates of psychotherapy and pharmacotherapy seen in affective and anxiety disorders (Linden, 2006).

4.2. Distinct neural targets of pharmacological and cognitive-based interventions

Although all therapeutic interventions were also associated with activation of the right anterior cingulate, right middle frontal gyrus, and left precuneus/posterior cingulate cortex (with direct overlap in the effects of cognitive-based and pharmacological interventions observed in the latter two), these regions were significantly more likely to be observed in studies of cognitive-based interventions than pharmacological interventions (Fig. 2B). This is consistent with theoretical models [e.g., as reviewed in Potenza et al. (2011)], which suggest that cognitive-based interventions may involve top-down control over bottom-up processes which facilitate addictive behavior (e.g., craving). Indeed, the anterior cingulate is involved in self-control during reward-related decision making (Hare et al., 2009) and in adjusting behavior following error (Kerns et al., 2004) and conflict (Morishima et al., 2010). In addition to its role in working memory (Leung et al., 2002), the middle frontal gyrus is also implicated in inhibitory control and emotion processing in addiction (Moreno-Lopez et al., 2012a), and it's direct modulation by noninvasive brain stimulation has been shown to be effective in reducing craving across substance addictions (Jansen et al., 2013). The precuneus supports cognitive flexibility and higher-order decision-making functions such as visual-spatial attention (Cavanna and Trimble, 2006) and delay discounting (Luhmann, 2009), both shown to be impaired in addiction (Crunelle et al., 2012). The precuneus/posterior cingulate cortex, along with the anterior cingulate, are also part of the brain's default mode network, which is a set of brain regions preferentially engaged during mentalizing processes (Laird et al., 2009) that need to be suppressed during task- or goal-relevant behavior (Buckner et al., 2008). Targeting these regions could increase goal-directed behavior in addicted individuals seeking to achieve abstinence, or insight into severity of illness in individuals not yet motivated for change, as has been previously suggested [e.g., Costello et al., 2010; Goldstein et al., 2009]. That is, differential augmentation of frontoparietal regions with cognitive-based interventions may enhance addicted individuals' ability to remain abstinent, as supported by studies that show longer duration of abstinence and treatment retention to correlate with cingulate (anterior and posterior) and middle frontal gyrus activation during inhibitory control tasks (Brewer et al., 2008).

4.3. Other neural targets of pharmacological and cognitive-based interventions

Additional effects of therapeutic interventions were detected in the analysis that pooled studies of pharmacological and cognitive-based interventions, but that were not observed in the conjunction and difference analyses described above. Of note, convergence in the effects of therapeutic interventions was observed in regions involved in sensory integration (e.g., inferior parietal lobule, cerebellum, and thalamus) and learning and memory (e.g., parahippocampal gyrus and amygdala). Modulation of activity in regions involved in sensory integration, attention, and motor control by therapeutic interventions could be important for treatment as addicted individuals must integrate and override bottom-up multisensory drug-related signals associated with object recognition (e.g., drug-related paraphernalia) and action knowledge (e.g., procedural memory processes related to drug consumption) that contribute to addiction severity and craving intensity (Yalachkov et al., 2009, 2010, 2012), with top-down cognitive and motor signals instrumental for changing behavior. In addition to aversive conditioning (Kim and Jung, 2006), the amygdala is associated with various forms of reward-related conditioning (Baxter and Murray, 2002), particularly via its interactions with the ventral striatum

(Di Ciano and Everitt, 2004). Activation of the amygdala correlates with subjective experience of craving (Chase et al., 2011) which increases the likelihood of relapse (Wrase et al., 2008). The amygdala and hippocampus also play a critical role in cue- (See, 2005) and context (Crombag et al., 2008)-induced relapse to drug-seeking. Thus, the ability of therapeutic interventions to modulate activity in these regions could be important for recognizing situations and automatized action plans that lead to relapse, or for modifying memory and learning away from drug taking and towards alternative behaviors.

4.4. Influence of study and sample characteristics

We performed a number of exploratory analyses to test whether our main findings were influenced by specific study (single-dose versus repeated administration interventions and use of a drug-related versus non-drug related task) and sample (primary drug of use) characteristics. With the exception of findings in the left precuneus however, our main results did not differ by any of these factors, suggesting that these results hold for a variety of contexts and addictions and might reflect a general mechanism of therapeutic interventions for addiction.

Nevertheless, our analyses comparing single-dose versus repeated administration studies identified the *right* ventral striatum as more likely to be observed in studies using the latter as compared to the former; in contrast, both types of interventions were associated with overlapping, non-differential, activation in the *left* ventral striatum. This suggests that repeated administration interventions may produce more diffuse striatal changes than single-dose interventions, compatible with dose effects in this region. The finding that single-dose studies detected similar activations in the left ventral striatum as repeated administration studies speaks to the potential of this neuroimaging target to serve as a *prognostic* tool for identifying longer-term response to treatment in addiction. For example, neural activity during a single-dose intervention has been shown to predict the success of longer-term treatment with the same intervention in other psychopathologies such as attention deficit hyperactivity disorder [e.g., An et al., 2013; Volkow et al., 2012].

Additional exploratory analyses also indicated that the left thalamus was more likely to be observed in studies that used non-drug related tasks, while the left ventral anterior cingulate was more likely to be observed in studies that used drug cue-related tasks (Fig. S2B). This is not surprising given that the thalamus is centrally involved in sensory processing and attention (Fan et al., 2005) and receives input from partly distinct dopamine pathways than those that innervate the ventral striatum and other limbic and cortical regions, including the ventral/pregenual anterior cingulate, involved in drug-cue processing (Garcia-Cabezas et al., 2007).

Lastly, our analyses identified that therapeutic interventions were more likely to activate the right ventral striatum in alcohol and stimulant users than in nicotine users and the left precuneus/posterior cingulate cortex in nicotine users than in alcohol and stimulant users (Fig. S3B). Striatal laterality has been previously reported in cocaine users (Volkow et al., 1999), where methylphenidate-induced glucose metabolism changes in the right but not left striatum and orbitofrontal cortex correlated with craving. In addition, in studies directly comparing cocaine and alcohol to other drugs, cocaine users exhibited right lateralized gray matter loss (Gardini and Venneri, 2012) and alcohol users, right lateralized abnormalities in striatal glucose metabolism (Moreno-Lopez et al., 2012b). Differences in the precuneus/posterior cingulate cortex may be related to nicotine's action on acetylcholine receptors in this region (Mamede et al., 2004) thought to mediate its attention-enhancing properties (Jasinska et al., 2013). However differences in the distribution of nicotine users across interventions (with nicotine users representing >80% of all substance users in studies of cognitive-based interventions) cannot be excluded from driving these addiction-specific effects in the left precuneus (see Table 1) and therefore this result warrants confirmation in future studies.

4.5. Limitations and future directions

Several caveats should be noted. Results for specific interventions should be considered preliminary as the number of studies included is relatively modest. This limitation also precluded our ability to perform more detailed analyses (e.g., successful versus unsuccessful interventions, pharmacological effects based on specific mechanisms of action or at different phases of treatment, etc.). Meta-analyses of neuroimaging data are particularly limited by the heterogeneity of the included studies (e.g., imaging and statistical parameters and the specific task paradigm used, although note that these factors did not appear to significantly influence our results). Our analyses are also susceptible to biases in the literature [e.g., lack of suitable studies exploring therapeutic interventions in marijuana users despite the efficacy of these interventions in this population in the clinical setting (Dutra et al., 2008) and the strong emphasis on single-session and pharmacological interventions and on populations of users of legal substances and especially nicotine]. Lastly, some of the included studies did not measure and/or report clinical correlates of a given intervention. In addition, most studies employed interventions that are still in the investigational phase (e.g., there are currently no FDA approved pharmacological treatments for stimulant addiction), and while these interventions show some promise clinically, they remain to be fully tested in their effectiveness for use as part of an addiction treatment strategy. Therefore, our analyses may have identified neural mechanisms that are not specific to the mechanisms of effective interventions for addiction. However, most regions identified by the analysis across all studies were also observed in sub-analyses that focused on established interventions or interventions that showed efficacy within a given study, increasing confidence that our results at least in part represent the neural mechanisms of effective interventions. Nevertheless, further studies are needed with larger addicted samples that use standardized treatment (e.g., randomized trials with appropriate controls) and imaging (e.g., pre- and post-intervention scanning) protocols, as well as studies that compare effects to abstinence without treatment [e.g., abstinence is associated with partial subcortical neurochemical (Ernst and Chang, 2008; Nordahl et al., 2005) and functional (Moeller et al., 2012) recovery] to clarify the specific neural changes that accompany the effects of therapeutic interventions. This latter comparison could also help elucidate whether the observed concurrence of regional brain activity, particularly in the regions of overlap, represents treatment effects or treatment response since changes in activation could be due to symptom improvement rather than serve as the mechanism of action of the intervention.

In addition, incorporating measures of brain connectivity [e.g., (Cole et al., 2010; Hong et al., 2009; Konova et al., 2013)], structure [e.g., (Froeliger et al., 2010)], electrocortical activity [e.g., (Horrell et al., 2010)], and neurochemistry [e.g., (Brody et al., 2010; Martinez et al., 2011; Schmaal et al., 2012b)], to these studies could provide further insights into the neural mechanisms of addiction treatment. Specifically, although in the present meta-analysis we focused on studies using fMRI and FDG-PET, the neuroimaging techniques most commonly used to study the neural correlates of addiction and its treatment, it is worth noting that techniques such as electroencephalogram (EEG) and magnetic resonance spectroscopy (MRS) can provide complementary information about the temporal aspects of and neurotransmitter systems affected by specific

interventions. Given the temporal resolution afforded by EEG (in the order of milliseconds versus seconds for fMRI and minutes for PET), EEG may be particularly suitable for capturing early sensory and attentional processes such as those involved in cognitive-based interventions. Notably, a recent EEG study (Horrell et al., 2010) employed 12 sessions of a neurofeedback-based intervention combined with motivational interviewing to modify electrical activity in the gamma frequency band in cocaine users, changes that were associated with a reduction in the number of positive cocaine urine screens and depressive symptoms. EEG-informed analysis of fMRI is another useful direction that can provide information about the underlying brain processes of treatment. Similarly, spectroscopy is a neuroimaging tool that allows *in vivo* measurement of concentrations of molecules such as glutamate and GABA (and their metabolites) in select brain regions. Like EEG, MRS is an emerging tool for monitoring the effects of therapeutic interventions in addiction, and particularly those acting on glutamate. Recent use of MRS in combination with therapeutic interventions in addiction has revealed that glutamate/glutamine disturbances in the insular cortex of smokers can be partly normalized by nicotine substitution treatment (Gutzeit et al., 2013) and in the anterior cingulate cortex of alcohol (Umhau et al., 2010) and cocaine (Schmaal et al., 2012a) users by treatment with acamprosate or a single dose of N-acetylcysteine, respectively.

5. Conclusion

In summary, our results provide novel, quantitative evidence that pharmacological and cognitive-based strategies target brain structures that are altered across substance addictions. In addition to common neural targets in the ventral striatum, inferior frontal gyrus, and orbitofrontal cortex, cognitive-based interventions were more likely to also target the anterior cingulate cortex, middle frontal gyrus, and precuneus/posterior cingulate cortex than pharmacological interventions. These findings suggest a potential mechanism by which the tandem use of pharmacological and cognitive-based strategies may produce synergistic (due to their common targets) or complementary (due to their distinct targets) therapeutic effects, as is suggested by controlled clinical trial data that shows the efficacy of pharmacotherapies in alcohol (Anton et al., 2006; Johansson et al., 2006) and opioid (Kosten et al., 2003; Poling et al., 2006) dependence is enhanced by the tandem use of behavioral interventions. In particular, the ability of cognitive-based interventions to target prefrontal and parietal regions may be important for treatment adherence, which is a key determinant of treatment success (Kampman et al., 2006; McClernon et al., 2007). *In vivo* imaging biomarkers may be useful for examining the neurobiological mechanisms of existing interventions and for designing improved treatments that optimally target the specific regions of dysfunction in this difficult-to-treat disorder (e.g., neuroimaging-based interventions such as neurofeedback and focal brain stimulation).

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We would like to thank Brenda J. Anderson, Hoi-Chung Leung, and Christian C. Luhmann for their thoughtful comments on earlier versions of this manuscript. This manuscript was prepared in part with grant support from the National Institute on Drug Abuse (1R01DA023579 and R21DA034954 to R.Z.G. and 1F32DA030017-01 to S.J.M).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2013.10.002.

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