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## Striatocortical pathway dysfunction in addiction and obesity: differences and similarities

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### Abstract

Neuroimaging techniques are starting to reveal significant overlap in the brain circuitry underlying addiction and disorders of dyscontrol over rewarding behaviors (such as binge eating disorder and obesity). Positron emission tomography (PET) has demonstrated impaired striatal dopamine (DA) signaling (decreased D2 receptors) in drug addiction and obesity that is associated with reduced baseline glucose metabolism in medial and ventral prefrontal brain regions. Functional magnetic resonance imaging (fMRI) has documented brain activation abnormalities that also implicate DA-modulated striato-cortical pathways. In this review we map findings from recent neuroimaging studies that differentiate brain activation in drug/food addiction from those in controls within brain networks functionally connected with ventral and dorsal striatum. We show that regions found to be abnormal in addiction and obesity frequently emerge at the overlap of the dorsal and the ventral striatal networks. Medial temporal and superior frontal regions functionally connected with dorsal striatum display greater vulnerability in obesity and eating disorders than in drug addictions, indicating more widespread abnormalities for obesity and eating disorders than for addictions. This corroborates involvement of both ventral striatal (predominantly associated with reward and motivation) and dorsal striatal networks (associated with habits or stimulus response learning) in addiction and obesity but also identify distinct patterns between these two disorders.

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Dopamine (DA) encodes prediction signals for natural and drug reinforcers and facilitates conditioning (learning of reward associations) by modulating brain activity in subcortical and cortical regions (Ikemoto, 2010). Drugs of abuse are compulsively consumed by humans or self-administered by laboratory animals because they are inherently rewarding (Di Chiara and Imperato, 1988; Volkow and Li, 2005). Drugs of abuse have been shown to cause abrupt increases in extracellular DA in the striatum (Volkow et al., 1997a) that parallel the time course of the subjective “high” (Volkow et al., 1997b). However, other neurotransmitters such as cannabinoids and opioids, and neuropeptides also play important roles in reward and addiction and are intimately involved in triggering the neuroplastic changes that follow repeated drug use and involve changes in glutamatergic signaling in striatocortical pathways (Kalivas, 2009; Koob and Le Moal, 2008; Lüscher and Malenka, 2011). Preclinical and clinical studies assessing the response to drug/food cues have shown increases in extracellular DA in striatum that were associated with enhanced motivation to consume drugs/foods. This evidences the involvement of DA in cue-induced overeating, just as it has been shown to underlie its involvement in cue-induced relapse in drug addiction (Avena et al., 2008; Volkow et al., 2008a). Thus, it has been postulated that DA-modulated

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#### Declaration of interest

The authors report no declarations of interest.

circuits showing drug-related impairments in drug addiction could also be implicated in pathologic, compulsive eating behaviors (Volkow et al., 2012b; Volkow et al., 2008a).

During the last two decades positron emission tomography (PET) studies have evaluated the role of DA in association with glucose metabolism in reward and addiction (Volkow et al., 2011c; Volkow et al., 2012b; Volkow et al., 2012a). The role of striatal DA on baseline brain activity, on the responses to drugs and on the responses to drug cues, has been studied with PET technology using multiple tracer approaches in both addicted and non addicted individuals (Fig 1). The combined use of D2 receptor (ie., [<sup>11</sup>C]raclopride, [<sup>18</sup>F]n-methylspiroperidol) and DA transporter (such as [<sup>11</sup>C]cocaine, [<sup>11</sup>C]d-threo-methylphenidate) radioligands with fludeoxyglucose ([<sup>18</sup>F]FDG, ligand used to measure brain glucose metabolism) demonstrated that the availability of DA D2 receptors (D2R) and transporters (DAT) in striatum is associated with metabolic activity in frontal and temporal cortices (Volkow et al., 1993; Volkow et al., 2008b; Volkow et al., 2006; Volkow et al., 1996c) (Fig 2). These studies have consistently demonstrated impaired DA function in striatum (decreases in D2R, reduced DA release) and its association with reduced baseline glucose metabolism (marker of brain function) in frontal (orbitofrontal cortex, anterior cingulate, dorsolateral prefrontal) and temporal cortices (most notable in insula) (Volkow et al., 1993).

In parallel functional magnetic resonance imaging (fMRI) studies have assessed changes in brain function and connectivity in addicted subjects (Goldstein and Volkow, 2011). The role of brain activation has been studied with fMRI using the endogenous blood-oxygenation-level-dependent (BOLD) contrast (Ogawa et al., 1990) and a plethora of task activation paradigms. These studies have shown that addiction affects not only the reward circuit, but also brain regions involved in attention, memory, motivation, executive function, mood and interoception (Volkow et al., 2011c).

More recently, PET and fMRI multimodality studies have documented an association between DA neurotransmission in striatum and fMRI responses in the default mode network (DMN; including ventral prefrontal cortex and precuneus) (Tomasi et al., 2009a; Braskie et al., 2011) that deactivates during task performance in healthy controls (Tomasi et al., 2006; Fox et al., 2005) (Fig 2). Pharmacological fMRI studies using stimulant drugs with DA enhancing effects such as modafinil and methylphenidate have also suggested an association between DA signaling and DMN function (Minzenberg et al., 2011; Tomasi et al., 2011). Other pharmacological PET and fMRI studies demonstrated that stimulants (methylphenidate) can attenuate limbic brain responses to cocaine cues (Volkow et al., 2010b) and normalize fMRI responses during a cognitive task (Goldstein et al., 2010; Li et al., 2010) in cocaine addicts. However, the association between impaired DA neurotransmission and abnormal activation in addiction and obesity is still poorly understood.

## Dopaminergic responses to drugs and food

All addictive drugs display ability to increase DA in striatum, particularly in the nucleus accumbens (ventral striatum), which underlies their rewarding effects (Koob, 1992). DA neurons located in the ventral tegmental area (VTA) and substantia nigra (SN) in the midbrain project to the striatum via the mesolimbic and nigrostriatal pathways. The rewarding and conditioning effects of drugs (and very likely to food too) seem to be predominantly driven by transient and pronounced increases in DA cell firing (Wise, 2009) that result in high DA concentrations that are necessary to stimulate the low affinity D1 receptors (Zweifel et al., 2009). In humans, PET studies have shown that several drugs increase DA in dorsal and ventral striatum and that these increases are associated with the

subjective rewarding effects of the drugs [stimulants (Drevets et al., 2001; Volkow et al., 1999), nicotine (Brody et al., 2009), alcohol (Boileau et al., 2003) and cannabis (Bossong et al., 2009)]. Dopaminergic responses might also play a role in the rewarding effects of foods and contribute to excessive consumption and obesity (Volkow et al., 2011b). Certain foods, particularly those rich in sugars and fat, are potently rewarding and can promote over-eating (Lenoir et al., 2007) because like drugs they increase striatal DA release (Norgren et al., 2006). Moreover, food can increase DA in ventral striatum solely on the basis of its caloric content and independent of palatability (de Araujo et al., 2008). Whereas food-reward associations were advantageous in environments where food sources were scarce and/or unreliable, this mechanism is now a liability in our modern societies where food is plentiful and constantly available.

Other neurotransmitters than dopamine (cannabinoids, opioids, and serotonin) as well as neuropeptide hormones (insulin, leptin, ghrelin, orexin, glucagon like peptide, agouti related protein, PYY) have been implicated in the rewarding effects of food and in the regulation of food intake (Atkinson, 2008; Cason et al., 2010; Cota et al., 2006). Furthermore, food-related striatal DA increases alone cannot explain the difference between normal food intake and excessive compulsive food consumption since these also occur in healthy individuals who do not overeat. Therefore, as for addiction, downstream adaptations are likely to be involved in the loss of control over food intake. These neuroadaptations might lead to decreases in tonic DA cell firing, enhanced phasic DA cell firing in response to drug or food cues and reduced executive function including impairments in self-control (Grace, 2000; Wanat et al., 2009).

## Striatocortical connectivity

Cortical correlates of striatal dopaminergic deficits in addition are not unexpected. Anatomical studies in non-human primates and in rodents documented that motor, somatosensory and dorsolateral prefrontal cortices project to dorsal striatum (Künzle, 1975; Künzle, 1977; Selemon and Goldman-Rakic, 1985; Middleton and Strick, 2002; Kelly and Strick, 2004; Künzle and Akert, 1977), and that anterior cingulate (ACC) and orbitofrontal (OFC) cortices project to ventral striatum (Ilinsky et al., 1985; Selemon and Goldman-Rakic, 1985; Ferry et al., 2000; Haber et al., 2006; Powell and Leman, 1976; Yeterian and Van Hoesen, 1978).

Recently, Di Martino and colleagues were able recapitulate these striatocortical circuits using brief (< 7 min) MRI scanning sessions at rest in 35 human subjects (Di Martino et al., 2008) and supported a meta-analysis of PET and fMRI studies that identified functional connectivity between the anterior dorsal striatum and the insula (Postuma and Dagher, 2006). Resting state functional connectivity (RSFC) is advantageous when studying patients with functional deficits because the data is collected at rest avoiding performance confounds (task stimulation paradigms require the subjects' cooperation and motivation), and has potential as a biomarker for diseases that affect the brain DA system.

Recent studies have documented impairments in functional connectivity both in drug addiction and in obesity. Specifically lower functional connectivity has been reported between dopaminergic midbrain nuclei (VTA and SN) with striatum and with the thalamus (Gu et al., 2010; Tomasi et al., 2010), between the hemispheres (Kelly et al., 2011), and between the striatum and cortex (Hanlon et al., 2011) in cocaine addicts. Abnormal striatocortical connectivity was also documented in social drinkers (Rzepecki-Smith et al., 2010), opioid abusers (Ma et al., 2010; Liu et al., 2009; Ma et al., 2011; Upadhyay et al., 2010) and obese subjects (Nummenmaa et al., 2012; Kullmann et al., 2012; García-García et al., 2012). Overall, these studies suggest that abnormal connectivity between cortical and subcortical

regions might underlie the pathological states in drug addiction and obesity. Open access to large RSFC databases integrating datasets from multiple studies promises increased statistical power and sensitivity to characterize the connectivity of the human brain (Biswal et al., 2010; Tomasi and Volkow, 2011). Here we reproduce the RSFC patterns from dorsal and ventral striatal seeds documented by Di Martino and colleagues (Di Martino et al., 2008) in a large sample of healthy subjects. The coordinates of the abnormal clusters documented by previous neuroimaging studies on food/drug addiction were projected into these striatal networks to assess their implication in addiction and obesity. Other striatal seed regions (i.e. dorsal caudate) were unnecessary because their functional connectivity patterns were largely included within the union of the ventral and dorsal RSFC patterns.

The RSFC patterns were computed using the three largest datasets (Beijing: N=198; Cambridge: N=198; Oulu: N=103) of the public image repository “1000 Functional Connectomes Project” ([http://www.nitrc.org/projects/fcon\\_1000/](http://www.nitrc.org/projects/fcon_1000/)), which included a total of 499 healthy subjects (188 males and 311 females; age: 18-30 years). We used the approach by Di Martino et al. to map dorsal and ventral striatal networks. The standard image post processing (realignment and spatial normalization to the MNI space) was carried with the statistical parametric mapping package (SPM5; Wellcome Trust Centre for Neuroimaging, London, UK). Then, seed-voxel correlation analysis with Gram-Schmidt orthogonalization (Margulies et al., 2007; Di Martino et al., 2008) was used to compute the functional connectivity of the bilateral dorsal ( $x = \pm 28$  mm,  $y = 1$  mm,  $z = 3$  mm) and ventral ( $x = \pm 9$  mm,  $y = 9$  mm,  $z = -8$  mm) striatal seed regions (0.73ml cubic volumes). In addition, the functional connectivity of a bilateral primary visual cortex seed ( $x = \pm 6$  mm,  $y = -81$  mm,  $z = 10$  mm; calcarine cortex, BA 17) was computed as a control network. These RSFC maps were spatially smoothed (8-mm) and included in a voxel-wise one-way analysis of variance (ANOVA) SPM5 model, independently for dorsal and ventral striatal seeds. Voxels with T-score  $> 3$  (p-value  $< 0.001$ , uncorrected) were considered to be significantly connected to the seed regions and were included as part of the networks.

The RSFC pattern of the dorsal striatal seeds (Fig 3) was bilateral and included dorsolateral prefrontal (BAs: 6, 8, 9, 44-46), inferior (BA: 47) and superior frontal (BAs: 8-10), temporal (BAs: 20, 22, 27, 28, 34, 36-38, 41-43), inferior and superior parietal (BAs: 2, 3, 4, 5, 7, 39, 40), occipital (BA: 19), and cingulate (BAs: 23, 24, 32), occipital (BA 19) and limbic (BA: 30) cortices, thalamus, putamen, globus pallidus, caudate, midbrain, pons, and cerebellum. The RSFC pattern of the ventral striatal seeds was also bilateral and included ventral orbitofrontal (BA: 11), superior frontal (BAs: 8-10), temporal (BAs: 20, 21, 27-29, 34, 36, 38), inferior parietal (BA: 39), and cingulate (BAs: 23-26, 32) and limbic (BA: 30) cortices, thalamus, putamen, globus pallidus, caudate, midbrain, pons, and cerebellum. These ventral and dorsal patterns overlapped in inferior (BA: 47) and superior frontal (BAs: 9), temporal (BAs: 20, 27, 28, 34, 36, 38), cingulate (BAs: 23, 24, 32) and limbic (BA: 30) cortices, thalamus, putamen, globus pallidus, caudate, midbrain, pons, and cerebellum. Thus, there was significant overlap as well as significant differences between these dorsal and ventral network patterns that corroborate those from Di Martino et al (Di Martino et al., 2008) and are consistent with the patterns reported by anatomical studies (Haber et al., 2000). The RSFC pattern of the primary visual cortex (V1) was also bilateral and included occipital (BAs 17-19), temporal (BA 37), superior parietal (BA 7), auditory (BAs 22 and 42) and premotor (BA 6) cortices and bilateral posterior superior cerebellum (Fig 3). Thus, the V1 connectivity pattern was smaller (volume of the V1 network = 16% gray matter volume) and partially overlapped the dorsal striatal network (6% gray matter volume in BAs 6, 7, 19 and 37) but not the ventral striatal network.

## Meta-analysis

In what follows we review functional neuroimaging studies on alcohol, cocaine, methamphetamine, and marijuana (Tables 1-4), as well as obesity and eating disorders (Tables 5 and 6) that were published between January 1, 2001 and December 31, 2011; nicotine addiction was not included because there were only five fMRI studies on nicotine addiction and none assessed brain activation differences between smokers and non-smokers. The words “activation”, “connectivity”, “dopamine”, “cocaine”, “marijuana”, “cannabis”, “methamphetamine”, “alcohol”, “PET”, and “MRI” were included in a search of peer-reviewed publications in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) to identify relevant brain imaging studies. Only studies that reported the spatial coordinates of the clusters (in the Montreal Neurological Institute (MNI) or Talairach stereotactic frames of references) showing significant activation/ metabolic differences between drug users/obese patients and controls ( $P < 0.05$ , corrected for multiple comparisons) were included in the analysis.

A coordinate-based meta-analysis was used to evaluate the degree of agreement between studies. We used an activation likelihood estimation approach (Wager et al., 2004) to build likelihood functions for each reported cluster. Specifically, a 3D Gaussian density (15-mm full-width-half-maximum) was centered at the MNI coordinates of each cluster that reported significant activation differences with respect to controls for drug users, obese individuals and eating disorder patients, regardless if they were increases or decreases. The SPM5 one-way ANOVA was used to analyze the statistical significance of the likelihood maps (3-mm isotropic resolution) corresponding to the 44 studies on drug addiction (Tables 1-4), and the 13 studies on obesity and eating disorders (Tables 5 and 6). The meta-analysis showed that the anterior and middle cingulate cortices frequently demonstrate activation abnormalities in neuroimaging studies on drug addiction, and that the putamen/posterior insula, hippocampus, superior prefrontal cortex (PFC), middle and inferior temporal cortices and cerebellum frequently demonstrate activation abnormalities in studies on obesity and eating disorders ( $P_{\text{FWE}} < 0.05$ , corrected for multiple comparisons in the whole brain using the random field theory with family-wise error correction; Fig 4; Table 7). This meta-analysis also showed that the likelihood of abnormal activation findings in putamen/posterior insula, hippocampus, parahippocampus and temporal cortices is usually higher for studies on obesity and eating disorders than for studies on drug addiction ( $P_{\text{FWE}} < 0.05$ ; Fig 4; Table 7). In ACC (BA 24 and 32), PFC (BA 8), putamen/posterior insula, hippocampus (BA 20), cerebellum, middle and superior temporal (BAs 21, 41 and 42) and supramarginal gyri the strength of the functional connectivity was stronger for the dorsal than for the ventral striatum and in the anterior medial frontal cortex (BAs 10 and 11) was stronger for the ventral than for the dorsal striatum ( $P_{\text{FWE}} < 0.05$ ; Table 7).

## Alcohol

In alcoholics, postmortem studies and brain imaging studies have reported reductions in D2R in striatum, including NAc (Freund and Ballinger, 1989). fMRI studies on alcoholics have reported abnormal responses to cue-reactivity, working memory, inhibition, and emotional paradigms in cortical and subcortical brain regions (Table 1). During cue-reactivity or with exposure to alcohol, more than 67% of the activation clusters that differentiated alcoholics from controls were included in the striatal networks (Fig 5). For instance, intravenous ethanol increased activation in ventral striatum and other limbic areas in social drinkers but not in heavy drinkers (Gilman et al., 2012) and alcohol taste cues activated PFC, striatum and midbrain in heavy drinkers (Filbey et al., 2008). Alcohol sips increased fMRI activation in dorsolateral PFC (DLPFC) and anterior thalamus when alcoholics were exposed to alcohol cues (George et al., 2001). Alcoholics also demonstrated



higher fMRI activation than controls in putamen, ACC and medial PFC and decreases in ventral striatum and PFC when viewing alcohol/control cues (Grüsser et al., 2004; Vollstädt-Klein et al., 2010b). Clusters reporting alcohol-related activation abnormalities during cue-reactivity tasks were more frequently located in the “overlapping” network defined by the intersection of the dorsal and ventral networks (Fig 3, magenta; 21% of the gray matter volume) than in regions that were functionally connected to V1, regardless if they overlapped (yellow) or not (green) with the striatal networks. These data suggests that exposure to alcohol-associated cues engage the intersection of the ventral and dorsal striatal networks in agreement with PET findings showing deficits in ventral and dorsal striatal D2R and in DA signaling in alcoholics (Volkow et al., 2007).

The striatal networks also included a large fraction of alcohol-related findings for working memory and memory encoding tasks. To assess the effect of alcohol intoxication on cognitive function, Gundersen et al. evaluated fMRI activation during n-back working memory when subjects drank alcohol versus when they drank soft drinks. They found that acute alcohol intake decreased activation in dorsal ACC and cerebellum, and that these decreases varied with cognitive load and blood alcohol concentrations (Gundersen et al., 2008). Alcoholics assessed with a working memory task demonstrated weaker lateralization of fMRI activation in parahippocampal regions, supporting the hypothesis that the right hemisphere is more vulnerable to alcohol-related damage than the left one (Yoon et al., 2009), and increased ACC activation compared to controls (Vollstädt-Klein et al., 2010a). More than 90% of the alcohol-related activation findings occurred in the striatal networks. These findings strongly support an association between activation abnormalities during working memory and striatal dysfunction in alcoholics.

The striatal networks also included a significant fraction of alcohol-related findings in studies on emotion and inhibitory control. During anticipation of monetary gain detoxified alcoholics exhibited lower activation in ventral striatum than controls but showed higher striatal activation during alcohol-cue exposure, which were correlated with alcohol craving in alcoholics but not in controls (Wrase et al., 2007). Studies on adolescents at risk for alcoholism (children of alcoholics, or COA) reported higher activation in dorsomedial PFC and less activation in ventral striatum and amygdala for alcohol-vulnerable subjects than for alcohol-resilient controls (Heitzeg et al., 2008). Studies on impulsivity reported greater fMRI activation in DLPFC and ACC during the Stroop interference test (Silveri et al., 2011), and lower deactivation in ventral striatum, ventral PFC, and OFC during an inhibitory go/no-go task (Heitzeg et al., 2010) for COA than for control adolescents. The high prevalence of findings within the striatal networks during these studies (> 83%) strongly suggests that alcohol vulnerability and related impairments in inhibitory capacity and control mechanisms are associated with striatal dysfunction. Indeed, we documented higher than normal availability of D2R in dorsal and ventral striatum associated with normal function in prefrontal brain regions (OFC, ACC, DLPFC) and anterior insula in COA who were not alcoholics as adults (Figure 2) (Volkow et al., 2006). We postulated that the striatal increases in D2R enabled them to maintain normal function in prefrontal brain regions, protecting them against alcoholism.

## Cocaine

The striatal networks captured 83% of the abnormal activation clusters in cocaine subjects suggesting cortico-striatal dysfunction in cocaine addiction. Drug cues (words) showed lower fMRI activation in rostral ventral and caudal dorsal ACC than neutral words in cocaine addicts (Goldstein et al., 2007b) who showed lower activation than controls in these ACC regions (Goldstein et al., 2009a) but higher activation in midbrain (Goldstein et al., 2009b). Administration of the DA enhancing medication methylphenidate (20 mg oral)

normalized the hypo ACC activation in cocaine addicts (Goldstein et al., 2010). During a cocaine-cue video, brain activation in left DLPFC and bilateral occipital cortex was stronger for cocaine subjects than for healthy controls (Wilcox et al., 2011). However, glucose metabolism in left insula, OFC and NAc, and right parahippocampus was lower when cocaine subjects watched a cocaine-cue video than when they watched a neutral-cue video and methylphenidate (20 mg, oral) reduced the abnormal response to the cocaine-cues (Volkow et al., 2010b). When instructed to inhibit their craving prior to exposure to cocaine-cues, cocaine abusers were able to reduce metabolism of the OFC and NAc (compared to the condition when they did not aim to control their craving), an effect that was predicted by baseline metabolism in the right inferior frontal cortex (BA 44) (Volkow et al., 2010a). In cocaine addicted women, but not in men, exposure to cocaine-cues (video and measured with PET and FDG) was associated with a significant reduction in metabolism in cortical brain regions that are located within the striatal networks and are also part of the control networks (Volkow et al., 2011a). Inasmuch as DA modulates control networks through striatal cortical pathways these findings support the involvement of control networks in addiction. Upon exposure to the stimulant drug itself (intravenous methylphenidate, which cocaine abusers reported to have similar effects to those of intravenous cocaine) cocaine abusers showed increased metabolic activation in OFC and ventral cingulate whereas control subjects decreased metabolic activity in these regions (Volkow et al., 1995).

The striatal networks also captured 71% of cocaine-related abnormal activation clusters during working memory and visual attention tasks and the control regions (functionally connected to V1) that overlapped the dorsal striatal network (Fig 3, yellow) had much higher likelihood of abnormalities than those that did not overlap the striatal networks (green). During verbal n-back working memory cocaine subjects demonstrated lower activation in thalamus and midbrain, dorsal striatum, ACC, and limbic regions (amygdala and parahippocampus) and hyper activation in PFC and parietal cortices (Tomasi et al., 2007a). Some of these abnormalities were accentuated in the cocaine abusers with positive urines for cocaine at time of study suggesting that the deficits may reflect in part early cocaine abstinence (Tomasi et al., 2007a). Indeed, during early abstinence treatment-seeking cocaine-dependent individuals exhibited hypo activation in striatum, ACC, inferior PFC, precentral gyrus, and thalamus compared to controls (Moeller et al., 2010). Other studies on working memory revealed that cocaine cues can increase brain activation in occipital cortex (Hester and Garavan, 2009). During visual attention tasks, cocaine abusers had lower thalamic activation and higher occipital cortex and PFC activation than controls (Tomasi et al., 2007b). The association between cortico-striatal dysfunction and abnormal fMRI activation during memory and attention tasks occurred predominantly at the intersection of the dorsal and ventral networks, which had 3 times higher likelihood (relative number of cluster normalized by network volume) than regions not functionally connected to the striatum (Fig 5).

During decision-making with the Iowa gambling task cocaine abusers demonstrated higher regional cerebral blood flow (rCBF; measured with  $^{15}\text{O}$ -water PET) in right OFC and lower rCBF in DLPFC and medial PFC compared to controls (Bolla et al., 2003). During a forced-choice task under three monetary value conditions cocaine subjects showed lower fMRI responses to monetary reward in OFC, PFC and occipital cortex, midbrain, thalamus, insula and cerebellum (Goldstein et al., 2007a). Lower than normal D2R availability in dorsal striatum was associated with decreased thalamic activation responses whereas in ventral striatum it was associated with increased medial PFC activation in cocaine addicted individuals (Asensio et al., 2010). Similarly to cognitive tasks, findings at the intersection of the dorsal and ventral networks exhibited higher likelihood than those in regions not functionally connected to the striatum.

Sixty-four % of the brain clusters reported by fMRI studies on inhibitory tasks were included in the striatal networks. During go/no-go inhibition cocaine addicts demonstrated lower activation than controls in OFC, supplementary motor area and ACC, regions that might be critical for cognitive control (Hester and Garavan, 2004). Short- and long-term abstinent cocaine users exhibited differential activation in PFC, temporal cortex, cingulum, thalamus and cerebellum (Connolly et al., 2011). During different inhibitory tasks (Stroop interference) cocaine addicts showed lower rCBF in left ACC and right PFC, and higher rCBF in right ACC than controls (Bolla et al., 2004). Striatal functional connectivity failed to explain brain activation differences from studies that used stop-signal tasks (Li et al., 2008). These studies showed lower activation in ACC, parietal and occipital cortices in cocaine abusers. PET studies measuring mu opioid receptors (using [<sup>11</sup>C]carfentanil) showed higher specific binding in frontal and temporal cortices for one-day abstinent cocaine dependent subjects than for controls, and these abnormalities decreased with abstinence and correlated with cocaine use (Gorelick et al., 2005;Ghitza et al., 2010).

## Methamphetamine

Compared to control subjects, methamphetamine abusers tested during early detoxification demonstrated decreased glucose metabolism in striatum and thalamus whereas they showed increased activity in parietal cortex (Volkow et al., 2001a). This suggested that both DA as well as non DA modulated brain regions are affected by chronic methamphetamine consumption (Volkow et al., 2001a). Moreover decreased striatal DA activity was associated with a greater likelihood of relapse during treatment (Wang et al., 2011b), protracted abstinence was associated with partial recovery of striatal DAT (Volkow et al., 2001b) and of regional brain metabolism (Wang et al., 2004), and reductions in striatal D2R were also associated with reduction in metabolism in OFC in recently detoxified methamphetamine abusers (Volkow et al., 2001a).

A large fraction (70%) of the methamphetamine-related fMRI findings was encompassed by the striatal networks (Fig 5). When compared to controls, methamphetamine dependent individuals exhibited higher ACC activation during go/no-go response inhibition (Leland et al., 2008), and lower right PFC activation during Stroop interference (Salo et al., 2009). Most of these abnormal activation clusters (88%) occurred within the dorsal network (including its overlap with the ventral network). During decision-making, however, a lower fraction (64%) of the clusters was encompassed by the striatal networks. Using a two-choice prediction task, Paulus and colleagues found that fMRI activation was lower in PFC (Paulus et al., 2002), OFC, ACC and parietal cortex for methamphetamine-dependent subjects than for controls (Paulus et al., 2003). Moreover, a combination of activation responses in these regions best predicted the time to relapse and showed different activation patterns as a function of error rate in left insula and DLPFC (Paulus et al., 2005).

## Marijuana

The involvement of striatal dysfunction in marijuana addiction is less clear because neither baseline striatal D2R nor striatal DA release (after amphetamine challenge) abnormalities were observed in recent PET studies with [<sup>11</sup>C]raclopride (Urban et al., 2012;Stokes et al., 2012). An FDG study showed that when given tetrahydrocannabinol (THC) chronic marijuana abusers showed increases in OFC and medial PFC and in striatum whereas controls did not, but it increased cerebellar metabolism in both abusers and controls suggesting that striatal networks are involved in marijuana addiction (Volkow et al., 1996b). Tactile marijuana-related cues versus neutral cues were shown to increase fMRI activation in VTA, thalamus, ACC, insula, and amygdala, supporting the involvement of striatal networks, as well as in other prefrontal, parietal and occipital cortices and cerebellum in



recently abstinent marijuana users (Filbey et al., 2009). During a visual attention task, marijuana abusers had lower fMRI activation in right PFC, parietal cortex and cerebellum (normalized with duration of abstinence) and higher activation in frontal, parietal and occipital cortices than controls (Chang et al., 2006). During working memory, however, marijuana abusers exhibited decreased activation in temporal lobes, ACC, parahippocampus and thalamus with increased task performance, a group  $\times$  performance interaction effect that was opposite in controls (Padula et al., 2007). During go/no-go inhibition, adolescents with histories of marijuana use showed higher fMRI activation in DLPFC, parietal and occipital cortices, and insula than adolescents without histories of marijuana use (Tapert et al., 2007). During visuomotor integration with a visually paced finger sequencing task cued by a flashing checkerboard, marijuana users had higher PFC activation and lower visual cortex activation than controls (King et al., 2011). Sixty-nine % of the abnormal activation clusters in studies on effects of marijuana on brain function were located in regions functionally connected to the striatum.

## Obesity

Compulsive-like feeding behavior in obese rats has been associated with downregulation of striatal D2R (Johnson and Kenny, 2010) and obesity has been linked to lower striatal D2R in humans (Wang et al., 2001), suggesting that common neuroadaptations in DA striatal pathway may underlie obesity and drug addiction. Baseline PET studies of brain glucose metabolism in obese individuals reported reductions in metabolic activity in OFC and ACC that were associated with lower than normal striatal D2R availability (Volkow et al., 2008b).

Brain activation in dorsal and ventral striatum, insula, hippocampus, OFC, amygdala, medial PFC and ACC elicited by visual exposures to high caloric foods was higher for obese than for control women (Rothmund et al., 2007;Stoeckel et al., 2008). Similarly, visual food cues elicited increased fMRI activation responses in frontal, temporal, and limbic regions for obese adults than for controls (Dimitropoulos et al., 2012), and hippocampal activation showed a correlation with fasting plasma levels of insulin and waist circumference in adolescents (Wallner-Liebmann et al., 2010). Striatal activation in response to chocolate milkshake intake was associated with gains in body weight and with the presence of the A1 allele of the TaqIA restriction fragment length polymorphism, which is associated with D2R gene binding in the striatum and compromised striatal DA signaling (Stice et al., 2008). Adolescents with high risk for obesity showed higher activation in caudate and operculum in response to chocolate milkshake intake than those with low risk for obesity (Stice et al., 2011). During gastric distention, as it occurs during meal ingestion, obese subjects had increased fMRI activation than normal weight subjects in cerebellum and posterior insula and decreased activation in amygdala, midbrain, hypothalamus, thalamus, pons, and anterior insula (Tomasi et al., 2009b). Eighty-two % of the activation clusters from these studies on cue-reactivity occurred in regions functionally connected to the striatum (Fig 6). Consistent with these activation response PET studies measuring D2R with [<sup>18</sup>F]fallypride in obese subject showed an inverse correlation between ghrelin and D2R in dorsal and ventral striatum and in inferior temporal cortex, temporal pole, insula and amygdala (Dunn et al., 2012).

## Food perception and control of food intake

In normal conditions food intake is thought to be determined by both homeostatic (balance of energy and nutrients in the body) and non-homeostatic (pleasure of eating) factors, and brain DA has been associated with eating behaviors (Volkow et al., 2003b). Pharmacological fMRI studies have shown that hypothalamic activation predicts food intake when the plasma level concentration of PYY, a peptide hormone that provides a

physiological gut-derived satiety signal to the brain, is low and that activation in OFC striatum, VTA, SN, cerebellum, PFC, insula and cingulum can predict feeding behavior when PYY plasma level concentration is high (Batterham et al., 2007).

Event-related studies contrasting brain responses to sucrose taste and tasteless water showed that hunger was associated with fMRI activation in insula, thalamus, cerebellum, cingulum, SN as well as cortical brain regions whereas satiety was associated with deactivation in parahippocampus, hippocampus, amygdala and ACC (Haase et al., 2009). In this study the differential effect of hunger versus satiety on brain activation to taste stimuli (salty, sour, bitter, sweet) was stronger for males than for females, particularly in dorsal striatum, amygdala, parahippocampus and posterior cingulum (Haase et al., 2011). PET studies on inhibitory control in hunger conditions that used real food stimulation revealed that purposeful inhibition of the desire for food decreased glucose metabolism in amygdala, hippocampus, insula, striatum and OFC in men but not in women (Wang et al., 2009). A large fraction (> 31%) of the activation clusters occurred in regions functionally connected to both dorsal and ventral striatum (Fig 6, magenta).

## Eating disorders

Pharmacological studies have shown that disruption of DA signaling in the striatum can inhibit normal feeding in rodents (Sotak et al., 2005; Cannon et al., 2004) and that DA signaling modulates reactivity to food cues in humans (Volkow et al., 2002). PET studies of patients suffering from anorexia (over control of eating habits) showed higher than normal striatal D2R availability (Frank et al., 2005). In contrast, a recent study in non-obese patients with binge eating disorder showed that while they did not differ in D2R availability from controls they showed enhanced striatal DA release during food stimulation (Wang et al., 2011a). fMRI studies showed that when exposed to pleasant food pictures patients with binge eating disorder had stronger medial OFC responses than controls whereas patients with bulimia nervosa had stronger ACC and insula responses than controls (Schienle et al., 2009). During go/no-go inhibition, binge eating/purging female adolescents showed higher activation in temporal cortex, PFC and ACC than controls, and anorexia nervosa patients exhibited higher activation in hypothalamus and lateral PFC (Lock et al., 2011). Since only one of these clusters was located outside the striatal networks, these data also corroborates a role of cortico-striatal networks in eating disorders.

## Prefrontal regions

The prefrontal cortex and the striatum are inter modulated via cortico-striatal networks modulated by DA (Haber, 2003). The frontal cortex plays a complex role in cognition, including inhibitory control, decision making, emotional regulation, purposefulness, motivation and salience attribution among others. It has been hypothesized that dysfunctions in frontal regions might impair the control over compulsive drug intake (Kalivas, 2004; Volkow and Fowler, 2000), and that frontal cortex disruptions can have serious consequences in drug addiction (Volkow et al., 2006).

The frontal abnormalities revealed by our meta-analysis are consistent with the correlations between striatal D2R reductions and decreased metabolic activity in ACC, OFC and DLPFC previously reported for cocaine and methamphetamine abusers and alcoholics (Volkow et al., 1993; Volkow et al., 2001a; Volkow et al., 2007). Since ACC, lateral OFC and DLPFC are involved with inhibitory control and decision making (Goldstein and Volkow, 2002; Phan et al., 2002), this association suggests that loss of control over drug intake (Volkow et al., 1996a) could reflect improper DA-regulation in these frontal regions. This hypothesis is supported by studies that associated striatal D2R reductions and impulsivity scores in methamphetamine abusers (Lee et al., 2009) and rodents (Everitt et al., 2008) and

by those that linked ACC impairments with obsessive compulsive behaviors and impulsivity (Rolls, 2000). However, another possibility is that early abnormalities in frontal regions trigger repeated drug use and neuroadaptations that decrease striatal D2R. For instance, non-alcoholic individuals with a family history of alcoholism had higher than normal striatal D2R that was associated with normal metabolism in ACC, OFC and DLPFC, suggesting that that normal activity in prefrontal regions promoting inhibitory control and emotional regulation could be the mechanism that protected these subjects against alcohol abuse (Volkow et al., 2006). Interestingly, a recent study that compared sibling discordant for stimulant addiction showed significant differences in volume of medial OFC (Ersche et al., 2012), suggesting that these differences reflected the exposure to the drug rather than genetic vulnerability (Volkow and Baler, 2012).

## Temporal regions

The striatum is also connected with medial temporal lobe structures (hippocampus parahippocampal gyrus) that are essential for explicit memory but also for conditioning (Haber et al., 2006). Brain activation studies on reward-motivated learning have documented the involvement of medial temporal lobe structures in subsequent memory enhancements (Adcock et al., 2006; Wittmann et al., 2005). Thus drug cues could trigger craving memory activating learning circuits in the medial temporal cortex, and this enhanced activation of memory circuits could contribute to overcome the inhibitory control exerted by the prefrontal cortex in food and drug addiction (Volkow et al., 2003a). Our meta-analysis revealed that drug addiction, obesity and eating disorders are characterized by common brain activation abnormalities in medial temporal cortex (hippocampus, parahippocampal gyrus and amygdala), superior and inferior temporal cortices and posterior insula ( $P_{FWE} < 0.05$ ). The pattern of brain activation abnormalities partially overlapped the dorsal (40%), ventral (10%) and overlapping (48%) networks; only 2% of the abnormalities did not show overlap with the striatal networks. Our meta-analysis also revealed stronger abnormalities in medial temporal lobe structures in obesity and eating disorders compared to drug addiction (Fig 4). This suggests that these temporal regions are involved in the regulation of eating behaviors to a greater extent than in the regulation of drug intake. Specifically food intake is regulated both by homeostatic and reward pathways and while the homeostatic system modulates the reward pathway, it also modulates other brain regions through the various peripheral hormones and neuropeptides that regulate hunger and satiety. Indeed medial temporal regions (hippocampus, parahippocampus) express leptin receptors (Williams et al., 1999) and insulin-like growth factor receptors (Wilczak et al., 2000) as well as mRNA for the ghrelin receptor gene (Guan et al., 1997). Thus greater involvement of medial temporal cortices in obesity than in addiction is consistent with the involvement of hormones and neuropeptides that regulate food intake via the homeostatic pathway.

## Reward and habits

For both drug and food intake reward processes in ventral striatum initially drive the motivation to repeat the behavior. However with repeated exposure conditioned responses and learned associations shift the incentive motivation to the conditioned stimulus that predicts the reward. This transition, along with the associated enhanced motivation to do the behaviors necessary to consume the reward (drug or food), requires involvement of the dorsal striatum (Belin and Everitt, 2008). In addition, repeated exposure to associated pairing results in habits that can further drive behavior (including eating or taking drugs or alcohol) also involve dorsal striatal regions. However in reviewing the significant overlap between ventral and dorsal striatal connectivity it is therefore not surprising that studies show activation of ventral and dorsal striatum both with reward and conditioning. Similarly

while the dorsal striatum is predominantly associated with habits their formation may also require a progression from ventral to dorsal striatal regions (Everitt et al., 2008).

## Vulnerable networks in addiction and obesity

An important finding from this study is that functional abnormalities in food or drug addiction tend to occur in brain regions functionally connected to both dorsal and ventral striatum. These vulnerable regions are essential for cognitive control (anterior cingulum and supplementary motor area), reward and motivation (striatum and medial OFC) and reward-motivated learning (hippocampus and parahippocampal gyrus). The overlap of striatal connectivity patterns suggests that dopaminergic modulation from both dorsal and ventral striatum is essential in these regions, and their higher vulnerability suggests that food/drug addiction might alter delicate striatal modulation balance and brain activation in these regions.

## Limitations

Our meta-analysis includes studies on acute effects of drugs and food (cues), as well as studies on cognition (memory, attention, inhibition, decision-making) and emotion when drugs or food are not present. Since the direct and the long-term effects of food/drug addiction are different the participants in the former studies may or may not be the most vulnerable to brain changes. These could have increased the variability, limiting the interpretation of the results. The over expression of the medial temporal lobe abnormalities in obesity and eating disorders compared to those in drug addiction may reflect the severity of the disorders as it is not easy to equate intensity, duration or age of initiation of the disorder.

In summary this analysis of recent brain imaging studies on different types of drug addiction and disorders characterized by behavioral dyscontrol over a rewarding behaviors (eating) shows that there is an over representation of abnormal activation (both to cues and during cognitive tasks) that frequently occur in areas where there is overlap between the ventral and the dorsal striatal pathways. This corroborates in humans that both the ventral striatum (predominantly associated with rewards processing) and the dorsal striatum (predominantly associated with habits and rituals in addiction) are disrupted in addictive disorders (Wise, 2009) and that these abnormalities influence processing of rewards (drugs and food) reward-associated stimuli (cues) and cognitive processes necessary for self-control (executive function). However medial temporal cortical regions that are part of the dorsal striatal pathway showed greater vulnerability to obesity and eating disorders than to drug addiction (Fig 4), indicating that there are also distinct pattern of abnormalities between these set of disorders.

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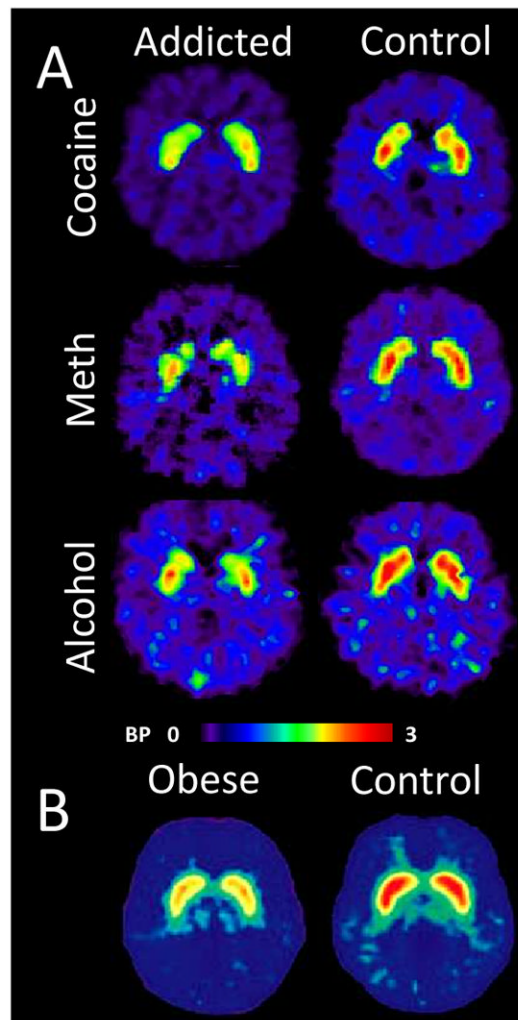
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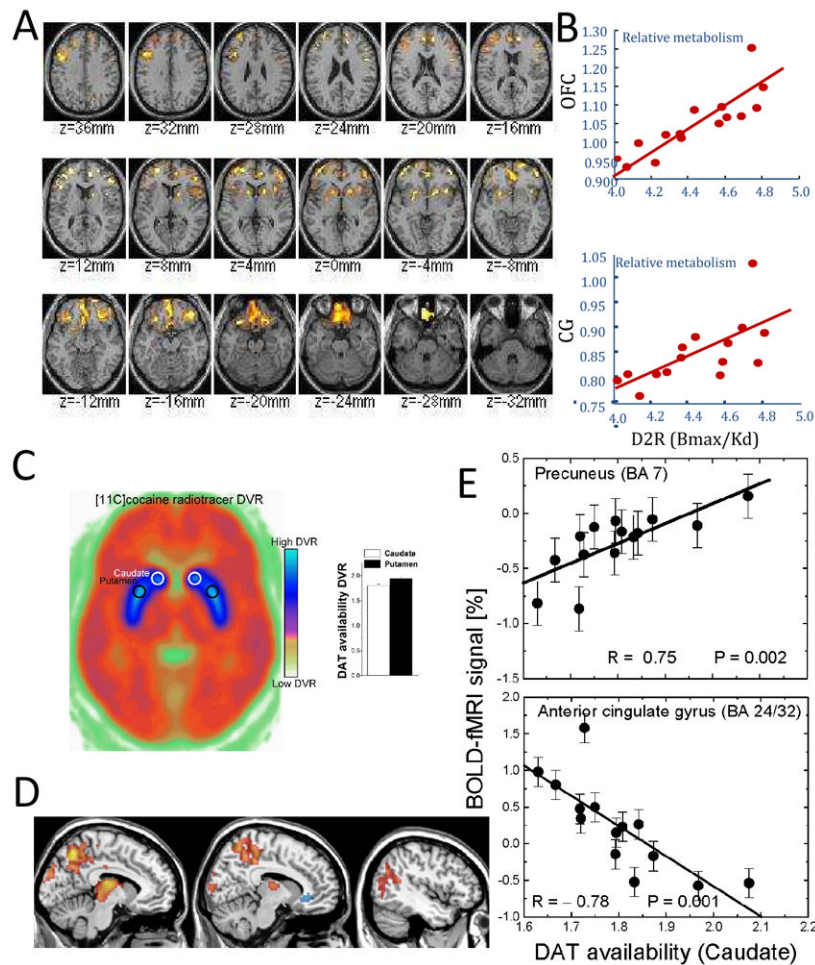
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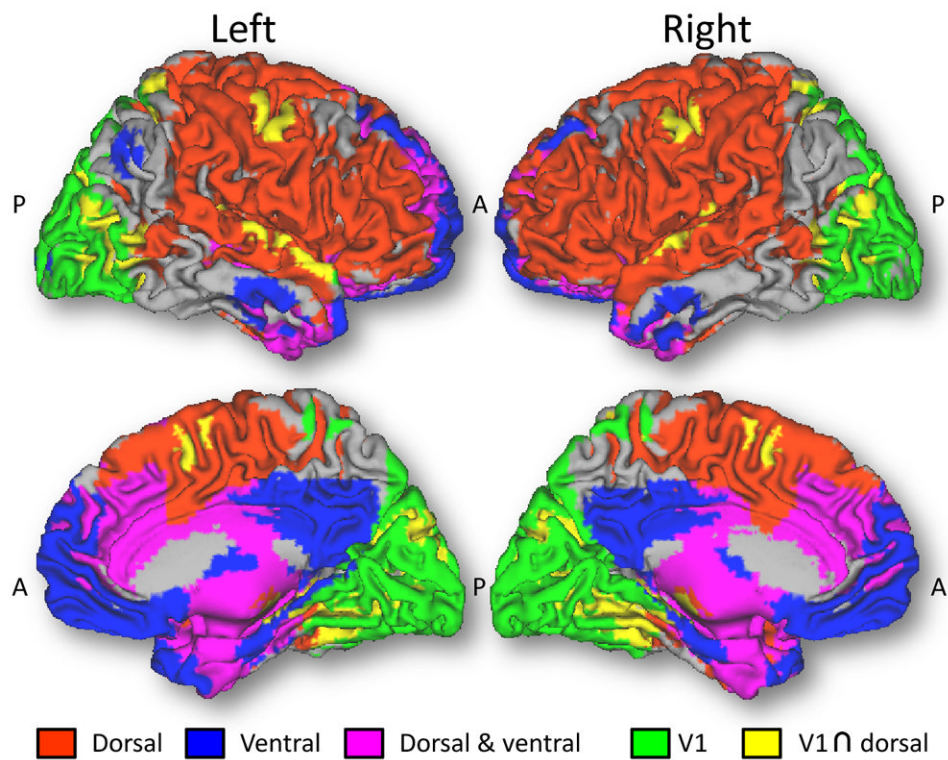
**Fig 1. Striatal DA neurotransmission abnormalities in addiction and obesity**

Positron emission tomography (PET) studies using [ $^{11}\text{C}$ ]raclopride, a 20 min half-life radiotracer that binds to DA D2/D3 receptors, have demonstrated reduced striatal binding potential (BP) in addicts to cocaine (Volkow et al., 1990; Volkow et al., 1997a; Volkow et al., 2002b; Martinez et al., 2009; Martinez et al., 2011), methamphetamine (Volkow et al., 2001a; Volkow et al., 2001c), alcohol (Volkow et al., 1996c; Martinez et al., 2005), heroin (Martinez et al., 2012), and nicotine (Brody et al., 2009) and also in morbidly obese subjects (Wang et al., 2001) when compared to healthy controls. Reduced striatal DA release has been found in alcoholics (Martinez et al., 2007) and cocaine (Martinez et al., 2007) addicts whereas higher striatal DA release was found in non-obese individuals suffering from a binge eating disorder (Wang et al., 2011a). Loss of striatal DA transporters has been reported in methamphetamine addicts (Volkow et al., 1999a; Volkow et al., 2001b; Volkow et al., 2001c).



**Fig 2.** **Association between brain metabolism and DA neurotransmission:** (A) Statistical axial maps of correlations between relative glucose metabolism and DA D2 receptors (D2R) in the striatum for subjects with a family history of alcoholism and (B) scatter plots exemplifying the linear association between relative metabolism in orbitofrontal cortex (OFC) and cingulate gyrus (CG) (vertical axis) and D2R in the striatum [data from (Volkow et al., 2006)]. **Association between brain activation and DA neurotransmission:** (C) Axial PET image at the level of the striatum (blue) showing the average availability DA transporters (DAT); (D) the correlation between DAT in striatum and fMRI activation during a visual attention task in 14 healthy humans; and (E) scatter plots exemplifying the correlation of DAT in striatum with the fMRI activation in precuneus and deactivation in ACC [data from (Tomasi et al., 2009a)].

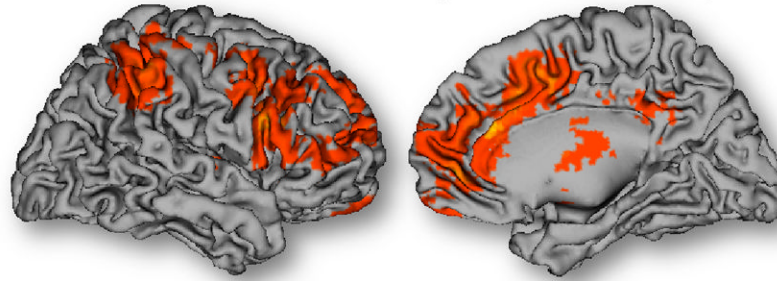




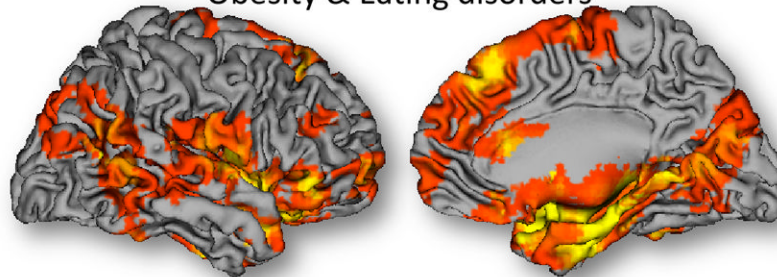
**Fig 3. RSFC networks from dorsal and ventral striatum**

Functional connectivity patterns from seed regions in dorsal (putamen;  $xyz = \pm 28, 1, 3$  mm) and ventral (nucleus accumbens;  $xyz = \pm 9, 9, -8$  mm) striatum. Red: brain regions functionally connected to the dorsal seed but not to the ventral seed; Blue: brain regions functionally connected to the ventral seed but not to the dorsal seed. Magenta: brain regions functionally connected to both ventral and dorsal seeds. The seed-voxel correlation approach with Gram-Schmidt orthogonalization proposed by Di Martino et al. was used to compute orthogonal functional connectivity patterns for the dorsal and ventral seeds in 499 healthy young adult subjects (188 males and 311 females) using resting-state datasets from the “1000 Functional Connectomes Project”.

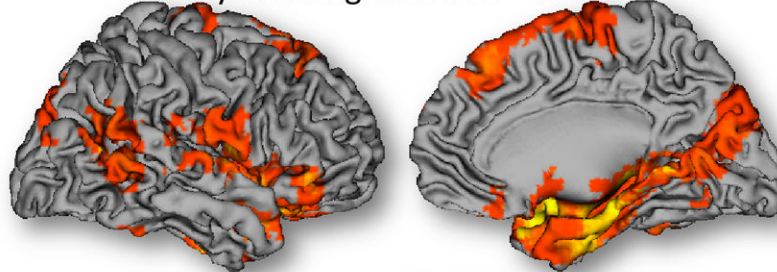
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Alcohol & cocaine & Methamphetamine & Marijuana



Obesity & Eating disorders



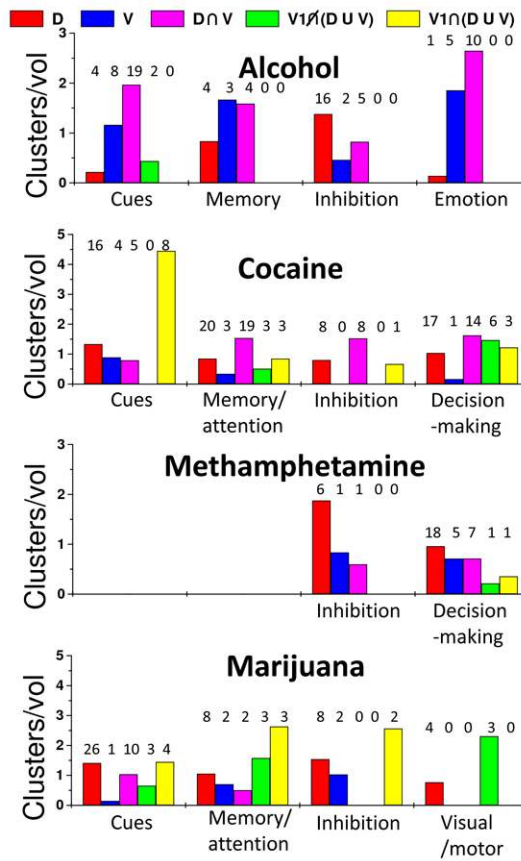
Obesity & Eating disorders > Addiction



T-score: 1.6  4

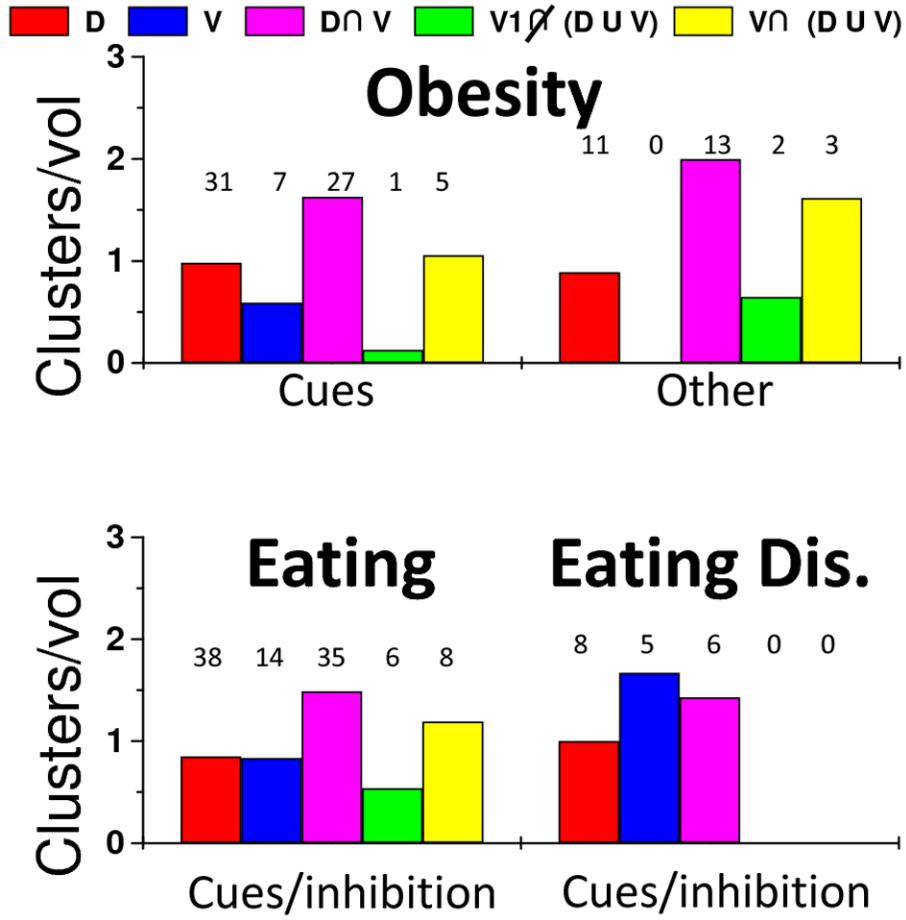
**Fig 4. Coordinate-based meta-analysis of neuroimaging studies on drug addiction, obesity and eating disorders**

Statistical significance of the activation likelihood estimation maps corresponding to the 44 studies on drug addiction (Tables 2-5), and the 13 studies on obesity and eating disorders (Tables 6-7). The activation likelihood estimation maps were computed using the coordinates of activation clusters reporting statistically significant increases or decreases in these populations with respect to matched controls ( $P_{FWE} < 0.05$ , corrected at the cluster level).



**Fig 5. Relative number of abnormal clusters per network: Drug addiction**

Cluster fractions normalized by network volume fractions were used as a metric to quantify how well the RSFC networks of the dorsal and ventral striatum included abnormal activation clusters reported in neuroimaging studies on drug addiction. Studies that used similar brain activation paradigms (horizontal axis) were grouped according to Tables 2-5. Numeric labels represent the number of clusters that overlapped the dorsal (D; red), ventral (V; blue) patterns and their overlap (D ∩ V; magenta), as well as those included in regions functionally connected with the primary visual cortex (V1) that did (gray) and did not (black) overlap the striatal networks.



**Fig 6. Relative number of abnormal clusters per network: Obesity and eating disorders**  
 Cluster fractions normalized by network volume fractions were used as a metric to quantify how well the RSFC networks of the dorsal and ventral striatum included abnormal activation clusters reported in neuroimaging studies on obesity and eating disorders. Studies that used similar brain activation paradigms (horizontal axis) were grouped according to Tables 6-7. Numeric labels represent the number of clusters that overlapped the dorsal (D; red), ventral (V; blue) patterns and their overlap (D U V; magenta), as well as those included in regions functionally connected to the primary visual cortex (V1) that did (gray) and did not (black) overlap the striatal networks.

**Table 1**

Summary of functional magnetic resonance imaging studies (conducted between 2001 and 2011) on effects of alcohol addiction on brain function that were included in Figs 4 and 5. Studies are grouped by stimulation paradigms into four major categories. Number of alcoholic (S) and control (C) subjects included and tasks are provided in addition to main results.

	Subjects	Task	Results
<b>Memory</b>			
Gundersen et. al; 2008	12S & 13C	Working memory	dACC; cerebellum ↓
Yoon et.al; 2009	12S & 12C	Word/face memory encoding	Temporal, parietal and cingulate cortices ↑
Vollstädt-Klein; 2010	11S & 19C	Spatial working memory	ACC ↑
<b>Cue-reactivity</b>			
George et. al; 2001	10S & 10C	Alcohol sip & cues	Left DLPFC and anterior thalamus ↑
Grusser et. al; 2004	10S & 10C	Visual alcohol cues	Striatum, ACC and medial PFC ↑
Filbey et. al; 2008	37S	Alcoholic taste	OFC, inf frontal, temporal, occipital, IPC, PCC, caudate and thalamus ↑
Vollstädt-Klein et. al; 2010	21S & 10C	Visual alcohol cues	Dorsal striatum ↑; ventral striatum and PFC ↓
Gilman et.al; 2012	14S & 14C	Emotional cues & IV ethanol	Nacc ↑ in social but not in heavy drinkers
<b>Inhibition</b>			
Heitzeg et.al; 2010	41S & 20C	Go/NoGo	OFC, VPFC and dmPFC ↑
Silven et. al; 2011	18S & 14C	Stroop interference	AC C and DLPFC ↑
<b>Emotion</b>			
Wrase et. al; 2007	16S & 16C	Emotion and monetary reward	Ventral and dorsal striatum ↓
Heitzeg et.al; 2008	22S & 6C	Emotion	OFC & insula/putamen ↑; Ventral striatum amygdala and dmPFC ↓

Arrows indicate activation increases (↑) or decreases (↓).



Table 2

Summary of functional neuroimaging studies (conducted between 2001 and 2011) on effects of cocaine addiction on brain function that were included in Figs 4 and 5. Studies are grouped by stimulation paradigm into five major categories. Number of cocaine (S) and control (C) subjects, tasks and imaging modality are provided in addition to main results.

	Subjects	Task; modality	Results
<b>Memory &amp; attention</b>			
Tomasi et al; 2007a	16S & 16C	Working memory; fMRI	Midbrain, thalamus, VPFC & limbic ↓; prefrontal & parietal ↑
Tomasi et al; 2007b	14S & 14C	Visual attention; fMRI	Thalamus, parietal and VPFC ↓; occipital & prefrontal ↑
Hester et al; 2009	16S	Working memory; fMRI	Cocaine cues -> Inf frontal, precuneus, PCC, occipital and cerebellum ↑
Moeller et al; 2010	19S & 14C	Working memory; fMRI	Striatum, Thalamus, PFC ↓
<b>Cue-reactivity</b>			
Goldstein et al; 2007b	14S	Drug/neutral word cues; fMRI	cdACC ↑; VPFC ↓
Goldstein et al; 2009a	17S & 17C	Drug/neutral word cues; fMRI	ACC ↓
Goldstein et al; 2009b	15S & 15C	Drug/neutral word cues; fMRI	Midbrain ↑
Volkow et al; 2010b	24S	Visual cocaine cues; PET MPH	Insula, OFC, Nacc and parahippocampus ↓ MPH attenuates this effect
Goldstein et al; 2010	13S & 14C	Drug/neutral word cues; fMRI	MPH normalizes ACC hypo-activation
Wilcox et al; 2011	14S & 16C	Visual cocaine cues; fMRI	ACC and PFC ↑
<b>Decision making</b>			
Bolla et al; 2003	13S & 13C	Gambling task; PET	OFC ↑; VPFC and DLPFC ↓
Goldstein et al; 2007a	16S & 13C	Monetary reward; fMRI	Cortical and subcortical regions ↓
Asensio et al; 2010	7S	M reward & D2R; PET & fMRI	Low striatal D2R; Thal ↓; ACC ↑
<b>Inhibition</b>			
Hester et al; 2004	15S & 15C	Go/no go task; fMRI	ACC and right PFC ↓
Bolla et al; 2004	13S & 13C	Stroop interference; PET	PFC ↑; ACC ↓
Connolly et al; 2011	18S & 9C	Go/NoGo; fMRI	PFC; inferior frontal, cingulate and cerebellum ↑
<b>Other (Stop signal &amp; molecular targets)</b>			
Gorelick et al; 2005	17S & 16C	mu-opioid receptor; PET	ACC and anterior frontal ↑ (elevated after 12 weeks abstinence)
Li et al; 2008	15S & 15C	Stop signal task; fMRI	VPFC ↓
Ghitza et al; 2010	25S	mu-opioid receptor; PET & CBT	VPFC and PFC ↑ mu-opioid receptor predict treatment outcome

Arrows indicate activation increases (↑) or decreases (↓).

**Table 3**

Summary of fMRI studies (conducted between 2001 and 2011) on effects of methamphetamine addiction on brain function that were included in Figs 4 and 5. Studies are grouped by stimulation paradigm into two major categories. Number of methamphetamine (S) and control (C) subjects and tasks are provided in addition to main results.

	Subjects	Task	Results
<b>Decision-making</b>			
Paulus et. al; 2002	10S & 10C	Two-choice prediction	DLPFC, VPFCC↓
Paulus et. al; 2003	14S & 14C	Two-choice prediction	OFC, DLPFC, ACC and superior parietal ↓
Paulus et. al; 2005	18S & 22C	Two-choice prediction	Relapsers: Insula, PCCC↓
Monterosso et.al; 2007	12S & 17C	Delay discounting	DLPFC, IPS↓
Paulus et. al; 2008	12S & 12C	Two-choice prediction	Insula (correlations with performance)
Hoffman et. al; 2008	19S & 17C	Delay discounting	Precuneus, caudate, DLPFC, ACC ↓
<b>Inhibition</b>			
Leland et. al; 2008	19S & 19C	Go/NoGo	ACC (correlations with false alarm rate)
Salo et. al; 2009	12S & 16C	Stroop interference	Right PFC↓

Arrows indicate activation increases (↑) or decreases (↓).

**Table 4**

Summary of functional magnetic resonance imaging studies (conducted between 2001 and 2011) on effects of marijuana addiction on brain function included in Figs 4 and 5. Studies are grouped by stimulation paradigm into four major categories. Number of marijuana (S) and control (C) subjects and tasks are provided in addition to main results.

	Subjects	Task	Results
<b>Memory &amp; attention</b>			
Chang et. al; 2006	24S & 19C	Visual attention	PFC, parietal and vermis↓; frontal, parietal & occipital ↑
Padula et.al; 2007	17S & 17C	Spatial working memory	Striatum, insula, precuneus and superior parietal ↑
<b>Cue-reactivity</b>			
Filbey et. al; 2009	31S & 21C	Tactile drug cues	VTA, thalamus, ACC, insula and amygdala ↑
<b>Inhibition</b>			
Tapert et. al; 2007	16S & 17C	Go/NoGo	DLPFC, parietal, occipital ↑
Roberts et. al; 2010	20S & 20C	Go/NoGo	Prefrontal, parietal, temporal and cingulate ↑
<b>visual &amp; motor</b>			
King et. al; 2011	30S & 30C	Finger tapping & checkerboard	Premotor and visual cortex↓

Arrows indicate activation increases (↑) or decreases (↓).

**Table 5**

Summary of functional magnetic resonance imaging studies (conducted between 2001 and 2012) on effects of obesity on brain function included in Figs 4 and 6. Studies are grouped by stimulation paradigm into two major categories. Number of obese (S) and control (C) subjects and tasks are provided in addition to main results.

	Subjects	Task	Results
<b>Cue reactivity</b>			
Rothmund et. al; 2007	13S & 13C	High/low calorie visual cues	striatum, HIPPO, INST <sup>↑</sup> (high calorie)
Stoeckel et. al; 2008	12S & 12C	High/low calorie visual cues	OFC, AMY, Nacc, VPFC, INS, ACC, GP, striatum, HIPPO <sup>↑</sup>
Wallner-Liebmann et al; 2010	12S & 12C	High/low calorie visual cues	Insulin plasma level was correlated with HIPPO activation
Dimitropoulos et. al; 2012	22S & 16C	High/low calorie visual cues	temporal and limbic <sup>↑</sup> after eating
<b>Other (Intake, reward, gastric distention)</b>			
Slice et. al; 2008	76S	Food intake & TaqIA A1 gene	TaqIA: no AI > AI: BMI correlate with striatal activation
Tomasi et. al; 2009b	24S	Gastric distention	Cerebellum and insula <sup>↑</sup> ; midbrain, hypothalamus, amygdala <sup>↓</sup>
Slice et. al; 2011	35S & 25C	Reward	Adolescents with high risk for obesity: caudate <sup>↑</sup>

Arrows indicate activation increases (<sup>↑</sup>) or decreases (<sup>↓</sup>).

**Table 6**

Summary of functional magnetic resonance imaging studies (conducted between 2001 and 2011) on effects of eating and eating disorders on brain function included in Figs 4 and 6. Number of patients (S) and control (C) subjects and tasks are provided in addition to main results.

	Subjects	Task; modality	Results
<b>Eating</b>			
Batterham et. al; 2007	8C	PYY/saline infusion; fMRI	Low PYY: HyTHA↑; high PYY: OFC↑
Haase et. al; 2009	18C	Taste paradigm; fMRI	Hunger: INS, THA, SN, pHipp, Hipp, AMY, ACC↑
Wang et. al; 2009	23C	Inhibition of food stimulation; PET	Males > females: AMY, HIPPO, INS, OFC and striatum ↓
Haase et. al; 2011	21C	Taste paradigm; fMRI	Males > females: Limbic regions, insula, OFC, and cerebellum↑
<b>Eating Disorders</b>			
Schienle et. al; 2009	31S & 36C	Food picture paradigm; fMRI	OFC, ACC and Insula↑
Lock et. al; 2011	27S & 13C	Go/NoGo; fMRI	Binge-eaters > control & anorexia: ACC, temporal, HyTHA and DLPFC↑

Arrows indicate activation increases (↑) or decreases (↓).



Table 7

Coordinate-base meta-analysis of neuroimaging studies on drug addiction, obesity and eating disorders published between 2001 and 2011 (Tables 2-7). MNI coordinates (x, y, z) and statistical significance (T-score) for clusters that demonstrated significant abnormalities (increases or decreases with respect to matched controls) across subjects ( $P_{FWE} < 0.05$ , corrected for multiple comparisons at the cluster level with the random field theory using a family-wise error) and for their functional connectivity with dorsal (D) and ventral (V) striatum.

Region	BA/nucleus	x[mm]	y[mm]	z[mm]	k	T	Functional Connectivity		
							V[T]	D[T]	D>V[T]
Addiction (Alcohol & Cocaine & Methamphetamine & Marijuana)									
<b>Anterior cingulum</b>	32	-12	30	24	841	3.52	14	26	5
Anterior cingulum	24	-3	30	21		3.45	20	16	-2
Middle cingulum	24	-9	12	36		3.37	NS	42	30
Eating disorders & Obesity									
<b>Putamen/posterior insula</b>		-30	-15	12	7440	6.87	NS	56	42
Hippocampus	20	-30	-9	-15		6.47	16	37	15
Putamen/posterior insula		27	3	-6		6.02	14	76	55
<b>Superior medial frontal</b>	9	0	36	42	334	3.91	NS	2	NS
Superior medial frontal	8	12	27	57		3.87	NS	14	4
Supplementary motor area	8	-3	24	60		3.8	NS	6	4
<b>Superior frontal</b>	11	24	57	3	114	3.81	6	NS	-10
Middle frontal	10	36	60	6		3.15	NS	NS	-6
Superior medial frontal	10	9	60	3		3	17	-9	-23
<b>Inferior temporal</b>	37	48	-48	-24	131	3.53	-9	-13	-6
Cerebellum		36	-57	-39		3.43	7	6	3
Cerebellum		27	-60	-33		3.18	4	13	8
<b>Middle Temporal</b>	21	45	-48	6	245	3.16	NS	10	16
Eating disorders & Obesity > Addiction									
<b>Putamen/posterior insula</b>		-30	-15	12	513	6.03	0	56	42
Hippocampus	20	-33	-6	-18	0	5.32	12	31	11
Fusiform	20	-36	-15	-24	0	4.74	9	13	NS
<b>Putamen</b>		27	3	-6	582	4.92	14	76	55
Hippocampus	20	39	-3	-18	0	4.87	3	21	11

Region	BA/nucleus	x[mm]	y[mm]	z[mm]	k	T	Functional Connectivity		
							V[T]	D[T]	D>V[T]
Parahippocampus	30	21	-33	-9	0	4.39	4	5	NS
<b>Superior temporal</b>	41	-39	-39	6	217	4.34	NS	17	15
Supramarginal	48	-54	-39	27	0	4.34	-10	28	25
Middle temporal	42	-54	-42	12	0	4.08	-5	22	17

k: cluster size (3-mm isotropic voxels). Statistical model one-way analysis of variance.