Addiction Biology

BRIEF REPORT

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Overlapping decline in orbitofrontal gray matter volume related to cocaine use and body mass index

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ABSTRACT

Loss of control over hedonically motivated actions is a defining component of impulse control disorders, such as drug dependence and the proposed 'food addiction' model of obesity. Devolution from goal-directed to compulsively maintained behaviors is partially attributed to abnormalities in the orbitofrontal cortex, an area critical in reward valuation. In the current study, overlapping reductions in orbitofrontal gray matter volume relating to body mass index were seen in healthy control and cocaine-dependent individuals, as well as in relation to duration of cocaine abuse, providing support for a shared neuropathology between the two conditions potentially related to dysfunctional reward-seeking behavior.

Keywords Body mass index, cocaine, orbitofrontal cortex.

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The orbitofrontal cortex (OFC) is critically involved in integrating emotion and behavior, e.g. reward valuation (Levy & Glimcher 2012). These abilities comprise goal-directed behavior, actions carried out to achieve an objective. Dysfunction in the OFC can impair these abilities, resulting in behavior that becomes compulsive, maintained despite attempts to stop or a shift in desired outcome. This overlap between reward valuation and motivated behavior makes the OFC a key target for impulsive/compulsive disorders, most notably drug addiction and compulsive overeating leading to obesity, as in cases of binge eating. Both conditions can be thought of as behaviors that were originally hedonically motivated but devolved into undesirable habits, and as such, both have been linked to variations in this region.

Gray matter reductions in the OFC have been seen in obese (Pannacciulli *et al.* 2006) and cocaine-dependent individuals (Ersche *et al.* 2011), and corresponding impairments in associated cognitive processes are present in both groups (Verdejo-Garcia *et al.* 2006; Gunstad *et al.* 2007). These neurobiological commonalities have led to the discussion of classifying overeating leading to obesity, particularly in instances of binge eating, as an addictive disorder (Smith & Robbins 2013). However, despite the reported overlap between these behavioral and structural deficits, no direct comparisons of cortical volume between the two conditions have been made.

We compared structural magnetic resonance imaging scans of a previously published sample of 60 healthy control volunteers with body mass indexes (BMI)s ranging from normal weight to obese (17.8–33.5, mean = 25.5) and 60 cocaine-dependent individuals with similar BMIs (16.6–32.7, mean = 24.2) and a span of 31 years of cocaine use (mean = 9.8 years) (Ersche *et al.* 2011). We hypothesized there would be overlapping regions of OFC volume decline corresponding to years of cocaine use and BMI in these individuals. To address this, gray matter data were newly processed to take into account the effects of BMI and cocaine use on brain volume, variables not previously modeled, focusing on the a priori designated region of the OFC. Control and cocaine-dependent participants did not differ in age, gender or BMI. Body weight from two controls was missing, resulting in 118 total participants.

We used voxel-based morphometry analysis, processed in FSL-v1.1 (Analysis Group, FMRIB, Oxford, UK) and statistically analyzed using CamBA-v2.3.0 (Cambridge Brain Activation; University of Cambridge,

Cambridge, UK) (see Supporting Information Appendix S1). BMI scores were regressed against gray matter volume within the OFC in both groups, and years of cocaine use were regressed against OFC gray matter in cocaine users, identifying correlations between OFC volume and these variables. Groups were analyzed separately to account for previously discovered differences in brain structure (Ersche *et al.* 2011). We compared affected areas, identifying shared regions of decline associated with both years of cocaine use and BMI, as well as comparing OFC volume between groups.

In control participants, four significant clusters negatively correlated with BMI bilaterally throughout the OFC ($r = -0.688$, $P < 0.001$; Fig. 1), whereas in cocaine users, two regions in the right OFC negatively correlated with BMI ($r = -0.624$, $P < 0.001$; Supporting Information Table S1). These areas overlapped in the right middle orbitofrontal gyrus, superior orbitofrontal gyrus and gyrus rectus (Brodmann Areas 10,11,25). Additionally, OFC volume negatively correlated with years of cocaine use in two bilateral clusters ($r = -0.705$, $P < 0.001$). The cocaine-related decline in gray matter overlapped with BMI-related reductions bilaterally in the superior orbitofrontal gyrus, middle orbitofrontal gyrus and left gyrus rectus (Brodmann Area 11).

In cocaine users, we observed a significant correlation between gray matter volume decline associated with both increased BMI and years of cocaine use ($r = 0.354$, $P = 0.006$; Supporting Information Fig. S1); however, cocaine use and BMI itself did not correlate ($r = -0.127$, $P = 0.338$). This suggests an overlapping reduction related to these variables, their effects on the brain potentially impacting the same regions.

When directly comparing total OFC volume between the two groups, cocaine-dependent individuals had significantly less gray matter than controls ($t = 7.694$, $P < 0.001$). This effect remained significant after including only overweight controls ($n = 34$) and lean cocaine-dependents ($n = 37$; $t = 4.097$, $P < 0.001$). However, the steepness of the linear regressions between the key variables (gray matter and BMI, and gray matter and cocaine years) did not significantly differ. This suggests that although the most pronounced effects on orbitofrontal structure were associated with cocaine use, this is perhaps more indicative of underlying differences rather than an accumulated effect of stimulant use.

Years of cocaine use and increased BMI both negatively correlated with OFC gray matter volume in healthy control and cocaine-dependent individuals. Additionally, select OFC regions showed decreases relating to both

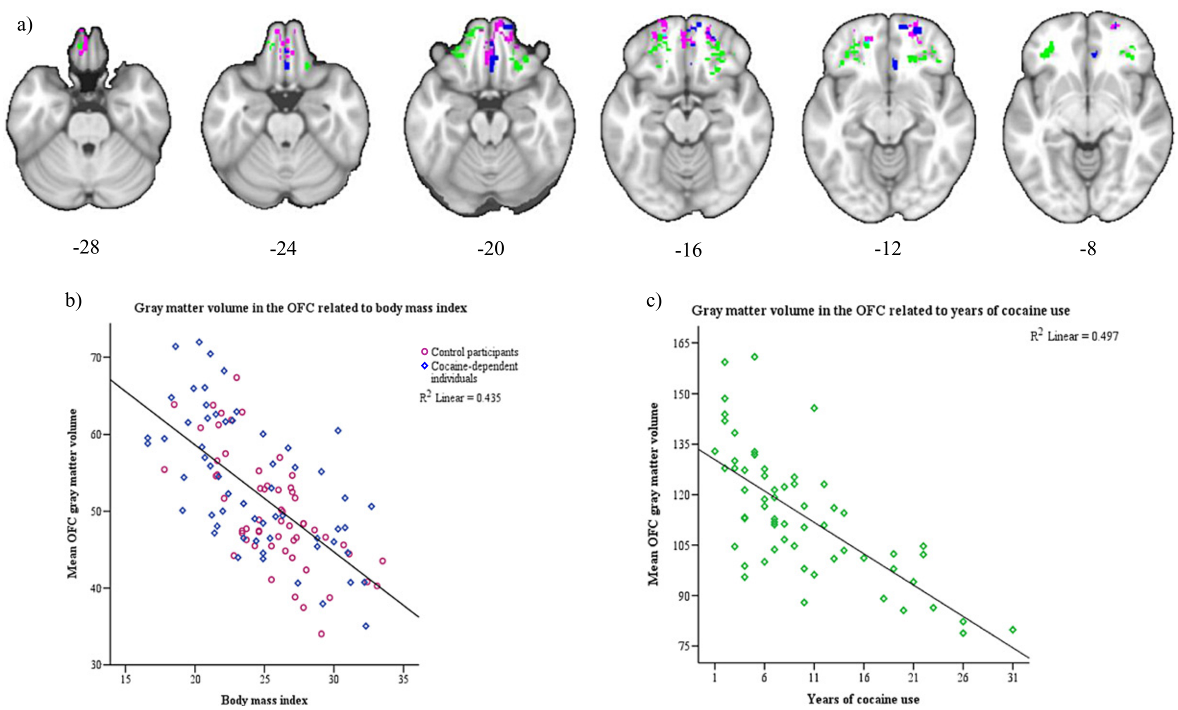

Figure 1 (a) Overlapping regions of orbitofrontal cortex (OFC) gray matter volume decline among healthy control and cocaine-dependent individuals, corresponding to increased body mass index (BMI) and years of cocaine use. Magenta—clusters for reduced gray matter with BMI in controls; Blue—clusters for reduced gray matter with BMI in cocaine users; Green—clusters for reduced gray matter with years of cocaine use; Cyan—overlapping voxels from magenta and green. (b) Correlation between OFC gray matter volume reductions and BMI in both healthy control and cocaine-dependent individuals. Participant groups were analyzed separately to account for underlying differences in structure volume and were overlaid to demonstrate similar trends of decreased OFC volume in association with increased BMI. (c) Correlation between OFC volume reductions and years of cocaine use

variables, suggesting an overlap between volume reductions associated with overconsumption of food and drugs of abuse. This decline may reflect underlying differences in the OFC's role in goal-directed behavior present in both groups, as both begin as motivated behaviors (taking drugs or eating high-caloric foods for hedonic reasons), but in some instances can become compulsive, habitually maintained after the behavior is no longer desired. Associated impairments in inhibitory control and decision making may also be implicated in OFC volume reduction.

Importantly, these participants were not recruited on the basis of their BMIs, and their range from normal weight to obese was representative of the general population. This demonstrates that the relationship with gray matter volume is present even in persons of normal or slightly elevated body weight and is not limited to obese individuals. Although these findings provide some support for the argument that some individuals who overeat may display characteristics similar to those of addictive disorders, this comparison has its limitations and is currently under debate (Ziauddeen, Farooqi & Fletcher 2012).

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Authors Contribution

DGS had the idea for this study, contributed to the design and data analysis, interpreted the data and drafted the manuscript. PSJ and GBW contributed to the data analysis. ETB and TWR provided funding for the study, contributed to the study design and reviewed the manuscript. KDE contributed to the design, acquired the data, contributed to the analysis and the interpretation of the data, and reviewed the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 The Supplementary Information contains an elaboration on the role of the orbitofrontal cortex in goal-directed behavior. Neuroimaging acquisition and analysis procedures for the current study are also detailed in this section. A table containing all of the voxel coordinates of the orbitofrontal areas identified as having volume reductions in the current study is included. Finally, a figure displaying the correlation between volume loss attributed to cocaine use and body mass index in the cocaine-using group is also shown

Figure S1 Correlation between orbitofrontal cortex (OFC) gray matter volume that is associated with years of cocaine use and OFC volume related to body mass index (BMI) in cocaine-dependent individuals. A significant positive correlation suggests there is a relationship between the effect these two variables (years of cocaine use and BMI) have on the OFC, and also confirms that there is a stable relationship in OFC volume within an individual in relation to these two separate variables

Table S1 Voxel coordinates of orbitofrontal clusters associated with either body mass index (BMI) or years of cocaine use in control and cocaine-dependent individuals. Regions overlapping, or nearly overlapping – no more than four voxels away in any direction, are highlighted as follows

