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Magnetic resonance imaging structural alterations in brain of alcohol abusers and its association with impulsivity

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ABSTRACT

Despite the suggestion that impulsivity plays a central role in the transfer from a recreational drug use to a substance use disorder, very few studies focused on neurobiological markers for addiction. This study aimed to identify volumetric alterations in a sample of patients with mild alcohol use disorder with a short history of alcohol use, compared with a control group, and also focused on its association with impulsivity levels. Most magnetic resonance imaging studies have focused on severe alcohol use disorder, formerly called alcohol-dependent patients, showing alcohol-related structural alterations and their association with alcohol use history variables but not with personality parameters like impulsivity. Our hypothesis is that our group of alcohol users may already display structural alterations especially in brain regions related to inhibitory control like medial-prefrontal regions, and that those structural alterations could be more associated to personality traits like impulsivity than to drug use variables. Our results clearly demonstrate that our population showed lower regional grey and white matter volumes in the medial-prefrontal and orbitofrontal cortices, as well as higher regional white matter volume in the ventral striatum and the internal capsule. Volumetric alterations were associated to the Barratt's impulsivity score: the more impulsive the subjects, the lower the medial-prefrontal cortex grey matter volume.

Keywords Alcohol, impulsivity, magnetic resonance imaging.

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INTRODUCTION

Alcohol abuse is a worldwide major public health problem with a long history but also with a large current impact. It is causing huge problems in the family and personal lives of drug users while treatment approaches are not of great effectiveness yet (EMCFDAA EMCFDADA 2009; SAMHSA 2010).

Neuroimaging studies show much evidence of long-term alcohol use alterations of brain structure and function (Pfefferbaum & Sullivan 2005). Many studies using non-biased automated voxel-based morphometry (VBM) and other volumetric magnetic resonance imaging (MRI) techniques show volumetric reductions of frontal, temporal and parietal cortices, insula, thalamus, cerebellum, hippocampus, amygdala, and the prefrontal cortex (PFC) including ventromedial PFC and orbitofrontal cortex (OFC), as well as white matter (WM) losses in brain stem, cerebral peduncles and periventricular WM in severe alcohol users (de Bruin *et al.* 2005; Monnig *et al.* 2013). More critically, several of these grey and white matter alterations seem to be associated with toxicological variables like the amount of lifetime alcohol use and time of alcohol use (Fein *et al.* 2006; Taki *et al.* 2006), and with impairment of cognitive functions (Jang *et al.* 2007). These associations with toxicological variables may account for the role of neurotoxicity and the subsequent neuronal loss (Harper 1998).

It is noteworthy that all above-mentioned studies only included alcohol-dependent patients suggesting that the neurotoxic effects of long-term ethanol intake on central nervous system are the main responsible for the observed

brain attrition. However, there is an increasing body of knowledge suggesting that previous brain alterations may predispose to alcohol use disorder. For instance, children exposed to alcohol during the fetal life display lower brain volumes compared with control children, but more interestingly, the former group showed a positive correlation between improved cognitive function and increased WM volume over time, while no such relationships were seen in controls (Gautam *et al*. 2014). This notion, combined with the fact that some personality traits such as impulsivity may be predisposing factors to addiction (Verdejo-Garcia, Lawrence & Clark 2008), raises the possibility that part of the grey matter (GM) and WM abnormalities found in alcohol-dependent subjects may relate to certain personality traits, such as impulsivity, present before the onset of alcohol abuse.

Contrary to alcohol dependence, the DSM-IV-TR described alcohol abuse diagnosis with different criteria excluding tolerance and abstinence, although DSM-V does not separate between alcohol abuse disorder and alcohol dependence, both now grouped from mild to severe alcohol use disorder. Clinicians often reported that alcohol abusers showed a compulsive alcohol drinking as a 'binge drinking' and high levels of impulsivity, suggesting an inhibition deficiency problem instead of a physical dependence. Impulsivity is now widely viewed as a multidimensional construct consisting of a predisposition towards rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions (Moeller *et al*. 2001). High impulsivity levels may cause problems in social life and predispose to a range of psychiatric disorders including addiction, now also revised in DSM-V.

In line with this, higher impulsivity rates had been observed in alcohol-dependent groups using auto-reported measures of impulsivity like Barratt Impulsivity Scale (BIS) (Patton, Stanford & Barratt 1995), Urgency, (lack of) Premeditation, (lack of) Perseverance, and Sensation Seeking (UPPS) and Sensation Seeking Scale (SSS) (Whiteside & Lynam 2003; Mitchell *et al*. 2005), as well as worse performance in objective measures of impulsivity like Continuous Performance Test, Go–No Go, stop signal, and delay discounting tests (Vuchinich & Simpson 1998; Petry 2001; Bjork *et al*. 2004; Kamarajan *et al*. 2005; Mitchell *et al*. 2005; Goudriaan *et al*. 2006), or worse risk taking and decision-making tests (Mazas, Finn & Steinmetz 2000; Bjork *et al*. 2004; Fein, Klein & Finn 2004; Dom *et al*. 2006).

In addicted individuals, continued use of stimulants is thought to further exacerbate impulsive traits (Ersche *et al*. 2010), and to possibly modify its neural underpinnings. In fact, the association between trait impulsivity levels and striatal dysfunction is stronger in methamphetamine-dependent individuals compared with healthy controls (Lee *et al*. 2009) and significant correlations between particular aspects of trait impulsivity (impulsive reward seeking) and, as mentioned above, GM reductions in cocaine-dependent subjects have been described (Verdejo-García *et al*. 2012), while other studies failed to find this correlation (Ersche *et al*. 2011). As far as we know, no study has addressed this question in alcoholic patients. Therefore, more studies are needed to specifically explore if, as expected, impulsivity is linked to GM or WM volume alterations in fronto-striatal regions in alcohol abusers.

It has been suggested that this high impulsivity may stem from the brain neurobiological effects of drug intake (consequence) or, conversely, may be a premorbid deficient inhibitory control (cause), predisposing individuals towards early recreational experiences with drugs of abuse (Verdejo-Garcia *et al*. 2008; de Wit 2009). Although these two approaches are not mutually exclusive, the characterization of vulnerability markers for addiction is essential for detecting at-risk individuals, and in order to implement early detection and treatment intervention and thereby avert the devastating effects of long-term use. Within this framework, this study aimed to examine possible relationships between structural brain alterations and impulsivity in a group of alcohol abusers, according to DSM-V: patients with mild-to-severe alcohol use disorder, with a short alcohol use history, and therefore, with lower lifetime neurotoxic alcohol impact compared with that of chronic or long-term alcohol use disorder individuals. The study aimed to: (1) show volumetric differences in a group of alcohol abusers compared with a control group; and (2) examine potential associations of these volumetric differences with both impulsivity and alcohol use variables.

METHODS

Subjects

Twenty-four patients with alcohol use disorder (formerly recruited as alcohol abusers, according to DSM-IV) and 24 healthy control subjects, all males, participated in the study. Eligibility for the study was initially established via a clinical interview screening that primarily assessed drug. Patients meeting the DSM-IV criteria for alcohol abuse (but not for alcohol dependence) according to the Structured Clinical Interview (SCID) were recruited from a Community Alcoholism Unit among those who asked for treatment between January 2009 and July 2010. Age range was between 18 and 55 years old. Exclusion criteria included any other Axis I psychiatric disorder including dependence of alcohol or other substance (except for nicotine), presence of structural brain abnormalities, any systemic or neurological disease, claustrophobia or any

other contraindication for MRI. Subjects refrained from alcohol use at least during 3 days prior to the scanning procedure.

Procedure

The study consisted of two sessions. General data were collected in the first session including demographic, drug use history, impulsivity and drinking-related compulsivity psychometric measures like Barratt's Impulsivity Scale (BIS-11) (Patton *et al.* 1995) and Obsessive Compulsive Disorder Scale (OCDS) (Anton, Moak & Latham 1995), respectively. After a maximum of 7 days, a second session took place at the hospital to perform a general neuropsychological assessment of verbal memory and fluency and executive functioning as well as motor skills of all participants. After 15 minutes of rest, subjects underwent the MRI session.

In accordance with the local institutional review board that approved the study, subjects provided written consent for their participation in the study; afterwards they were fully informed of all procedures and risks associated with this MRI study.

MRI acquisition and analysis

The structural data were collected on a 1.5 T Siemens Symphony scanner (Maestro Class, Siemens, Erlangen, Germany) equipped with a head volume coil. High-resolution anatomical T1-weighted volume scans were obtained with a standard three-dimensional Fast Spin Gradient sequence (FSPGR) with 160 contiguous sagittal slices of 1.5 mm thickness across the entire brain, matrix = 256 × 256, TE/TR = 4.2/11.3 ms, field of view = 240 mm, flip angle = 15° and read bandwidth = 12.5 kHz.

All MRI data were processed using Statistical Parametric Mapping (SPM5) (Wellcome Department of Cognitive Neurology; http://www.fil.ion.ucl.ac.uk/spm/) and a voxel-based morphometry (VBM5) toolbox (http://www.dbm.neuro.uni-jena.de/vbm/) in MATLAB v.7.0 (The Mathworks, Natick, MA, USA) using the VBM-optimized protocol (Good *et al.* 2001). Briefly, study-specific templates of grey and white matter were created for automated segmentation and spatial normalization of the initial images. Then, the original T1-weighted images were segmented into GM and WM images that were then spatially normalized to the same stereotactic space (i.e. the customized template) through 16-parameter affine and non-linear transformations, and medium regularization. Then, the normalization parameters were applied to the original T1-weighted images and a second segmentation was performed to the normalized images followed by an additional Hidden Markov Random Field model (weighting of 0.3) to minimize noise by removing the isolated voxels that may have been misclassified. Next, a Jacobian modulation was applied to the segmented images by multiplying the voxel intensities by the Jacobian determinants derived from the non-linear component of the spatial normalization step (Ashburner & Friston 2000; Good *et al.* 2001). Modulated data were used to test for regional differences in tissue volume (Ashburner & Friston 2000; Good *et al.* 2001). This procedure was carried out for both GM and WM images. Finally, both segments (GM and WM) of all subjects were smoothed using a full width at half maximum Gaussian kernel of 8 mm.

Between-group analysis

Between-group comparison of GM and WM was carried out on a voxel basis using the general linear model (Friston *et al.* 1995). To test hypotheses with respect to regionally specific group effects, the smoothed GM and WM images were compared by using two linear contrasts (more or less GM or WM in patients than in controls) (Friston *et al.* 1995).

Age and total GM or WM volume were entered as covariates in an analysis of covariance to focus on the regional differences in GM or WM, respectively. The resulting set of voxel values for each contrast constituted a statistical parametric map of the *t*-statistic [SPM (t)]. For controlling Type I error, we accepted as significant only clusters of a cluster-corrected $P < 0.05$ with the extent threshold consisting of 50 voxels per cluster.

Bivariate and partial correlations were used to examine the relationships between impulsivity (including data of all subjects) or drug use variables (only including patients' group) and the averaged beta value of voxels of the clusters showing between-group local volume differences (GM and WM) ($P < 0.05$).

RESULTS

Psychological and general data

Table 1 shows all neuropsychological, personality, volumetric and general data of the two groups and its comparison. There were no significant differences in age or race but the groups were not matched on years of education so this variable was included as covariate in subsequent analyses together with total GM.

No differences were observed in motor and reading skills, colour sensitivity, verbal memory, Stroop interference, phonetic fluency, mental flexibility and executive functioning. However, patients displayed lower verbal phonetic and semantic fluency ($P = 0.04$ and $P = 0.01$, respectively) than controls. As expected, alcohol group displayed higher scores than controls in OCDS and all three BIS-11 subscales.

Table 1 Mean values and SD of general volumetric, impulsivity and neuropsychological data, and between-group comparison using *t*-test or χ^2.

		Controls			*Patients*			
		Mean		*SD*	*Mean*		*SD*	P-*value*
General	Age (years)	31,91	±	9,34	35,62	±	4,81	0,121
	Years of education	15,60	±	3,14	13,06	±	3,63	0,030
	Race (Caucasian/Hispanic)	23	/	1	20	/	4	0,156
	Age at first use (years)	15,60	±	2,20	16,21	±	6,72	0,790
	Grams of pure alcohol per session	12,90	±	23,79	179,60	±	63,79	<0,001
	Last use (days)	24,52	±	43,56	40,88	±	29,07	0,382
	Alcohol craving (EMCA)	14	±	2,48	18,33	±	8,06	0,07
	Years of abuse	NA			4,71	±	2,93	NA
Volumetric	Grey matter (mm^3)	692,53	±	66,92	644,52	±	52,05	0,007
	White matter (mm^3)	524,56	±	50,42	508,27	±	51,39	0,268
	CSF (mm^3)	822,45	±	111,24	833,50	±	150,14	0,770
	Intracranial volume (mm^3)	2039,54	±	195,05	1986,30	±	198,35	0,348
Impulsivity	BIS-11 cognitive	10,94	±	3,61	14,89	±	5,04	0,014
	BIS-11 motor	9,53	±	4,16	19,00	±	7,53	<0,001
	BIS-11 non-planning	17,47	±	5,46	22,16	±	6,88	0,036
	BIS-11 total	37,65	±	10,16	56,05	±	16,35	<0,001
	OCDS	2,17	±	1,95	11,15	±	5,61	<0,001
Neuropsychological	Reading skills test	24,13	±	11,34	26,79	±	4,19	0,42
	Fluency (COWAT). Semantic	69,54	±	33,56	44,15	±	31,17	0,01
	Fluency (COWAT). Phonetic	25,45	±	5,6	21,43	±	4,81	0,04
	Trail Making Test (TMT)	37,6	±	16,37	31,67	±	6	0,19
	Verbal memory	18,67	±	40,31	4	±	3,37	0,36
	Stroop (interference)	2,83	±	8,53	0,48	±	7,96	0,42

BIS = Barratt's Impulsivity Scale; CSF = cerebrospinal fluid; COWAT = Control Oral Word Association Test; EMCA = Spanish Alcohol Craving Multidimensional Scale; NA = not applicable; OCDS = Obsessive Compulsive Disorder Scale; SD = standard deviation; TMT = Trail Making Test.

Table 2 Brain regions showing differential between-group local volumes in GM and WM.

							Coordinates MNI		
	Anatomic region	*BA*	*Hemisphere*	k	T	*Corrected* P-*value*	x	y	z
Controls > Patients									
GM	vmPFC	10/32	Bilateral	1298	4.53	0.035	−2	55	-2
	dmPFC	32/24/8	Bilateral	1879	4.51	0.006	5	19	48
WM	Inferior/medial Frontal	(11/32/10)	Left	5737	5.39	<0.001	−18	37	0
	Inferior/medial Frontal	(10)	Right	1219	4.88	0.029	32	40	12
Patients > Controls									
GM	NS								
WM	External capsule/ventral striatum	NA	Left	3502	6.29	<0.001	−31	−5	10
	WM next to ventral striatum	NA	Right	1842	5.03	0.005	17	−12	−6

BA = Brodmann areas; dmPFC = dorsomedial pre-frontal cortex; GM = grey matter; NA = not applicable; NS = not significant; vmPFC: ventro medial = ventromedial pre-frontal cortex; WM = white matter.

VBM results

Optimized VBM whole-brain analysis detected regions with different between-group local GM and WM volumes (Table 2, Fig. 1). In the GM analysis, patients displayed lower local volumes in a number of clusters located along the medial-prefrontal wall [Brodmann areas (BA) 32/24/8] and a trend was observed at anterior OFC (BA 10/11) ($P = 0.067$). Inverse comparison did not reveal significant results. However, a non-significant cluster observed at the right nucleus accumbens (NAcc) was included in the subsequent correlational analysis because of its role in impulsivity.

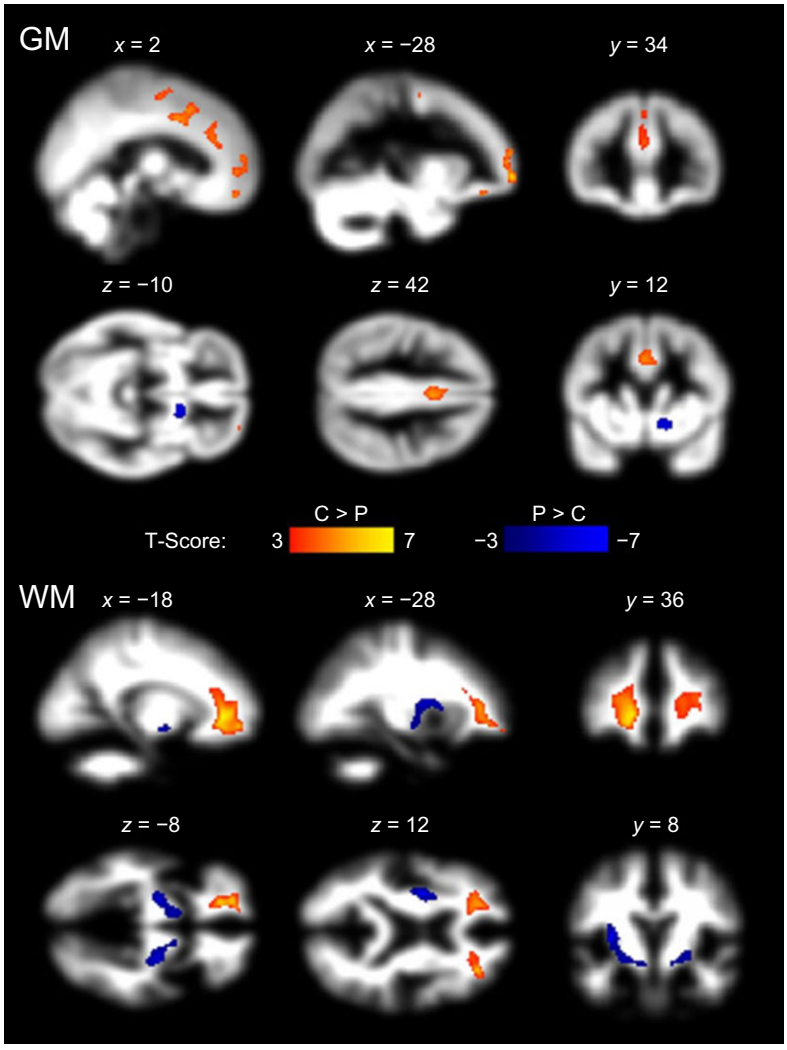

Figure 1 VBM results: maps of brain regions showing differential between-group local volumes in GM (top) and WM (bottom). Hot colours indicate regions with lower local volume in patients compared with controls (C > P). Cold colours indicate regions with higher local volume in patients relative to controls (P > C). Maps are displayed on the averaged GM and WM image from the own template. Right is right. For display purposes, threshold was set at $P < 0.005$ uncorrected

WM analysis revealed a similar but stronger pattern. Alcohol subjects showed lower local volume in the inferior and medial frontal WM. A manual exploration using Talairach atlas and the West Forest University-Pick Atlas in SPM showed that these WM coordinates were underlying BA 11/32/10. Again, inverse comparison revealed greater WM local volume in the bilateral WM of ventral striatum and the internal capsule. A manual WM atlas (Mori *et al.* 2005) revealed that external capsule, and medial telencephalic fascicle which connects mesencephalon (ventral tegmental area and substantia nigra) with ventral striatum and frontal regions were included in this cluster.

Correlational analysis, including subjects of both groups, showed that impulsivity (total, motor and non-planning BIS) and local GM volume were negatively correlated in several brain regions, primarily in the left OFC (cluster with local maxima coordinates: $x = -28$, $y = 64$, $z = -4$, $R = -0.527$, $P < 0.001$) and some clusters within the mPFC ($x = 1$, $y = 34$, $z = 25$, $R = -0.504$, $P = 0.002$; $x = -2$, $y = 55$, $z = -2$, $R = -0.384$, $P = 0.024$; $x = 5$, $y = 19$, $z = 48$, $R = -0.406$, $P = 0.014$) (Fig. 2), and were positively correlated bilaterally with the local volume of the NAcc ($x = 15$, $y = 11$, $z = -10$, $R = 0.383$, $P = 0.021$; $x = -16$, $y = 10$, $z = -10$, $R = 0.331$, $P = 0.048$). WM analysis only revealed a trend for a negative correlation between left frontal WM and motor impulsivity ($x = -18$, $y = 37$, $z = 0$, $R = -0.301$, $P < 0.078$). However, several of these correlations became non-significant after controlling for years of abuse and amount of alcohol intake per session. In fact, only left OFC cluster showed a tendency ($P = 0.083$) (cf. Supporting Information).

Among toxicological variables, only the amount of alcohol intake per session was negatively correlated with left OFC GM ($x = -28$, $y = 64$, $z = -4$, $R = -0.580$, $P < 0.019$) using only alcohol group data (cf. Supporting Information).

DISCUSSION

As expected, alcohol abusers displayed higher impulsivity scores in all three Barratt Impulsivity subscales and

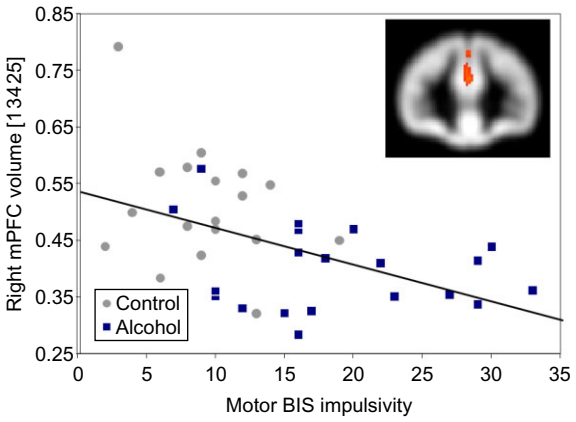

Figure 2 Scatterplot showing the negative correlation between Motor BIS impulsivity score and the relative volume of a GM cluster at the right mPFC (local maxima: $x = 1$, $y = 34$, $z = 25$) of both controls (dots) and alcohol abusers (squares)

OCDS, congruent with a deficient inhibitory control and high compulsivity of the abusers at this stage of addiction.

After controlling for age and total grey or white matter volumes, the between-group comparisons revealed three main results: (1) a lower GM regional volume in the mPFC and OFC in alcohol abusers compared with controls; (2) a lower WM regional volume in the inferior and medial frontal WM underlying mPFC and OFC in the alcohol group; and (3) a higher WM local volume of the ventral striatum at the localization of telencephalic fascicles, and internal capsule compared with controls. From these brain abnormalities, while only the toxicological variable 'amount of alcohol intake per session' was negatively correlated with left OFC GM, several prefrontal brain regions (dmPFC and OFC) were negatively correlated with impulsivity levels, although only OFC showed a tendency after controlling for both years of abuse and amount of alcohol intake.

As exposed earlier, virtually all structural MRI studies have focused on alcohol dependence diagnosis (alcoholic patients) and many of the volumetric reductions have been associated to alcohol use history variables (lifetime alcohol use, years of alcohol use, etc.) (Fein *et al.* 2006; Taki *et al.* 2006) and impaired cognitive functioning (Jang *et al.* 2007). Our results demonstrate that patients with shorter alcohol use histories, not fulfilling criteria for DSM-IV alcohol dependence, also show prefrontal brain attrition although these reductions seem to be more related with impulsivity variables than toxicological.

Given that impulsivity is defined as a trait variable of human personality that is stable within an individual and varies normatively across the healthy population (Barratt 1959; Patton *et al.* 1995), these results suggest that the lower GM and WM prefrontal volumes observed in this sample may be associated to differences in impulsivity. This interpretation is in line with similar volumetric studies: Matsuo *et al.* (2009) scanned 62 healthy subjects and showed that those subjects with higher impulsivity scores (also measured with BIS-11) displayed lower OFC and mPFC GM volumes. There were also negative associations between non-planning and motor impulsivity and volume of left and right OFC, respectively (Matsuo *et al.* 2009). Note that also our correlations were with some BIS-11 factors (i.e. total, motor and non-planning). Although BIS-11 is arguably the most widely used scale reporting impulsivity, the factor structure has been problematic and it has been suggested to be less robust in high impulsivity samples (including those with addictive disorders), so caution should be taken in using the three factors of BIS-11 (Reid *et al.* 2013).

Also supporting our results, Ersche and colleagues (Ersche *et al.* 2011) used VBM to compare the brain of 60 cocaine-dependent patients and 60 healthy controls and examined the relationship of structural alterations with several impulsivity measures and alcohol use variables. Similar to our results, they found abnormally decreased GM volume in OFC, anterior cingulate cortex and insula (which was correlated with greater duration of cocaine dependence) and increased GM in the basal ganglia. Compulsivity of drug use was correlated with reduced volume of OFC too. Similarly, the OFC cluster of our patients' group was also negatively associated to OCDS, a measure of compulsivity related with alcohol drinking. Although impulsivity and compulsivity are different traits, these may overlap and share underlying brain systems (Dalley, Everitt & Robbins 2011).

Medial PFC is involved in behaviour monitoring (including error and conflict detection) (van Veen & Carter 2002) and cognitive control (Ridderinkhof *et al.* 2004). It also constitutes the core of the anterior attentional system which is involved in selective or executive attention (Pardo, Fox & Raichle 1991). It supports consciousness and therefore is involved in controlling automated behaviours arising from unconscious layers of the brain such as those arising from limbic and striatal structures. Previous fMRI studies showed some functional alterations of this region during cognitive tasks including response inhibition studies on addicted patients (Tomasi *et al.* 2007; Li & Sinha 2008). Therefore, lower GM tissue density in the mPFC may underlie both an impaired attentional system responsible for monitoring function and an impaired cognitive control over emotional and compulsive reactions, deficits so related with impulsivity and so common in alcohol abusers.

We also observed a greater WM density next to the ventral striatum of the alcohol group. This, together with the GM striatal increase observed in OCD studies (Gilbert *et al.* 2008; Yoo *et al.* 2008), suggests that this alteration may be related to the between-group impulsivity differences. It is known that the ventral striatum plays an important role in addiction development, is involved in reward processing, and a wrong functioning of this system has been associated to impulsivity in alcoholic patients (Beck *et al.* 2009; Tomasi & Volkow 2013).

Like most drugs of abuse, alcohol exerts its neurobiological effects on the ventral striatum (Gilpin & Koob 2008). Enlarged striatal structures have been reported previously in chronic cocaine users (Jacobsen *et al.* 2001; Ersche *et al.* 2011) and methamphetamine users (Chang *et al.* 2005). However, the neuropathology underlying this enlargement is not fully understood. Blockade of dopamine D2 receptors by antipsychotic drugs has been shown to increase the volume of basal ganglia structures in humans (Keshavan *et al.* 1994; Scherk & Falkai 2006), possibly indicating that striatal enlargement is associated with an under-active dopamine system. It has recently been shown in humans that variation in GM volume correlates both positively and negatively with individual differences in the expression of D2-like receptors in various brain regions, including the caudate (Woodward *et al.* 2009). Alcohol dependence has also been associated with significant reduction in striatal dopamine D2 receptor density (Volkow *et al.* 1996). In addition, during a monetary incentive delay task, alcoholic patients, compared with controls, show increased ventral striatum activity (measured with fMRI) when the gained money is confirmed on the screen and deactivated if after a correct response, the trial was cancelled and they were asked to repeat the trial (frustration) (Bjork, Smith & Hommer 2008), suggesting a hypersensitive mesolimbic system to monetary reward gains and losses. Nonetheless, a reduced activation of the ventral striatum during the anticipation phase of monetary gain relative to healthy controls and a correlation of low activation of the ventral striatum and anterior cingulate during gain anticipation with high impulsivity have been observed in detoxified alcohol patients (Beck *et al.* 2009). This suggests that reduced ventral striatal recruitment during anticipation of conventional rewards in alcoholics may be related to their increased impulsivity while similar results have been observed in other disorders like attention deficit hyperactivity disorder (Scheres *et al.* 2007).

The increased WM region included some fascicles including medial telencephalic fascicle connecting mesencephalic regions (i.e. ventral tegmental area, substantia nigra) to the striatum and frontal regions. It is supposed that this connection signals the rewarding value of the stimuli for a good evaluation of multiple choices in making decision. Perhaps, this increased striatal region together with the frontal decreased regions contributes to the high impulsivity rate and impairs decision-making processes. This may lead patients to choose smaller immediate rewards instead of delayed bigger rewards. Binge alcohol drinking (compulsive use) may also be explained in terms of these cortico-striatal alterations. This would also facilitate habit development leading to addictive disorders (Vollstadt-Klein *et al.* 2010; Tomasi & Volkow 2013).

In line with this, other studies demonstrated smaller volumes of superior frontal, cingulate and parahippocampal gyri, amygdala, thalamus and cerebellum in high-risk young alcohol-naive subjects. These GM volumes correlated negatively with externalizing symptoms scores suggesting these to represent key endophenotypes of alcoholism (Benegal *et al.* 2007). Similar studies found smaller areas of the corpus callosum in subjects with high risk compared with low risk for alcoholism, also correlating with externalizing symptoms, suggesting, again, this as another marker of susceptibility to alcoholism in high-risk subjects of possible neurodevelopmental origin (Venkatasubramanian *et al.* 2007).

Many authors propose neuropsychological training (including functions like inhibitory control, attention and memory) as part of the behavioural treatment of addiction. This can be understood on the basis of the need for rehabilitation of impaired mental functions caused by the neurotoxic drug effects. However, further research is certainly needed to elucidate whether neuropsychological deficiencies could be present in addicted individuals prior to addiction onset. If so, neuropsychological training should be taken in even higher consideration for behavioural treatment.

Limitations

A limitation of this and other similar studies is that impulsivity was measured in a few ways. A more comprehensive evaluation of impulsivity should include more direct and indirect auto-reported and behavioural tests. In fact, Ersche and colleagues were able to link different components of impulsivity (built from a number of varied measures and an independent component analysis) to volumetric alterations in a sample of cocaine-dependent subjects (Ersche *et al.* 2011). Collecting many aspects of the impulsivity leads to more reliable results.

In addition, most of these correlations were only significant when including both groups. This can be due to the increase of the number of subjects and of variance on the impulsivity scale (when including both groups in the analysis), which increases the statistical power to detect

association between variables. Despite the absence of correlations with alcohol use variables, we cannot rule out the alcohol toxic effect on the volumetric differences during these (not many) years of alcohol abuse (mean of years of alcohol abuse = 4.71, SD = 2.9). Moreover, while correlations with impulsivity score included all subjects of both groups (24 controls and 24 patients), correlations with toxicology variables only included subjects of the alcohol group (controls did not abuse alcohol) decreasing statistical power. Note that use of psychoactive medication was not an explicit exclusion criterion; however, no one of the patients used any other medication than disulfiram and/or naltrexone. More studies, including longitudinal ones, are needed to elucidate at what extent previous personality traits and experience are predisposing subjects to alcohol use and how these interact with toxicological effects of drug use.

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Disclosure/Conflict of Interest

None.

Authors Contribution

SA, JMB and FJR were responsible for the study concept and design. JLM and IS contributed to the acquisition of neuropsychological data, and MJR helped performing MRI. SA and MAB assisted with data analysis and interpretation of findings. FJR drafted the manuscript. SA, JMB and MF-B provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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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:

Figure S1 Scatterplot showing the negative correlation between Motor BIS impulsivity score and the relative volume of a GM cluster at the left OFC (local maxima at $x = -28$, $y = 64$, $z = -4$) of both controls (dots) and alcohol abusers (squares)

Figure S2 Scatterplot showing the negative correlation between Motor BIS impulsivity score and the relative volume of a GM cluster at the right mPFC (local maxima at $x = 5$, $y = 19$, $z = -48$) of both controls (dots) and alcohol abusers (squares)

Figure S3 Scatterplot showing the positive correlation between NP BIS impulsivity score and the relative volume of a GM cluster at the right ventral striatum (local maxima at $x = 15$, $y = 11$, $z = -10$) of both controls (dots) and alcohol abusers (squares)

Table S1 Table showing significant correlations between volumetric measures (including between-group differential clusters and total volumes) and impulsivity, toxicological and demographical variables

