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A voxel-based morphometry study comparing problem gamblers, alcohol abusers, and healthy controls☆

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ABSTRACT

Background: Alcohol use disorders (AUDs) are associated with smaller grey matter volumes in cortical and subcortical brain regions which are related to cognitive impairments often found in these disorders. Similar cognitive impairments have been found in patients suffering from problem gambling behaviour. However, in contrast to AUDs, gambling behaviour does not entail brain exposure to toxic agents. Although there are many clinical, neuropsychological, and neurobiological similarities between PG and substance use disorders it has not yet been established whether pathological gambling, similar to alcohol use disorders, is associated with abnormal regional grey matter volumes.
Methods: With whole-brain voxel-based morphometry we compared a group of 40 treatment seeking problem gamblers, 36 subjects with an alcohol use disorder, and 54 healthy controls to evaluate potential group differences in regional grey matter volumes, corrected for age, IQ, smoking status, and total intracranial volume (TIV).
Results: Significantly smaller grey matter volumes in left superior frontal cortex, left precentral cortex, right insula, right putamen, left thalamus, bilateral superior parietal cortex and right supramarginal cortex were present in subjects with an alcohol use disorder compared to healthy controls and problem gamblers. No significant grey matter volume differences were present between problem gamblers and healthy controls.
Conclusion: In conclusion, we replicated previous findings of smaller grey matter volumes in subjects with an alcohol use disorder and found no significant morphological brain abnormalities in problem gamblers.

1. Introduction

It is well documented that long-term alcohol use disorders (AUDs: alcohol abuse or alcohol dependence) are associated with brain atrophy and cognitive impairments such as reduced working memory, verbal memory, visuospatial abilities, and impaired response inhibition (Moselhy et al., 2001; for a review see Sullivan et al., 2000). Similar cognitive impairments have been found in patients suffering from pathological gambling (PG) or problem gambling (e.g., Goudriaan et al., 2006; for a review see van Holst et al., 2010). Because of clinical, neuropsychological, and neurobiological similarities between PG and substance dependence (Holden, 2001; Petry, 2007; Potenza, 2006), the DSM-IV classification of PG as an impulse-control disorder not otherwise categorized is challenged and PG is likely to be classified in the Addiction and Related Disorders section in DSM-V (http://www.dsm5.org). In contrast to AUDs, gambling behaviour does not entail brain exposure to toxic agents. However, in theory regional grey matter (GM) volume abnormalities in problem gamblers could result from neuroadaptations due to chronic, repetitive gambling behaviour, and/or the existence of a common underlying neurobiological vulnerability for addictive behaviours. Moreover, if GM volume reductions would also be present in pathological gamblers, comparable to GM reductions in subjects with AUDs (Fein et al., 2002b, 2006, 2009; Jang et al., 2007) this might explain similarities in neurocognitive impairments found in both disorders. However, no studies on morphological brain abnormalities in pathological gambling have yet been reported.

☆ Supplementary material can be found by accessing the online version of this paper. Please see Appendix A for more information.

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Magnetic resonance imaging (MRI) studies with AUD cohorts have consistently demonstrated widespread morphological abnormalities involving sulcal widening and volume loss in cortical GM and white matter (Fein et al., 2009; Jang et al., 2007; Kril and Halliday, 1999; Mechtcheriakov et al., 2007; Sullivan et al., 1995, 2005; Visser et al., 1999). Whole-brain voxel-wise analyses have likewise shown GM reductions in cortical and subcortical areas, including precentral, prefrontal, insula, parietal and occipital cortex and thalamus and cerebellar regions (Cardenas et al., 2007; Chanraud et al., 2007; Mechtcheriakov et al., 2007; Rando et al., 2011).

Furthermore, recent research indicates that cigarette smoking, which is highly prevalent among AUDs (Romberger and Grant, 2004), is associated with region specific brain volume reductions (Durazzo et al., 2004; Gallinat et al., 2006; Gazdzinski et al., 2005; Kuhn et al., 2010; Liao et al., 2010). Compared to never-smokers, smokers (without other dependencies) showed regional GM volume reductions in the prefrontal cortex, anterior cingulate cortex, temporal lobe (including the parahippocampal gyrus), thalamus, cerebellum and substantia nigra (Gallinat et al., 2006; Kuhn et al., 2010; Liao et al., 2010). In addition, studies have demonstrated that in alcohol dependent individuals, chronic cigarette smoking is associated with larger cortical GM reduction and that chronic smoking is associated with impaired neurocognitive function in both alcoholic and non-alcoholic samples (Durazzo et al., 2007; Gazdzinski et al., 2005; Mon et al., 2009). Because cigarette smoking is also highly prevalent in PG (McGrath and Barrett, 2009) and because smoking may have a positive effect on neurocognitive functions in PG (Mooney et al., 2011), controlling for smoking behaviour is necessary when assessing specific associations of problem gambling behaviour with abnormal brain morphology.

The present voxel-based morphometry (VBM) study aimed to investigate whether problem gambling behaviour is associated with reduced regional GM volumes similar to those found in AUDs. We, therefore, compared treatment seeking problem gamblers (PRGs), AUDs, and healthy comparison subject (HCs) to detect regional GM volume differences controlling for demographical differences such as age, IQ, total intracranial volume and smoking status.

2. Methods

2.1. Participants

Forty treatment seeking PRGs, 36 AUDs, and 54 HCs participated in the study. All PRGs were recruited from Dutch addiction treatment centres. AUDs were recruited either through advertisement in local newspapers or from Dutch addiction treatment centres. All HCs were recruited through advertisements in local newspapers. Because most treatment-seeking PRGs were men, only male subjects were included in the study. The ethical review board of the Academic Medical Centre approved the study, and all subjects provided written informed consent.

The main inclusion criterion for PRGs was a score >5 on the South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987), indicating probable pathological gambling in the past 12 months. This scale was used to facilitate comparisons with other studies using the SOGS. In addition, PRGs were interviewed with section T of the Diagnostic Interview Schedule to assess the diagnostic criteria for DSM-IV-TR Pathological Gambling.

AUDs were included when meeting DSM-IV-TR criteria for alcohol abuse or dependence assessed with section J of the Dutch version of the Clinical International Diagnostic Inventory (CIDI; World Health Organisation, 1997). A measure of alcohol problem severity was obtained with the Alcohol Use Disorders Identification Test (AUDIT; Bush et al., 1998). Furthermore, to ensure that all participants were detoxified from alcohol, AUD participants had to be fully abstinent for at least two weeks to be included in the study (mean abstinence duration: 18 days), which was assessed by self-report. HCs and PRGs were asked to limit their alcohol use to a maximum of 2 alcoholic consumptions the day before the study. Furthermore, the urine screen for alcohol (and other drugs, see below), assessed at the testing day, had to be negative.

Exclusion criteria for all groups were: lifetime diagnosis of schizophrenia or psychotic episodes, 12-month diagnosis of manic disorder (CIDI, section F), OCD (CIDI, section E), and post-traumatic stress disorder (CIDI, section K), other substance use disorders than those under study (except for nicotine) (CIDI, section L), treatment for mental disorders other than those under study in the past 12 months, use of psychotropic medication, difficulty reading Dutch, age under 18 years, IQ below 80 (measured by the Dutch Adult Reading Test; Schmand et al., 1991), positive urine screen for alcohol, amphetamines, benzodiazepines, opioids or cocaine, history or current treatment for neurological disorders, major internal disorders, brain trauma, or exposure to neurotoxic factors.

Groups were mutually exclusive with regard to the psychiatric disorder under study, i.e. PRGs and HCs did not drink more than 21 standard units (10 g) of alcohol per week and AUDs and HCs did not gamble more than twice a year. Participants were allowed to smoke.

2.2. MRI data acquisition and preprocessing

MRI was performed on a 3.0 T Intera MR system (Philips Medical Systems, Best, the Netherlands) with a standard SENSE multichannel receiver head coil. The anatomical scan consisted of 170 coronal slices with a three-dimensional T1-weighted gradient-echo sequence (flip angle 8°; repetition time = 9 ms; echo time = 4.20 ms; matrix, 256 × 256 pixels; voxel size, 1.00 mm × 1.00 mm × 1.00 mm). 3D geometry correction was performed during reconstruction of the images. Image segmentation and registration were performed using the segmentation algorithm (the New Segment procedure) and the DARTEL registration algorithm incorporated in the current release of Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm).

As a first processing step, to provide better initial estimates for the segmentation algorithm, the SPM8 Display function was used to manually set the image space origin to the anterior commissure and align each image with the plane of the anterior and posterior commissures. Default settings were used for segmentation. No skull stripping was applied prior to segmentation. The resulting segmentations were validated visually. The segmentation procedure produced rigid-body aligned tissue segments for each image. The grey and white matter segments were fed into DARTEL. DARTEL registers the tissue segments to a template generated from their own mean.

Because these images have been warped to the space of the mean image, an additional step normalized the warped images to Montreal Neurological Institute template space. The warped images were also visually validated before continuing with the registration step. The default parameter settings were also used in the DARTEL registration, which includes resampling to 1.5-mm^3 voxels to reduce memory demands for the large number of parameters estimated by the registration algorithm. Final outputs were modulated (i.e., preserving the total amount of grey matter of the original image), GM segments (1.5-mm^3 voxels) smoothed using an 8-mm Gaussian filter. Gaussian smoothing reduces the effects of residual misregistration on potential group differences and reduces departures from normality that may occur at some voxels (Ashburner and Friston, 2000).

2.3. Data analysis

Statistical parametric maps were created in SPM8 to perform between-group comparisons using the smoothed, modulated, normalized GM tissue segments output by DARTEL. A general linear model was created with diagnostic group (AUDs, PRGs, HCs) as the factor of interest. Covariates included age, IQ, smoking status (yes or no) and estimated total intracranial volume, which was calculated by voxel-wise summing of the native space grey, white and CSF segments for each subject. All our analyses compared regional GM volume differences adjusted for age, estimated IQ, smoking status and individual differences in global brain size.

The whole-brain statistical analysis was conducted using voxel based false discovery rate (FDR) correction (Genovese et al., 2002), $p < 0.05$, for multiple comparisons to detect differences between groups.

3. Results

3.1. Sample characteristics

Except for 5 PRGs, all PRGs met criteria of a current DSM-IV-TR pathological gambling diagnosis (PG). Table 1 shows that PRGs and AUD groups did not differ in the duration of their disorder. However, the AUD group was significantly older and as expected scored higher on the AUDIT than the HC and the PRG groups. The PRG group had a significantly lower IQ compared to the other groups and as expected PRGs scored significantly higher on the SOGS compared to the HC and AUD groups. There were no significant group differences on total intracranial volume, GM or WM volume. There were significantly more smokers in the HC and the AUD groups compared to the PRG group.

3.2. Regional GM differences between groups

Smaller regional GM volumes in AUDs relative to HCs were observed in left superior frontal cortex, right insula, left precentral

Table 1
Sample characteristics.

	HCs	PRGs	AUDs	Stats
n	54	40	36	
IQ[a,b], Mean (sd)	101 (14)	95 (13)	105 (16)	$F(2,129) = 5.63$, $p = 0.05$
Age[c,b], Mean (sd)	35.3 (10.1)	36.5 (10.67)	43.2 (11.03)	$F(2,129) = 6.05$, $p = 0.002$
TIV volume, Mean ml (sd)	1647 (121)	1633 (95)	1631 (91)	$F(2,129) = 0.35$, $p = 0.71$
GM volume, Mean (sd)	709 (57)	698 (44)	696 (41)	$F(2,129) = 0.93$, $p = 0.40$
WM volume, Mean (sd)	517 (45)	511 (40)	511 (41)	$F(2,129) = 0.30$, $p = 0.74$
Number (%) current smokers in group	25 (46)	10 (25)	20 (56)	$H(2) = 7.85$, $p = 0.02$
Duration target disorder in years	–	12.2 (9.7)	11.69 (9.7)	$F(1,66) = 0.07$, $p = 0.79$
SOGS[d,e], Mean (sd)	0 (0)	9.92 (2.95)	0.22 (.72)	$F(2,67) = 475.22$, $p < 0.001$
AUDIT[b,c], Mean (sd)	4.39 (3.31)	4.74 (2.80)	22.75 (8.12)	$F(2,67) = 166.33$, $p < 0.001$

HCs = healthy controls; PRGs = problematic gamblers; AUDs = alcohol use disorder group; TIV = Total intracranial volume; GM = Grey matter, WM = White matter; SOGS = South Oaks Gambling Screen; AUDIT = Alcohol Use Disorders Identification Test.
[a] HCs = AUDs > PRGs; [b] AUDs > PRGs; [c] AUDs > HCs; [d] PRGs > HCs; [e] PRGs > AUDs.

cortex, right putamen, left thalamus, bilateral superior parietal cortex and right supramarginal cortex (Fig. 1, see also Table 2). We did not find regional GM volumes in AUDs that were significantly larger compared to HCs. Finally, no volume differences were found between PRGs and HCs and no volume differences between PRGs and AUDs. GM clusters that were significantly smaller in AUDs compared to HCs were extracted to visualize the proportional average GM volume per group (see Fig. 2).

3.3. Analyses between HCs, AUDs and PRGs with matched age subgroups

Although we corrected for possible age effects by including age as covariate in our analyses, age could have influenced our findings of smaller GM volumes in AUDs. We re-analysed our group differences with a younger subset of AUDs, i.e., AUDs with an age above 47 ($n = 15$) were excluded from this analysis. This resulted in a group

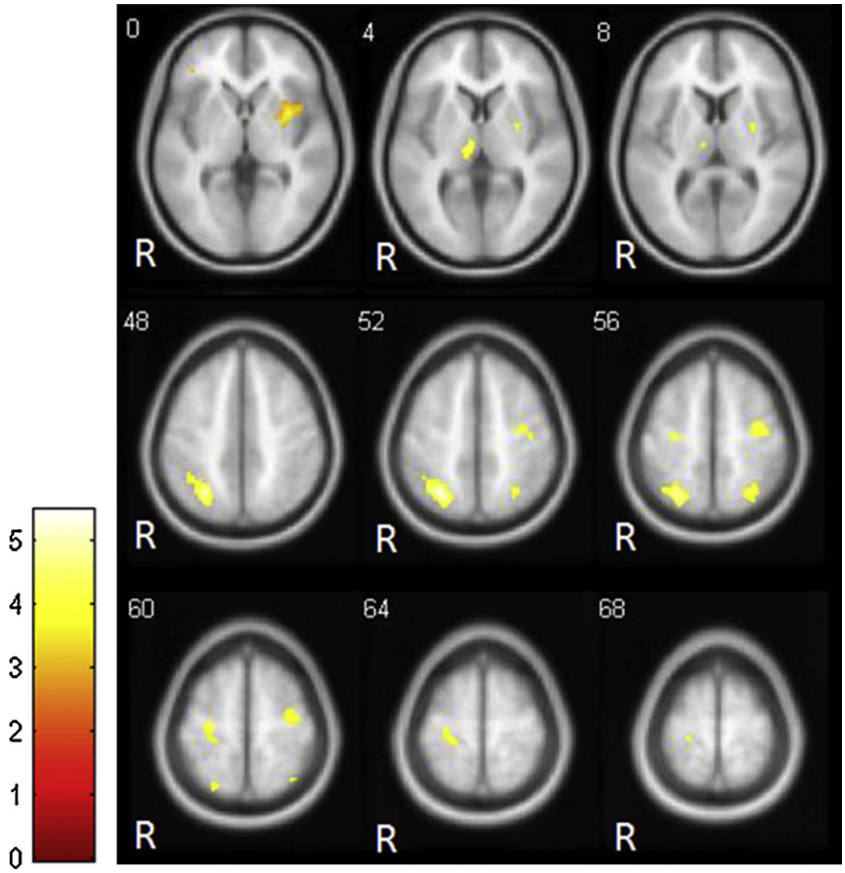

Fig. 1. GM comparisons between AUDs and HCs. Smaller grey matter volumes in right and left superior frontal cortex, left precentral cortex, right putamen, right insula, left thalamus, bilateral superior parietal cortex and right supramarginal cortex were found in AUDs compared to HCs, Numbers are *Z* coordinates corresponding to the MNI space.

Table 2
Overall grey matter differences between groups.

AUDs < HCs						
	L/R	MNI coordinates				
		x	*y*	*z*	*Z* value	Voxels
Frontal lobe						
Superior frontal cortex	L	−23	−12	72	4.08	46
Precentral cortex	L	−29	−19	30	4.41	294
Parietal lobe						
Superior parietal cortex	R	30	−60	56	4.07	197
	L	−29	−61	51	5.17	942
Supramarginal cortex	R	45	−46	36	3.96	85
Insula	R	33	5	2	4.15	310
Subcortical lobe						
Thalamus	L	−9	−18	3	4.27	195
Putamen	R	−29	−3	6	3.74	44

Results reported whole brain false discovery rate corrected $p < 0.05$. MNI = Montreal Neurological Institute; HCs = healthy controls; AUDs = alcohol use disorder group.

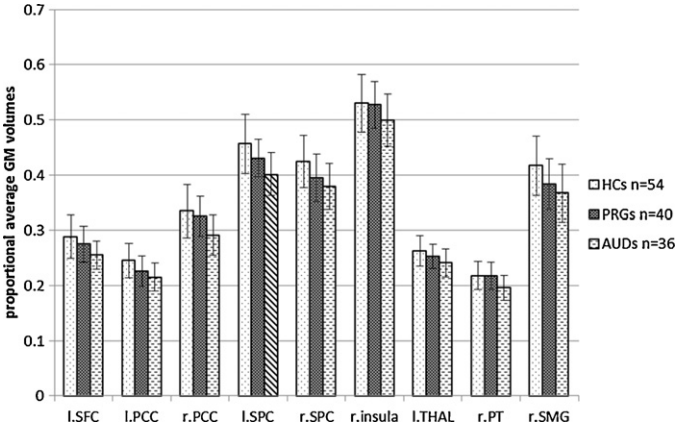

Fig. 2. Proportional average GM volumes in AUDs, PRGs and HCs. GM clusters that were significantly smaller in AUDs compared to HCs were extracted to visualize the proportional average GM volume per group with error bars. GM = grey matter; l.SFC = left superior frontal cortex; l.PCC = left precentral cortex; r.PCC = right precentral cortex; l.SPC = left superior parietal cortex; r.SPC = right superior parietal cortex; l.THAL = left thalamus; r.PT = right putamen; r.insula = right insula; r.SMG = right supra marginal gyrus.

with 54 HCs, 40 PRGs and 21 AUD participants. TIV and smoking status were again included as covariate. Please see Supplementary data Table 1[1] for the demographic information of this group. No group differences were detected with our conservative voxel based whole brain correction threshold of $p < 0.05$ FDR, probably caused by a loss of power due to a smaller number of subjects in the AUD group. However, with a more lenient threshold of FDR $p < 0.1$ we found very similar results as reported in the total group analyses. AUDs still showed smaller GM volumes in the left superior frontal cortex, postcentral cortex, thalamus and superior parietal cortex (see Table 3). There were still no group differences between HCs and PRGs at this more lenient significance threshold.

3.4. Analyses comparing pathological gamblers to HCs

We re-analysed our group omitting PRGs who did not meet the diagnostic criteria for pathological gambling based on the CIDI (see supplementary data Table 2 for demographic information). This resulted in a PG group of $n = 35$. Smoking status, IQ and TIV were included as covariates in the VBM analyses. Our analyses with this smaller subgroup showed similar results as our main findings. Also, no significant group differences between HCs and PRGs were present at a more lenient threshold of $p < 0.1$ FDR.

[1] Supplementary material can be found by accessing the online version of this paper. Please see Appendix A for more information.

Table 3
Grey matter differences between age-matched HCs and AUDs.

AUDs < HCs						
	L/R	MNI coordinates				
		x	*y*	*z*	*Z* value	Voxels
Frontal lobe						
Superior frontal cortex	L	−23	−12	72	3.83	6
Post central cortex	L	−24	−28	64	4.10	127
Parietal lobe						
Superior parietal cortex	L	−29	−61	51	4.32	134
Subcortical lobe						
Thalamus	L	−8	−18	0	4.53	224

A younger subset of AUDs compared to HCs: AUDs with an age above 47 ($n = 15$) were excluded from this analysis. Results reported whole brain false discovery rate corrected $p < 0.1$. MNI = Montreal Neurological Institute; $n = 54$ HCs = healthy controls; $n = 21$ AUDs = alcohol use disorder group.

4. Discussion

The present VBM study investigated whether problem gambling behaviour was associated with reduced GM volumes similar to those that were previously found in AUDs. Although we observed widespread GM reductions in AUDs vs HCs, we did not find any GM abnormalities in PRGs when compared with HCs.

4.1. Regional GM reductions in AUDs but not in PRGs

As expected we found significantly smaller regional GM volumes in AUDs relative to HCs in the left superior frontal cortex, left precentral cortex, right insula, right putamen, left thalamus, bilateral superior parietal cortex and right supramarginal cortex. These reductions are consistent with previous morphological studies in treatment seeking AUDs (Fein et al., 2009; Jang et al., 2007; Kril and Halliday, 1999; Mechtcheriakov et al., 2007; Sullivan et al., 2005; Visser et al., 1999). Of these regions, superior frontal cortex and precentral cortex are involved in top-down cognitive control of processing sensory inputs and actions that guide behaviour (Miller and Cohen, 2001). In addition, precentral cortex and supramarginal cortex are associated with response inhibition abilities, such as those measured with stop signal tasks (Chambers et al., 2009). Although this study did not establish a link with functional impairment, the volume deficits in these cortical regions would suggest disruption of cognitive control functions associated with atrophy in these regions, congruent with previous findings of cognitive impairments in AUDs (Moselhy et al., 2001). Furthermore, smaller parietal cortex volumes have been associated with frequent findings of impairments in visual spatial abilities and sensory integration in AUDs (Sullivan et al., 2000). GM reduction in the insula, thalamus and putamen is also consistent with previous studies (Durazzo et al., 2004; Harding et al., 2000; Kril et al., 1997; Mechtcheriakov et al., 2007), regions associated with emotion regulation, arousal, attention and appetitive behaviour, functions that have been found to be disrupted in AUDs (e.g., George et al., 2001; Heinz et al., 2007; Vollstadt-Klein et al., 2010). As expected, we did not find brain regions showing larger volumes in AUDs compared to HCs.

In contrast to previous VBM studies in AUD, our AUD group consisted of treatment seeking and community based AUDs (Fein et al., 2009; Jang et al., 2007; Kril and Halliday, 1999; Mechtcheriakov et al., 2007; Sullivan et al., 2005; Visser et al., 1999). Compared to treatment-seeking alcoholics, treatment-naïve alcoholics have been reported to demonstrate a different drinking trajectory

and less severe levels of lifetime alcohol consumption (Fein and Landman, 2005), as well as lower magnitudes of alcohol-induced cerebral morphological abnormalities (Fein et al., 2002a). We found consistent GM volume reductions in our mixed treatment seeking and community based AUD group. This could be explained by the fact that, although overall our AUD group may have been less severely afflicted, the AUDs had shorter abstinence duration than in most other VBM studies including treatment seeking AUDs (Cardenas et al., 2007; Chanraud et al., 2007; Mechtcheriakov et al., 2007; Rando et al., 2011). Indeed, abstinence has been shown to lead to a (partial) recovery of GM volumes (Agartz et al., 2003; Bartsch et al., 2007; Wobrock et al., 2009; Gazdzinski et al., 2005). Further research is needed to test whether AUDs with longer abstinence duration resemble PRGs more on GM volumes than our current AUDs.

Based on similarities in neuropsychological profiles between PRGs and AUDs (e.g., Goudriaan et al., 2006), we expected to find a similar pattern of reduced GM volumes in PRGs as in AUDs. However, we found no GM volume differences between PRGs and AUDs, but our post hoc analyses of proportional grey matter density in all groups revealed a pattern showing that PRGs had grey matter density levels intermediate between HCs and AUDs – with the PRG group not differing significantly from both HCs and AUDs. Thus, perhaps with larger samples it might be possible to detect statistically significant differences between PRGs and HCs. The current lack of significant volume differences in PRGs compared to HCs, indicate that problem gambling behaviour is dissimilar from an alcohol use disorder with regard to brain morphology. Also, our subgroup analyses comparing the gamblers who met the DSM criteria for pathological gambling to the other groups, suggest that the lack of GM volume reductions in PRGs compared to HCs could not be explained by less severe addiction problems in the PRG group. Possibly, neuropsychological impairments in a behavioural addiction like problem gambling are associated with more subtle changes in receptor density and neurotransmitter levels, or changes in functional connectivity between brain regions. Future research is needed to specifically test the relation between neuropsychological performance and regional GM volume in PRGs and AUDs.

5. Limitations, strengths and suggestions for future research

A limitation of this study is the lack of detailed information on certain clinical characteristics that could have influenced our findings. For example, we did not have detailed information about smoking using validated instruments such as The Fagerström interview (Heatherton et al., 1991), in order to investigate the association between the level of smoking and nicotine dependence and GM reductions. Also no specific information was available on the family history of addictive disorders. This is important because several studies have shown GM reductions in adolescents from high risk families without having an addiction themselves (Benegal et al., 2007; Gilman et al., 2007; Hill et al., 2009). Moreover, information on externalizing disorders such as antisocial personality disorders (ASPD) which have high incidence in addictive disorders (Bowden-Jones et al., 2004; Petry et al., 2005; Verheul et al., 1998) could have provided extra information on the relation between GM abnormalities and addictive disorders. For instance, smaller prefrontal cortex volumes were found in subjects with ASPD but not in substance dependent subjects without ASPD (e.g., Raine et al., 2000). The generalizability of our findings is limited to AUDs and PRGs without comorbid substance dependence (apart from nicotine dependence) or other psychiatric disorders. Additionally, because we did not include female participants our findings are also limited to the male population. Finally, our study is cross-sectional and, therefore, our findings provide only indirect evidence that smaller regional brain volumes are caused by alcohol abuse or addictive behaviour. It is possible that the observed group differences are pre-morbid or that potential unrecorded group differences in nutrition, exercise, overall physical health or genetic predisposition contributed to our findings. Lastly, previous studies have also shown interactions between alcohol dependence and age, indicating that differences in age-related rates of grey matter volume loss may differ across groups even when mean age is not different between groups (Fein et al., 2010).

An important strength of the present study is that by including three groups, we could compare our new findings in PRGs with well-documented GM reductions found in AUDs and show that our method was sensitive enough to replicate these GM findings in our AUDs. Because of our mixed AUD group our findings could be more generalizable to all AUDs than previous studies, because previous studies have indicated that treatment-seeking individuals constitute only a small fraction of persons afflicted with alcohol use disorders, whereas non-treatment seeking AUDs are in the vast majority. In addition, we controlled for important aspects such as IQ, age, intracranial volume, smoking status and included PRGs and AUDs that did not suffer from any other substance dependence (except for nicotine) that are known to influence GM volumes as well (Franklin et al., 2002; Sachdev et al., 2008; e.g., Tanabe et al., 2009). However, our age-matched subgroup analyses of HCs and AUDs indicated no group differences with our conservative voxel based whole brain correction threshold of $p < 0.05$ FDR, probably caused by a loss of power due to a smaller number of subjects in the AUD subgroup. However, with a more lenient threshold of FDR $p < 0.1$ we found very similar results as reported in the total group analyses.

The next step in morphology studies will be to include multimodal imaging protocols to understand the complex relationship between biochemistry, brain structure and function in relation to specific addictive behaviours. In addition, pharmacological MRI studies using effective medications for the treatment of specific addictions (e.g. acamprosate) or medications effective for a range of addictions (e.g. naltrexone) could improve our understanding of the underlying mechanisms for the development of and the recovery from addictive behaviours.

5.1. Conclusion

In this study, no regional GM volume abnormalities in PRGs compared with HCs were present. Our findings indicate that problem gambling behaviour is not associated with grey matter reductions as those found in the AUDs. In addition, we replicated previous findings of smaller regional GM volumes in AUDs. Future longitudinal studies could shed light on the causal role of abnormalities in these brain structures on the development and course of addictive behaviours.

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Contributors

AG, DV, RvH, and WvB were responsible for the study concept and design. RvH, MdR and AG contributed to data acquisition. RvH, MdR and DV performed the MRI analyses. RvH, MdR, DV, WvB and AG interpreted findings. RvH drafted the first version of this

manuscript. AG, MdR, WvB and DV provided critical revision of the manuscript for important intellectual content. All authors critically reviewed the content and approved the final version of this manuscript.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2011.12.025.

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