Imaging studies in pathological gambling: similarities and differences with alcohol dependence
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Chapter 7

A voxel-based morphometry study comparing problematic gamblers, alcohol abusers, and healthy controls
Chapter 7

Abstract
Alcohol use disorders are associated with smaller gray matter (GM) volumes in various cortical and subcortical brain regions. Whether pathological gambling, similar to alcohol use disorders, is associated with abnormal regional GM volumes has not yet been established.

We used whole-brain voxel-based morphometry (VBM) to compare a group of 40 treatment seeking problematic gamblers (PRGs), 36 subjects with an alcohol use disorder (AUDs), and 54 healthy controls (HCs) to evaluate potential group differences in regional GM volumes (corrected for possible effects of age, IQ, smoking status, and total intracranial volume).

Significantly smaller GM 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 AUDs compared to HCs and PRGs. No significant GM volume differences were present between PRGs and HCs. However, conjunction analyses indicated that irrespective of the type of addiction, addicted subjects (smoking HCs, PRGs, and AUDs) had significantly smaller volumes of the left orbitofrontal cortex compared to non-smoking HCs.

In conclusion, we replicated previous findings of smaller GM volumes in AUDs and showed that morphological brain abnormalities typical for AUDs are not present in PRGs. Thus problematic gambling, with cognitive deficits similar to those found in AUDs, is not associated with GM volume reductions. Furthermore, the left orbitofrontal cortex volume reduction found across addictions, suggests that decreased orbitofrontal cortex volume is a vulnerability marker for addictive behaviours in general.
**Introduction**

It is well documented that long-term alcohol use disorders (AUD: 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 (and Moselhy et al., 2001; for a review see Sullivan et al., 2000). Similar cognitive impairments have been found in patients suffering from problematic gambling behaviour (e.g., Goudriaan et al., 2006; and 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 NOS 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, regional gray matter (GM) volume abnormalities in gamblers may result from neuroadaptations due to chronic, repetitive gambling behaviour, and/or the existence of a common underlying neurobiological vulnerability for addictive behaviours. Moreover, cognitive impairments found in pathological gamblers suggest morphological brain differences compared to healthy controls, similar to AUDs (Fein et al., 2002; Fein et al., 2006; Fein et al., 2009; Jang et al., 2007). However, no studies on morphological brain abnormalities in pathological gambling have yet been reported.

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; Sullivan et al., 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 individuals with AUD (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 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 problematic gambling behaviour with abnormal brain morphology.

The present VBM study aimed to investigate whether problematic gambling behaviour is associated with reduced regional GM volumes similar to those found in AUDs. We, therefore, compared treatment seeking problematic gamblers (PRGs), subjects with an alcohol use disorder (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.
Method

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.

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, AUDs had to be abstinent for at least two weeks to be included in the study (mean abstinence duration: 18 days). 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.

MRI data acquisition and pre-processing
Imaging data were obtained using a 3.0 T Intera full-body MRI scanner (Philips Medical Systems, Best, the Netherlands) with a phased array SENSE RF six or eight-channel receiver head coil. For each participant, a sagittal high-resolution T1-weighted magnetization-prepared rapid gradient echo scan was acquired (voxel size=1 mm³, 170 slices).

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 gray 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 default parameter settings were also used in the DARTEL registration, which include resampling to 1.5-mm³ 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-mm³ 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).

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 gray, 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 on global brain size.

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

Post-hoc, a conjunction analysis was performed to investigate whether common volume reductions irrespective of type of addiction could be identified. For this purpose, we incorporated the following contrasts that were tested against the “conjunction null hypothesis”: smoking HCs < non-smoking HCs, AUDs < non-smoking HCs, and PRGs < non-smoking HCs. Results from this analysis detected with an threshold of \( P<0.001 \) uncorrected and surviving a threshold set at \( P<.05 \), FDR corrected for multiple comparisons across the search volume of a sphere of 10 mm [small volume correction (SVC)] (Friston et al., 1996; Worsley et al., 1996) were reported.

Results
Sample characteristics
Table 1 shows that PRG 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 white matter (WM) volume. There were significantly more smokers in the HC and the AUD groups compared to the PRG group.

<table>
<thead>
<tr>
<th></th>
<th>HCs</th>
<th>PRGs</th>
<th>AUDs</th>
<th>Stats</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>54</td>
<td>40</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>IQ*</td>
<td>101 (14)</td>
<td>95 (13)</td>
<td>105 (16)</td>
<td>F(2,129)= 5.63, ( P=0.05 )</td>
</tr>
<tr>
<td>Age*</td>
<td>35.3 (10.1)</td>
<td>36.5 (10.67)</td>
<td>43.2 (11.03)</td>
<td>F(2,129)=6.05, ( P=0.002 )</td>
</tr>
</tbody>
</table>
Chapter 7

<table>
<thead>
<tr>
<th></th>
<th>HCs</th>
<th>PRGs</th>
<th>AUDs</th>
<th>F(2,129)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIV volume Mean ml (sd)</td>
<td>1647 (121)</td>
<td>1633 (95)</td>
<td>1631 (91)</td>
<td>0.35</td>
<td>0.71</td>
</tr>
<tr>
<td>GM volume Mean (sd)</td>
<td>709 (57)</td>
<td>698 (44)</td>
<td>696 (41)</td>
<td>0.93</td>
<td>0.40</td>
</tr>
<tr>
<td>WM volume Mean (sd)</td>
<td>517 (45)</td>
<td>511 (40)</td>
<td>511 (41)</td>
<td>0.30</td>
<td>0.74</td>
</tr>
<tr>
<td>Number (%) current</td>
<td>25 (46)</td>
<td>10 (25)</td>
<td>20 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>smokers in group*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration target</td>
<td>-</td>
<td>12.2 (9.7)</td>
<td>11.69 (9.7)</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td>disorder in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOGS* Mean (sd)</td>
<td>0 (0)</td>
<td>9.92 (2.95)</td>
<td>0.22 (.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUDIT* Mean (sd)</td>
<td>4.39 (3.31)</td>
<td>4.74 (2.80)</td>
<td>22.75 (8.12)</td>
<td>166.33</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 1: Sample characteristics
HCs = healthy controls; PRGs = problematic gamblers; AUDs = alcohol use disorder group; TIV= Total intracranial volume; GM= Gray matter, WM= White matter; SOGS: South Oaks Gambling Screen; AUDIT: Alcohol Use Disorders Identification Test. * Significant differences between groups, with p<0.05; **HCs>AUDs > PRGs; ^AUDs > PRGs; † AUDs > HCs; ‡ PRGs > HCs; § PRGs > AUDs

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 cortex, right putamen, left thalamus, bilateral superior parietal cortex and right supramarginal cortex (Figure 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.

<table>
<thead>
<tr>
<th>AUDs &lt; HCs</th>
<th>MNI coordinates</th>
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<tbody>
<tr>
<td></td>
<td>L/R</td>
</tr>
<tr>
<td>Prefrontal lobe</td>
<td></td>
</tr>
<tr>
<td>Superior frontal cortex</td>
<td>L</td>
</tr>
<tr>
<td>Insula</td>
<td>R</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td></td>
</tr>
<tr>
<td>Precentral cortex</td>
<td>L</td>
</tr>
<tr>
<td>Limbic lobe</td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>R</td>
</tr>
<tr>
<td>Thalamus</td>
<td>L</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td></td>
</tr>
<tr>
<td>Superior parietal cortex</td>
<td>R</td>
</tr>
<tr>
<td>Supramarginal cortex</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 2: Overall gray matter differences between groups
Results reported whole brain false discovery rate corrected p<0.05. MNI=Montreal Neurological Institute
Gray matter differences between problematic gamblers, alcoholics and controls

Figure 1: GM comparisons between AUDs and HCs
Smaller gray matter volumes in right left superior frontal cortex, left precentral cortex, right putamen, left thalamus, bilateral superior parietal cortex and right supramarginal cortex were found in AUDs compared to HCs (right insula not shown). Numbers are Z coordinates corresponding to the MNI space.

Common GM reductions in addicted participants: a conjunction analysis
To test whether there were significant regional brain volumes reductions that were associated with the presence of any addictive behaviour, we performed a conjunction analysis (conjunction null) incorporating the following contrasts: smoking HCs < non-smoking HCs, AUDs < non-smoking HCs, and PRGs < non-smoking HCs. The left orbitofrontal cortex (peak voxel: x, y, z = -41, 36, 14, Z= 3.45, FDR=0.011, cluster size = 41) was a region that was conjointly smaller in all groups displaying addictive behaviour compared to the subgroup of non-smoking HCs (see Figure 2).
Figure 2: Results of conjunction analyses of smaller volumes in all addicted groups
The left orbitofrontal cortex was a region that was conjointly smaller in all addicted groups compared to the non-smoking subgroup of HCs. Colour bar indicates T-scores.

Discussion
The present VBM study investigated whether problematic 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. Furthermore, a common area of reduced GM volume was found across addicted participants (PRGs, AUDs, smoking HCs) compared to non-smoking HCs.

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 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.

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, no significant volume differences were found in PRGs compared to HCs, indicating that problematic gambling behaviour is dissimilar from an alcohol use disorder with regard to brain morphology. Possibly, such neuropsychological impairments in a behavioural addiction like problematic 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.

Common GM reductions in addicted participants irrespective of type of addiction
Our conjunction analyses indicated the left orbitofrontal cortex as the area that showed decreased GM volume in all addicted participants compared to non-smoking HCs, irrespective of addiction type, i.e. nicotine, gambling or alcohol. Although this finding was post-hoc and therefore needs to be interpreted with caution, our findings are consisted with several other studies on the role of the orbitofrontal cortex in drug addiction (Dom et al.,...
Gray matter differences between problematic gamblers, alcoholics and controls

2005; Everitt et al., 2007; Koob and Volkow, 2010; Winstanley, 2007). First, the compulsive drug-seeking behaviour of addicts and its persistence despite negative consequences is similar to the behaviour of individuals with damage or dysfunction of the orbitofrontal cortex (Bechara, 2005; e.g., Bechara and Van Der Linden, 2005; Rogers et al., 1999). Second, functional imaging studies have demonstrated aberrant activation of the orbitofrontal cortex during decision making tasks and hyperactivity (Bolla et al., 2003; and see Dom et al., 2005 for a review; e.g., Ersche et al., 2006) along with other limbic cortical areas when addicts are exposed to drug-associated stimuli that elicit craving (Childress et al., 1999; McClernon et al., 2008; Wrase et al., 2007). Third, persistent metabolic or neurochemical changes have been demonstrated in the orbitofrontal cortex of drug addicts (Volkow et al., 2002; Volkow et al., 2004). Fourth, abnormalities in orbitofrontal cortex functioning associated with failure of self control, have also been found as a pre-existing vulnerability factor for the development of an addiction (e.g., Bechara, 2005; Hill et al., 2009). For instance, young adolescents with a family history of alcohol dependence performed worse on a response inhibition task in a functional magnetic resonance imaging study and showed less activation in the inferior frontal cortex and part of the orbitofrontal cortex (Schweinsburg et al., 2004). Moreover, deficits in frontal cortex regulation in children or young adolescent are known to predict later drug and alcohol consumption, especially in families with a history of drug and behavioral disorders (Dawes et al., 1997; Tarter et al., 2003). Thus, we suggest that our finding of reduced left orbitofrontal cortex volume among subjects with various types of addiction may be a vulnerability marker for the acquisition of an addiction, although this interpretation is in need of empirical confirmation.

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 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 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 externalising 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.

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. 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).

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.

**Conclusion**

In this study, no regional GM volume abnormalities in PRGs compared with HCs were present. Our findings show that problematic gambling behaviour is not associated with gray matter reductions as those found in the AUDs. In addition, we replicated previous findings of smaller regional GM volumes in AUDs. Finally, the left orbitofrontal cortex was found to be smaller than in non-addicted controls across the different types of addiction, i.e. smoking, alcohol or gambling. This suggests that the left orbitofrontal cortex may be a pre-existing factor indicating an underlying vulnerability for addictive behaviours, including non-substance related addictive behaviours. Future longitudinal studies could shed light on the causal role of abnormalities in these brain structures on the development and course of addictive behaviours.

**Acknowledgments**

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Gray matter differences between problematic gamblers, alcoholics and controls

Reference List


Gray matter differences between problematic gamblers, alcoholics and controls


Gray matter differences between problematic gamblers, alcoholics and controls


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