








AKADÉMIAI KIADÓ

# Frontal white and gray matter abnormality in gambling disorder: A multimodal MRI study

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## FULL-LENGTH REPORT



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## ABSTRACT

**Background:** Changes in brain structural connections appear to be important in the pathophysiology of substance use disorders, but their role in behavioral addictions, such as gambling disorder (GD), is unclear. GD also offers a model to study addiction mechanisms without pharmacological confounding factors. Here, we used multimodal MRI data to examine the integrity of white matter connections in individuals with GD. We hypothesized that the affected areas would be in the fronto-striatal-thalamic circuit. **Methods:** Twenty individuals with GD (mean age: 64 years, GD duration: 15.7 years) and 40 age- and sex-matched healthy controls (HCs) underwent detailed clinical examinations together with brain 3T MRI scans (T1, T2, FLAIR and DWI). White matter (WM) analysis involved fractional anisotropy and lesion load, while gray matter (GM) analysis included voxel- and surface-based morphometry. These measures were compared between groups, and correlations with GD-related behavioral characteristics were examined. **Results:** Individuals with GD showed reduced WM integrity in the left and right frontal parts of the corona radiata and corpus callosum ( $p_{FWE} < 0.05$ ). WM gambling symptom severity (SOGS score) was negatively associated to WM integrity in these areas within the left hemisphere ( $p < 0.05$ ). Individuals with GD also exhibited higher WM lesion load in the left anterior corona radiata ( $p_{FWE} < 0.05$ ). GM volume in the left thalamus and GM thickness in the left orbitofrontal cortex were reduced in the GD group ( $p_{FWE} < 0.05$ ). **Conclusions:** Similar to substance addictions, the fronto-striatal-thalamic circuit is also affected in GD, suggesting that this circuitry may have a crucial role in addictions, independent of pharmacological substances.

## KEYWORDS

gambling disorder, MRI, neuroimaging

## BACKGROUND

Gambling disorder (GD) is a prevalent behavioral addiction affecting 1–3.5% of the adult population (Shaffer, Hall, & Vander Bilt, 1999; Shaffer & Hall, 2001; Welte, Barnes, Wieczorek, Tidwell, & Parker, 2002). According to the current diagnostic criteria (DSM-5), GD is a nonsubstance-related addiction disorder characterized by an alteration in reward processing, compulsion, withdrawal, and a lack of executive control, among other clinical characteristics (Koob & Volkow, 2016). Importantly, although GD is a major problem worldwide and the prevalence is thought to be increasing (Abbott, 2020), there are no available specific pharmacological or neuromodulation treatments for this disorder.

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However, opioid antagonists such as naltrexone have shown some promise in treating GD (Di Nicola et al., 2020; Lupi et al., 2014).

The pathophysiology of GD is largely unknown but shares many clinical features with substance use disorders (SUDs) (Koob & Volkow, 2016; Leeman & Potenza, 2012). The nucleus accumbens (NAcc), located in the ventral striatum, is known to play an important role in reward processing involving the neurotransmitter dopamine. Studies have established extensive alterations of the NAcc in SUDs, affecting the reward system, such as a blunted dopamine release (Koob & Volkow, 2010). Furthermore, SUDs have typically been characterized as a disorder involving altered cortico-striatal-thalamic circuitry that leads to compulsive drug use (Goldstein & Volkow, 2002; Huang, Yang, Luo, Yan, & Liu, 2020; Kalivas, 2008; Koob & Volkow, 2010; W. Wang et al., 2018; Zorlu et al., 2013). In GD, the NAcc also exhibits abnormalities affecting fronto-striatal function (Bellmunt-Gil, Majuri, Arponen, Kaasinen, & Joutsa, 2023; Koehler et al., 2013; Limbrick-Oldfield et al., 2017; Miedl, Fehr, Meyer, & Herrmann, 2010; Reuter et al., 2005), but it does not present the same impact on the dopaminergic response as SUDs, suggesting that GD is neurobiologically different or, alternatively, that the findings in SUDs are driven by the pharmacological effects of substances of abuse (Boileau et al., 2013; Clark et al., 2012; Joutsa et al., 2012; Majuri et al., 2017). In addition, dopamine-based treatments have not shown promising results for either SUDs or GD (Álvarez, Pérez-Mañá, Torrens, & Farré, 2013; Fong, Kalechstein, Bernhard, Rosenthal, & Ruggle, 2008; McElroy, Nelson, Welge, Kaehler, & Keck, 2008; Verrico, Haile, Newton, Kosten, & Garza, 2013). Recent findings in SUDs studies have suggested that the target for addictions is likely to be at the brain network level rather than a specific cortical region or neurotransmitter (Joutsa et al., 2022).

Given the apparent structural brain circuitry abnormalities in SUDs (Goldstein & Volkow, 2002; Huang et al., 2020; Kalivas, 2008; Koob & Volkow, 2010; W. Wang et al., 2018; Zorlu et al., 2013), we aimed to investigate this issue in a behavioral addiction (GD). We hypothesized that the same mechanistic alterations would be observed in both behavioral addictions and SUDs, and thus, potential effective therapeutic neuromodulation approaches would be similar. Very few studies have focused on circuit abnormalities in GD, and only one previous study used multimodal MRI in individuals with GD (van Timmeren, Jansen, Caan, Goudriaan, & van Holst, 2017). Furthermore, previous neuroimaging studies on GD have mainly been performed in young GD subjects and have had relatively small sample sizes. Here, we recruited a sample of older adults with more age-related white matter (WM) degeneration, thus increasing analysis sensitivity, as aging is associated with variable degrees of brain atrophy and small vessel disease, as represented by WM lesions (Fjell et al., 2009; Pantoni, 2010). We hypothesized that, in relation to previous SUDs findings, a similar circuitry-level abnormality would be present in older people with GD with aging-related brain changes.

We investigated whole-brain structural abnormalities in GD using several complementary MRI techniques.

## METHODS

### Subjects

The sample consisted of 60 subjects: 20 older people with GD and 40 age- and sex-matched healthy controls (HCs), as detailed in Table 1. The subjects with GD had diagnoses confirmed using the DSM-5 criteria. The exclusion criteria were evidence of serious neurological disorders such as neurodegenerative diseases, multiple sclerosis, myasthenia gravis, brain tumors, epilepsy or stroke, as well as other psychiatric disorders (apart from GD). All participants underwent the same standardized procedure, which comprised an evaluation of electronic health records and a clinical interview to assess the following psychiatric comorbidities: behavioral addictions; current alcohol or other SUDs within the last 6 months (DSM-5); ADHD; current other Axis I disorders such as major depressive disorder, bipolar disorder or psychotic disorder; current treatment with amphetamine derivatives, methylphenidate, bupropion or other medications known to interfere with dopamine transporter (DAT) imaging; and possible psychiatric problems without diagnoses. All subjects were clinically examined 3–5 h before MRI scans. DAT imaging results of the sample have been reported previously (Kaasinen et al., 2023).

### Clinical and behavioral measures

Clinical and behavioral data (including nicotine use, smoking, alcohol use, and drug use) were collected via clinical interviews and validated questionnaires. Alcohol and nicotine doses were defined the following way: An alcohol dose was defined as 330 mL of beer (~5% alcohol), 150 mL of wine (~12% alcohol), or 40 mL of distilled spirit (~40% alcohol). A dose of nicotine was defined as one cigarette, one nicotine pouch, or one nicotine gum. A gambling behavior interview including the South Oaks Gambling Screen (SOGS) was completed, and gambling-related variables (gambling hours per week, gambling euros per week, problematic gambling years, and SOGS score) were obtained from the GD group. Other questionnaires administered to participants were the Mini-Mental State Examination (MMSE), the Barratt Impulsiveness Scale (BIS-11), the Beck Anxiety Inventory (BAI), and the Beck Depression Inventory (BDI).

### Image acquisition

MRI data were acquired with a Siemens 3T Skyra Fit scanner (Siemens Medical Imaging, Erlangen, Germany), and the imaging protocol involved three-dimensional T1, T2 and FLAIR images. For T1w images, a repetition time (TR) of 2,300.0 ms and an echo time (TE) of 2.98 ms were used. T2 images were acquired with a TR of 5,000 ms and a TE of 386 ms. Additionally, FLAIR imaging utilized a TR of 3,200 ms and a TE of 408 ms. Common parameters across



all sequences included a voxel size of  $1 \times 1 \times 1$  mm, a field of view of 256 mm, and a slice thickness of 1 mm. DWI data were collected with a single-shot spin-echo echo-planar sequence using TR/TE = 7,600/85 ms, voxel size of  $2 \text{ mm}^3$ , matrix size of  $116 \times 116 \times 80$ , and 60 gradient directions. For each participant, 60 DWI images with a b-value of  $1,000 \text{ s mm}^{-2}$ , 9 null images ( $b = 0 \text{ s mm}^{-2}$ ) and 8 inverse phase-encoding null images were acquired. The DWI data from 39 controls and 20 GD participants were analyzed. One control subject was excluded due to technical difficulties.

### White matter integrity

The DWI images were denoised and Gibbs ringing artifacts were removed with MRTrix3 (<https://www.mrtrix.org>), corrected for eddy current, head motion, and phase-related distortions within a brain mask using FMRIB Software Library (FSL, v.6.0.4) software ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)), and corrected for B1 field inhomogeneity using the ANTs toolbox (<https://www.nitrc.org/projects/ants>). The diffusion tensor voxelwise model was fitted, and the individual fractional anisotropy (FA) maps were calculated using FSL's "dtifit" algorithm.

The tract-based spatial statistics (TBSS) procedure (Smith et al., 2004, 2006) implemented in FSL was used to map individual FA data on a WM skeleton (centers of WM tracts) and spatially transform the images to the FMRIB58\_FA template in the Montreal Neurological Institute (MNI) standard space.

The group difference was estimated in a voxelwise manner on the skeletonized FA data using FSL's "randomize" nonparametric algorithm with 5,000 permutations. Age, sex, and the ratio between cerebrospinal fluid volume and total intracranial volume (CSF/TIV) were included as nuisance covariates. The analysis volume was constrained by the main WM pathways using a mask created from the "JHU ICBM-DTI-81 White-Matter Labels" atlas of 48 WM tracts. Threshold-free cluster enhancement (TFCE) (Smith & Nichols, 2009) and familywise error (FWE)-corrected  $p < 0.05$  thresholds were used to determine significant effects. To better explain the nature of between-group differences in relation to GD, individual mean FA values for each cluster with significant group differences were extracted for the GD group and analyzed in JMP Pro (SAS Institute Inc., Cary, NC) using regression models that included nuisance covariates (age, sex, and CSF/TIV) and predictors of interest related to gambling behavior: the duration of problem gambling (years), SOGS score, BDI score, BIS score, MMSE score, average total duration of gambling per week (hours) and average monetary loss due to gambling per week (€).

As there were 10 possible predictors and 20 observations in the GD group, we first applied data-driven variable selection based on a generalized regression model with an adaptive version of the least absolute shrinkage and selection operator (LASSO) (Zou, 2006) along with the corrected Akaike information criterion for model validation (Sugiura, 1978). The resulting set of predictors was included in a multiple linear regression model with the standard least

squares method, and significant ( $p < 0.05$ ) effects were identified with two-tailed  $t$  tests (Table 1S). This variable selection algorithm resembled the "screen and clean" procedure (Wu, Devlin, Ringquist, Trucco, & Roeder, 2010).

### White matter lesion locations

WM lesions were segmented on FLAIR images using an automated multistage segmentation method (Y. Wang et al., 2012) based on the expectation-maximization algorithm (Koikkalainen et al., 2016). The total lesion volume was normalized for intracranial volume (Buckner et al., 2004), age, and sex (Cole & Green, 1992).

The T1 images were normalized to the MNI template using the default normalization pipeline in SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>) using a MATLAB 2021b platform (MathWorks, Natick, MA, USA). Since WM lesions were not visible in the T1 images, they were not included in the normalization pipeline and therefore did not affect T1 image normalization. Transformations from the native T1 images to MNI space were applied to the lesions, which were then resampled to a voxel size of  $3 \times 3 \times 3$  mm. A between-groups comparison of the number and locations of the normalized lesions was performed in a voxelwise manner over the whole brain with NiiStat software ([www.nitrc.org/projects/niistat/](http://www.nitrc.org/projects/niistat/)). Age and sex were included as nuisance covariates. In addition, these findings were confirmed by controlling for the potential effect of the cardiovascular diseases present in both groups. The Freedman-Lane method was used with 2 000 permutations and a corrected  $p$  threshold of 0.05. The total lesion volume was calculated from the ROI (the left anterior corona radiata, JHU ICBM-DTI-81 White-Matter Labels), where a significant group difference was observed, to verify the findings at the tract level. A one-tailed Mann-Whitney U test was used to compare the WM lesion load between groups within this ROI, as the GD group was hypothesized to have more WM lesions than the control group.

### Voxel-based and surface-based morphometry

Voxel-based morphometry (VBM) and surface-based morphometry (SBM) analyses were conducted with the Computational Anatomy Toolbox 12 (CAT12) (<http://www.neuro.uni-jena.de/cat/>) (Gaser et al., 2022) implemented in SPM12. The default preprocessing pipeline for both analyses was used (<http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf>). Briefly, for VBM, the 3D T1 volumes were segmented in the subjects' native space, which produced separate files for GM, WM, and CSF. Then, images were spatially normalized using the DARTEL algorithm. Finally, images were smoothed by an isotropic Gaussian kernel of 8 mm full-width at half-maximum (FWHM). The resulting images were inspected visually. Age, sex and total intracranial volume (TIV) were included as covariates in the model for group analyses. As cortical analyses were conducted separately, volumetric analyses were restricted to subcortical areas using a mask created with the WFU Pickatlas toolbox



([https://www.nitrc.org/projects/wfu\\_pickatlas/](https://www.nitrc.org/projects/wfu_pickatlas/)), dilated  $\times 1$ . The mask included the bilateral caudate, putamen, accumbens, globus pallidus, thalamus, amygdala and hippocampus.

For surface-based morphometry (SBM), the default protocol from CAT12 was again used. This included surface and thickness estimation, in which projection-based thickness was used to estimate cortical thickness and to create the central cortical surface for the left and right hemispheres, and surface resampling, which included smoothing with a 12 mm FWHM filter. In this between-group analysis, age and sex were included as covariates. Effects with Family-Wise Error (FWE)-corrected  $p$  values  $< 0.05$  were considered significant for both VBM and SBM analyses.

## Statistical analyses

Statistical analyses of demographic and clinical data were performed with SPSS (IBM SPSS Statistics, version 27, Armonk, NY, USA). Independent-sample  $t$  tests, Fisher's exact tests and Mann-Whitney tests were used to identify group differences, as appropriate. To investigate relationships between behavioral/clinical data and imaging data, Pearson and Spearman correlation analyses were used.

## Ethics

Written informed consent was obtained from all participants. The study was approved by the local ethics committee and was conducted according to the Declaration of Helsinki at Turku University Hospital, Finland.

## RESULTS

### Demographic and clinical data

The demographic and clinical data are presented in Table 1. No group differences were observed in age, sex proportion,

or general cognitive capacity (MMSE scores). Along with differences in gambling-related variables, GD subjects consumed more alcohol and nicotine per week and had higher BDI scores than HCs. The prevalence of cardiovascular diagnoses (hypertension, type 2 diabetes, hypercholesterolemia, and coronary heart disease) was higher in the GD group compared to controls ( $p = 0.01$ , Table 1).

### White matter integrity

Individuals with GD had lower FA values in three clusters containing the right and left genu of the corpus callosum, right and left anterior corona radiata (CR), right superior CR, and right body of the corpus callosum (Fig. 1A, Table 2). FA values in the left anterior CR cluster were higher in smokers compared to non-smokers ( $p = 0.02$ ) and not significantly associated with alcohol use or BDI scores, indicating that the lower FA in GD compared to HC were not driven by these factors. The other 2 clusters were not significantly associated with smoking, alcohol use or BDI scores. Of gambling-related variables, SOGS scores were negatively correlated with FA values in the anterior CR (Cluster 2) ( $r = -0.51$ ,  $p = 0.02$ ) (Fig. 1B) but not with FA values of the other clusters.

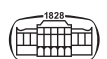
### White matter lesion locations

In the voxel-level analysis, individuals with GD had more WM lesions than HC subjects in the left anterior CR (peak at  $-21, 30, 0$ ;  $p < 0.05$ ). This result remained when controlling for cardiovascular diseases, showing also a difference in the right anterior CR and right superior CR (Fig. 1S). This was also supported by the ROI analysis results, in which individuals with GD showed an increase in lesion load in the left anterior CR ( $p < 0.05$ ) (Fig. 2). No correlation was found between the anterior CR WM lesion load and gambling-related variables. In addition, these results were not significantly associated with smoking, alcohol use or BDI scores.

Table 1. Demographic and clinical data

Variables (mean $\pm$ SD or median[IQR] or n)	GD ( $n = 20$ )	HC ( $n = 40$ )	$p$ -value
Age (years)	64.0 $\pm$ 5.7	66.8 $\pm$ 9.0	0.20
Sex (male/female)	12/8	21/19	0.78
Gambling hours per week	9.5 $\pm$ 9.3	n.a.	–
Gambling euros per week	262 $\pm$ 328	n.a.	–
Problematic gambling years	15.7 $\pm$ 14.3	n.a.	–
SOGS	9.2 $\pm$ 2.9	n.a.	–
MMSE	27.7 $\pm$ 2.1	28.0 $\pm$ 2.1	0.54
BIS score	66.8 $\pm$ 8.7	57.4 $\pm$ 6.4	<0.001
Smoking (smoker/non-smoker)	5/15	2/38	0.04
Nicotine use (doses per week)	0 [8]	0 [0]	0.04
Alcohol use (doses per week)	6.2 $\pm$ 9.2	2.8 $\pm$ 3.1	0.04
BDI	7.5 $\pm$ 9.3	2.5 $\pm$ 3.8	<0.001
Subjects with cardiovascular risk factors	16	18	0.01

SD: Standard Deviation; GD: Gambling Disorder; HC: Healthy Controls; SOGS: South Oaks Gambling Screen; MMSE: Mini-Mental State Examination; BIS: Barratt Impulsiveness Scale; BDI: Beck Depression Inventory.  $p$ -values are from independent samples  $t$ -tests, Mann-Whitney and Fisher's exact tests. IQR: Interquartile Range.



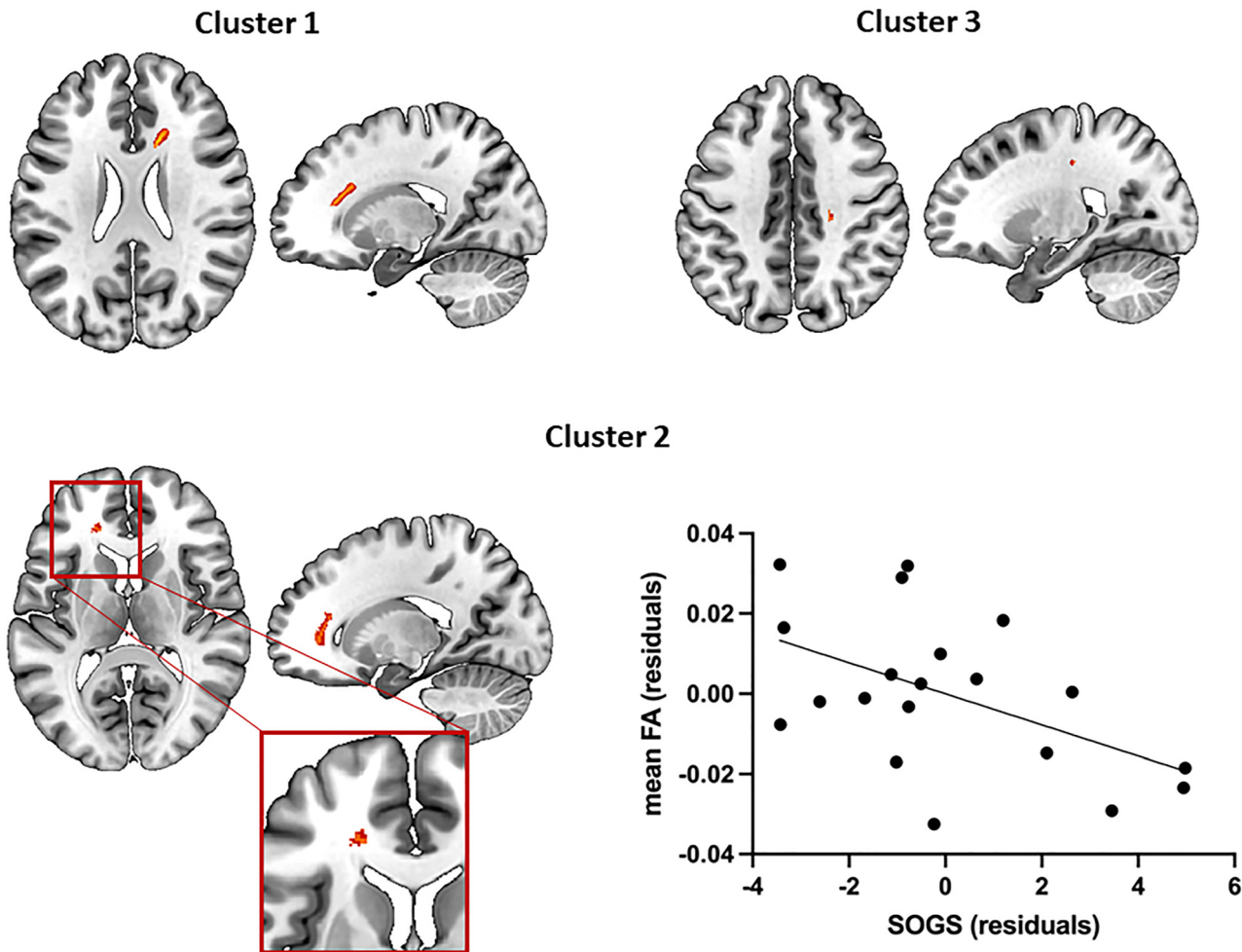


Fig. 1. FA differences between groups and correlation with SOGS scores

Location of the three clusters with lower FA values in GD group than in the HC group. The cluster indices are the same as in Table 2. The mean FA value in Cluster 2 (the left corona radiata) was negatively correlated with SOGS scores (gambling severity), as illustrated by the plot of the partial regression (corrected for confounding effects of age and CSF/TIV).

Table 2. Clusters showing lower fractional anisotropy in individuals with GD compared to controls

Cluster size (voxels)	WM atlas structure	Cluster/atlas overlap (voxels)	peak $p$ -value (TFCE)	x (mm)	y (mm)	z (mm)	Cluster index
295	R. Genu of Corpus Callosum	145	0.039	17	24	22	1
	R. Anterior Corona Radiata	118					
	R. Body of Corpus Callosum	32					
219	L. Anterior Corona Radiata	210	0.039	-19	39	5	2
	L. Genu of Corpus Callosum	9					
33	R. Superior Corona Radiata	33	0.049	21	-25	40	3

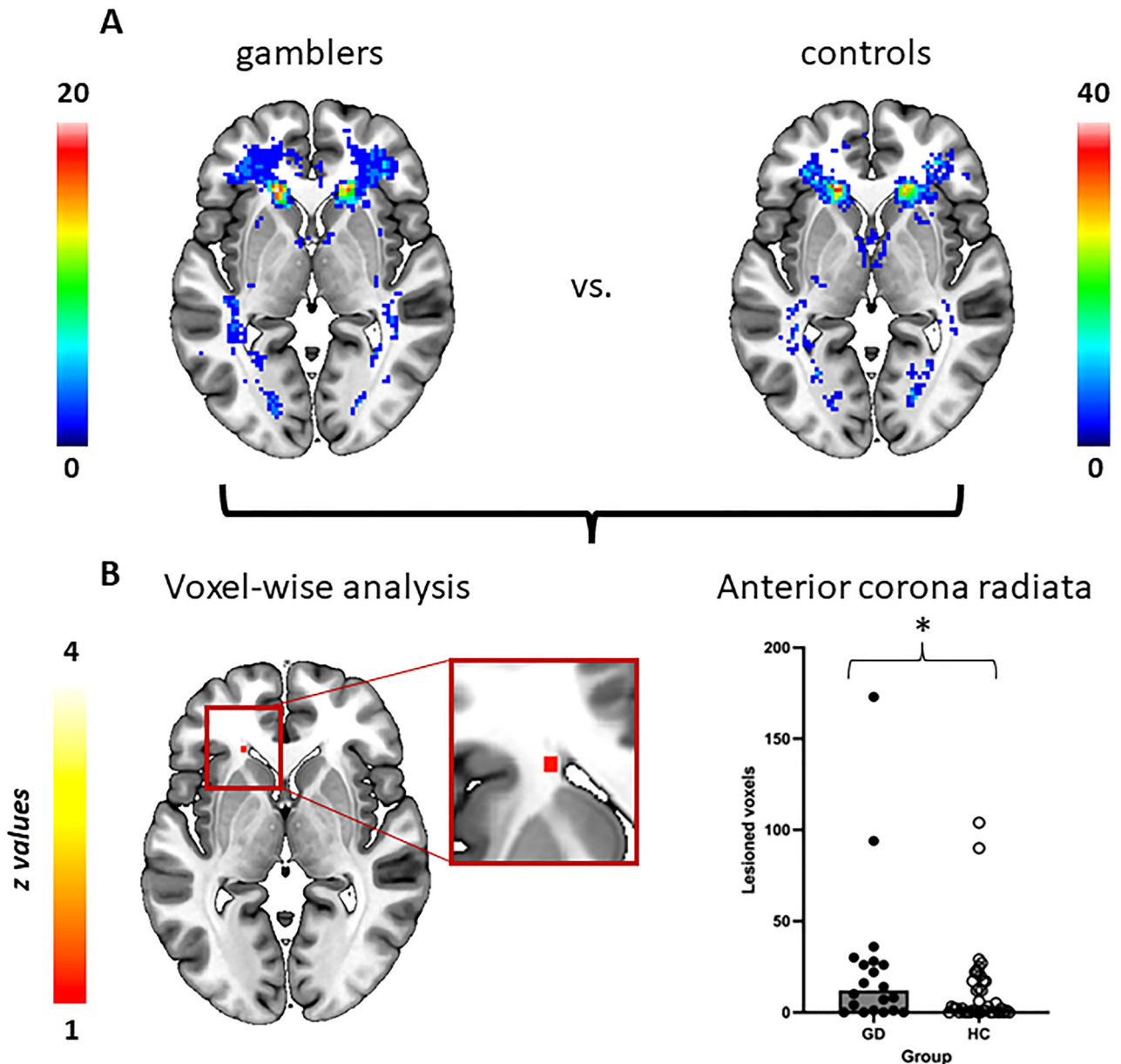
WM: White matter. TFCE: Threshold-free cluster enhancement.  $p$ -values are Family-Wise Error (FWE)-corrected. R: right. L: left.

### Voxel-based and surface-based morphometry

Within the fronto-striatal-thalamic areas, the GD group showed regional reduced cortical thickness with the largest cluster in the left orbitofrontal cortex and frontal operculum than the HC group ( $p_{FWE} < 0.001$ ) (Fig. 3A); and lower gray matter volume in the left thalamus ( $p_{FWE} = 0.042$ ) (Fig. 3B).

No correlation was found between any of these cluster values and gambling-related variables. In addition, these clusters did not show significant associations with smoking, alcohol or BDI scores, except for the intracalcarine cortex cluster in the surface-based analysis, which was thicker in smokers compared to non-smokers ( $p = 0.02$ ) and therefore unlikely to bias the observed group differences.





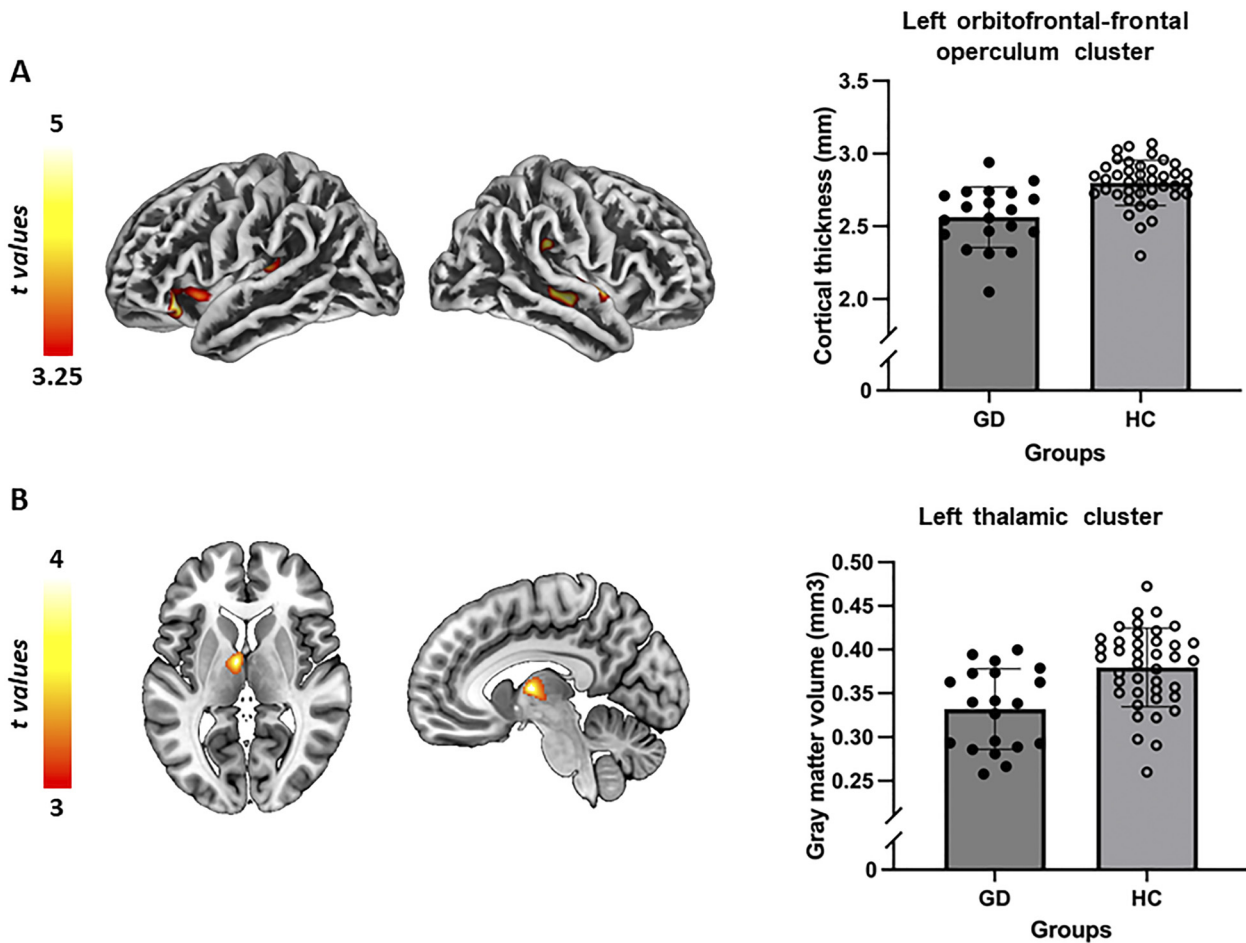
**Fig. 2. Group-differences in white matter lesion load.** A. Total lesion load in each group, representing the number of subjects with lesions in each voxel. B. Lesion locations associated with gambling disorder in the voxelwise analysis (1 significant voxel at  $-21\ 30\ 0\ \text{mm}$ ). The number of lesioned voxels in the left anterior corona radiata was higher in the GD group compared to the control group (right panel). The result remained significant even without 3 subjects with the highest values ( $p = 0.04$ )

## DISCUSSION

The present study employed a multimodal neuroimaging approach to investigate possible circuitry abnormalities in GD. The results across multiple methods converged on the fronto-striatal-thalamic circuit, involving the orbitofrontal cortex, frontal operculum, anterior CR and thalamus. This is one of the very few multimodal MRI studies in GD, showing converging findings across different modalities, highlighting the involvement of the fronto-striatal-thalamic circuitry. This circuitry has thalamic projections from the internal capsule that relay information to areas of the prefrontal

cortex and has been implicated in inhibitory control and reward seeking (Feltenstein & See, 2013; Kalivas & Volkow, 2005).

Previous studies have suggested involvement of multiple different brain structures in GD but the results vary study-by-study (Balodis et al., 2012; Choi et al., 2012; De Ruiter et al., 2009; Fuentes et al., 2015; Grant, Odlaug, & Chamberlain, 2015; Koehler et al., 2013; Miedl et al., 2010; Reuter et al., 2005; Tanabe et al., 2009; van Holst, Veltman, Büchel, van den Brink, & Goudriaan, 2012; Yip et al., 2018; Zois et al., 2017). However, most of the previous work has focused on findings with single imaging modalities. The findings of the present study show converging evidence from



**Fig. 3. Cortical surface thickness and subcortical volumetric differences between groups.** A) Clusters where individuals with GD had significantly ( $p_{FWE} < 0.05$ ) lower cortical thickness than healthy controls: Left orbitofrontal cortex and frontal operculum (peak coordinates at  $-39\ 21\ -12$  mm, cluster size 169 voxels)/Right medial temporal gyrus (peak coordinates at  $48\ -15\ -13$  mm, cluster size 140 voxels)/Intracalcarine cortex (peak coordinates at  $-14\ -66\ 8$  mm, cluster size 128 voxels)/Left superior temporal gyrus (peak coordinates at  $-43\ -20\ 1$  mm, cluster size 112 voxels)/Right temporoparietal junction (peak coordinates at  $48\ -34\ 25$  mm, cluster size 98 voxels)/Right superior temporal gyrus (peak coordinates at  $59\ 7\ -15$  mm, cluster size 84 voxels). B) Left thalamic cluster in which individuals with GD had lower gray matter volume than healthy controls (peak coordinates at  $-8\ -6\ 8$  mm, cluster size 433 voxels,  $p_{FWE} < 0.05$ ). Gamblers (GD) 0.33(0.046) vs Healthy controls (HC) 0.38 (0.045), 95% CI [0.023, 0.072]. The bar charts show the group mean, SD and individual cluster mean values for the left orbitofrontal-frontal operculum (Gamblers (GD) 0.33(0.046) vs Healthy controls (HC) 0.38 (0.045), 95% CI [0.023, 0.072]) (A) and for the left thalamus (Gamblers (GD) 2.56(0.21) vs Healthy controls (HC) 2.8 (0.16), 95% CI [0.14, 0.33]) (B).

several different MRI modalities, converging on the fronto-striatal-thalamic circuitry. In agreement with our findings, prior fMRI studies have demonstrated abnormal function in regions associated with this circuit (Balodis et al., 2012; Choi et al., 2012; De Ruiter et al., 2009; Fuentes et al., 2015; Grant et al., 2015; Koehler et al., 2013; Miedl et al., 2010; Power, Goodyear, & Crockford, 2012; Reuter et al., 2005; van Holst et al., 2012; Yip et al., 2018; Zois et al., 2017). Our findings support GD as a condition associated with disruption of the fronto-striatal-thalamic circuit, highlighting the involvement of the left anterior CR. Decreased integrity in the anterior CR has also previously been associated with SUDs, such as alcohol or cocaine dependence (Lane et al., 2010; Smith et al., 2006; Yeh, Simpson, Durazzo, Gazdzinski, & Meyerhoff, 2009; Yip

et al., 2017). Furthermore, while the fronto-striatal-thalamic circuitry was primarily impacted in our findings, additional regions in the brain demonstrated differences in the surface-based analysis.

There are few previous studies on older adults with GD (Kaasinen et al., 2023). This is notable, particularly regarding the results on WM lesions associated with aging. Here, we showed that individuals with GD had more WM lesions in the anterior CR than controls. Our results differ from some of the results reported on WM integrity in younger gamblers (Chamberlain et al., 2016; Joutsa, Saunavaara, Parkkola, Niemelä, & Kaasinen, 2011; van Timmeren et al., 2017; Yip et al., 2013), possibly due to improved power to detect age-related WM abnormalities or age-related differences in GD neurobiology between early- and late-onset GD. Our



findings align with the recently identified circuit mediating addiction remission and the targets of noninvasive brain stimulation that have been demonstrated to treat SUDs (Harel et al., 2022; Joutsa et al., 2022; Zangen et al., 2021). It is therefore possible that addictive behaviors are regulated and modulated by the same circuitry in both substance and behavioral addictions. Based on the clear involvement of the fronto-striatal-thalamic regions across addictive behaviors, an intervention targeting this circuit (e.g. indirectly modulating the circuit by targeting the frontal cortex) may effectively rebalance the network. Further clinical trials are needed, also including functional connectivity measurements.

There are certain limitations to consider when interpreting the results. First, although other research using similar methodology included a comparable or even lower number of subjects, the present total sample ( $n = 60$ ) can be considered small for a structural MRI study; thus, we may have lacked the power to detect more subtle differences between the groups or correlations with behavioral variables. Second, this was a cross-sectional study; therefore, we cannot determine causality and further longitudinal neuroimaging studies are needed. Third, the GD group had more cardiovascular diagnoses, consistent with prior findings linking gambling to increased cardiovascular disease risk, often associated with white matter hyperintensities and their distribution in the brain (Habes et al., 2018; Pilver & Potenza, 2013). Our findings remained the same when controlling for the prevalence of cardiovascular risk factors, suggesting that the findings are not driven by underlying differences in these factors. However, due to the available data and small sample size, we could not explore the effect of how different vascular risk factors are associated with specific patterns of white matter hyperintensities (Habes et al., 2018).

In summary, the results of the present study revealed disrupted fronto-striatal-thalamic circuit structure in GD, as demonstrated by a multimodal approach investigating WM integrity, WM lesion load and GM structure. The similarity of our findings in GD to those of studies on SUDs may indicate a shared mechanism between behavioral and substance addictions and highlights the role of the frontal cortex and its connections in GD.

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**Authors' contribution:** Study concept and design: JJ, VK, data collection: VK, analysis and interpretation of data: ABG, VV, JJ, VK, RP, JL, statistical analysis: ABG, JJ, obtained funding: VK, supervision: JJ, VK. ABG and VK wrote the first draft, and all authors critically reviewed the paper and approved the final version.

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## SUPPLEMENTARY MATERIALS

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## REFERENCES

- Abbott, M. W. (2020). The changing epidemiology of gambling disorder and gambling-related harm: Public health implications. *Public Health*, 184, 41–45. <https://doi.org/10.1016/j.puhe.2020.04.003>.
- Álvarez, Y., Pérez-Mañá, C., Torrens, M., & Farré, M. (2013). Antipsychotic drugs in cocaine dependence: A systematic review and meta-analysis. *Journal of Substance Abuse Treatment*, 45(1), 1–10. <https://doi.org/10.1016/j.jsat.2012.12.013>.
- Balodis, I. M., Kober, H., Worhunsky, P. D., Stevens, M. C., Pearlson, G. D., & Potenza, M. N. (2012). Diminished frontostriatal activity during processing of monetary rewards and losses in pathological gambling. *Biological Psychiatry*, 71(8), 749–757. <https://doi.org/10.1016/j.biopsych.2012.01.006>.
- Bellmunt-Gil, A., Majuri, J., Arponen, E., Kaasinen, V., & Joutsa, J. (2023). Abnormal frontostriatal connectivity and serotonin function in gambling disorder: A preliminary exploratory study. *Journal of Behavioral Addictions*, 1(aop). <https://doi.org/10.1556/2006.2023.00037>.
- Boileau, I., Payer, D., Chugani, B., Lobo, D., Behzadi, A., Rusjan, P. M., ... Zack, M. (2013). The D2/3 dopamine receptor in pathological gambling: A positron emission tomography study with [11C]-(+)-propyl-hexahydro-naphtho-oxazin and [11C]raclopride. *Addiction*, 108(5), 953–963. <https://doi.org/10.1111/add.12066>.



- Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., & Snyder, A. Z. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: Reliability and validation against manual measurement of total intracranial volume. *NeuroImage*, 23(2), 724–738. <https://doi.org/10.1016/J.NEUROIMAGE.2004.06.018>.
- Chamberlain, S. R., Derbyshire, K., Daws, R. E., Odlaug, B. L., Leppink, E. W., & Grant, J. E. (2016). White matter tract integrity in treatment-resistant gambling disorder. *The British Journal of Psychiatry*, 208(6), 579–584. <https://doi.org/10.1192/bjp.bp.115.165506>.
- Choi, J.-S., Shin, Y.-C., Jung, W. H., Jang, J. H., Kang, D.-H., Choi, C.-H., ... Kwon, J. S. (2012). Altered brain activity during reward anticipation in pathological gambling and obsessive-compulsive disorder. *Plos One*, 7(9), e45938. <https://doi.org/10.1371/journal.pone.0045938>.
- Clark, L., Stokes, P. R., Wu, K., Michalczuk, R., Benecke, A., Watson, B. J., ... Lingford-Hughes, A. R. (2012). Striatal dopamine D2/D3 receptor binding in pathological gambling is correlated with mood-related impulsivity. *NeuroImage*, 63(1), 40–46. <https://doi.org/10.1016/j.neuroimage.2012.06.067>.
- Cole, T. J., & Green, P. J. (1992). Smoothing reference centile curves: The lms method and penalized likelihood. *Statistics in Medicine*, 11(10), 1305–1319. <https://doi.org/10.1002/sim.4780111005>.
- De Ruiter, M. B., Veltman, D. J., Goudriaan, A. E., Oosterlaan, J., Sjoerds, Z., & Van Den Brink, W. (2009). Response perseveration and ventral prefrontal sensitivity to reward and punishment in male problem gamblers and smokers. *Neuropsychopharmacology*, 34(4), 1027–1038. <https://doi.org/10.1038/npp.2008.175>.
- Di Nicola, M., De Crescenzo, F., D'Alò, G. L., Remondi, C., Panaccione, I., Moccia, L., ... Janiri, L. (2020). Pharmacological and psychosocial treatment of adults with gambling disorder: A meta-review. *Journal of Addiction Medicine*, 14(4), e15. <https://doi.org/10.1097/ADM.0000000000000574>.
- Feltenstein, M. W., & See, R. E. (2013). Systems level neuroplasticity in drug addiction. *Cold Spring Harbor Perspectives in Medicine*, 3(5), a011916. <https://doi.org/10.1101/cshperspect.a011916>.
- Fjell, A. M., Walhovd, K. B., Fennema-Notestine, C., McEvoy, L. K., Hagler, D. J., Holland, D., ... Dale, A. M. (2009). One-year brain atrophy evident in healthy aging. *Journal of Neuroscience*, 29(48), 15223–15231. <https://doi.org/10.1523/JNEUROSCI.3252-09.2009>.
- Fong, T., Kalechstein, A., Bernhard, B., Rosenthal, R., & Rugle, L. (2008). A double-blind, placebo-controlled trial of olanzapine for the treatment of video poker pathological gamblers. *Pharmacology Biochemistry and Behavior*, 89(3), 298–303. <https://doi.org/10.1016/j.pbb.2007.12.025>.
- Fuentes, D., Rzezak, P., Pereira, F. R., Malloy-Diniz, L. F., Santos, L. C., Duran, F. L. S., ... Gorenstein, C. (2015). Mapping brain volumetric abnormalities in never-treated pathological gamblers. *Psychiatry Research: Neuroimaging*, 232(3), 208–213. <https://doi.org/10.1016/j.psychres.2015.04.001>.
- Gaser, C., Dahnke, R., Thompson, P. M., Kurth, F., Luders, E., & Initiative, A. D. N. (2022). CAT – A computational anatomy toolbox for the analysis of structural MRI data (p. 2022.06.11.495736). bioRxiv. <https://doi.org/10.1101/2022.06.11.495736>.
- Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, 159(10), 1642–1652. <https://doi.org/10.1176/appi.ajp.159.10.1642>.
- Grant, J. E., Odlaug, B. L., & Chamberlain, S. R. (2015). Reduced cortical thickness in gambling disorder: A morphometric MRI study. *European Archives of Psychiatry and Clinical Neuroscience*, 265(8), 655–661. <https://doi.org/10.1007/s00406-015-0592-2>.
- Habes, M., Sotiras, A., Erus, G., Toledo, J. B., Janowitz, D., Wolk, D. A., ... Davatzikos, C. (2018). White matter lesions. *Neurology*, 91(10), e964–e975. <https://doi.org/10.1212/WNL.0000000000006116>.
- Harel, M., Perini, I., Kämpe, R., Alyagon, U., Shalev, H., Besser, I., ... Zangen, A. (2022). Repetitive transcranial magnetic stimulation in alcohol dependence: A randomized, double-blind, sham-controlled proof-of-concept trial targeting the medial prefrontal and anterior cingulate cortices. *Biological Psychiatry*, 91(12), 1061–1069. <https://doi.org/10.1016/j.biopsych.2021.11.020>.
- Huang, S., Yang, W., Luo, J., Yan, C., & Liu, J. (2020). White matter abnormalities based on TBSS and its correlation with impulsivity behavior of methamphetamine addicts. *Frontiers in Psychiatry*, 11. <https://www.frontiersin.org/articles/10.3389/fpsy.2020.00452>.
- Joutsa, J., Johansson, J., Niemelä, S., Ollikainen, A., Hirvonen, M. M., Piepponen, P., ... Kaasinen, V. (2012). Mesolimbic dopamine release is linked to symptom severity in pathological gambling. *NeuroImage*, 60(4), 1992–1999. <https://doi.org/10.1016/j.neuroimage.2012.02.006>.
- Joutsa, J., Moussawi, K., Siddiqi, S. H., Abdolahi, A., Drew, W., Cohen, A. L., ... Fox, M. D. (2022). Brain lesions disrupting addiction map to a common human brain circuit. *Nature Medicine*, 28(6), Article 6. <https://doi.org/10.1038/s41591-022-01834-y>.
- Joutsa, J., Saunavaara, J., Parkkola, R., Niemelä, S., & Kaasinen, V. (2011). Extensive abnormality of brain white matter integrity in pathological gambling. *Psychiatry Research: Neuroimaging*, 194(3), 340–346. <https://doi.org/10.1016/j.psychres.2011.08.001>.
- Kaasinen, V., Honkanen, E. A., Lindholm, K., Jaakkola, E., Majuri, J., Parkkola, R., ... Seppänen, M. (2023). Serotonergic and dopaminergic control of impulsivity in gambling disorder. *Addiction Biology*, 28(2), e13264. <https://doi.org/10.1111/adb.13264>.
- Kalivas, P. W. (2008). Addiction as a pathology in prefrontal cortical regulation of corticostriatal habit circuitry. *Neurotoxicity Research*, 14(2), 185–189. <https://doi.org/10.1007/BF03033809>.
- Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: A pathology of motivation and choice. *American Journal of Psychiatry*, 162(8), 1403–1413. <https://doi.org/10.1176/appi.ajp.162.8.1403>.
- Koehler, S., Ovadia-Caro, S., van der Meer, E., Villringer, A., Heinz, A., Romanczuk-Seiferth, N., & Margulies, D. S. (2013). Increased functional connectivity between prefrontal cortex and reward system in pathological gambling. *Plos One*, 8(12), e84565. <https://doi.org/10.1371/journal.pone.0084565>.



- Koikkalainen, J., Rhodius-Meester, H., Tolonen, A., Barkhof, F., Tijms, B., Lemstra, A. W., ... Lötjönen, J. (2016). Differential diagnosis of neurodegenerative diseases using structural MRI data. *NeuroImage: Clinical*, 11, 435–449. <https://doi.org/10.1016/J.NICL.2016.02.019>.
- Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, 35(1), 217–238. <https://doi.org/10.1038/npp.2009.110>.
- Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet Psychiatry*, 3(8), 760–773. [https://doi.org/10.1016/S2215-0366\(16\)00104-8](https://doi.org/10.1016/S2215-0366(16)00104-8).
- Lane, S. D., Steinberg, J. L., Ma, L., Hasan, K. M., Kramer, L. A., Zuniga, E. A., ... Moeller, F. G. (2010). Diffusion tensor imaging and decision making in cocaine dependence. *Plos One*, 5(7), e11591. <https://doi.org/10.1371/journal.pone.0011591>.
- Leeman, R. F., & Potenza, M. N. (2012). Similarities and differences between pathological gambling and substance use disorders: A focus on impulsivity and compulsivity. *Psychopharmacology*, 219(2), 469–490. <https://doi.org/10.1007/s00213-011-2550-7>.
- Limbrick-Oldfield, E. H., Mick, I., Cocks, R. E., McGonigle, J., Sharman, S. P., Goldstone, A. P., ... Clark, L. (2017). Neural substrates of cue reactivity and craving in gambling disorder. *Translational Psychiatry*, 7(1), Article 1. <https://doi.org/10.1038/tp.2016.256>.
- Lupi, M., Martinotti, G., Acciavatti, T., Pettorruso, M., Brunetti, M., Santacroce, R., ... Di Giannantonio, M. (2014). Pharmacological treatments in gambling disorder: A qualitative review. *BioMed Research International*, 2014, e537306. <https://doi.org/10.1155/2014/537306>.
- Majuri, J., Joutsa, J., Johansson, J., Voon, V., Alakurtti, K., Parkkola, R., ... Kaasinen, V. (2017). Dopamine and opioid neurotransmission in behavioral addictions: A comparative PET study in pathological gambling and binge eating. *Neuropsychopharmacology*, 42(5), Article 5. <https://doi.org/10.1038/npp.2016.265>.
- McElroy, S. L., Nelson, E. B., Welge, J. A., Kaehler, L., & Keck, P. E. (2008). Olanzapine in the treatment of pathological gambling: A negative randomized placebo-controlled trial. *The Journal of Clinical Psychiatry*, 69(3), 13214. <https://doi.org/10.4088/jcp.v69n0314>.
- Miedl, S. F., Fehr, T., Meyer, G., & Herrmann, M. (2010). Neurobiological correlates of problem gambling in a quasi-realistic blackjack scenario as revealed by fMRI. *Psychiatry Research: Neuroimaging*, 181(3), 165–173. <https://doi.org/10.1016/j.pscychresns.2009.11.008>.
- Pantoni, L. (2010). Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology*, 9(7), 689–701. [https://doi.org/10.1016/S1474-4422\(10\)70104-6](https://doi.org/10.1016/S1474-4422(10)70104-6).
- Pilver, C. E., & Potenza, M. N. (2013). Increased incidence of cardiovascular conditions among older adults with pathological gambling features in a prospective study. *Journal of Addiction Medicine*, 7(6), 387. <https://doi.org/10.1097/ADM.0b013e31829e9b36>.
- Power, Y., Goodyear, B., & Crockford, D. (2012). Neural correlates of pathological gamblers preference for immediate rewards during the Iowa gambling task: An fMRI study. *Journal of Gambling Studies*, 28(4), 623–636. <https://doi.org/10.1007/s10899-011-9278-5>.
- Reuter, J., Raedler, T., Rose, M., Hand, I., Gläscher, J., & Büchel, C. (2005). Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nature Neuroscience*, 8(2), 147–148. <https://doi.org/10.1038/nn1378>.
- Shaffer, H. J., & Hall, M. N. (2001). Updating and refining prevalence estimates of disordered gambling behaviour in the United States and Canada. *Canadian Journal of Public Health*, 92(3), 168–172. <https://doi.org/10.1007/BF03404298>.
- Shaffer, H. J., Hall, M. N., & Vander Bilt, J. (1999). Estimating the prevalence of disordered gambling behavior in the United States and Canada: A research synthesis. *American Journal of Public Health*, 89(9), 1369–1376. <https://doi.org/10.2105/AJPH.89.9.1369>.
- Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., ... Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, 31(4), 1487–1505. <https://doi.org/10.1016/j.neuroimage.2006.02.024>.
- Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., ... Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, 23, S208–S219. <https://doi.org/10.1016/j.neuroimage.2004.07.051>.
- Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, 44(1), 83–98. <https://doi.org/10.1016/j.neuroimage.2008.03.061>.
- Sugiura, N. (1978). Further analysts of the data by akaike' s information criterion and the finite corrections. *Communications in Statistics - Theory and Methods*, 7(1), 13–26. <https://doi.org/10.1080/03610927808827599>.
- Tanabe, J., Tregellas, J. R., Dalwani, M., Thompson, L., Owens, E., Crowley, T., & Banich, M. (2009). Medial orbitofrontal cortex gray matter is reduced in abstinent substance-dependent individuals. *Biological Psychiatry*, 65(2), 160–164. <https://doi.org/10.1016/j.biopsych.2008.07.030>.
- van Holst, R. J., Veltman, D. J., Büchel, C., van den Brink, W., & Goudriaan, A. E. (2012). Distorted expectancy coding in problem gambling: Is the addictive in the anticipation? *Biological Psychiatry*, 71(8), 741–748. <https://doi.org/10.1016/j.biopsych.2011.12.030>.
- van Timmeren, T., Jansen, J. M., Caan, M. W. A., Goudriaan, A. E., & van Holst, R. J. (2017). White matter integrity between left basal ganglia and left prefrontal cortex is compromised in gambling disorder. *Addiction Biology*, 22(6), 1590–1600. <https://doi.org/10.1111/adb.12447>.
- Verrico, C. D., Haile, C. N., Newton, T. F., Kosten, T. R., & Garza, R. D. L. (2013). Pharmacotherapeutics for substance-use disorders: A focus on dopaminergic medications. *Expert Opinion on Investigational Drugs*, 22(12), 1549–1568. <https://doi.org/10.1517/13543784.2013.836488>.
- Wang, Y., Catindig, J. A., Hilal, S., Soon, H. W., Ting, E., Wong, T. Y., ... Qiu, A. (2012). Multi-stage segmentation of white matter hyperintensity, cortical and lacunar infarcts. *NeuroImage*, 60(4), 2379–2388. <https://doi.org/10.1016/J.NEUROIMAGE.2012.02.034>.



- Wang, W., Worhunsky, P. D., Zhang, S., Le, T. M., Potenza, M. N., & Li, C.-S. R. (2018). Response inhibition and fronto-striatal-thalamic circuit dysfunction in cocaine addiction. *Drug and Alcohol Dependence*, 192, 137–145. <https://doi.org/10.1016/j.drugalcdep.2018.07.037>.
- Welte, J. W., Barnes, G. M., Wieczorek, W. F., Tidwell, M.-C., & Parker, J. (2002). Gambling participation in the U.S.—results from a national survey. *Journal of Gambling Studies*, 18(4), 313–337. <https://doi.org/10.1023/A:1021019915591>.
- Wu, J., Devlin, B., Ringquist, S., Trucco, M., & Roeder, K. (2010). Screen and clean: A tool for identifying interactions in genome-wide association studies. *Genetic Epidemiology*, 34(3), 275–285. <https://doi.org/10.1002/gepi.20459>.
- Yeh, P.-H., Simpson, K., Durazzo, T. C., Gazdzinski, S., & Meyerhoff, D. J. (2009). Tract-based spatial statistics (TBSS) of diffusion tensor imaging data in alcohol dependence: Abnormalities of the motivational neurocircuitry. *Psychiatry Research: Neuroimaging*, 173(1), 22–30. <https://doi.org/10.1016/j.psychresns.2008.07.012>.
- Yip, S. W., Lacadie, C., Xu, J., Worhunsky, P. D., Fulbright, R. K., Constable, R. T., & Potenza, M. N. (2013). Reduced genual corpus callosal white matter integrity in pathological gambling and its relationship to alcohol abuse or dependence. *The World Journal of Biological Psychiatry*, 14(2), 129–138. <https://doi.org/10.3109/15622975.2011.568068>.
- Yip, S. W., Morie, K. P., Xu, J., Constable, R. T., Malison, R. T., Carroll, K. M., & Potenza, M. N. (2017). Shared microstructural features of behavioral and substance addictions revealed in areas of crossing fibers. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2(2), 188–195. <https://doi.org/10.1016/j.bpsc.2016.03.001>.
- Yip, S. W., Worhunsky, P. D., Xu, J., Morie, K. P., Constable, R. T., Malison, R. T., ... Potenza, M. N. (2018). Gray-matter relationships to diagnostic and transdiagnostic features of drug and behavioral addictions. *Addiction Biology*, 23(1), 394–402. <https://doi.org/10.1111/adb.12492>.
- Zangen, A., Moshe, H., Martinez, D., Barnea-Ygael, N., Vapnik, T., Bystritsky, A., ... George, M. S. (2021). Repetitive transcranial magnetic stimulation for smoking cessation: A pivotal multicenter double-blind randomized controlled trial. *World Psychiatry*, 20(3), 397–404. <https://doi.org/10.1002/wps.20905>.
- Zois, E., Kiefer, F., Lemenager, T., Vollstädt-Klein, S., Mann, K., & Fauth-Bühler, M. (2017). Frontal cortex gray matter volume alterations in pathological gambling occur independently from substance use disorder. *Addiction Biology*, 22(3), 864–872. <https://doi.org/10.1111/adb.12368>.
- Zorlu, N., Gelal, F., Kuserli, A., Cenic, E., Durmaz, E., Saricicek, A., & Gulseren, S. (2013). Abnormal white matter integrity and decision-making deficits in alcohol dependence. *Psychiatry Research: Neuroimaging*, 214(3), 382–388. <https://doi.org/10.1016/j.psychresns.2013.06.014>.
- Zou, H. (2006). The adaptive lasso and its oracle properties. *Journal of the American Statistical Association*, 101(476), 1418–1429. <https://doi.org/10.1198/016214506000000735>.

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