Psychiatry. The definitive publisher-authenticated version is available online at http://bjp.rcpsych.org.

For resubmission to the BJP as an Article

Word Count: abstract 158; body 2583

Tables: 1; Figures: 3

Supplementary Online Figures: 2

White Matter Tract Integrity in Treatment-Resistant Gambling Disorder

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ABSTRACT

Background: Gambling disorder is a relatively common psychiatric disorder recently re-classified within the DSM-5 under the category of "Substance-Related and Addictive Disorders".

Aims: To compare white matter integrity in patients with gambling disorder to healthy controls; to explore relationships between white matter integrity and disease severity in gambling disorder.

Method: 16 subjects with treatment-resistant gambling disorder and 15 healthy controls underwent Magnetic Resonance Imaging. White matter integrity was analyzed using tract based spatial statistics (TBSS).

Results: Gambling disorder was associated with reduced fractional anisotropy in the corpus callosum and superior longitudinal fasciculus. Fractional anisotropy in distributed white matter tracts elsewhere correlated positively with disease severity.

Conclusions: Reduced corpus callosum fractional anisotropy is suggestive of disorganized/damaged tracts in patients with gambling disorder, and this may represent a trait/vulnerability marker for the disorder. Future research should explore these measures in a larger sample, ideally incorporating a range of imaging markers (e.g. functional MRI), and enrolling unaffected first-degree relatives of patients.

Declaration of Interest(s): This research was supported by a grant from the National Center for Responsible Gaming to Dr. Grant, and by a grant from the Academy of Medical Sciences to Dr. Chamberlain (UK). Dr. Grant has received research grants from NIMH, National Center for Responsible Gaming, and Forest and Roche Pharmaceuticals Dr. Grant receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the Journal of Gambling Studies and has received royalties from Oxford University Press, American Psychiatric Publishing, Inc., Norton Press, and McGraw Hill. Dr. Chamberlain consults for Cambridge Cognition. Mr. Odlaug has received a research grant from the Trichotillomania Learning Center, consults for H. Lundbeck A/S, and has received royalties from Oxford University Press. Mr. Leppink and Ms. Derbyshire report no conflicts of interest.

Keywords: compulsivity; gambling; imaging; impulsivity; white matter

INTRODUCTION

Gambling is a commonplace recreational activity dating back thousands of years, yet for between 1-3% of the population, it develops into a dysfunctional pattern of behavior (1). In those who develop gambling disorder, the behavior is associated with significant personal, financial, and relationship difficulties (2, 3) as well as elevated rates of suicide (4). Despite the morbidity and mortality associated with gambling disorder, brain architecture in gambling disorder has received limited research attention.

To the knowledge of the authors, only two studies to date have explored white matter tract integrity in gambling disorder. Joutsa and colleagues found reduced white matter integrity (reduced fractional anisotropy) in multiple regions, using tract based spatial statistics (TBSS), in 12 patients with gambling disorder compared to 12 controls (5). Regions of abnormality included the corpus callosum, cingulum, superior longitudinal fascicle, inferior fronto-occipital fascicle, anterior limb of internal capsule, anterior thalamic radiation, inferior longitudinal fascicle and the uncinate/inferior fronto-occipital fascicle. The authors found no significant grey matter volume abnormalities in the patients. A separate study focusing on the corpus callosum (region of interest rather than whole-brain approach) found reductions of white matter integrity (reduced fractional anisotropy) in sectors of the corpus callosum in 19 subjects with gambling disorder versus 19 controls (6).

Thus, tentative evidence for white matter abnormalities in gambling disorder has been reported in two previous studies. Neither study, however, explored possible relationships between white matter abnormalities and disease severity, or used a treatment-resistant sample. While little is known about the clinical differences between patients with non-treatment-resistant and treatment-resistant gambling disorder, research into other psychiatric disorders such as

depression indicate that treatment-resistant patients are more severe and place a larger burden on the health care system than non-treatment-resistant patients with depression (7). We therefore explored white matter in treatment-resistant gambling disorder versus healthy controls, and relationships between white matter parameters and disease severity in gambling disorder. Based on the previous literature, we hypothesized that those with gambling disorder would show reduced white matter integrity in the corpus callosum.

METHOD

Subjects

Subjects with gambling disorder were recruited from an outpatient psychiatry clinic and from media advertisements on the basis of meeting DSM-5 criteria (i.e., minimum of 4 of 9 DSM-5 criteria) (8). Inclusion criteria across all subjects were: 18-65 years old, right-handedness, no current or past month use of psychotropic medications, not pregnant or breast-feeding, a negative urine drug screen, and no contraindication to MRI. Subjects with gambling disorder were required to be treatment-resistant, which we defined as having completed at least 6 sessions of cognitive behavioral therapy and a trial of naltrexone for their gambling disorder with limited or no success. Cognitive behavioral therapy was delivered by trained psychologists using a manualized treatment. Treatment consisted of 6 sessions (psychoeducation, motivational enhancement, functional analysis and behavioural strategies, coping with gambling urges and changing irrational thinking, imaginal desensitization, and relapse prevention) (9)Naltrexone treatment comprised at least 12 weeks at an adequate treatment dose (defined as 50mg/day or higher) (10). Limited or no success was operationalized as a less than 35% reduction from baseline in total disease severity scores, measured using the Yale Brown Obsessive Compulsive

Scale modified for Pathological Gambling (PG-YBOCS) (11). Previous literature indicates that naltrexone treatment is unsuccessful in approximately 25% of cases (12), and that CBT is ineffective in approximately 7-32% of cases (13).

Exclusion criteria for patients included any current psychotic, bipolar or substance use disorder, or any lifetime substance use disorder.

Healthy controls were recruited via word of mouth or media advertisements. They were required to have no current or lifetime psychiatric disorders and no family history of either substance or behavioral addiction. Family members were not interviewed directly and report of family history was based on self-report by the control subjects.

Procedures

All subjects underwent a semi-structured psychiatric evaluation by a board certified psychiatrist. Gambling symptomatology was assessed using the Structured Clinical Interview for Pathological Gambling (SCI-PG) (11) which was adapted for DSM-5 (8), the Yale Brown Obsessive Compulsive Scale modified for Pathological Gambling (PG-YBOCS) (clinician-administered scale of gambling severity for the past week with two subscales gambling behavior and gambling urges) (14), and the Gambling Symptom Assessment Scale (G-SAS) (self-report scale of gambling severity for the past week) (15). Psychiatric comorbidity was assessed using the Mini International Neuropsychiatric Inventory (MINI) (16). Other assessments included the Hamilton Depression Scale (17), the Sheehan Disability Scale (18), and the Quality of Life Inventory (QoLI) (19).

All subjects underwent a comprehensive safety assessment for magnetic resonance imaging (MRI). Upon completion of these assessments, structural imaging was conducted on the same day using a 3-Tesla (3T) Siemen's system.

All study procedures were conducted in accordance with the ethical standards established by the latest version of the Declaration of Helsinki. A full Institutional Review Board approved the study and all consent procedures. After complete description of the study to the subjects, participants provided written informed consent. No secondary consent (i.e., parent or guardian) was allowed for this study.

Data Analysis

Demographic characteristics

Between-group differences in salient demographic characteristics were explored using independent sample t-tests, with statistical significance defined as $p<0.05$ uncorrected.

Diffusion MRI scans and preprocessing

Imaging data were acquired using a 3-T system. Diffusion-weighted imaging data were obtained (25 directions) with slice thickness of 4 mm, temporal resolution of 12 s, echo time of 93 ms, matrix size of 128 × 128, field of view of 30 × 24 cm2, and B-value of 1000 s/mm2. One volume without diffusion weighting (b=0) was also acquired. To provide a reference, axial three-dimensional T1-weighted images were obtained using a spoiled-gradient recall sequence with slice thickness of 2 mm, temporal resolution of 33 ms, echo time of 3 ms, field of view of 24 cm, flip angle of 40°, and matrix size of 256 × 256.

Individuals raw diffusion and b = 0 volumes were concatenated into a single 4D file prior to being corrected for geometric and eddy current distortions, and subject motion (20,21). Following this, affine transformations were used to warp each diffusion volume within each subjects timeseries to the b = 0 reference image. Subject specific brain masks were created to demarcate voxels to be modeled with the diffusion tensor. Tensors were fit to each voxel within each subject's brain mask using a least squares weighted approach. From this, whole brain maps of Fractional Anisotropy (FA), Mean Diffusivity (MD), and EigenValue1, 2 and 3 were generated. FA is a measure of directionality of water diffusion, while MD is the mean of the three eigenvalues and provides a measure of average water mobility.

Tract Based Spatial Statistics (TBSS)

Analyses were conducted using previously validated procedures as implemented in TBSS software (20,21). Voxel outliers from the 4D files were removed and each subject's FA images were then aligned to each other subjects FA image. This process selected the most representative target image of the group which was then affine aligned into MNI space. Subsequently, all of the other images were registered into MNI space based on the nonlinear transformations that were carried out on the representative image. From this a mean FA image was created and thinned to form a white matter skeleton that represents the centers of all tracts common to the group.

Group Level and correlational analyses

Voxelwise statistics were used to test for group differences in measures of diffusivity using a significance threshold of $p < 0.05$). Each subject's aligned FA data were projected onto this skeleton and the resulting data were fed into voxel-wise cross-subject statistics.

Group differences in each measure of diffusion were tested for using a permutation-based analysis with 10,000 permutations. The resulting statistical maps were corrected for using Threshold-Free Cluster Enhancement (TFCE) and Family Wise Error (FWE – $p < 0.05$). Unless stated, age was mean centered and was included as a covariate of no interest. This process was repeated within the Gambling patient group to investigate whether gambling measures correlated with voxel-wise measurement of diffusion. Variables were mean-centered and each analysis included age as a covariate of no interest. For visualization, voxels showing significant differences were filled. All maps were rendered using the lowest probability values possible.

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RESULTS

Demographic and clinical characteristics of the sample are shown in Table 1. A total of 16 patients with DSM-5 gambling disorder (mean age 47.0±13.9 years) and 15 healthy controls (mean age 32.9±14.7 years) were enrolled and underwent brain imaging. The gambling disorder subjects were significantly older than the controls ($p=0.007$). There were no other significant demographic differences between groups. The gambling disorder sample had a mean PG-YBOCS score of 24.2±4.7 and a mean G-SAS score of 33.8±7.1 both of which corresponded to a severe gambling disorder. Gambling disorder subjects had a low quality of life (mean total score of 29.8±12.6) according to the QoLI but relatively low depression scores on the HAM-D (mean total score 8.3±4.5).

Between Group differences in measures of diffusion

TBSS analysis demonstrated significantly reduced fractional anisotropy (FA) in gambling disorder subjects versus controls (Figure 1, shown in red). This cluster of reduced FA in the gambling subjects is interpreted as corpus callosal fibres including the middle and middle posterior body of the corpus callosum, which either extend from the corpus callosal proper or is also present in an independent aspect of the superior longitudinal fasciculus / cortico spinal tract. When age was not included as a covariate in the analysis, this difference in these regions remained significant, but also extended across a broader range of areas (Figure 1, shown in blue). No significant group differences were observed based on Mean Diffusivity (MD).

* FIGURE 1 AROUND HERE PLEASE *

Relationships with gambling measures in gambling disordered subjects

In subjects with treatment-resistant gambling disorder, there was a significant positive correlation (p=0.03) between theurge subscale of the PG-YBOCS and FA in distributed white matter tracts (Figure 2); and a significant positive correlation (p=0.01) between G-SAS and FA within large right hemisphere white matter tracts (Figure 3). Representative scatter plots are provided in Supplementary Online Figures 1 and 2 respectively. No significant correlations were found between FA and the gambling behavior subscale of the PG-YBOCS nor were significant correlations found between Mean Diffusivity and any of these clinical measures.

***** FIGURES 2 & 3 AROUND HERE PLEASE *

DISCUSSION

To our knowledge, this is the first study to examine white matter tract integrity in treatment-resistant gambling disorder subjects versus controls. Gambling disorder was associated with significant reductions of fractional anisotropy in the corpus callosum, suggestive of damaged and/or disorganized white matter. Additionally, fractional anisotropy was positively correlated with symptom severity in other white matter regions in the gambling disordered participants. No group differences were identified with respect to mean diffusivity, suggesting that the white matter abnormalities were more related to microarchitecture of tracts (i.e. tract integrity) than local lesions.

Our finding of reduced fractional anisotropy in the corpus callosum (Figure 1) is in broad agreement with reductions in fractional anisotropy seen in this region in two previous gambling disorder studies. Yip and colleagues used a region-of-interest approach, exploring white matter in distinct sectors of the corpus callosum. They found reduced fractional anisotropy values in the left body and left and right genu in particular, versus controls (6). By contrast, Joutsa et al. used a whole brain approach (TBSS) as we did here; the authors reported reduced fractional anisotropy not just in the corpus callosum but also elsewhere, in patients with gambling disorder compared to controls (5). It is unclear why our group-level differences are more restricted in anatomical scope as compared to this second study. There were several differences between the current study and (5): we included men and women while the other study was male only, our study had a larger sample size; finally, age differed between groups in our study but not in the other study.

Our data add to a growing body of evidence implicating aberrant white matter tracts of the corpus callosum across impulsive and compulsive disorders. Similar abnormalities of fractional anisotropy in this region have been found in obsessive compulsive disorder (22), kleptomania (23), trichotillomania (24), and in various substance use disorders (25). The white

matter of the corpus callosum enables communication and integration of information across distributed grey matter nodes, and is heavily implicated in cognitive functioning, including in top-down inhibitory control (26). Thus it is conceivable, but has yet to be demonstrated, that diminished integrity of the corpus callosum in gambling disorder may underpin some of the cognitive deficits observed in gambling disorder across studies (27).

While reduced fractional anisotropy was found in the corpus callosum, fractional anisotropy was positively (rather than negatively) associated with worse symptom severity in the gambling disordered participants, across a broad swathe of other white matter regions (Figures 2 & 3). One interpretation of these findings is disorganized white matter tracts in the corpus callosum may represent a vulnerability marker (or trait marker) in gambling disorder, which does not relate directly to symptom severity, while more organized white matter tracts elsewhere are associated with worse symptom severity and so correspond to the state nature of the illness. Given that the positive correlation between symptom severity and FA was contrary to our expectations, replication will be important in future work to confirm or refute this relationship. It is not possible, on the basis of the current study, to establish whether this positive relationship between symptom severity and higher FA in certain regions is intrinsic to the illness, or rather represents some form of adaptive brain changes / compensatory mechanisms. These issues should be further addressed in larger studies, ideally incorporating not just DTI but also functional neuroimaging, including analysis of functional connectivity across salient neural nodes. Future work could include unaffected first-degree relatives of patients to confirm or refute the trait-like nature of the corpus callosum abnormalities.

There are several limitations that should be considered. First, the overall sample size was small and primarily Caucasian in ethnic origin. Larger sample sizes with greater diversity would

be ideal for future studies in order to provide a more population-representative overview of gambling disorder. Second, gambling disorder patients were significantly older than the healthy control population. Age is known to be an important factor when considering measurements of diffusivity in the brain (e.g. 28). Fractional anisotropy has been found to vary in normal ageing, with the direction of effect and magnitude of such changes varying considerably depending on the region considered (29). For example, age has been reported to be negatively correlated with fractional anisotropy in the corpus callosum genu, but not significantly correlated (in either direction) with fractional anisotropy in the corpus callosum body (29). Despite the significant age differences, however, the between-group differences in FA in the corpus callosum were evident whether or not age was included as a covariate in the analysis, suggesting that the result was not driven by this potential confound. Future studies, however, should aim to provide a sample of age- and gender-matched controls in order to more robustly address the questions at hand. Another caveat of the current study, relevant to all DTI studies, is that fractional anisotropy can be influenced by a variety of factors apart from myelination, such as crossing fiber tracts (30). While we refer to the reduced FA in gambling disorder as being consistent with reduced structural integrity of white matter tracts, this does necessarily imply an underlying specific structural pathology, such as that seen with advancing age, or in the case of demyelinating neurological disorders; put differently, the underlying causes of reduced FA seen here cannot be addressed using the current neuroimaging techniques.

Table 1. Demographic and Clinical Characteristics of Gamblers versus Controls

	Gambling Disorder (n=16)	Healthy Controls (n=15)	Statistic	p-value
Age, years	47.4 (13.7)	32.5 (14.9)	2.889t	**0.007**
Sex, female, n (%)	10 (62.5)	12 (80)	1.151c	0.283
Ethnicity, Caucasian, n (%)	13 (81.5)	14 (93.3)	1.006c	0.316
Education, ≥College, n (%)	8 (50)	11 (73.3)	1.777c	1.823
HAM-D	8.3 (4.5)			
PG-YBOCS, urges	12.2 (2.8)			
PG-YBOCS, behaviors	12 (3.6)			
PG-YBOCS, total score	24.2 (4.7)			
G-SAS	33.8 (7.1)			
Sheehan Disability Scale	17.8 (8.2)			
Quality of Life Score	29.8 (12.6)			

Data refer to mean (standard deviation) unless otherwise specified.
t=independent sample t-test; c=chi-square
PG-YBOCS: Yale-Brown Obsessive Compulsive Scale for Pathological Gambling; HAM-D: Hamilton Depression Rating Scale; G-SAS: Gambling Symptom Assessment Scale

REFERENCES

1. Hodgins DC, Stea JN, Grant JE. Gambling disorders. Lancet 2011;378(9806):1874-84.

2. Black DW, Shaw M, McCormick B, Allen J. Pathological gambling: relationship to obesity, self-reported chronic medical conditions, poor lifestyle choices, and impaired quality of life. Compr Psychiatry. 2013 Feb;54(2):97-104.

3. Grant JE, Kim SW. Demographic and clinical features of 131 adult pathological gamblers. J Clin Psychiatry. 2001 Dec;62(12):957-62.

4. Thon N, Preuss UW, Pölzleitner A, Quantschnig B, Scholz H, Kühberger A, Bischof A, Rumpf HJ, Wurst FM; Austrian Society for the research of non-substance related Addiction. Prevalence of suicide attempts in pathological gamblers in a nationwide Austrian treatment sample. Gen Hosp Psychiatry. 2014 May-Jun;36(3):342-6.

5. Joutsa J, Saunavaara J, Parkkola R, Niemelä S, Kaasinen V. Extensive abnormality of brain white matter integrity in pathological gambling. Psychiatry Res 2011;194(3):340-6.

6. Yip SW, Lacadie C, Xu J, Worhunsky PD, Fulbright RK, Constable RT, Potenza MN. Reduced genual corpus callosal white matter integrity in pathological gambling and its relationship to alcohol abuse or dependence. World J Biol Psychiatry 2013;14(2):129-38

7. Greenberg P, Corey-Lisle PK, Birnbaum H, Marynchenko M, Claxton A. Economic implications of treatment-resistant depression among employees. Pharmacoeconomics 2004;22(6):363-73.

8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (5th ed.) (DSM-5). Arlington, VA: American Psychiatric Publishing; 2013.

9. Grant JE, Donahue CB, Odlaug BL, Kim SW, Miller MJ, Petry NM. Imaginal desensitisation plus motivational interviewing for pathological gambling: randomised controlled trial. Br J Psychiatry. 2009;195(3):266-267.

10. Grant JE, Kim SW, Hollander E, Potenza MN. Predicting response to opiate antagonists and placebo in the treatment of pathological gambling. Psychopharmacology (Berl). 2008; 200(4):521-527.

11. Grant JE, Steinberg MA, Kim SW, Rounsaville BJ, Potenza MN. Preliminary validity and reliability testing of a structured clinical interview for pathological gambling. Psychiatry Res 2004;128(1):79-88.

12. Kim SW, Grant JE, Adson DE, Shin YC. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. Biol Psychiatry. 2001 Jun 1;49(11):914-21.

13. Oei TP, Raylu N, Casey LM. Effectiveness of group and individual formats of a combined motivational interviewing and cognitive behavioral treatment program for problem gambling: a randomized controlled trial. Behav Cogn Psychother. 2010 Mar;38(2):233-8.

14. Pallanti S, DeCaria CM, Grant JE, Urpe M, Hollander E. Reliability and validity of the pathological gambling adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS). J Gambl Stud 2005;21(4):431-43.

15. Kim SW, Grant JE, Potenza MN, Blanco C, Hollander E. The Gambling Symptom Assessment Scale (G-SAS): a reliability and validity study. Psychiatry Res. 2009 Mar 31;166(1):76-84.

16. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. The Journal of clinical psychiatry. 1998;59 Suppl 20:22-33.

17. Hamilton M. A rating scale for depression. Journal of neurology, neurosurgery, and psychiatry. 1960;23:56-62.

18. Sheehan DV. The Anxiety Disease. New York: Scribner. 1983.

19. Frisch MB, Cornell J, M V. Clinical validation of the Quality of Life Inventory: a measure of life satisfaction for use in treatment planning and outcome assessment. Psychol Assess. 1993;4(1):92-101.

20. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004;23 Suppl 1:S208-19.

21. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006 Jul 15;31(4):1487-505.

22. Koch K, Reess TJ, Rus OG, Zimmer C, Zaudig M. Diffusion tensor imaging (DTI) studies in patients with obsessive-compulsive disorder (OCD): a review.J Psychiatr Res. 2014 Jul;54:26-35.

23. Grant JE, Correia S, Brennan-Krohn T. White matter integrity in kleptomania: a pilot study. Psychiatry Res. 2006 Oct 30;147(2-3):233-7.

24. Chamberlain SR, Hampshire A, Menzies LA, Garyfallidis E, Grant JE, Odlaug BL, Craig K, Fineberg N, Sahakian BJ. Reduced brain white matter integrity in trichotillomania: a diffusion tensor imaging study. Arch Gen Psychiatry. 2010 Sep;67(9):965-71.

25. Salo R, Nordahl TE, Buonocore MH, Natsuaki Y, Waters C, Moore CD, Galloway GP, Leamon MH. Cognitive control and white matter callosal microstructure in methamphetamine-dependent subjects: a diffusion tensor imaging study. Biol Psychiatry. 2009 Jan 15;65(2):122-8.

26. King AV, Linke J, Gass A, Hennerici MG, Tost H, Poupon C, Wessa M. Microstructure of a three-way anatomical network predicts individual differences in response inhibition: a tractography study. Neuroimage. 2012 Jan 16;59(2):1949-59.

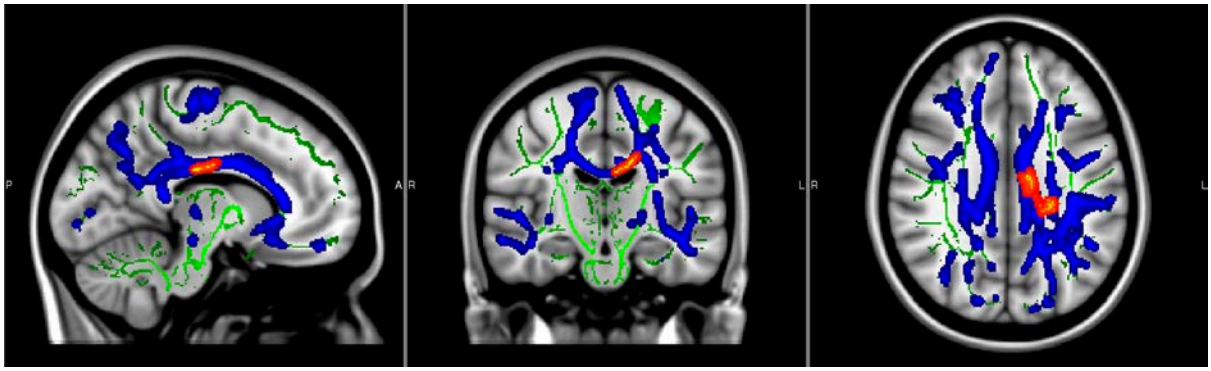
27. Goudriaan AE, Yücel M, van Holst RJ. Getting a grip on problem gambling: what can neuroscience tell us? Front Behav Neurosci. 2014 May 20;8:141.

28. Bhagat YA, Beaulieu C. Diffusion anisotropy in subcortical whitematter and cortical gray matter: Changes with aging and the role of CSF-suppression. J Magn Reson Imaging 2004; 20(2): 216-27

29. Yang Y, Bender AR, Raz N. Age related differences in reaction time components and diffusion properties of normal-appearing white matter in healthy adults. Neuropsychologia. 2015 Jan;66:246-58.

30. Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. Neuroimage. 2013 Jun;73:239-54.

Figure 1. Results of permutation cluster analysis of fractal anisotropy (FA). In red (top and bottom figure), regions of significantly reduced FA in gambling disorder versus controls, after controlling for age. In blue (top figure), regions of significantly reduced FA in gambling disorder versus controls, without including age as a covariate.



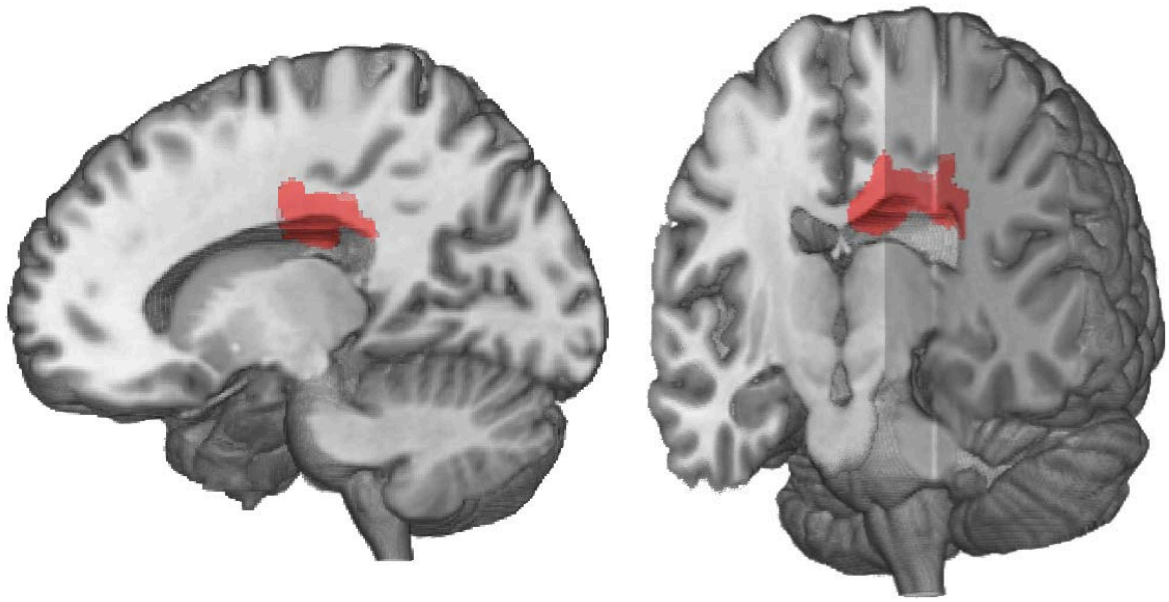


Figure 2. Results of permutation analysis for clinical measures in the gamblers. In red, regions in which fractal anisotropy (FA) correlated positively against the urge subscale of the PG-YBOCS ($p<0.03$).

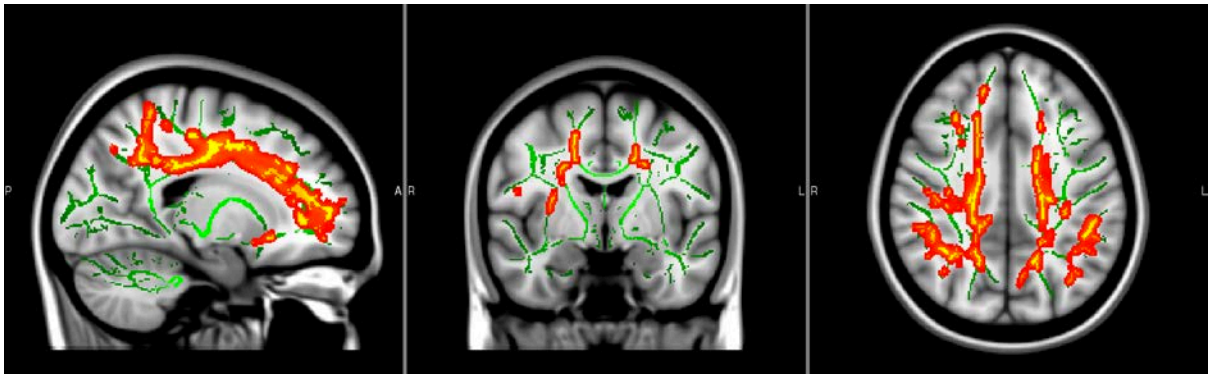


Figure 3. Results of permutation analysis for clinical measures in the gamblers. In red, regions in which fractal anisotropy (FA) correlated positively against the G-SAS ($p<0.01$).