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Reduced genual corpus callosal white matter integrity in pathological gambling and its relationship to alcohol abuse or dependence

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Abstract

Objective—Magnetic resonance imaging (MRI) studies have demonstrated functional prefrontal cortical (PFC) abnormalities in pathological gambling (PG) and other psychiatric disorders characterized by impaired impulse control; e.g. cocaine dependence and bipolar disorder. These abnormalities are accompanied by impairments in white matter microstructures in the anterior (genual) corpus callosum (CC) in cocaine dependence and bipolar disorder. Prior studies have not examined white matter integrity in PG.

Methods—19 participants with PG and 19 matched control participants underwent diffusion tensor imaging (DTI) to compare white matter integrity in the CC, as assessed using fractional anisotropy (FA).

Results—In PG subjects as compared to control subjects, reduced FA values in the left and right genu of the CC were observed. Multiple regression analyses confirmed that PG status - in addition to age and past alcohol abuse/dependence (AA/AD) – was a significant predictor of genual FA values.

Conclusion—Findings of decreased FA values in the genu of the CC in PG subjects suggest that, like with other disorders of behavioral dyscontrol, white matter microstructural abnormalities contribute to the pathophysiology of PG. These differences appear particularly relevant to individuals with remitted AA/AD, highlighting the importance of considering co-occurring substance use disorders when investigating PG.

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Authors contribution:
Marc Potenza was responsible for the study concept and design. Sarah Yip and Cheryl Lacadie conducted the diffusion tensor analyses. Sarah Yip conducted the statistical comparisons of FA values and impulsivity measures, wrote the first draft of the manuscript and worked with Marc Potenza on subsequent drafts. Robert Fulbright advised on ROI identification. Patrick Worhunsky, Jiansong Xu and Todd Constable advised on imaging acquisition and analysis. All authors have reviewed and revised the manuscript during preparation and approved the content of this submission.

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Keywords

corpus callosum; diffusion tensor imaging; fractional anisotropy; impulse control disorder; pathological gambling; substance use

Introduction

Pathological gambling (PG) is characterized in the Diagnostic and Statistical Manual 4th Edition (DSM-IV; American Psychiatric Association, 1995) as an impulse control disorder (ICD). Consistently, individuals with PG have scored high on measures of impulsivity (Blaszczynski et al., 1997; Potenza et al., 2003b). Functional magnetic resonance imaging (fMRI) studies have reported abnormalities in prefrontal cortex (PFC - particularly in its ventromedial component), particularly as related to function underlying impulse control (e.g., in risk/reward decision-making and cognitive control) in PG (Tanabe et al., 2007; Potenza et al., 2003a), and in other disorders characterized by impulsivity; e.g. cocaine dependence (Volkow and Fowler, 2000) and bipolar disorder (Blumberg et al., 2003). Studies using diffusion tensor imaging (DTI) - a technique allowing for the *in vivo* assessment of white matter integrity based on the directionality of diffusion of water molecules in the brain (Mori and Zhang, 2006) - have demonstrated microstructural abnormalities in the inferior frontal cortex and anterior corpus callosum (CC) in cocaine dependence (Lim et al., 2002; Lim et al., 2008; Moeller et al., 2005; Moeller et al., 2007), bipolar disorder (Yurgelun-Todd et al., 2007; Wang et al., 2008; Chaddock et al., 2009; Barnea-Goraly et al., 2009; Kafantaris et al., 2009), alcohol dependence (AD; Pfefferbaum et al., 2000; Pfefferbaum et al., 2002; Pfefferbaum et al.,2004) and ICDs, including kleptomania (Grant et al., 2006) and trichotillomania (Chamberlain et al., 2010). The extent to which white matter abnormalities exist in PG has not been previously assessed.

Clinical and population-based studies report elevated rates of drug and alcohol use disorders in PG (Desai and Potenza, 2008; Petry et al., 2005; Ladd and Petry, 2002). Clinical similarities between PG and substance use disorders have also been noted (Tavares et al., 2005), with the DSM-IV diagnostic criteria for PG sharing features with those for substance dependence (American Psychiatric Association, 1995). Based on these similarities, it has been proposed that PG might be best characterized as a behavioral addiction (Grant et al., 2006; Yip and Potenza, 2009) and is currently being considered for re-categorization as an addictive disorder in DSM-V (Holden, 2010). Given white matter deficits associated with AD (Pfefferbaum et al., 2000; Pfefferbaum et al., 2002; Pfefferbaum et al., 2004), elevated prevalence rates of AD in PG (Desai and Potenza, 2008; Petry et al., 2005), and the similarities between PG and substance addictions, research into the relationship between alcohol use disorders and CC white matter integrity in PG may inform the understanding of the pathophysiology of PG, and studies of white matter integrity in PG should consider alcohol use disorders.

Previous DTI studies suggest a complex relationship between white matter integrity and impulsivity measures across psychiatric disorders. For example in cocaine dependence, reduced anterior CC FA has been associated with Barratt Impulsiveness Scale (BIS-11) scores in some (Lim et al., 2008) but not other studies (Moeller et al., 2005). In contrast, more consistent findings have been observed between white matter integrity measures and BIS-11 scores in other populations; e.g., individuals with schizophrenia (Hoptman et al., 2002; Hoptman et al., 2004). These findings suggest that associations between FA and impulsivity measures may vary in groups of individuals with different psychiatric disorders, and, given the relevance of impulsivity to ICDs, further research is needed to better

determine the relationship between anterior CC white matter integrity (e.g., genual FA) and impulsivity in individuals with PG.

As impulsivity is a complex entity (Moeller et al., 2001), the use of measures covering multiple domains of impulsivity and theoretically related constructs may help link aspects of impulsivity with specific anatomical features. For example, the Behavioral Inhibition System and Behavioral Activation System (BIS/BAS; Carver and White, 1994) scale – particularly the BAS subscales – may be helpful in identifying different aspects of behavioral activation (e.g., reward responsiveness versus fun-seeking), whereas the BIS-11, a widely used measure of impulsivity, may help in distinguishing between different aspects of impulsivity (e.g., cognitive versus motor impulsiveness; Patton et al., 1995).

This study used DTI to assess CC white matter integrity in PG subjects in comparison to healthy control subjects and to explore relations with impulsivity and consider potential contributions of substance addictions. We hypothesized that: 1) in comparison to controls, PG subjects would have reduced FA in the genu of the CC, a region linked to the functional abnormalities identified in PG in ventromedial PFC and implicated in other disorders characterized by impaired impulse control; 2) in comparison to controls, PG subjects would score higher on measures of impulsivity and behavioral activation (e.g., BIS-11, BIS/BAS subscales; 3) across all subjects, FA values would correlate inversely with measures of impulsivity and behavioral activation, as assessed by the BIS-11 and BIS/BAS subscales.

Methods

Participants and recruitment procedures

Participants were 19 individuals who met DSM-IV-TR diagnostic criteria for PG (12 men and 7 women) and 19 control participants (11 men and 8 women). Participants were screened using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995). PG diagnoses were confirmed using the Structured Clinical Interview for Pathological Gambling (SCI-PG; Grant et al., 2004). For the PG subjects, the mean (standard deviation) South Oaks Gambling Screen (SOGS; Lesieur and Blume, 1987) scores ranged between 6–18 (median score = 13) and the mean (standard deviation) score was 12.47 (3.16). Control subjects' SOGS scores ranged between 0–2, and the mean (standard deviation) score was 1.06 (0.24). Exclusion criteria for controls included pregnancy, a current Axis I disorder apart from nicotine dependence or unstable medical condition.

Participants were recruited by media ads seeking adults for participation in a university-based research study. All participants provided written informed consent and the study protocols were approved by the Yale Human Investigations Committee.

Demographic measures

Gender, race/ethnicity, age and education information were obtained via self-report during intake.

Substance use history

One of the PG subjects and two of the controls reported current recreational marijuana use. Twelve of the PG subjects and four of the controls reported current daily cigarette smoking. Two of the PG subjects had a history of substance abuse/dependence: one subject reported past lifetime cocaine and sedative dependence, one subject reported past lifetime opioid dependence. Three of the PG subjects had a history of alcohol abuse (AA) and two had a history of AD. Two of the PG subjects with a history of AA also had a history of substance abuse/dependence: one subject reported past lifetime opiate prescription drug dependence,

one subject reported past lifetime cocaine abuse. Alcohol and substance use history were not available for one PG subject, and this subject was excluded from analyses related to past substance and alcohol use.

Non-substance psychiatric comorbidity

Two of the PG subjects had current Axis I disorders: one of the PG subjects had current comorbid major depressive disorder, panic disorder, social phobia, specific phobia, obsessive-compulsive disorder and post-traumatic stress disorder. One of the PG subjects had comorbid anxiety disorder NOS. Complete Axis I histories were not available for three of the PG participants.

Impulsivity, behavioral inhibition and activation measures

The Barratt Impulsiveness Scale (BIS-11)—The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) is a self-report measure designed to assess impulsivity. The 30-item scale factors into three subscales: Motor Impulsiveness (BIS-11-MI), Cognitive Impulsiveness (BIS-11-CI), Non-planning Impulsiveness (BIS-11-NPI).

The Behavioral Inhibition System and Behavioral Activation System (BIS/BAS) scales

Based on Gray's theory of personality, the Behavioral Inhibition System and Behavioral Activation System (BIS/BAS; Carver and White, 1994) scale is self-report measure that factors into one BIS subscale and three BAS subscales: Fun-Seeking (BAS-FS), Drive (BAS-D), Reward Responsiveness (BAS-RR). Participants rate each of the 20 items on a four point Likert-type scale ranging from 'strongly disagree' to 'strongly agree.'

Image acquisition

DTI data were acquired with a 3T Siemens Trio scanner at Yale's Magnetic Resonance Research Center, and each participant underwent two separate image acquisitions. Diffusion sensitizing gradients were applied along 32 non-collinear directions using b values of 0 (b_0 image = 1) and 1000 s/mm^2 (TR = 7400, TE = 115, bandwidth = 1396, matrix = 128 × 128, FOV = 256 × 256 mm^2), and 40 contiguous slices parallel to AC-PC line were acquired, and each slice was 3.0 mm thick.

Image processing

Diffusion-weighted images were visually inspected to ensure sufficient quality. Images were motion corrected using SPM5 (www.fil.ion/ucl.ac.uk/spm/software/spm5). All other image processing was conducted using the Yale BioImage Suite (www.bioimagesuite.org), following previously described techniques (Constable et al., 2008). For each subject, two separate image acquisitions were combined and averaged and used to compute the diffusion tensor. Intensity thresholds of the T2-weighted b_0 image were matched on background value. Individual subject tensors were masked outside the brain. FA was calculated from the tensor data and individual subject FA maps were nonlinearly registered to a single control subject's FA map. Parallel diffusivity values were defined as λ_1, and perpendicular diffusivity values were defined as the mean of λ_2 and λ_3.

A composite tricolor directionality map was generated using the mean tensor of the control participants, and this map was used to manually parcellate the CC into six distinct regions of interest (ROIs; Fig. 1): the left and right genu, splenium and body. The genu was defined as the anterior curved aspect of the CC. The fiber tracts in the genu curved anterior to form, in part, the forceps minor. The posterior boundary of the genu (anterior aspect of body) was defined as where the fiber tracts became transverse in orientation with minimal or no curvature. The splenium was defined as the posterior curved aspect of the corpus callosum.

The fiber tracts of the splenium curved posterior to form, in part, the forceps major. The anterior border of the splenium (posterior border of the body) was where fiber tracts became transverse in orientation, with minimal or no curvature. The body of the CC was defined by where the fiber tracts had a transverse orientation. ROIs were then applied directly to single-subject FA maps and used to generate individual FA values for each ROI on an individual subject basis as in previous DTI studies using the Yale BioImage Suite software package (Constable et al., 2008).

Statistical comparisons

Demographic comparisons were conducted using chi-square and student's *t*-tests. Individual subject FA values and parallel and perpendicular diffusivity values for each of the six ROIs were entered into SPSS 16.0. Normality was assessed using Kolmogorov Smirnov tests. BIS-11, BIS/BAS scores, FA and diffusivity values were compared using one-way analyses of variance analyses (ANOVAs). Age, gender, presence or absence of PG, substance use history, alcohol use history and tobacco-smoking status were entered into a multiple regression analyses to explore further the relationship between PG and diffusion parameters. Correlational analyses were conducted using Pearson's r.

Results

Demographic measures

The results of between-group comparisons of demographic characteristics are shown in Table 1. Controls and PGs did not differ with respect to gender ($x^2 = 0.11$, $p = 0.74$), ethnicity ($x^2 = 1.05$, $p = 0.31$), age ($t = 0.09$, $p = 0.93$) or years of education ($t = 1.50$, $p = 0.14$).

Impulsivity, behavioral inhibition and activation

The results of between-group comparisons of impulsivity-related measures are shown in Table 1. In comparison to controls, PGs had higher scores on the BIS-11-CI ($F = 8.71$, $p = 0.006$), BIS-11-MI ($F = 6.23$, $p = 0.02$), BIS-11-NPI ($F = 7.50$, $p = 0.01$), BAS-FS ($F = 9.06$, $p = 0.005$) and BAS-D ($F = 8.71$, $p = 0.006$).

FA and diffusivity values

Mean values and between-group comparisons of FA within the six sub-regions of the CC are shown in Table 2. In comparison to controls, PG subjects had reduced FA values in the left body ($F = 4.33$, $p = 0.045$) and left ($F = 9.45$, $p = 0.004$) and right genu ($F = 8.59$, $p = 0.006$). In comparison to controls, PG subjects also had significantly increased perpendicular diffusivity values in the left ($F = 6.19$, $p = 0.018$) and right ($F = 5.48$, $p = 0.025$) genu. No significant between group differences were observed for parallel diffusivity values.

Results of multiple regression analyses are displayed in Table 3. In these models, presence or absence of PG was a significant predictor of left and right genual FA (L: $\beta = -0.38$, $p = 0.02$; R: $\beta = -.36$, $p = 0.03$), and of left and right genual perpendicular diffusion values ($\beta = 0.40$, $p = 0.03$; $\beta = 0.39$, $p = 0.04$). Age was also a significant predictor of both left and right genual FA values ($\beta = -0.37$, $p = 0.01$; $\beta = -0.39$, $p = 0.009$), but did not significantly predict perpendicular genual diffusion values. Presence or absence of past AA/AD was not a significant predictor of left or right genual FA or perpendicular diffusion values, although a trend toward significance was observed for FA values ($\beta = -0.30$, $p = 0.065$; $\beta = -0.30$, $p = 0.063$). Gender, current tobacco smoking status and presence or absence of past SUDs did not significantly contribute to genual FA or perpendicular diffusion values. The only significant predictor of left body FA values was the presence or absence of past AA/AD ($\beta = -0.37$, $p = 0.044$).

Correlations between clinical characteristics and FA

Among controls, BIS scores were positively correlated with right corpus body FA values ($r = 0.47$, $p = 0.046$). Among PG participants, BAS-FS scores were negatively correlated with FA values in the left and right genu ($r = -0.46$, $p = 0.049$; $r = -0.52$, $p = 0.02$; Fig. 2).

No significant correlations between BIS-11 scores and CC FA values were observed.

Discussion

This study used DTI to compare CC white matter integrity in individuals with PG versus healthy controls. Our first hypothesis was largely supported. Consistent with this hypothesis, reduced FA values were observed in the genu of the CC among PG subjects, suggesting impairments in connectivity between frontal regions in PG. We additionally compared parallel versus perpendicular diffusivity values, and found increased perpendicular – but not parallel - diffusivity in the genu among PG subjects, suggesting decreased mylenation in this region (Song et al., 2002). Findings of reduced FA values in the genu persisted after controlling for age, gender, current tobacco smoking status, past AA/AD and SUDs using multiple regression. These findings are consistent with the other published DTI studies of ICDs (Grant et al., 2006; Chamberlain et al., 2010), and together suggest that deficits in frontal white matter microstructures might contribute to the pathophysiology of a range of impulsive disorders.

A significant effect of past AA/AD status was also observed on left body FA values, as well as a trend toward significance for genual FA values. These findings are consistent with prior DTI studies in chronic AD (Pfefferbaum et al., 2000; Pfefferbaum et al., 2002; Pfefferbaum et al.,2004), which found a significant main effect of past AA/AD on CC FA. Together, these results suggest that impairments in white matter integrity in PG could be exacerbated by the presence of prior AA/AD. However, future studies using a comparison group of controls with a history of AA/AD is needed to further substantiate this theory. The present findings complement neuropsychological research demonstrating ventral PFC deficits in both PG and AD - which have been hypothesized to reflect a shared pathophysiology - and AD-specific impairments in dorsal PFC functioning - hypothesized to reflect structural damage resultant from AD (Lawrence et al., 2009). Given the elevated rates of AA/AD in PG (Desai and Potenza, 2008; Petry et al., 2005), further research is needed to better characterize the interaction between PG and AA/AD with respect to white matter integrity. Additionally, the extent to which reduced white matter integrity in the genu in PG may be related to heavy alcohol exposure or represents an *a priori* vulnerability factor for PG and other disorders characterized by behavioral dyscontrol warrants additional investigation (e.g., in longitudinal studies).

Consistent with our second hypothesis, PG subjects scored significantly higher than controls on multiple measures related to impulsivity and behavioral activation. Consistent with previous studies, PG subjects scored significantly higher than controls on all three BIS-11 subscales (Motor, Cognitive, and Non-planning Impulsiveness; Fuentes et al., 2006; Ledgerwood et al., 2009). In contrast to a previous report of elevated BIS and BAS subscale (Reward-Responsiveness) scores among treatment-seeking individuals with PG (Goudriaan et al., 2006), we observed significant between-group differences for two of the BAS subscales (Fun-Seeking, Drive), but not for the third BAS subscale (Reward Responsiveness) or for the BIS subscale. Additional research is needed to better understand specific individual difference factors that may underlie differences amongst PG subjects with respect to impulsivity and behavioral inhibition and activation.

Partially consistent with our third hypothesis, reduced FA values were associated with higher scores on some but not all measures related to impulsivity and behavioral activation. Analogous to findings of some (Moeller et al, 2005) but not other studies of cocaine dependence (Lim et al., 2008), no significant correlations between FA values and BIS-11 scores were observed. These findings suggest that aspects of impulsivity assessed by the BIS-11 might be more closely related to specific functional brain activation differences (e.g., related to gray matter structure and function), consistent with findings in individuals with alcoholism (Beck, et al., 2009). A significant negative correlation between left and right genu FA values and BAS-FS subscale scores was observed among PG subjects. Elevated BAS-FS and BAS-D scores have been reported previously in other impulsive disorders with documented white matter deficits; e.g. substance use disorders (Franken et al., 2006) and bipolar disorder (Alloy et al., 2009). To our knowledge, this is the first study to explore the relationship between BIS/BAS subscale scores and white matter integrity as assessed via DTI.

In conjunction with prior reports in cocaine dependence (Moeller et al., 2005), findings in PG subjects of reduced FA values in the genu of the CC which negatively correlate with impulsivity-related measures suggest that deficits in genual CC white matter integrity might contribute to multiple disorders characterized by poor impulse control. Findings of an association between BIS scores and CC body FA values among control subjects are consistent with one previous report of a negative correlation between CC FA and cognitive control among methamphetamine users (Salo et al., 2009) and suggest that associations between white matter integrity and impulsivity-related measures extend to non-psychiatric populations.

Previous studies using fMRI have demonstrated functional impairments in frontal gray matter structures (e.g. ventromedial PFC) in PG (Tanabe et al., 2007; Potenza et al., 2003a). Findings of reduced FA in the genu of the CC among PG subjects suggest that these impairments may be partially accounted for by impairments in connectivity between frontal regions; however, further research is needed to examine directly relationships between white matter microstructural integrity and gray matter functional impairments in PG. Additionally, research is needed to determine whether the more severe white matter impairments observed among PG subjects with a history of comorbid AA/AD are best construed as vulnerability factors for multiple impulsive disorders, outcomes of engagement in multiple risk behaviors, or a direct effect of extensive alcohol exposure, or whether alternate explanations might account for the findings.

Clinically, these findings may inform data from treatment trials in which drugs (e.g., naltrexone and nalmefene) with efficacy in the treatment of AD appear beneficial in the treatment of PG (Grant et al., 2006; Grant et al., 2008), particularly among individuals with a familial history of alcoholism (Grant et al., 2008). Future studies are warranted to investigate directly how white matter microstructural integrity relates to the treatment of individuals with PG, particularly with respect to treatments with drugs like naltrexone that may target neural pathways underlying motivated behaviors in addictions. Additionally, white matter integrity may be altered by pharmacological or behavioral means (Harsan et al, 2008; Schlaug et al, 2009). For example, mindfulness based therapies have been associated with improved white matter integrity in the corona radiata, white tracts connecting the anterior cingulate cortex (implicated in self-control) to other brain regions (Tang et al., 2010). As mindfulness-based therapies have shown early promise in the treatment of substance addictions (Brewer et al, 2009), future studies of PG should evaluate the efficacy of mindfulness-based interventions as well as the behavioral factors (including impulsivity) and biological factors (including white matter integrity) that may mediate and/or moderate its effects.

Strengths and Limitations

This study has several limitations, including its reliance on self-report measures of impulsivity and related constructs, the relatively small sample size of PG subjects with past drug abuse/dependence and AA/AD and the absence of control subjects with a history of AA/AD, which prevented us from exploring directly for PG-by-AA/AD interaction effects on FA values. Our DTI analyses also include limitations, as we did not control for possible partial volume effects, or for the effects of individual variability in the fitting of the ROIs. These limitations are nonetheless similar to those in some other previously published DTI papers (e.g., Constable et al., 2008). It is additionally possible that our finding of no significant effect of past AA/AD on genual FA values might be due to Type II error, and future research including a larger sample of individuals with PG and remitted AA/AD is needed to further explore interactions between FA values and alcohol use disorders in PG. This study additionally included one PG subject and two controls with current recreational marijuana use. Although previous studies do not suggest decreased CC FA in marijuana use (*reviewed in* Arnone et al., 2006), there has been one previous report of increased mean diffusivity (MD) in the anterior CC among heavy marijuana users (Arnone et al., 2006). As such, future studies are needed to investigate the possible influence of marijuana use on white matter integrity in PG. However, the number of PG participants with a history of drug abuse/dependence and AA/AD is comparable to that reported in previously published fMRI studies of PG (e.g., Potenza et al., 2003b) and DTI studies of CD (Moeller et al., 2005). Additionally, there is heterogeneity amongst individuals with PG, with some groups proposed as being less impulsive than others (Blasczcynski and Nower, 2002; Ledgerwood and Petry, 2006). As the PG subjects in our group scored relatively highly on measures of impulsivity, the extent to which the findings are relevant to groups with lower levels of impulsivity warrants additional investigation. Future studies of larger samples could also investigate further the nature of the relationship between impulsivity and white matter integrity using larger sample, alternate analytical approaches, and a wider range of impulsivity measures (including behavioral assessments). A final limitation of this study is that it did not assess for a complete range of psychiatric disorders and some disorders characterized by impaired impulse control (e.g., attention-deficit/hyperactivity disorder; personality disorders) were not formally assessed.

This study also has several strengths, including a larger sample size comparable to several previous DTI studies (e.g. Moeller et al., 2005; Grant et al., 2006; Paul et al., 2008), the use of multiple impulsivity-related measures. To our knowledge, this is also the first study of white matter integrity in PG. Future research should explore further the interaction between PG, AA/AD and white matter integrity, identify the extent to which white matter differences are relevant to sub-groups of individuals with PG and the extent to which they relate to other clinically relevant measures (e.g. treatment outcome, neuropsychological task performance).

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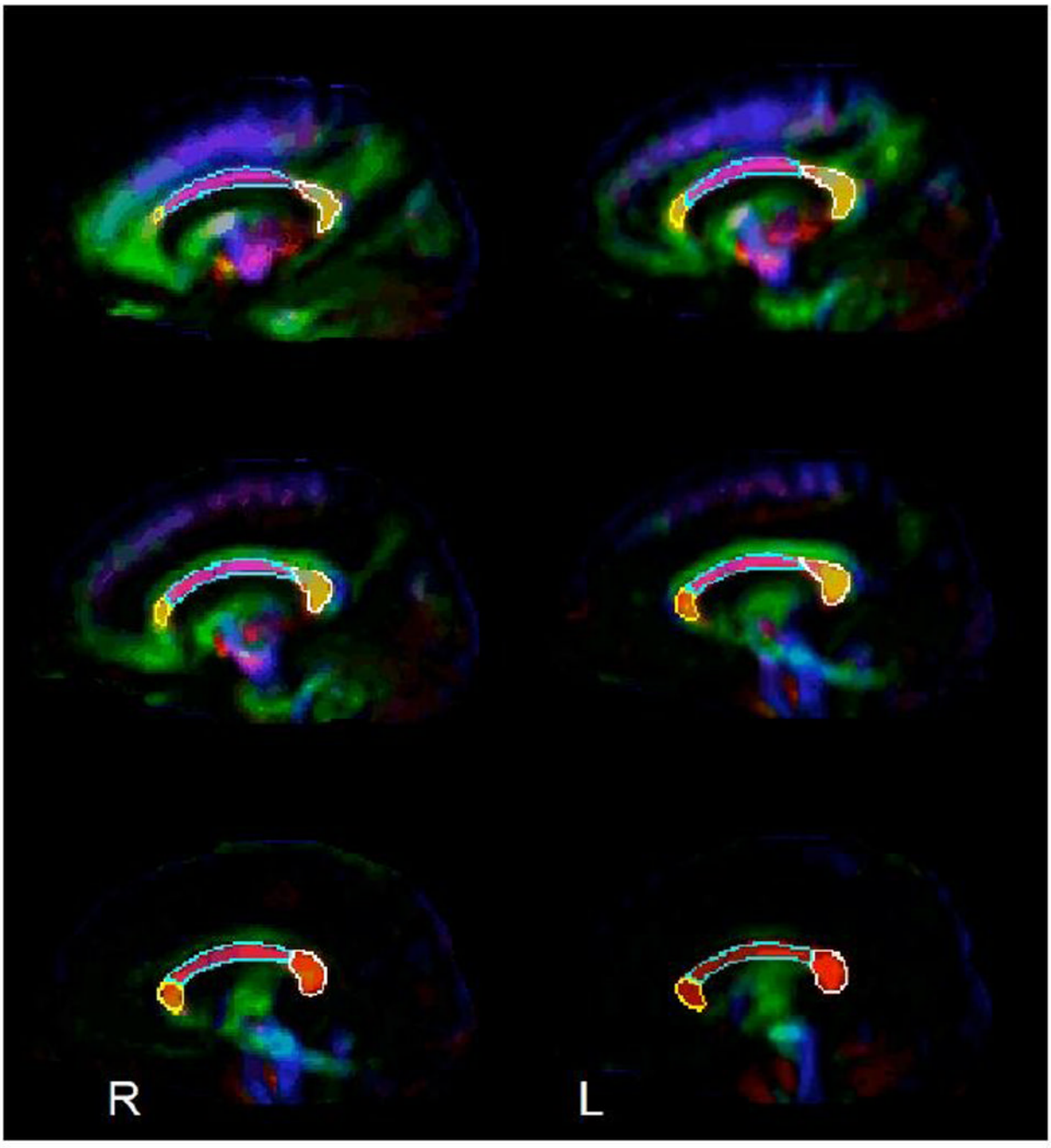

Figure 1.

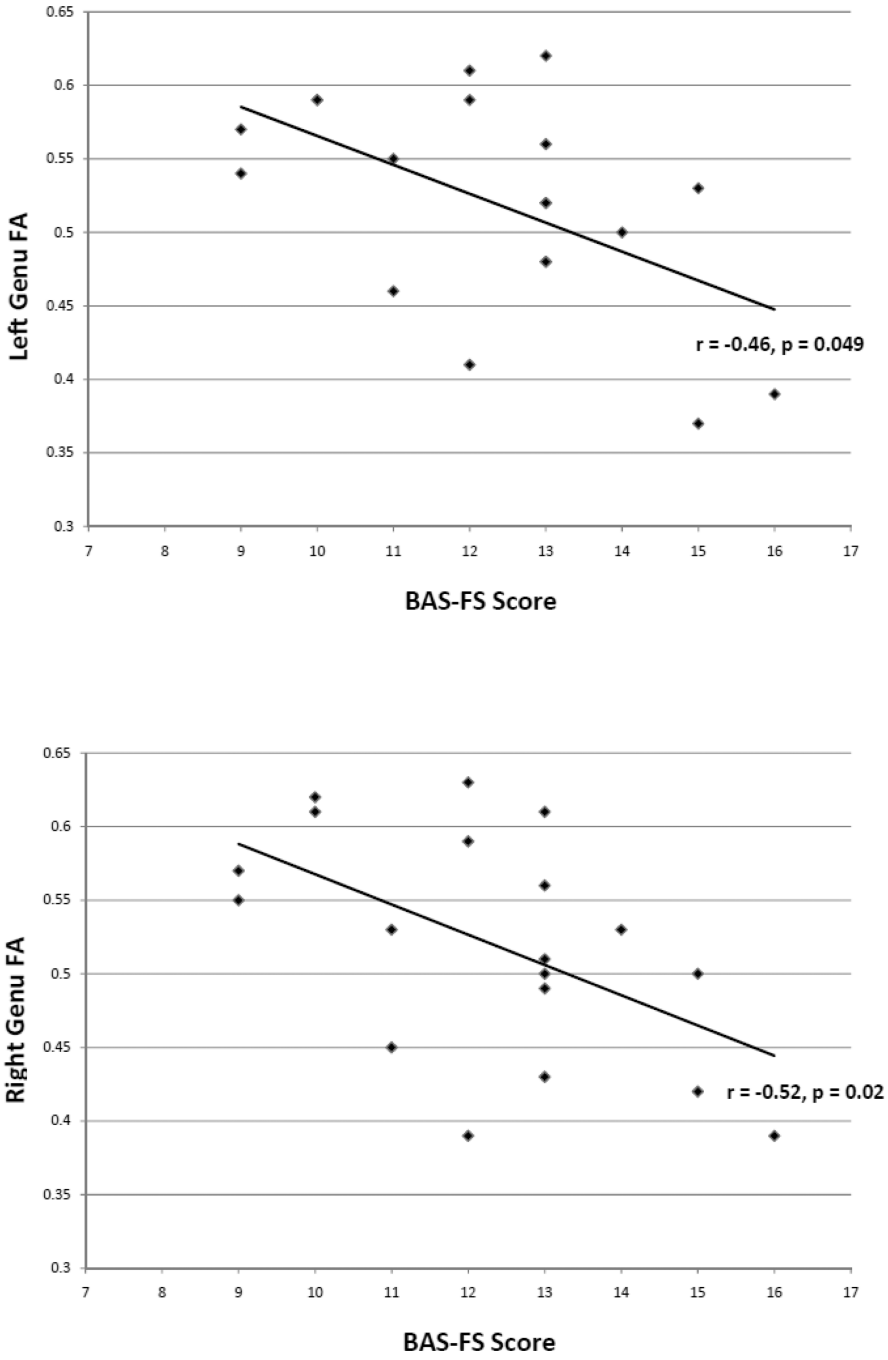

Figure 2.

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Table 1

Results of demographic and clinical comparisons between HC and PG subjects

	HCs (n = 19)	**PGs (n = 19)**	X^2	p	df
Variables	N, %				
Female	8, 42.1%	7, 36.8%	0.11	0.74	1
Non-Caucasian	8, 42.1%	5, 26.3%	1.05	0.31	1
	Mean Values ± St. Dev.		t	p	df
Age, years	36.53 ± 11.21	36.84 ± 11.76	0.09	0.93	1
Education, years	13.68 ± 1.97	12.74 ± 1.91	1.50	0.14	1
Measures	Mean Values ± St. Dev.		**F**	**p**	df
SOGS	1.06 ± 0.24	12.47 ± 3.12	**240.08**	**<0.001**	1
BIS-11	56.44 ± 10.93	69.47 ± 13.26	**10.57**	**0.003**	1
BIS-NPI	22.56 ± 5.68	27.68 ± 5.71	**7.50**	**0.010**	1
BIS-MI	20.94 ± 4.07	24.79 ± 5.20	**6.23**	**0.017**	1
BIS-CI	12.94 ± 3.51	17.00 ± 4.73	**8.71**	**0.006**	1
BIS	18.42 ± 3.06	19.32 ± 3.27	**0.76**	**0.389**	1
BAS	36.37 ± 5.64	41.89 ± 5.73	**8.97**	**0.005**	1
BAS-FS	10.21 ± 2.32	12.32 ± 1.97	**9.06**	**0.005**	1
BAS-D	9.58 ± 2.67	12.16 ± 2.71	**8.71**	**0.006**	1
BAS-RR	17.58 ± 1.71	17.42 ± 2.19	1.74	0.195	1

HC = Healthy control

PG = Pathological gambling

SOGS = South Oaks Gambling Screen

BIS-11 = Barratt Impulsiveness Scale total score

BIS-NPI = Barratt Impulsiveness Scale Non-planning Impulsiveness

BIS-MI = Barratt Impulsiveness Scale Motor Impulsiveness

BIS-C = Barratt Impulsiveness Scale Cognitive Impulsiveness

BIS = Behavioral Inhibition System

BAS = Behavioral Activation System total score

BAS-FS = Behavioral Activation System Fun-Seeking (BAS-FS),

BAS-D = Behavioral Activation System Drive

BAS-RR = Behavioral Activation System Reward Responsiveness

Table 2

Results of between group comparisons of CC diffusion parameters

	PGs versus matched HCs				
	HCs (n = 19)	PGs (n = 19)			
ROIs	Mean FA values ± St. Dev.		F	p	df
L Genu	0.587 ± 0.060	0.520 ± 0.073	**9.446**	**0.004**	1
R Genu	0.587 ± 0.063	0.519 ± 0.078	**8.585**	**0.006**	1
L Body	0.557 ± 0.050	0.521 ± 0.057	**4.326**	**0.045**	1
R Body	0.536 ± 0.047	0.506 ± 0.058	3.098	0.087	1
L Splenium	0.620 ± 0.047	0.610 ± 0.060	0.328	0.570	1
R Splenium	0.609 ± 0.050	0.506 ± 0.058	0.242	0.626	1
	Mean Perpendicular ± St. Dev.				
L Genu	0.512 ± 0.075	0.589 ± 0.113	**6.186**	**0.018**	1
R Genu	0.508 ± 0.077	0.580 ± 0.110	**5.483**	**0.025**	1
L Body	0.534 ± 0.063	0.575 ± 0.080	3.080	0.088	1
R Body	0.561 ± 0.064	0.591 ± 0.086	1.498	0.229	1
L Splenium	0.510 ± 0.086	0.523 ± 0.120	0.140	0.710	1
R Splenium	0.542 ± 0.105	0.531 ± 0.089	0.124	0.727	1
	Mean Parallel ± St. Dev.				
L Genu	1.410 ± 0.162	1.338 ± 0.122	2.376	0.132	1
R Genu	1.416 ± 0.162	1.339 ± 0.120	2.825	0.101	1
L Body	1.385 ± 0.082	1.351 ± 0.111	1.172	0.286	1
R Body	1.372 ± 0.082	1.329 ± 0.095	2.253	0.142	1
L Splenium	1.533 ± 0.122	1.498 ± 0.145	0.655	0.424	1
R Splenium	1.553 ± 0.123	1.482 ± 0.126	3.106	0.086	1

St. Dev. = Standard deviation

FA = Fractional anisotropy

HC = Healthy control

PG = Pathological gambling

ROI = Regions of interest

L = Left

R = Right

Table 3

Results of multiple regression analyses exploring the effects gender, age, current cigarette smoking, past SUDs, past AA/AD and current PG on CC diffusion parameters

ROIs	Gender	Age	Current Cigarette Smoking	Past SUDs	Past AA/AD	PG
	B (p)	B (p)	B (p)	B (p)	B (p)	B (p)
Fractional anisotropy						
L Genu	0.092 (0.526)	**−0.365 (0.012)**	0.188 (0.238)	0.119 (0.464)	−0.296 (0.065)	**−0.379 (0.021)**
R Genu	0.073 (0.616)	**−0.390 (0.009)**	0.160 (0.319)	0.082 (0.618)	−0.300 (0.063)	**−0.362 (0.029)**
L Body	−0.048 (0.771)	−0.225 (0.157)	0.256 (0.157)	0.092 (0.615)	**−0.365 (0.044)**	−0.274 (0.130)
Perpendicular diffusion						
L Genu	−0.081 (0.626)	0.250 (0.120)	−0.188 (0.298)	0.078 (0.676)	0.266 (0.141)	**0.398 (0.033)**
R Genu	−0.019 (0.908)	0.289 (0.072)	−0.201 (0.263)	0.083 (0.651)	0.270 (0.131)	**0.390 (0.035)**

L = Left

R = Right

SUDs = Substance use disorders

AA/AD = Alcohol abuse or dependence