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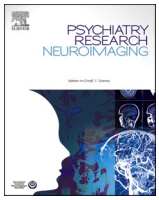

Neural fingerprints of gambling disorder using diffusion tensor imaging

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ABSTRACT

Gambling disorder (GD) is a behavioral addiction associated with personal, social and occupational consequences. Thus, examining GD's clinical relationship with its neural substrates is critical. We compared neural fingerprints using diffusion tensor imaging (DTI) in GD subjects undergoing treatment relative to healthy volunteers (HV). Fifty-three (25 GD, 28 age-matched HV) males were scanned with structural magnetic resonance imaging (MRI) and DTI. We applied probabilistic tractography based on DTI scanning data, preprocessed and analyzed using permutation testing of individual connectivity weights between regions for group comparison. Permutation-based comparisons between group-averaged connectomes highlighted significant structural differences. The GD group demonstrated increased connectivity, and striatal network reorganisation, contrasted by reduced connectivity within and to frontal lobe nodes. Modularity analysis revealed that the GD group had fewer hubs integrating information across the brain. We highlight GD neural changes involved in controlling risk-seeking behaviors. The observed striatal restructuring converges with previous research, and the increased connectivity affects subnetworks highly active in gambling situations, although these findings are not significant when correcting for multiple comparisons. Modularity analysis underlines that, despite connectivity increases, the GD connectome loses hubs, impeding its neuronal network coherence. Together, these results demonstrate the feasibility of using whole-brain computational modeling in assessing GD.

1. Introduction

Gambling disorder (GD) is a behavioral addiction marked by detrimental personal, social, and psychological consequences, and is relatively frequent affecting an estimated 1–2% (Wardle et al., 2015; Welte et al., 2011) of the western population with a marked increase in prevalence in young adults (Nowak and Aloe, 2014). The suicide attempt rate within GD is the highest of any addictive disorder at approximately 20% (Bischof et al., 2015), and GD has marked neural and behavioral similarities with other disorders of addiction such as substance use disorders (SUD) (Petry, 2007; Potenza, 2008; Potenza et al., 2003) and impulse control disorders such as compulsive sexual behavior disorder (Gola et al., 2017). In clinical settings, GD has been proposed as a beneficial clinical group of examining addiction, as it bypasses the confounding effects of repeated substance use on brain functioning (Fineberg et al., 2014). Thus, it is critical to examine GD's clinical relationship with its neural substrates, which has been previously examined using functional magnetic resonance imaging (fMRI). Several fMRI studies have identified key neural regions associated with GD. One tentative concept in GD is that of incentive salience, where motivational biasing to specific reward forms dominates motivation over others (Goldstein et al., 2007; Goldstein and Volkow, 2002),

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leading to asymmetrical reward processing across different reward forms. This form of motivation has shown to be mediated by cues predicting anticipated rewards with enhanced activity in the ventral striatum (VS) and orbitofrontal cortex (OFC) (Berridge, 2007), and GD has been associated with amplified striatal responses to near-miss outcomes in gambling situations (Sescousse et al., 2016). Furthermore, the monetary incentive delay (MID) task, which examines reward processing, allows for the dissociation of reward phases such as anticipation and outcome, as well as reward forms such as monetary and erotic rewards. Meta-analyses of the MID task has shown the VS to be specifically implicated in reward anticipation , which has been similarly implicated in GD with increased VS activity to monetary relative to erotic reward anticipation (Knutson and Greer, 2008). This highlights the role of monetary cues as a reward reinforcer in GD, where oppositely, erotic rewards are not as highly regarded. In extension, GD is generally marked by increased activity to monetary cues in reward-related brain regions (Crockford et al., 2005; Goudriaan et al., 2010; Sescousse et al., 2016; Vickery and Jiang, 2009) although neuroimaging and behavioral reviews have reported divergent findings in reward-related regions (Balodis et al., 2012). Recent findings have reported that GD subjects undergoing cognitive behavioral therapy (CBT) treatment exhibit neural biases towards sexual rewards away from gambling cues (Schmidt et al., 2021), suggesting that the therapeutic markers of CBT as an intervention changes their reward preference as has been demonstrated to be solely specific to monetary rewards (Sescousse et al., 2013). Out research group has also used this task to examine the role of dopaminergic and serotonergic transmission in sexual and monetary reward processing in healthy volunteers (Schmidt et al., 2020). The divergent findings on the MID task have generated support for the reward deficiency theory, building on the idea that hypoactivity of the brain's reward system, resulting from a chronic hypodopaminergic state in subcortical brain regions, conditions the behavioral correlate of being reward-seeking; also characteristic of GD symptomatology (Vickery and Jiang, 2009; Volkow et al., 2002).

Despite the multitude of fMRI studies (van Holst et al., 2010, 2012), relatively little is known about the structural neural connectivity in GD, using diffusion tensor imaging (DTI). One study examining white matter integrity on GD ($N = 12$) using DTI (Joutsa et al., 2011) found lower mean diffusivity in multiple brain regions, including the corpus callosum, the cingulum, the superior longitudinal fascicle, the inferior fronto-occipital fascicle, the anterior limb of internal capsule, the anterior thalamic radiation, the inferior longitudinal fascicle and the uncinate/inferior fronto-occipital fascicle, showing that GD is associated with extensive reductions in the integrity of several brain white matter tracts, mimicking previous evidence in groups with substance addictions, including alcohol (Yeh et al., 2009; Yip et al., 2013), cocaine (Xu et al., 2010), and heroin (Liu et al., 2008). The study was not specific regarding whether GD subjects received active treatment through GD treatment centers, although they were recruited from an internet site for excessive gambling use. Another study (Yip et al., 2013) examining DTI using fractional anisotropy (FA) in GD ($N = 19$) compared WM integrity in the corpus callosum (CC), and found reduced FA values in the left and right genu of the CC, and GD was a significant predictor of genual FA values, warranting future studies to investigate how white matter (WM) tract integrity relates to GD treatment. Unfortunately, neither did this study report treatment-status of its GD subjects.

Here, we examine structural connectivity patterns in GD subjects undergoing treatment in the form of cognitive behavioral therapy at the Danish Center for Gambling Disorder and compare them with healthy volunteers (HV) using a novel DTI approach developed in Oxford, which is outlined below.

2. Material and methods

2.1. Participants

Twenty-five male treatment active GD subjects were recruited via the Danish Centres of Gambling Disorder. Twenty-eight age-matched male healthy volunteers (HV) were recruited via advertisement-based methods, including television, newspapers, university notices, as well as social media portals for university students. GD subjects were screened by an expert clinician in order to ensure they fulfilled diagnostic criteria for GD (American Psychiatric Association, 2013). Gambling severity was represented using the South Oaks Gambling Screen (SOGS). HV were screened by a psychologist and included if between 18 and 50 years of age, free of psychiatric illnesses, substance, and behavioural addictions, as well as meeting MR safety criteria. GD subjects were included if they were between 18 and 50 years of age, with no history of SUD, including using illicit substances such as cannabis, or major psychiatric disorders (including current moderate/severe major depression). All participants were screened by three trained psychologists and underwent questionnaires on impulsivity using the UPPS-P (Lynam et al., 2006), depression using Beck's Depression Inventory (BDI) (Beck et al., 1996), gambling using the SOGS (Lesieur and Blume, 1987), nicotine using Fagerström Test for Nicotine Addiction (FTNA) (Heatherton et al., 1991), alcohol using Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993), severe illicit substance use using Drug Abuse Screening Test (DAST-20) (Skinner, 1982), and anxiety using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). Short-term memory was assessed using a digit span test from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2014) and a proxy of intelligence using a Danish version of the National Adult Reading Test (DART) (Nelson and Willison, 1991). All participants were further screened for compatibility with the MRI environment, as we have done previously (Schmidt et al., 2016) and gave written informed consent to participate. The study was approved by the Middle Jutland Scientific Ethical Committee. All participants were paid approximately 500–700 DKK for their participation.

2.2. Neuroimaging acquisition

Structural T1-weighted MRI scans and DTI scans were performed with a three tesla (3T) Siemens Skyra MRI scanner with a 32-channel head coil at the center of Functionally Integrative Neuroscience (CFIN) in Aarhus, Denmark. The structural T1 scans had a voxel size of 1 $\times$ 1 $\times$ 1 mm, slice thickness of 1 mm, matrix size 256 $\times$ 256, FoV 256 $\times$ 256, repetition time (TR) 2300 ms, echo time (TE) 3.8 ms, pixel bandwidth 170 Hz/ Px, and a flip angle of 8°. The DTI echo planar imaging (EPI) sequence had a voxel size of 1.98 $\times$ 1.98 $\times$ 2 mm, slice thickness of 2 mm, matrix size 106 $\times$ 106, FoV 210 $\times$ 210, TR 9000 ms, TE 84 ms, b-value 1500 s/ mm^2, diffusion directions 62 (9 b0 scans interspersed throughout the scans, every 8 vol), two phase encoding directions (anterior-posterior and posterior-anterior), pixel bandwidth 1745 Hz/ Px, and a flip angle of 90°

2.2.1. Structural connectivity

In order to enable comparison of whole-brain connectivity, a probabilistic tractography strategy was applied based on DTI scanning data of GD and HV groups. We replicated a novel method that makes use of a brain atlas in order to construct a region-to-region structural connectome characterizing the main neuronal pathways between grey matter areas. Construction of individualized structural connectivity measures was carried out in 4 major steps. This is what entails the fingerprinting method.

2.2.2. Preprocessing of DTI images and fiber orientation estimation

The DTI data was preprocessed using the guidelines available for FSL (FMRIB Software Library, Oxford, version 5.0, www.fmrib.ox.ac.

uk/fsl/). This involves use of the diffusion toolbox FDT, that makes use of BET, BEDPOSTX, and PROBTRACKX in order to produce individual whole-brain connectomes. Preprocessing involves various artifact removal procedures. Initially we performed removal of gibbs-ringing artefacts with the tool unring (https://bitbucket.org/reisert/unring), followed by FSL's TOPUP that estimates and corrects for susceptibility artefacts, and lastly FSL's EDDY, an algorithm that corrects for subject movements and eddy-current induced distortions.

In order to model the neuronal fiber orientation for each voxel we employed a Markov Chain Monte Carlo sampling algorithm that relies on the diffusion parameters in the DTI data. We configured the estimation to model two fiber directions within BEDPOSTX, to allow for crossing fibers, providing us with a voxel-detail fiber orientation scaffold later used for running the probabilistic tractography.

2.2.3 Defining parcellation of brain regions

In this study we chose to use the Automated Anatomical Labelling (AAL) atlas, discarding the 26 cerebellar regions, which leaves us with 90 cortical and subcortical regions. In order to transform the atlas into native space for each individual subject we used FSL's FLIRT registration tool (FMRIB, Oxford, UK) to perform a set of linear registrations. Following a principle of registering from low-resolution into high-resolution both DTI and the standard ICBM152 in MNI space were registered into subject-specific T1 native space. This resulted in two transformation matrices: DTI to T1 native space, and MNI to T1 native space. The DTI to T1 matrix was inverted to obtain a T1 to DTI transformation matrix. Lastly the MNI to T1 and T1 to DTI matrices were concatenated to obtain a MNI to DTI transformation matrix. One such transformation matrix was produced for each subject and used to register the AAL from MNI to native DTI space, using a nearest-neighbor interpolation in order to preserve discrete labels. Registrations were manually inspected to assure acceptable quality.

2.2.4. Estimating structural connectomes

Employing the AAL atlas (now in native DTI space) each region was extracted and used as a seed region for the probabilistic tractography algorithm. We used a sampling of 5000 streamlines per voxel within each region, and ran the algorithm with the remaining 89 regions as a target. This process was repeated using each of the 90 regions as a seed. The strength of connectivity between a seed region, i and a target region j was defined as the number of streamlines from voxels in the seed region, i that reach a voxel in target region j. In this way a regional fingerprint of connectivity to the rest of the brain is obtained for each region in our atlas. This estimate, however, allows a maximum connectivity that depends on the number of voxels within a region, so normalization with respect to voxels in a region was performed bringing the maximum possible structural connectivity to 5000. Using in-house perl scripts the resulting fingerprints were collected into a structural connectome for each individual. To correct for false positives, we imposed a minimum threshold of 1% of the maximum connectivity strength between any regions within a subject's connectome, thus removing spurious connections.

2.2.5. Connectome analysis

To analyze potential significant differences between the GD and HV groups we used permutation testing of individual connectivity weights between regions. Correction for multiple comparison was carried out using Bonferroni correction, and a family-wise error correction method used by the network-based statistics toolbox (NBS, https://sites.google.com/site/bctnet/comparison/nbs) was further employed to detect any significantly altered sub networks. Further analysis of the mean GD and HV 90 × 90 connectivity matrices was carried out using the brain connectivity toolbox (BCT, https://sites.google.com/site/bctnet/) which use graph metrics to characterize network features.

Modularity represents the degree to which subdivisions of the mean group network into non-overlapping communities is possible. We employed the Louvain algorithm for detection of an optimal community structure that minimizes between-community connectivity and maximizes within-community connectivity. Hub classification was carried out by employing graph measures of the within-community and between-community connections to specify regions of particular importance to GD or HV networks. To classify as a hub, the within-module degree centrality, measured by within module z-score, must exceed the mean plus standard deviation for regions within that community. This indicates that the region plays a central role in intra-community communication. The hubs are then split into provincial and connector hubs depending on the proportion of cross-community connections, namely the participation coefficient p. A hub with a $p<0.3$ denotes a provincial hub and a $p>0.3$ denotes connector hubs. Connector hubs thus carry a vital role in integrating information between the communities detected in the structural connectivity profile of mean GD and HV brains.

2.3. Statistical analysis of behavioural outcomes

Subjects' characteristics and questionnaire scores were compared across groups with two-tailed t-tests. We also used reaction time (RT) data from the same population to correlate RT to mean diffusivity. When comparing RTs to different reward types we compared differences in RTs to erotic and monetary versus neutral with an improved scoring algorithm developed by Greenwald and colleagues (Greenwald et al., 2003). The algorithm reduces the biases due to variability of RTs by standardizing the differences in response latencies and dividing an individual's difference in RTs by a personalized standard deviation of these differences. We compared Group × Reward RT differences using a two-way ANOVA. All statistical analyses were performed using R (version 3.5.1) (Team R, 2014).

3. Results

3.1. Behavioural

Compared with HV, GD subjects had increased scores on gambling, pornography craving, impulsivity (and two of its subcomponents), depression, anxiety, and decreased digit span (Table 1). When examining RT differences, we found no main effect of Group. When comparing RTs to erotic versus monetary reward types across groups, we found a main effect of Reward, with lower RTs to erotic versus monetary cues in both GD subjects and HV ($F(1,92) = 4.020$, $P = 0.047$). We found no interaction effects in RT differences as a function of Group × Reward.

3.2. Connectivity differences

The permutational comparison between GD and HV elucidated 37 connections of significance ($p < 0.01$, uncorr.). These connections did not survive correction for multiple comparisons. As seen in Fig. 1, the changes were primarily characterized by an increase in connection strength, with 24 increases and 13 losses of connectivity. The largest differences amounted to roughly 10% of the maximum connectivity strength found in HV. Relative decreases spanned reductions of 10–69%, whilst relative increases were as high as 2.5-fold increases.

The decreases were most pronounced within the frontal lobe, the connections between the frontal lobe and right hemisphere basal ganglia, as well as ipsilateral connections between the frontal lobes and the rolandic opercula.

The increases in connectivity were found primarily strengthening a network including the putamen, thalamus, precuneus, posterior cingulum, hippocampal structures, and left temporal pole. Notably there was also an increase in connectivity between the amygdala and olfactory cortex. The NBS analysis did not find any significant networks within a t-statistics threshold range of 1.0–3.0.

Table 1
Subject characteristics.

Variable	Healthy volunteer subjects	Gambling disorder subjects	Group Comparison
Age	26.8 (5.8)	27.9 (9.3)	t(46) = 0.63 *P* = 0.53
DART	27.9 (6.6)	25.9 (7.7)	t(46) = 1.39 *P* = 0.17
Digit span test	16.5 (3.0)	14.3 (3.1)	t(46) = 2.10 *P* = 0.04*
SOGS	0.4 (0.8)	11.1 (2.8)	t(46) = 17.64 *P* = 0.00*
PCQ	4.1 (1.2)	5.0 (1.4)	t(42) = 2.10 *P* = 0.04*
UPPS-P total	131.2 (20.3)	148.6 (19.6)	t(46) = 3.62 *P* = 0.00*
Negative Urgency	24.4 (5.5)	35.0 (5.8)	t(46) = 6.90 *P* = 0.00*
Lack of Perseverance	19.3 (3.8)	20.4 (4.1)	t(46) = 1.72 *P* = 0.09
Lack of Premeditation	22.8 (5.6)	24.6 (5.7)	t(46) = 1.48 *P* = 0.15
Sensation Seeking	37.3 (4.6)	33.6 (7.6)	t(46) = 1.49 *P* = 0.14
Positive Urgency	27.4 (7.8)	35.1 (9.6)	t(46) = 3.63 *P* = 0.00*
BDI	7.2 (8.5)	15.2 (10.7)	t(46) = 3.10 *P* = 0.00*
STAI	66.8 (17.4)	81.5 (16.3)	t(46) = 3.31 *P* = 0.00*
AUDIT	7.9 (3.9)	7.1 (4.7)	t(46) = 0.19 *P* = 0.85
DAST	0.7 (0.9)	0.9 (1.3)	t(46) = 0.49 *P* = 0.63
FTNA	0.7 (1.7)	1.4 (2.5)	t(46) = 1.26 *P* = 0.21
Monetary RT	441.8 (32.8)	454.6 (47.7)	t(46) = 0.42 *P* = 0.67
Erotic RT	456.0 (32.5)	473.3 (44.1)	t(46) = 0.94 *P* = 0.35
Neutral RT	492.0 (37.9)	522.4 (63.9)	t(46) = 1.52 *P* = 0.13
Erotic Liking	6.1 (1.1)	6.0 (1.8)	t(46) = 0.69 *P* = 0.49
Erotic Wanting	5.7 (1.3)	5.7 (2.3)	t(46) = 0.45 *P* = 0.66

All values are mean (SD). Groups were compared using independent two sample t-tests. Due to a technical error, PCQ was not collected for three healthy volunteers and one gambling disorder subject.
Abbreviations: SD, standard deviation; DART, Danish Adult Reading Test; SOGS, South Oaks Gambling Scale; PCQ, Pornography Craving Questionnaire; UPPS-P, see Table 1 below abbreviation; BDI, Beck's Depression Inventory; STAI, State-Trait Anxiety Inventory; AUDIT, Alcohol Use Disorder Identification Test; DAST, Drug Abuse Screening Test; Profile of Mood States (POMS) nicotine using (FTNA), Fagerström Test for Nicotine Addiction; RT, reaction time.

3.3. Modularity

The Louvain method for community detection revealed an optimal community structure for both groups (see Fig. 2). This structure is nearly identical for both groups, with only two nodes being attributed to different modules. The modules show a high degree of symmetry around the midline, with module 3 and 5 being primarily ventral modules comprising most of the temporal lobes, 2 and 6 being dorsolateral modules, module 4 comprising the occipital cortex, and module 1 constituting an interconnected medial module extending into the frontal lobe.

Hub classification revealed connector and provincial hubs crucial for the integration and processing of information. We identified module 1, 2, 3, and 5 to contain connector hubs while for the provincial hubs we observed a complimentary distribution across the modules with 2, 3, 4, 5, and 6 containing provincial hub nodes in HV. In GD subjects, the right cuneus and left parahippocampal gyrus no longer obtain the provincial hub classification, and the medial frontal superior area of the AAL atlas is impacted to no longer be a connector hub. Taken together, GD subjects end up with three fewer hubs classified despite increased connectivity strengths; yet the overall the modularity of the groups is near identical.

4. Discussion

Since this, to the best of our knowledge, is the first paper looking into structural whole-brain connectivity in GD, there is a paucity of literature to lean on and contrast with. For this reason, most of this discussion will include functional studies and lesion studies and follow the accepted argumentation that while structure provides a scaffold for function, function also shapes structure (Cabral et al., 2017). Further limitations to the discussion section involve the loss of significance by correction for multiple comparisons, a typical issue in connectomics that can sometimes be overcome by NBS. However, in this study, the network fragments are too scattered for NBS to detect significant sub networks within a reasonable t-statistic threshold range of 1–3 (Rubinov and Sporns, 2010). Thus, we highlight our results as exploratory in nature and warrant future studies to further assess these network hubs, highlighting the importance of multiple comparisons correction.

4.1. Behavioral results

In our behavioural results, GD subjects elicited higher scores on the measures of gambling severity (through SOGS), pornography craving (through PCQ), two subcomponents of impulsivity (through negative and positive urgency), as well as depression- (through BDI) and anxiety-(through STAI) related severity, and finally lower scores on the digit span test.

In line with the validation of the SOGS, gambling severity scores were naturally higher, as GD was an inclusion criterion to be in this group. Much more striking were the similarly elevated PCQ scores observed in GD subjects. This goes very well in line with what we have observed functionally in the same group of active-treatment GD subjects, who no longer elicit biases towards monetary rewards, but are more motivated by sexual or erotic rewards. We observed a generalised reward-bias in RT scores, again with no monetary reward RT bias present in GD subjects. Thus, our behavioural findings of elevated PCQ scores and lowered RTs to general reward outcomes fits in well with the role of a shift in reward bias towards reward-generalisation in treatment-active GD, supporting the idea that the effect of active treatment in GD can indeed be measured behaviourally. Our observation of increased positive and negative urgency goes well in line with core components of GD symptomatology in the form of impulsivity-driven behaviour resulting in negative consequences. Lastly, three GD subjects exhibited borderline moderate-severe depression scores on BDI without previous diagnosis, which drove the increased BDI scores in GD subjects; a known co-morbidity associated with GD.

4.2. Restructuring of striatal network

As our present findings did not survive correction for multiple comparisons, we highlight the relative weak results of our analyses and interpret the following discussion of our results as exploratory discussion for future assessment of this method.

The recorded differences indicate a restructuring of the connectivity fingerprint with respect to right striatum in the GD group. The loss of connectivity from thalamus to medial OFC and inferior parietal is offset by a marked increase in connectivity to the medial cingulate cortex. This loss of connectivity in orbitofrontal cortex could very well be related to the classical finding that patients with damage to the OFC consistently pick from the high-risk pile in the Iowa Gambling Task, even if able to predict the most likely outcome (Bechara et al., 1994, 1996). Conversely people with larger OFC grey matter volume have been shown to manage

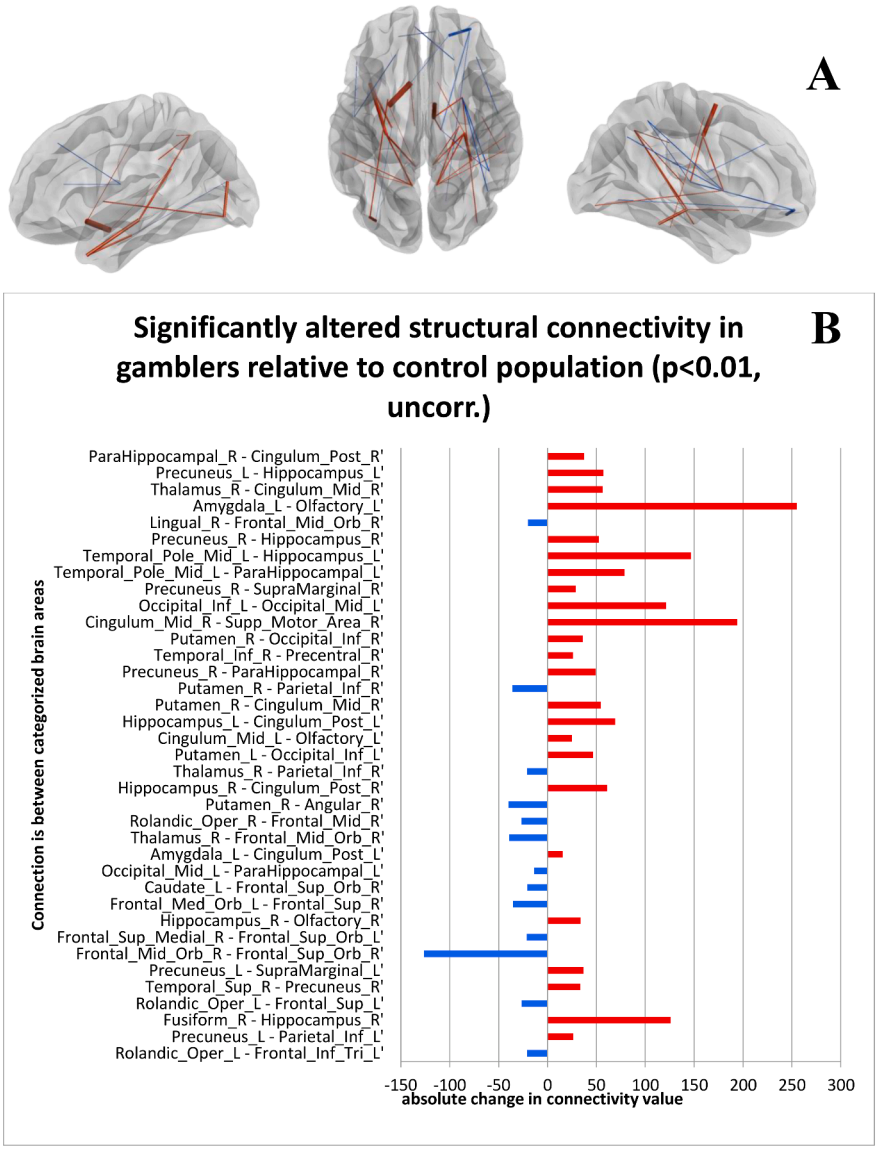

Fig. 1. Detail of the altered connectivity in the GD group as compared to HV. A) 37 significantly altered connections between regions ($p<0.01$, uncorr.) are overlaid on a glass brain showing (left to right) left hemisphere, top view of both hemispheres, and right hemisphere sections. Increased connectivity in the GD group is color coded in red, while decreases are coloured blue. The thickness indicate the absolute change in connectivity value between groups, with thicker lines showing higher difference. B) List form of the 37 connections ranked by significance (not shown), with the respective regions on the y-axis and the corresponding change in connectivity for the GD group compared to HV. color coding is kept the same.

risk better (Wang et al., 2019). While the loss seems to correspond to a dysfunctional OFC, the medial cingulate is classically associated with increased activity during craving across many addiction forms, as well as the "loss chasing" behavior (Potenza, 2013). This increased activation could afford the increased connectivity we observe.

Like thalamus, the putamen has increased medial cingulate connectivity, whilst the parietal cortex and angular gyrus connectivity is significantly decreased. The angular gyrus has a strong role in risk assessment during decision-making as well as a key role in mental arithmetic (Sacré et al., 2017; Zarnhofer et al., 2012), demonstrating increased activity in the cases where decisions were made under uncertainty (Vickery and Jiang, 2009). Similarly, the inferior parietal lobe is strongly related to the assessment of odds of winning, particularly showing most involvement in cases where winning is almost guaranteed (Studer et al., 2012). In GD however, the addictive behavior in essence erodes the uncertainty of choice, and the valuation of what constitutes a "safe win" is dramatically impaired.

These findings suggest an overall restructuring of the striatal network where activity in agreement to symptomatology has shaped stronger connections for the GD group whilst the connections to areas associated with risk aversion and risk assessment have weakened to some extent, possibly due to atrophy. Regions that in lesion studies are associated with gambling-like behavior also reveal reduced connectivity in the GD group.

4.3. Reduced frontal connection strengths

Within the frontal lobe, there is a notable drop in connectivity to OFC. This is both within the GD group, from medial to lateral parts of the OFC, as well as from the superior frontal gyrus to the OFC. This strongly supports the dysfunction explanations previously alluded to. Further enforcing this theory is the right hemisphere laterality, which has previously been shown in lesion studies to exist within the Iowa gambling task (Clark et al., 2003). While the amygdala has been shown to play a role in loss aversion through mediated signaling to the rolandic operculum, we observe reduced connection strength between the ipsilateral rolandic operculum and frontal areas. This could potentially be related to the lack of control over impulsive behaviors known to be associated with GD (Bechara et al., 1996; Gelskov et al., 2015; Studer et al., 2012).

4.4. Increased connectivity in a subnetwork

The differences in connectivity profile of the GD subjects relative to the HV demonstrate, in addition to striatal reconfiguration and frontal

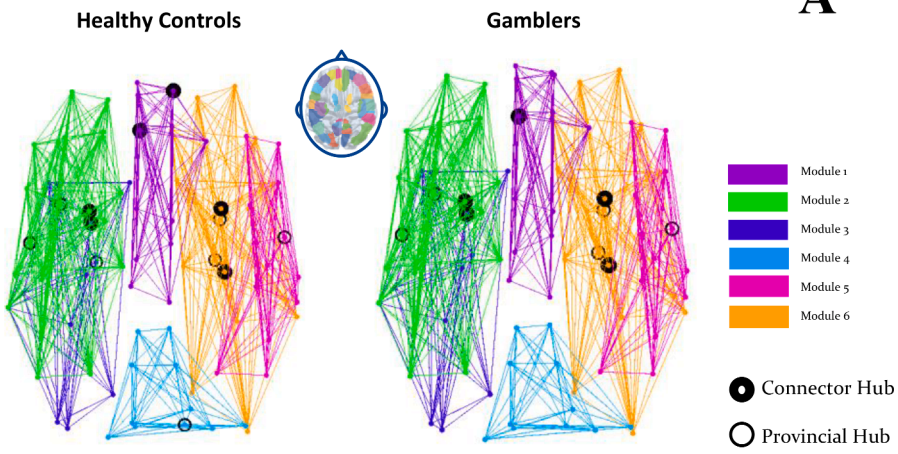

Fig. 2. Modularity of the GD and HV group respectively.
A) Top-down view of the modularity results drawn as a flattened image of lines connecting the centres of gravity of each other 90 regions in the AAL atlas. Filled and unfilled black circles denote hub regions into connector and provincial hubs respectively. As can be seen, the modularity is near identical, however the GD group have lost a connector hub in module 1, and provincial hubs in module 3 and 4.
B) Table showing the classified hubs for each group. As shown, the HC group modules contain the same hubs as the GD group in addition to the 3 hubs mentioned above. This points to that the overall brain structure of the two groups is quite similar with some more specific regional differences.

B

Hubs			
Connector Hubs		Provincial Hubs	
Gambling	Controls	Gambling	Controls
Cingulum_Ant_L	Frontal_Sup_Med_R	Rolandic_Oper_L	Rolandic_Oper_L
Hippocampus_R	Cingulum_Ant_L	Rolandic_Oper_R	Rolandic_Oper_R
Amygdala_L	Hippocampus_R	Insula_L	Insula_L
Putamen_L	Amygdala_L	ParaHippocamp_R	ParaHippocamp_L
Putamen_R	Putamen_L	Amygdala_R	ParaHippocamp_R
	Putamen_R		Amygdala_R
			Cuneus_R

connectivity strength losses, a widespread increase in connectivity strength. Among the 24 uncovered significant alterations, several regions involved in decision-making processes are predominant.

The hippocampus region which show increased connections to the precuneus, posterior cingulate, and bilateral temporal lobes have recently been suggested to play a larger role in value-based decision-making (Palombo et al., 2015).

GD is associated with increased parahippocampal activity during stimulation with gambling related scenery, consolidating the finding that parahippocampus has several increases in connectivity strength, similar to that of the hippocampus (Crockford et al., 2005).

As a key region in the default mode network, the precuneus is well studied. In our study it shows increased connectivity to the temporal lobe and hippocampus, a finding in direct contrast to previously reported decreases in resting state functional connectivity within GD (Jung et al., 2014). On the other hand, precuneus activity correlates positively with GD behavior in a mixed gamble task setting (Gelskov et al., 2015) and has recently been suggested to encode irrational betting behavior through high frequency gamma activity (Sacré et al., 2016). These findings on the role of the precuneus point to a lowered activity at rest, but increased activity in GD related tasks / settings.

Similarly to the precuneus, the posterior cingulate cortex is found in macaques to encode subjective valuation of outcomes, driving an irrational preference for risky behavior (McCoy and Platt, 2005), adding to which both precuneus and posterior cingulate activity is often found in self-referencing tasks (Cavanna and Trimble, 2006). Finally, previous studies have reported bilateral temporal lope activation to be correlated to subjective gambling urges (Balodis et al., 2012).

Taken together, these edges with increased connectivity connect areas that are associated with similar brain activation increases in relation to gambling related tasks, actions, and sceneries.

4.5. Modular similarity and hub differences

The findings in the modularity analysis show that there is no marked difference in modularity across GD and HV. This may come off as surprising initially since there is precedence for this type of analysis to reflect the reorganization patterns within mental illness (Deco and Kringelbach, 2014). However, the GD group in this study are all treatment-active, which could explain that there is very little difference to detect in terms of overall organizational graph representation.

More subtle changes are evident from the hub classification results. While there is a large degree of overlap in the hub classification as well, the GD group have three hubs fewer than the HV. These comprise two provincial hubs, the right cuneus and the left parahippocampus, and one connector hub, the medial superior frontal gyrus in the right hemisphere. As briefly discussed before, the latter frontal region has been shown to be involved in risk avoidance behavior and has consistently been reported to exhibit decreased activation during loss conditions of the MID task (Balodis et al., 2012). For it to no longer be classified as a connector hub, it stands that not only is it less well connected to module 1, which contains limbic and medial OFC nodes; it also has reduced effective connectivity to the other modules. This reduction in the GD group in the role of the right medial superior frontal gyrus as a node for information integration could be due to synaptic atrophy.

6. Conclusions

In conclusion we find that the treatment-active GD group, relative to HV, demonstrate reduced connectivity to brain areas whose dysfunction

heavily impacts risk seeking behavior, a restructured striatal connectivity profile in accordance with the literature on functional neuroimaging, and a general reinforcement of connectivity strength between regions that exhibit increased activity in gambling situations. However, we highlight our results as exploratory in nature as they did not survive multiple comparisons correction. While the superior frontal gyrus of the right hemisphere loses status as a connector hub, alongside the two provincial hubs of right cuneus and left parahippocampus, the overall modularity of the GD subjects were indistinguishable from that of HV. These findings corroborate existing literature on active GD. Considering our group of GD subjects in this study are all undergoing treatment for their behavioral addiction, this may explain the lack of statistical power. The behavioral results further suggest a directly measurable effect of treatment, with monetary appraisal being down-regulated, in favor of a generalized reward-bias. We encourage future studies to assess this method in both treatment-naïve and treatment-active GD subjects in order to further explore the effect of treatment as a biomarker for intervention strategies within GD.

CRediT authorship contribution statement

Casper Schmidt: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Carsten Gleesborg:** Formal analysis, Methodology, Software, Validation. **Hema Schmidt:** Data curation, Methodology, Software. **Timo L. Kvamme:** Data curation, Methodology, Software. **Valerie Voon:** Project administration, Supervision. **Arne Møller:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

We, all authors, declare no conflicts of interest in connection with this manuscript or journal.

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