Abnormalities of functional brain networks in pathological gambling: a graph-theoretical approach

Melanie Tschernegg1,†, Julia S. Crane1,†, Tina Eigenberger3, Philipp Schwartenbeck1,2, Mira Fauth-Böhler4, Tagrid Lemnäger4, Karl Mann5, Natasha Thon1, Friedrich M. Wurst1,2 and Martin Kronbichler1,2,*

1Centre for Neurocognitive Research and Department of Psychology, University of Salzburg, Salzburg, Austria
2Neuroscience Institute and Centre for Neurocognitive Research, Christian-Doppler-Klinik, Paracelsus Medical University Salzburg, Salzburg, Austria
3Department of Psychiatry and Psychotherapy II, Christian-Doppler-Klinik, Paracelsus Medical University Salzburg, Salzburg, Austria
4Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany
5020 Salzburg, Austria

together with substance addiction

*Correspondence: Martin Kronbichler, Centre for Neurocognitive Research and Department of Psychology, University of Salzburg, Hellbrunnerstrasse 34, 5020 Salzburg, Austria. e-mail: martin.kronbichler@sbg.ac.at
†Melanie Tschernegg and Julia S. Crane, as well as Friedrich M. Wurst and Martin Kronbichler have contributed equally to this work. Melanie Tschernegg and Julia S. Crane are joint first authors, and Friedrich M. Wurst and Martin Kronbichler are joint last authors.

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INTRODUCTION

Patients suffering from pathological gambling (PG) show persistent gambling behavior despite negative consequences resulting in a wide-range of psychosocial impairments (Goudriaan et al., 2004). PG is classified as an impulse control disorder in DSM-IV (American Psychiatric Association, 2000), but is increasingly conceptualized as a behavioral addiction with striking similarities to substance addictions such as withdrawal symptoms and signs of tolerance (Petry, 2007). Therefore, PG (besides being renamed as disordered gambling) has been reclassified under the chapter “Addiction and related disorders” (together with substance addictions) in DSM 5 (American Psychiatric Association, 2013; Petry et al., 2013).

Most functional neuroimaging studies in PG up to date have examined brain activity abnormalities using paradigms such as reward processing, reactivity to gambling related cues, learning, decision making, and executive functions (for reviews, see Potenza, 2008, 2013; van Holst et al., 2010). In line with brain imaging studies on substance addiction, activation abnormalities in regions of the mesolimbic reward system (mainly in orbitofrontal, medial and lateral prefrontal regions, and the ventral striatum) were consistently found in patients with PG (Cavedini et al., 2002; Potenza et al., 2003; Reuter et al., 2005; Tanabe et al., 2007; Balodis et al., 2012; Choi et al., 2012; Miedl et al., 2012; van Holst et al., 2012a; Hudgens-Haney et al., 2013; Limbrick-Oldfield et al., 2013).

Brain activation differences in fronto-striatal regions in PG have also been found in executive function tasks and been commonly interpreted as reflecting impairments in cognitive control and inhibitory functions (Potenza et al., 2003) which contribute to maladaptive decision making in PG, comparable to such impairments in substance addiction (Tanabe et al., 2007).

Recent interest in functional neuroimaging studies on neuropsychiatric disorders has focused on analyzing resting state functional connectivity (Fox and Grecius, 2010; van den Heuvel and Hulshoff Pol, 2010; Menon, 2011; Xia and He, 2011;
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between frontal areas (Ma et al., 2010). Two studies using graph-theoretical approaches provide important information on the architecture of brain networks. Small-world networks are characterized by dense local connectivity and short path length linking individual network nodes in a short and efficient way (e.g., brain regions based on a parcellation atlas; Bullmore and Sporns, 2009). Short pathways between one node and any other node as well as a high density of connections between nearest neighbors are necessary for efficient segregation and functional integration (Salvador et al., 2005; Achaer et al., 2016; Bassett and Bullmore, 2009). Network graphs are based on structural or functional data and quantify the structural and functional organization of the brain (Stam and Reijneveld, 2007).

Studies have shown that the small-world architecture and topological network properties of the brain exhibit abnormalities in neuropsychiatric disorders (e.g., He et al., 2009; Lynall et al., 2010; Zhang et al., 2011a, Cocchi et al., 2012; Cai et al., 2013; for a review, see Xia and He, 2011). For example, patients with schizophrenia show lower cortical integration (lower amount of connections, longer path lengths, and lower clustering coefficients) in the frontal, parietal, and temporal pole (Liu et al., 2009). Zhang et al. (2011b) found global integration differences between HCs and patients with major depressive disorder, and differences in nodal centrality for frontal areas, and regions of the default mode network as well as for subcortical regions like the caudate. Furthermore, patients with obsessive-compulsive disorder (OCD) show altered functional connectivity and small worldliness properties (Zhang et al., 2011b). OCD patients demonstrate higher local clustering in the brain’s cognitive control network (posterior temporal regions and the cingulate cortex). Differences in brain topology are also reported for young adults with ADHD (Cocchi et al., 2012). Functional segregation of the orbitofrontal cortex via advertisements and mailings. Behavioral assessment: The German version of the short questionnaire on gambling behavior (Karzfagebogen zum Glücksspielverhalten – KFG; Petry, 1996) and The South Oaks Gambling Screen (SOGS) by Lesieur and Blume (1987) were used to quantify gambling behavior. Furthermore, all participants completed the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2006), the Fagerstrom Test for Nicotine Dependence (FTND; Fagerstrom, 1978), the Behavioral Inhibition Scale (BIS; Carver and White, 1994), and the Beck Depression Inventory (BDI; Beck et al., 1996).

**Materials and methods**

**Subjects**

This study has been approved by the local ethics committee. Nineteen patients with PG and 19 age-matched HCs with no history of neurological or psychiatric disorders participated in this study. Written informed consent was provided by all participants. All patients were seeking treatment and have been recruited at the Pathological Gambling out-patient clinic at the Department of Psychiatry and Psychotherapy II. Control subjects were recruited via advertisements and mailings.

**Imaging data acquisition**

Resting state fMRI was performed with a 3 Tesla Siemens Tim Trio MRI using a 32-channel head coil. All participants were asked for Nicotine Dependence (FTND; Fagerstrom, 1978), the Behavioral Inhibition Scale (BIS; Carver and White, 1994), and the Beck Depression Inventory (BDI; Beck et al., 1996).
to quietly rest in the scanner with their eyes closed and not to think of anything specific. Two-hundred and fifty T2*-weighted images were acquired (including six dummy scans which were discarded) with a gradient echo-planar imaging sequences with the following parameters: TR: 2.25 s; TE: 30 ms; flip angle: 78°; field of view (FOV): 192 mm × 192 mm; matrix size: 64 × 64; 36 slices; slice thickness: 3 mm; slice gap 0.3 mm; voxel size: 3 mm × 3 mm × 3 mm. Additionally, a high-resolution structural scan (sagittal T1-weighted MPRAGE sequence; TR: 2300 ms; TE: 2.91 ms; voxel size: 1 mm × 1 mm × 1.2 mm; slice thickness: 1.20 mm; FOV: 356 mm × 356 mm; 160 slices; flip angle: 9°) and fieldmaps were obtained from each participant.

Functional magnetic resonance imaging data were preprocessed using Statistical Parametric Mapping (SPM 8, Wellcome Department of Imaging Neuroscience, London, UK). The following procedures were included: realignment and unwarping to compensate for movement-related artifacts; slice timing correction; coregistration of the EPI scans to the skull-stripped T1-weighted structural scan; normalization to standard stereotaxic anatomical Montreal Neurological Institute (MNI) space; smoothing with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel; voxel size was resampled to isotropic 3 mm × 3 mm × 3 mm.

To address the problem of confounds due to small head motion which may influence resting state connectivity, we ensured that all data sets did not exhibit movements larger than 3 mm for translations or 3° for rotations. Movement parameters were compared between patients and HCs using two-tailed t-tests. There are no significant differences in any of the six movement parameters (all rs < 1, all ps > 0.3).

For further analyses, noise correction and filtering with a band-pass filter between 0.01 and 0.1 Hz was performed with the conn toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). For noise correction all six movement parameters and the first derivative of the time-series were removed from the data by regression. For further noise reduction, noise signals were estimated from white matter and CSF signal and removed from the data with the CompCor method (Behzadi et al., 2007) as implemented in the conn toolbox. These noise removal steps have been shown to substantially reduce noise from non-neural sources and increase the sensitivity and reliability of functional connectivity analysis (Whitfield-Gabrieli and Nieto-Castanon, 2012). No global signal regression was performed as it may result in lower reproducibility of network metrics (see Telesford et al., 2013).

NETWORK CONSTRUCTION

The Harvard–Oxford Atlas was used to extract the preprocessed fMRI data from 48 left and 48 right hemisphere cortical regions, as well as from seven left and seven right subcortical regions. Time-series of the low-frequency BOLD signal were extracted for each subject, the time-series of all 110 regions were correlated as well as from seven left and seven right subcortical regions. Time-series of the low-frequency BOLD signal were extracted for each of the 110 regions and averaged over all voxels in each node. For each subject, the time-series of all 110 regions were correlated with each other to create an undirected and weighted correlation matrix using Pearson correlation. These steps were performed with the conn toolbox. In contrast to partial correlation, the Pearson correlation coefficient is gaining higher values of reproducibility (Telesford et al., 2013). In this network, each region represents a node with the correlation coefficients of the time-series between the different regions defining the edges resulting in a 110 × 110 connectivity matrix.

GRAPH ANALYSES

Algorithms of network properties were performed with the GAT2 (Hosseini et al., 2012), which uses routines of the Brain Connectivity Toolbox for network metrics calculation (Rubinov and Sporns, 2010).

Threshold selection

To make groups comparable, we ensured that all graphs had the same number of edges by applying an individual threshold to each correlation matrix. This was done by calculating the ratio of the number of actual connections divided by the maximum number of all possible connections described as the so-called cost of the network (connection density). Since there is still no consensus of the best threshold to be chosen, a wide range of threshold values were applied in this study (0.11 ≤ T ≤ 0.55 with an increment of 0.02). To verify that the selection of the threshold range is not too wide which may produce disconnected nodes and networks without small-worldness features on either ends of the range, we ensured that all subjects (a) had an averaged degree value of 2 * log(N) with N = number of nodes and (b) showed network properties of small-worldness with σ > 1.1 in all threshold values (Zhang et al., 2011a).

Network metrics

For each threshold, the following global metrics were calculated: characteristic path length (L); the average of the clustering coefficient (C); global efficiency (EG); small-worldness (σ); additionally, the following local metrics were calculated for each threshold: degree (k); local efficiency (EL); node betweenness (NB); clustering coefficient (C).

The degree describes the number of edges linking one node to the rest of the network and gives information on how functionally connected a node is. The clustering coefficient is a measure of degree to which nodes in a graph are forming a cluster. The characteristic path length describes the number of edges between one node and any other node in a network giving an overview of the effectiveness of information transfer. The global efficiency is inversely related to the characteristic path length. The local efficiency is computed on node neighborhood and gives an overview of the clustering coefficient reflecting the efficiency of parallel information transfer, robustness, and fault tolerance of a network. Compared to the clustering coefficient and the characteristic path length, measures of efficiency have the advantage of including disconnected nodes with a value of 0 while the former remove them from the analysis, and therefore, may falsify the results when disconnected nodes are present (Adcock and Bullmore, 2007). The node betweenness is a measure of centrality and specifies the fraction of all shortest pathways in a network that contain a given node. The so-called small-worldness is the ratio of the averaged and normalized clustering coefficient (γ) to the normalized characteristic path length (λ) and assesses the small-world properties of a network characterized by high clustering coefficient and a
low characteristic path length. Small-worldness properties of a network are usually given when sigma (σ) is greater than 1.

All metrics were compared with the corresponding values obtained and averaged from 20 random networks with the same number of nodes, total edges, and degree distribution resulting in, for example, γ = C/(1−γ) and λ = L/(1−γ) (Maslov and Sneppen, 2002).

Statistical analyses
Group comparisons of the metrics were conducted with permutation tests implemented in the GAT toolbox using the area under the curve (AUC) calculated over the threshold for each metric (Bruno et al., 2012; Hosseini et al., 2012; Singh et al., 2013). All results were corrected for multiple comparisons using a false positive correction, p < 1/N (Alexander-Bloch et al., 2010). All p-values corrected for multiple comparisons have been transformed and are reported as pcorr.

Since this study is an exploratory study and the first in PG using graph theoretical approaches to assess network properties in resting state data, we also report significant results with uncorrected p-values.

To examine possible alterations of functional connectivity strength between regions, the correlation values of all regions were compared between both groups to find significant differences in connectivity. Analyses of functional connectivity were performed with the conn toolbox and corrected for multiple comparisons using an FDR-threshold, p < 0.05.

RESULTS
SAMPLE CHARACTERISTICS
Sample characteristics are shown in Table 1. No statistically significant group differences were found for sex ratio, years of education, or age. Furthermore, PG patients were comparable to HCs with respect to tobacco and alcohol consumption as assessed by the FTND and the AUDIT.

Large group differences were found in gambling behavior (KFG, SOGS). PG patients also demonstrated a larger number of depressive symptoms as measured by the BDI and higher impulsivity as measured by the BIS.

GLOBAL METRICS
Both groups showed small worldness properties with σ > 1 and there were no significant differences between groups (p = 0.845). Compared to random networks, both groups showed a higher averaged clustering coefficient (γ > 1) and similar values for the characteristic path length (λ ~ 1). None of the global metrics differed between patients and controls (Edgeloop: p = 0.646; λ: p = 0.797; γ: p = 0.817). Results for all global metrics are displayed in Figure 1.

NODAL METRICS
At the corrected significance threshold, differences in nodal metrics were found in medial frontal regions. As can be seen in Figure 2, patients with PG demonstrated a decreased clustering coefficient for the left juxtapostriate lobe (supplementary motor area, SMA; pcorr = 0.038) and the left paracingulate gyrus (pcorr = 0.044). Additionally, local efficiency for the left juxtapostriate lobe (SMA) was decreased for PG patients (pcorr = 0.022). Node betweenness was increased in the right paracingulate gyrus (pcorr = 0.05) as well as in the left paracingulate gyrus (pcorr = 0.011) in PG patients. Further differences in regional metrics at an uncorrected significance level are shown for exploratory purposes in Table 2.

FUNCTIONAL CONNECTIVITY ANALYSES
Functional connectivity was increased in patients between frontal regions and between frontal and temporal regions (see Table 3). Furthermore, we found increased connectivity in patients between the left caudate and the right anterior cingulum as well as the left anterior cingulum. Additionally, the left amygdala with the left subcallosal cortex demonstrated weaker connectivity in patients than in controls.

DISCUSSION
In this exploratory study, we investigated the functional network properties of patients with PG during the resting state using a graph-theoretical approach. While several studies could demonstrate functional abnormalities in PG during tasks associated with gambling, executive functions, and reward processing (Reuter et al., 2005; Tanabe et al., 2007; Balodis et al., 2012; Choi et al., 2012; Medić et al., 2012; van Holst et al., 2012a; Hugdens-Haney et al., 2013; Limbrick-Oldfield et al., 2013), for a review, see Potenza, 2013), we are the first to show that patients with a behavioral addiction such as PG exhibit alterations in the topology of resting state networks in regions associated with reward processing and self-regulation.

Network properties at the global level showed no differences between patients and HCs. Global efficiency of information transfer and fault tolerance, for example, were similarly high in both groups. This is in line with a previous graph-theoretical study investigating the global topology of subjects suffering from internet addiction (Hong et al., 2013).

In contrast to global network properties, we found significant differences between healthy subjects and patients in network.
properties at the nodal level. Corrected for multiple comparisons, only medial frontal regions were affected in patients with PG. The SMA and the paracingulate cortex both showed a reduced clustering coefficient and impaired local efficiency of information transfer and fault tolerance. Furthermore, the contribution to the number of shortest paths was increased in both regions suggesting that these regions seem to adopt a more central position in the network than in healthy subjects. Note that the results for local efficiency in the paracingulate cortex and for betweenness centrality in the SMA are only tendencies, since they are not significant at a corrected level. These findings indicate that in medial frontal regions the balance between integration and segregation seem to be altered.

Medial frontal regions like the paracingulate cortex are associated with reward processing (Knutson et al., 2001; van den Bos et al., 2007; Fujiwara et al., 2009). Dysfunctions in reward processing are typical findings of previous investigations in PG (Reuter et al., 2005; Clark and Limbrick-Oldfield, 2013). The cingulate cortex is also important for gambling situations especially for specific processes of gambling (Campbell-Meiklejohn et al., 2008) like loss-chasing and quitting gambling.

Another frontal region which was found to be affected in PG is the SMA. The SMA demonstrated the same pattern of impairments as the paracingulate cortex with decreased clustering and efficiency of local information transfer but an increase in betweenness centrality.

The SMA is associated with motor execution and vigilance performance (Hinds et al., 2013) but is also involved in error detection and reward expectancy (McClure et al., 2004). Thus, the findings of this study demonstrating alterations...
Table 2 | Significant differences in all metrics using area under the curve (AUC) for pathological gamblers (PG) and healthy controls (HCs).

| Hemisphere | Region                          | Metric | p-Value | p_cor | Group comparison |
|------------|--------------------------------|--------|---------|-------|------------------|
| Right      | Paracingulate                  | NB     | 0.009   | 0.050*| PG > HC          |
|            | Insular                        | LE     | 0.057   | 0.316 | HC > PG          |
|            | Precentral                     | NB     | 0.027   | 0.150 | PG > HC          |
|            | Supramarginal (anterior)       | NB     | 0.019   | 0.105 | HC > PG          |
|            | Temporal fusiform (anterior)   | DG     | 0.022   | 0.122 | PG > HC          |
|            | Caudate                        | NB     | 0.041   | 0.227 | PG > HC          |
|            | Hippocampus                    | NB     | 0.036   | 0.200 | HC > PG          |
| Left       | Juxtapositional (SMA)          | CC     | 0.007   | 0.038*| HC > PG          |
|            |                                 | LE     | 0.004   | 0.022*| HC > PG          |
|            |                                 | NB     | 0.041   | 0.227 | PG > HC          |
|            | Paracingulate                  | CC     | 0.008   | 0.044*| HC > PG          |
|            |                                 | LE     | 0.033   | 0.183 | HC > PG          |
|            |                                 | NB     | 0.002   | 0.011*| PG > HC          |
|            | Middle temporal (anterior)     | CC     | 0.039   | 0.216 | PG > HC          |
|            | Middle temporal (temporooccip) | DG     | 0.013   | 0.072 | PG > HC          |
|            | Middle temporal (anterior)     | NB     | 0.037   | 0.205 | PG > HC          |
|            | Inferior temporal (anterior)   | CC     | 0.034   | 0.188 | PG > HC          |
|            |                                 | LE     | 0.035   | 0.194 | PG > HC          |
|            | Inferior temporal (temporooccip)| NB   | 0.034   | 0.188 | PG > HC          |
|            | Lateral occipital superior     | CC     | 0.025   | 0.138 | HC > PG          |
|            |                                 | LE     | 0.016   | 0.088 | HC > PG          |
|            | Temporal fusiform (anterior)   | CC     | 0.045   | 0.250 | PG > HC          |
|            |                                 | LE     | 0.024   | 0.133 | PG > HC          |

CC, clustering coefficient; DG, degree; LE, local efficiency; NB, node betweenness; p_cor: corrected for multiple comparisons; *Statistically significant at p < 0.05, corrected for multiple comparisons.

...in integration and segregation of medial frontal regions may underlie specific behavioral difficulties patients with PG exhibit.

Since this was an exploratory study, we also want to discuss findings which do not exceed the threshold selected to correct for multiple comparisons.

We found a reduced fraction of path length in the left inferior frontal gyrus which also contributes to the general findings of impairments in frontal regions in gambling and addiction. A previous study showed that PG patients exhibit alterations in inferior frontal activity during gambling cue presentation (Crocker et al., 2010). The inferior frontal gyrus has been associated with executive control and response inhibition (Hamshire et al., 2010). Interestingly, while medial frontal regions showed an increase in betweenness centrality, in lateral frontal regions, this metric was decreased. This pattern may support previous findings demonstrating deficits in self-regulation and working memory in PG (Forbush et al., 2008), but enhanced involvement of the reward system.

Additionally, we further found alterations in subcortical regions at an uncorrected threshold level. The right caudate plays a more central role as a main hub for integration of information compared to HCs while the hippocampus is less involved. Again, this points out the enhanced involvement of the reward system in PG. The caudate is part of the striatum which is an important part of the mesolimbic reward system. The alterations found in network properties of the hippocampus, are in line with deficits in heroin addicts identified in a previous study (Liu et al., 2009).

This pattern of impaired topology in regions which were previously associated with the executive control network and the reward system (Potenza et al., 2003; Reuter et al., 2005; Tanabe et al., 2007; Limbrick-Oldfield et al., 2013) is complemented by our findings of increased functional connectivity of fronto-striatal...
Table 3 | Significant differences between pathological gamblers (PG) and healthy controls (HC) in functional connectivity.

| Region                  | Region                  | Group          | p-Value* |
|-------------------------|-------------------------|----------------|----------|
| Right inferior frontal (parasagittal) | Right hippocampus       | HC < PG        | <0.001   |
| Right frontal operculum | Right inferior temporal (temporooccipital) | HC < PG        | <0.001   |
| Right frontal operculum | Right cingulate cortex  | HC < PG        | <0.001   |
| Right frontal operculum | Right temporal fusiform (anterior) | HC < PG        | 0.003    |
| Right frontal operculum | Left inferior temporal (temporooccipital) | HC < PG        | 0.001    |
| Right frontal operculum | Left middle frontal     | HC < PG        | <0.001   |
| Right frontal operculum | Left middle temporal (temporooccipital) | HC < PG        | <0.001   |
| Right frontal operculum | Left frontal pole       | HC < PG        | 0.003    |
| Left caudate            | Left cingulate (anterior) | HC < PG        | 0.001    |
| Right angular           | Left lateral occipital (superior) | HC < PG        | <0.001   |
| Right temporal fusiform (posterior) | Left inferior temporal (temporooccipital) | HC < PG        | 0.001    |
| Left middle temporal (anterior) | Left parahippocampal (anterior) | PG < HC        | <0.001   |
| Left subcallosal        | Left amygdala           | PG < HC        | 0.004    |

*Statistically significant at FDR-corrected threshold, p < 0.05.

There are no available standards for a uniform application of graph theories at present (Bullmore and Sporns, 2009). One methodological limitation when investigating network topology with a graph-theoretical approach, for example, is the choice of thresholds. There are several possibilities to select the threshold and no golden standard has been defined yet. When comparing groups it should be ensured that each network has the same number of edges. However, the problem with a global threshold is that it may lead to disconnected graphs. Comparing network properties of one graph with the other is problematic if the one is connected at a given node and the other is disconnected. To address this problem, we ensured that the averaged degree is above the selected threshold and all subjects show small-world properties. Furthermore, we also investigated the global and local efficiency in addition to the clustering coefficient and the characteristic path length. These metrics have some methodological advantages when dealing with disconnectedness (Achard and Bullmore, 2007).

Another limitation is the wide range of thresholds selected. Depending on the range, results differ between studies and make comparison of findings and their interpretation difficult. However, we have implemented strategies which have been successfully applied in previous studies using graph-theoretical approaches (e.g., Zhang et al., 2011a; Bruno et al., 2012). Since this is a first exploratory study in PG using graph-theoretical analyses of resting state fMRI data, further research must be conducted to confirm these results.

Moreover, Zalesky et al. (2012) has shown that the type of randomization (topology randomization, correlation matrix randomization, or time-series randomization) influences the normalization process of the metrics. For a low density of around 7% the authors identified a discrepancy of approximately 60% when applying topology randomization compared to correlation matrix randomization to estimate the normalized clustering coefficient. In addition, using correlation matrix randomization to normalize characteristic path length may lead to longer path lengths due to the randomization of hub nodes since the degree distribution is not preserved. These limitations affect especially low density thresholds around 7% and are evident when looking at absolute small-world properties of the networks in each group. However, they are less essential for the comparison of network metrics between groups which is the focus of this study.
This first study in PG using graph-theoretical approaches to investigate network properties demonstrates that alterations of regions associated with the reward system and executive functions are not only present in task-related activity but also during rest. Alterations are reflected in a decrease in segregation and an increase of information integration in specific regions of the reward system.

This may contribute to the ongoing discussion whether PG is characterized by a hyper- or a hyporeactive reward system. Furthermore, our results suggest deficits of integration in regions associated with executive functions. These alterations may provide further explanation for several symptoms and previous findings in PG (for a review see Goudriaan et al., 2004; van Hoist et al., 2010).

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