Increased functional connectivity in gambling disorder correlates with behavioural and emotional dysregulation: evidence of a role for the cerebellum

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ABSTRACT

Gambling disorder (GD) is a psychiatric disease that has been recently classified as a behavioural addiction. So far, a very few studies have investigated the alteration of functional connectivity in GD patients, thus the concrete interplay between relevant function-dependent circuitries in such disease has not been comprehensively assessed.

The aim of this research was to investigate resting-state functional connectivity in GD patients, searching for a correlation with GD symptoms severity.

GD patients were assessed for gambling behaviour, impulsivity, cognitive distortions, anxiety and depression, in comparison with healthy controls (HC). Afterwards, they were assessed for resting-state functional magnetic resonance imaging; functional connectivity was assessed through a data-driven approach, by using independent component analysis. The correlation between gambling severity and the strength of specific resting-state networks was also investigated.

Our results show that GD patients displayed higher emotional and behavioural impairment than HC, together with an increased resting state functional connectivity in the network including anterior cingulate cortex, the caudate nucleus and nucleus accumbens, and within the cerebellum, in comparison with the control group. Moreover, a significant correlation between behavioural parameters and the strength of the resting-state cerebellar network was found. Overall, the functional alterations in brain connectivity involving the cerebellum observed in this study underpin the emotional and behavioural impairment recorded in GD patients. This evidence suggests the employment of novel neuromodulatory therapeutic approaches involving specific and salient targets such as the cerebellum in addictive disorders.

Keywords: cerebellum, fMRI, functional connectivity, gambling disorder, psychological assessment, resting-state

Highlights

- GD patients displayed impulsivity, cognitive distortions, anxiety and depression.
- GD patients showed high functional connectivity in reward and cerebellar networks.

1. INTRODUCTION

Gambling disorder (GD) is a psychiatric disease characterized by maladaptive and excessive gambling behaviour. Due to the striking similarities to substance addiction in terms of cognitive and personality features, psychiatric comorbidities, neurobiological processes, and genetic vulnerability, it is accounted for a behavioural addiction [1-6], and reclassified under the chapter "Addiction and related disorders", in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) [7]. Pathogenetic interpretations of (drug) addiction have included different theories: reward deficiency hypothesis [8], incentive-sensitization theory [9], impaired response inhibition and salience attribution hypotheses [10]. All of them converge towards aberrant functioning of the reward network (prefrontal and mesolimbic cortex) which underlies the symptom clusters shared between drug addiction and GD: loss of control, withdrawal and craving, and "neglect other areas in life" .

The overlapping of the main symptom clusters is confirmed by the results from behavioural and functional Magnetic Resonance Imaging (fMRI) studies. In particular, subjects affected by GD and heroin addicts display reduced executive functioning such as diminished response inhibition and cognitive flexibility and impaired decision making [1], which have been paralleled to fMRI evidence of hypo-responsiveness of the frontal midline structures [11-13]. A hyper-reactivity of the brain to gambling-related cues, associated with craving and withdrawal, is evidenced by an increased activity in the prefrontal and limbic structures [14,15]. Indeed, fMRI findings suggest that an imbalance between prefrontal brain activity and mesolimbic function may account for an alteration in reward (gain/loss) processing at the basis of the chasing one's losses in GD, which may be an important factor in the development of GD. As a matter of fact, the prefrontal cortex is not the only player involved in tuning behavioural responses that need optimizing the efficacy of the predictions about internal events and the external cues [16-18], since other areas, like the cerebellum, take part to the process [19].

It is apparent that focusing on brain activation within specific brain regions is limitative to comprehend the neurobiological underpinnings of GD, where the actual interplay between relevant function-dependent circuitries has not been comprehensively assessed so far. To accommodate the idea of the brain as a complex network, neuroimaging studies have been carried out with the aim at investigating functional connectivity during the resting state (RS-FC) in GD. All this makes it possible to distinguish particular brain circuitries that are involved in the development and maintenance of psychiatric disorders, such as addictions. Most of the studies that have already explored RS-FC in GD, took advantage of a seed-based approach which focused on reward and cognition-related areas [20,21,22] or with a graph theoretical analysis [23]. As far as we know, only one study applied a data-driven Independent Components Analysis (ICA) to RS-FC in GD showing an increased integration of the right middle insula within the ventral attention network; however, the authors chose the networks to be compared between the two groups, on the basis of their a priori hypothesis [24].

Indeed, the aim of this research was to investigate altered intrinsic RS-FC in patients with GD, by an independent component analysis (ICA) approach. This may lead to the identification of unexpected alterations in network connectivity that are not apparent by a priori fMRI approach. In addition, the search for correlation between altered brain RS-FC and GD symptoms severity has been carried out.

Since gambling disorder can be considered an addiction in its pure form, i.e. without the influence of a drug of abuse, investigation of addiction-related modifications in brain RS-FC can help to define the whole picture and implement therapeutic strategies.

2. MATERIALS AND METHODS

2.1. Participants and procedure

Fourteen GD patients and fourteen healthy controls (HCs), both right-handed, ranging from 23 to 56 years old were involved in the study. GD patients were recruited from the Italian Addiction

Center (Dept. of Pathological Addiction, ASP Palermo) and from the Psychiatry Unit of Policlinico "P. Giaccone", Palermo, Italy. HCs were recruited through advertisements. Since most treatment seeking GD patients were men, only male participants (both GD and HC) were included in the study. For this reason, exclusion criteria for both groups were: lifetime diagnosis of any major psychiatric illness, including substance dependent disorder and post-traumatic stress disorder; treatment for mental disorders other than GD in the past 12 months; history or current treatment for neurological disorders, major internal disorders, brain trauma, or exposure to neurotoxic factors; use of psychotropic medication; reading difficulty; age under 18 years. In addition, HCs were excluded if they gambled more than twice a year.

All subjects underwent a psychological assessment and a brain resting state fMRI (RS-fMRI). All measures were administered under respect of privacy. This study was carried out in accordance with the protocol approved by the Ethics Committee of the Policlinico "P. Giaccone", Palermo, Italy (Prot. 14910A). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

2.2. Psychological measures

2.2.1. Gambling Behaviour Assessment

All participants completed the South Oaks Gambling Screen (SOGS). The SOGS is a 20-item questionnaire that measures gambling behaviour. The total score on the SOGS ranges from 0 to 20: scores higher than 5 indicate probable pathological gambling [25]. We used the Italian version of the Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale (PG-YBOCS) [26]. The PG-YBOCS is a 10-item clinician-administered questionnaire that measures the severity of gambling disorder over a recent time interval (usually within the past two weeks).

2.2.2. Impulsivity

To evaluate impulsiveness, we used the Barratt Impulsiveness Scale, 11th version (BIS-11)

[27]. The BIS-11 total score indicates the level of impulsiveness. The higher the BIS-11 total score, the higher the impulsiveness level. The BIS-11 is the most frequently used self-report measure of impulsivity.

2.2.3. Cognitive Distortions

In order to evaluate the cognitive distortions, we used the Italian version of the Gambling Attitudes and Beliefs Survey (GABS) [28]. The GABS is a self-report questionnaire, which contains 35 questions related to possible cognitive distortions or different kinds of thinking.

2.2.4. Anxiety

In order to evaluate anxiety, we used the Italian version of the State-Trait Anxiety Inventory (STAI). The STAI is a scale of considerable construct and concurrent validity, and a commonly used measure of trait and state anxiety [29]. Moreover, a measure of perceived stress (MPS) scale was employed to score emotional, behavioural, and cognitive aspects of distress [30].

2.2.5. Depression

The mood valence was evaluated by the Beck Depression Inventory – second version (BDI-II) [31]. The BDI-II is a widely used 21-item self-report inventory measuring the severity of depression in adolescents and adults. The BDI-II was revised in 1996 to be more consistent with DSM-IV criteria for depression.

2.3. Statistical analysis

One-way analysis of variance (ANOVA) was used to evaluate significant differences between GD patients and HCs in age, BIS-11, MSP, STAI, GABS, BDI-II, Y-BOCS and SOGS scores. Pearson's correlation was used to assess a correlation between behavioural data (gambling severity) and the mean functional connectivity value of specific resting-state networks in GD patients. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY: IBM Corp.) and Graphpad Prism version 6.1 for MacOS (GraphPad Software, La Jolla California USA).

2.4. MRI acquisition and preprocessing

All subjects underwent brain scan using a 1.5T MRI scanner (Signa HDxt; GE Medical System, Milwaukee, Wisconsin, USA) at the Radiology Section of the Department of Biomedicine, Neuroscience and Advanced Diagnostics of the University of Palermo; an eight-channel brain phased array coil was used. Foam pads were placed on both sides of the head, within the head coil, to limit head motion during the scan. Structural images were obtained via a T1-weighted sagittal three-dimensional (3D) 1.2 mm thick Fast Spoiled GRadient-echo (FSPGR) prepped inversion recovery pulse sequence (acquisition matrix 256×256; slice thickness 1.2 mm; TR 12.4 ms; TE 5 ms; IT 450 ms; FA 20; parallel imaging method: Array coil Spatial Sensitivity Encoding, ASSET). RS-fMRI data were acquired with a two-dimensional (2D) axial T2*-weighted gradient-echo Echo-Planar (EP) pulse sequence parallel to the anterior commissure–posterior commissure (AC–PC) line over the entire brain (acquisition matrix 64 x 64; 33 slices; slice thickness 3 mm; gap 1 mm; TR 3000 ms; TE 60 ms; FA 90); the first five scans were discarded to allow T1 saturation to reach equilibrium. All participants were explicitly instructed not to move during the MRI scan and quietly rest in the scanner with their eyes open and not to think of anything specific. A ten-minute (200 volumes) fMRI scan was performed on each participant. Scan parameters were consistent for all imaging sessions.

All the preprocessing was performed, at the Department of Physics and Chemistry of the University of Palermo, using FSL's recommended preprocessing pipeline from FMRIB's Software Library (FSL version 5.0.9 www.fmrib.ox.ac.uk/fsl). The following preprocessing procedure was applied by employing different modules of the FSL-software package. The preprocessing of the resting-state data consisted of the following steps: motion correction though MCFLIRT tool [32], slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal using BET [33], spatial smoothing using a Gaussian kernel of FWHM 6.0mm, multiplicative mean intensity normalization of the volume at each timepoint, high pass temporal filtering with sigma =

100.0 s, pre-whitening and global spatial smoothing using a Gaussian kernel with a full width at a half maximum of 6 mm. After preprocessing, the functional images were registered to the corresponding high-resolution echo planar images, (co-registered to T_1-weighted images,) which were registered to the 2 mm isotropic MNI-152 standard space image using non-linear registration with 12 degrees of freedom as implemented in FMRIB's Linear Image Registration Tool (FLIRT), followed by nonlinear (FMRIB's nonlinear image registration tool, FNIRT) warping [32]. Individual time-series were assessed for motion contamination prior to deciding whether fMRI data should be included or excluded in final group analyses. In this work excessive motion was considered if the estimated translation was larger than 0.5 mm along any axis; no significant difference in movement parameters between patients and controls was observed.

2.5. ICA Analysis and Dual Regression

Independent Component Analysis (ICA) was carried out using FSL's MELODIC toolbox implementing probabilistic independent component analysis (PICA).

Multi-session temporal concatenated ICA (Concat-ICA) approach, as recommended for resting state data analysis [34], was chosen. This approach allowed the inputting of all subjects from the two groups in a temporally concatenated fashion for the ICA analysis. Concat-ICA yielded different components without the need for specifying any explicit time series model. A total of 40 independent components (IC) maps were extracted. A mixture model approach was used to perform the inference on estimated maps. Variance normalization was used and IC maps were thresholded using an alternative hypothesis test based on fitting a Gaussian/gamma mixture model to distribution of voxel intensities within spatial maps [34] and controlling the local false-discovery rate at $p < 0.5$.

As a statistical analysis the different component maps are tested voxel-wise for statistically significant differences between the groups using FSL dual regression, which allows for a voxel-wise comparison of RS-fMRI. In particular, FSL randomized non parametric permutation testing,

with 10000 permutations, was performed using a threshold-free cluster enhanced (TFCE) [35] technique to control for multiple comparisons and corrected for multiple comparisons (across space) within the permutation framework. The TFCE has the advantage to identify cluster-like structures but the image remains fundamentally voxelized. This cluster enhancement is therefore more sensitive than voxel-wise thresholding.

Correction for multiple comparisons across space was applied assuming an overall significance of $p < 0.05$ using permutation testing and TFCE.

3. RESULTS

Participant demographic and clinical characteristics are summarized in Table 1.

No significant differences in age were found between GD patients and HCs whereas education level was significantly different. GD patients showed higher levels of perceived stress ($F(1, 27) = 72.337$, $p < 0.001$), trait anxiety ($F(1, 27) = 103.363$, $p < 0.001$), depression ($F(1, 27) = 43.931$, $p < 0.001$), impulsivity ($F(1,27) = 95.797$, $p < 0.001$) and cognitive distortions ($F(1, 27) = 47.459$, $p < 0.001$).

Visual inspection of IC maps allowed us to identify common resting state networks reported in literature [36,37]. For example, figure 1 reports some RS-networks (such as default mode network, auditory network, right fronto-parietal network, left fronto-parietal network, sensory-motor network and visual network) obtained through the ICA performed in this work.

Our dual regression analysis showed an increased RS-FC in GD patients compared to HCs in the following components: IC00, IC08, IC09, IC11, IC21 and IC22. Among these, IC00 and IC22 will not be discussed because located mainly within the brain white matter, and interpreted as noise.

We will describe and discuss in detail the results regarding the reward network, the cerebellum and the visual networks:

- reward network (IC 009), specifically within: Caudate Nucleus (CN), Nucleus Accumbens (NA) (peak at x, y, z: 51, 74, 33, p = 0.01, cluster size = 251 voxels; figure 2), Subcallosal Cortex (SC) and ParaCingulate Cortex (ParaCC) of the left hemisphere; ParaCC, and anterior Cingulate Gyrus (CG) of the right hemisphere (peak at x, y, z: 43, 85, 38, p = 0.031, cluster size = 20 voxels; figure 3);

- cerebellum (IC 011), specifically within: crus II and lobules VIIb and VI of the right hemisphere (peak at x, y, z: 37, 29, 18, p = 0.033, cluster size = 37 voxels; figure 4); lobules V and VI of the right hemisphere (peak at x, y, z: 32, 40, 21, p = 0.036, cluster size = 16 voxels; figure 5); lobules VIIIa, VIIIb, IX of the left hemisphere (peak at x, y, z: 52, 35, 14, p = 0.038, cluster size = 10 voxels; figure 6);

- visual networks (IC008 and IC021), specifically within: bilateral intracalcarine cortex, supracalcarine cortex and lingual gyrus (peak at x, y, z: 49, 16, 44, p = 0.016, cluster size = 715 voxels (IC008 - primary visual network); occipital pole, lateral occipital cortex, lingual gyrus and occipital fusiform gyrus of the right hemisphere (peak at x, y, z: 38, 13, 34, p = 0.024, cluster size = 112 voxels; occipital pole, lateral occipital cortex and occipital fusiform gyrus of the left hemisphere (peak at x, y, z: 56, 15, 30, p = 0.039, cluster size = 24 voxels (IC021 - ventral visual network).

In GD patients, a significant positive correlation was found between gambling severity, in terms of PG-YBOCS score, and mean functional connectivity value extracted from the significant clusters in the cerebellar network (r = 0.579, p = 0.03) (figure 7).

4. DISCUSSION

This study was aimed at exploring brain intrinsic resting state functional connectivity in a population of GD patients and at searching for a correlation between RS-FC and GD symptoms. Using a data driven approach we found an increased RS-FC within specific brain regions in GD patients compared with HC. More precisely, we found a stronger connectivity in the networks

including Anterior Cingulate Cortex (ACC), the head of the Caudate Nucleus (hCN) and Nucleus Accumbens (NA), and within the cerebellum involving: the right crus II, right lobules V, VI, VIIb and left lobules VIIIa, VIIIb, IX.

Moreover, the strength of functional connectivity in the cerebellar network significantly correlated with the severity of gambling disorder over the last 2 weeks – in terms of PG-YBOCS. As a matter of fact, most of the neuroimaging studies on GD brains revealed abnormal activations in response to specific cognitive/behavioural tasks, mainly in the decision-making and reward-related brain regions (for a review see [38]). As the human brain is organized in dynamically interacting functional networks [39,40], more recent studies are focusing on functional connectivity. Earlier publications [20-22], that took advantage of a seed-based approach, showed an increased functional connectivity between ventral striatum and amygdala bilaterally during a decision-making task. Koehler [41] studied RS-FC between the middle frontal gyrus and ventral striatum, showing an increased functional connectivity between these two regions in GD patients compared to controls.

The involvement of the fronto-striatal networks in reward processing and decision-making is well-established [42-47] as well as their impairment in addicted patients [6]. Indeed, the symptom clusters of addiction find their neurofunctional basis in those aberrant circuitries. For instance, withdrawal and craving, experienced as feeling distress when attempting to cut down or stop gambling, may be induced by a hyper-reactivity of the brain to gambling-related cues, which is evidenced by an increased activity in the prefrontal and limbic structures, including the dorsolateral prefrontal cortex, anterior cingulate, ventral striatum, and parahippocampal gyrus [14, 15]. Accordingly, Ma et al. [48] found an increased connectivity between ACC and NA and between ACC and the orbito-frontal cortex in chronic heroin users; moreover a complex alteration of the cortical-subcortical balance has also been shown in GD patients [38].

From a neurobiological perspective, all the symptom clusters related to excessive gambling activity may develop due to fundamental changes in the activity of the brain's reward system with an

overestimation of the short-term value of drug/gambling related rewards combined with an underestimation of long-term losses [7]. This imbalance may lead to increased impulsivity/diminished self-regulation, a behavioural bias towards the pursuit of immediate rewards instead of the accomplishment of long-term goals [6]. Gambles are always associated with a potential gain and a potential loss of money, which have to be weighed up against each other. Consistently, those executive functions that normally enable abdication of the immediate satisfaction of needs in favor of a prediction of a future greater satisfaction are compromised in GD [49]. Notably, emotional and affective dysregulations have been reported [3-5], further confirmed by higher levels of anxiety, perceived stress and depression observed in this study.

Intriguingly, the novelty of the current research is the interesting finding of an alteration of the cerebellar connectivity in our population of GD patients. Specifically, the connectivity strength of the cerebellar functional network in GD patients was positively correlated with gambling severity in terms of PG-YBOCS scores. These data further support the notion that the role of the cerebellum is not exclusively related to motor control. Evidence obtained from clinical and neuroimaging studies has shown that the cerebellum is involved in a series of cognitive functions, such as verbal and working memory, executive functions, language, emotion processing, and attention [50] as well as in neurodegenerative dementias with cognitive and behavioural symptoms [51]. Interestingly, the cerebellum shows connections with fear and anxiety-related brain areas and functional involvement in such processes has been shown in preclinical models [52].

In addition, though traditionally overlooked in the addiction field, a growing amount of data suggests the involvement of the cerebellum in many of the aberrant brain functions in addicts [41,53]. Indeed, the cerebellum is known to be strongly connected with the basal ganglia and the prefrontal cortex, to be co-activated during reward related tasks and influence their activity.

Evidence for GD patients report that "the right ventral striatum demonstrates increased connectivity to the right superior and middle frontal gyrus and left cerebellum compared to controls. The

increased connectivity to the cerebellum is positively correlated with smoking" [41] emphasizing a participation of the cerebellum in substance use behaviour.

A recent work by an Italian group [54] has appointed the cerebellum as a master regulatory structure for integrating motor, emotional, and sensory information that affects “mind–world synchronization”. In this context, the cerebellar cortex would be in charge of rapid unconscious processes, while other cortical brain areas would address the slow conscious ones [41]. Cerebellar processing thus contributes to the generation of coherent and conscious representations of self-perception and the external world and to the conscious recognition of negative feelings caused by the sense of self-responsibility for an incorrect decision [54].

Overall, it is reasonable to speculate that the functional alterations in cerebellum-related connectivity observed in this study might underpin the occurrence of severe gambling behaviour recorded in GD patients. Indeed, the typical “chasing behaviour”, and at a larger scale “neglect of other areas in life” might arise from an internal discrepancy between internally perceived and externally generated signals. Strengthening this point of view, patients with cerebellar damage have been recently reported to be unable to feel conscious emotions of regret as a consequence of their disadvantageous choices in a gambling task exacerbating their addictive behaviour [54].

Optimal internal balance at the unconscious and conscious levels is necessary to ensure an emotional behaviour that is coherent with the environment and a self-perception of one’s emotional state that is consistent with the context. The evidence of an aberrant connectivity engaging the cerebellum, besides the reward network, opens new perspectives on cerebellar role in the etiopathology of GD and addiction, and suggests the employment of novel neuromodulatory therapeutic approaches [55,56] that may be helpful in ameliorating gambling severity and co-morbid emotional and cognitive dysfunctions.

We also found an increased RS-FC within the visual network in PG compared to HC. Early studies found an over-activation of a set of brain areas, including the reward network and the occipital

cortex, after the presentation of specific addiction-related pictures [15,57], interpreted as cue-reactivity related activations. All the subjects participating in our study underwent a fMRI Go-noGo task, including gambling-related pictures, immediately before the resting block. The GD patients showed an overactivation of the middle frontal gyrus, the ACC as well as the occipital cortex compared to HC that we also interpreted as a cue reactivity effect [58]. In such a context, as suggested by van Timmeren [24], even the RS-FC could be influenced by previous task-related paradigms as a "sustained cue reactivity effect".

In our knowledge, only one earlier study used a data driven approach [24] with results that differ from ours. van Timmeren et al. found an increased functional connectivity only within the ventral attention network. This could depend on a different methodological approach: at the first place, the authors performed an ICA to identify the functional networks from their data but subsequently they selected their networks of interest to be compared between GD and HC. Secondly, we generated a different number of components (40 vs 51 IC) from the same number of brain volume scans (200) and, at last, we used a 1.5T scanner while they used a 3T one. Furthermore, our choice of analyzing the whole body of data, without any a priori selection, allowed us to find, besides the well-known involvement of the fronto-striatal network, unexpected and original results, such as the cerebellar involvement in our GD population.

5. LIMITATIONS

Our study has some limitations that need to be acknowledged. The main limitation of the study is the small sample size. Further studies should be carried out recruiting a larger number of subjects including also women. Another limitation is related to the use of a 1.5T scanner. However, it should be underlined that, even though high (3T) or ultra high field (7T) MRI scanners would favor a significant increase in terms of contrast, spatial and temporal resolutions, there are plenty of fMRI studies published in the english literature reporting the use of a 1.5T MRI scanner. Moreover, not all these published studies reported robust fMRI data analyses as the one described above. Another

limitation, related to the use of a 1.5 T MRI scanner, is the choice of a TR value of 3000 ms which could be criticized for being too high. This value is indeed strictly related to the MRI scanner we used since it is the lowest TR that allowed a whole brain fMRI scan with the reported acquisition parameters. Although a shorter TR could provide a larger temporal resolution, other published articles used this TR value with a 1.5T scanner [59,60]. Even with these limitations, we obtained a valid representation of the neural networks most commonly reported in the literature, supporting the validity of our study. After all, in order to achieve more accuracy in RS-networks reconstruction we chose a total number of 200 measurements for resting state fMRI scans (10 minutes sessions).

6. CONCLUSIONS

In conclusion, our findings confirm the already known involvement of the reward network and support a possible role of the cerebellum in GD. The role of the cerebellum in cognition and behaviour is well established and, more recently, some studies have implicated the cerebellum in substance addiction. GD can be considered an optimal model for functional studies, because of the lack of any substance related influence on functional connectivity. To our knowledge this is the first study demonstrating an involvement of cerebellar connectivity in gambling disorder.

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8.AUTHOR STATEMENT

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All the authors contributed to manuscript revision and read and approved the submitted version.

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FIGURE LEGEND

Figure 1 - Examples of resting state networks identified by ICA: default mode network (A), auditory network (B), right fronto-parietal network (C), left fronto-parietal network (D), sensory-motor network (E) and visual network (F).

Figure 2 - Increased RS-FC in GD patients compared to HCs in the left CN, NA, SC, ParaCC (peak at x, y, z: 51, 74, 33, p = 0.01, cluster size = 251 voxels)

Figure 3 - Increased RS-FC in GD patients compared to HCs in the right ParaCC, and right CG (peak at x, y, z: 43, 85, 38, p = 0.031, cluster size = 20 voxels)

Figure 4 - Increased RS-FC in GD patients compared to HCs in the right crus II and right lobules VIIb and VI (peak at x, y, z: 37, 29, 18, p = 0.033, cluster size = 37 voxels)

Figure 5 - Increased RS-FC in GD patients compared to HCs in the right lobules VI and V (peak at x, y, z: 32, 40, 21, p = 0.036, cluster size = 16 voxels)

Figure 6 - Increased RS-FC in GD patients compared to HCs in the left lobules VIIIa, VIIIb and, IX (peak at x, y, z: 52, 35, 14, p = 0.038, cluster size = 10 voxels)

Figure 7 - In GD patients, mean functional connectivity value (PE = parameter estimate) extracted from the significant cluster in the cerebellar network (IC011) correlated with PG-YBOCS score of gambling behaviour.

Table 1. **Demographic and clinical statistics of the subjects.** NS: Non-significant; *p < .05; **p < .01; ***p < .005; ****p < .001.

	PATHOLOGICAL GAMBLERS (n=14) Mean (SD)	**HEALTHY CONTROL GROUP (n=14) Mean (SD)**	**TEST ANOVA**
AGE (years)	40.57 (8.12)	33.64 (9.71)	F = 4.191NS
EDUCATION (years)	12.29 (1.81)	14.43 (3.05)	F = 5.087*
SOGS	11.5 (2.87)	.5 (.65)	F = 194.885****
PG-YBOCS	20.85 (6.67)	.00 (.00)	F = 136.574****
STAI-TRAIT	62.42 (12.42)	26.50 (4.51)	F = 103.363****
BDI-II	21.71 (10.26)	3.35 (1.39)	F = 43.931****
BIS-11	70.71 (7.65)	47.85 (4.22)	F = 95.797****
GABS	80.92 (9.90)	61.78 (3.16)	F = 47.459****
MSP	119.85 (16.78)	76.28 (9.26)	F = 72.337****

Figure 1

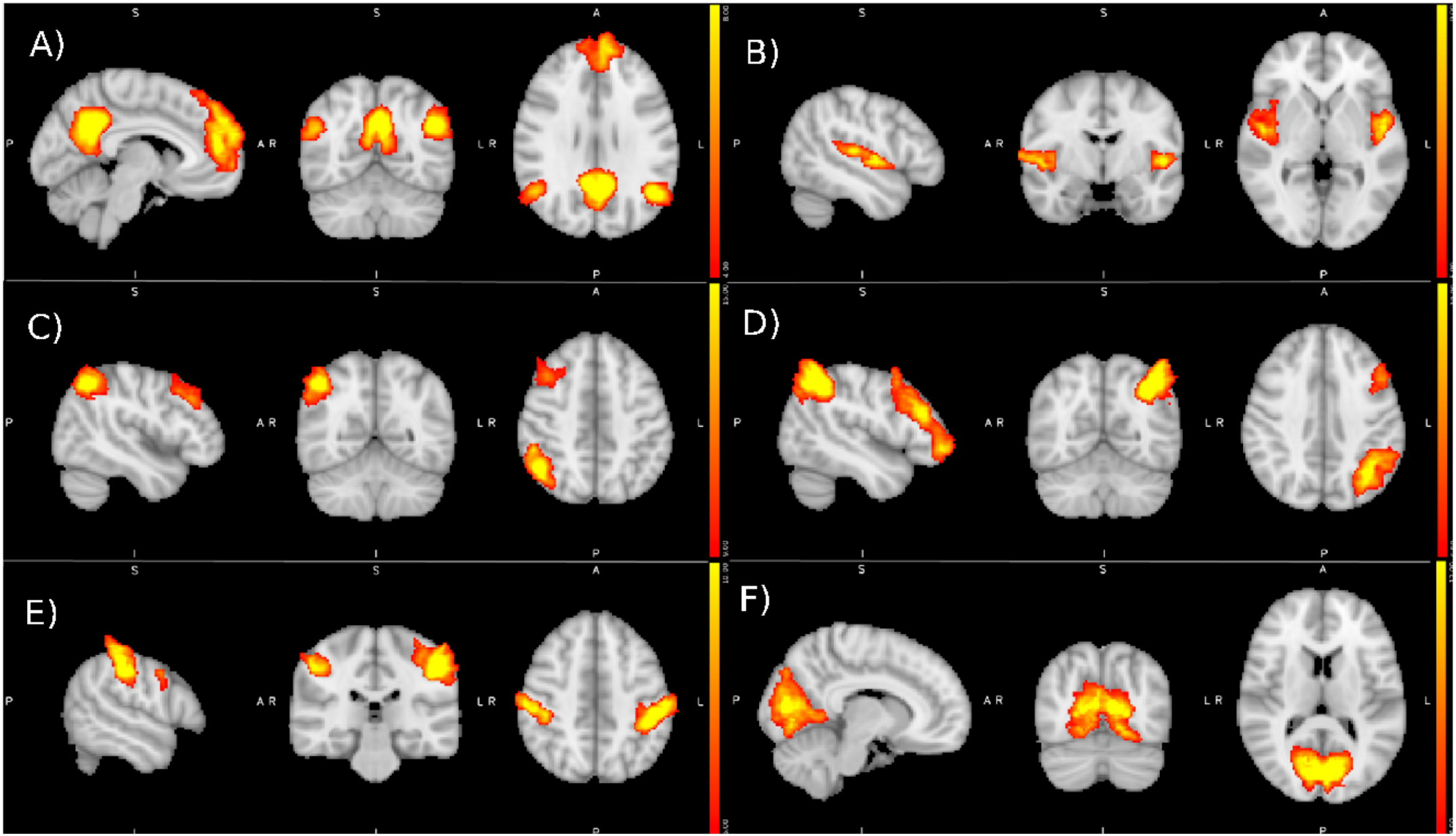

Figure 2

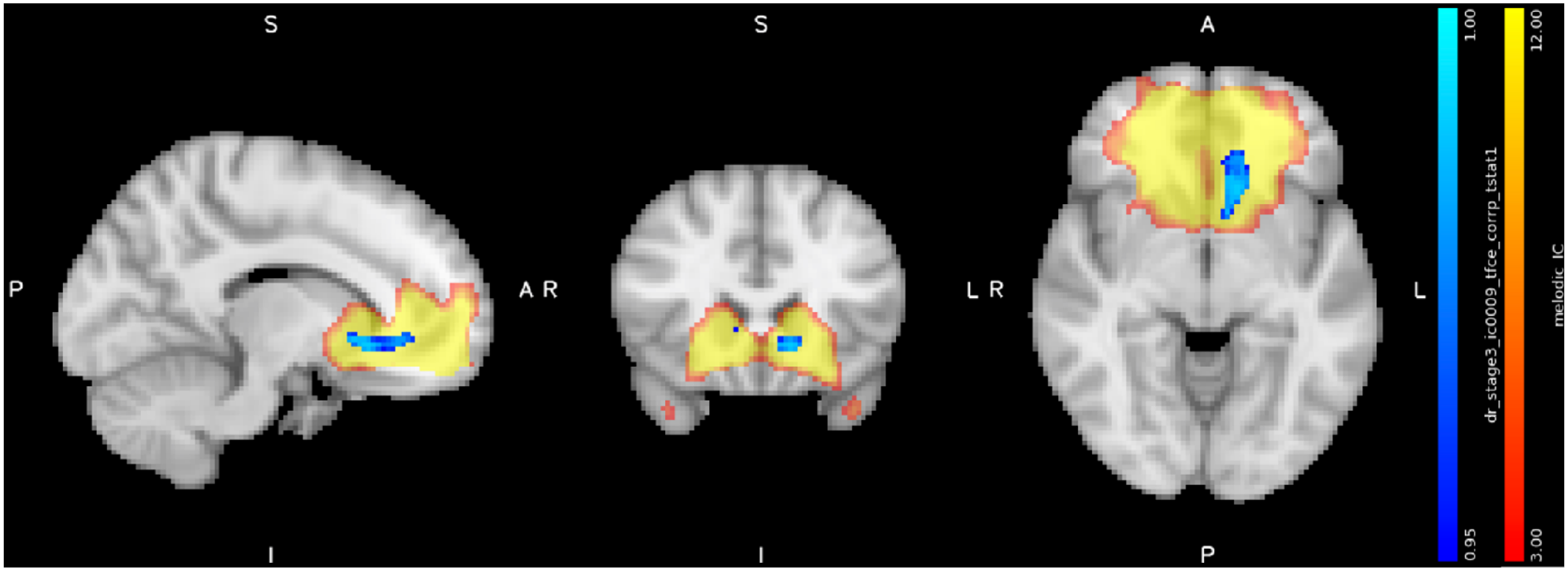
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Figure 3

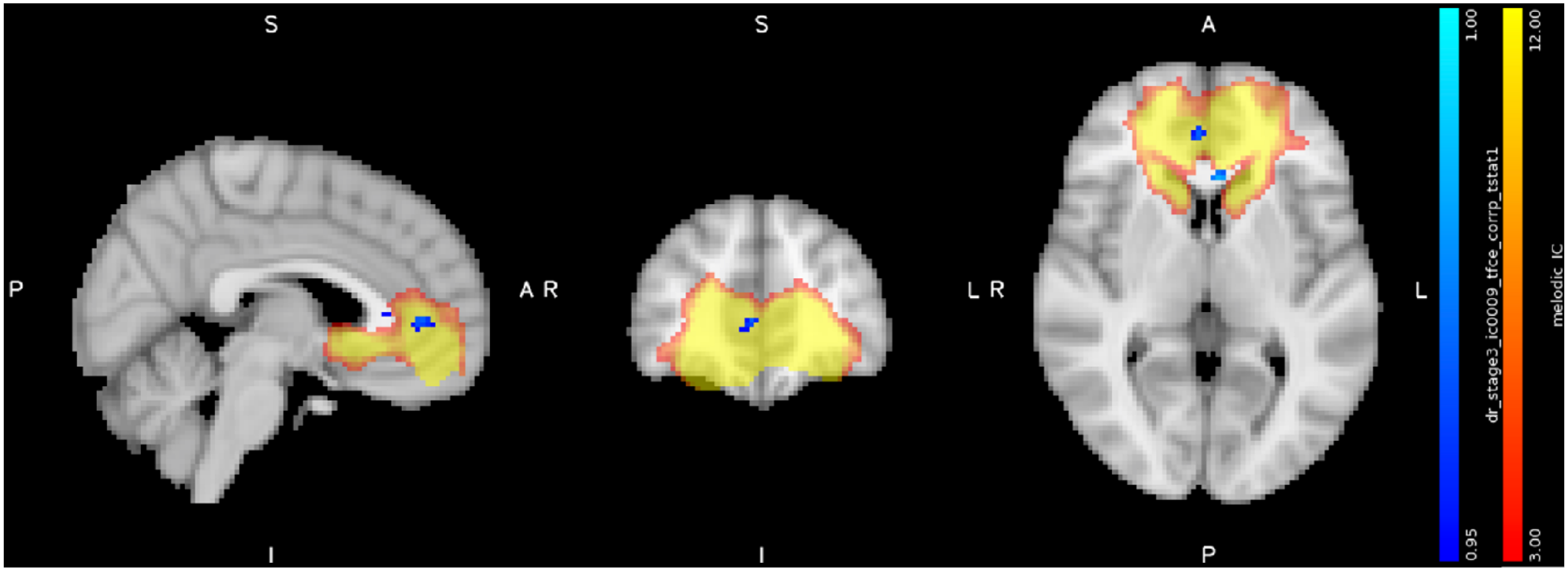
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Figure 4

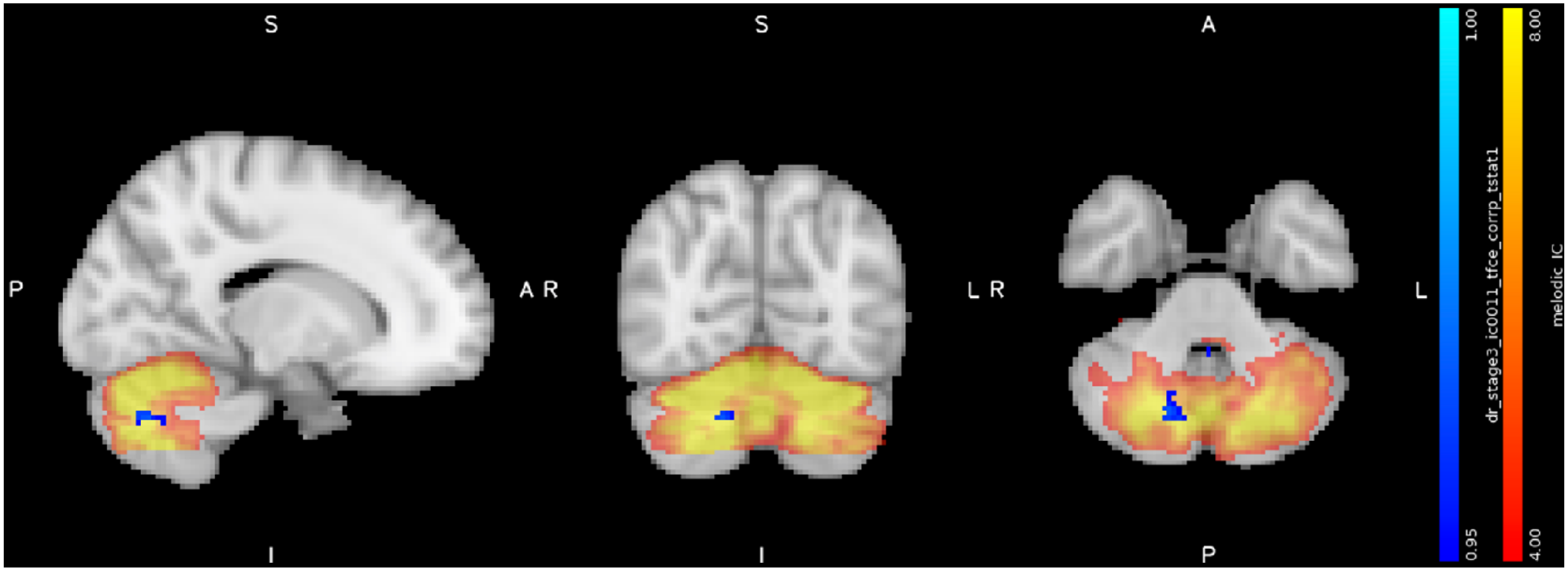
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Figure 5

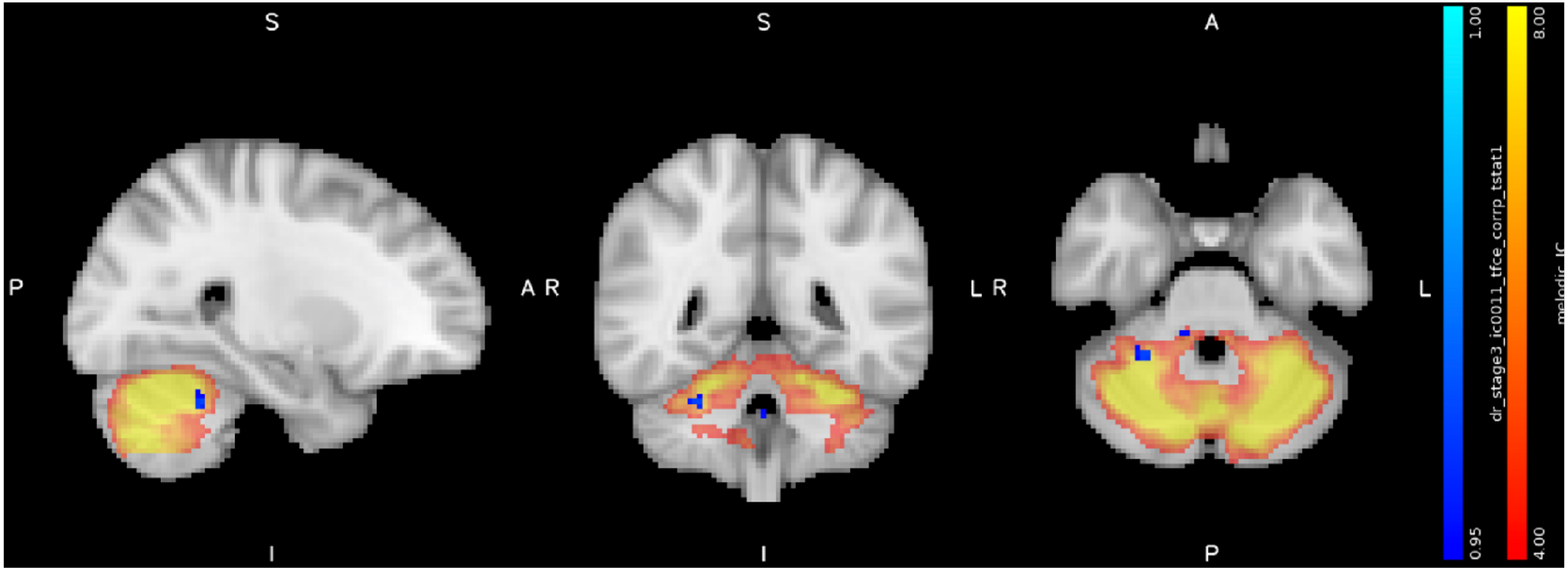
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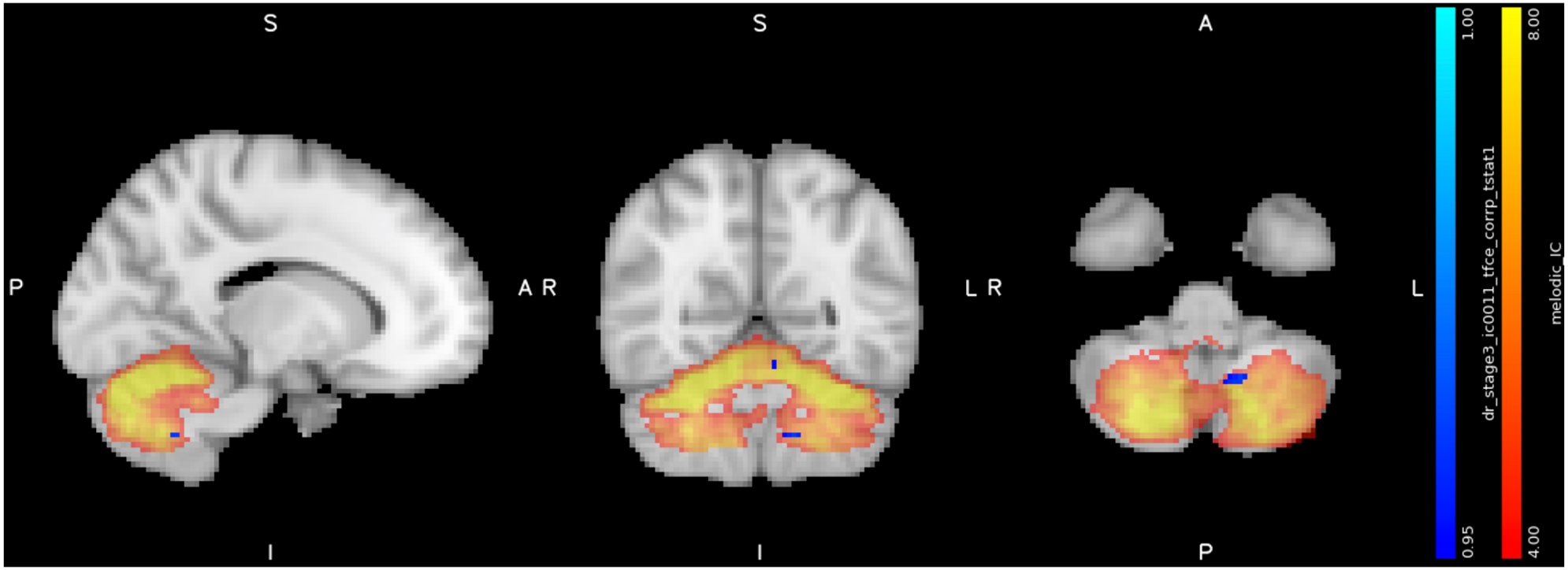
Figure 6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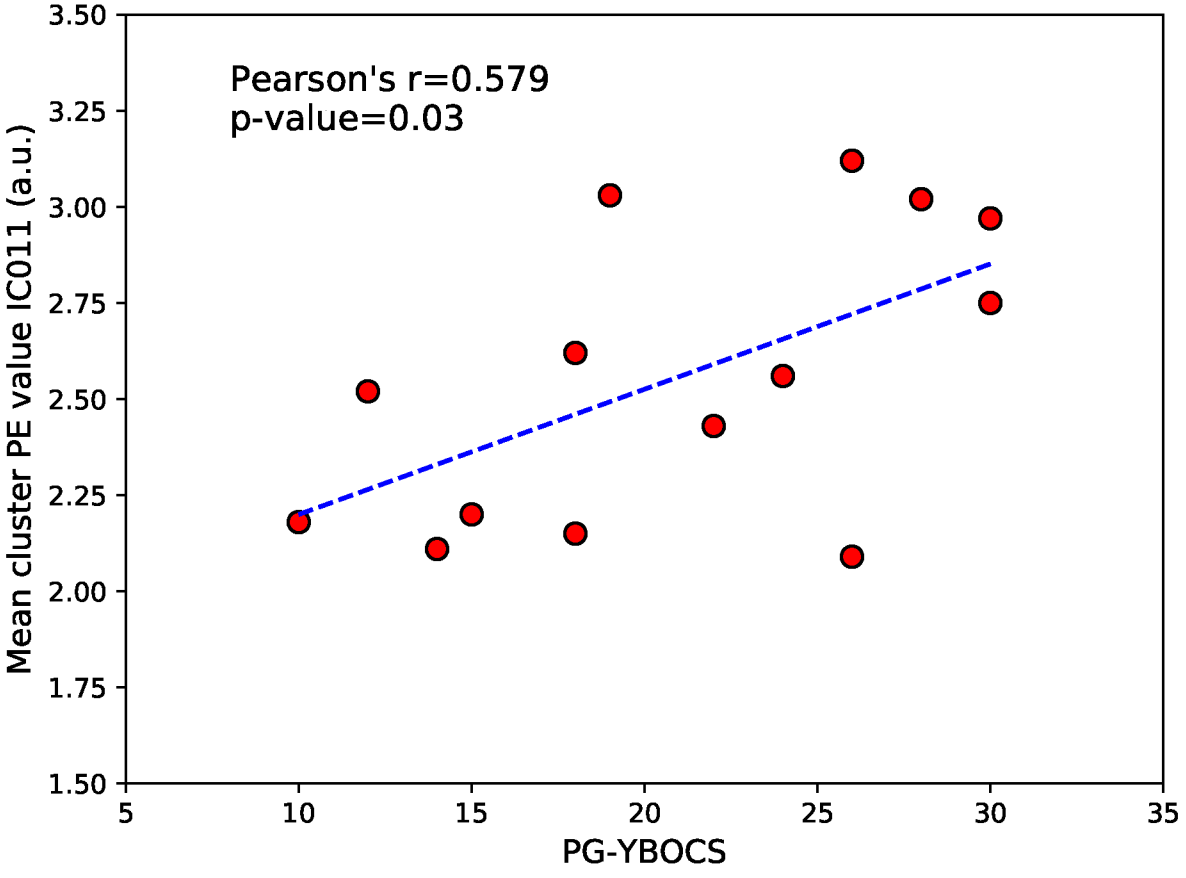
Pearson's r=0.579
p-value=0.03
Mean cluster PE value IC011 (a.u.)
PG-YBOCS
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