Journal of Psychiatric Research 182 (2025) 122–131

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Mapping alterations in the local synchrony of the cerebral cortex in Prader Willi syndrome

Laura Blanco-Hinojo [a,b,*], Jesus Pujol [a], Gerard Martínez-Vilavella [a], Olga Giménez-Palop [c], Laia Casamitjana [c], Jesús Cobo [d,e], Rocío Pareja [c], Susanna Esteba-Castillo [f,g], Joan Deus [a,h], Assumpta Caixàs [c]

[a] MRI Research Unit, Department of Radiology, Hospital del Mar, 08003, Barcelona, Spain
[b] Barcelona Institute for Global Health, ISGlobal, 08003, Barcelona, Spain
[c] Endocrinology and Nutrition Department, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí I3PT, Medicine Department, Universitat Autònoma de Barcelona, 08208, Sabadell, Spain
[d] Mental Health Department, Corporació Sanitària Parc Taulí-CIBERSAM, Institut d'Investigació i Innovació Parc Taulí I3PT, Centres de Recerca de Catalunya (CERCA), 08208, Sabadell, Spain
[e] Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, 08193, Bellaterra, Spain
[f] Specialized Service in Mental Health and Intellectual Disability, Institut Assistència Sanitària (IAS), Parc Hospitalari Martí i Julià, 17190, Girona, Spain
[g] Neurodevelopmental Disorders Group, Girona Biomedical Research Institute, 17190, Girona, Spain
[h] Department of Clinical and Health Psychology, Universitat Autònoma de Barcelona, 08193, Bellaterra, Spain

ARTICLE INFO

Keywords:
Brain mapping
Cerebral cortex
Functional connectivity
Gamma-aminobutyric acid
Obsessive-compulsive
Prader Willi syndrome

ABSTRACT

Individuals with Prader Willi syndrome (PWS) often exhibit behavioral difficulties characterized by deficient impulse regulation and obsessive-compulsive features resembling those observed in obsessive-compulsive disorder. The genetic configuration of PWS aligns with molecular and neurophysiological findings suggesting dysfunction in the inhibitory gamma-aminobutyric acid (GABA) interneuron system may contribute to its clinical manifestation. In the cerebral cortex, this dysfunction is expressed as desynchronization of local neural activity. We used functional connectivity MRI to examine potential alterations in the local synchrony of the cerebral cortex in PWS. Whole-brain functional connectivity maps were generated using iso-distance average correlation (IDAC) measures in 22 patients with PWS and 22 control participants. Patients with PWS showed reduced local connectivity (weaker synchrony) in frontal areas, including the orbitofrontal cortex, ventral medial and lateral frontal regions, the anterior cingulate cortex, and sensory areas. The presence of obsessive-compulsive symptoms was significantly associated with the degree of functional structure alteration in part of the orbitofrontal and sensory cortices. In addition, abnormally heightened functional connectivity (stronger synchrony) was identified in the posterior cingulate cortex and the bilateral angular gyri, core components of the default mode network, with distance-dependent effects. Our findings of cortical synchrony alterations indicate a degree of overlap with the anatomy of the alterations previously observed in primary obsessive-compulsive disorder, while also suggesting the implication of GABAergic dysfunction in the pathophysiology of the disorder. Our observations may support the rational development of more specific therapeutic strategies in the treatment of behavioral disinhibition characteristic of PWS.

1. Introduction

Prader Willi syndrome is a rare genetic disorder resulting from the loss of paternally expressed imprinted genes on chromosome 15's long arm (Cassidy et al., 2012). It is characterized by neonatal hypotonia and feeding difficulties that progress to insatiable appetite and hyperphagia, developmental delay, and mild intellectual disability (Cassidy et al., 2012). Individuals with Prader Willi syndrome also exhibit a spectrum of behavioral difficulties notably characterized by deficient impulse regulation (Holland et al., 2003; Sinnema et al., 2011; Rice et al., 2018; Schwartz et al., 2021). These may manifest as impulsivity and episodes of severe temper outbursts. Additionally, the behavioral phenotype of

* Corresponding author. Laura Blanco. MRI Department, Hospital del Mar, Passeig Marítim 25-29. 08003, Barcelona, Spain.
E-mail address: laura.blanco02@gmail.com (L. Blanco-Hinojo).

https://doi.org/10.1016/j.jpsychires.2025.01.012
Received 26 September 2024; Received in revised form 10 December 2024; Accepted 6 January 2025
Available online 7 January 2025

the syndrome often encompasses obsessive-compulsive features such as rigid adherence to routines, repetitive rituals, and self-injurious behaviors like compulsive skin picking and nail biting, as well as compulsive ordering, hoarding tendencies and concerns with symmetry and exactness (Dykens et al., 1996; State et al., 1999; Dimitropoulos et al., 2001; Clarke et al., 2002; Novell-Alsina et al., 2019; Whittington and Holland, 2020). These behavioral patterns partially overlap with the characteristic symptoms of patients with obsessive-compulsive disorder (OCD), suggesting potential shared underlying mechanisms of impaired inhibitory control.

The Prader Willi syndrome chromosomal region 15q11-13 encompasses a cluster of three genes encoding subunits of the type-A receptor for gamma-aminobutyric acid (GABA) (Wagstaff et al., 1991), the main inhibitory neurotransmitter in the adult brain. Dysfunction in this genetic configuration may impact the modulation of GABAergic neurotransmission, potentially contributing to the behavioral manifestation of the syndrome (Dhossche et al., 2005). Notably, GABA neuronal dysfunction has been implicated in various neurodevelopmental and psychiatric disorders that share common features with Prader Willi syndrome, including autism, psychosis, and mood and anxiety disorders (Brambilla et al., 2003; Lewis et al., 2005; Chao et al., 2010; Marín, 2012).

While data remains relatively sparse, studies have indicated specific defects in the GABAergic system among patients with Prader Willi syndrome, including elevated plasma GABA levels (Ebert et al., 1997), reduced cerebral GABA levels in the parietal region (Rice et al., 2016), as well as decreased GABAa receptor binding in frontal areas (Lucignani et al., 2004). Moreover, evidence for GABAergic dysfunction in the disorder is supported by neurophysiological studies demonstrating deficiencies in specific event-related potentials related to inhibition during tasks (Stauder et al., 2005) and abnormal excitability in cortical motor areas (Civardi et al., 2004). Animal studies have also shown deficient sensorimotor gating and abnormal startle responses in mice models of the syndrome (Relkovic et al., 2010; Zahova et al., 2021). Nevertheless, the precise anatomical distribution of the GABA defect within the cerebral cortex is not fully characterized.

Inhibitory GABAergic interneurons play a crucial role in providing inhibitory inputs and shaping synchronized oscillations within local neural assemblies of glutamatergic principal pyramidal cells (Marín, 2012). Their function in maintaining the excitation-inhibition balance is essential for proper cortical function (Marín, 2012). Functional magnetic resonance imaging (fMRI) local connectivity measures may provide information about cortical functioning insofar as variations in local MRI signal synchrony are related to variations in neural activity (Niessing et al., 2005; Chen et al., 2017). That is, changes in intracortical activity coupling observed through fMRI may reflect the synchronization effect of GABA inhibitory neurons on local neural activity in the cerebral cortex (Blanco-Hinojo et al., 2021). Despite previous studies indicating alterations in large-scale neural networks in patients with Prader Willi syndrome (Huang et al., 2024; Pujol et al., 2016), functional connectivity at the local level has not been examined in this population.

In this study, we used a combination of iso-distance average correlation (IDAC) measures of local, short-distance, functional connectivity (Macià et al., 2018) to capture the anatomy of changes in the cerebral cortex's local MRI signal synchrony in a sample of individuals with Prader Willi syndrome compared to a control group. In contrast to other commonly used metrics in resting-state fMRI, such as the amplitude of low-frequency fluctuations (ALFF), which reflects the amplitude of spontaneous neural activity within specific regions (Zou et al., 2008), or traditional measures of local functional connectivity like regional homogeneity (Zang et al., 2004) and local functional connectivity density (Tomasi and Volkow, 2010), IDAC provides a more complete characterization of local connections by capturing distance-graded changes in functional connectivity. Our IDAC measures represent the average functional MRI temporal correlation of a given brain unit, or voxel, with other units situated at increasingly separated iso-distant intervals (Macià et al., 2018). Essentially, we expanded well-established MRI measures of local functional connectivity (Zang et al., 2004; Tomasi and Volkow, 2010; Sepulcre et al., 2010) by combining the connectivity maps across varying distances to uniquely inform on the rich spatial structure of the cerebral cortex functional connections. Indeed, this multi-distance approach has proven effective in distinguishing between major classical anatomofunctional cortical areas (Macià et al., 2018; Pujol et al., 2019). In previous studies using such mapping approach, reduced local cortical synchrony was evident in patients with OCD involving the orbitofrontal cortex and all sensory cortex modalities (Pujol et al., 2019). Conversely, we identified a local synchronization effect in the cerebral cortex induced by a typical GABA agonist (alprazolam) with inhibitory action, manifesting as enhanced local connectivity (Blanco-Hinojo et al., 2021).

In this context, we hypothesized that individuals with Prader Willi syndrome would demonstrate alterations in local functional connectivity in the form of weaker intracortical coupling akin to those observed in patients with typical OCD, but anticipated that the spectrum of changes might extend further, reflecting the syndrome's diverse behavioral manifestations. We additionally investigated potential associations between local connectivity and measures of behavioral symptoms.

2. Methods and materials

2.1. Participants

Adults with Prader Willi syndrome were recruited between June 2017 and October 2019 from the Endocrinology Department of a reference center for Prader Willi syndrome (Corporació Sanitària Parc Taulí, Sabadell, Barcelona, Spain). Patients underwent a complete medical and clinical assessment, including a comprehensive interview with a senior psychiatrist. Patients under 18 years, those with non-stable medical conditions, and those considered unable to follow MRI instructions were not eligible to participate. Genetic testing to confirm the chromosome 15 anomaly was conducted for all patients by procedures fully described elsewhere (Pujol et al., 2016).

A control group matched for age and sex was recruited from hospital staff or acquaintances who volunteered to participate. A complete medical interview was conducted to exclude individuals with relevant medical or neurological conditions, substance abuse, psychiatric disorders, or those undergoing medical treatment.

The study protocol was approved by the local ethics committee (Institutional Ethics Committee of Institut Universitari Parc Taulí of Sabadell, Barcelona; ref. END-GH-2017) and complied with all provisions in The Code of Ethics of the World Medical Association (Declaration of Helsinki). All patients agreed to participate after being informed together with their parents or caregivers; their parents/legal guardians signed the consent form before enrollment. Written informed consent was provided by all control participants.

2.1.1. Behavioral assessment

Behavioral symptoms over the preceding two weeks were assessed using an ad hoc questionnaire, which determined the presence or absence of obsessive-compulsive behaviors, self-harm/scratching and onychophagia symptoms, psychological rigidity and sensory-perceptive alterations (Cobo et al., 2021). Current behavioral and emotional symptoms in participants with Prader Willi syndrome were evaluated using the Spanish version of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), a 25-item screening questionnaire for behavioral problems in childhood and adolescence, completed by parents. Although primarily intended for younger populations, the SDQ was chosen due to challenges in finding an optimal and adapted adult-specific questionnaire valid for these patients. The SDQ has been used in other adult populations with developmental disabilities (Glenn et al., 2013). It comprises five subscales: Emotional Symptoms, Conduct Problems, Hyperactivity, Problems with Peers, and Prosocial Behavior.

Each subscale consists of five items reflecting the past six months, with responses measured on a 3-point Likert scale (0 = not true, 1 = somewhat true, and 2 = certainly true). Raw SDQ scores were categorized as normal, borderline, or clinical (Goodman, 1997).

2.2. MRI acquisition

The fMRI data were acquired using a 3.0 T Philips Achieva magnet (Philips Healthcare, Best, The Netherlands; RRID:SCR_008656) equipped with an eight-channel phased-array head coil. The functional sequence consisted of a single-shot gradient recalled echo planar imaging acquisition in the steady state (repetition time, 2000 ms; echo time, 35 ms; pulse angle, 70°) in a field of view of 230 × 230 mm, with a 64 x 64-pixel matrix and a slice thickness of 3.59 mm (inter-slice gap, 0 mm). Thirty-four interleaved slices parallel to the anterior-posterior commissure line were acquired covering the whole brain. The total sequence duration was 8 min, corresponding to 240 consecutive image volumes. The first four (additional) image volumes in each run were discarded to allow for signal equilibration. Participants were instructed to lie still with their eyes closed for the duration of the scan.

High-resolution 3D anatomical images were also acquired for each participant based on a T1-weighted three-dimensional fast spoiled gradient inversion-recovery prepared sequence to assist functional timeseries coregistration. A total of 160 contiguous slices were acquired with repetition time 8.2 ms, echo time, 3.792 ms, flip angle 8°, field of view 25.6 cm, 256 x 256-pixel matrix, and a slice thickness of 1 mm.

2.3. Iso-Distant Average Correlation (IDAC) maps

Imaging data were processed using MATLAB 2016a (The MathWorks Inc., Natick, USA; RRID:SCR_001622) and Statistical Parametric Mapping (SPM) (The Wellcome Department of Imaging Neuroscience, London, UK; RRID:SCR_007037). Preprocessing followed previously reported steps for IDAC analysis (Macià et al., 2018; Pujol et al., 2023). A

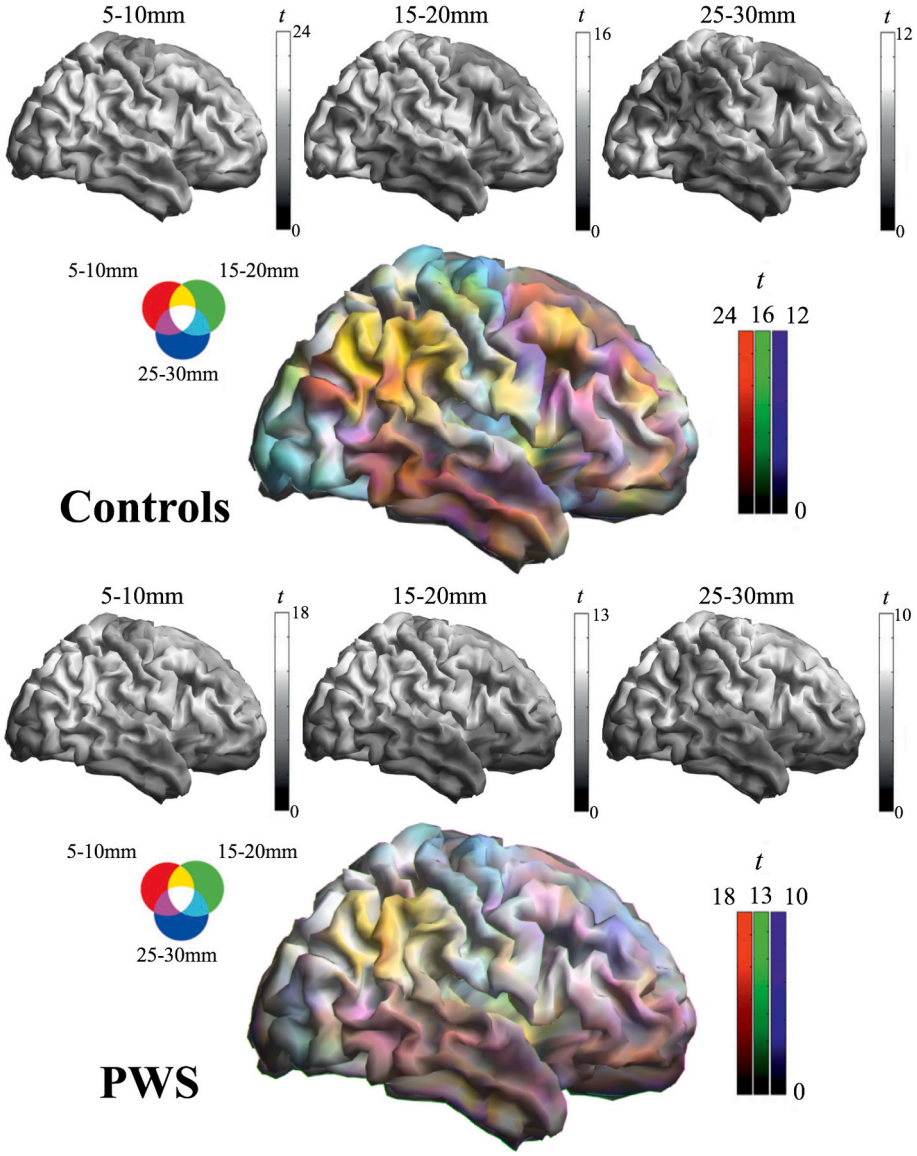

Fig. 1. Illustration of Iso-Distant Average Correlation (IDAC) brain mapping. The images represent the results obtained in one-sample *t*-test analyses from control subjects and patients at three IDAC measures. In each case, the gray images (top) correspond to the individual distance IDAC maps. The color images (bottom) show the result of superimposing the three IDAC maps from the top row using an RGB (red, green and blue) display. The composite images are thus made up of primary RGB colors and their secondary combinations. This visualization is intended solely to illustrate the differentiation of anatomofunctional regions using the RGB combination and does not serve a quantitative purpose. PWS, Prader Willi syndrome. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

detailed description is provided in Supplementary Material. In brief, for each subject functional MRI images underwent slice-time correction, realignment, coregistration to corresponding anatomical image using an affine transformation, reslicing to 3 x 3 × 3 mm resolution, and smoothing by convolving the image with a 4 x 4 × 4 mm full width at half maximum Gaussian kernel. Motion-affected image volumes were discarded using conventional scrubbing procedures (Power et al., 2014).

IDAC measures were then estimated in native space, computed in a gray matter mask split into left and right hemispheres. Whole-cortex IDAC maps were generated by estimating the average temporal correlation of each voxel with all neighboring voxels placed at increasingly separated Euclidean iso-distant lags. Three IDAC maps were obtained at distance intervals 5–10 mm, 15–20 mm and 25–30 mm. The analyses were adjusted by including 6 rigid body realignment parameters, their first-order derivatives, average white matter, cerebrospinal fluid, and global brain signal as regressors. A discrete cosine transform filter was applied for frequencies outside the 0.01–0.1 Hz interval.

Finally, the resulting IDAC maps in native space were normalized to the Montreal Neurological Institute (MNI) space using a back-transformation process to enable group inference. That is, individual 3D anatomical image had previously been segmented and registered to the MNI space and the inverse deformation fields provided by SPM in this step were applied to the IDAC maps.

Multi-distance IDAC color maps were obtained from the overlay of the three IDAC maps using an RGB color codification (see Fig. 1). RGB color channels enabled the display of three values simultaneously. Red represented results from 5 to 10 mm IDAC maps, green from 15 to 20 mm and blue from 25 to 30 mm. The overlapping of these primary colors produces a full range of secondary colors. This visualization is intended solely to illustrate the differentiation of anatomofunctional regions using the RGB combination and does not serve a quantitative purpose. Composite RGB maps were generated from one-sample t-maps obtained for each distance in both study groups and from between-group comparison t-maps.

2.4. Statistical analysis

We compared patients with Prader Willi syndrome to the control group to map brain areas with altered connectivity and assess whether the alterations involve the spatial structure (i.e., differential implication of distinct local distances). Between-group analyses were conducted using a 2 x 3 mixed design ANOVA (ANCOVA) model (i.e., group [healthy control and Prader Willi syndrome] by distance [5–10, 15–20, and 25–30 mm]). A motion summary measure (mean inter-frame motion (Pujol et al., 2014)) for each participant was included as a covariate in these analyses. We examined the main effect of group and group × distance interaction. Following examination of the main effect of group F contrast, post hoc t-tests (Con < Prader Willi syndrome/Con > Prader Willi syndrome) were performed to determine the direction of effects for each of the three IDAC maps. Voxel-wise analyses in SPM were also performed to map the correlation between whole-brain IDAC functional connectivity and selected (those with sufficient variability and abnormal scores within this sample) behavioral symptoms (i.e., presence of obsessive-compulsive behaviors, onychophagia, and SDQ Conduct Problems and Peer Problems subscales).

Thresholding criteria. To correct our results for multiple comparisons, significance was established when clusters formed at a threshold of $p < 0.005$ survived whole-brain family-wise error (FWE) correction ($p < 0.05$), calculated using SPM.

3. Results

Following MRI preprocessing, one patient was excluded due to insufficient imaging data collection, resulting in a final sample of 22 patients with a genetically confirmed diagnosis of Prader Willi syndrome and 22 control participants. A total of 15 patients were taking psychiatric medication (antidepressants, anticonvulsants, or both, occasionally combined with antipsychotics [n = 5]). None of the patients were undergoing rehabilitative therapy or receiving growth hormone treatment. Treated patients were on a stable medication regime for at least 3 months prior to imaging assessment. Table 1 provides demographic and clinical characteristics of the study participants.

Among the reported behavioral symptoms in patients with Prader Willi syndrome, the most prevalent were psychological rigidity (19 out of 20 patients, 95%), onychophagia (56%), and obsessive-compulsive behaviors (50%). In the SDQ, the majority of patients exhibited abnormal or borderline scores in the Conduct Problems (81%) and Peer

Table 1
Demographic and clinical details of the sample.

	Group: mean ± SD (range)	
	Prader Willi (n = 22)	Control (n = 22)
Age, yr	31.1 ± 10.0 (18–53)	29.8 ± 9.2 (19–46)
Sex, M/F	10/12	10/12
Body mass index, kg/m^2	34.9 ± 7.6 (23.3–53.2)	22.0 ± 1.8 (18.7–25.2)
Laterality (R/L)	15/7	17/4[a]
IQ KBIT-2, Total score	70.3 ± 14.3 (48–99)[b]	
Genetic diagnosis, no.		
Type I deletion	7	
Type II deletion	6	
Atypical deletion	2	
Uniparental disomy	4	
Imprinting defect	3	
Metabolic syndrome[c]		
Type 2 diabetes mellitus	3	
Dyslipidemia	4	
Arterial hypertension	1	
GH treatment in childhood – Yes, n	12	
APW-SUD – Yes, n (%)		
Obsessive-Compulsive behaviors	10 (50%)	
Hyperactivity	0 (0%)	
Self-harm/Scratching	16 (80%)	
Onychophagia	10 (56%)[c]	
Heteroaggressivity	4 (20%)	
Cognitive impairment	17 (85%)	
Language difficulties	3 (15%)	
Daytime sleepiness	11 (55%)	
Psychological rigidity	19 (95%)	
Sensory-perceptive alterations	4 (20%)	
Anxiety/Depression	3 (16%)	
SDQ Total score[d,e]	15.0 (10.5–21)	
Emotional Symptoms[f,d]	2.0 (1.0–4.0)	
Conduct Problems[g,d]	4.0 (3.0–5.0)	
Hyperactivity[h,d]	4.0 (2.0–5.0)	
Problems with Peers[i,d]	5.0 (2.5–7.0)	
Prosocial Behaviors[j,d]	7.0 (5.5–9.0)	

SD, standard deviation. IQ-KBIT, Intelligence Quotient – Kaufman Brief Intelligence Test. APW-SUD, Adapted Prader Willi Scale for the Unawareness of the Disorder. SDQ, Strengths and Difficulties Questionnaire.

[a] n = 21.

[b] n = 18.

[c] n = 20.

[d] Values are expressed as group: median (interquartile range).

[e] SDQ Total Interpretation: Normal (0–13), Borderline (14–16), Out of the norm (17–40).

[f] SDQ Emotional Symptoms Subscale Interpretation: Normal (0–3), Borderline (4), Out of the norm (5–10).

[g] SDQ Conduct Problems Subscale Interpretation: Normal (0–2), Borderline (3), Out of the norm (4–10).

[h] SDQ Hyperactivity Subscale Interpretation: Normal (0–5), Borderline (6), Out of the norm (7–10).

[i] SDQ Problems with Peers Subscale Interpretation: Normal (0–2), Borderline (3), Out of the norm (4–10).

[j] SDQ Prosocial Behaviors Subscale: Normal (6–10), Borderline (5), Out of the norm (0–4).

Problems (76%) subscales, as well as in the SDQ total score (52%), while scores in the Emotional Symptoms, Hyperactivity, and Prosocial Behavior Subscales were within the normal range.

Whole-brain group maps of cerebral cortex functional connectivity were generated from combined IDAC measures using RGB composition display for short (5–10 mm), middle (15–20 mm) and long (25–30 mm) distances (Fig. 1). In both groups, distinct anatomofunctional areas demonstrated a varying functional structure determined by the relative connectivity strength at each distance. For example, the lateral occipital cortex displayed consistent high connectivity across all local distance ranges (depicted as white in the maps) in the control group, whereas the inferior parietal lobule (angular and supramarginal gyri) predominantly showed connectivity at short and medium distances. However, upon visual inspection, cortical area differentiation was less apparent in patients with Prader Willi syndrome, suggesting reduced functional heterogeneity in these measures.

The main effect of group contrast revealed significant differences in IDAC functional connectivity measures across the three connectivity distances (Fig. 2, Table S1). The effect was most predominantly observed in the orbitofrontal cortex bilaterally extending to lateral and medial prefrontal and cingulate cortices, the bilateral inferior (opercular) level of the somatosensory cortex, the auditory cortex in the temporal lobe, the bilateral insula/frontal operculum, and visual areas in the occipital cortex.

Subsequent post hoc analyses reporting simple effects were conducted for each local connectivity distance 5-10, 15-20, and 25-30mm) (Fig. 3). Overall, the analyses showed that between-group differences were driven by both weaker local connectivity (i.e., lower functional MRI signal synchrony) in participants with Prader Willi syndrome compared to controls in orbitofrontal and prefrontal cortices, somatosensory, auditory and visual areas, predominantly at short local distances (5–10, 15–20 mm), as well as stronger functional connectivity in the patient group in the posterior cingulate cortex and the inferior parietal region encompassing the supramarginal and angular gyri, at long local distance (25–30 mm). The group-by-distance interaction test revealed significant results in frontal and sensory regions and in posterior elements of the default mode network, confirming such a distance effect (Fig. 4, Fig. S1 and Table S2) and indicating changes particularly in the functional structure of the regions rather than expressing a general tendency of functional connectivity reduction. An integrated display of RGB maps of IDAC differences is provided in Fig. 3 to summarize the functional alterations identified in Prader Willi syndrome.

Finally, correlations between IDAC measures and behavioral scores were examined in the patient group through a voxelwise regression analysis for each of the 3 whole-brain IDAC maps at distances 5–10, 15–20, and 25–30 mm. The presence of obsessive-compulsive behaviors and onychophagia was associated with weaker functional connectivity in visual areas in all three IDAC distances, and in the lateral aspect of the orbitofrontal cortex in the middle and long local distance maps (Fig. 5, Table S3). Conduct problems measured by the SDQ negatively correlated with functional connectivity in the right frontal operculum at long local distances, while peer problems ratings were positively associated with connectivity in the medial prefrontal cortex at short distance. A distance effect was also observed in the latter correlation pattern, such that the correlation between peer problems ratings and IDAC measures was significantly greater at short than long distance in the right supra marginal gyrus. That is, the association was positive at the short distance and negative at the long local distance.

4. Discussion

We used functional connectivity MRI measures to investigate potential alterations in the local synchrony of the cerebral cortex in patients with Prader Willi syndrome. Anomalies in local functional connectivity were identified across several cortical regions, including the ventral frontal cortex, primary sensory areas, and components of the default mode network. Notably, changes in areas showing weaker synchrony, such as the orbitofrontal cortex, were significantly associated with the presence of obsessive-compulsive behaviors in these patients. These findings support our hypothesis, indicating a degree of overlap with the alterations seen in patients with typical OCD (Pujol et al., 2019). Furthermore, at longer local distances, we observed stronger synchrony within the posterior elements of the default mode network, which additionally showed a significant distance-dependent effect,

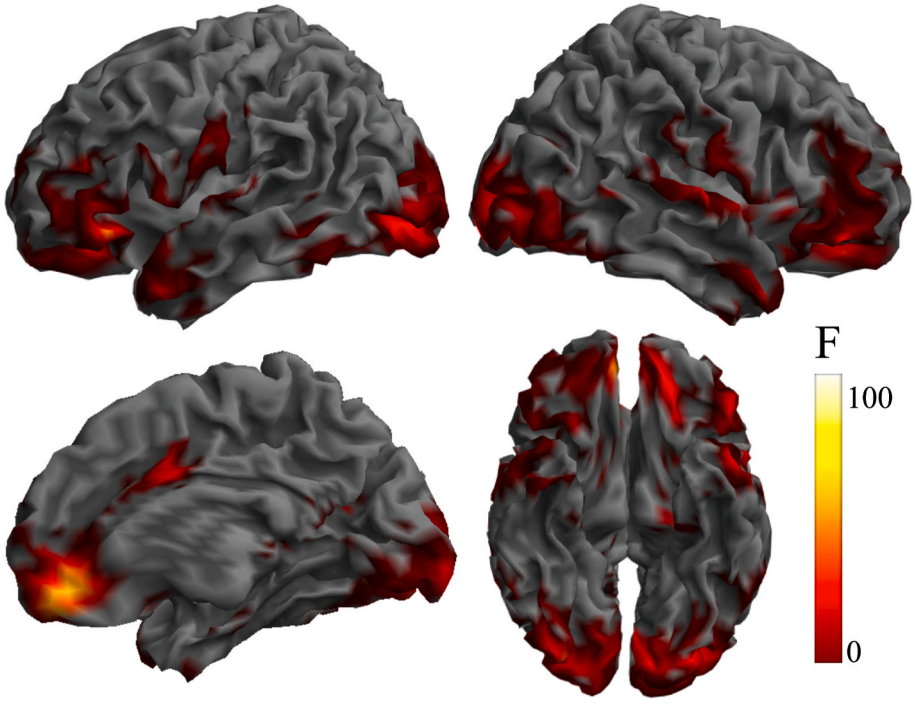

Fig. 2. Main effect of group illustrating the differences between patients with Prader Willi syndrome and control subjects in Iso-Distant Average Correlation (IDAC) measures across the three distance maps (ANOVA). Top row: lateral view of left and right hemispheres. Bottom row: medial and ventral surfaces.

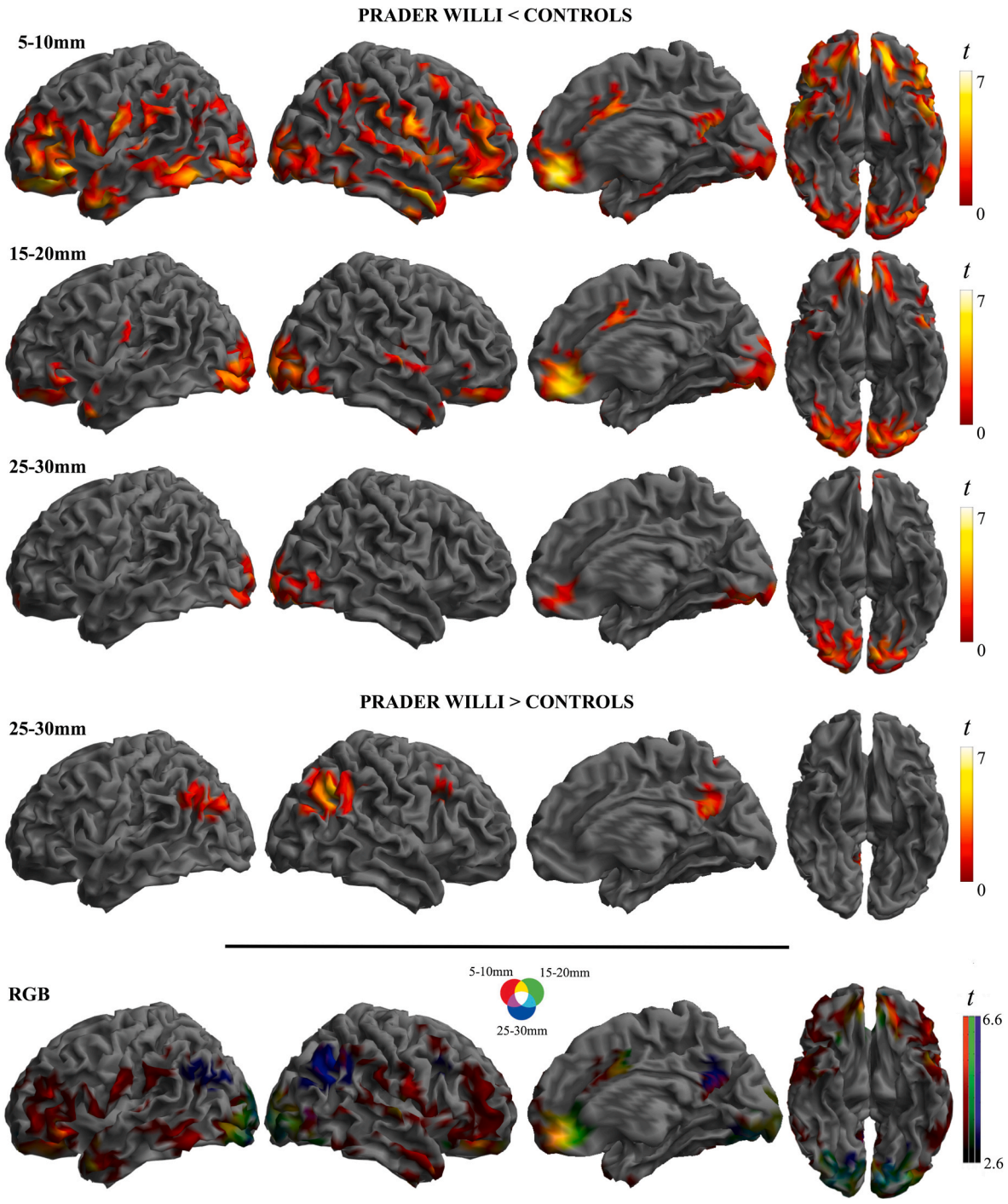

Fig. 3. Single effects illustrating differences between patients with Prader Willi syndrome and control subjects in IDAC measures at each local connectivity distance. Bottom row: Composite RGB (red, green, and blue) display summarizing alterations shown above. The color map corresponds to the superimposition of between-group differences in IDAC measures at functional connectivity distances 5–10 mm (red), 15–20 mm (green), and 25–30 mm (blue). Data are displayed on the lateral, medial and ventral surfaces. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

underscoring a complex pattern of cortical dysfunction.

Our findings revealed weaker local functional connectivity (lower MRI signal synchrony) in the frontal cortex of patients with Prader Willi syndrome, particularly in the ventromedial, orbitofrontal, and ventral lateral areas. These ventral prefrontal regions play a crucial role in behavioral regulation through their involvement in impulsive control and inhibition (Fuster, 2019). The reduced local connectivity observed may potentially indicate decreased activity in both excitatory neurons, indicating fewer active neurons, and inhibitory interneurons, leading to reduced synchronization. Previous imaging studies in individuals with Prader Willi syndrome have shown increased basal metabolism (Kim et al., 2006) and heightened neural activity in response to (food) stimuli involving the frontobasal brain (Holsen et al., 2006; Miller et al., 2007; Dimitropoulos and Schultz, 2008). Our findings of lower prefrontal local connectivity would thus arguably be consistent with impaired regulation of GABA interneurons, which could contribute to alterations in inhibitory control observed in patients with the disorder. Specifically, dysregulated GABAergic signaling may reduce the ability to suppress compulsive behaviors, exacerbating the behavioral disinhibition characteristic of the syndrome.

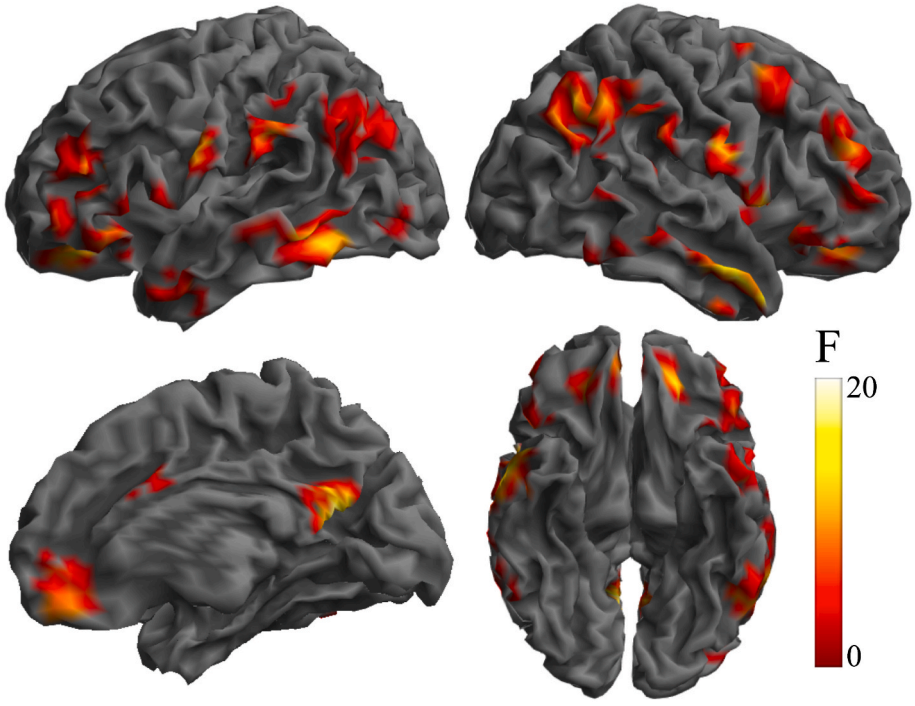

Fig. 4. ANOVA group (Prader Willi syndrome vs. Controls) by distance (5–10 mm, 15–20 mm and 25–30 mm) interactions as to local functional connectivity IDAC measures [(Controls > Prader Willi syndrome at short distances) > (Controls < Prader Willi syndrome at long distances)]. See Fig. 3 and Fig. S1.

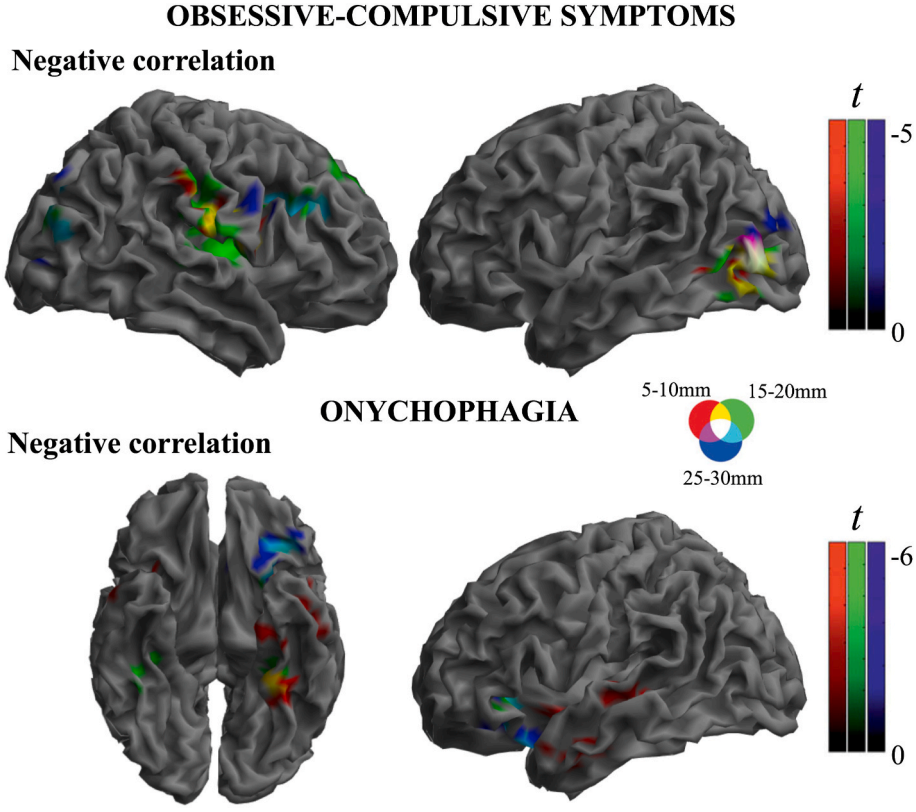

Fig. 5. Illustration of the correlation analysis results. Brain areas showing a negative correlation between behavioral measures and local functional connectivity as measured by IDAC in the Prader Willi syndrome sample. Multi-distance IDAC color maps are generated from the overlay of the separate correlation maps at three distances using an RGB (red, green, and blue) color codification. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Dysfunction in ventral prefrontal areas, particularly the orbitofrontal cortex, has consistently been implicated in various aspects of OCD symptomatology (Chamberlain et al., 2008; Harrison et al., 2009; Beucke et al., 2013; van den Heuvel et al., 2016; Robbins et al., 2024). Notably, in a previous study using identical functional connectivity measures, we reported a similar functional alteration in the orbitofrontal cortex, characterized by weaker local synchrony, in patients with OCD, which was associated with the severity of compulsions (Pujol et al., 2019). The obsessive-compulsive behaviors characteristic of OCD, driven by an inability to inhibit repetitive thoughts and actions, share similarities with the compulsive features observed in Prader Willi syndrome, such as body-focused repetitive behaviors (Grant and Chamberlain, 2022). In our present study, we found that the presence of onychophagia, a repetitive behavior associated with the disorder, predicted lower synchrony in the lateral orbitofrontal region. Overall, these findings suggest that Prader Willi syndrome exhibits pathophysiological parallels with typical OCD. Nevertheless, the specific manifestation of disinhibited behaviors may vary due to syndrome-specific mechanisms.

In addition to frontal anomalies, abnormal intracortical coupling was identified in sensory cortices involving visual, somatosensory and auditory areas. These regions exhibited reduced local functional connectivity, similarly suggesting decreased inhibitory neuron function. Moreover, the presence of obsessive-compulsive behaviors predicted lower synchrony in a part of the altered sensory areas. These findings are consistent with reports of specific sensory deficits in Prader Willi syndrome (Priano et al., 2009; Salles et al., 2016; Debladis et al., 2019; Strenilkov et al., 2020; Saima et al., 2022), accompanied by neurophysiological abnormalities of sensory processing (Stauder et al., 2002; Gabrielli et al., 2018). Building upon our previous contribution in OCD (Pujol et al., 2019), where similar impairments were observed in sensory cortices, it was proposed that insufficient inhibitory control over primary sensory inputs could ultimately contribute to enhanced neural activity in orbitofrontal regions responsible for regulating motivated behavior, thereby increasing the urge to respond to heightened sensations. In individuals with Prader Willi syndrome, this notion is exemplified by somatic sensations believed to initiate or sustain skin picking behaviors (Whittington and Holland, 2020; Hustyi et al., 2013; Klabunde et al., 2015). Indeed, we had previously observed an association between alterations in the degree of functional connectivity of the somatosensory cortex and the severity of skin picking behaviors in these patients (Pujol et al., 2016). Our current findings, showing sensory cortical dysregulation in Prader Willi syndrome, reinforce the idea that deficient sensory filtering may play an important role in the behavioral manifestations of the disorder.

Functional connectivity changes in the Prader Willi syndrome group additionally implicated the posterior cingulate cortex, adjacent precuneus, and the bilateral inferior parietal cortex encompassing the supramarginal and angular gyri. These regions, along with the medial prefrontal cortex, are core components of the default mode network (Buckner et al., 2008; Davey et al., 2016). This network, as a functional unit, has been broadly implicated in situations involving self-referential mental activity and social cognitive processing, as in self-judgments, emotion perception, and conceiving the viewpoint of others (Buckner et al., 2008; Davey et al., 2016; Li et al., 2014), areas where individuals with Prader Willi syndrome often exhibit difficulties (Schwartz et al., 2021; Cobo et al., 2021; Debladis et al., 2019; Lo et al., 2013; Whittington and Holland, 2017; Dykens et al., 2019). In our correlation analysis, stronger functional connectivity in parts of the default network was associated with ratings of peer-related problems.

Finally, our multidistance connectivity measure was able to capture local distance-specific differences. In particular, we observed a distance effect in local functional connectivity in the posterior cingulate and inferior parietal cortices, with reduced connectivity in the Prader Willi syndrome group at the shortest local connections (5–10 mm) and increased connectivity at the longest local connections (25–30 mm). The default network shows prominent synchronized activity at rest and typically deactivates during engagement in complex external tasks (Buckner et al., 2008). Imaging studies in individuals with Prader Willi syndrome have demonstrated anomalies in regions associated with this network, including increased metabolism (Ogura et al., 2013), greater activation during skin picking (Klabunde et al., 2015), and failure to deactivate during tasks requiring attention switching (Woodcock et al., 2010). Notably, there is also evidence of reduced GABA concentration in the posterior cingulate cortex associated with self-absorbed behaviors and social relating difficulties in these patients (Rice et al., 2016), which still points to abnormalities in local circuit inhibitory processing and suggests compromised regulation of cortical neural activity at this level. Taken together, these findings indicate an altered functional structure within the default network in Prader Willi syndrome.

The present study is limited by its cross-sectional design and relatively small sample size, potentially limiting the generalizability of our findings. Additionally, our assessment of obsessive-compulsive behaviors in the Prader Willi syndrome sample was constrained to identifying the presence or absence of symptoms. A more comprehensive obsessive-compulsive behavior evaluation could have better characterized the alterations in the functional structure of the cerebral cortex in relation to the severity of symptoms. Finally, we must also consider the medication status of patients, as a subgroup was undergoing treatment with psychiatric medication, which has demonstrated effects on neural inhibition (e.g. (Minzenberg and Leuchter, 2019),). However, medication in our study may more likely have attenuated differences in functional connectivity between patients and controls rather than caused them. Indeed, antidepressants, such as selective serotonin reuptake inhibitors, and anticonvulsants, particularly those affecting GABAergic neurotransmission, have been shown to normalize network dynamics by enhancing connectivity (Arnone et al., 2018), or stabilize excitatory-inhibitory imbalances in neural activity (Schousboe et al., 2014) potentially normalizing functional connectivity patterns.

In conclusion, our study using functional connectivity MRI measures in Prader Willi syndrome revealed significant reductions in local connectivity (cortical activity desynchronization) across ventral frontal and sensory cortices. The observed changes in the orbitofrontal and sensory regions, associated with obsessive-compulsive behaviors, underscore similarities with typical OCD pathophysiology and suggest the involvement of disrupted GABAergic neurotransmission as a potential underlying mechanism of the syndrome's behavioral manifestations. Furthermore, our results identified increased local functional connectivity (stronger synchrony) within elements of the default mode network, indicating alterations in the functional structure of the cerebral cortex at this level and highlighting the complex nature of cortical dysfunction in the disorder. Our observations may support the rational development of more specific therapeutic strategies by further suggesting the targeting of GABAergic neurotransmission in the treatment of Prader Willi syndrome. Nevertheless, further research is needed to specifically identify which elements of the interneuron system are affected, a crucial step that could inform these targeted strategies and potentially improve associated behavioral symptoms.

CRediT authorship contribution statement

Laura Blanco-Hinojo: Writing – original draft, Formal analysis, Data curation. **Jesus Pujol:** Writing – review & editing, Data curation, Conceptualization. **Gerard Martínez-Vilavella:** Writing – review & editing, Investigation. **Olga Giménez-Palop:** Writing – review & editing, Investigation. **Laia Casamitjana:** Writing – review & editing, Investigation, Data curation. **Jesús Cobo:** Writing – review & editing, Investigation, Data curation. **Rocío Pareja:** Writing – review & editing, Investigation. **Susanna Esteba-Castillo:** Writing – review & editing, Investigation. **Joan Deus:** Writing – review & editing, Conceptualization. **Assumpta Caixàs:** Writing – review & editing, Supervision, Conceptualization.

Disclosures

The authors declare no biomedical financial interests or potential conflicts of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by Fondo de Investigación Sanitaria del Instituto Carlos III and Fondo Europeo de Desarrollo Regional (grant numbers PI-18/00734, PI-21/00459 awarded to AC). The funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

We thank the Associació Catalana de Síndrome de Prader-Willi and the Associació Valenciana de Síndrome de Prader-Willi, also all the patients and their families for kindly agreeing to participate. We want to acknowledge A. Caixàs for being the corresponding author at Parc Taulí Hospital Universitari (acaixas@tauli.cat). The Agency of University and Research Funding Management of the Catalonia Government participated in the context of Research Group SGR2014-1673.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.01.012.

References

Arnone, D., Wise, T., Walker, C., Cowen, P.J., Howes, O., Selvaraj, S., 2018. The effects of serotonin modulation on medial prefrontal connectivity strength and stability: a pharmacological fMRI study with citalopram. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 84, 152–159.

Beucke, J.C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., et al., 2013. Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. JAMA Psychiatr. 70, 619–629.

Blanco Hinojo, L., Pujol, J., Macià, D., Martínez-Vilavella, G., Martín-Santos, R., Pérez-Sola, V., et al., 2021. Mapping the synchronization effect of gamma- aminobutyric acid inhibition on the cerebral cortex using magnetic resonance imaging. Brain Connect. 11, 393–403.

Brambilla, P., Perez, J., Barale, F., Schettini, G., Soares, J., 2003. GABAergic dysfunction in mood disorders. Mol Psychiatry 8, 721–737.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. 1124, 1–38.

Cassidy, S.B., Schwartz, S., Miller, J.L., Driscoll, D.J., 2012. Prader-Willi syndrome. Genet. Med. 14, 10–26.

Chamberlain, S.R., Menzies, L., Hampshire, A., Suckling, J., Fineberg, N.A., del Campo, N., et al., 2008. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. Science 321, 421–422.

Chao, H.T., Chen, H., Samaco, R.C., Xue, M., Chahrour, M., Yoo, J., et al., 2010. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. Nature 468, 263–269.

Chen, L.M., Yang, P.F., Wang, F., Mishra, A., Shi, Z., Wu, R., et al., 2017. Biophysical and neural basis of resting state functional connectivity: evidence from non-human primates. Magn. Reson. Imaging 39, 71–81.

Civardi, C., Vicentini, R., Grugni, G., Cantello, R., 2004. Corticospinal physiology in patients with Prader-Willi syndrome: a transcranial magnetic stimulation study. Arch. Neurol. 61, 1585–1589.

Clarke, D.J., Boer, H., Whittington, J., Holland, A., Butler, J., Webb, T., 2002. Prader-Willi syndrome, compulsive and ritualistic behaviours: the first population-based survey. Br. J. Psychiatry 180, 358–362.

Cobo, J., Coronas, R., Pousa, E., Oliva, J.C., Giménez-Palop, O., Esteba-Castillo, S., et al., 2021. Multidimensional evaluation of awareness in prader-willi syndrome. J. Clin. Med. 10, 2007.

Davey, C.G., Pujol, J., Harrison, B.J., 2016. Mapping the self in the brain's default mode network. Neuroimage 132, 390–397.

Debladis, J., Valette, M., Strenilkov, K., Mantoulan, C., Thuilleaux, D., Laurier, V., et al., 2019. Face processing and exploration of social signals in Prader-Willi syndrome: a genetic signature. Orphanet J. Rare Dis. 14, 262.

Dhossche, D.M., Song, Y., Liu, Y., 2005. Is there a connection between autism, Prader-Willi syndrome, catatonia, and GABA? Int. Rev. Neurobiol. 71, 189–216.

Dimitropoulos, A., Schultz, R.T., 2008. Food-related neural circuitry in Prader-Willi syndrome: response to high- versus low-calorie foods. J. Autism Dev. Disord. 38, 1642–1653.

Dimitropoulos, A., Feurer, I.D., Butler, M.G., Thompson, T., 2001. Emergence of compulsive behavior and tantrums in children with Prader-Willi syndrome. Am. J. Ment. Retard. 106, 39–51.

Dykens, E.M., Leckman, J.F., Cassidy, S.B., 1996. Obsessions and compulsions in Prader-Willi syndrome. JCPP (J. Child Psychol. Psychiatry) 37, 995–1002.

Dykens, E.M., Roof, E., Hunt-Hawkins, H., Daniell, C., Jurgensmeyer, S., 2019. Profiles and trajectories of impaired social cognition in people with Prader-Willi syndrome. PLoS One 14, 1–19.

Ebert, M., Schmidt, D., Thompson, T., Butler, M., 1997. Elevated plasma gamma-aminobutyric acid (GABA) levels in individuals with either Prader-Willi Syndrome or Angelman Syndrome. J. Neuropsychiatry Clin. Neurosci. 9, 75–80.

Fuster, J.M., 2019. The prefrontal cortex in the neurology clinic. Handb. Clin. Neurol. 163, 3–15.

Gabrielli, A., Poje, A.B., Manzardo, A., Butler, M.G., 2018. Startle response analysis of food-image processing in prader-willi syndrome. J Rare Disord 6, 18–27.

Glenn, S., Cunningham, C., Nananidou, A., Prasher, V., Glenholmes, P., 2013. Using the strengths and difficulties questionnaire with adults with Down syndrome. Res. Dev. Disabil. 34, 3343–3351.

Goodman, R., 1997. The strengths and difficulties questionnaire: a research note. JCPP (J. Child Psychol. Psychiatry) 38, 581–586.

Grant, J.E., Chamberlain, S.R., 2022. The role of compulsivity in body-focused repetitive behaviors. J. Psychiatr. Res. 151, 365–367.

Harrison, B.J., Soriano-Mas, C., Pujol, J., Ortiz, H., López-Solà, M., Hernández-Ribas, R., et al., 2009. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. Arch. Gen. Psychiatr. 66, 1189–1200.

Holland, A.J., Whittington, J.E., Butler, J., Webb, T., Boer, H., Clarke, D., 2003. Behavioural phenotypes associated with specific genetic disorders: evidence from a population-based study of people with Prader-Willi syndrome. Psychol. Med. 33, 141–153.

Holsen, L.M., Zarcone, J.R., Brooks, W.M., Butler, M.G., Thompson, T.I., Ahluwalia, J.S., et al., 2006. Neural mechanisms underlying hyperphagia in Prader-Willi syndrome. Obesity 14, 1028–1037.

Huang, Z., Zhang, X., Yang, X., Ding, S., Cai, J., 2024. Aberrant brain intra- and internetwork functional connectivity in children with Prader-Willi syndrome. Neuroradiology 66, 135–144.

Hustyi, K.M., Hammond, J.L., Rezvani, A.B., Hall, S.S., 2013. An analysis of the topography, severity, potential sources of reinforcement, and treatments utilized for skin picking in Prader-Willi syndrome. Res. Dev. Disabil. 34, 2890–2899.

Kim, S.E., Jin, D.K., Cho, S.S., Kim, J.H., Hong, S.D., Paik, K.H., et al., 2006. Regional cerebral glucose metabolic abnormality in Prader-Willi syndrome: a 18F-FDG PET study under sedation. J. Nucl. Med. 47, 1088–1092.

Klabunde, M., Saggar, M., Hustyi, K.M., Hammond, J.L., Reiss, A.L., Hall, S.S., 2015. Neural correlates of self-injurious behavior in Prader-Willi syndrome. Hum. Brain Mapp. 36, 4135–4143.

Lewis, D.A., Hashimoto, T., Volk, D.W., 2005. Cortical inhibitory neurons and schizophrenia. Nat. Rev. Neurosci. 6, 312–324.

Li, W., Mai, X., Liu, C., 2014. The default mode network and social understanding of others: what do brain connectivity studies tell us. Front. Hum. Neurosci. 8, 74.

Lo, S.T., Siemensma, E., Collin, P., Hokken-Koelega, A., 2013. Impaired theory of mind and symptoms of autism spectrum disorder in children with Prader-Willi syndrome. Res. Dev. Disabil. 34, 2764–2773.

Lucignani, G., Panzacchi, A., Bosio, L., Moresco, R.M., Ravasi, L., Coppa, I., et al., 2004. GABA A receptor abnormalities in Prader-Willi syndrome assessed with positron emission tomography and [11C]flumazenil. Neuroimage 22, 22–28.

Macià, D., Pujol, J., Blanco-Hinojo, L., Martínez-Vilavella, G., Martín-Santos, R., Deus, J., 2018. Characterization of the spatial structure of local functional connectivity using multi-distance average correlation measures. Brain Connect. 8, 276–287.

Marín, O., 2012. Interneuron dysfunction in psychiatric disorders. Nat. Rev. Neurosci. 13, 107–120.

Miller, J.L., James, G.A., Goldstone, A.P., Couch, J.A., He, G., Driscoll, D.J., et al., 2007. Enhanced activation of reward mediating prefrontal regions in response to food stimuli in Prader-Willi syndrome. J. Neurol. Neurosurg. Psychiatry 78, 615–619.

Minzenberg, M.J., Leuchter, A.F., 2019. The effect of psychotropic drugs on cortical excitability and plasticity measured with transcranial magnetic stimulation: implications for psychiatric treatment. J. Affect. Disord. 253, 126–140.

Niessing, J., Ebisch, B., Schmidt, K.E., Niessing, M., Singer, W., Galuske, R.A.W., 2005. Hemodynamic signals correlate tightly with synchronized gamma oscillations. Science 309, 948–951.

Novell-Alsina, R., Esteba-Castillo, S., Caixàs, A., Gabau, E., Giménez-Palop, O., Pujol, J., et al., 2019. Compulsions in prader-willi syndrome: occurrence and severity as a function of genetic subtype. Actas Esp. Psiquiatr. 47, 79–87.

Ogura, K., Fujii, T., Abe, N., Hosokai, Y., Shinohara, M., Fukuda, H., et al., 2013. Regional cerebral blood flow and abnormal eating behavior in Prader-Willi syndrome. Brain Dev. 35, 427–434.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84, 320–341.

Priano, L., Miscio, G., Grugni, G., Milano, E., Baudo, S., Sellitti, L., et al., 2009. On the origin of sensory impairment and altered pain perception in Prader-Willi syndrome: a neurophysiological study. Eur. J. Pain 13, 829–835.

Pujol, J., Macià, D., Blanco-Hinojo, L., Martínez-Vilavella, G., Sunyer, J., de la Torre, R., et al., 2014. Does motion-related brain functional connectivity reflect both artifacts and genuine neural activity? Neuroimage 101, 87–95.

Pujol, J., Blanco-Hinojo, L., Esteba-Castillo, S., Caixàs, A., Harrison, B.J., Bueno, M., et al., 2016. Anomalous basal ganglia connectivity and obsessive-compulsive behavior in patients with Prader Willi syndrome. J. Psychiatry Neurosci. 41, 261–271.

Pujol, J., Blanco-Hinojo, L., Macià, D., Alonso, P., Harrison, B.J., Martínez-Vilavella, G., et al., 2019. Mapping alterations of the functional structure of the cerebral cortex in obsessive-compulsive disorder. Cerebr. Cortex 29, 4753–4762.

Pujol, J., Pujol, N., Mané, A., Martínez-Vilavella, G., Deus, J., Pérez-Sola, V., et al., 2023. Mapping alterations in the local synchrony of the cerebral cortex in schizophrenia. Eur. Psychiatr. 66, e84.

Relkovic, D., Doe, C.M., Humby, T., Johnstone, K.A., Resnick, J.L., Holland, A.J., et al., 2010. Behavioural and cognitive abnormalities in an imprinting centre deletion mouse model for Prader-Willi syndrome. Eur. J. Neurosci. 31, 156–164.

Rice, L.J., Lagopoulos, J., Brammer, M., Einfeld, S.L., 2016. Reduced gamma-aminobutyric acid is associated with emotional and behavioral problems in Prader-Willi syndrome. Am J Med Genet B Neuropsychiatr Genet 171, 1041–1048.

Rice, L.J., Woodcock, K., Einfeld, S.L., 2018. The characteristics of temper outbursts in Prader-Willi syndrome. Am. J. Med. Genet. 176, 2292–2300.

Robbins, T.W., Banca, P., Belin, D., 2024. From compulsivity to compulsion: the neural basis of compulsive disorders. Nat. Rev. Neurosci. 25, 313–333.

Saima, S., Ihara, H., Ogata, H., Gito, M., Murakami, N., Oto, Y., et al., 2022. Relationship between sensory processing and autism spectrum disorder-like behaviors in prader-willi syndrome. Am. J. Intellect. Dev. Disabil. 127, 249–263.

Salles, J., Strelnikov, K., Carine, M., Denise, T., Laurier, V., Molinas, C., et al., 2016. Deficits in voice and multisensory processing in patients with Prader-Willi syndrome. Neuropsychologia 85, 137–147.

Schousboe, A., Madsen, K.K., Barker-Haliski, M.L., White, H.S., 2014. The GABA synapse as a target for antiepileptic drugs: a historical overview focused on GABA transporters. Neurochem. Res. 39, 1980–1987.

Schwartz, L., Caixàs, A., Dimitropoulos, A., Dykens, E., Duis, J., Einfeld, S., et al., 2021. Behavioral features in prader-willi syndrome (PWS): consensus paper from the international PWS clinical trial consortium. J. Neurodev. Disord. 13, 25.

Sepulcre, J., Liu, H., Talukdar, T., Martincorena, I., Yeo, B.T., Buckner, R.L., 2010. The organization of local and distant functional connectivity in the human brain. PLoS Comput. Biol. 6, e1000808.

Sinnema, M., Einfeld, S.L., Schrander-Stumpel, C.T., Maaskant, M.A., Boer, H., Curfs, L. M., 2011. Behavioral phenotype in adults with Prader-Willi syndrome. Res. Dev. Disabil. 32, 604–612.

State, M.W., Dykens, E.M., Rosner, B., Martin, A., King, B.H., 1999. Obsessive-compulsive symptoms in prader-willi and "Prader-Willi-Like" patients. J. Am. Acad. Child Adolesc. Psychiatry 38, 329–334.

Stauder, J.E., Brinkman, M.J., Curfs, L.M., 2002. Multi-modal P3 deflation of event-related brain activity in Prader-Willi syndrome. Neurosci. Lett. 327, 99–102.

Stauder, J.E., Boer, H., Gerits, R.H., Tummers, A., Whittington, J., Curfs, L.M., 2005. Differences in behavioural phenotype between parental deletion and maternal uniparental disomy in Prader-Willi syndrome: an ERP study. Clin. Neurophysiol. 116, 1464–1470.

Strenilkov, K., Debladis, J., Salles, J., Valette, M., Mantoulan, C., Thuilleaux, D., et al., 2020. A study of voice and non-voice processing in Prader-Willi syndrome. Orphanet J. Rare Dis. 15, 22.

Tomasi, D., Volkow, N.D., 2010. Functional connectivity density mapping. Proc Natl Acad Sci U S A 107, 9885–9890.

van den Heuvel, O.A., van Wingen, G., Soriano-Mas, C., Alonso, P., Chamberlain, S.R., Nakamae, T., et al., 2016. Brain circuitry of compulsivity. Eur. Neuropsychopharmacol 26, 810–827.

Wagstaff, J., Knoll, J.H., Fleming, J., Kirkness, E.F., Martin-Gallardo, A., Greenberg, F., et al., 1991. Localization of the gene encoding the GABAA receptor beta 3 subunit to the Angelman/Prader-Willi region of human chromosome 15. Am. J. Hum. Genet. 49, 330–337.

Whittington, J., Holland, A., 2017. Cognition in people with Prader-Willi syndrome: insights into genetic influences on cognitive and social development. Neurosci. Biobehav. Rev. 72, 153–167.

Whittington, J., Holland, A., 2020. Developing an understanding of skin picking in people with Prader-Willi syndrome: a structured literature review and re-analysis of existing data. Neurosci. Biobehav. Rev. 112, 48–61.

Woodcock, K.A., Humphreys, G.W., Oliver, C., Hansen, P.C., 2010. Neural correlates of task switching in paternal 15q11-q13 deletion Prader-Willi syndrome. Brain Res. 1363, 128–142.

Zahova, S.K., Humby, T., Davies, J.R., Morgan, J.E., Isles, A.R., 2021. Comparison of mouse models reveals a molecular distinction between psychotic illness in PWS and schizophrenia. Transl. Psychiatry 11, 433.

Zang, Y., Jiang, T., Lu, Y., He, Y., Tian, L., 2004. Regional homogeneity approach to fMRI data analysis. Neuroimage 22, 394–400.

Zou, Q., Zhu, C., Yang, Y., Zuo, X., Long, X., Cao, Q., et al., 2008. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J. Neurosci. Methods 172, 137–141.