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Hormone levels are related to functional compensation in prolactinomas: A resting-state fMRI study

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ABSTRACT

Prolactinomas are tumors of the pituitary gland, which overproduces prolactin leading to dramatic fluctuations of endogenous hormone levels throughout the body. While it is not fully understood how endogenous hormone disorders affect a patient's brain, it is well known that fluctuating hormone levels can have negative neuropsychological effects. Using resting-state functional magnetic resonance imaging (rs-fMRI), we investigated whole-brain functional connectivity (FC) and its relationship with hormone levels in prolactinomas. By performing seed-based FC analyses, we compared FC metrics between 33 prolactinoma patients and 31 healthy controls matched for age, sex, and hand dominance. We then carried out a partial correlation analysis to examine the relationship between FC metrics and hormone levels. Compared to healthy controls, prolactinoma patients showed significantly increased thalamocortical and cerebellar-cerebral FC. Endogenous hormone levels were also positively correlated with increased FC metrics, and these hormone-FC relationships exhibited sex differences in prolactinoma patients. Our study is the first to reveal altered FC patterns in prolactinomas and to quantify the hormone-FC relationships. These results indicate the importance of endogenous hormones on functional compensation of the brain in patients with prolactinomas.

1. Introduction

Prolactin-secreting pituitary tumors (prolactinomas) are the most common subtype of pituitary tumors [1]. Prolactinomas are characterized by a dramatic surge of prolactin that suppresses the secretion of various hormones including sex steroid hormones, resulting in galactorrhea, amenorrhea, fertility disorders, and impaired sexual function [2]. Although most prolactinomas are benign, they can present with debilitating symptoms, including cognitive dysfunction, affective disorders, and impaired psychological well-being leading to reduced social interactions and poor quality of life [3,4]. The underlying pathophysiology is not fully understood; however, clinical evidence has shown that disturbances in endogenous hormones can lead to cognitive impairments in executive function [5], attention [6], verbal memory [7], processing speed [8] and working memory [9].

Hormones affect brain development, organization, and plasticity. Numerous studies have shown that high levels of endogenous hormones can alter both gray and white matter structures in patients with Cushing's disease [10,26], prolactinomas [5], acromegaly [11], hormonal transition periods in women [12,13], pubertal boys and girls

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[14], and healthy elderly men [15]. These studies provide evidence that altered hormone levels have a substantial effect on brain structure and likely corresponding brain function. The mechanism by which endogenous hormones influence brain cognitive function has been increasingly investigated [16–19]. The effect of estradiol on memory consolidation has been shown to occur through membrane interactions and activation of inter-cellular signaling pathways in addition to known genetic changes [16]. In menopausal females over 60 years old, early-initiation hormone therapy can lead to improved visual working memory further demonstrating the importance of estrogen in memory consolidation [18]. Interestingly, even during the normal menstrual cycle of a healthy patient, there is evidence of subtle fluctuation of hormone levels affecting brain regional activity [20]. Children with isolated growth hormone deficiency show structural abnormalities of the white matter of the brain, which can lead to cognitive impairments [17]. Prolactin receptors are widely distributed in the brain and can regulate neuronal circuits, neurotransmission and neuronal signaling pathways [21]. Elevated levels of prolactin can suppress levels of sex hormones, such as estrogen, progesterone, and testosterone. Therefore, this disturbance of endogenous hormones can lead to altered brain structure [5], and modification of functional connectivity (FC) in the brain [22–24].

Brain networks have large and diverse functional motifs [25,26]. We have previously investigated the influence of endogenous hormones on brain gray matter and neurocognition in prolactinoma patients [5]. However, functional connections in prolactinoma patients have not been explored. Based on previous studies investigating the relationship between hormones and brain function [16–19], we speculated that determining the FC patterns in prolactinoma patients may be useful in the clinical setting. Exploring the FC patterns in prolactinomas allows us to perform quantitative assessments of cognitive dysfunction, which has been previously investigated in other diseases such as Cushing's disease [8–10,27]. Thus, altered intrinsic FC reflecting fundamental brain functional organization is currently under investigation as a potential imaging biomarker in the selection of a course of treatment in a variety of psychiatric disorders [28–30]. Importantly, it is widely adopted that resting-state functional magnetic imaging (rs-fMRI) is a useful tool to measure the temporal dependence of neuronal activation patterns of spatially distributed brain areas to characterize FC patterns of intrinsic networks [31–33]. Therefore, the aim of the current study was to determine FC patterns in prolactinoma patients using rs-fMRI. We hypothesized that altered hormone levels in patients with prolactinomas can alter functional network connectivity.

2. Materials and methods

2.1. Participants

Thirty-three preoperative prolactinoma patients and 31 healthy controls participated in this study. Patients were enrolled in the study if they met the following criteria: (1) clinically diagnosed with prolactinoma according to the patient's symptoms, elevated prolactin levels, and MRI features [34]; (2) physically able to take part in structural MRI, rs-MRI, and conventional MRI scans including T1-weighted MRI, T2-weighted MRI, and fluid-attenuated inversion recovery (FLAIR) images for clinical diagnosis; (3) with over 5 years' education. The exclusion criteria were: (1) left-handed; (2) over 65 years old or in pubertal stage (less than 18 years old); (3) a history of other neurological or psychiatric disorders, acquired brain injury, smoke, drug/alcohol abuse, or medication intake (including dopamine agonist and oral contraceptives); and (4) any contraindication for MRI scanning. All patients were initially diagnosed in the neurosurgery clinic and did not receive any treatment prior to their functional MRI scans.

All procedures of this study comply with the Declaration of Helsinki and were approved by the Ethical Committee of Wuhan General Hospital (Approved ID: [2017] 024–1). The study protocol was fully explained to all participants, and written informed consent was obtained.

2.2. Hormone assays and visual assessments

Fasting peripheral venous blood samples from the patients were obtained between 8:00 a.m. and 9:30 a.m. to measure endogenous hormone levels with minimal circadian effect. Serum levels of prolactin (PRL, ng/ml), estradiol (E2, pg/ml), follicle-stimulating hormone (FSH, mIU/ml), luteinizing hormone (LH, mIU/ml), progesterone (P, ng/ml), testosterone (T, ng/ml), growth hormone (GH, ng/ml), thyroid-stimulating hormone (TSH, uIU/ml), and cortisol (nmol/l) were determined by chemiluminescent immunoassays (Roche, cobas® 8000, Switzerland). Serum dilution for the PRL measurement (1:100) was performed to rule out the “hook effect,” if necessary.

All patients routinely underwent complete ophthalmologic examination at admission. The E chart was used to measure the best-corrected visual acuity. The visual field parameters were obtained using the standardized, automated perimetry (Octopus 900 Perimetry, Switzerland).

2.3. Image acquisition

All participants were placed in a supine position with bilateral earplugs to attenuate MRI scanning noise. and their head were fixed by custom-fit multiped positioning cushions to minimize head motion. High resolution structural MR images were acquired on a 1.5 Tesla GE scanner (GE EXCITE, Milwaukee, WI, USA) using an 8-channel head coil. Three-dimensional T1-weighted images were acquired using the axial Fast Spoiled Gradient Echo sequence with the following parameters: repetition time (TR) = 11.5 ms, echo time (TE) = 5.1 ms, flip angle = 15°, matrix = 256 × 256, field of view (FOV) = 240 mm × 240 mm, slice thickness = 0.6 mm, voxel size = 1 × 1 × 1 mm^3, and 230–240 contiguous transverse slices.

A 7-min resting-state blood oxygen level dependent (BOLD) fMRI data were acquired using single-shot T2*-weighted echo-planar imaging with the following parameters: TR = 2000 ms, TE = 30 ms, matrix size = 64 × 64, slice thickness = 4.0 mm, slice gap = 0.5 mm, voxel size = 3.75 × 3.75 × 4.5 mm^3, 33 axial slices. During the rs-fMRI scanning, all participants were instructed to keep their eyes open with a central fixation condition.

Based on the T1-enhancement MRI images, pituitary tumor volumes were semi-automatically segmented by both a neurosurgeon with three years of clinical experience and a professor specializing in brain tumor segmentation using 3D Slicer (https://www.slicer.org/). The segmentation results were further reviewed by an associate neurosurgeon. Raters were blinded to patients' rs-fMRI data and clinical information. None of the healthy participants demonstrated abnormal brain structures as assessed by the two neurosurgeons.

2.4. fMRI preprocessing

fMRI data were preprocessed using the CONN Toolbox (v.18.a; http://www.nitrc.org/projects/conn) based on SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) in MATLAB R2018a (MathWorks, Inc., MA, USA). Data preprocessing was carried out using the default pipeline in the CONN toolbox including: (1) realignment of functional images to the first functional image of the run (head motion estimation and correction); (2) slice-timing correction of corrected functional volumes; (3) functional outlier detection using the artifact detection tool (ART) to identify the outlier scan for scrubbing with the threshold for global signal above z = 5 and for head motion above 1.0 mm; (4) structural image segmentation and normalization (non-linear transformation to Montreal Neurological Institute (MNI) space); (5) co-registration of functional images to the normalized structural images; (6) smoothing using a full-width half-maximum Gaussian kernel of 6 mm;

(7) bandpass filtering of 0.008–0.09 Hz, and regression of white matter and cerebrospinal fluid signal; and (8) cleaning of motion and physiological noise using the CompCor method [35], which is performed to address potential subject-movement and physiological confounding effects without the risk of artificially introducing anti-correlations into our functional connectivity estimates [36].

2.5. Whole-brain FC analysis

The region of interest (ROI)-to-ROI FC analysis across whole brain was performed using the CONN toolbox to explore the characteristics of spatial isolation and temporal synchronizing from rs-fMRI data [37]. For the whole-brain FC analysis, the ROIs were defined on the basis of a complete brain parcellation implemented in CONN, including 91 cortical areas and 15 subcortical areas from the FSL Harvard-Oxford Atlas as well as 26 cerebellar areas from the ALL atlas [37]. This default atlas in CONN toolbox is adopted to explore whole brain functional connectivity and graph theory in patients with psychological or psychiatric disease [30]. The mean time series of each ROI was subsequently extracted from the preprocessed functional data. Then the ROI-to-ROI correlation matrices representing the level of FC between each pair of the 132 ROIs were calculated and converted to z-scores using Fisher's r-to-z-transformation. Finally, the whole-brain FC metrics were compared between prolactinoma patients and healthy controls, and a partial correlation analysis was performed between FC metrics and clinical variables. To control the type 1 error, we approached this in the way controlling false discovery rate (FDR) at seed-level with a significant threshold of $p < .05$ when we were comparing whole brain FC metrics between prolactinoma patients and healthy controls.

2.6. Statistical analyses

Baseline clinical characteristics were described using mean values and ranges (minimum and maximum values) for continuous variables and using median and interquartile range for continuous variable with highly skewed distributions. Group differences were compared using the non-parametric Mann-Whitney *U* test, two-sample student's *t*-test or Pearson's Chi-Squared test, as appropriate. The partial correlation analysis was performed to determine the relationship between FC metrics and hormone levels controlling for age, tumor volume, and the duration of disease. Significance was set at $p < .05$ (two-tailed). Statistical analyses were performed using JASP version 0.10.2 (https://jasp-stats.org/).

2.7. Data availability

Any anonymized data not presented within this article will be available upon request from any qualified investigators.

3. Results

There were no statistically significant differences between prolactinoma patients and healthy controls in age ($p = .266$), sex ($p = .477$), and education ($p = .909$). Other clinical characteristics are described in Table 1.

Compared to healthy controls, prolactinoma patients showed increased FC between the left thalamus and visual cortex/association areas [bilateral lingual gyrus (LG), right intra-calcarine cortex (ICC), right supra-calcarine cortex (SCC), right cuneal cortex, and bilateral lateral occipital cortex (LOC)] and right cerebellum, the right cerebellum and cerebral cortex [precuneus, posterior cingulate gyrus (PC), bilateral temporal fusiform cortex (TFusC)], and the left supplementary motor area (SMA) and right lingual gyrus (Fig. 1). In addition, the increased FC of the thalamus and right ICC were significantly prominent in patients without visual field impairments (VFI) compared to patients with VFI ($p = .013$) (Table 2).

Table 1
Demographical information of prolactinomas patients and healthy controls.

Clinical categories	Prolactinoma patients ($n = 33$)	Healthy controls ($n = 31$)	*P value*
Age (years)	43.76 ± 10.87	46.74 ± 10.38	0.266[a]
Gender (F/M)	22/11	18/13	0.477[b]
Education (years), median (IQR)	10.0 (6.0–12.0)	10.0 (6.0–14.0)	0.909[c]
Duration of Disease (months), median (IQR)	12.0 (6.0–24.0)	N/A	N/A
Volume of Pituitary Tumor (cc), median (IQR)	4.4 (1.7–9.8)	N/A	N/A
Clinical symptoms			
Headache	24.3% (8/33)	N/A	N/A
Visual impairments	45.5% (15/33)	N/A	N/A
Sexual dysfunction	48.5% (16/33)	N/A	N/A
Hormone levels			
Estradiol (pg/ml)	40.5 ± 79.31	N/A	N/A
FSH (mIU/ml)	8.31 ± 9.08	N/A	N/A
LH (mIU/ml)	3.65 ± 3.39	N/A	N/A
Progesterone (ng/ml)	1.20 ± 3.76	N/A	N/A
Prolactin (ng/ml)	190.3 ± 177.6	N/A	N/A
Testosterone (ng/ml)	0.92 ± 1.37	N/A	N/A
TSH (uIU/ml)	2.96 ± 2.57	N/A	N/A
Cortisol (nmol/l)	291.9 ± 174.4	N/A	N/A
GH (ng/ml)	0.57 ± 0.93	N/A	N/A

Abbreviations: F, female; M, male; IQR, interquartile range; cc, cubic centimeter; FSH, follicle-stimulating hormone; LH, luteinizing hormone; THS, thyroid-stimulating hormone; GH, growth hormone.
[a] Two-sample student's t-test.
[b] Pearson Chi-Squared test of Fisher's exact test.
[c] Non-parametric Mann-Whitney *U* test.

There was a significantly positive correlation between the prolactin level and the FC of left thalamus and right LG in female patients with prolactinomas (Fig. 2). There was positive correlation between the testosterone level and the FC of right cerebellum and left TFusC (Fig. 2B), and positive correlation between the LH level and the FC of left SMA and right LG in male patients (Fig. 2C).

4. Discussion

To our knowledge, this study is the first to demonstrate altered whole-brain FC patterns and their relationships with endogenous hormone levels in patients with a prolactinoma. Compared to healthy controls, prolactinoma patients showed an increase in thalamocortical and cerebellar-cerebral connectivity, suggesting a relationship between abnormal endogenous hormone levels and FC patterns. Furthermore, the FC-hormone relationships showed sex differences in patients, indicating a sex-dependent influences of endogenous hormones on brain compensation.

Our first notable finding was the illustration of increased FC between the left thalamus and visual cortex/association areas (lingual gyrus, ICC, SCC, cuneal cortex, and LOC). The thalamus is both the primary integrator in neural information processing of the central nervous system and the gateway of sensory input to the cerebral cortex, such as the visual cortex/association areas, which involve visual perception receiving signal input from the retina via the lateral geniculate nucleus of the thalamus [38]. Connected with widespread cortical-subcortical and cortico-cerebellar areas, the thalamus plays a critical role in modulating the communication within these neural circuits, forming the extensive thalamocortical connections [39]. While all patients exhibited an increase in visual-related FC patterns, those patients without visual field impairments exhibited substantially more hyperactive intrinsic connections that may illustrate compensatory activity within the thalamocortical circuits, and also indicated that there existed other underlying mechanisms for the increased FC other than the

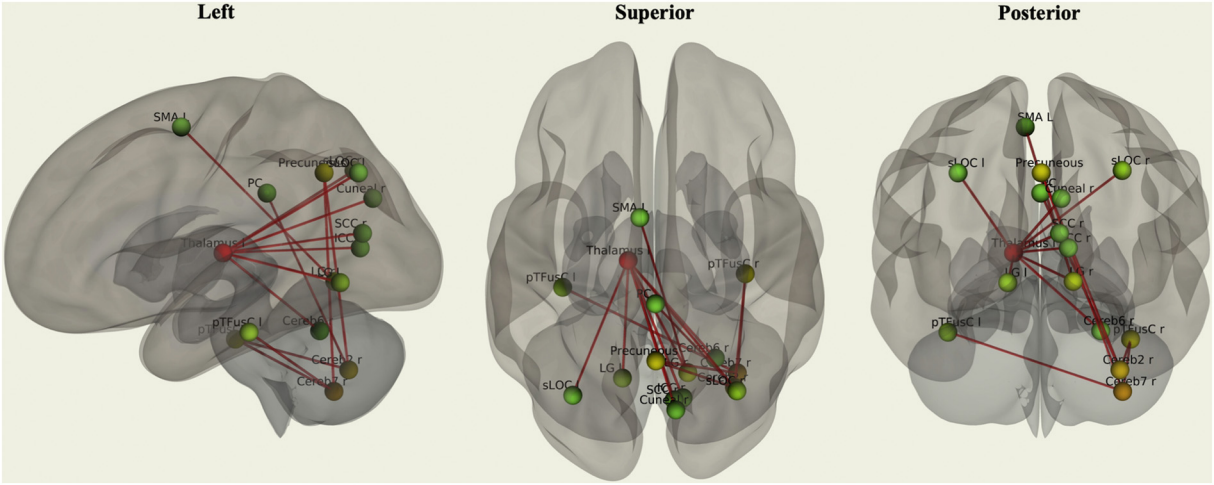

Fig. 1. ROI-to-ROI analysis results of the resting-state functional connectivity across the whole-brain. Compared to healthy controls, significantly increased functional connectivity was shown in patients with prolactinomas. The false discovery rate (FDR) method was used to perform the seed-level correction at a significant level of $p < .05$ (two-sided). In the whole-brain connectivity patterns, the red nodes have more connections with other nodes, the green nodes have less connections with other nodes, and the yellow nodes have the mediate number of connections with other nodes. Abbreviations: ROI, region-of-interest; Cereb, Cerebellum; pTFusC, temporal fusiform cortex, posterior division; LG, lingual gyrus; sLOC, lateral occipital cortex, superior division; ICC, intra-calcarine cortex; SCC, supra-calcarine cortex; PC, cingulate gyrus, posterior division; SMA, supplementary motor area.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

possibility by the tumor. Another important finding was the increased cerebellar-cerebral connectivity that occurred primarily between the right cerebellum and the areas within the default mode network (DMN), including posterior cingulate cortex (PCC), precuneus and bilateral TFusC. The PCC/precuneus together plays a critical role in controlling the state of arousal and maintaining attention [40]. TFusC mediates a variety of higher cognitive and emotional functions that relate to facial and object perception [41]. The cerebellum is also activated during the control of negative emotional processing with activation occurring concomitantly with the mirror neuron system, including TFusC and precuneus [42]. Therefore, the increased cerebellar-DMN connectivity could be a potential imaging biomarker for cognitive impairment in prolactinomas [43].

Prolactinoma patients are a good study population to investigate the relationship between prolactin and brain FC in vivo. Prolactinoma is the leading cause of hyperprolactinemia, which is a common condition in the population with a series of psychiatric disorders, mainly when the subject is under antipsychotic treatment [44]. Our team also has demonstrated impaired verbal memory and executive function in prolactinoma patients with a significant decrease in the gray matter volumes of the left hippocampus, left orbitofrontal cortex, right middle frontal cortex, and right medial frontal cortex [5]. One of the underlying mechanisms of cognitive impairments in prolactinomas may be an altered relationship between prolactin and dopamine, which are critical for the development and maintenance of cognitive function [45]. Normally, dopamine neurotransmitters reach the pituitary gland and regulate the prolactin production via hypophyseal portal blood from the hypothalamus. However, the pituitary gland will overproduce prolactin in dopamine deficiency [46]. Dopamine receptors are widely distributed in brain particularly the midbrain (substantia nigra, ventral tegmental area, and dorsal striatum) and neocortex, which are key brain areas for higher-order brain function [47,48]. Therefore, considering the possibility of existing dopamine deficiency in prolactinomas, the effect of prolactin on the FC may be indirect via the dopamine-mediated pathway [44]. Our novel findings on the hyperactive connections within the thalamocortical and cerebellar-cerebral circuits may be one of the underlying pathophysiological changes underlying cognitive impairments and emotional disorders in prolactinomas.

Various studies have demonstrated the role of sex steroid hormones in regulating the organization of structural and functional connectivity in the brain, facilitating information communication within a large-scale brain network [49]. For example, testosterone has been shown to display neuroprotective effects on FC and structural connectivity by allowing increased engagement of the actin cytoskeleton and increased growth of white matter in the brain [50]. LH is another sex steroid that is related to the development of white matter volume and density in the prefrontal and temporal cortices [51]. Since testosterone and LH sex hormones can be suppressed by excess prolactin in serum due to prolactinomas, the relationship between hormone levels and the increased FC may illustrate the potential influence of endogenous hormones in brain compensation in prolactinoma patients.

There are several limitations to this study. First, the mass effect of

Table 2
Comparison of the altered functional connectivity related to the visual system in patients with and without visual field impairment.

FC metric	Non-VFI patients (mean ± SD)	VFI patients (mean ± SD)	Statistic	*P* – value[a]
Left thalamus – right LOC	−0.044 ± 0.124	−0.030 ± 0.148	−0.308	0.760
Left thalamus – left LOC	0.070 ± 0.116	0.105 ± 0.127	−0.815	0.422
Left thalamus - left lingual gyrus	0.181 ± 0.135	0.083 ± 0.147	1.988	0.056
Left thalamus – right lingual gyrus	0.157 ± 0.140	0.065 ± 0.135	1.889	0.068
Left thalamus – right ICC	0.181 ± 0.137	0.053 ± 0.138	2.647	0.013
Left thalamus – right SCC	0.125 ± 0.157	0.033 ± 0.117	1.857	0.073
Left thalamus – right Cuneal	0.012 ± 0.199	−0.037 ± 0.115	0.844	0.405

Abbreviations: LOC, lateral occipital cortex; ICC, intra-calcarine cortex; SCC, supra-calcarine cortex; SD, standard deviation;VFI, visual field impairment.
[a] Non-parametric Mann-Whitney *U* test.

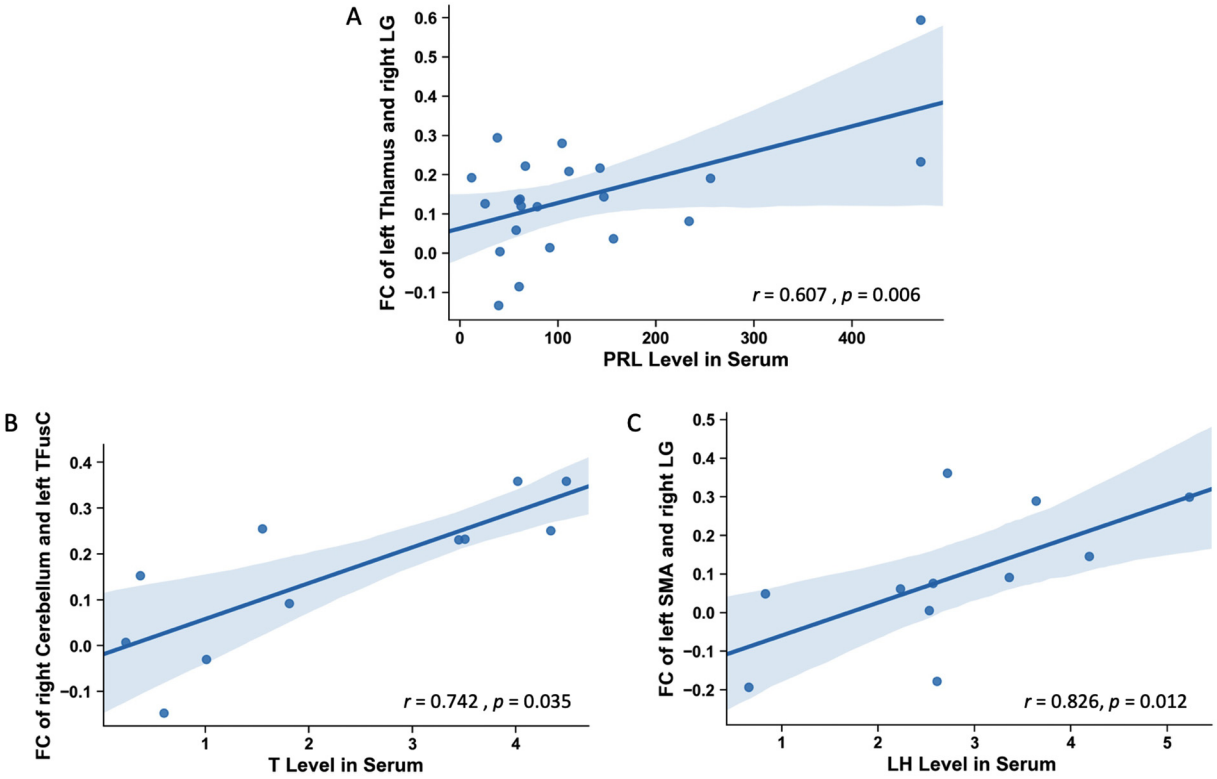

Fig. 2. Partial correlation analysis results between endogenous hormone levels and altered functional connectivity metrics. (A) The PRL level in serum is positively correlated with the FC of the left thalamus and the right LG in female patients. (B) The T level in serum is positively correlated with the FC of the right cerebellum and the left TFusC in male patients. (C) The LH level in serum is positively correlated with the FC of the left SMA and the right LG in male patients. The shading area indicates the 95% confidence interval of a correlation line. Abbreviations: PRL, prolactin; T, testosterone; LH, luteinizing hormone; LG, lingual gyrus; TFusC, temporal fusiform cortex; SMA, supplementary motor area.

the bulky tumor on surrounding structures in some patients may effect the results, however we adjusted for the the tumor size in the data analysis. Second, the relationship between hormone levels and the altered FC in males may have been biased due to the relatively small sample size. Third, in our study, we did not perform neuropsychological assessments and therefore we cannot directly measure the relationship between neuropsychological deficits and altered FC metrics. Future study should include a neurocognitive assessment to supplement our findings and quantify the effects of altered FC in prolactinoma patients should be undertaken. Fourth, it is well known that hand dominance does not determine hemispheric dominance. In our recent language task fMRI study, we measured hand dominance in 36 patients and found two patients (5.6%) with right handedness showing right hemispheric dominance [52]. The missing information about hemisphere dominance should be addressed in future studies. Fifth, we did not measure hormone levels in healthy participants as many did not wish to undergo invasive biochemical tests, and saliva tests for hormone levels were not available in this hospital. However, we did not find any structural abnormalities of the pituitary glands in these patients using MRI scans and we therefore believe there is low probability of hormonal imbalance in these patients. Thus, a follow-up study with fully matched controls should be taken into account in the study design. Finally, advances in neuroimaging techniques provide a noninvasive approach to identifying potential biomarkers for psychological, psychiatric, and neurological diseases. However, the neuroimaging metrics (i.e. gray/white matter, activated clusters/regions or functional connectivity) cannot always provide a clearly direct relationship to biological changes and can therefore be difficult to interpret. Future studies investigating changes in genetic expression related to altered neuroimaging results, may provide useful clues to the underlying pathobiology of our observed findings.

5. Conclusion

Our findings demonstrate increased FC within the thalamocortical and cerebellar-cerebral circuits in prolactinoma patients and these are associated with altered endogenous hormone levels. We therefore speculate whether altered FC patterns may be a promising imaging biomarker for hormone-related neurological and psychological symptoms in prolactinoma patients. FC-hormone relationships were also different in males and females, indicating a sex-dependent influence of endogenous hormones on brain compensation. Overall, our findings provide new insights into the altered FC patterns and the important role of endogenous hormones in brain compensation in prolactinomas.

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Author contributions

Drs. Guozheng Xu, Jian Song, Shun Yao, Alexandra J. Golby, and Yanmei Tie provided the majority of research funding. Shun Yao and Jian Song were responsible for the study design. Shun Yao collected data, undertook fMRI data analysis, and drafted the manuscript. Pan Lin did the brain tumor segmentation and fMRI preprocessing analysis. Jian Song reviewed all lesion masks. Ru-Yuan Zhang did the partial correlation analysis and created figures. Matthew Vera, Farhana Akter,

Ailiang Zeng, Alexandra J. Golby, and Yanmei Tie contributed to results interpretation, manuscript preparation, and critical revision.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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