Functional Status of Hypothalamic-pituitary-thyroid axis and Prolactin level in Patients with First-episode of Bipolar Disorder in Mania State

Fang Wang
Shanghai Yangpu Mental Health Center
Huaihui Zhang
Shanghai Yangpu Mental Health Center
Jun Wang
Shanghai Yangpu Mental Health Center
Dongmei Zhao
Shanghai Mental Health Center
Yuncheng Zhu (hellfiregenius@163.com)
shanghai mental health center https://orcid.org/0000-0003-4686-8887

Research article

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Abstract

Background

Bipolar disorder (BD)-mania symptoms are stimulated by disease of the thyroid.

Methods

This study included 70 patients diagnosed with first-episode BD-mania and 70 healthy controls (HC) matched for age and sex. We aimed to determine upstream thyroid hormone interactions on the anterior pituitary, and find differences between thyroid-stimulating-hormone (TSH) and Prolactin (PRL) in the patients with first-episode of BD-mania. There were significant changes in triiodothyronine (TT3), total thyroxin (TT4), and free thyroxine (FT4) concentrations between the BD-mania and HC groups ($p < 0.0167$ with Bonferroni correction).

Results

After being grouped by sex, higher PRL in the male and female BD-mania subgroup were observed compared to each isosexual HC ($p's < 0.01$). Higher FT4 in the male BD-mania group was observed compared to the HC males ($p < 0.01$) while the female BD-mania group showed lower TT3 and TT4 compared to the HC females ($p's < 0.01$). In the female BD-mania group, correlation analysis established an inverse relationship between PRL and TSH ($r^2 = 0.25$, $F = 11.11$, $p < 0.01$).

Conclusions

The findings demonstrate that sex impacts the concentration of hormones secreted by the anterior pituitary of patients with first-episode BD-mania. The increased PRL may be a putative mechanism that underlies the onset in female patients with a moderate inverse relationship between TSH and PRL.

Background

Bipolar disorder (BD) is a complex, recurrent, and severe illness characterized by bipolar mood and abnormal behavioral symptoms. There has long been a debate between the interactive change of the pathophysiology in the hypothalamus-pituitary-thyroid axis (HPTA)[1–3] and prolactin (PRL)[4, 5] during the treatment and maintenance of mood. Bipolar disorder is strongly associated with immune dysfunction[6] that may impact the function of the anterior pituitary, however, the reference range of the anterior pituitary hormone levels which are related to recurrent BD's have yet to be defined. Metabolic dysregulation of the axis at any part of the storage, secretion, activity, or bypass can affect the function of normal neural connections resulting in a psychotic symptom cluster. Thyroid hormones (THs) can strongly affect mood and behavior through phenotypic symptom clusters related to the illness[7]. Thus, THs can

modulate intrinsic neuronal activity to lower thresholds, which play permissive roles in the expression of affective “pacemakers”, and potentially impact vulnerability set points to switch between over-activity (BD-mania) and under-activity (BD-depression)[8]. Moreover, THs and PRL could impact the expression of abnormal neuronal activity within the affective circuits, and as a result, increase suicide attempts[9] by reducing serum brain-derived neurotrophic factor (BDNF) levels[10].

Bipolar disorder is interrelated with many neuroendocrine diseases and biologic studies have suggested that the relationship between mood disorder and medical illness is bidirectional in nature[11]. This provides support for the multiplayer of shared and specific etiologic factors interlinking these clinical conditions[12]. On the other hand, clinical manifestation, course, and prognosis of neuroendocrine disease are closely associated with affective symptoms[13].

The pituitary and the hypothalamus serve as a functional unit in controlling the secretion of various hormones. Bipolar disorder-related symptoms could be either worsened by an acute change in thyroid hormones, or compensated for by the maintenance of stable levels below a critical threshold, through regulation by the anterior pituitary. The function of the HPTA plays an important role in neuropsychiatric disorders, for example, hyperthyroidism (Graves' disease) is characterized by typical emotional irritability, increased activity, and sleep deprivation[14], similar to mania syndrome.

Varying from traditional biomedicine, the theory of the classical neuroendocrine feedback states that physiological feedback systems are mostly modulated by negative feedback and self-protection. The self-regulatory mechanism of BD-mania is aimed at relieving symptoms through the hyposecretion of TH’s, thus decreasing it’s physiological affective symptoms, and hyperactivates the regulating of the pituitary axis by negative feedback mechanism. Thus, the process increases not only the release of thyroid-stimulating-hormone (TSH) [15, 16] but also the sensitivity of the anterior pituitary[17]. Compensatory enhancement of the pituitary function is developed in the process of spontaneous hyposecretion of hormones during the remission of symptoms. In a bibliographic search on PUBMED of all MRI studies exploring the pituitary gland before 2016, structural MRI studies showed evidence of pituitary gland enlargement in BD[18]. Thus, after the review of current literature, we considered TSH and PRL to be of high potential value for research. Furthermore, anterior pituitary dysfunction was found in patients taking lithium, or patients with additional psychiatric and medical conditions[16]. Therefore, our study on patients with medicine-naïve first-episode BD is more accurate in reflecting the effect of the anterior pituitary mechanism of BD.

Methods

Setting

This study was reviewed and approved on 11/01/2016 by the Institutional Ethical Committee for clinical research of the corresponding institutes from the Changning District (2016001). Data of the patients with BD-mania were collected at the psychiatric departments of Shanghai Changning Mental Health Center

(SCMHC) from November 2016 to October 2017. Written informed consent was obtained from participants or their next of kin after a complete description of the study was given.

Study design

The diagnosis of BD-mania was ascertained through the International Statistical Classification of Diseases and Related Health Problems, the Tenth Revision (ICD-10). Three-level ward rounds were rigorously operated and diagnosed by two experienced psychiatrists independently. The diagnosis of BD was ascertained according to the ICD-10 criteria recognized by the Mini-International Neuropsychiatric Interview (M.I.N.I)[19]. For this study, we analyzed patients at reproductive age with discrimination of anterior pituitary function between sex[20]. Inclusion criteria were: Chinese Han; aged from 16 to 40 with secondary sex characteristic; medicine-naïve first-episode BD-mania including the diagnostic code (F31.0, F31.1 or F31.2) without comorbid diagnosis; Bipolar Spectrum Diagnostic Scale (BSDS) ≥ 12[21]. Exclusion criteria were: History of central nervous system disease; central nervous system disease; confirmed nervous system disease through MRI examination; history of thyroid diseases, adrenal diseases, or gonad diseases tested from B-ultrasonography or immunoserology; taking levothyroxine, antithyroid, glucocorticoid, estrogen, progestin, oral contraceptive, bromocriptine, or other medicine related to pituitary diseases in the past six months; alcohol or tobacco abuse; history of antipsychotic medications; pregnant or in postpartum period; estrus cycle in women (luteinizing hormone > 14 IU/L); taking medication records within two weeks.

The samples of healthy controls (HC) were selected randomly from a name list of approximately 300 individuals screened in the physical examination center of Tongren Hospital Affiliated to Shanghai Jiaotong University School of Medicine. All the data was gathered by the SCMHC Information Department. The patients' personally identifiable information was redacted in order to protect patient privacy and anonymity before being provided for analysis. In order to understanding the research content, education needed to be above high school. They were matched to a group based on age, sex, ethnicity and without diagnosis recognized by the M.I.N.I.. Exclusion criteria were the same as those of the BD patients, in addition, with BSDS ≥ 6. Seventy patients (35 male and 35 female) were enrolled in the BD-mania group and 70 healthy records (35/35) were collected in HC group (see Fig. 1 for a flow diagram of sample selection).

Measures

General self-made questionnaire

The general self-made questionnaire contained questions on age, sex, ethnicity, course of disease, level of education, family history, alcohol or tobacco abuse, medication history, and review of recent drug use.

Young manic rating scale (YMRS)

The YMRS symptom rating scale has been shown to be a reliable and valid instrument in the assessment of the severity of psychopathology of manic symptoms [22]. The scale is divided into two parts. The first

part consists of 7 items, each rated using a 4-point scale while the other 4 items are rated on an 8-point scale. The higher the score, the more severe the manic state is likely to be.

Bipolar Spectrum Diagnostic Scale (BSDS)

The Chinese version of the BSDS has reached a high standard of reliability and validity in BD patients[21]. The scale is divided into two parts. The first part is a description of 19 BD symptoms (answered by yes (score 1) or no (score 0)) and the second part is a general assessment, which provides a scale rating from 0 to 6 for the total compliance of symptoms, with a combined total of 0 to 25. The higher the score, the more likely BD is to be diagnosed. The diagnosis of BD was almost excluded with results less than 6.

Hemoconcentration of neuroendocrine test

The evaluation of THs and PRL included TSH, free triiodothyronine (FT3), free thyroxine (FT4), triiodothyronine (TT3), total thyroxin (TT4), and PRL. We collected venous blood from patients meeting the above criteria at 7:00 in the next morning. An electrochemical luminescence immunoassay was carried out by the Roche Cobas e601 automatic electrochemiluminescence immunoassay system, which was provided by Shanghai lanwei clinical testing co., LTD. The above analysis system was measured as TSH (range, 0.27–4.20 mIU/L), TT3 (range, 1.3–3.1 nmol/L), TT4 (range, 66–181 nmol/L), FT3 (range, 2.8–7.1 pmol/L), FT4 (range, 12–22 pmol/L), and PRL (range, male: 86–390; female: 72–511 mIU/L).

Statistical analysis

All statistical computations were performed using IBM SPSS Statistics Version 18.0 for windows (Chicago Inc, USA). All measurement data were inspected for normality by Kolmogorov-Smirov tests. Normal distribution metering data was represented as mean (standard deviation (SD)) while skewed distribution measurement data was represented as medians and quartiles. A *Chi-square* test was conducted to analyze demographic data. An independent sample *T*-tests was used for age, BSDS, and YMRS evaluation. Excluding TSH, covariance analysis was used for THs, with age set as the covariance. Two sample *rank sum* tests were used for TSH and PRL between groups. Linear regression and curve estimation were conducted to make correlation analysis of TSH and PRL in each group. All statistical analyses were defined as two-tailed *p* values, significance level of 5% ($\alpha = 0.05$). Bonferroni corrections for multiple comparisons were applied, and the level was $\alpha = \alpha'/c$, c (number of pairwise comparisons) = $(k(k-1)/2)$ [23].

Results

Demographic characteristics

There was no difference in age between the two groups ($p > 0.05$). Higher BSDS in BD-mania was observed compared to HC, as well as gender subgroups ($p's < 0.01$). See Table 1.

Table 1
Demographic characteristics of patients with BD-mania and HC

	BD-mania (*n* = 70)	HC (*n* = 70)	*t value*	*p*
Age (y)	24.3 (5.1)	24.7 (4.3)	0.52	0.60
Male	24.9 (5.5)	25.3 (4.7)	0.38	0.71
Female	23.7 (4.7)	24.1 (3.8)	0.36	0.72
Length of illness (m)	8.3 (3.9)	/	/	/
BSDS total	17.9 (2.6)	2.3 (1.3)	44.71	< 0.01
Male	17.8 (2.3)	2.5 (1.2)	34.13	< 0.01
Female	18.1 (2.9)	2.1 (1.4)	29.59	< 0.01
YMRS total	28.2 (3.4)	/	/	/

BD-mania, Bipolar disorder in mania state; HC, Healthy control; BSDS, Bipolar Spectrum Diagnostic Scale; YMRS, Young Manic Rating Scale; SD, standard deviation.

Within the BD-mania group, we recruited 3 patients with BD-hypomania, 45 with BD-mania without psychotic symptoms, and 21 with BD-mania with psychotic symptoms. There was no significant difference in the subtypes of BD, age, length of illness, BSDS, or YMRS between the gender subgroup of BD-mania (*p's* > 0.05). See Table 2.

Table 2
Demographic comparison between genders in the BD-mania group

	BD-mania		*χ2/ t* value	*p*
	Male (*n* = 35)	Female (*n* = 35)		
Subtypes (*n,%*)	1 (2.9%)	3 (8.6%)	1.25	0.54
Hypomania	24 (68.6%)	21 (60.0%)		
Mania without PS	10 (28.5%)	11 (31.4%)		
Mania with PS				
Age (y)	24.9 (5.5)	23.7 (4.7)	0.96	0.34
Length of illness (m)	8.7 (3.5)	7.9 (4.2)	0.90	0.39
BSDS total	17.8 (2.3)	18.1 (2.9)	0.46	0.65
YMRS total	28.8 (3.8)	27.6 (2.8)	1.47	1.47

BD-mania, Bipolar disorder in mania state; HC, Healthy control; PS, psychotic symptoms; BSDS, Bipolar Spectrum Diagnostic Scale; YMRS, Young Manic Rating Scale; SD, standard deviation.

Hormone hemoconcentrations of the thyroid and PRL

Bonferroni correction for multiple comparisons was applied, the level was 0.05/3 = 0.0167. There were significant differences in TT3 ($p < 0.01$), TT4 ($p = 0.014$) and FT4 ($p < 0.01$) between the BD-mania and HC groups. After being grouped by sex, higher PRL in the male and female BD-mania subgroup were observed compared to each isosexual HC ($p's < 0.01$). Higher FT4 in the male BD-mania group was observed compared to the HC males ($p < 0.01$) while the female BD-mania group showed lower TT3 and TT4 compared to the HC females ($p's < 0.01$). See Table 3.

Table 3
The hormone hemoconcentration of HPTA and PRL in BD-mania and HC groups [mean (SD)/M (Q1,Q3)].

Valuable	Total BD ($n = 70$)	Male ($n = 70$)		Total HC ($n = 70$)	Female ($n = 70$)	
		BD ($n = 35$)	HC ($n = 35$)		BD ($n = 35$)	HC ($n = 35$)
TSH (mIU/L)	1.88 (1.00,2.68)	1.70 (0.60,2.45)	1.83 (1.05,2.57)	1.78 (1.07,2.44)	1.95 (1.32,2.93)	1.77 (1.07,2.04)
FT3 (pmol/L)	4.44 (0.76)	4.75 (0.72)	4.67 (0.96)	4.42 (0.95)	4.12 (0.68)	4.17 (0.88)
FT4 (pmol/L)	18.23 (3.52)[a]	19.24 (3.49)[a]	16.29 (3.05)	16.56 (2.98)	17.22 (3.31)	16.84 (2.93)
TT3 (nmol/L)	1.56 (0.28)[a]	1.67 (0.26)	1.75 (0.24)	1.74 (0.36)	1.45 (0.24)[a]	1.72 (0.45)
TT4 (nmol/L)	102.1 (22.1)[a]	105.3 (20.7)	105.1 (20.7)	111.5 (22.9)	98.8 (23.2)[a]	118.0 (23.5)
PRL (mIU/L)	/	513.8 (188.0,597.5)[a]	243.6 (141.0,334.8)	/	616.1 (367.9,1049.0)[a]	320 (229.4,433.2)

BD, Bipolar disorder in mania state; HC, Healthy control. Compared with HC, there was statistical significance showed [a] $p < 0.0167$.

Linear regression and curve estimation for PRL and TSH in BD-mania

Linear regression was used to determine the relationship between PRL and TSH. There was no linear relationship in the male BD-mania group ($F = 0.42$, $p = 0.52$) (Fig. 2a) whereas PRL and TSH were linearly dependent in the female BD-mania group with weak correlation ($r^2 = 0.13$, $F = 4.71$, $p = 0.037$). Using a scatter diagram for correlation (TSH set as independent variable on the x-axis and PRL as the dependent variable on the y-axis), further curve estimation showed an inverse relationship between PRL and TSH in the female BD-mania group with a moderate correlation ($r^2 = 0.25$, $F = 11.11$, $p = 0.002$), the inverse function equation[24]: $y = b_0 + b_1/x$ ($b_0 = 294.5$, $b_1 = 772.0$). (Fig. 2b).

Discussion

At the endocrine glandular level, we found that patients with BD-mania had overall lower TT3 and TT4 and higher FT4 levels. After comparing the subgroups, we found that sex may be responsible for the differences. Male patients had higher FT4 levels, while female patients had lower TT3 and TT4. The increase in peripheral secreted THs leads to high risk of hyperthymia, irritability, and distractibility, thus, the increase of FT4 in the male BD-mania group was consistent with symptoms of a mania-like state[25]. The hypothyroidism theory in BD is usually explained by the compensatory mechanism of the thyroid[26]. It is important to note that the results of the female BD-mania group were inconsistent with the biological peripheral roles of T3 and T4. Although there were no differences between men and women shown in the BSDS and YMRS for the clinical diagnosis of BD[27], our data of the female BD-mania group supported the compensatory hyposecretion of TT4 in BD-mania. In addition, the decreased TT3 level may result from the simultaneous decrease in TT4 as high-functioning T3 mainly originates from the deiodination of T4. Thus both may reduce the release of TT3[28]. As a result, this negative feedback increases long term TSH secretion in the anterior pituitary[15]. This trend was seen in the female patient subgroup (1.95 mIU/L VS. 1.77 mIU/L), however it was not significant in the acute first-episode after Bonferroni correction. In the disease condition, BD-mania neuroendocrine regulation may differ among genders[29]. A previous study found that the compensatory feedback of the HPTA may decline with chronic deferment of the disease. Thus, increased FT4 and TSH becomes a comparatively steady state under chronic psychiatric stress, and the sex differences may disappear[25].

At the anterior pituitary level, there is no evident difference of TSH level in BD-mania, on the other hand, the negative feedback regulation of the anterior pituitary gland might not be established so soon in the onset of BD-mania. Özerdem et al[16] found that TSH increased more frequently in female patients and that self-regulation triggers the compensation mechanism of the thyroid gland in the disease. As previously mentioned, the classic negative feedback regulation is in contrast to the traditional biomedical model that states hyperthyroidism can lead to clinical manifestations of manic symptoms. A higher prevalence of thyroid dysfunction was found in BD, with 11.4–24.5% being above or below the RR of TSH considered for BD-mania[30]. Therefore, the current explanation hardly fits both theories. If these theories are not accepted simultaneously, then according to the monism analysis of the disease, abnormal thyroid function and BD-mania are not due to comorbidity.

In order to discuss the relationship between the differences of sex in thyroid disease and hyperprolactinemia, we needed to know whether they both significantly correlated to sex[16] [31]. We thus recruited patients aged 16 to 40 with sexual characteristics set as a confounding factor. Due to the physiological effects of PRL, sex differences were evident. Post-pubertally, the expression of growth hormone and PRL is sexually dimorphic with males exhibiting higher growth hormone levels and females higher PRL levels[32]. The aberrant increase of PRL causes side effects on the pathological lactation and menstruation of women. Additionally, thyroid-stimulating hormone level might be sensitive to changes in circulating estrogen in women and increases after an induced acute increase of estradiol with PRL, which is a classic estradiol-upregulated pituitary hormone[33]. Previous studies have indicated that women with

BD are at a higher risk for mood episodes during periods of intense hormonal fluctuation (e.g., postpartum, premenstrual, perimenopause)[34]. Profound interactions between the immune system and the HPTA exist and both immune and endocrine factors mediate neuroplastic effects[35].

Furthermore, several neuropeptides, vasoactive intestinal peptides, and TSH have been reported to stimulate the release of PRL under psychological stress. The TSH acts on the pituitary PRL cells to stimulate the expression of PRL mRNA[36], thus promoting it's synthesis and secretion, which may explain the correlation between TSH and PRL in females with BD-mania. The increase of PRL may lead to galactorrhea, sexual dysfunction, osteoporosis and other pathological changes that should be paid serious attention, particularly in women. Bromocriptine, a dopamine agonist widely used in the treatment of hyperprolactinemia may further explain elevated PRL as it blocks the dopamine channel in the tubero-infundibular system and the dopamine antagonist effects of antipsychotic drugs[37]. Studies have shown that BD does not change the sensitivity of dopamine neurons in the hypothalamus-pituitary system anomalies[5]. In our study, there might be a correlation between the increased PRL in BD-mania and the onset of manic symptoms. Therefore, a correlation study of the hormones secreted by PRL and the pituitary is expected to be a potential biomarker for clinicians to use in medical treatment.

In order to discuss the interactions of pituitary hormones, we needed to know whether anterior pituitary dysfunction effected only certain kinds of anterior pituitary cells or several kinds[38]. Theoretically, in the condition that hyposecretion of peripheral glands occurs, feedback information is transmitted to the hypothalamus, then positive or negative feedback of the hypothalamus secretes hormone releasing factors that stimulate both peripheral glands and the hypersecretion of PRL[39]. Neuroimmunology research has found that TSH interacts with PRL through tumor necrosis factor-α and interleukin-1β to affect the neural immune system[40]. Although female neural diseases of the immune system are more common, the relationship is not clear yet. A recently published systematic literature search indicated that most of the previous studies ignored the complexity and timeliness of the effects of medicine on the neuroendocrine of BD-mania[41]. Benvenga S et al [33] found that women with an estradiol-dependent increase in TSH do however exist, as do PRL-dependent increases. Based on the above theory, we attempted to make a related analysis of TSH and PRL in first-episode BD-mania. We found that PRL in female patients with BD-mania might have a weak negative and a moderate inverse relationship with TSH even when TSH secretion did not increase. Thus, we assume that the increase in both is not easily synchronized, with the loss of synchrony previously found during prolonged critical illness[42]. Aromatase expression in TSH and PRL may have a regulatory role on the synthesis and secretion of these hormones[43]. Capozzi A et al [44] indicated that BD-mania, as an acute stress reaction, together with hypothyroidism, renal failure, or interruption of hypothalamic-pituitary dopaminergic pathways are other frequent conditions of hyperprolactinemia.

Conclusions

Neuroendocrine diseases are closely associated with mental disorders. It enlightens us that future work on BD should not be limited to dual variable regression analysis[45], but to multivariate regression analysis.

Targeting pituitary dysfunctions might be a novel strategy to improve the outcomes of BD. There are several limitations in the current study. First, the medicine-naïve design was the highlight of our research. Therefore, a large sample study was compromised to ensure the homogeneity of samples. The conclusions can thus only be applied for a first-episode patient. Some confounding factors are difficult to eliminate, for instance, most clinical researches can not exclude lithium, which is a strong confounding factor of thyroid dysregulation, while the menstrual cycle may be related to PRL levels. Second, the patients came from in-patient department with medical insurance, and so the family economics and environment factors are difficult to identify, thus the research has its limitation in reflecting only the family economic status in this population. Furthermore, recruited volunteers may also have their selective bias.

Abbreviations

BD: bipolar disorder; HPTA :hypothalamus-pituitary-thyroid axis; PRL: prolactin; THs: Thyroid hormones; BDNF: brain-derived neurotrophic factor; TSH: thyroid-stimulating-hormone; ICD-10: the International Statistical Classification of Diseases and Related Health Problems, the Tenth Revision; SCMHC: Shanghai Changning Mental Health Center; M.I.N.I: the Mini-International Neuropsychiatric Interview; BSDS: Bipolar Spectrum Diagnostic Scale; YMRS: Young manic rating scale; FT3: free triiodothyronine; : FT4: free thyroxine;TT3: triiodothyronine; TT4:total thyroxine

Declarations

Ethics approval and consent to participate

Our study was based on approval by the Institutional Ethical Committee for clinical research of Shanghai Changning Mental Health Center, Shanghai, China. Written informed consent was provided according to the Declaration of Helsinki.

Consent to publish

Not applicable.

Availability of data and materials

All data mentioned in this article are available in the published article.

Competing Interests

The authors declare that they have no conflicts of interest.

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sources had no role in the design of the study, the collection, analysis and interpretation of the data, and the writing of the manuscript.

Authors' contributions

Fang Wang, Huaihui Zhang, Jun Wang, and Dongmei Zhao collected the data. Yuncheng Zhu designed the study, performed the analysis, interpreted the data and wrote the manuscript. All authors read and approved the final manuscript.

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Figures

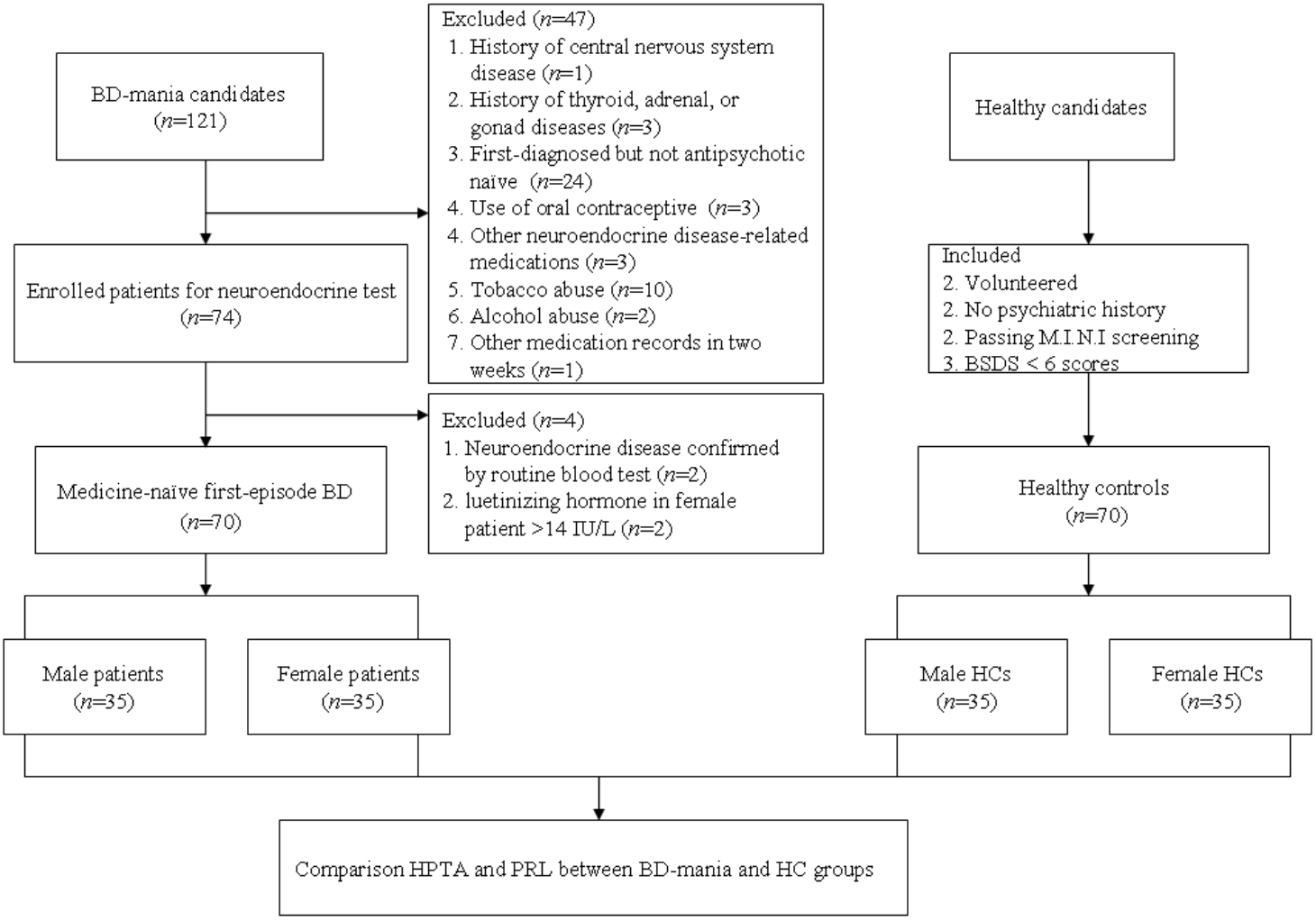

Figure 1

Flowchart of screening process and data classification

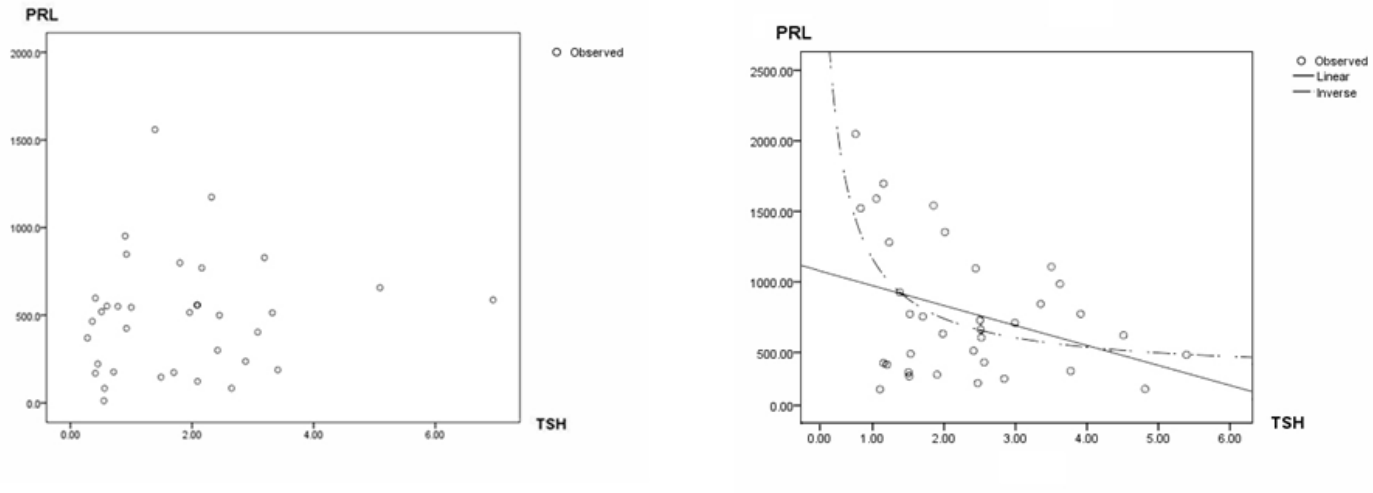

Figure 2

a. The scatter plot of TSH and PRL in male patients with BD-mania. b. The linear regression and curve estimation for TSH and PRL in female patients with BD-mania.