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Pituitary gland shrinkage in bipolar disorder: The role of gender

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ABSTRACT

Background: Hyperactivity of the Hypothalamic-Pituitary-Adrenal Axis (HPAA) has been consistently reported in mood disorders. However, only few studies investigated the Pituitary gland (PG) in Bipolar Disorder (BD) and the results are so far contrasting. Therefore, the aim of this study is to explore the integrity of the PG as well as the role of gender and the impact of clinical measurements on this structure in a sample of BD patients compared to healthy controls (HC).

Methods: 34 BD patients and 41 HC underwent a 1.5 T MRI scan. PG volumes were manually traced for all subjects. Psychiatric symptoms were assessed by means of the Brief Psychiatry Rating Scale, the Hamilton Depression Rating Scale and the Bech Rafaelsen Mania Rating Scale.

Results: We found decreased PG volumes in BD patients compared to HC ($F = 24.9$, $p < 0.001$). Interestingly, after dividing the sample by gender, a significant PG volume decrease was detected only in female BD patients compared to female HC ($F = 9.1$, $p < 0.001$), but not in male BD compared to male HC ($F = -0.12$, $p = 0.074$). No significant correlations were observed between PG volumes and clinical variables.

Conclusions: Our findings suggest that BD patients have decreased PG volumes, probably due to the long-term hyperactivity of the HPAA and to the consequent strengthening of the negative feedback control towards the PG volume itself. This alteration was particularly evident in females, suggesting a role of gender in affecting PG volumes in BD. Finally, the absence of significant correlations between PG volumes and clinical variables further supports that PG disruption is a trait feature of BD, being independent of symptoms severity and duration of treatment.

1. Introduction

Bipolar disorder (BD) is a neurobiological disorder characterized by the alternation of manic/hypomanic episodes with depressive ones, interspersed with euthymic phases [1]. In the last two decades, several Magnetic Resonance Imaging (MRI) studies investigated the neurobiological substrates of BD in order to identify putative neurobiological markers of this disabling illness [2,3]. In this regard, although it has been consistently suggested the presence of gray matter (GM) volume reductions within the prefronto-temporo-limbic network [4–6], the volumetric investigation of the hypothalamo-pituitary-adrenal axis (HPAA) components in BD is still under-examined. The HPAA is the main neuroendocrine system involved in the response to stress factors [7] and it has been consistently found to be disrupted in BD [8–10]. Specifically for the Pituitary Gland (PG), it has been shown that this structure plays a crucial role by modulating behavioural responses and by promoting neuroplasticity and neurogenesis, which can influence cognitive and mood functions [11].

Therefore, MRI investigations have driven their attention towards the investigation of PG integrity in order to identify its potential role in the pathophysiology of BD. However, over the last years, only a handful of MRI studies investigated PG volumes in BD and the results are still far

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to be conclusive [12]. Indeed, although the majority of these studies showed that BD patients had larger PG volumes [13–17], some others found a reduction [18] or no differences [19–21].

Interestingly, Clark et al. [17] recently performed a meta-analysis, which included nine studies and reached a final sample of 552 subjects ($N = 244$ BD patients and $N = 308$ HC) [17]. The results seem to point towards the hypothesis that a small increase in PG volumes might be a putative biomarker of BD [17]. However, although the authors demonstrated the presence of larger PG among BD subjects compared to matched HC, the effect was small and did not reach statistical significance (effect size: 0.23, CI: −0.14, 0.59) [17], therefore suggesting the need of further studies to confirm PG alterations in BD.

Furthermore, it has also been suggested that the gender could play an important role in modulating PG volumes in normal populations, with young healthy females consistently showing larger PG volumes than young healthy males [22–28]. Similarly, the same gender effect on PG volume has also been detected in subjects with Schizophrenia and in individuals at ultra-high-risk of developing psychosis [29].

Specifically for BD, although it has been reported the presence of gender-related effects on PG volumes in this disabling disorder, the direction of these effects is still conflicting [12], with some studies reporting a key role of gender on PG disruptions [18,20] and some others reporting non-significant gender impact [13,15–17,19,30].

Finally, a general consensus on the effects of chronicity on PG volumes in BD has not been reached yet. Indeed, while some studies reported a significant correlation between duration of illness and PG volume reductions [14,31–33], some others found no significant associations [18–21].

In this context, the aim of this study was to further investigate the integrity of PG volumes in BD and to provide evidence of the putative role of gender and chronicity on this structure. Considering the volumetric findings of the meta-analysis by Clark et al. [17], we expect a small increase in PG volumes in BD patients compared to HC. However, given to the limited number of investigations and to the lack of specific and univocal findings in BD and in other psychiatric disorders [34], we can only hypothesize that BD patients will show altered PG volumes compared to HC, with a potential effect of gender and duration of illness, based on the evidence that pathological modifications in hormone secretion could affect PG volumes [35].

2. Material and methods

2.1. Sample

We enrolled 34 subjects affected by BD (21 with BD type I and 13 with BD type II) according to DMS-IV-R criteria and 41 HC (see Table 1). Patients were recruited from the South-Verona psychiatric case register (PCR) [36], a community-based mental health register. Clinical diagnoses were confirmed using the Item Group Checklist of the Schedule for Clinical Assessment in Neuropsychiatry (IGC-SCAN), a semi-structured standardized checklist encompassing 41 psychopathological item groups [37], and confirmed with the clinical consensus of two staff psychiatrists. Exclusion criteria were a) any other Axis I psychiatric disorders, b) substance or alcohol abuse, c) history of lifetime traumatic head injury with loss of consciousness, and d) epilepsy or other neurological or medical diseases were excluded from the study. All subjects underwent a clinical and socio-demographical interview. Psychiatric symptoms were assessed by means of the Brief Psychiatry Rating Scale (BPRS) [38], the Hamilton Depression Rating Scale (HDRS) [39], and the Bech Rafaelsen Mania Rating Scale (BRMRS) [40]. At the time of the MRI scan, 24 BD patients were euthymic, 3 were manic and 7 were depressed.

Additionally, 13 patients were using antipsychotics ($n = 4$ first generation antipsychotics, $n = 6$ second generation antipsychotics, $n = 3$ both first and second generation antipsychotics) and 13 patients were taking mood stabilizers ($n = 7$ carbolithium, n = 3 valproate, $n = 1$ lamotrigine, n = 1 carbamazepine, n = 1 both carbolithium and valproate).

Table 1
Demographic and clinical data of the sample.

	Healthy controls ($N = 41$)	BD patients ($N = 34$)	Statistics
Age, years ± SD	48.1 ± 8.2	50.1 ± 10.8	$t = 0.9$, $P > 0.3$
Gender (M/F)	15/26	15/19	$\chi^2 = 0.4$, $P > 0.5$
Age of onset ± SD	–	33.8 ± 12.0	–
Duration of illness ± SD	–	15.5 ± 10.0	–
Illness phase		24 Euthymic 3 Manic 7 Depressed	–
Duration of AP treatment, years ± SD	–	15.6 ± 9.8	–
Medication		4 FGA 6 SGA 3 FGA + SGA 7 LIT 3 VPA 1 CAR 1 LAM 1 LIT + VPA	
BPRS total ± SD	–	30.9 ± 6.2	–
BPRS-anxiety/depression ± SD	–	9.5 ± 3.8	–
BPRS-positive symptoms ± SD	–	6.2 ± 2.3	–
BPRS-negative symptoms ± SD	–	7.9 ± 1.5	–
BPRS-mania ± SD	–	10.5 ± 1.8	–
HDRS total ± SD	–	6.6 ± 5.4	–
BRMRS total ± SD	–	2.6 ± 4.5	–

AP = Antipsychotics; BPRS = Brief Psychiatric Rating Scale; HDRS = Hamilton Depression Rating Scale; BRMRS = Bech Rafaelsen Mania Rating Scale; FGA = first generation antipsychotics; SGA = second generation antipsychotics; LIT = Carbolithium, VPA = Valproate, CAR = Carbamazepine, LAM = Lamotrigine; SD = Standard deviation.

HC were recruited through advertisements and the inclusion criteria were: no DSM-IV axis I disorders, as determined by a brief interview modified from the SCID-I for DSM-IV non-patient version (SCID I-NP) [41], no history of psychiatric disorders among first-degree relatives, alcohol or substance abuse, and no current neurological or medical illness. This research study was approved by the biomedical Ethics Committee of the Azienda Ospedaliera of Verona. All subjects provided signed informed consent, after having understood all issues involved in study participation.

2.2. MRI procedures

MRI scans were acquired with a 1.5 T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B (Siemens, Erlangen, Germany). A standard head coil was used for RF transmission and reception of the MR signal and restraining foam pads were used to minimize head motion. Initially, exploratory T1-weighted images (TR =450 ms, TE = 14 ms, flip angle = 90°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 192 × 256) were obtained to verify the subject's head position and the quality of the image. A sequence of DP/T2-weighted images were then obtained (TR = 2620 ms, TE = 24/121 ms, flip angle = 180°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 205 × 256) according to an axial plane parallel to the anterior–posterior commissures (AC–PC), in order to exclude focal lesions. Subsequently, a coronal 3D MPR sequence was acquired (TR = 2140 ms, TE = 3.9 ms, flip angle = 15°, FOV = 176 × 235, slice thickness = 1.25 mm, matrix size = 270 × 512 with interpolation, TI = 1100) to obtain 144 images covering the entire brain.

2.3. PG measurements

A trained evaluator blind to subjects' assignment to group and identity was enrolled to measure PG volume by tracing it in reference to standard brain atlases [42,43]. Two evaluators established the inter-rater reliability by tracing 10 training scans (intra-class correlation coefficient = 0.95). PG volumes were measured in cm^3 and calculated through multiplication of the measured areas by the slice thickness