Journal of Affective Disorders 169 (2014) 197–202

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research report

Pituitary gland volumes in bipolar disorder

Ian A. Clark, Clare E. Mackay, Guy M. Goodwin *

University Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, United Kingdom

ARTICLE INFO

Article history:
Received 7 April 2014
Received in revised form
8 August 2014
Accepted 13 August 2014
Available online 23 August 2014

Keywords:
Pituitary gland
Bipolar disorder
Mood disorder
Cortisol
Stress

ABSTRACT

Background: Bipolar disorder has been associated with increased Hypothalamic–Pituitary–Adrenal axis function. The mechanism is not well understood, but there may be associated increases in pituitary gland volume (PGV) and these small increases may be functionally significant. However, research investigating PGV in bipolar disorder reports mixed results. The aim of the current study was twofold. First, to assess PGV in two novel samples of patients with bipolar disorder and matched healthy controls. Second, to perform a meta-analysis comparing PGV across a larger sample of patients and matched controls.
Methods: Sample 1 consisted of 23 established patients and 32 matched controls. Sample 2 consisted of 39 medication-naïve patients and 42 matched controls. PGV was measured on structural MRI scans. Seven further studies were identified comparing PGV between patients and matched controls (total *n*; 244 patients, 308 controls).
Results: Both novel samples showed a small (approximately 20 mm^3 or 4%), but non-significant, increase in PGV in patients. Combining the two novel samples showed a significant association of age and PGV. Meta-analysis showed a trend towards a larger pituitary gland in patients (effect size: .23, CI: −.14, .59).
Limitations: While results suggest a possible small difference in pituitary gland volume between patients and matched controls, larger mega-analyses with sample sizes greater even than those used in the current meta-analysis are still required.
Conclusions: There is a small but potentially functionally significant increase in PGV in patients with bipolar disorder compared to controls. Results demonstrate the difficulty of finding potentially important but small effects in functional brain disorders.

1. Introduction

Hypercortisolaemia is commonly observed in a range of psychiatric conditions and especially in mood disorders. In bipolar disorder, hypercortisolaemia has been reported in both manic and depressive episodes (Cervantes et al., 2001) and there is evidence of functional disruption of the Hypothalamic–Pituitary–Adrenal (HPA) axis during euthymia (Watson et al., 2004). While the importance of cortisol dysregulation is not established it may explain some of the long term sequelae of mood disorder like loss of grey matter (Arnone et al., 2009; Ellison-Wright and Bullmore, 2010; Selvaraj et al., 2012) and enduring cognitive impairment (Bourne et al., 2013). The mechanism underlying increased cortisol secretion in mood disorder is uncertain. One suggestion is that it arises from increased pituitary function (i.e. secretion of somatotrophin or ACTH) and is associated with objectively increased pituitary volume (e.g. Axelson et al., 1992; MacMaster et al., 2008). However, animal studies on growth of cells in the anterior pituitary gland have shown that the effects of both sex hormones and adrenal steroids are complicated and will depend upon both tonic levels of hormone and their phasic increases (Nolan and Levy, 2006; Nolan et al., 1998)

However, the relatively few studies that have compared pituitary gland volume (PGV) between patients with bipolar disorder and healthy controls have suggested mixed results. Indeed, the first published study comparing PGV counterintuitively reported smaller PGV in patients with bipolar disorder (Sassi et al., 2001), while following studies have reported no difference in PGV (e.g. Cousins et al., 2010) and greater PGV (e.g. MacMaster et al., 2008). Obvious confounds like age, duration and burden of illness and medication may go some way to explaining these mixed results. However, most biological studies of this type have used sample sizes powered to detect relatively large effects. Mixed results may therefore represent the difficulty of finding small effects in studies with small samples and expected large variability in outcome measures. However, even a small increase in PGV may be highly functionally significant and controlled studies using medication naïve patients and larger samples may help to determine any differences in PGV between patients and controls.

We therefore sought, first, to assess PGV in two new samples of matched controls and patient groups, one of which was composed of young neuroleptic and mood stabilizer naïve bipolars. The

* Corresponding author. Tel.: +44 1865 226451; fax: +44 1865 793101.
E-mail address: guy.goodwin@psych.ox.ac.uk (G.M. Goodwin).

http://dx.doi.org/10.1016/j.jad.2014.08.022
0165-0327/

sample sizes were representative of those often used in biological studies, powered to detect relatively large effects. We then performed a meta-analysis using published experimental data for pituitary gland volume together with our data presented here. The results illustrate the challenge of demonstrating potentially important but small effects in functional brain disorders.

2. Method

2.1. Comparison of pituitary gland volume in two new data sets

2.1.1. Participants

Following complete description of study procedures, all participants provided written informed consent. All participants were screened at the University of Oxford's Department of Psychiatry and underwent structural imaging protocols at University of Oxford's Centre for Clinical Magnetic Resonance Research (OCMR). The study protocols were approved by the National Health Service Research Ethics Committee (NHS REC).

2.1.1.1. Sample 1: established bipolar I disorder and controls. Potential participants with a history of psychotic episodes and a primary diagnosis of bipolar disorder were identified from Oxfordshire and Berkshire Mental Healthcare Trusts. Diagnosis was confirmed using the Structured Clinical Interview for DSM-IV Disorders (SCID; First et al., 1997) for 23 patients with bipolar disorder; all patients were taking antipsychotic and/or mood regulating medication.

Thirty-two healthy age and sex matched controls were recruited by advertisement from the general population and were screened for psychiatric disorder using the SCID. Exclusion criteria for all participants were history of head injury or any neurological condition, substance abuse, age outside of the range 18–50 years, and English not their first language. Controls were excluded if they had any history of psychiatric disorder.

All participants were scanned at the University of Oxford Centre for Clinical Magnetic Resonance Research (OCMR) on a 1.5T Siemens Sonata system (Siemens Medical Systems, Erlangen) using an imaging protocol consisting of a coronal T1 weighted 3D structural (TR=12 ms; TE=5.6 ms, flip angle=19°; 1 mm isotropic voxels; matrix=256 × 160 × 208; 3 averages; elliptical sampling; acquisition time=15 m 42 s).

2.1.1.2. Sample 2: medication-naïve bipolar II/NOS and controls. Thirty nine unmedicated individuals with BD II/NOS (NOS=13) and 42 healthy control participants were matched on age, gender and cognitive ability. In order to ensure homogeneity across control and BD participant groups, all participants were recruited from the same population.

All participants were screened using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). This identified the formal criteria for diagnosis of bipolar disorder for participants in the BD II/NOS group. Exclusion criteria for BD II/NOS participants were: (1) any history of head injury or neurological condition; (2) other contraindication to scanning; (3) current major depressive, manic or hypomanic episodes at the time of scanning (as assessed using the MINI); (4) any current psychotropic medication; (5) any past treatment with an antipsychotic or mood stabilizer (e.g., lithium and anticonvulsants); (6) any current psychiatric disorder (with the exception of BD and anxiety disorders). Among the BD II/NOS participants, four met criteria for past alcohol abuse, two met criteria for past marijuana abuse and one met criteria for past codeine abuse and past anorexia. Two of the BD II/NOS participants reported a family history of bipolar disorder. Three of the participants in the BD II/NOS group had received previous SSRI treatment, and all had been medication-free for a minimum of 3 months prior to scanning. Control participants were excluded for: (1) any history of head injury or neurological condition; (2) other contraindication to scanning; (3) history of psychotropic medication; (4) current or past psychiatric disorder, as assessed using the MINI.

Participants were scanned using a 3T Siemens Trio system (Siemens Medical Systems, Erlangen) using an axial T1-weighted 3D structural (TR=2040 ms; TE=4.7 ms, TI=900 ms, flip angle=8°; 1 mm isotropic voxels; acquisition time=5 m 56 s), and an axial multi-slice diffusion weighted EPI (TR=9300 ms; TE=94 ms; B values=0, 1000 s/mm^2; bandwidth=1628 Hz/px; directions=60 [+0]; averages=3; 2.5 mm isotropic voxels; no. slices=50 (whole brain); acquisition time: 21 m 02 s).

2.1.2. Measurement of pituitary gland volume

The pituitary gland was measured in both samples using previously employed methodology (MacMaster et al., 2008; Sassi et al., 2001). The superior border of the pituitary gland was identified as the optic chiasm and infundibular recess of the third ventricle, while the inferior border was identified as the sphenoid sinus. The infundibular stalk was excluded, while the bright posterior pituitary was included as it is believed to represent hyperintense signals from the neurosecretory vesicles or intracellular lipids in the posterior pituitary cells, as specified by Sassi et al. (2001). The pituitary gland was located using the sagittal view and traced in coronal view. To ensure that all scans were observed in the same conditions an average intensity was taken for the MRI scan of each individual which was then used to determine the intensity of the image observed by the rater. Average intensity was obtained from MRI images that had first had the skull removed (using BET) and then undergone FAST to separate the grey matter (both tools from the FMRIB FSL library; www.fmrib.ox.ac.uk/fsl).

A single trained rater, the first author, made all measurements blind to any clinical or participant information (intra-class consistency single measure r=.91; absolute single measure r=.91).

2.2. Meta-analysis

2.2.1. Data sources

Pub Med, Scopus and Web of Knowledge databases were searched in December 2013 using the terms ("bipolar disorder"[MeSH Terms] OR ("bipolar"[All Fields] AND "disorder"[All Fields]) OR "bipolar disorder"[All Fields]) AND ("pituitary gland"[MeSH Terms] OR ("pituitary"[All Fields] AND "gland"[All Fields]) OR "pituitary gland"[All Fields]) AND "volume"[All Fields]. Titles and Abstracts were used to screen suitable articles for inclusion. The reference lists of all relevant articles were searched to identify additional suitable articles.

2.2.2. Study selection

Inclusion criteria were 1) studies measuring pituitary gland volume in patients with bipolar disorder and 2) inclusion of a healthy control group for comparison.

2.3. Data extraction

The first author examined each article for eligibility. The method and results section of each relevant article were analysed. Pituitary gland volumes (mean ± SD) were extracted for patients with bipolar disorder and matched controls. Any missing data were requested from the corresponding author of the publication.