Diagnosis of bipolar disorders and body mass index predict clustering based on similarities in cortical thickness-ENIGMA study in 2436 individuals

ENIGMA Bipolar Disorders Working Group; McWhinney, Sean R; Abé, Christoph; Alda, Martin; Benedetti, Francesco; Bøen, Erlend; Del Mar Bonnin, Caterina; Borgers, Tiana; Brosch, Katharina; Canales-Rodríguez, Erick J

Published in:
Bipolar Disorders

DOI:
10.1111/bdi.13172

Publication date:
2022

DOI: 10.1111/bdi.13172

ORIGINAL ARTICLE

BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES
WILEY

Diagnosis of bipolar disorders and body mass index predict clustering based on similarities in cortical thickness—ENIGMA study in 2436 individuals

Sean R. McWhinney[1] | Christoph Abé[2] | Martin Alda[1] | Francesco Benedetti[3,4] | Erlend Bøen[5] | Caterina del Mar Bonnin[6] | Tiana Borgers[7] | Katharina Brosch[8] | Erick J. Canales-Rodríguez[9] | Dara M. Cannon[10] | Udo Dannlowski[7] | Ana M. Diaz-Zuluaga[11] | Lorielle Dietze[1] | Torbjørn Elvsåshagen[12,13,14] | Lisa T. Eyler[15,16] | Janice M. Fullerton[17,18] | Jose M. Goikolea[6] | Janik Goltermann[7] | Dominik Grotegerd[7] | Bartholomeus C. M. Haarman[19] | Tim Hahn[7] | Fleur M. Howells[20,21] | Martin Ingvar[2] | Tilo T. J. Kircher[8] | Axel Krug[8,22] | Rayus T. Kuplicki[23] | Mikael Landén[24,25] | Hannah Lemke[7] | Benny Liberg[2] | Carlos Lopez-Jaramillo[11] | Ulrik F. Malt[5,26] | Fiona M. Martyn[10] | Elena Mazza[3,4] | Colm McDonald[10] | Genevieve McPhilemy[10] | Sandra Meier[1] | Susanne Meinert[7] | Tina Meller[8,27] | Elisa M. T. Melloni[3,4] | Philip B. Mitchell[28] | Leila Nabulsi[10] | Igor Nenadic[8] | Nils Opel[7] | Roel A. Ophoff[29,30] | Bronwyn J. Overs[17] | Julia-Katharina Pfarr[8] | Julian A. Pineda-Zapata[31] | Edith Pomarol-Clotet[9] | Joaquim Raduà[2,6,32] | Jonathan Repple[7] | Maike Richter[7] | Kai G. Ringwald[8] | Gloria Roberts[28] | Alex Ross[1] | Raymond Salvador[9] | Jonathan Savitz[23,33] | Simon Schmitt[8,27,34] | Peter R. Schofield[17,18] | Kang Sim[35,36] | Dan J. Stein[20,21,37] | Frederike Stein[8] | Henk S. Temmingh[21] | Katharina Thiel[7] | Sophia I. Thomopoulos[38] | Neeltje E. M. van Haren[39,40] | Holly Van Gestel[1] | Cristian Vargas[11] | Eduard Vieta[6] | Annabel Vreeker[39] | Lena Waltemate[7] | Lakshmi N. Yatham[41] | Christopher R. K. Ching[38] | Ole A. Andreassen[12] | Paul M. Thompson[38] | Tomas Hajek[1,42] | for the ENIGMA Bipolar Disorders Working Group

[1]Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada

[2]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[3]Vita-Salute San Raffaele University, Milan, Italy

[4]Psychiatry and Psychobiology Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy

[5]Unit for Psychosomatics/CL Outpatient Clinic for Adults, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

[6]Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain

[7]Department of Psychiatry, University of Münster, Münster, Germany

[8]Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Marburg, Germany

[9]FIDMAG Germanes Hospitalàries Research Foundation, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain

[10]Clinical Neuroimaging Laboratory, Centre for Neuroimaging & Cognitive Genomics (NICOG), NCBES Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland Galway, Galway, Ireland

[11]Research Group in Psychiatry GIPSI, Department of Psychiatry, Faculty of Medicine, Universidad de Antioquia, Medellín, Colombia

[12]Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[13]Division of Clinical Neuroscience, Department of Neurology, Oslo University Hospital, Oslo, Norway

[14]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[15]Department of Psychiatry, University of California, San Diego, La Jolla, California, USA

[16]Desert-Pacific MIRECC, VA San Diego Healthcare, San Diego, California, USA

[17]Neuroscience Research Australia, Randwick, New South Wales, Australia

[18]School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia

[19]Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[20]Neuroscience Institute, University of Cape Town, Cape Town, South Africa

[21]Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

[22]Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany

[23]Laureate Institute for Brain Research, Tulsa, Oklahoma, USA

[24]Department of Neuroscience and Physiology, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

[25]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[26]Department of Neurology, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[27]Center for Mind, Brain and Behavior (CMBB), University of Marburg and Justus Liebig University Giessen, Marburg, Germany

[28]School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia

[29]UCLA Center for Neurobehavioral Genetics, Los Angeles, California, USA

[30]Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands

[31]Research Group, Instituto de Alta Tecnología Médica, Ayudas Diagnósticas SURA, Medellin, Colombia

[32]Institute of Psychiartry, King's College London, London, UK

[33]Oxley College of Health Sciences, The University of Tulsa, Tulsa, Oklahoma, USA

[34]Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany

[35]West Region, Institute of Mental Health, Singapore, Singapore

[36]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

[37]South African MRC Unit on Risk & Resilience in Mental Disorders, University of Cape Town, Cape Town, South Africa

[38]Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Marina del Rey, California, USA

[39]Department of Child and Adolescent Psychiatry and Psychology, Erasmus University Medical Center, Rotterdam, The Netherlands

[40]Department of Psychiatry, University Medical Center Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[41]University of British Columbia, Vancouver, British Columbia, Canada

[42]National Institute of Mental Health, Klecany, Czech Republic

Correspondence
Tomas Hajek, Department of Psychiatry, Dalhousie University, QEII HSC, A.J. Lane Bldg., Room 3093, 5909 Veteran's Memorial Lane, Halifax, NS B3H 2E2, Canada.
Email: tomas.hajek@dal.ca

Funding information
NIH, Grant/Award Number: U54 EB020403; NIA, Grant/Award Number: T32AG058507; Biogen, Inc.; Swedish Research Council, Grant/Award Number: 2018-02653; Swedish Foundation for Strategic Research, Grant/Award Number: KF10-0039; Swedish Brain Foundation; Swedish Federal Government, Grant/Award Number: ALF 20170019 and ALFGBG-716801; Deutsche Forschungsgemeinschaft DFG, Grant/Award Number: FOR2107, KI 588/14-1, KI 588/14-2, DA 1151/5-1, DA 1151/5-

Abstract

Aims: Rates of obesity have reached epidemic proportions, especially among people with psychiatric disorders. While the effects of obesity on the brain are of major interest in medicine, they remain markedly under-researched in psychiatry.

Methods: We obtained body mass index (BMI) and magnetic resonance imaging-derived regional cortical thickness, surface area from 836 bipolar disorders (BD) and 1600 control individuals from 14 sites within the ENIGMA-BD Working Group. We identified regionally specific profiles of cortical thickness using K-means clustering and studied clinical characteristics associated with individual cortical profiles.

Results: We detected two clusters based on similarities among participants in cortical thickness. The lower thickness cluster (46.8% of the sample) showed thinner cortex, especially in the frontal and temporal lobes and was associated with diagnosis of BD, higher BMI, and older age. BD individuals in the low thickness cluster were more likely to have the diagnosis of bipolar disorder I and less likely to be treated with lithium. In

2, KR 3822/5-1, KR 3822/7-2, NE 2254/1-1, NE 2254/2-1, KO 4291/3-1, SFB-TRR58, HA7070/2-2, HA7070/3 and HA7070/4; Interdisciplinary Center for Clinical Research (IZKF), Grant/Award Number: Dan3/012/17, SEED11/18 and MzH 3/020/20; Health Research Board, Grant/Award Number: HRA_POR/2011/100, HRA-POR-324 and HRA_POR/2011/100; UNIVERSIDAD DE ANTIOQUIA; HOSPITAL SAN VICENTE FUNDACIÓN; Italian Ministry of Health, Grant/Award Number: RF-2011-02350980; Irish Research Council (IRC); William K. Warren Foundation; National Institute of Mental Health, Grant/Award Number: R21MH113871 and R01 MH090553; National Institute of General Medical Sciences, Grant/Award Number: P20GM121312; EU-FP7-HEALTH-222963; Singapore Bioimaging Consortium, Grant/Award Number: RP C009/2006; Australian National Health and Medical Research Council, Grant/Award Number: 1037196, 1063960 and 1066177; Lansdowne Foundation; Spanish Ministry of Science and Innovation, Grant/Award Number: PI15/00283 and PI18/00805; Fondo Europeo de Desarrollo Regional (FEDER); Instituto de Salud Carlos III; CIBER of Mental Health (CIBERSAM); Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement, Grant/Award Number: 2017 SGR 1365; Departament de Salut de la Generalitat de Catalunya, Grant/Award Number: SLT006/17/00357; Canadian Institutes of Health Research, Grant/Award Number: 103703, 106469 and 142255; Nova Scotia Health Research Foundation; Abbvie; Alkermes; Allergan; AstraZeneca; CANMAT; CIHR; Dainippon Sumitomo Pharma; Janssen; Lundbeck; Otsuka; Sunovion; Teva

contrast, clustering based on similarities in the cortical surface area was unrelated to BD or BMI and only tracked age and sex.

Conclusions: We provide evidence that both BD and obesity are associated with similar alterations in cortical thickness, but not surface area. The fact that obesity increased the chance of having low cortical thickness could explain differences in cortical measures among people with BD. The thinner cortex in individuals with higher BMI, which was additive and similar to the BD-associated alterations, may suggest that treating obesity could lower the extent of cortical thinning in BD.

KEYWORDS

bipolar disorders, body mass index, cortical thickness, heterogeneity, obesity, surface area

1 | INTRODUCTION

Bipolar disorders (BD) affect an estimated 45 million people worldwide[1] and are among the most disabling and expensive psychiatric illnesses.[2] Brain alterations are frequently reported in BD, yet the differences between BD and control individuals in brain structure are surprisingly small,[3] especially when considering the major clinical impact of the illness. Furthermore, across studies, the same neurostructural variables may be smaller, comparable, or even larger in BD relative to control individuals.[4] This clearly indicates that whereas the illness may be one source of brain imaging alterations in BD, additional extra-diagnostic factors also play a role. Medical comorbidities, which affect the brain, such as obesity, may help explain why some individuals with BD show more pronounced brain alterations than others.

Rates of obesity have grown to epidemic proportions, especially among people with psychiatric disorders. Between one-half and two-thirds of individuals with BD are overweight or obese, which is a 1.6 times greater risk of obesity relative to the general population.[5,6] The devastating effects of obesity on morbidity and life expectancy in those with psychiatric disorders are beginning to be well recognized. Much less appreciated, but equally important, are the negative effects of these medical conditions on psychiatric and brain outcomes. Long before obesity contributes to premature mortality, it may worsen psychiatric prognosis, possibly through its impact on brain structure/cognitive functioning.[7–11]

Indeed, the brain is one of the targets for obesity-related end-organ damage, long before the development of cardiovascular complications.[12] Obesity is consistently associated with lower cortical thickness in large studies[13,14] and meta-analyses.[12,15]

Obesity-related alterations tend to be most pronounced in frontal and temporal regions, where alterations are also typically observed in individuals with BD.[3] Thus, the study of metabolic comorbidities in psychiatric disorders could help us better understand the heterogeneity of findings and identify modifiable risk factors for neurobiological alterations, which may yield adverse psychiatric sequalae. Yet, few studies have investigated the interplay between obesity and brain structure in BD. These studies have suggested that obesity may be associated with brain alterations in BD, possibly with a stronger effect size or with some regional specificity compared to controls.[16–20] However, many questions remain.

As the initial studies have been relatively small (76–112 participants) and included highly selected groups, that is, first episode of mania,[16–18] adolescent BD participants,[19] or offspring of people with BD,[20] we need replications in larger, more generalizable samples. Prior findings suggested a possible interaction between obesity and BD,[16] which would be particularly concerning and highly clinically relevant. At the same time, testing for interactions requires large sample sizes. In addition, previous studies have typically separately focused on individual regions, or used mass-univariate methods of magnetic resonance imaging (MRI) data analysis, thus targeting relatively large and localized alterations.[21] Yet, brain changes in BD or obesity are characterized by patterns of subtle neurostructural changes across many regions of interest.[3,22] Clustering techniques, which target multivariate alterations distributed throughout the whole brain, require large sample size, but may better capture the neuroanatomy of complex disorders, reduce the number of comparisons and increase the effect size.[23–25] To address these issues, we jointly investigated the association between BD, body mass index (BMI), and cortical brain structure using multivariate, clustering analysis in a large, highly generalizable, international multicenter sample from the ENIGMA-BD Working Group.

2 | MATERIALS AND METHODS

2.1 | Participating sites

The ENIGMA-BD Working Group brings together researchers with brain imaging and clinical data from people with BD.[3,26,27] Fourteen site members of this group from 13 countries on six continents contributed individual subject structural MRI data, clinical information, and BMI values from a total of 836 individuals with BD and 1600 healthy controls. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Tables S1 and S2 lists the demographic/clinical details for each cohort. Table S3 provides the diagnostic instruments used to obtain diagnosis and clinical information. Table S4 lists exclusion criteria for study enrolment. Briefly, all studies used standard diagnostic instruments, including SCID ($N = 12$), MINI ($N = 1$), and DIGS ($N = 1$). Most studies ($N = 8$) included both bipolar I (BDI) and bipolar II (BDII) disorders, five studies included only BDI and one study only BDII participants. At the time of scanning, the vast majority of individuals with BD were euthymic (81%), with some depressed (15%), manic (2%), hypomanic (1%), or mixed (<1%). Substance abuse was an exclusion criterion in seven studies. Most studies did not exclude comorbidities, other than substance abuse. Consequently, the sample is a broad, ecologically valid, and generalizable representation of BD. All participating sites received approval from local ethics committees, and all participants provided written informed consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2 | MRI acquisition and processing

High-resolution T1-weighted brain anatomical MRI scans were acquired at each site, see Table S5. All groups used the same analytical protocol to derive region of interest (ROI) estimates of cortical thickness and surface area and performed the same visual and statistical quality assessment, as detailed at: http://enigma.ini.usc.edu/protocols/imaging-protocols/. These protocols are standardized across the consortium, are open-source, and available online to foster open science/replication/reproducibility. They were applied in prior publications by our group,[3,26] and more broadly in large-scale ENIGMA studies of major depression, schizophrenia, attention deficit hyperactivity disorders, obsessive-compulsive disorders, post-traumatic stress disorders, epilepsy, and autism.

Briefly, using the freely available and extensively validated FreeSurfer software, we performed segmentations of 34 cortical regions per hemisphere, based on the Desikan–Killiany atlas. Visual quality controls were performed on a ROI level aided by a visual inspection guide including pass/fail segmentation examples. We also generated diagnostic histogram plots for each site and outliers that deviated from the site mean for each structure at >3 standard deviations were flagged for further review. All ROIs failing quality inspection were withheld from subsequent analyses, see Table S6. Prior analyses from the ENIGMA-BD Working Group showed that scanner field strength, voxel volume, and the version of FreeSurfer used for segmentation did not significantly influence the effect size estimates.[22]

2.3 | Statistical analyses

Understanding neuroanatomy of BD or obesity requires multivariate approaches, which consider patterns of changes across the whole cortex first and then attempt to link these patterns to individual clinical characteristics. Accordingly, we first identified regionally specific profiles of cortical thickness using clustering analyses and subsequently studied clinical characteristics associated with individual cortical profiles.

Specifically, using the cortical thickness of all regions across both hemispheres (68 regions total), we calculated the Euclidean distance between each pair of participants as a single measure of brain dissimilarity. We a priori chose to use the K-means clustering, which is among the most common and well-established clustering techniques. We tested for up to nine clusters to identify clusters of participants within the data based on similarities in cortical thickness, and chose the best solution based on the highest average silhouette and the proportion of the total sum of squared error (SS) that is accounted for by within-cluster SS. Clustering was performed with R version 4.1.1 and the base *stats* package, which includes the K-means clustering function (kmeans). To characterize each cluster, we used linear regression to compare cortical thickness in each region between the clusters, controlling for multiple comparisons using false discovery rate-adjusted *p* values. All models also included a random effect of data collection site to control for variability between scanners. This process was repeated separately using surface area of the same regions. As in our study, these two measures are typically analyzed separately,[3] which is also more informative as changes in each measure index different processes.[28] Combining the measures would also be complicated by differences in their measurement scales and dependence on whole brain size.

Subsequently, we used logistic regression modeling to test whether the cluster could be predicted using group (BD or control), BMI as a continuous measure, while controlling for age, and sex. We also tested for an interaction between group and BMI, and only included it if significant. This same procedure was subsequently done in participants with BD using BMI as a continuous measure, age, sex, diagnosis (BD-I or BD-II), age of onset, history of psychosis (Y/N), and prescribed medications at the time of scanning (antidepressant, antipsychotic, antiepileptic, and/or lithium), coded as yes or no for each medication class separately, as in prior ENIGMA BD analyses.[27] All models also included a random effect of data collection site to control for variability between scanners. The model's receiver operating characteristic curve provided estimates of predictive accuracy, sensitivity, and specificity. We additionally controlled for total intracranial volume (ICV) in models where surface area was the dependent variable. We ensured that multicollinearity among predictors, age included, was acceptable, by calculating the variance inflation factor of all predictors. All modeling was completed using the package *lme4* (v1.1-21) in R version 3.6.2.

3 | RESULTS

This sample included 2436 participants (1600 healthy controls and 836 individuals with BD), see Table 1. Clinical and demographic associations with BMI are shown in Table S7.

3.1 | Clustering based on similarities in cortical thickness

Within the full sample, division into two clusters based on similarities in regional cortical thickness resulted in the highest average silhouette, at 0.196 (standard deviation [SD] = 0.105), indicating the

TABLE 1 Demographic, diagnostic, and treatment characteristics of sample

	Controls $N = 1600$	Cases $N = 836$	Difference
Sex—*N* (%) female	916 (57%)	483 (58%)	$\chi^2 = 0.06$, $p = 0.804$
Age—mean (SD)	35.47 (12.63)	40.57 (12.81)	$t(2433) = 7.05$, $p < 0.001$
BMI—mean (SD) [95% CI]	24.43 (4.12) [18.50; 34.63]	27.10 (5.30) [18.83; 38.72]	$t(2378) = 11.67$, $p < 0.001$
Normal weight, overweight, obese—*N* (%)	1014 (63%), 437 (27%), 149 (9%)	331 (40%), 298 (36%), 207 (25%)	$\chi^2 = 158.55$, $p < 0.001$
Diagnosis: BD-I, BD-II, BD-NOS—*N* (%)	n/a	572 (68%), 234 (28%), 5 (1%)	
Age of onset—mean (SD)	n/a	23.88 (10.64)	
History of psychosis—*N* (%)	n/a	305 (37%)	
Treatment at time of scan—*N* (%) polytherapy/*N* (%) monotherapy			
None	n/a	79 (9%)	
Lithium	n/a	373 (45%)/112 (13%)	
Antiepileptic	n/a	244 (29%)/51 (6%)	
First-gen. antipsychotic	n/a	37 (4%)/5 (1%)	
Second-gen. antipsychotic	n/a	262 (31%)/39 (5%)	
Antidepressant	n/a	225 (27%)/28 (3%)	

Abbreviations: BD, bipolar disorders; BMI, body mass index; CI, confidence interval; SD, standard deviation.

best fit of this solution to the data (Figure S1). Cluster 1 (n = 1139, 47%) consistently showed lower cortical thickness than cluster 2 (n = 1 297, 53%), in every region in both hemispheres (Figure 1), with largest differences in the frontal cortex and temporal lobes. Regional differences were highly consistent between hemisphere, with a Spearman rank-order correlation of $\rho = 0.933$ ($p < 0.001$).

3.2 | Predictors of cortical thickness

Individuals in the two clusters formed solely based on brain imaging data also differed in relevant clinical and demographic variables, see Table 2. In the whole sample, multiple regression confirmed that those in the low thickness cluster were more likely to have the diagnosis of BD, have higher BMI and were older, see Table 3. Both groups and clusters included a wide age distribution (Figure S2). There were no significant interactions between any of diagnosis, BMI, or age, see Data S1 for details. The effect of BD and BMI was additive. Specifically, the odds of belonging to the low thickness cluster were lowest in normal weight control participants, and increased in overweight control participants (odds ratio [OR] = 1.08 [0.81; 1.44]), normal weight participants with BD (OR = 1.60 [1.11; 2.31]), to the highest odds among overweight participants with BD (OR = 2.31 [1.67; 2.31]), as shown in Figure S3. There was no significant interaction between diagnosis of BD and BMI in predicting cluster ($Z = 0.21$, $p = 0.831$).

Among individuals with BD, those in the low-thickness cluster were more likely to have the diagnosis of BDI as opposed to BDII, and were less likely to be treated with lithium. Treatment with antipsychotic, antiepileptic, or antidepressant medications, age of onset, and history of psychosis were not significant predictors of cluster, see Table 3.

3.3 | Clustering based on similarities in surface area

As with cortical thickness, similarities in regional surface area also yielded two clusters, with an average silhouette of 0.305 (SD = 0.142). Cluster 1 (n = 1590) showed significantly lower surface area in each region when compared with cluster 2 (n = 846). Regional effect sizes for between-cluster differences in surface area are shown in Figure S4.

3.4 | Predictors of surface area

In the whole sample, participants in the low surface area cluster were more likely to be older, and female, see Table 4. Diagnosis of BD or BMI were both unrelated to cluster assignment. There were no significant interactions between any of diagnosis, BMI, or age, see Data S1 for details. Within those with BD only, while controlling for age, BMI, sex, and ICV, cluster was not significantly associated with diagnosis (BDI or BDII), treatment at the time of scanning, age of onset, or history of psychosis, see Table 4.

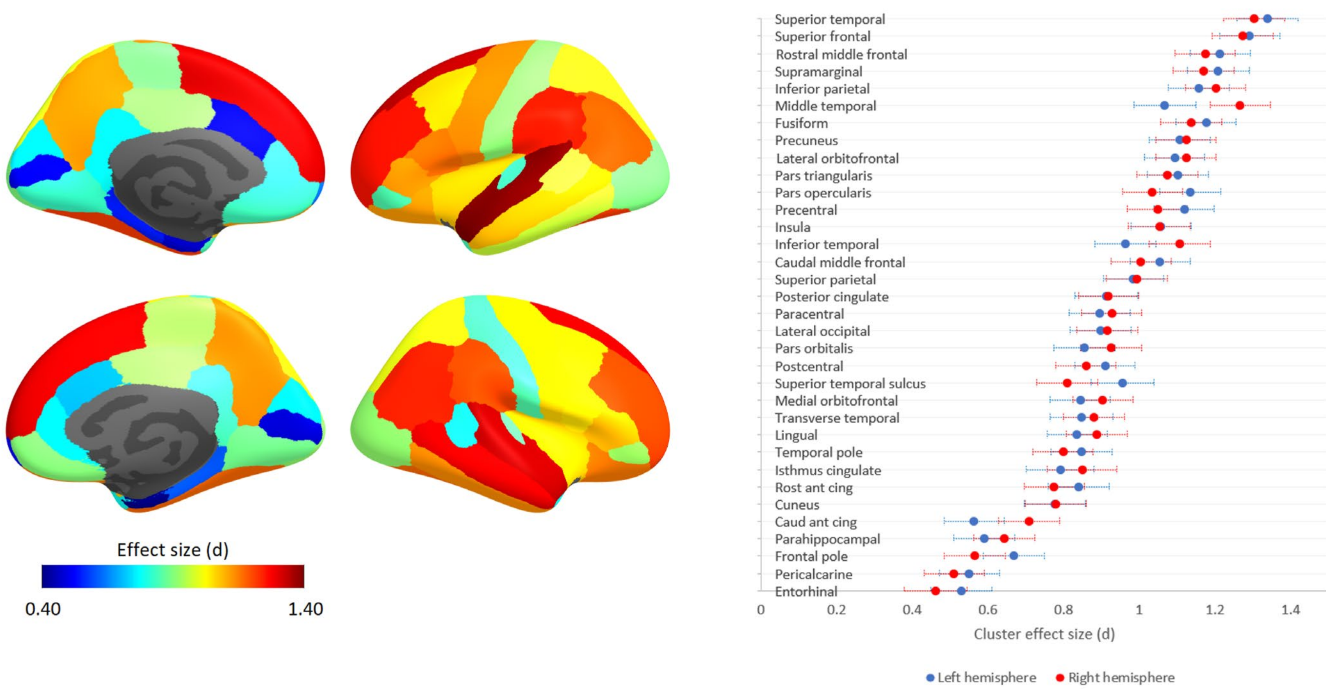

FIGURE 1 Effect size (d) of cortical thickness differences between clusters in each brain region

TABLE 2 Demographic, diagnostic, and treatment characteristics of each cluster

	Low thickness N = 1139	High thickness N = 1297	Difference
Patients—N (%)	458 (40%)	378 (29%)	$\chi^2 = 32.46$, $p < 0.001$
Sex—N (%) female	612 (54%)	787 (61%)	$\chi^2 = 11.69$, $p < 0.001$
Age—mean (SD)	42.59 (12.37)	32.49 (11.46)	$t(2432) = 21.98$, $p < 0.001$
BMI—mean (SD) [95% CI]	26.10 (4.80) [18.82; 37.92]	24.68 (4.57) [18.36; 36.58]	$t(2164) = 7.19$, $p < 0.001$
Normal weight, overweight, obese—N (%)	541 (47%), 396 (35%), 202 (18%)	804 (62%), 339 (26%), 154 (12%)	$\chi^2 = 52.29$, $p < 0.001$
Diagnosis: BD-I, BD-II, BD-NOS—N (%)	329 (72%), 102 (22%), 3 (1%)	243 (64%), 132 (35%), 2 (1%)	$\chi^2 = 13.03$, $p = 0.002$
Age of onset—mean (SD)	26.77 (10.94)	20.32 (9.08)	$t(674) = 5.38$, $p < 0.001$
History of psychosis—N (%)	170 (37%)	135 (36%)	$Z = 1.09$, $p = 0.274$
Treatment at time of scan—N (%)			
None	36 (8%)	43 (11%)	$\chi^2 = 26.41$, $p < 0.001$
Lithium	190 (41%)	183 (48%)	
Antiepileptic	137 (30%)	107 (28%)	
First-generation antipsychotic	31 (7%)	6 (2%)	
Second-generation antipsychotic	164 (36%)	98 (26%)	
Antidepressant	112 (24%)	113 (30%)	

Abbreviations: BD, bipolar disorders; BMI, body mass index; CI, confidence interval; SD, standard deviation.

TABLE 3 Model estimates for associations between demographic, clinical, and treatment characteristics and being assigned to the lower cortical thickness cluster

Sample	Predictor	Estimate (SE)	Odds ratio	95% CI
Full sample[a]	Age (Quartile)	1.42 (0.08)	4.13	3.50–4.88[c]
	BD diagnosis	0.61 (0.13)	1.83	1.41–2.39[c]
	BMI (Quartile)	0.23 (0.11)	1.25	1.01–1.55[c]
	Sex (F)	−0.21 (0.11)	0.81	0.65–1.01
BD only[b]	Age (Quartile)	1.53 (0.23)	4.64	2.95–7.29[c]
	Diagnosis (BDI)	1.05 (0.52)	2.87	1.04–7.90[c]
	Antipsychotic	0.41 (0.29)	1.51	0.85–2.67
	Antiepileptic	0.25 (0.32)	1.28	0.69–2.38
	Age of onset	0.00 (0.02)	0.99	0.97–1.03
	BMI (Quartile)	−0.06 (0.23)	0.94	0.60–1.47
	Sex (F)	−0.12 (0.26)	0.89	0.53–1.48
	History of psychosis	−0.15 (0.35)	0.86	0.43–1.72
	Antidepressant	−0.52 (0.29)	0.59	0.34–1.05
	Lithium	−0.58 (0.29)	0.56	0.31–0.99[c]

Abbreviations: AUC, area under the curve; BD, bipolar disorders; BDI, bipolar disorder I; BMI, body mass index; CI, confidence interval; ROC, receiver operating characteristic; SE, standard error.

[a]ROC AUC = 0.892 (sensitivity 0.773, specificity 0.856), $\chi^2 = 432.08$, df = 4, $p < 0.001$.

[b]ROC AUC = 0.888 (sensitivity 0.750, specificity 0.882), $\chi^2 = 80.16$, df = 10, $p < 0.001$.

[c]Terms with odds ratios that significantly differ from 1.0 (95% confidence interval).

TABLE 4 Model estimates for associations between demographic, clinical and treatment characteristics and being assigned to the lower cortical surface area cluster

Sample	Predictor	Estimate (SE)	Odds ratio	95% CI
Full sample[a]	Age (Quartile)	0.73 (0.10)	2.07	1.72–2.50[c]
	Sex (F)	0.58 (0.14)	1.8	1.37–2.36[c]
	BMI (Quartile)	−0.11 (0.13)	0.9	0.70–1.77
	BD diagnosis	0.27 (0.15)	0.84	0.32–2.23
BD only[b]	Age (Quartile)	1.23 (0.27)	3.41	2.01–5.78[c]
	Sex (F)	1.17 (0.33)	3.22	1.67–6.21[c]
	Antipsychotic	0.46 (0.34)	1.59	0.81–3.10
	History of psychosis	0.12 (0.40)	1.13	0.51–2.50
	Antidepressant	0.00 (0.33)	1.00	0.52–1.92
	BMI (Quartile)	−0.01 (0.27)	0.99	0.58–1.68
	Age of onset	−0.01 (0.02)	0.99	0.95–1.02
	Diagnosis (BDI)	−0.04 (0.53)	0.96	0.34–2.71
	Antiepileptic	−0.11 (0.35)	0.89	0.44–1.80
	Lithium	−0.46 (0.34)	0.63	0.32–1.24

Abbreviations: AUC, area under the curve; BD, bipolar disorders; BDI, bipolar disorder I; BMI, body mass index; CI, confidence interval; ROC, receiver operating characteristic; SE, standard error.

[a]ROC AUC = 0.921 (sensitivity 0.823, specificity 0.872), $\chi^2 = 1373.20$, df = 4, $p < 0.001$.

[b]ROC AUC = 0.930 (sensitivity 0.828, specificity 0.889), $\chi^2 = 266.23$, df = 11, $p < 0.001$.

[c]Terms with odds ratios that significantly differ from 1.0 (95% confidence interval).

4 | DISCUSSION

In this study of 2436 individuals, we detected two clusters based on similarities among participants in regional cortical thickness. The lower regional thickness cluster encompassed 46.8% of the sample and compared to the second cluster showed consistently thinner cortex especially in the frontal and temporal lobes. Importantly, the two clusters, which were identified purely based on the brain imaging data, also differed in relevant clinical and demographic variables. Specifically, individuals in the low thickness cluster were more likely to be diagnosed with BD, have higher BMI, and be older. BD individuals in the low thickness cluster were more likely to have the diagnosis of BDI as opposed to BDII and were less likely to be treated with lithium. Importantly, this large study showed no interaction between BD and BMI in their effect on cortical thickness. In contrast to the cortical thickness, clustering based on similarities in regional cortical surface area was unrelated to the diagnosis of BD or BMI and only tracked age and sex.

A purely data driven, regional brain structure-based approach, identified subgroups that differed in relevant clinical characteristics. Specifically, the low thickness cluster was characterized by the presence of BD and by higher BMI. Importantly, some controls were categorized into this low thickness cluster, together with BD individuals. These controls predominantly had higher BMI. This is in keeping with other studies showing that higher BMI is associated with lower cortical thickness.[29–32] In addition, this demonstrates similarities in cortical thickness between individuals with high BMI or BD. Indeed, the regions which most differed between the clusters, that is, frontal and temporal lobes, are also most strongly associated with BD[3] or obesity.[14,31]

Importantly, the association between BD or BMI and brain structure was additive, that is, overweight or obese individuals with BD were 2.31 times more likely than normal weight controls to be represented in the low-thickness cluster. This is in keeping with previous study in first episode of psychosis.[33] The fact that obesity increased the chance of having low regional cortical thickness could explain differences in cortical measures among people with the same diagnosis of BD. Conversely, we do not expect that this pattern is specific to BD, and the large proportion of healthy controls in both clusters suggests that BMI or other factors may influence this pattern of reduced cortical thickness, regardless of psychiatric disorder. At the same time, in this large sample, we did not find a significant interaction between BD, BMI, and brain structure. In other words, there was no specific BMI effect on brain in BD beyond what was observed in the general population. This is in keeping with other large studies in BD[30] or major depressive disorders.[31,34]

We do not know the direction or pathophysiology of the association between lower cortical thickness and obesity. It is possible that overweight/obesity caused the observed changes through a range of mechanisms, including effects of adipokines, oxidative stress, systemic inflammation, insulin resistance/diabetes,[12,35] hypertension, atherosclerosis[36,37] or dyslipidemia,[38] but also lower mobility/

fitness or sedentary lifestyle.[39] However, the reverse causality is also possible, where neurostructural alterations cause obesity, possibly through impulsivity, conditioning, or impaired homeostatic regulation. The diffuse and uniform nature of the BMI-related brain alterations may be more congruent with cortical thinning as a consequence of obesity. The negative effects of BMI on brain structure are supported by a Mendelian randomization study,[40] several longitudinal studies, demonstrating that obesity or obesity-related metabolic alterations precede and accelerate brain changes over time[18,41] and by improvement of brain indices following a successful treatment of obesity.[42–44]

This study expands our knowledge about neuroanatomy of BD. Individuals with BD had 1.83 times greater odds to be in the low than in the high-thickness cluster. Other studies have also shown a diffuse pattern of lower cortical thickness in BD relative to control individuals, possibly with a greater extent in frontal and temporal regions.[3] At the same time and perhaps most remarkably, 45% of BD individuals were categorized into the higher-thickness cluster, together with most of the controls (57%). This clearly demonstrates the heterogeneity of brain alterations in BD, where many individuals with BD have comparable cortical morphology to controls. In addition, the boundaries between neurotypical and atypical phenotypes may be less clear than we had anticipated. It also raises important questions as to why some individuals with BD resemble controls, while others show diffusely lower cortical thickness.

In this study, people treated with lithium were 1.79 times more likely to be in the high relative to the low-thickness cluster. This is very much in keeping with previous studies showing neuroprotective effects of lithium.[4,45] In contrast, individuals with BDI were 2.87 times more likely to be categorized into the lower thickness cluster. Interestingly, large previous studies[3] and meta-analyses[46] generally failed to find significant differences between individuals with BDI and BDII. Perhaps this is because previous studies focused on individual brain regions using mass univariate analyses. These univariate analyses are sensitive to large and localized alterations, but not too small, but diffuse changes. Here we used the structure of all cortical regions in a truly multivariate analysis. Our findings suggest that there are subtle, but diffuse differences between BDI and BDII in cortical thickness, which may be difficult to capture when focusing on one region at a time.

Interestingly, we also found broad differences among individuals in surface area, but these were only related to age and sex and did not track BD, BMI, or BD-related clinical factors. Alterations in surface area are less consistently reported in BD or in obesity. Indeed previous large studies also found comparable surface are in individuals with BD versus controls[3,47] and no[48] or less pronounced/inconsistent[31] associations between obesity and surface area. It is also in keeping with the evidence suggesting that cortical thickness is the more plastic of the two indices,[3] whereas surface area may be a more static marker of genetic risk[28] and further supports the hypothesis that obesity leads to cortical alterations and not vice versa. The greater plasticity of cortical thickness relative to surface area and the positive associations between Li treatment and cortical thickness,[3] may also suggest that these brain correlates of BD may be amenable to treatment.

In terms of the clinical impact, the association between BMI and diffuse cortical thinning is concerning. While we do not yet understand whether brain changes are a cause or consequence of obesity, each of these directions has important clinical implications. Obesity may represent a risk factor for neuroprogression in BD which can be modified or managed. Obesity-related cortical alterations might be preventable or even reversible through weight management by dietary, lifestyle, surgical, or pharmacological interventions.[42–44] Furthermore, the current psychiatric medications have a very limited range of pharmacodynamic properties and the number of mechanistically different medications is proportional to efficacy in managing severe, multifactorial disorders. Perhaps some anti-obesity medications could be neuroprotective and could address some of the currently difficult to treat outcomes, such as cognitive impairments, residual symptoms, and poor functioning, which have also been associated with obesity[49] or neurostructural alterations.[50] On the other hand, if certain brain alterations predispose individuals to obesity, then this pattern of brain changes could help identify individuals who are at increased risk of obesity and related medical issues. Regardless of the direction of association, knowing that obese individuals with BD are especially likely to demonstrate cortical thinning is relevant. Considering the high rates of obesity in severe mental disorders, this additive effect is concerning and emphasizes the need to improve weight monitoring and integrate psychiatric and medical management.

The advantages of this study include the large sample size (2436 individuals), which allowed us to test for interactions among relevant clinical factors and focus analyses on specific comparisons, such as BDI relative to BDII. The multivariate approach made this study more sensitive to the diffuse, but relatively small alterations, which characterize BD better than large and highly localized changes, as targeted by mass univariate approaches. These results may be considered highly generalizable, as the study participants represented a broad spectrum of BD from around the world. This study provides a novel approach to analyzing complex brain imaging data. It is particularly encouraging that the clusters, which were purely based on brain imaging data and acquired by running a single clustering technique, differed in relevant clinical/demographic variables. These results, while novel, had excellent face validity and replicated many previous findings.

This study has the following limitations. More detailed markers beyond BMI were not broadly available throughout the ENIGMA BD-working group. Waist circumference or waist-hip-ratio may show more extensive associations with gray matter than BMI, but usually in the same regions.[14] At the same time, BMI is much easier to acquire and is by far the most frequently used measure,[12,15] thus allowing for a more direct comparison with previous work. Due to confidentiality reasons related to legacy datasets, we could not access raw, whole-brain data and could not use methods, such as voxel-based morphometry. Aside from the standardization of methods, we also addressed any differences between scanners statistically by using mixed models and including site as a random factor in all analyses. While there are other approaches, this is still by far the most utilized and accepted method for dealing with site effects.[27,51] Information about medications was limited to current usage at the time of scan. The study was not designed to test the effects of medication, which would require a randomized controlled design. Therefore, the medication findings should be interpreted with caution, as medication prescriptions in clinical practice are not random. For example, clinicians may choose not to prescribe lithium to those that are overweight because of the weight gain side effect. Fat content near the MRI coil may lead to slight signal intensity changes, but the vast majority of individuals in this study were normal weight to overweight. Psychiatric and other medical comorbidities, which might not be available for all the patients enrolled, may influence the interplay between BMI, BD and neuroimaging findings. Whole-brain clustering may depend on the definition of the regions. Comparing clustering results based on different atlases is beyond the scope of this paper and would be more appropriate for a methodological journal. Similarly, future methodological studies should investigate how K-means compares with other clustering techniques. For our purposes, that is, to apply previously tested and validated methods to learn about neuroanatomy of BD and obesity, performing only a single, a priori selected clustering technique was preferable. Finally, using other neuroimaging modalities could provide further insights into the mechanisms of the BMI effect.

To conclude, we provide evidence that both BD and obesity are associated with similar regional cortical alterations, especially in the frontal and temporal cortex. Clustering based on similarities among individuals in brain imaging data, yielded two clusters, which differed in cortical thickness. Interestingly, these neuroanatomical differences closely tracked differences at the system level. Specifically, the low regional cortical thickness cluster predominantly included individuals with BD, those with higher BMI, and older age. Interestingly, a large proportion of individuals with BD were categorized into the higher regional cortical thickness cluster, together with controls, and these individuals were predominantly treated with lithium or diagnosed with BDII. In this large study, there was no interaction between BD and BMI. Clustering based on cortical surface area was unrelated to clinical variables and did not differentiate individuals with BD from controls. The diffuse effect of BMI on cortical thickness, which was additive and similar to the BD associated alterations, suggests the possibility that targeting BMI could lower the extent of cortical thinning in BD. We need prospective studies to investigate whether obesity is a modifiable risk factor for neuroprogression and related adverse clinical outcomes in BD.

ACKNOWLEDGMENTS

We gratefully acknowledge the following contributions and research funding sources that made this study possible: PT and CRKC of the Marina del Rey studies were supported by NIH grant U54 EB020403 from the Big Data to Knowledge (BD2K) Program; CRKC also acknowledges, NIA T32AG058507, and partial research support from Biogen, Inc. (Boston, USA) for work unrelated to the topic of this manuscript. The St. Göran study was supported by grants from the Swedish Research Council (2018-02653), the Swedish Foundation for Strategic Research (KF10-0039), the Swedish Brain Foundation, and the Swedish Federal Government under the LUA/ALF agreement (ALF 20170019, ALFGBG-716801). This work is also part of the German multicenter consortium “Neurobiology of Affective Disorders. A translational perspective on brain structure and function”, funded by the German Research Foundation (Deutsche Forschungsgemeinschaft DFG; Forschungsgruppe/Research Unit FOR2107). Principal investigators (PIs) with respective areas of responsibility in the FOR2107 consortium are: Work Package WP1, FOR2107 cohort and brain imaging: TK (speaker FOR2107; DFG grant numbers KI 588/14-1, KI 588/14-2), UD (co-speaker FOR2107; DA 1151/5-1, DA 1151/5-2), AK (KR 3822/5-1, KR 3822/7-2), IN (NE 2254/1-1 and NE 2254/2-1), CK (KO 4291/3-1). Further support from the German sites were provided by MNC and FOR2107-Muenster: This work was funded by the German Research Foundation (SFB-TRR58, Project C09 to UD) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/012/17 to UD and grant SEED11/18 to NO); FOR2107-Muenster: This work was supported by grants from the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant MzH 3/020/20 to TH) and the German Research Foundation (DFG grants HA7070/2-2, HA7070/3, HA7070/4 to TH). The NUIG sample was supported by the Health Research Board (HRA_POR/2011/100). The Medellin studies (GIPSI) were supported by the PRISMA UNION TEMPORAL (UNIVERSIDAD DE ANTIOQUIA/HOSPITAL SAN VICENTE FUNDACIÓN), Colciencias-INVITACIÓN 990 de 3 de agosto de 2017, Codigo 99059634. The San Raffaele site was supported by the Italian Ministry of Health RF-2011-02350980 project. This research was also supported by the Irish Research Council (IRC) Postgraduate Scholarship, Ireland awarded to LN and to GM, and by the Health Research Board (HRA-POR-324) awarded to DMC. We thank the participants and the support of the Welcome-Trust HRB Clinical Research Facility and the Centre for Advanced Medical Imaging, St. James Hospital, Dublin, Ireland. The NUIG sample was supported by the Health Research Board (HRA_POR/2011/100). JS and RTK received support from the William K. Warren Foundation National Institute of Mental Health (R21MH113871); JS also acknowledges the National Institute of General Medical Sciences (P20GM121312). This study was also funded by EU-FP7-HEALTH-222963 “MOODINFLAME” and EU-FP7-PEOPLE-286334 “PSYCHAID.” The Barcelona group would like to thank CIBERSAM (EPC) and the Instituto de Salud Carlos III (PI18/00877, and PI19/00394) for their support. This work was supported by the Singapore Bioimaging Consortium (RP C009/2006) research grant awarded to KS. The CIAM group (FMH—PI) was supported by the University Research Committee, University of Cape Town and South African funding bodies National Research Foundation and Medical Research Council; DJS from CIAM was supported by the SAMRC. The Sydney studies were supported by the Australian National Health and Medical Research Council (NHMRC) Program Grant 1037196, Project Grants 1063960 and 1066177, the Lansdowne Foundation, Good Talk and Keith Pettigrew Family; as well as the Janette Mary O’Neil Research

Fellowship to JMF. The study was also supported by NIMH grant number: R01 MH090553 (to RAO). Funding for the Oslo-Malt cohort was provided by the South Eastern Norway Regional Health Authority (2015-078), the Ebbe Frøland foundation, and a research grant from Mrs. Throne-Holst. EV acknowledges the support of the Spanish Ministry of Science and Innovation (PI15/00283, PI18/00805) integrated into the Plan Nacional de I+D+I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365), the CERCA Programme, and the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357. Lastly, this study was supported by the Canadian Institutes of Health Research (103703, 106469, and 142255), Nova Scotia Health Research Foundation, Dalhousie Clinical Research Scholarship to TH, Brain and Behavior Research Foundation (formerly NARSAD); 2007 Young Investigator and 2015 Independent Investigator Awards to TH. PMT and CRKC received a grant from Biogen, Inc., for research unrelated to this manuscript. DJS has received research grants and/or consultancy honoraria from Lundbeck and Sun. LNY has received speaking/consulting fees and/or research grants from Abbvie, Alkermes, Allergan, AstraZeneca, CANMAT, CIHR, Dainippon Sumitomo Pharma, Janssen, Lundbeck, Otsuka, Sunovion, and Teva. TE received speaker's honoraria from Lundbeck and Janssen Cilag. EV has received grants and served as consultant, advisor, or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda.

CONFLICT OF INTERESTS

The co-authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Christoph Abé https://orcid.org/0000-0002-1680-8480
Martin Alda https://orcid.org/0000-0001-9544-3944
Francesco Benedetti https://orcid.org/0000-0003-4949-856X
Erick J. Canales-Rodríguez https://orcid.org/0000-0001-6421-2633
Torbjørn Elvsåshagen https://orcid.org/0000-0001-9991-1610
Janice M. Fullerton https://orcid.org/0000-0003-4014-4490
Bartholomeus C. M. Haarman https://orcid.org/0000-0002-9006-8863
Philip B. Mitchell https://orcid.org/0000-0002-7954-5235
Igor Nenadic https://orcid.org/0000-0002-0749-7473
Bronwyn J. Overs https://orcid.org/0000-0002-7138-5556
Edith Pomarol-Clotet https://orcid.org/0000-0002-8159-8563
Joaquim Raduà https://orcid.org/0000-0003-1240-5438
Gloria Roberts https://orcid.org/0000-0002-1966-5120
Peter R. Schofield https://orcid.org/0000-0003-2967-9662
Cristian Vargas https://orcid.org/0000-0002-2621-2920
Eduard Vieta https://orcid.org/0000-0002-0548-0053
Ole A. Andreassen https://orcid.org/0000-0002-4461-3568
Tomas Hajek https://orcid.org/0000-0003-0281-8458

REFERENCES

1. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7
2. Begley CE, Annegers JF, Swann AC, et al. The lifetime cost of bipolar disorder in the US. *Pharmacoeconomics*. 2001;19(5 Pt 1):483-495.
3. Hibar DP, Westlye LT, Doan NT, et al. Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. *Mol Psychiatry*. 2018;23(4):932-942. doi:10.1038/mp.2017.73
4. Hajek T, Kopecek M, Hoschl C, Alda M. Smaller hippocampal volumes in patients with bipolar disorder are masked by exposure to lithium: a meta-analysis. *J Psychiatry Neurosci*. 2012;37(5):333-343.
5. Vancampfort D, Vansteelandt K, Correll CU, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. *Am J Psychiatry*. 2013;170(3):265-274. doi:10.1176/appi.ajp.2012.12050620
6. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry*. 2015;14(3):339-347. doi:10.1002/wps.20252
7. Calkin CV, Ruzickova M, Uher R, et al. Insulin resistance and outcome in bipolar disorder. *Br J Psychiatry*. 2015;206(1):52-57.
8. Calkin C, van de Velde C, Růžičková M, et al. Can body mass index help predict outcome in patients with bipolar disorder? *Bipolar Disord*. 2009;11(6):650-656.
9. Hajek T, Hahn M, Slaney C, et al. Rapid cycling bipolar disorders in primary and tertiary care treated patients. *Bipolar Disord*. 2008;10(4):495-502.
10. McIntyre RS, Danilewitz M, Liauw SS, et al. Bipolar disorder and metabolic syndrome: an international perspective. *J Affect Disord*. 2010;126(3):366-387.
11. Salvi V, Di Salvo G, Korčáková J, et al. Insulin resistance is associated with verbal memory impairment in bipolar disorders. *J Affect Disord*. 2020;266:610-614. doi:10.1016/j.jad.2020.01.145
12. Willette AA, Kapogiannis D. Does the brain shrink as the waist expands? *Ageing Res Rev*. 2015;20:86-97.
13. Dekkers IA, Jansen PR, Lamb HJ. Obesity, brain volume, and white matter microstructure at MRI: a cross-sectional UK Biobank Study. *Radiology*. 2019;291(3):763-771. doi:10.1148/radiol.2019181012
14. Janowitz D, Wittfeld K, Terock J, et al. Association between waist circumference and gray matter volume in 2344 individuals from two adult community-based samples. *NeuroImage*. 2015;122:149-157.
15. García-García I, Michaud A, Dadar M, et al. Neuroanatomical differences in obesity: meta-analytic findings and their validation in an independent dataset. *Int J Obes*. 2019;43(5):943-951. doi:10.1038/s41366-018-0164-4
16. Bond DJ, Lang DJ, Noronha MM, et al. The association of elevated body mass index with reduced brain volumes in first-episode mania. *Biol Psychiatry*. 2011;70(4):381-387.
17. Bond DJ, Ha TH, Lang DJ, et al. Body mass index-related regional gray and white matter volume reductions in first-episode mania patients. *Biol Psychiatry*. 2014;76(2):138-145

18. Bond DJ, Su W, Honer WG, et al. Weight gain as a predictor of frontal and temporal lobe volume loss in bipolar disorder: a prospective MRI study. *Bipolar Disord*. 2019;21(1):50-60.
19. Islam AH, Metcalfe AWS, MacIntosh BJ, Korczak DJ, Goldstein BI. Greater body mass index is associated with reduced frontal cortical volumes among adolescents with bipolar disorder. *J Psychiatry Neurosci*. 2018;43(2):120-130. doi:10.1503/jpn.170041
20. Mansur RB, McIntyre RS, Cao BO, et al. Obesity and frontal-striatal brain structures in offspring of individuals with bipolar disorder: results from the global mood and brain science initiative. *Bipolar Disord*. 2018;20(1):42-48. doi:10.1111/bdi.12559
21. Davatzikos C. Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. *NeuroImage*. 2004;23(1):17-20.
22. Hibar DP, Westlye LT, van Erp TG, et al. Subcortical volumetric abnormalities in bipolar disorder. *Mol Psychiatry*. 2016;21(12):1710-1716.
23. Reddan MC, Lindquist MA, Wager TD. Effect size estimation in neuroimaging. *JAMA Psychiatry*. 2017;74(3):207-208
24. Atluri G, Padmanabhan K, Fang G, et al. Complex biomarker discovery in neuroimaging data: finding a needle in a haystack. *Neuroimage Clin*. 2013;3:123-131.
25. Davatzikos C, Shen D, Gur RC, et al. Whole-brain morphometric study of schizophrenia revealing a spatially complex set of focal abnormalities. *Arch Gen Psychiatry*. 2005;62(11):1218-1227.
26. Nunes A, Schnack HG, Ching CRK, et al. Using structural MRI to identify bipolar disorders - 13 site machine learning study in 3020 individuals from the ENIGMA Bipolar Disorders Working Group. *Mol Psychiatry*. 2020;25(9):2130-2143. doi:10.1038/s41380-018-0228-9
27. McWhinney SR, Abé C, Alda M, et al. Association between body mass index and subcortical brain volumes in bipolar disorders–ENIGMA study in 2735 individuals. *Mol Psychiatry*. 2021. doi:10.1038/s41380-021-01098-x
28. Drobinin V, Slaney C, Garnham J, et al. Larger right inferior frontal gyrus volume and surface area in participants at genetic risk for bipolar disorders. *Psychol Med*. 2019;49(08):1308-1315. doi:10.1017/S0033291718001903
29. Caunca MR, Gardener H, Simonetto M, et al. Measures of obesity are associated with MRI markers of brain aging: the Northern Manhattan Study. *Neurology*. 2019;93(8):e791-e803. doi:10.1212/WNL.0000000000007966
30. Laurent JS, Watts R, Adise S, et al. Associations among body mass index, cortical thickness, and executive function in children. *JAMA Pediatr*. 2020;174(2):170. doi:10.1001/jamapediatrics.2019.4708
31. Opel N, Thalamuthu A, Milaneschi Y, et al. Brain structural abnormalities in obesity: relation to age, genetic risk, and common psychiatric disorders. *Mol Psychiatry*. 2021;26(9):4839-4852. doi:10.1038/s41380-020-0774-9
32. Binnewies J, Nawijn L, van Tol M-J, van der Wee NJA, Veltman DJ, Penninx BWJH. Associations between depression, lifestyle and brain structure: a longitudinal MRI study. *NeuroImage*. 2021;231:117834. doi:10.1016/j.neuroimage.2021.117834
33. Kolenic M, Franke K, Hlinka J, et al. Obesity, dyslipidemia and brain age in first-episode psychosis. *J Psychiatr Res*. 2018;99:151-158. doi:10.1016/j.jpsychires.2018.02.012
34. Cole JH, Boyle CP, Simmons A, et al. Body mass index, but not FTO genotype or major depressive disorder, influences brain structure. *Neuroscience*. 2013;252:109-117.
35. Hajek T, Calkin C, Blagdon R, Slaney C, Uher R, Alda M. Insulin resistance, diabetes mellitus, and brain structure in bipolar disorders. *Neuropsychopharmacology*. 2014;39(12):2910-2918.
36. Cox SR, Lyall DM, Ritchie SJ, et al. Associations between vascular risk factors and brain MRI indices in UK Biobank. *Eur Heart J*. 2019;40(28):2290-2300. doi:10.1093/eurheartj/ehz100
37. Goldstein BI, Baune BT, Bond DJ, et al. Call to action regarding the vascular-bipolar link: a report from the Vascular Task Force of the International Society for Bipolar Disorders. *Bipolar Disord*. 2020;22(5):440–460. doi:10.1111/bdi.12921
38. Kolenič M, Španiel F, Hlinka J, et al. Higher body-mass index and lower gray matter volumes in first episode of psychosis. *Front Psychiatry*. 2020;11. doi:10.3389/fpsyt.2020.556759
39. Zavala-Crichton JP, Esteban-Cornejo I, Solis-Urra P, et al. Association of sedentary behavior with brain structure and intelligence in children with overweight or obesity: the ActiveBrains Project. *J Clin Med*. 2020;9(4):1101. doi:10.3390/jcm9041101
40. Debette S, Wolf C, Lambert J-C, et al. Abdominal obesity and lower gray matter volume: a Mendelian randomization study. *Neurobiol Aging*. 2014;35(2):378-386.
41. McWhinney S, Kolenic M, Franke K, et al. Obesity as a risk factor for accelerated brain ageing in first-episode psychosis—a longitudinal study. *Schizophr Bull*. 2021;47(6):1772-1781. doi:10.1093/schbul/sbab064
42. Tuulari JJ, Karlsson HK, Antikainen O, et al. Bariatric surgery induces white and grey matter density recovery in the morbidly obese: a voxel-based morphometric study. *Hum Brain Mapp*. 2016;37(11):3745-3756.
43. Mueller K, Möller HE, Horstmann A, et al. Physical exercise in overweight to obese individuals induces metabolic- and neurotrophic-related structural brain plasticity. *Front Hum Neurosci*. 2015;9:372. doi:10.3389/fnhum.2015.00372
44. Shan H, Li P, Liu H, et al. Gray matter reduction related to decreased serum creatinine and increased triglyceride, hemoglobin A1C, and low-density lipoprotein in subjects with obesity. *Neuroradiology*. 2019;61(6):703-710. doi:10.1007/s00234-019-02202-3
45. Hajek T, Weiner MW. Neuroprotective effects of lithium in human brain? Food for thought. *Curr Alzheimer Res*. 2016;13(8):862-872
46. Arnone D, Cavanagh J, Gerber D, Lawrie SM, Ebmeier KP, McIntosh AM. Magnetic resonance imaging studies in bipolar disorder and schizophrenia: meta-analysis. *Br J Psychiatry*. 2009;195:194-201.
47. Madre M, Canales-Rodríguez EJ, Fuentes-Claramonte P, et al. Structural abnormality in schizophrenia versus bipolar disorder: a whole brain cortical thickness, surface area, volume and gyrification analyses. *Neuroimage Clin*. 2020;25:102131. doi:10.1016/j.nicl.2019.102131
48. Medic N, Ziauddeen H, Ersche KD, et al. Increased body mass index is associated with specific regional alterations in brain structure. *Int J Obes (Lond)*. 2016;40(7):1177-1182. doi:10.1038/ijo.2016.42
49. Hajek T, Slaney C, Garnham J, Ruzickova M, Passmore M, Alda M. Clinical correlates of current level of functioning in primary care-treated bipolar patients. *Bipolar Disord*. 2005;7:286-291.
50. Akudjedu TN, Tronchin G, McInerney S, et al. Progression of neuroanatomical abnormalities after first-episode of psychosis: a 3-year longitudinal sMRI study. *J Psychiatr Res*. 2020;130:137-151. doi:10.1016/j.jpsychires.2020.07.034
51. Thompson PM, Jahanshad N, Ching CRK, et al. ENIGMA and global neuroscience: a decade of large-scale studies of the brain in health and disease across more than 40 countries. *Transl Psychiatry*. 2020;10(1):100. doi:10.1038/s41398-020-0705-1

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: McWhinney SR, Abé C, Alda M, et al; for the ENIGMA Bipolar Disorders Working Group. Diagnosis of bipolar disorders and body mass index predict clustering based on similarities in cortical thickness—ENIGMA study in 2436 individuals. *Bipolar Disord*. 2021;00:1–12. doi:10.1111/bdi.13172