IRIS AperTO

UNIVERSITÀ DEGLI STUDI DI TORINO

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Identifying neuroanatomical signatures of anorexia nervosa: a multivariate machine learning approach

This is the author's manuscript

Original Citation:

Availability:

This version is available http://hdl.handle.net/2318/1520885 since 2015-06-23T16:10:50Z

Published version:

DOI:10.1017/S0033291715000768

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

12 October 2024

UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:
Questa è la versione dell'autore dell'opera:

Psychological Medicine 45 (13) 2015 : 2805-2812

DOI: *http://dx.doi.org/10.1017/S0033291715000768*

The definitive version is available at:
La versione definitiva è disponibile alla URL:

http://search.proquest.com/docview/1710157486?accountid=14368

Identifying neuroanatomical signatures of anorexia nervosa: a multivariate machine learning approach

L. Lavagnino[1*], F. Amianto[2], B. Mwangi[1], F. D'Agata[2], A. Spalatro[2], G. B. Zunta-Soares[1], G. Abbate Daga[2], P. Mortara[2], S. Fassino[2], J. C. Soares[1]

[1] UT Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, UT Houston Medical School, Houston, TX, USA

[2] Department of Neuroscience, AOU San Giovanni Battista, Turin, Italy

* Address for correspondence: L. Lavagnino, Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, 1941 East Road, Houston, TX 77054, USA. (Email: luca.lavagnino@uth.tmc.edu)

Abstract

Background. There are currently no neuroanatomical biomarkers of anorexia nervosa (AN) available to make clinical inferences at an individual subject level. We present results of a multivariate machine learning (ML) approach utilizing structural neuroanatomical scan data to differentiate AN patients from matched healthy controls at an individual subject level.

Method. Structural neuroimaging scans were acquired from 15 female patients with AN (age = 20, s.d. = 4 years) and 15 demographically matched female controls (age = 22, s.d. = 3 years). Neuroanatomical volumes were extracted using the FreeSurfer software and input into the Least Absolute Shrinkage and Selection Operator (LASSO) multivariate ML algorithm. LASSO was 'trained' to identify 'novel' individual subjects as either AN patients or healthy controls. Furthermore, the model estimated the probability that an individual subject belonged to the AN group based on an individual scan.

Results. The model correctly predicted 25 out of 30 subjects, translating into 83.3% accuracy (sensitivity 86.7%, specificity 80.0%) ($p < 0.001$; χ^2 test). Six neuroanatomical regions (cerebellum white matter, choroid plexus, putamen, accumbens, the diencephalon and the third ventricle) were found to be relevant in distinguishing individual AN patients from healthy controls. The predicted probabilities showed a linear relationship with drive for thinness clinical scores ($r = 0.52$, $p < 0.005$) and with body mass index (BMI) ($r = -0.45$, $p = 0.01$).

Conclusions. The model achieved a good predictive accuracy and drive for thinness showed a strong neuroanatomical signature. These results indicate that neuroimaging scans coupled with ML techniques have the potential to provide information at an individual subject level that might be relevant to clinical outcomes.

Key words: anorexia, drive for thinness, machine learning, magnetic resonance imaging.

Original Articles

Introduction

Anorexia nervosa (AN) is a potentially life-threatening eating disorder characterized by intense body dissatisfaction and a relentless pursuit of thinness, to the point of starvation. Treatments for anorexia are often ineffective (Steinhausen, 2002; Fassino & Abbate Daga, 2013; Walsh, 2013), and this makes research into the brain mechanisms that trigger and maintain the disorder critical in order to develop targeted approaches and new treatment options (Schmidt &Campbell, 2013). Several authors have investigated the presence of structural brain alterations that could be linked to the symptoms of anorexia. For example, volumetric decreases have been found in the gray matter in the cerebellum (Boghi et al. 2011; Brooks et al. 2011; Amianto et al. 2013a; Fonville et al. 2014), frontal cortex (Joos et al. 2010), anterior cingulate (Muhlau et al. 2007; Friederich et al. 2012), temporal and parietal areas (Castro-Fornieles et al. 2009; Joos et al. 2010; Gaudio et al. 2011), occipital areas (Suchan et al. 2010; Amianto et al. 2013a ; Fonville et al. 2014) and localized white matter regions (Kazlouski et al. 2011; Frank et al. 2013). In addition, total white matter (Boghi et al. 2011; Bomba et al. 2013; Fonville et al. 2014) and total gray matter (Katzman et al. 1996; Bomba et al. 2013) reductions have beenreported in some studies. In contrast, volumetric increases in specific gray matter regions (Brooks et al. 2011; Amianto et al. 2013a; Frank et al. 2013) and in cerebrospinal fluid and ventricles (Castro-Fornieles et al. 2009; Bomba et al. 2013; Fonville et al. 2014) have also been reported. However, results from these studies have not been translated into clinical practice. A major limitation has been the fact that previous studies have largely utilized univariate data analytic techniques - which compute statistical inferences at a voxel-by-voxel basis and cannot utilize multiple measurements to make predictions at an individual subject level. Consequently, in this study, we adopted a multivariate machine learning approach, which has two noticeable benefits: first, the ability to utilize multiple neuroanatomical measurements to classify or predict individual subjects; second, this method allows the researcher to select neuroanatomical measurements most relevant in predicting individual subjects through a feature reduction process (Mwangi et al. 2012). These techniques have recently been developed and applied successfully in neuroimaging research (Mwangi et al. 2012, 2014b). Notably, these techniques are usually implemented in two stages: first, neuroanatomical measurements from multiple subjects and corresponding diagnostic labels (e.g. 1 = healthy controls, 2 = anorexia) are used to 'train' a classifier. Second, the classifier accuracy (sensitivity and specificity) is evaluated using 'novel' data not utilized during the classifier 'training' stage. This process is referred to as 'cross-validation', which in this study was implemented using the 'leave-one-out' method. This entails 'training' the classifier using all subjects but one, a process which is repeated until all subjects are left out at least once and prediction results are aggregated as well as reported. These techniques have been successfully applied in multiple disorders such as major depression (Mwangi et al. 2012), bipolar disorder (Mwangi et al. 2014a), attention-deficit/hyperactivity disorder (Johnston et al. 2014) and autism (Ingalhalikar et al. 2011). Most notably, some machine learning techniques provide probabilistic outcomes at the individual subject level, which quantify the probability of a subject

having a disorder (Mwangi et al. 2014a). These probabilities may be useful clinically to guide individualized treatments (Fu & Costafreda, 2013).

In this study T1-weighted magnetic resonance imaging (MRI) scans of 15 AN patients and 15 matched healthy controls were acquired from the Center for Eating Disorders in Turin, Italy. These data have previously been reported elsewhere (Amianto et al. 2013a). Our primary aim in this study was to develop and apply a highly accurate predictive classifier able to discriminate neuroanatomical scans from AN patients and healthy controls. Specifically, the Least Absolute Shrinkage and Selection Operator (LASSO) algorithm (Tibshirani, 1996) was used. The second aim was to compute the probability of a subject of belonging in the AN group based on the subject's MRI scan and establish whether there is a relationship between individual subjects' probabilities and key symptoms of anorexia. This aim was investigated by testing the correlation of the probability with two dimensions of the Eating Disorder Inventory 2 (EDI-II) (Garner, 1991): 'drive for thinness' and 'body dissatisfaction', which express the core psychopathology of AN (Russell, 1970; Bruch, 1973; Vansteelandt et al. 2010), and with the BMI.

Method

Participants

Patients were recruited after being diagnosed with AN at their first visit at the out-patient service of the Center for Eating Disorders of the University of Turin. Matched healthy controls were recruited through local advertisements. Diagnosis was established for all subjects by a psychiatrist expert in the assessment of eating disorders using the Structured Clinical Interview for DSM-IV-TR (SCID). A further assessment for Axis II disorders was also performed with the SCID-II for DSM-IV-TR. A total of 15 AN patients (12 restricting-type, three binge-purging type) and 15 healthy controls were enrolled. Inclusion criteria were: female sex, age 16-30 years, right-handedness, no past or present neurological diseases, no psychiatric Axis I or Axis II co-morbidity for patients, no drug or alcohol abuse or dependence, no psychiatric diagnosis for controls, no past or present medication or psychotherapeutic treatment, duration or illness shorter than 2 years, BMI > 15 kg/m 2 for patients. The EDI-II (Garner, 1991) was administered to all participants. All subjects provided their written informed consent to the study. The study was approved by the Ethical Committee of the San Giovanni Battista Hospital, Turin. Statistical analyses were conducted using SPSS 20.0 (USA). Demographic and clinical group differences between patients and healthy controls were assessed with t tests.

MRI scan acquisition

Data were acquired at the Neuroscience Department, San Giovanni Battista Hospital, Turin, on a Philips Achieva1.5 T scanner (The Netherlands). T1-weighted three-dimensional turbo gradient-echo sequences (image matrix = 256 × 256; voxel size = 1 × 1 × 1 mm 3; number of slices = 190; repetition time (TR) = 7 ms; echo time (TE) = 3 ms; turbo spin echo, TFE shots = 89) were acquired with full

brain coverage and isotropic voxels. This sequence was equivalent to a magnetic prepared rapid acquisition gradient echo (MPRAGE). The acquisition time was approximately 5 min.

MRI scan pre-processing

All T1-weighted scans were inspected to ensure no presence of gross artefacts and subsequently preprocessed using the FreeSurfer software library (http://surfer.nmr.mgh.harvard.edu/) version 5.3.0 (Fischl, 2012). This process was achieved using an automated method which is described in detail elsewhere (Desikan et al. 2006; Rosas et al. 2010). Lastly, neuroanatomical volumes were extracted using a brain atlas of 109 anatomical regions (41 subcortical and 68 cortical) as described elsewhere (Fischl et al. 2004; Desikan et al. 2006) and tabulated in the online Supplementary material. All anatomical volumes were scaled with the total intracranial volume (ICV) and used as predictor variables or features in the ensuing machine learning analyses.

Multivariate machine learning

Predictor variables were normalized by subtracting the mean and dividing by the standard deviation. The LASSO algorithm was set up to perform a prediction task of classifying or distinguishing healthy controls from AN patients. Anatomical volumes (ICV normalized) also referred to as predictor variables or features were represented as x_{ij}. Target group membership labels (1 = healthy controls, 2 = anorexia) were represented as y_i, where i = 1, 2, 3,... N represents study subjects (healthy controls, AN) and j = 1,2,3,... M stands for the number of predictor variables (anatomical volumes - ICV normalized). Consequently, the LASSO algorithm (Tibshirani, 1996, 2011) computed a set of coefficients $(\hat{\beta})$ by minimizing the following objective function:

$$\sum_{i=1}^{N}\left(y_i - \sum_{j=1}^{M} x_{ij}\beta_j\right)^2 + \lambda \sum_{j=1}^{M} |\beta_j|$$

where λ is a parameter used to encourage model sparsity - meaning few model coefficients $(\hat{\beta})$ with non-zero weighting values and high model prediction accuracy (Tibshirani, 1996; Bunea et al. 2011; Mwangi et al. 2014b). In the present study, the λ parameter was selected through a 5-fold cross-validation using training data only and the parameter which maximized prediction accuracy was selected. The LASSO objective function was solved using the coordinate descent optimization algorithm as explored in detail elsewhere (Friedman et al. 2010). This optimization was solved using a Matlab (The Mathworks, Inc.) routine freely provided by Friedman et al. (2010). Most notably, in the current study the LASSO algorithm was preferred as compared to equivalent algorithms (e.g. ridge regression or non-regularized ridge) as it promotes 'sparsity' - meaning few model coefficients with non-zero weighting values (Bunea et al. 2011; Mwangi et al. 2014b). Sparse models are reportedly more accurate as they remove non-redundant predictor variables and are more interpretable as there are few anatomical regions to consider when interpreting the model (Mwangi et al. 2014b).

The model was 'trained' to estimate the probability of a subject belonging to the AN or the healthy control group. Importantly, the leave-one-out cross-validation (LOOCV) method as introduced below was used to train and test the models shown in Fig. 1 b. This process entailed training the model using all subjects but one and this was repeated until all subjects had been left out at least once (Johnston et al. 2013). Lastly, the validity of the model was assessed using multiple metrics such as accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under receiver operating characteristic curve (AUROC). These predictive classifier quantification metrics are explored in detail elsewhere (Mwangi et al. 2012). The model probability, which quantifies whether the subject belongs to the patient or healthy control group, was tested for correlations with the drive for thinness and body dissatisfaction scores of the EDI-II and the BMI. This calculation was performed to establish the relationship between the machine learning model probability outcome and dimensions that define the key diagnostic criteria for AN. Furthermore, partial correlations using weight as a covariate were performed, in order to assess whether the relationship between the model probability and psychopathology at an individual subject level was accounted for by BMI.

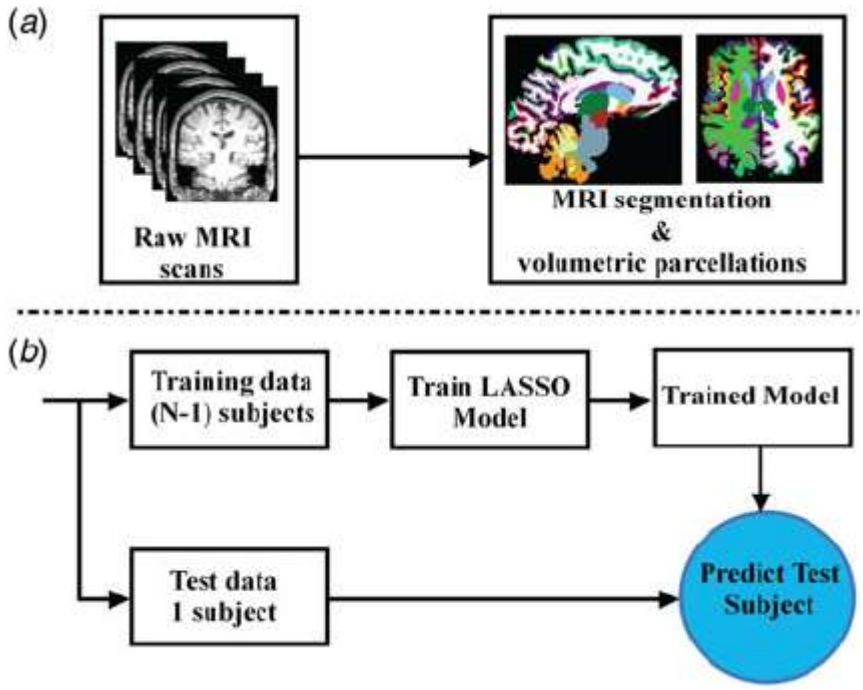

Fig. 1. Flow diagrams showing both the magnetic resonance imaging (MRI) scan during the pre-processing stage and during the model training/testing process. *(a)* Volumetric measurements were extracted using FreeSurfer software version 5.3. *(b)* A leave-one-out cross-validation process was used to separate training and testing data and the model was trained using training data only. The model was used to predict the left-out subject (circled in blue). LASSO, Least Absolute Shrinkage and Selection Operator.

Results

Table 1 summarizes the sociodemographic and clinical details of the participants. There were no significant differences between groups with regards to age. As expected, AN patients had a significantly lower weight and a higher drive for thinness. There was a trend for higher body dissatisfaction in AN patients (p = 0.061).

Table 1. Clinical and demographic characteristics and differences between means (*t test*)

	Controls (*n* = 15)	AN (*n* = 15)	*t*	*p*
Age, years	22 (3)	20 (4)	1.6	0.1
Duration of illness, months	-	13 (8)	-	-
BMI, kg/m^2	21.4 (2.4)	15.9 (1.0)	7.9	<0.001
Drive to thinness	2.3 (2.8)	12.8 (7.1)	-5.2	<0.001
Body dissatisfaction	7.9 (6.9)	12.8 (6.9)	-1.9	0.061

Data are given as mean (standard deviation).

AN, Anorexia nervosa; BMI, body mass index.

The LASSO multivariate machine learning model assigned 25 out of 30 subjects the correct label (12 AN patients and 13 controls were correctly classified). This result translated to a sensitivity of 86.7%, 80.0% specificity and overall accuracy of 83.3%. In addition, the model reported a PPV = 85.7%, NPV = 81.2%, and an AUROC of 0.796. These predictions were statistically significant ($p < 0.001$) through a χ^2 test between actual categorical labels and the model's predicted labels. Anatomical regions that were most relevant to the model predictions are shown in Fig. 2*b*. Anatomical regions that presented volumetric reductions in AN patients include white matter of the left cerebellum, and the left accumbens area. Conversely, the left choroid plexus, the right putamen, the third ventricle and the right ventral diencephalon presented volumetric increases in AN patients as compared with healthy controls as shown in Fig. 1*b*. The individual score of probability of being assigned to the group of anorectic patients showed a linear relationship with the drive for thinness scale ($r = 0.52$, $p < 0.005$) (see Fig. 3) and with BMI ($r = -0.45$, $p = 0.01$). No relationship was found with body

dissatisfaction. A partial correlation between the probability score and drive for thinness controlling for the BMI indicated a persisting trend towards a positive correlation (r = 0.35, p = 0.060).

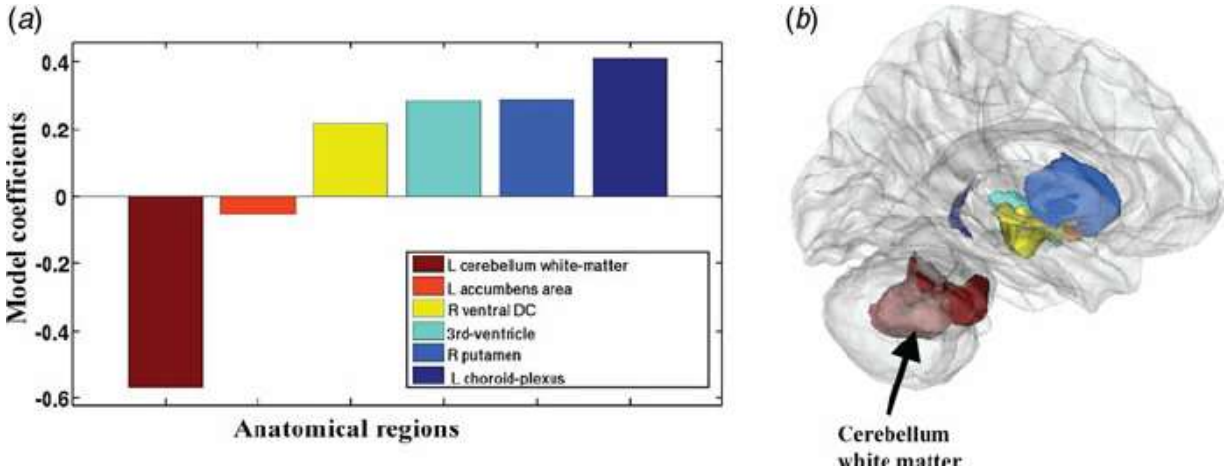

Fig. 2. *(a)* Anatomical regions that were most relevant to model predictions. The dimensions of the bars represent the β weights of the regions (= relative contribution to the model). *(b)* The same regions are shown in the brain. L, Left; R, right; DC, diencephalon.

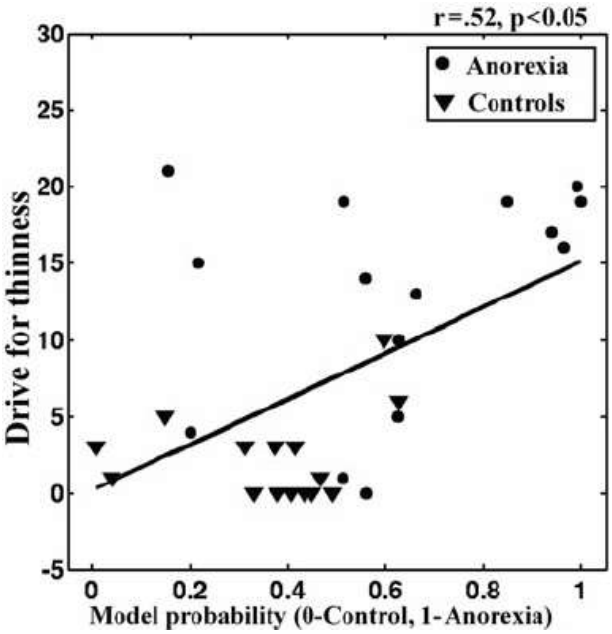

Fig. 3. Scatterplot showing the relationship between model probability and Eating Disorder Inventory 2 drive for thinness scores for patients with anorexia and controls.

Discussion

AN is a serious psychiatric disorder that affects mainly adolescent and young adult women. It is associated with medical complications (Fairburn & Harrison, 2003) and it has one of the highest mortality rates among all psychiatric disorders (Sullivan, 1995).

To the best of our knowledge, this is the first neuroimaging study utilizing a machine learning technique to predict AN diagnosis at an individual subject level. Markedly, probabilities assigned to individual subjects by the machine learning model showed a linear relationship with the drive for thinness scores and with the BMI.

Brain regions identified by the model as most relevant in classifying AN patients from healthy controls are consistent with published group-level studies and with findings of the previous study performed on this dataset: one example of this is the presence of alterations in the cerebellum.

The cerebellum is involved in feeding, behavior and emotion regulation (Schmahmann & Sherman, 1998; Zhu & Wang, 2008), and several recent studies point to alterations in the cerebellum in eating disorder patients (Boghi et al. 2011; Brooks et al. 2011; Fonville et al. 2014; Amianto et al. 2013a, b). The reduction in the white matter of the left cerebellum in particular dovetails with a recent diffusion tensor imaging study by Nagahara et al. (2014) which found lower fractional anisotropy in the white matter of the left cerebellum in anorectic patients compared with controls. However, there were also differences from previous results. Group differences that the previous voxel-based morphometry (VBM) analysis showed in this database (e.g. in the paracentral lobule and the supplementary motor area) (Amianto et al. 2013a) were not found to be relevant in distinguishing individual AN patients and healthy controls using a multivariate machine learning approach. This may be due to the process of feature selection or 'regularization' (Bunea et al. 2011; Mwangi et al. 2014b): LASSO 'prunes' (assigns zero β weight to) variables that may be 'redundant', meaning that they may not provide significant improvement to the model (Bunea et al. 2011).

The increased volume in the choroid plexus was an unanticipated result. This could be attributed to the fact that multivariate machine learning techniques may be more sensitive to volumetric patterns, as compared with conventional mass-univariate approaches (Fu & Costafreda, 2013). The choroid plexus has been implicated in recent studies as a relevant and understudied area of investigation in psychiatry (Sathyanesan et al. 2012; Turner et al. 2014). Sathyanesan et al. (2012) showed that chronic stress alters the expression of several genes and down-regulates 5HT2C receptors in the choroid plexus; the authors suggest that these mechanisms play a role in stress-induced decrease in glucose intake in rats. Alterations of serotonergic circuits and the effects of stress are thought to be involved in the neurobiology of AN (Kaye et al. 2013). Another study in rats showed that the stimulation of melanocortin receptors in circumventricular organs, among which the choroid plexus, has potent inhibitory effects on food intake (Trivedi et al. 2003). Further investigation of this anatomical region in anorexia is warranted. Lastly, the putamen and accumbens are regions involved in reward processing and alterations in the reward system have been repeatedly reported in this patient

population (Frank, 2013; Frank et al. 2013; Titova et al. 2013). In addition, ventricular enlargement confirms previous studies (Swayze et al. 2003; Fonville et al. 2014).

Some structural alterations reported in AN are thought to be related to stage of illness (e.g. early versus chronic), lowest illness-related attained BMI and current BMI status (as can be expected since low BMI is a criterion for AN diagnosis) (Roberto et al. 2011; Fonville et al. 2014; Fuglset et al. 2015; King et al. 2015). Consequently, it is unclear whether the pattern identified by the model expresses trait or state features of the illness. However, the patient population of this study is characterized by a short duration of illness; therefore our findings are not likely to be due to effects of prolonged/chronic illness. A longitudinal study is currently underway with the aim of investigating structural changes related to BMI increase after treatment as well as testing whether individual differences in the model probability among AN patients at the time of diagnosis will predict course of illness and response to treatment.

The relationship between the model probability and drive for thinness and BMI shows that the model is able to capture relevant dimensions of AN at an individual subject level. The partial correlation between the probability score and drive for thinness was close to significance after controlling for BMI ($r = 0.35$, $p = 0.06$). Therefore, it is plausible that the relationship between the model probability and the psychological dimension of drive for thinness is independent of weight. Noticeably, the two subjects in the healthy comparison group that were misclassified by the model as anorectics had the highest drive for thinness scores among healthy controls (10 and 6, respectively), and their BMIs were within normal limits. These findings support current efforts to integrate dimensional models to the categorical diagnostic systems in use with the aim of elucidating underlying neurobiological mechanisms (Cuthbert, 2014).

The model's selection of the choroid plexus was unexpected and the accuracy, sensitivity and specificity dropped to 57, 53 and 60%, respectively, after removing this region from the model. This finding suggests that drive for thinness might be encoded within a distributed network of brain regions, which makes a multivariate data analysis approach most appropriate as compared with a univariate approach.

Neuroimaging research in eating disorders has substantially increased in the last few years (Eddy & Rauch, 2011), but it has so far failed to have an impact on clinical practice. The identification of neuroimaging-based biomarkers for anorexia could present significant potential for clinical translation: individually targeted treatments, a more accurate individual prognosis and the prediction of clinical response to treatment are paramount to find new approaches in treatment of eating disorders and improve outcomes (Schmidt & Campbell, 2013). An example of a possible application could be to use neuroanatomical indicators of a more severe illness to initiate more intensive or combined therapies at an earlier stage (Fu & Costafreda, 2013). Techniques like LASSO that provide significant information at an individual level are ideally suited to provide an added value to clinical management and decision making.

Some limitations of this study must be noted. Our sample of AN patients were mostly restricting AN subjects (AN-R), with three binge-purging AN subjects (AN-BP). Although this might have introduced some degree of inhomogeneity in the sample, the presence of substantial differences between AN-R and AN-BP is still debated. These two subtypes might reflect variations on a continuum instead of distinct categories (Murphy et al. 2010; Olatunji et al. 2012). The small sample size is also a limitation. Some of our results (i.e. the choroid plexus contributing to the model) have not previously been reported in the literature and require replication. However, the sample of AN patients recruited for this study has several desirable features, among which the absence of relevant psychiatric co-morbidities, no psychopharmacological or psychotherapeutic previous treatment, and a short illness duration, that allowed us to exclude the effects of chronic illness in interpreting the results. Also, strong points of the study are the use of FreeSurfer to implement an automated well-validated procedure (Fischl et al. 2004, 2009; Fischl, 2012; Cardinale et al. 2014) and the use of a multivariate machine learning approach. Future studies will consider machine learning algorithms able to account for non-linear relationships (e.g. nonlinear support vector machines) as compared with a LASSO which is linear.

In summary, we report highly accurate prediction of individual subjects with AN using T1 MRI scan data. The model presented here assigned a probability score to each individual which correlated with drive for thinness and BMI. Individual measures derived from brain structure with a machine learning approach appear promising for clinical translation: future studies should investigate the relevance of these measures for predicting illness course and response to treatment at an individual subject level, in order to make neuroimaging approaches relevant in the clinical management of anorexia.

Supplementary material

For supplementary material accompanying this paper visit:
http://dx.doi.org/10.1017/S0033291715000768

Acknowledgements

The present study was sponsored by the 'Compagnia di San Paolo' Bank Foundation with the 'Bando Neuroscienze' grant (code: 3929IT/PF2008.2242) assigned in 2009 to S.F. and F.A. and by IARPsrl generic 20BW320110719008513915033 Casale Monferrato 'Resistenza ai trattamenti nei DCA'. The study was also supported in part by the Pat Rutherford, Jr. Endowed Chair in Psychiatry (J.C.S.).

Declaration of Interest

J.C.S. has participated in research funded by Forest, Merck, BMS and GSK and has been a speaker for Pfizer and Abbott. All the other authors report no biomedical financial interests or potential conflicts of interest.

References

Amianto F, Caroppo P, D'Agata F, Spalatro A, Lavagnino L, Caglio M, Righi D, Bergui M, Abbate Daga G, Rigardetto R, Mortara P, Fassino S (2013a). Brain volumetric abnormalities in patients with anorexia and bulimia nervosa: a voxel-based morphometry study. *Psychiatry Research* 213, 210-216.

Amianto F, D'Agata F, Lavagnino L, Caroppo P, Abbate-Daga G, Righi D, Scarone S, Bergui M, Mortara P, Fassino S (2013b). Intrinsic connectivity networks within cerebellum and beyond in eating disorders. *Cerebellum* 12, 623-631.

Boghi A, Sterpone S, Sales S, D'Agata F, Bradac GB, Zullo G, Munno D (2011). In vivo evidence of global and focal brain alterations in anorexia nervosa. *Psychiatry Research* 192, 154-159.

Bomba M, Riva A, Veggo F, Grimaldi M, Morzenti S, Neri F, Nacinovich R (2013). Impact of speed and magnitude of weight loss on the development of brain trophic changes in adolescents with anorexia nervosa: a case control study. *Italian Journal of Pediatrics* 39, 14.

Brooks SJ, Barker GJ, O'Daly OG, Brammer M, Williams SC, Benedict C, Schioth HB, Treasure J, Campbell IC (2011). Restraint of appetite and reduced regional brain volumes in anorexia nervosa: a voxel-based morphometric study. *BMC Psychiatry* 11, 179.

Bruch H (1973). *Eating Disorders: Obesity, Anorexia Nervosa and the Person Within*. Basic Books: New York.

Bunea F, She Y, Ombao H, Gongvatana A, Devlin K, Cohen R (2011). Penalized least squares regression methods and applications to neuroimaging. *NeuroImage* 55, 1519-1527.

Cardinale F, Chinnici G, Bramerio M, Mai R, Sartori I, Cossu M, Lo Russo G, Castana L, Colombo N, Caborni C, De Momi E, Ferrigno G (2014). Validation of FreeSurfer-estimated brain cortical thickness: comparison with histologic measurements. *Neuroinformatics* 12, 535-542.

Castro-Fornieles J, Bargallo N, Lazaro L, Andres S, Falcon C, Plana MT, Junqué C (2009). A cross-sectional and follow-up voxel-based morphometric MRI study in adolescent anorexia nervosa. *Journal of Psychiatric Research* 43, 331-340.

Cuthbert BN (2014). The RDoC framework: facilitating transition from ICD/DSM to dimensional approaches that integrate neuroscience and psychopathology. *World Psychiatry* 13, 28-35.

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage* 31, 968-980.

Eddy KT, Rauch SL (2011). Neuroimaging in eating disorders: coming of age. *American Journal of Psychiatry* 168, 1139-1141.

Fairburn CG, Harrison PJ (2003). Eating disorders. *Lancet* 361, 407-416.10.

Fassino S, Abbate Daga G (2013). Resistance to treatment in eating disorders: a critical challenge. *BMC Psychiatry* 13, 282.

Fischl B (2012). FreeSurfer. *NeuroImage* 62, 774-781.

Fischl B, Stevens AA, Rajendran N, Yeo BT, Greve DN, Van Leemput K, Polimeni JR, Kakunoori S, Buckner RL, Pacheco J, Salat DH, Melcher J, Frosch MP, Hyman BT, Grant PE, Rosen BR, van der Kouwe AJ, Wiggins GC, Wald LL, Augustinack JC (2009). Predicting the location of entorhinal cortex from MRI. *NeuroImage* 47, 8-17.

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex* 14, 11-22.

Fonville L, Giampietro V, Williams SC, Simmons A, Tchanturia K (2014). Alterations in brain structure in adults with anorexia nervosa and the impact of illness duration. *Psychological Medicine* 44, 1965-1975.

Frank GK (2013). Altered brain reward circuits in eating disorders: chicken or egg? *Current Psychiatry Reports* 15, 396.

Frank GK, Shott ME, Hagman JO, Mittal VA (2013). Alterations in brain structures related to taste reward circuitry in ill and recovered anorexia nervosa and in bulimia nervosa. *American Journal of Psychiatry* 170, 1152-1160.

Friederich HC, Walther S, Bendszus M, Biller A, Thomann P, Zeigermann S, Katus T, Brunner R, Zastrow A, Herzog W (2012). Grey matter abnormalities within cortico-limbic-striatal circuits in acute and weight-restored anorexia nervosa patients. *NeuroImage* 59, 1106-1113.

Friedman J, Hastie T, Tibshirani R (2010). Regularization paths for generalized linear models via coordinate descent. *Journal of Statistical Software* 33, 1-22.

Fu CH, Costafreda SG (2013). Neuroimaging-based biomarkers in psychiatry: clinical opportunities of a paradigm shift. *Canadian Journal of Psychiatry* 58, 499-508.

Fuglset TS, Endestad T, Landrø NI, Rø O (2015). Brain structure alterations associated with weight changes in young females with anorexia nervosa: a case series. *Neurocase* 21, 169-177.

Garner DM (1991). *Eating Disorder Inventory-2 Professional Manual*. Psychological Assessment Resources: Odessa, FL.

Gaudio S, Nocchi F, Franchin T, Genovese E, Cannata V, Longo D, Fariello G (2011). Gray matter decrease distribution in the early stages of anorexia nervosa restrictive type in adolescents. *Psychiatry Research* 191, 24-30.

Ingalhalikar M, Parker D, Bloy L, Roberts TP, Verma R (2011). Diffusion based abnormality markers of pathology: toward learned diagnostic prediction of ASD. *NeuroImage* 57, 918-927.

Johnston BA, Mwangi B, Matthews K, Coghill D, Konrad K, Steele JD (2014). Brainstem abnormalities in attention deficit hyperactivity disorder support high accuracy individual diagnostic classification. *Human Brain Mapping* 35, 5179-5189.

Johnston BA, Mwangi B, Matthews K, Coghill D, Steele JD (2013). Predictive classification of individual magnetic resonance imaging scans from children and adolescents. *European Child and Adolescent Psychiatry* 22, 733-744.

Joos A, Kloppel S, Hartmann A, Glauche V, Tuscher O, Perlov E, Saum B, Freyer T, Zeek A , Tebartz van Elst L (2010). Voxel-based morphometry in eating disorders: correlation of psychopathology with grey matter volume. *Psychiatry Research* 182, 146-151.

Katzman DK, Lambe EK, Mikulis DJ, Ridgley JN, Goldbloom DS, Zipursky RB (1996). Cerebral gray matter and white matter volume deficits in adolescent girls with anorexia nervosa. *Journal of Pediatrics* 129, 794-803.

Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A (2013). Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. *Trends in Neuroscience* 36, 110-120.

Kazlouski D, Rollin MD, Tregellas J, Shott ME, Jappe LM, Hagman JO, Pryor T, Yang TT, Frank GK (2011). Altered fimbria-fornix white matter integrity in anorexia nervosa predicts harm avoidance. *Psychiatry Research* 192, 109-116.

King JA, Geisler D, Ritschel F, Schober I, Seidel M, Roschinski B, Soltwedel L, Zwipp J, Pfuhl G, Marxen M, Roessner V, Ehrlich S (2015). Global cortical thinning in acute anorexia nervosa normalizes following long-term weight restoration. *Biological Psychiatry* 77, 624-632.

Muhlau M, Gaser C, Ilg R, Conrad B, Leibl C, Cebulla MH, Backmund H, Gerlinghoff M, Lommer P, Schnebel A, Wohlschläger AM, Zimmer C, Nunnemann S (2007). Gray matter decrease of the anterior cingulate cortex in anorexia nervosa. *American Journal of Psychiatry* 164, 1850-1857.

Murphy R, Straebler S, Cooper Z, Fairburn CG (2010). Cognitive behavioral therapy for eating disorders. *Psychiatric Clinics of North America* 33, 611-627.

Mwangi B, Ebmeier KP, Matthews K, Steele JD (2012). Multi-centre diagnostic classification of individual structural neuroimaging scans from patients with major depressive disorder. *Brain* 135, 1508-1521.

Mwangi B, Spiker D, Zunta-Soares GB, Soares JC (2014a). Prediction of pediatric bipolar disorder using neuroanatomical signatures of the amygdala. *Bipolar Disorders* 16, 713-721.

Mwangi B, Tian TS, Soares JC (2014b). A review of feature reduction techniques in neuroimaging. *Neuroinformatics* 12, 229-244.

Nagahara Y, Nakamae T, Nishizawa S, Mizuhara Y, Moritoki Y, Wada Y, Sakai Y, Yamashita T, Narumoto J, Miyata J, Yamada K, Fukui K (2014). A tract-based spatial statistics study in anorexia nervosa: abnormality in the fornix and the cerebellum. *Progress in Neuropsychopharmacology and Biological Psychiatry* 51, 72-77.

Olatunji BO, Broman-Fulks JJ, Ciesielski BG, Zawilinski LL, Shewmaker S, Wall DA (2012). Taxometric investigation of the latent structure of eating disorders. *Psychiatry Research* 197, 97-102.

Roberto CA, Mayer LE, Brickman AM, Barnes A, Muraskin J, Yeung LK, Steffener J, Sy M, Hirsch J, Stern Y, Walsh BT (2011). Brain tissue volume changes following weight gain in adults with anorexia nervosa. *International Journal of Eating Disorders* 44, 406-411.

Rosas HD, Lee SY, Bender AC, Zaleta AK, Vangel M, Yu P, Fischl B, Pappu V, Onorato C, Cha JH, Salat DH, Hersch SM (2010). Altered white matter microstructure in the corpus callosum in Huntington's disease: implications for cortical "disconnection". *NeuroImage* 49, 2995-3004.

Russell GFM (1970). Anorexia nervosa: its identity as an illness and its treatment. In *Modern Trends in Psychological Medicine* (ed. J. H. Price), pp. 131-164. Butterworths: London.

Sathyanesan M, Girgenti MJ, Banasr M, Stone K, Bruce C, Guilchicek E, Wilczak-Havill K, Nairn A, Williams K, Sass S, Duman JG, Newton SS (2012). A molecular characterization of the choroid plexus and stress-induced gene regulation. *Translational Psychiatry* 2, e139.

Schmahmann JD, Sherman JC (1998). The cerebellar cognitive affective syndrome. Brain 121, 561-579.

Schmidt U, Campbell IC (2013). Treatment of eating disorders can not remain 'brainless': the case for brain-directed treatments. *European Eating Disorders Reviews* 21, 425-427.

Steinhausen HC (2002). The outcome of anorexia nervosa in the 20th century. *American Journal of Psychiatry* 159, 1284-1293.

Suchan B, Busch M, Schulte D, Gronemeyer D, Herpertz S, Vocks S (2010). Reduction of gray matter density in the extrastriate body area in women with anorexia nervosa. *Behavioural Brain Research* 206, 63-67.

Sullivan PF (1995). Mortality in anorexia nervosa. *American Journal of Psychiatry* 152, 1073-1074.

Swayze VW II, Andersen AE, Andreasen NC, Arndt S, Sato Y, Ziebell S (2003). Brain tissue volume segmentation in patients with anorexia nervosa before and after weight normalization. *International Journal of Eating Disorders* 33, 33-44.

Tibshirani R (1996). Regression shrinkage and selection via the LASSO. *Journal of the Royal Statistical Society Series B (Methodology)* 58, 267-288.

Tibshirani R (2011). Regression shrinkage and selection via the LASSO: a retrospective. *Journal of the Royal Statistical Society* 73, 273-282.

Titova OE, Hjorth OC, Schioth HB, Brooks SJ (2013). Anorexia nervosa is linked to reduced brain structure in reward and somatosensory regions: a meta-analysis of VBM studies. *BMC Psychiatry* 13, 110.

Trivedi P, Jiang M, Tamvakopoulos CC, Shen X, Yu H, Mock S, Fenyk-Melody J, Van der Ploeg LH, Guan XM (2003). Exploring the site of anorectic action of peripherally administered synthetic melanocortin peptide MT-II in rats. *Brain Research* 977, 221-230.

Turner CA, Thompson RC, Bunney WE, Schatzberg AF, Barchas JD, Myers RM, Akil H, Watson SJ (2014). Altered choroid plexus gene expression in major depressive disorder. *Frontiers of Human Neuroscience* 8, 238.

Vansteelandt K, Pieters G, Vanderlinden J, Probst M (2010). Body dissatisfaction moderates weight curves in the inpatient treatment of anorexia nervosa. *International Journal of Eating Disorders* 43, 694-700.

Walsh BT (2013). The enigmatic persistence of anorexia nervosa. *American Journal of Psychiatry* 170, 477-484.

Zhu J-N, Wang J-J (2008). The cerebellum in feeding control: possible function and mechanism. *Cellular and Molecular Neurobiology* 28, 469-478.