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Brain-gut microbiome profile of neuroticism predicts food addiction in obesity: A transdiagnostic approach

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Abstract

Neuroticism is one of the most robust risk factors for addictive behaviors including food addiction (a key contributor to obesity), although the associated mechanisms are not well understood. A transdiagnostic approach was used to identify the neuroticism-related neuropsychological and gut metabolomic patterns associated with food addiction. Predictive modeling of neuroticism was implemented using multimodal features (23 clinical, 13,531 resting-state functional connectivity (rsFC), 336 gut metabolites) in 114 high body mass index (BMI ≥25 kg/m^2) (cross-sectional) participants. Gradient boosting machine and logistic regression models were used to evaluate classification performance for food addiction. Neuroticism was significantly associated with food addiction ($P < 0.001$). Neuroticism-related features predicted food addiction with high performance (89% accuracy). Multimodal models performed better than single-modal models in predicting food addiction. Transdiagnostic alterations corresponded to rsFC involved in

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Declaration of Competing Interest

AG is a scientific consultant to Yamaha. All other authors have nothing to disclose.

CRediT authorship contribution statement

Xiaobei Zhang : Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Ravi R. Bhatt :** Methodology, Formal analysis, Writing – original draft, Visualization. **Svetoslav Todorov :** Formal analysis, Writing – original draft, Visualization. **Arpana Gupta :** Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – original draft, Supervision, Funding acquisition.

Ethical statement

All procedures complied with institutional guidelines and were approved by the Institutional Review Board at UCLA's Office of Protection for Research Subjects. All participants provided written informed consent.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2023.110768.

the emotion regulation, reward, and cognitive control and self-monitoring networks, and the metabolite 3-(4-hydroxyphenyl) propionate, as well as anxiety symptoms. Neuroticism moderated the relationship between BMI and food addiction. Neuroticism drives neuropsychological and gut microbial signatures implicated in dopamine synthesis and inflammation, anxiety, and food addiction. Such transdiagnostic models are essential in identifying mechanisms underlying food addiction in obesity, as it can help develop multiprong interventions to improve symptoms.

Keywords

Omics; Neuroticism; Food addiction; Brain-gut-microbiome; Machine learning

1. Introduction

Neuroticism is a fundamental domain of personality with public health implications. Neuroticism is defined as a relatively stable propensity to experience negative emotions and is associated with intense emotional hyperarousal (Goldberg, 1993). Neuroticism contributes the greater economic burden than most common mental disorders combined (Cuijpers et al., 2010). Neuroticism is one of the most robust risk factors contributing to psychiatric symptoms and substance-related and addictive disorders (Anderson et al., 2007; Feldman et al., 2011; Kotov et al., 2010; Sutin et al., 2013).

Neuroticism is also related to obesity risk and various altered eating behaviors (Gerlach et al., 2015). High neuroticism has been associated with inflammatory markers (C-reactive protein) and other environmental and social risk factors related to obesity such as sedentary lifestyle and less physical activity (Sutin and Terracciano, 2017). One study demonstrated a link between high neuroticism and food addiction (FA) in individuals with obesity (Brunault et al., 2018). FA is characterized by similar patterns of substance-dependence symptoms toward highlypalatable foods (Gearhardt et al., 2009a). As a maladaptive eating behavior, FA plays an important role in the pathophysiology of obesity (Gearhardt et al., 2011a).

The association between neuroticism and FA (or addiction in general) is not well understood. Given the important implications of neuroticism and FA for the field of obesity, it is crucial to delineate the underlying mechanisms involved. One possible pathway underlying this association is the alterations in the brain-gut-microbiome (BGM) system (Gupta et al., 2020). Unhealthy diet-induced gut signaling based on the overconsumption of unhealthy foods disrupts the balance between homeostatic and hedonic regulatory mechanisms in the brain and the gut microbiome (Gupta et al., 2020). The compromised inhibitory regulation of the reward and emotional–arousal networks in the brain reinforces gut dysbiosis (Dong et al., 2020a; Gupta et al., 2020; Ravichandran et al., 2021). Preclinical studies have also linked BGM alterations with mental health (Dinan and Cryan, 2017). Accumulating evidence supports that neuroticism and psychiatric disorders (such as depression and anxiety) may be associated with alterations in the gut microbiome, which could impact the brain and behavior through neuronal, endocrine, and immune pathways (Liang et al., 2018). Dysregulation of the core stress system, the hypothalamic-pituitary-adrenal axis (HPA), is particularly relevant within the context of neuroticism (Dinan and

Cryan, 2017; Park et al., 2021). Overall, these studies highlight that alterations within the BGM system might play a role in connecting neuroticism to FA.

Reward processing underlies FA (Dong et al., 2020b; Gearhardt et al., 2011b; Gupta et al., 2020; Ravichandran et al., 2021). According to the reward deficiency theory (Volkow et al., 2017; Wang et al., 2001), individuals with blunted dopaminergic transmission demonstrate compulsive overeating of highly palatable foods to compensate for the dopamine deficits (Blum et al., 2014), increasing the risk of developing FA and obesity (Volkow et al., 2008). Other addiction-related theories also propose alterations in reward processing as a key factor in the development and maintenance of addiction. The incentive-sensitization theory (Robinson and Berridge, 1993) proposes that repeated drug use leads to an increase in the sensitivity of the brain's reward system to the drug and drug-related cues, while the allostatic adaptation model (Koob, 2015) suggests that excessive activation of the brain reward systems through repeated use of addictive substances leads to dysregulation of the brain's reward and stress systems, leading to chronic allostatic dysregulation. These theories have also been discussed in the context of FA (De Ridder et al., 2016; Joyner et al., 2017). A few studies have suggested that high levels of neuroticism are associated with attenuated or blunted reward processing (Bondy et al., 2021; Mobbs et al., 2005). Similarly, reward-related neural alterations have been observed in depression and anxiety (Caouette and Guyer, 2014; Keren et al., 2018), which may help explain how neuroticism increases the risk of developing comorbid disorders (Weinstock and Whisman, 2006).

Behavioral and neuroimaging evidence also suggest that alterations in the emotion regulation brain network (amygdala, insula, and prefrontal cortex) may contribute to the development, persistence, and severity of FA (Pivarunas and Conner, 2015; Ravichandran et al., 2021; Wolz et al., 2016). Although not directly measured in the context of FA, neuroticism has been associated with increased amygdala–ventromedial prefrontal cortex connectivity during an emotional face matching task, highlighting the failure in top-down frontal control of emotion regulation processes (Silverman et al., 2019), similarly observed in structural and functional studies (Cremers et al., 2010; Xu and Potenza, 2012).

Decreased cognitive control is another important hallmark of FA, as evidenced by alterations in the prefrontal cortex during both food cue and cognitive control tasks (Franken et al., 2018; Michaud et al., 2017). Similar patterns have been observed with neuroticism as characterized by increased impulsivity (i.e., lack of controlled inhibitory processing) (Whiteside and Lynam, 2001). Highly neurotic individuals have demonstrated decreased efficiency in information processing within the cognitive control subnetworks (Servaas et al., 2015). Damage to these cognitive control regions has led to higher neuroticism (Banich, 2009).

Altered gut microbiome composition has been associated with FA and neuroticism (Dong et al., 2020b; Gupta et al., 2020). The neurotransmitters dopamine, serotonin, and their metabolites (associated trace amines, etc.) play an essential role in regulating energy metabolism, feeding behavior, movement, feeling, and motivation (Gainetdinov et al., 2018). The abnormality of these neurotransmitters or their precursors including amino acids tyrosine and tryptophan have been linked to obesity, FA and psychological problems such

as neuroticism, depression and anxiety (DeYoung, 2010; Handakas et al., 2022; Huang and Wu, 2021). In addition, people with FA/obesity or high neuroticism have also demonstrated altered microbial composition related to the increased stress responses and inflammatory processes (Gupta et al., 2020; Johnson, 2020; Kim et al., 2018).

Utilizing a multimodal, data-driven approach, the current study aims to elucidate the association between neuroticism and FA in people who are overweight or obese, by exploring their transdiagnostic components in resting-state functional connectivity (rsFC), gut microbial metabolites and related clinical features (summarized in Fig. 1). We hypothesize that 1). Self-reported neuroticism is associated with FA; 2) Neuroticism will moderate the relationship between body mass index (BMI) and FA. 3) A multimodal classification profile based on the selection of unique brain-gut microbiome and clinical profiles for neuroticism, and increased risk for FA will be delineated with high accuracy in individuals with high BMI. Brain features will include regions related to reward processing, cognitive control, and emotion regulation, metabolite signatures will include dopamine and inflammation related pathways relevant to neuroticism.

2. Methods

2.1. Participants

Participants comprised 114 participants (78 females) recruited from the Los Angeles community. All participants were overweight or obese (listed as high BMI individuals henceforth with BMI ≥25 kg/m^2). Inclusion and exclusion criteria are detailed in Supplemental Methods. All procedures complied with institutional guidelines and were approved by the Institutional Review Board at UCLA's Office of Protection for Research Subjects. All participants provided written informed consent. Basic participant data included BMI, age, and sex. Multimodal data including resting-state MRI, fecal metabolomics and clinical and behavioral measures were collected.

2.2. Clinical and behavioral assessments

Trait neuroticism was assessed using the International Personality Item Pool (IPIP) (Goldberg et al., 2006). Scores were dichotomized into "neurotic group" (Neuroticism score > 20.8) and "non-neurotic group" (Neuroticism score ≤ 20.8) based on sample mean.

FA was evaluated using Yale Food Addiction Scale (YFAS), a 25-item scale developed to measure FA by assessing signs of substance-dependence symptoms in eating behavior (Gearhardt et al., 2009b). FA was defined as having a YFAS symptom count ≥ 3 with clinically significant impairment or distress. See details of diagnostic criteria for FA in Supplemental Methods.

Other measures collected included the Early Trauma Inventory (ETISR)(Bremner et al., 2005), Spielberger State Trait Anxiety Inventory (STAI) (Marteau and Bekker, 1992), Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith, 1983), Perceived Stress Scale (PSS) (Cohen et al., 1983), Short-Form Health Survey (SF-12) (Gandek et al., 1998), Connor-Davidson Resilience Scale (CD-RISC) (Connor and Davidson, 2003), and

Positive Affect Negative Affect Schedule (PANAS) (Watson et al., 1988) (Supplemental Methods).

2.3. Magnetic resonance imaging

Whole brain rsFC data were acquired using a 3.0 T Prisma MRI scanner (Siemens, Erlangen, Germany). See Supplemental Methods for details on neuroimaging acquisition parameters and data preprocessing. A whole brain region of interest (ROI) approach was used to create the datasets used. For cortical regions, the Destrieux atlas was used. For subcortical regions, the Harvard-Oxford subcortical atlas was used. Based on these ROIs, measures of rsFC were derived.

2.4. Fecal metabolomics

Fecal metabolomics collection and processing have been described in a previous publication (Coley et al., 2021) and are detailed in Supplemental Methods.

2.5. Data analyses

2.5.1. Baseline characteristics—Baseline demographic and clinical characteristics were compared using Student *t*-tests for continuous variables and Chi-squared tests for categorical variables. *P* values were adjusted for multiple comparisons using the false discovery rate (FDR).

2.5.2. Correlation between food addiction and neuroticism—Partial correlations were calculated between neuroticism and FA scores (all subscales), controlling for BMI, sex, age, ETI Total Score, CDRISC Score, HAD Anxiety, HAD Depression, STAI Trait Anxiety, PSS Score, SF12 Mental Component Score, and PANAS Positive Affect Score. These scores showed baseline differences as a function of FA and neuroticism. *P* values were adjusted for multiple comparisons using FDR. The YFAS translates the diagnostic criteria for substance dependence as stated in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 2000) to apply to the consumption of calorie-dense foods. The scale assesses several specific criteria, including tolerance, withdrawal symptoms, consumption more than intended, persistent cravings or unsuccessful reduction attempts, spending too much time using or recovering from the substance, continuous use despite knowledge of negative consequences, and abandonment of activities due to FA. Each criterion reveals a different aspect of FA, and by including the results of individual subscales in relation to FA, we can gain a better understanding of the specific factors driving the association.

2.5.3. Predictive modeling of neuroticism: gradient boosting machine (GBM) —GBM was used to train the optimal machine learning model to predict the binary neuroticism outcome, for its robustness against high dimensionality and collinearity, using ‘gbm’ package in R.

Multimodal datapoints were passed to GBM calls in as concatenated data matrices, containing 23 columns of clinical features, 13,531 columns of rsFC features, and 336 columns of gut metabolomic features (13,887 columns total). 92 individuals were assigned

to the training set, and 22 individuals were assigned to the testing set. Training of the classifier occurred in the following steps. The training data was passed to a 1000-iteration call of the GBM algorithm. Out-of-bag error was used for the optimal number of iterations needed to build an accurate classifier on the given train set. This iteration count was used for a second invocation of the GBM, which produced the final model. To generate Receiver operating characteristic (ROC) curves, the model's predictions on the testing set were compared to the true neuroticism scores using Mann-Whitney U statistic (https://cran.r-project.org/web/packages/gbm/index.html). The features that best predicted neuroticism were the input features into a FA classifier. Partial dependence plots for the most important features of the GBM were also created.

2.5.4. Classification modeling of food addiction: logistic regression with cross-validation—The most important 15 features derived from GBM were the resulting dataset used to predict FA diagnoses. For the classification of FA, the logistic regression machine learning algorithm from the R caret package was used to train and evaluate the classification model. Classification performance was validated using 10-fold cross validation repeated 50 times on a training set of data (80% of data), the validated model was then tested on a separate evaluation set of data (20% heldout sample). All the evaluation metrics reported were based on model predictions using the evaluation set of data. The following are steps used to address class imbalance, determine which 'omic type was contributing to accurate classification, and relevant feature selection.

1. Resampling to Address Class Imbalance using Synthetic Minority Over Sampling Technique. (specific details in Supplemental Methods).
2. Model Comparisons of Different 'Omics. All possible combinations of feature modalities (brain features only, clinical assessments only, metabolite only, brain+clinical, brain+metabolite, clinical+metabolite, and brain+clinical+metabolite) were considered as inputs to select the best model to predict FA.
3. Significant Predictors in Predicting Food Addiction in All Models. Significant predictors ($P < 0.05$) from each cross-validated model in predicting FA were presented. Feature reduction was further conducted by using only the significant predictors as predictors.

The variance inflation factor (VIF) was used to diagnose multicollinearity (Supplemental Methods). The area under the curve (AUC), sensitivity (true positive rate), specificity (true negative rate) and accuracy were reported as the performance metrics. The same model comparisons procedure was repeated to predict neuroticism to confirm GBM selected features could robustly predict neuroticism.

2.5.5. Moderation effect of neuroticism on food addiction symptoms—To evaluate whether neuroticism moderated the relation between BMI and FA symptoms, 'pequod' package in R (https://cran.r-project.org/web/packages/pequod/index.html) was used. Linear regression model included the main effects of BMI and neuroticism score and their interaction, controlling for sex, age, ETI Total Score, CD-RISC Score, HAD Anxiety,

HAD Depression, STAI Trait Anxiety, PSS Score, SF12 MCS, and PANAS Positive Affect Score. BMI and neuroticism scores were centered before creating the interaction terms. Simple slope tests were conducted to evaluate whether separate slopes within a given high (+1 SD) or low (−1 SD) range of neuroticism scores were significantly different from zero.

3. Results

3.1. Baseline characteristics by neuroticism and food addiction

The neurotic group, relative to the non-neurotic group, exhibited significantly or marginally significantly higher scores in several YFAS subscales, early trauma, anxiety, depression, perceived stress, and negative affect; and significantly lower scores in resilience, mental health, and positive affect. The comparison patterns between people with and without FA were similar to the comparison between the neurotic and non-neurotic groups (Table 1).

3.2. Correlation between FA and neuroticism

Partial correlations between Neuroticism and all YFAS subscales were significant (*Ps* < 0.05), except for unsuccessful reduction ($r = 0.02$, $P = 0.83$)(Supplemental Table S1).

3.3. Predictive modeling of neuroticism: GBM

The most important features derived from GBM algorism predicted Neuroticism with good performance (Fig. 2A, AUC = 0.88). Relative importance measures the effect of each feature on the variation of the prediction over the joint input variable distribution. Fig. 2B visualized the relative importance of the most important features generated by GBM (Partial dependence plots for each feature in Supplemental Fig. S1).

3.4. Classification modeling of food addiction: logistic regression with cross-validation

Model comparisons (Table 2 & Supplemental Table S2) showed that most predictive models considered performed well in predicting FA (AUCs>0.77). The best model was the multimodal model with brain and clinical features (AUC = 0.91), followed by the model with features in all three modalities (AUC = 0.89). Several simplified models (Supplemental Table S2) also had good performance in predicting FA using less predictors. In general, multimodal models performed better than single-modal models.

3.5. Significant predictors in all models in predicting food addiction

Across all models, brain features consistently predicted FA included rsFC of R Central Sulcus to L Superior temporal gyrus, R Precentral gyrus to R Posterior-ventral cingulate, R Parahippocampal gyrus to L Inferior temporal gyrus, R Temporal pole to L Middle temporal gyrus, and R Ventrolateral prefrontal cortex to L Temporal pole. Among them, R Precentral gyrus to R Posterior-ventral cingulate connectivity was significantly lower in people with FA, and the rest of the brain features were significantly higher in people with FA. Individuals with FA had significantly higher anxiety and lower levels of 3-(4-hydroxyphenyl) propionate (Supplemental Table S3).

3.6. Moderation effect of neuroticism on food addiction symptoms

The overall model investigating BMI predicting FA symptoms with neuroticism score as the moderator, significantly accounted for 47% of the variance ($R^2 = 0.47$, $F_{(13,100)} = 6.85$, $P < 0.001$). Results (Fig. 3) indicated that higher BMI ($B = 0.22$, $SE = 0.03$, $\beta = 0.07$, $P = 0.008$) and neuroticism scores ($B = 0.43$, $SE = 0.03$, $\beta = 0.09$, $P < 0.001$) were associated with more FA symptoms. The interaction between neuroticism and BMI was significant ($B = 0.16$, $SE = 0.003$, $\beta = 0.16$, $P = 0.04$), suggesting the moderation effect of neuroticism. Specifically, significant positive associations between BMI and FA symptoms for people with high levels (+1 SD above the mean)($B = 0.12$, $t_{(100)} = 3.54$, $P < 0.001$) of neuroticism were observed, but not for people with low levels (−1 SD below the mean) of neuroticism ($B = 0.02$, $t_{(100)} = 0.57$, $P = 0.57$).

3.7. Classification modeling of neuroticism: logistic regression with cross-validation

The GBM derived neuroticism related features were used to predict neuroticism (high vs. low) using the same logistic regression procedures. Model comparisons (Table 3 & Supplemental Table S4) showed that most predictive models considered (except for metabolite only model) performed well in predicting neuroticism (all AUCs > 0.76). The best model was the multimodal model with features in all three modalities (AUC = 0.98), followed by the model with brain and clinical features (AUC = 0.97). Several simplified models (Supplemental Table S4) had good performance in predicting FA using less predictors.

3.8. Significant predictors in all models in predicting neuroticism

Among all the rsFC brain features consistently predicted neuroticism, R Postcentral gyrus to L Caudate nucleus and L Orbitofrontal cortex to L Pallidum are lower in highly neurotic individuals, and R Central Sulcus to L Superior temporal gyrus, R Precentral gyrus to R Posterior-ventral cingulate, and L Orbitofrontal cortex to L Parahippocampal gyrus were significantly higher in highly neurotic individuals. In addition, highly neurotic people had significantly higher levels of anxiety and 3-(4-hydroxyphenyl) propionate, and lower resilience (details in Supplemental Table S5). The directionality of these significant features in predicting neuroticism are the same as the GBM generated results (Supplemental Fig. S1).

4. Discussion

We investigated the brain-gut-microbiome profile of the personality trait neuroticism in relation to FA. We found a significant association between neuroticism and FA symptoms. The most important neuroticism-related features derived from within the brain-gut-microbiome predicted FA diagnoses with high accuracy (AUC = 0.89). Models comparing all the combinations of data modalities in predicting FA revealed that multimodal models performed better than single-modal models. Across all models, transdiagnostic alterations corresponded prominently to rsFC involved in the emotion regulation, reward processing, and cognitive control and self-monitoring networks, the metabolite 3-(4-hydroxyphenyl) propionate, and anxiety symptoms. Further, neuroticism was found to moderate the relationship between BMI and FA symptoms.

Neuroticism was positively associated with FA in participants with high BMI, consistent with a study that also found the same relationship in individuals with obesity (Brunault et al., 2018). Neuroticism was also linked to other maladaptive eating behavior (e.g., emotional eating) related to FA in people with obesity (Elfhag and Morey, 2008). FA defined as compulsive consumption of palatable food items beyond homeostatic energy requirements (Gearhardt et al., 2009a), is not limited to people with obesity and is prevalent in people who are underweight or obese (Hauck et al., 2017). The presence of FA in individuals that are underweight may be due to underlying disordered eating (Granero et al., 2014), suggesting that confounding factors such as psychological and eating disorders could be considered in relating neuroticism to FA.

When we used multimodal models, we found that they performed better than the single-modal models, and clinical and brain features outperformed the metabolite feature in predicting FA. These results suggest that multimodal data might lead to more accurate classification models, as it provides more comprehensive knowledge of the relationship between neuroticism and FA in the context of brain signatures, metabolite features, and clinical symptoms.

Across all models, transdiagnostic patterns of altered connectivity in regions involved in emotion regulation (ventral lateral prefrontal cortex, temporal pole, superior temporal gyrus), reward processing (caudate, orbitofrontal cortex, parahippocampal gyrus and pallidum), and cognitive control and self-monitoring (precentral gyrus and posterior cingulate) were identified for both FA and neuroticism. FA was associated with decreased connectivity between precentral gyrus and posterior-ventral cingulate, two regions involved in motor-related cognitive control and self-monitoring respectively (Andrews-Hanna et al., 2014; Congdon et al., 2010), possibly suggesting the dissociation of self-reflection and motor control in FA. However, the increase of such connectivity predicted neuroticism, which might indicate an overmodulation of self-processing and control. As such, the directionality difference in neural alteration might reflect differential mechanisms contributing to neuroticism and FA. In fact, both emotional task-elicited hyper- and hypoactivation of the prefrontal cortex have been observed across and within disorder categories, such as PTSD and depression (Lanius et al., 2010; Nejad et al., 2013). One meta-analytic study (McTeague et al., 2020) identified common neural circuits underlying emotional processing across psychiatric disorders (schizophrenia, bipolar or unipolar depression, anxiety, and substance use relative to healthy control), but also showed notable differences in patterns of hyper- and hypoactivation across diagnoses. Therefore, finding alterations that converge on the same regions between FA and neuroticism (across diagnostic categories), regardless of directionality, is essential to identify common impairments relevant to understanding psychopathology as a whole and why they are associated (Barch, 2020).

Alterations in brain regions implicated in emotion regulation, reward processing, and cognitive control were observed across different models. Ventral lateral prefrontal cortex is a core region involved in the down-regulation of negative emotions (Buhle et al., 2014). The temporal pole is a cortical area involved in multiple sensory modalities as well as episodic memory processing and retrieval (Barredo et al., 2015) in social emotional situations. Thus, the observed increased connectivity between ventral lateral prefrontal

cortex and temporal pole in people with FA and higher levels of neuroticism might reflect the enhanced frontal regulation of emotional responses. In addition, the frontotemporal pathway has been implicated in the cognitive control of memory (Barredo et al., 2015), which is fundamental to cognitive emotion regulation (i.e., controlling retrieval of intrusive memories to regulate emotions). Compromised emotion regulation has been reflected in counter-regulatory maladaptive eating behaviors, such as external or emotional eating, in people with FA and higher neuroticism (Gearhardt et al., 2011b; Keller and Siegrist, 2015). In particular, negative urgency, the tendency to act rashly when experiencing extremely negative emotions, has been implicated in both neuroticism and FA (Settles et al., 2012; Wolz et al., 2017). Specifically, negative urgency and emotion dysregulation are positively associated with food addiction in the general population, as well as in individuals who are obese or have eating disorders (Ouellette et al., 2017; Pivarunas and Conner, 2015; Wolz et al., 2017). This evidence implies that compromised emotion regulation may become further deteriorated in distressed situations." Together, these results suggest alterations in top-down regulation of emotional responses or memories associated with neuroticism and FA.

The caudate, orbitofrontal cortex, parahippocampal gyrus and pallidum are brain regions innervated by dopaminergic pathways and they play important roles in reward, motivation (Carnell et al., 2012; Kringelbach, 2005), and appetitive responses (urges, cravings) (Dagher, 2010). According to the reward deficiency theory, individuals with blunted dopaminergic transmission might show compulsive overeating to balance their dopamine deficits (Volkow et al., 2017; Wang et al., 2001). This theory has also been supported by recent neural evidence on FA (Gearhardt et al., 2011b; Ravichandran et al., 2021). Blunted reward processing in neuroticism has also been observed. And the genetic variation in the production and uptake of dopamine may play a role in the heritability of neuroticism (DeYoung, 2015). Similarly, our study demonstrated functional connectivity alterations in these reward regions, suggesting high BMI individuals with FA or high neuroticism have altered reward processing. Thus, compromised emotion and reward regulation, might suggest changes in motivation, cravings, and consumption of foods to balance brain dopamine function. Since resting-state data do not differentiate between anticipatory and consummatory rewards, we are unable to evaluate the relevance of other addiction-related reward processing models (e.g., Incentive Sensitization theory, Allostatic model) (Koob and Le Moal, 2001; Robinson and Berridge, 1993). Future studies with appropriate task design are warranted to further test these hypothesized theories in relation to FA and neuroticism.

The posterior cingulate cortex and the precentral gyrus are involved in self-monitoring and cognitive control (Congdon et al., 2010; Leech et al., 2011). Cognitive control is also an essential part of emotion regulation (Ochsner et al., 2012). Therefore, altered cognitive control observed in both FA and neuroticism, could be contributing to the exacerbated hedonic eating and weight gain observed in individuals with obesity.

Trait anxiety predicted neuroticism and FA. The comorbidity of FA and anxiety disorders has been observed (Piccinni et al., 2021). Trait Anxiety has been correlated with neuroticism (Gonda et al., 2009). Some researchers have even suggested that trait anxiety is synonymous with neuroticism (Barlow et al., 2014). There is also substantial overlap between the genetic factors influencing individual variation in both traits (Hettema et al., 2004). Individuals with

anxiety or neuroticism have a tendency to experience negative affect (Bishop and Forster, 2013), which could explain the processing alterations observed in FA. Thus maladaptive eating behaviors such as FA may work as a coping strategy to regulate negative emotions (Schneider et al., 2010).

We found that 3-(4-hydroxyphenyl) propionate (an amino acid metabolite associated with tyrosine metabolism (O'Neill et al., 2018)) predicted FA and neuroticism. 3-(4-hydroxyphenyl) propionate is structurally similar to tyrosine, which is associated with dopamine synthesis (Daubner et al., 2011), has antioxidant, anti-inflammatory, and anti-cancer properties, and has been increased in amniotic fluid from women with gestational diabetes (O'Neill et al., 2018). Changes in the dopaminergic system, neuroticism, and FA have been linked to increased oxidative stress and inflammation. This suggests that changes in 3-(4-hydroxyphenyl) propionate could be due to links with altered dopaminergic reward processing and inflammation related to stress responses and negative affect from both FA and neuroticism (Hemmingsson, 2014).

Neuroticism moderated the relationship between BMI and FA symptoms, with a stronger association in people with higher levels of neuroticism, and no association in people with low levels of neuroticism. One recent study (Vainik et al., 2020) compared obesity, uncontrolled eating and addiction on the strength of associations between personality traits and showed that obesity is less addiction-centered than uncontrolled eating. Interestingly, the similarity between uncontrolled eating and addiction was found to be driven by trait neuroticism. Together, these findings imply the added value in incorporating the big five personality domains, especially neuroticism, when considering problematic eating behaviors (including FA) in relation to overeating and obesity.

Using a fully data-driven method, we identified a highly predictive, transdiagnostic multimodal biomarker for both FA and neuroticism, emphasizing the shared pathways involved in impairments in reward processing, emotion regulation (stress response), and cognitive control. These findings have valuable implications in identifying common factors to target prevention and therapeutic interventions that are transdiagnostic. The Unified Protocol for transdiagnostic treatment of emotional disorders (UP) is an emotion-focused, cognitive behavioral intervention that targets neuroticism and resulting emotion dysregulation, by simultaneously accommodating comorbid emotional disorders (i.e., anxiety, depression)(Barlow et al., 2014). The UP can be modified and implemented to treat eating and substance disorders, with preliminary results suggesting improvements in emotional conditions and treatment outcomes (Thompson-Brenner et al., 2019). Such an approach could be utilized to improve FA, together with neuroticism. In addition, targeting the microbiota in therapy is a promising approach. Preliminary studies illustrated the short-term benefits of using fecal microbiota transplantation in people with metabolic syndrome (Kootte et al., 2017). Fermented food intake has shown success in lowering anxiety symptoms in highly neurotic individuals (Hilimire et al., 2015). Calorie restriction, which can modify gut microbial composition and global metabolism, has shown to improve weight loss and mood (Martin et al., 2016).

5. Limitations and future directions

Since this study was focused on delineating patterns in obesity, people who are normal weight and underweight were not included in this study. As such confounding factors should be addressed differently according to the weight group in larger studies. The sample size of our resting state data is relatively small especially for the FA group (Grady et al., 2021), therefore future studies with larger samples should attempt to replicate these results and explore the potential moderating effects of gender and race/ethnicity. Although neuroticism is a very strong personality predictor of negative health outcomes, future studies could evaluate the other dimensions of the big five personality traits in the context of FA and obesity. While our study specifically examined the association between neuroticism and FA, our findings have broader implications for other addictive disorders such as alcohol addiction, substance addiction, and internet addiction (Dean et al., 2020; Kuss et al., 2013; Valero et al., 2014). These findings highlight the importance of incorporating the personality domain when considering addictive behaviors and developing transdiagnostic treatment plans.

6. Conclusions and clinical implications

Our study suggests that neuroticism-related brain-gut-clinical features predict FA in individuals with high BMI and potentially modulates clinical symptoms. We demonstrate a neuroticism-based pattern driving neuropsychological and gut microbiota perturbations and increased FA. Such transdiagnostic dysfunctions are critical to identifying the core maladaptive mechanisms that underlie a broad array of diagnostic presentations in order to develop potential targeted multidimensional interventions to improve comorbid symptoms and treatment outcomes in obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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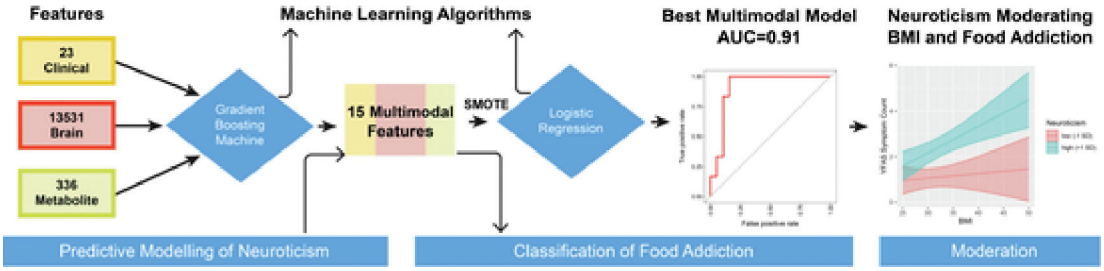

Fig. 1.

Overview of study. This graph illustrated the study overview.

Abbreviations: SMOTE, Synthetic Minority Over Sampling Technique; AUC, Area Under the Curve; BMI, Body Mass Index; YFAS, Yale Food Addiction Scale.

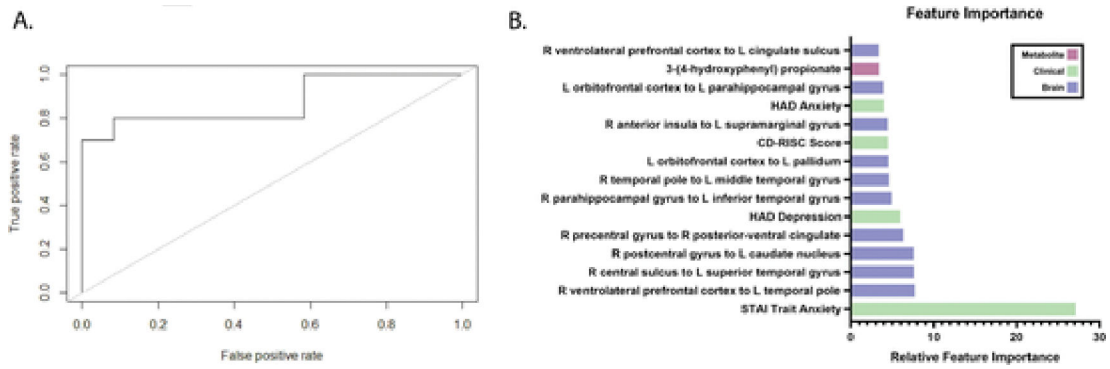

Fig. 2.

Predictive modeling of neuroticism using gradient boosting machine (GBM). (A) showed the model performance of predictive modeling of neuroticism. (B) showed the most important multi-modal features predicting neuroticism via GBM. Green = Clinical, Blue = Brain, Purple = Metabolite. Abbreviations: R, right; L, left; HAD, Hospital Anxiety and Depression Scale; CD-RISK, Connor-Davidson Resilience Scale; STAI, State-Trait Anxiety Inventory. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

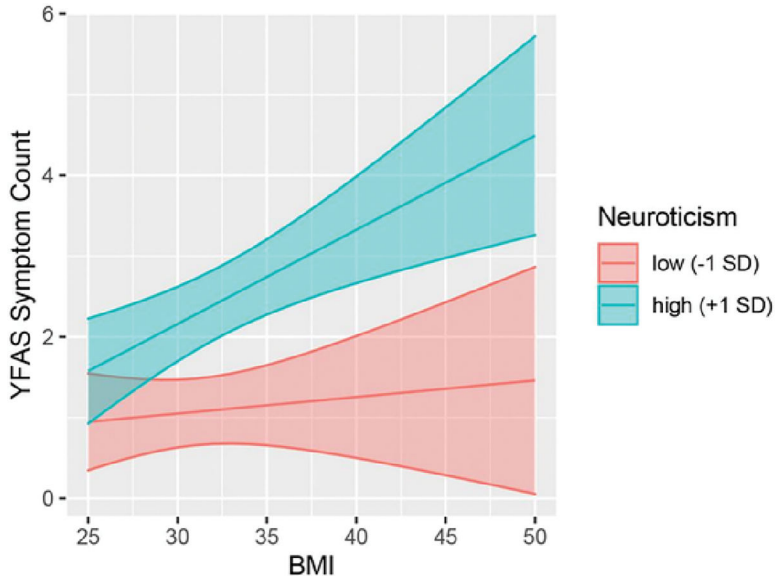

Fig. 3.

Neuroticism moderating the relation between BMI and food addiction symptoms.

A linear model included the main effects of BMI and neuroticism score and their interaction, controlling for confounding factors (Materials and Methods). We observed a significant interaction between neuroticism and BMI, such that the relationship between BMI and food addiction symptoms was especially pronounced among individuals with higher level of neuroticism (Results). Shaded areas represent 95% confidence intervals. Abbreviations: BMI, Body Mass Index; YFAS, Yale Food Addiction Scale.

Table 1

Baseline characteristics by neuroticism and food addiction.

Parameter	Neurotic (*N* = 51)	Non-neurotic (*N* = 63)	*T*	*P*	*P* (FDR-corrected)
Age, mean (SD) [range], y	30.8 (9.70) [19, 54]	33.6 (10.8) [18, 60]	1.46	0.148	
Sex				0.394	
Men	14	22			
Women	37	41			
BMI, mean (SD) [range], kg/m^2	31.9 (5.05) [25.3, 47.5]	31.0 (4.38) [25.1, 45.3]	−0.99	0.324	
Food Addiction				0.002 *	
Food addiction	14	4			
Without food addiction	37	59			
YFAS Withdrawal	0.333 (0.792)	0.127 (0.336)	−1.74	0.087	0.102
YFAS Tolerance	0.242 (0.549)	0.0978 (0.390)	−1.58	0.119	0.132
YFAS Continued Use	0.294 (0.460)	0.127 (0.336)	−2.17	0.033	0.05
YFAS Activities Given Up	0.333 (0.864)	0.0635 (0.396)	−2.06	0.043	0.054
YFAS Time Spent	0.373 (0.692)	0.127 (0.381)	−2.27	0.026	0.043 *
YFAS Loss of Control	0.216 (0.541)	0.0176 (0.126)	−2.56	0.013	0.027 *
YFAS Unsuccessful Reduction	1.56 (0.820)	1.60 (0.879)	0.29	0.772	0.813
YFAS Clinically Significant Impairment	0.176 (0.518)	0 (0)	−2.43	0.019	0.034 *
YFAS Symptom Count	2.14 (1.83)	1.33 (0.880)	−2.88	0.005	0.015 *
ETI Total Score	5.96 (4.85)	4.11 (4.31)	−2.13	0.036	0.05
CD-RISC Score	73.0 (11.8)	84.4 (9.86)	5.47	< 0.001	< 0.001 *
HAD Anxiety	6.98 (3.37)	2.73 (2.74)	−7.27	< 0.001	< 0.001 *
HAD Depression	3.43 (2.86)	1.22 (1.75)	−4.83	< 0.001	< 0.001 *
STAI Trait Anxiety	54.1 (8.62)	41.5 (5.73)	−8.94	< 0.001	< 0.001 *
PSS Score	15.7 (7.07)	8.91 (4.95)	−5.84	< 0.001	< 0.001 *
SF12 Physical Component Score	54.3 (4.30)	54.2 (3.11)	−0.23	0.817	0.817
SF12 Mental Component Score	48.1 (8.85)	54.8 (4.59)	4.89	< 0.001	< 0.001 *
PANAS Positive Affect Score	30.8 (8.09)	33.9 (7.41)	2.11	0.037	0.05
PANAS Negative Affect Score	13.2 (3.87)	11.5 (2.80)	−2.67	0.009	0.022 *
Parameter	Food addiction (*N* = 18)	No food addiction (*N* = 96)	*T*	*P*	*P* (FDR-corrected)
Age, mean (SD) [range], y	27(6.7)[18, 60]	33.31(10.68) [18,60]	3.29	0.002 *	
Sex				0.861	
Men	6	30			
Women	12	66			
BMI, mean (SD) [range], kg/m^2	35.95 (5.5) [26.99, 47.54]	30.56 (4.02) [25.11, 43.71]	−3.97	0.001 *	
Neuroticism	27.67(7.19)	19.47(5.81)	−4.56	< 0.001 *	
ETI Total Score, mean (SD)	7.22(5.34)	4.51(4.39)	−2.03	0.055	0.076

Parameter	Neurotic (*N* = 51)	Non-neurotic (*N* = 63)	*T*	*P*	*P* (FDR-corrected)
CD-RISC Score	73.11(12.2)	80.44(11.84)	2.35	0.028	0.043 *
HAD Anxiety	8.11(3.36)	3.98(3.39)	−4.78	< 0.001	< 0.001 *
HAD Depression	4.22 (2.9)	1.83 (2.31)	−3.3	0.003	0.006 *
STAI Trait Anxiety	57.11(8.39)	45.3(8.53)	−5.47	< 0.001	< 0.001 *
PSS Score	18.33 (5.25)	10.78(6.49)	−5.39	< 0.001	< 0.001 *
SF12 Physical Component Score	53.72(5.38)	54.33 (3.29)	0.46	0.651	0.716
SF12 Mental Component Score	43.41 (9.58)	53.39(5.99)	4.27	< 0.001	0.001 *
PANAS Positive Affect Score	26.61 (8.2)	33.63(7.3)	3.39	0.003	0.006 *
PANAS Negative Affect Score	12.11(1.88)	12.31 (3.64)	0.35	0.73	0.73

Baseline demographic and clinical characteristics were compared using Student t-tests for continuous variables and Chi-squared tests for categorical variables. *P* values were adjusted for multiple comparisons using the false discovery rate (FDR).

* indicates $P < 0.05$.

Abbreviations: BMI, Body Mass Index; YFAS, Yale Food Addiction Scale; ETI, Early Trauma Inventory; CD-RISK, Connor-Davidson Resilience Scale; HAD, Hospital Anxiety and Depression Scale; STAI, State-Trait Anxiety Inventory; PSS, Perceived Stress Scale; SF12, 12-Item Short Form Survey; PANAS, Positive Affect Negative Affect Schedule; FDR, False Discovery Rate.

Table 2

Model comparisons of classification modeling of food addiction using logistic regression (without feature reduction).

Model	AUC	Accuracy	Sensitivity	Specificity	No. of predictors
Model: Brain + Clinical	0.91	0.81	0.89	0.72	14
Model: All modalities	0.89	0.84	0.84	0.83	15
Model: Metabolite + Clinical	0.85	0.78	0.79	0.78	5
Model: Clinical	0.85	0.7	0.79	0.61	4
Model: Brain	0.82	0.73	0.79	0.67	10
Model: Brain + Metabolite	0.8	0.76	0.74	0.78	11
Model: Metabolite	0.36	0.49	0.32	0.67	1

Collinearity diagnostics indicated that multicollinearity was not a concern in our predictive models of food addiction.

Abbreviations: Area Under the Curve.

Table 3

Model comparisons of classification modeling of neuroticism using logistic regression (without feature reduction).

Model	AUC	Accuracy	Sensitivity	Specificity	No. of predictors
Model: All modalities	0.98	0.91	0.83	1.00	14
Model: Brain + Clinical	0.97	0.91	0.92	0.90	14
Model: Brain	0.87	0.77	0.75	0.80	10
Model: Clinical	0.86	0.82	0.83	0.80	4
Model: Metabolite + Clinical	0.86	0.82	0.83	0.80	5
Model: Brain + Metabolite	0.86	0.73	0.67	0.80	11
Model: Metabolite	0.70	0.64	0.92	0.30	1

One clinical feature (State-Trait Anxiety Inventory (STAI) trait anxiety) was removed in the “Model: All modalities” predicting neuroticism due to its variance inflation factor (VIF) >10.

Abbreviations: Area Under the Curve.