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Altered orbitofrontal and pars opercularis cortical thickness in betel quid dependence chewers

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Abstract

Background: Altered cerebral cortex's structural organization has been found in individuals with betel quid dependence (BQD). However, the neurological underpinnings of the BQD-related abnormalities in cortical thickness and brain circuitry deficit are largely unknown.

Objective: This study aimed to investigate potential abnormalities of brain circuitry in the cortical thickness of BQD individuals by applying the surface-based morphometry (SBM) method.

Design: Cross-sectional study.

Methods: High spatial resolution, three-dimensional T1-weighted structural imaging data were collected from 53 individuals with BQD and 37 healthy controls (HCs) who were similar to the BQD group in terms of age, sex, and educational level. The SBM method was applied to analyze the cortical thickness alterations in BQD-related areas. Independent-samples *t*-test was used to assess the cortical thickness difference between the two groups. Pearson correlation analysis was used to investigate the correlation between cortical thickness changes and clinical characteristics, including BQD scale scores and duration of BQD.

Results: The BQD group had a higher cortical thickness than the HC group at the lateral orbitofrontal ($t = 4.703$, $p = 0.0028$) and pars opercularis ($t = 3.602$, $p = 0.0403$) clusters in the right cerebral hemisphere, with age, sex, and education duration as covariates ($p < 0.05$, Monte Carlo). There were no significant differences in age, sex, or education duration-adjusted cortical thickness of the left cerebral hemisphere between BQD chewers and HCs ($p > 0.05$, Monte Carlo). Correlation analysis revealed that the cortical thickness of the right pars opercularis was negatively correlated with the BQD duration ($r = -0.274$, $p = 0.047$). The cortical thickness of the right lateral orbitofrontal cluster was not significantly correlated with Betel Quid Dependence Scale (BQDS) or BQD duration ($p > 0.05$).

Conclusion: This study demonstrated that BQD might be associated with changes in the orbitofrontal and pars opercularis cortical thickness, which may be related to the neurobiological basis of BQD.

Keywords: betel quid, betel quid dependent, cortical thickness, drug dependence, surface-based morphometry

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Introduction

In addition to ethanol, nicotine, and caffeine, the psychoactive stimulant betel quid (BQ) is one of the most broadly consumed addictive substances worldwide.[1] BQ is chewed by approximately 10% of the global population, mainly in Asia and the Pacific islands.[2] Areca nut (AN), piper betel leaf (a common vine), and slaked lime (calcium hydroxide) are the primary components of "betel quid." However, the exact

ingredients differ according to the region and community.[3,4]

Alkaloids are the principal biologically active components of BQ. Approximately 2% of BQ composition comprises significant alkaloids such as arecoline, arecaidine, guavacine, and guavacoline. Arecoline has the greatest physiological significance. It functions as a monoamine oxidase-A inhibitor, significantly raising the serotonin (5-hydroxytryptamine, or 5-HT) levels, a neurotransmitter that causes euphoria and impulsivity. 5-HT also contributes to betel quid dependence (BQD).[5] Frequent BQ chewing causes a dependence syndrome characterized by heightened concentration, mild pleasure, comfort, and postprandial satisfaction, as well as a withdrawal syndrome characterized by insomnia, mood swings, anxiety, and irritation.[6]

According to a review of BQ-related systemic adverse effects, nearly every organ in the body can be impacted by BQ, including the brain, heart, lungs, gastrointestinal tract, and reproductive system.[7] BQD can worsen pre-existing conditions such as metabolic syndrome or cause myocardial infarction and neurological damage. Infertility, prostatic enlargement, and hypothyroidism are all consequences of BQ's impact on the endocrine system. Immune system involvement can result in T-cell activation and decreased cytokine secretion. Moreover, BQ can result in fetal abnormalities during pregnancy. BQ has been designated as a human carcinogen by the International Agency for Research on Cancer.[3,8] Many health issues, including oral cavity cancer and several precancerous lesions linked to leukoplakia and submucosal fibrosis of the oral cavity, can also result from extended BQ use.[9] Determining BQD's mechanism for causing addiction and creating appropriate solutions to lessen its possible risks are urgently needed.

Magnetic resonance imaging (MRI) has been extensively utilized to examine neuropsychiatric illnesses due to its noninvasive nature, easy-to-signal acquisition, high spatial and temporal resolution, and minimal patient workload. Voxel-based morphometry (VBM) and surface-based morphometry (SBM), two currently used techniques for structural imaging investigations of the brain cortex related to substance addiction, enable observation of minute variations in brain structure through the quantitative analysis of brain tissue.

Previous studies showed that BQ addiction causes alterations in the cerebral cortex's structural organization.[10–13] Table 1 presents a summary of brain areas with altered cortex's structure in BQD chewers. Our VBM study of BQD indicated that compared with controls, BQD individuals had significantly decreased gray matter volume (GMV) in the bilateral dorsolateral prefrontal cortex (dlPFC), right anterior cingulate cortex (ACC), right superior temporal gyrus, and midbrain. In contrast, the GMV of the right hippocampus and right precuneus were significantly increased. The GMV in dlPFC and right ACC were negatively correlated with the BQD duration in BQD patients.[10]

Using VBM analysis, Yuan et al. demonstrated that GMV was lower in three critical brain regions

Table 1. Brain areas with altered cortex's structure in BQD chewers.

Source	Area of brain cortex's structural alteration	
Chen et al.[10]	↑ GMV in right hippocampal and right precuneus	↓ GMV in in the midbrain, right ACC, dlPFC, and rSTG
Yuan et al.[11]	NA	↓ GMV in bilateral vmPFC, bilateral dlPFC/insula, and left OFC
Zhu et al.[12]	NA	↓ Cortical thickness in bilateral dlPFC
Sariah et al.[13]	NA	↓ Cortical thickness in left precuneus, left entorhinal, right paracentral, middle temporal, and caudal middle frontal gyri

↑, increased; ↓, decreased; NA, not applicable; ACC, anterior cingulate cortex; BQD, betel quid dependence; dlPFC, dorsal lateral prefrontal cortex; GMV, gray matter volume; OFC, orbital frontal cortex; rSTG, right superior temporal gyrus; vmPFC, ventral medial prefrontal cortex.

in BQD patients than in the controls: the left orbitofrontal cortex, the bilateral dlPFC/insula, and the ventral medial prefrontal cortex. Reduced GMV in the dlPFC may also predict the BQD degree score, daily betel quid eating, and chewing history.[11] In addition, these findings may benefit the investigation of potential structural foundations for BQD.

Notably, VBM is particularly sensitive to the level of smoothing, the alignment method, and the normalizing template selected.[14,15] Additionally, VBM considers the entirety of the brain's gray matter, assessing for a variety of gray matter features, such as cortical thickness, cortical surface area, and cortical folding.[16,17] These elements may lessen the VBM method's sensitivity in identifying the substantial consequences of brain structural abnormalities in BQD patients. FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging, Boston) comprises a popular and freely available set of tools for deriving neuroanatomical volume and cortical thickness measurements using automated brain segmentation (http://surfer.nmr.mgh.harvard.edu), which is the most widely used SBM software. SBM analysis approaches have been put forward as an alternative method for probing cortical gray matter group changes. Compared with VBM, SBM separates GMV into the cortical thickness and area using a geometric model of the cortical surface to acquire morphometric measures, which are confounded in VBM approaches. Therefore, when evaluating morphological anomalies in brain regions, cortical thickness might be more relevant than GMV. SBM is likely to yield more precise information about underlying disease mechanisms and may contribute to our understanding of the neuropathophysiology of dependence-related brains.

Only a few studies have examined cortical thickness changes in BQD chewers. In one study, BQD chewers had reduced cortical thickness in the precuneus, entorhinal, right paracentral, middle temporal, and caudal middle frontal gyri compared to healthy controls (HCs).[13] The results showed that BQD chewers had aberrant cortical thickness. Moreover, according to a systematic review of BQD-related neuroimaging effects, the duration and severity of BQD significantly impacted the structure, metabolism, and function of the cognitive, reward, and impulsive circuits in the brain.[18] However, the neurological underpinnings of the BQD-related abnormalities in cortical thickness and brain circuitry deficit are largely unknown.

In this study, we hypothesized that BQD individuals may have potential abnormalities in the cortical thickness. To verify this hypothesis, the SBM method based on high spatial resolution 3D structural images was used to detect cortical thickness changes in BQD chewers on whole-brain analysis, which may expand our knowledge of the neurological basis of BQD. The post hoc tests of correlational analyses were then conducted.

Materials and methods

Inclusion and exclusion criteria

Betel Quid Dependence Scale (BQDS) for self-report was applied to assess the use of BQ. BQD individuals conformed to the criteria for present BQ addiction, as diagnosed by BQDS >4. The BQD volunteers' inclusion criteria were: (1) aged 18–60 years; (2) the Fagerstrom Test for Nicotine Dependence (FTND) was used to screen broadly for nicotine use. It was considered to be high nicotine dependence when FTND $\geqslant 6$. To avoid nicotine dependence, individuals in the BQD group must be nonsmokers or have used nicotine minimally (once or twice a month) over the past 3 years. Additionally, only individuals with an FTND score of less than 6 were included in the BQD group. (3) Addiction often co-occurs with mental illnesses, especially affective (e.g., depression) and anxiety (social anxiety disorder and generalized anxiety disorder) disorders; to rule out the influences of depression and anxiety, the Hamilton Depression Rating Scale-24 item (HAMD-24) and Hamilton Anxiety Rating Scale-14 item (HAMA-14) for self-report were applied for participant evaluation; (4) BQD subjects had a BQDS >4, HAMD-24 $\leqslant 7$, HAMA-14 $\leqslant 7$, and FTND <6; (5) complete imaging data available, and (6) righthandedness.

The HC individuals' inclusion criteria were: (1) aged 18–60 years; (2) no use of BQ, AN, or cigarettes in any form; (3) complete imaging data available, and (4) righthandedness.

The exclusion criteria for all subjects were: (1) use of any addictive or psychoactive medications, such as antidepressants and abuse of any other substances; (2) systemic disorders, family history of mental illness or history of psychosis, either

past or present; and (3) contraindications to MRI assessment, structural abnormalities, or aberrant signals in the craniocerebral MRI.

Initially, 65 BQD individuals and 45 HC participants from the local Hainan provincial population were recruited for MRI scanning. Four participants (one from BQD groups and three from controls) had brain pathologies such as angiocavernoma, arachnoid cyst, and lacunar infarction were excluded. Eight participants (five from BQD groups and three from controls) with head motion >1.5 mm translation and/or >1.5 rotation were excluded. In addition, eight participants (six from BQD groups and two from controls) withdrew from the study due to their inability to endure prolonged MRI scans. Ultimately, only 53 BQD individuals and 37 HC participants were included in this study. The reporting of this study conforms to the STROBE cross-sectional reporting guidelines.[19]

Questionnaire

Before the MRI examination, we conducted a questionnaire evaluation of each individual to determine their age, gender, educational level, daily BQ dosage, BQD duration, and use of alcohol and tobacco. To evaluate BQD, the BQDS was employed. The reliance level of people taking BQD was quantified using this scale, which has been shown to have strong internal consistency and validity.[20,21] BQD has been evaluated using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, and several dependent measures for other substances.[18] However, the most popular BQD evaluation technique was BQDS.[22] FTND was used to assess the nicotine addiction status. Last, the HAMD-24 and HAMA-14 scales were applied to measure depression and anxiousness on the scanner day.

MRI data acquisition

The 3-T MRI scanner with a conventional 32-channel head coil was used to collect the MRI data (TIM Skyra, Siemens Medical Solutions, Erlangen, Germany). All participants were instructed to keep their heads still in the MRI scanner, their eyes open while remaining unfocused, and to use foam headrests to minimize head movement. High-resolution T1-weighted structural imaging was acquired using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence (repetition time = 2530 ms, echo time = 2.98 ms, field of view = 256×256 mm^2, in-plane matrix = 256×256, and 192 sagittal slices with a 1 mm thickness). Then, a routine MRI scan was performed to screen out any substantial cerebral pathology.

Cortical thickness analysis

To estimate cortical thickness, images were processed with the FreeSurfer software package (version 6.0, https://surfer.nmr.mgh.harvard.edu). Briefly, processing included intensity normalization, removal of non-brain tissue, transformation to Talairach-like space, segmentation of gray-white matter tissue, and tessellation and smoothing of the white matter boundary with a Gaussian kernel with a FWHM of 10 mm. The white matter surfaces were then deformed toward the gray matter boundary at each vertex. Subsequently, cortical thickness was calculated based on the distance between the white and gray matter boundaries at each vertex. Each study subject's entire cortex was visualized, and inaccuracies in segmentation were manually edited.

Statistical analysis

The BQD and HC individuals' demographic and clinical characteristics were assessed using IBM SPSS Statistic Software (version 25.0, IBM Corp, Armonk, NY, USA). For continuous variables, the normality test was conducted before the comparison analysis. If the variables satisfied the requirements for normal distribution, an independent two-sample *t*-test was used. Otherwise, the data were examined using an independent two-sample nonparametric test. Age, education, HAMA-14, and HAMD-24 were all evaluated using an independent two-sample *t*-test, whereas sex was assessed using a chi-squared test. Statistical significance was defined as $p < 0.05$.

Sex, age, and educational level were used as covariates in a two-sample *t*-test using the FreeSurfer software to confirm the significant between-group variations in cortical thickness. In addition, the Monte Carlo was used in multiple comparisons and was considered statistically significant if $p < 0.05$.

Regions of interest (ROIs) were defined purely on the basis of brain anatomy. The cortical thickness data for each individual were extracted from each ROI that significantly differed between groups on

Table 2. Demographics and clinical characteristics of participants.

Variables	BQD ($n=53$)	HC ($n=37$)	p-Value
Sex (males/females)	37/16	24/13	0.621[a]
Age (year)	38.2 ± 11.0	41.9 ± 11.6	0.125[b]
Education (year)	12.2 ± 2.8	12.9 ± 2.9	0.158[b]
BQDS (score)	8.8 ± 3.0	N/A	
BQD duration (year)	14.1 ± 8.3	N/A	
Daily BQ dosage	7.7 ± 7.0	N/A	
% Reporting no use of alcohol	45.3	N/A	
% Reporting no use of tobacco	47.2	N/A	
HAMA-14 (score)	1.6 ± 1.8	2.2 ± 1.9	0.117[b]
HAMD-24 (score)	2.1 ± 2.2	2.6 ± 2.5	0.283[b]

Values are expressed as means ± standard deviation except for sex. Sex is presented as a number.
[a]p-Value between the two groups was obtained by the chi-squared test.
[b]p-Value between the two groups was obtained by an independent-samples t-test.
BQ, betel quid; BQD, betel quid dependence; BQDS, betel quid dependence scale; HAMA-14, Hamilton anxiety rating scale-14 item; HAMD-24, Hamilton depression rating scale-24 item; HC, healthy control; N/A, not applicable.

whole-brain analysis. The selection of functional data by this criterion cannot bias the results statistics, and all results statistics are independent of the selection criteria under the null hypothesis.[23] Furthermore, selective analysis is a powerful tool and is perfectly justified whenever the results are statistically independent of the selection criterion under the null hypothesis. Therefore, we argue that the correlational analyses with ROI defined purely based on brain anatomy may not be "double dipping" and will not result in distorted descriptive statistics and invalid statistical inference. Pearson's correlation analysis was conducted between the cortical thickness values of ROIs and BQDS, duration, daily BQ dosage, BQ-years, HAMA-14, and HAMD-24, with a significance value of $p < 0.05$.

Results

Demographic and clinical data

In this study, 90 volunteers (53 BQD chewers and 37 controls) were included. BQD chewers had an average age of 38.2 ± 11.0 years and a mean educational duration of 12.2 ± 2.8 years. The average age and educational background of the controls were 41.9 ± 11.6 years and 12.9 ± 2.9 years, respectively. BQD chewers reported having been doing so for an average of 14.1 ± 8.3 years (range 5.8–22.4 years). The BQD chewers had an average BQDS score of 8.8 ± 3.0. On average, HAMA-14 and HAMD-24 failed to meet the threshold for clinical significance. The average and SD of the FTND scores of the BQD group was 1.6 ± 1.7. Regarding age, sex, educational status, HAMA-14, or HAMD-24, there was no statistically significant difference between the BQD chewers and HCs (all $p > 0.05$). The demographic details of both groups are summarized in Table 2.

Group differences in cortical thickness

A significant difference between the BQD chewers and HCs in the cortical thickness of the right cerebral hemisphere was noted using an independent-sample t-test, with age, sex, and educational duration as covariates. The BQD group had a higher cortical thickness than the HC group in two clusters, namely, at the lateral orbitofrontal ($t = 4.703$, $p = 0.0028$) and pars opercularis ($t = 3.602$, $p = 0.0403$) of the right cerebral hemisphere (Figure 1 and Table 3). There were no significant differences between the BQD chewers and HCs in the age, sex, or educational duration-adjusted cortical thickness of the left cerebral hemisphere.

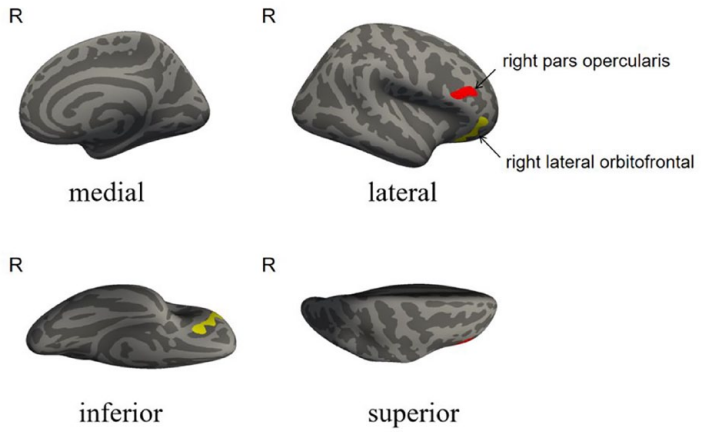

Figure 1. Cortical thickness maps show differences between BQD individuals and HC subjects ($p < 0.05$, Monte Carlo). The BQD group showed significantly higher cortical thickness values in the right lateral orbitofrontal and right pars opercularis regions relative to the HC group. Colors in red and yellow indicate a significant increase in cortical thickness values in the right pars opercularis and right lateral orbitofrontal regions in the 2-sample *t*-test, respectively.
BQD, betel quid dependence; HC, healthy control; R, right hemisphere.

Table 3. Summary of FreeSurfer cortical thickness results (BQD > HC) ($p < 0.05$, Monte Carlo).

Brain region	Side	Cluster size	MNI coordinates			*t* Value	*p*-Value
		(mm^2)	*X*	*Y*	*Z*		
Lateral orbitofrontal	Right	555.53	26.5	26.8	−15	4.703	0.0028
Pars opercularis	Right	366.4	44.5	26.1	17.9	3.602	0.0403

BQD, betel quid dependence; HC, healthy control; MNI, Montreal Neurological Institute coordinate system or template; *x*, *y*, *z*, coordinates of primary peak locations in the MNI space.

Correlation analysis results

Using Pearson correlation analysis, the BQD duration was found to be negatively correlated with the cortical thickness of the right pars opercularis ($r = -0.274$, $p = 0.047$; Figure 2). There was no correlation between BQDS, daily BQ dosage, BQ-years, and cortical thickness alterations. In addition, no correlation was identified between HAMA-14 or HAMD-24 and cortical thickness changes.

Discussion

In our study, the BQD group exhibited higher cortical thickness than the HC group in the lateral orbitofrontal and pars opercularis of the right cerebral hemisphere, which contradicts some prior reports in BQD chewers.[12,13] One study reported significantly decreased cortical thickness in the precuneus, entorhinal, right paracentral, middle temporal, and caudal middle frontal gyri in 24 male BQD chewers.[13] Furthermore, in a recent investigation, BQD chewers displayed thinner cortex in the bilateral dorsolateral prefrontal cortex compared to HCs.[12] In addition, greater cortical thickness of the right pars opercularis was negatively associated with BQD duration in our study.

Increased cortical thickness in the orbitofrontal region of the right cerebral hemisphere might be attributed to the long-term enhanced reward system. Our earlier research identified that BQ chewing was associated with changes in spontaneous brain activity in this reward system, evidenced by a higher percent fluctuation amplitude in the right orbitofrontal cortex.[24] Furthermore, Sariah et al. documented increased functional connectivity (FC) in the orbitofrontal cortex.[25,26] These data suggested that BQ addiction fosters the enhancement of the orbitofrontal network, which is critical for regulating emotions, monitoring rewards, and evaluating punishment.[27] Its disruption by addictive drugs is

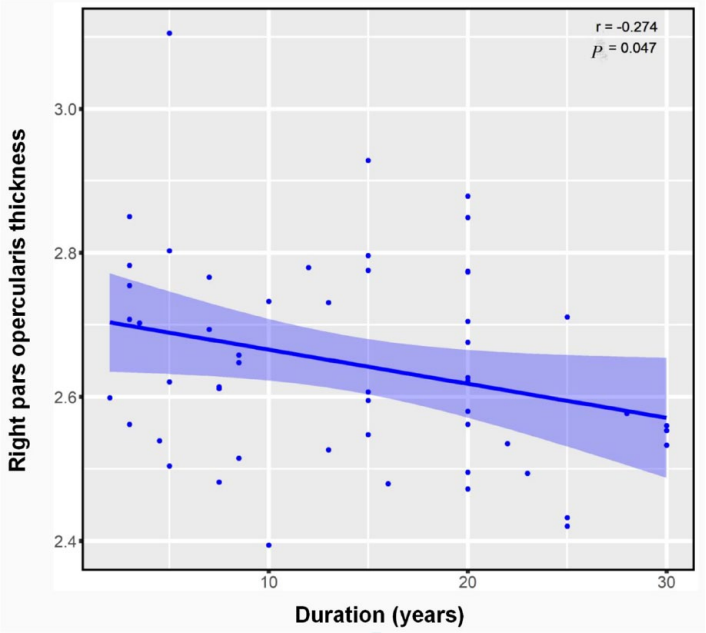

Figure 2. Correlation results between cortical thickness value and duration of BQD. Pearson correlation analyses reveal that the cortical thickness value of the right pars opercularis was negatively correlated with BQD duration in BQD individuals ($p < 0.05$).
BQD, betel quid dependence.

correlated with maladaptive and impulsive decision-making.[28]

The orbitofrontal cortex and the dorsal lateral prefrontal cortex play a pivotal role in reward processing,[27] potentially explaining the noted abnormalities in observed decision-making and goal-driven behavior abnormalities in BQD chewers.[29] However, contradictory findings have been reported in two studies, where a reduction in frontal (middle frontal and prefrontal) cortical thickness was presented in BQD chewers.[12,13] These disparities might stem from the varied effects of BQ on different functional brain systems, including those governing impulsivity, cognition, and reward responses. Specifically, the cortical thickness of the bilateral dlPFC appears to play a role in mediating the correlation between BQ chewing and executive function, suggesting a decline in executive function believed to be associated with impaired inhibitory control of reward-related behavior.[12] Consequently, alterations in the dlPFC may influence impaired decision-making, cognitive control, and memory processing, fostering habitual and compulsive BQ chewing.

Furthermore, inconsistencies in cortical thickness might be attributed to the varying compositions of BQ consumed among diverse populations and regions. BQ can be prepared and consumed raw, boiled, roasted, or cured and often involves the combination of thinly sliced AN with slaked lime in a betel leaf, optionally accompanied by tobacco.

The sex of the participants and the duration of BQ chewing are other crucial factors potentially influencing the observed variations in cortical thickness. It is worth noting that some studies exclusively enrolled male participants.[12,13] In this study, we restricted our enrollment to individuals with a BQ chewing history exceeding 3 years to analyze the long-term effects on cortical thickness. These findings imply that anatomical shifts in the brain's reward system could be associated with BQ dependence. However, further exploration to determine whether these changes are precursors or consequences of BQ addiction is needed.

Notably, an increase in the right pars opercularis cortical thickness was observed in the BQD group. The pars opercularis is part of Broca's area and is instrumental in speech production/language articulation. Aberrations in this area are associated with phenomena such as hallucinations and auditory manifestations,[30] suggesting a potential link with BQD neurobiology. Broca's area is generally in the left hemisphere (in ~90%

of right-handers and 70% of left-handers), whereas the pars opercularis region identified in the current study is in the right hemisphere. The pars opercularis in the right hemisphere is most typically associated with inhibitory control and self-regulation functions,[31] including in a gray matter study of addiction.[32] Therefore, a region associated with self-regulation would be abnormal in a disorder characterized by difficulties in self-regulation.

Interestingly, a reverse correlation was found between BQD duration and the cortical thickness of the right pars opercularis in the BQD group, suggesting BQD individuals with prolonged BQ usage may develop tolerance. In the early stages of BQD duration, chewing BQ caused a significantly greater cortical thickness. However, the increase in cortical thickness caused by the same dosage of BQ became less noticeable over the duration of BQD due to the tolerance. Therefore, the increased cortical thickness in the right pars opercularis in BQD chewers may be a risk marker for early BQ addiction. An earlier structural MRI study suggested that methamphetamine prenatal exposure reduced pars opercularis cortical thickness in BQD chewers compared to HCs, indicating that different forms of psychoactive substances may have a range of effects on the brain.[30] Correlation was only found between cortical thickness alteration and duration of BQD and no was found in BQDS suggesting that BQD duration may have a greater impact on brain structure or that it may be due to the relatively low BQD score (BQDS, 8.8 ± 3.0). The small sample size might also have accounted for the results. In addition, no correlation was identified between cortical thickness changes with HAMA-14 or HAMD-24, suggesting that anxiety or depressive mood in the BQD group might not contribute to the cortical thickness changes. There's also no statistical difference in HAMA-14 and HAMD-24 between the BQD and HC groups.

Morphometric alterations related to BQD are only found in the right hemisphere, suggesting that the right hemisphere is more susceptible to BQD. This may be attributed to the right-handed participants in our research. The duration of BQ chewing may be a potential factor influencing the observed variations in cortical thickness. In this study, We limited our study's participant pool to individuals who have a history of chewing BQ for more than 3 years. In addition, the small sample size could have influenced the results observed.

While the carefully selected samples in this study ensured the relative specificity of BQD-related problems and the low use of other addictive substances, alcohol, and nicotine consumption is still widespread in BQD subjects and their effects could not be fully excluded. Moreover, addiction often co-occurs with mental illnesses, especially affective (e.g., depression) and anxiety (social anxiety disorder and generalized anxiety disorder) disorders. Although depression and degrees of anxiety failed to meet the threshold for clinical significance, and there's also no statistical difference in HAMA-14 and HAMD-24 between the BQD and HC groups, the average and SD of the HAMA-14 and HAMD-24 scores of the BQD group were relatively lower than HC group. These factors may have a potential impact on the observed variations in cortical thickness. In future research design, we should take these potential confounding factors into account and avoid their effects as much as possible.

In summary, our study demonstrated abnormalities in cortical thickness in individuals with BQD, enhancing our understanding of the neurological mechanisms underlying BQD. We theorized that the orbitofrontal cortex is a significant component in the brain's reward system associated with BQ dependency, influencing an individual's decision to continue or cease BQ consumption and thereby sustaining BQ-dependent behavior. Future longitudinal neuroimaging studies on BQ could shed light on whether the observed alterations in cortical thickness are precursors, risk factors, or direct results of BQD use.

Limitations

This study had several limitations. First, we could not definitively link BQD to specific regional anomalies in cortical thickness in this cross-sectional study. Therefore, a longitudinal investigation is required in future research to elucidate the concerns about causality when using a comprehensive experimental method. Second, since we did not perform complex neuropsychological testing, providing a more thorough justification for the abnormal MRI data was challenging. Third, this is a single-center study and thus the results could not be further validated by the external validation dataset. Although the carefully selected samples in this study ensured the relative specificity of BOD-related issues and minimal tobacco use, nicotine consumption remains prevalent among BOD subjects, and its effects cannot

be entirely excluded. Other mental illnesses, such as schizophrenia and autism, were evaluated through self-report rather than specific assessment scales. To achieve a more comprehensive exclusion of these mental diseases and minimize their potential impact, standardized assessment tools should be used in future research to screen for these related mental illnesses. Last, a thorough examination of BQD brain structure, function, and metabolism using multimodal fusion techniques and a more comprehensive explanation of genetic pathways are lacking in the current study. In future studies, we plan to use multimodal fusion techniques and genetic imaging to learn more about how gene-environment-brain network behavior cross-information regulates BQ addiction at the molecular level.

Conclusion

This study demonstrated a notable augmentation in the cortical thickness of the orbitofrontal and pars opercularis regions of the right cerebral hemisphere in individuals afflicted with BQD. This finding of morphometric alterations significantly broadens our comprehension of the neurological complexities underlying BQD.

Declarations

Ethics approval and consent to participate

Based on the Declaration of Helsinki (2000), the Research Ethics Review Committee of the Hainan General Hospital formally approved this study (Number 2017 - 4). Before being included in the study, each participant provided written informed consent.

Consent for publication

Not applicable.

Author contributions

Li Li Fu: Conceptualization; Investigation; Methodology; Software; Supervision; Validation; Writing – original draft; Writing – review & editing.

Hui Juan Chen: Conceptualization; Investigation; Methodology; Software; Supervision; Validation; Writing – original draft; Writing – review & editing.

Wei Yuan Huang: Conceptualization; Methodology; Validation; Writing – review & editing.

Yihao Guo: Conceptualization; Methodology; Validation; Writing – review & editing.

Li Ting Liu: Data curation; Methodology; Project administration; Writing – review & editing.

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Hao Dong Qin: Data curation; Methodology; Project administration; Writing – review & editing.

Tao Liu: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

Feng Chen: Conceptualization; Investigation; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets in this study are not available currently because the present data is part of an ongoing longitudinal study and most data are still in collection and ought to be protected. Reasonable requests to obtain the data could be emailed to FC, fenger0802@163.com.

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Supplemental material

Supplemental material for this article is available online.

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