



A multivariate pattern analysis of resting-state functional MRI data in Naïve and chronic betel quid chewers

Zeqiang Linli^{1,2} · Xiaojun Huang³ · Zhening Liu³ · Shuixia Guo^{1,2} · Adellah Sariah^{3,4}

© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Betel quid (BQ) is the fourth most commonly consumed psychoactive substance in the world. However, comprehensive functional magnetic resonance imaging (fMRI) studies exploring the neurophysiological mechanism of BQ addiction are lacking. Betel-quid-dependent (BQD) individuals ($n = 24$) and age-matched healthy controls (HC) ($n = 26$) underwent fMRI before and after chewing BQ. Multivariate pattern analysis (MVPA) was used to explore the acute effects of BQ-chewing in both groups. A cross-sectional comparison was conducted to explore the chronic effects of BQ-chewing. Regression analysis was used to investigate the relationship between altered circuits of BQD individuals and the severity of BQ addiction. MVPA achieved classification accuracies of up to 90% in both groups for acute BQ-chewing. Suppression of the default-mode network was the most prominent feature. BQD showed more extensive and intensive within- and between-network dysconnectivity of the default, frontal-parietal, and occipital regions associated with high-order brain functions such as self-awareness, inhibitory control, and decision-making. In contrast, the chronic effects of BQ on the brain function were mild, but impaired circuits were predominately located in the default and frontal-parietal networks which might be associated with compulsive drug use. Simultaneously quantifying the effects of both chronic and acute BQ exposure provides a possible neuroimaging-based BQ addiction foci. Results from this study may help us understand the neural mechanisms involved in BQ-chewing and BQ dependence.

Keywords Betel-quid addiction · Functional magnetic resonance imaging · Multivariate pattern analysis · Acute effect · Chronic effect

Zeqiang Linli and Xiaojun Huang contributed equally to this work.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11682-020-00322-6>) contains supplementary material, which is available to authorized users.

✉ Shuixia Guo
guoshuixia75@163.com

✉ Adellah Sariah
adellahsariah@gmail.com

¹ MOE-LCSM, School of Mathematics and Statistics, Hunan Normal University, Changsha, People's Republic of China

² Key Laboratory of Applied Statistics and Data Science, Hunan Normal University, College of Hunan Province, Changsha, People's Republic of China

³ Mental Health Institute of the Second Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China

⁴ Department of Mental Health and Psychiatric Nursing, Hubert Kairuki Memorial University, Dar es Salaam, Tanzania

Introduction

Drug addiction encompasses a relapsing cycle of intoxication, bingeing, withdrawal, and craving that results in excessive drug use despite adverse consequences (Goldstein and Volkow 2011), and has been identified as a chronic brain disease (Leshner 1997). With the development of neuroimaging techniques such as functional magnetic resonance imaging (fMRI), researchers began to investigate the neurobiological mechanisms of substance addiction, in which psychoactive substances such as nicotine, alcohol, and caffeine have attracted wide attention (Doyle et al. 2010; Zahr et al. 2011; Lerman et al. 2014; Cheng et al. 2019). Betel quid (BQ), the fourth most commonly consumed psychoactive substance in the world after the three drugs above (Boucher and Mannan 2002), is a mixture of ingredients that typically includes areca nut, *Piper betel* leaf, slaked lime (calcium hydroxide), tobacco, and a Chinese herb (*Acacia catechu*) for flavor, but the ingredients vary considerably from region to region (Lee et al. 2014.). Chewing BQ has produced positive effects such as

increased concentration, mild euphoria, and relaxation, postprandial satisfaction, heightened alertness, and increased capacity to work for habitual users, but long-term BQ exposure has also been associated with negative effects such as habituation, addiction, and withdrawal (Osborne et al. 2017). However, such a neuroimaging study on BQ is not as extensive compared with that of the above substances because of the limited geographical localization of BQ users (Gupta and Warnakulasuriya 2002). Independent of stimulus-biased responses, resting-state fMRI (rs-fMRI) provides useful information about the natural mode of brain function, which has been proven immensely valuable for neuroimaging study.

Recently, a review systematically assessed previous rs-fMRI studies on BQ addiction (Sariah et al. 2019). Using functional connectivity density (FCD), Liu et al. (2016a) reported that addicts had altered long-range and short-range FCD in the right anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC) and part of the default-mode network (DMN). With ACC as the seed region, Liu et al. (2016b) found that functional connectivity (FC) from ACC to reward networks was enhanced in addicts, while FC from ACC to DMN was weakened. They also showed that the PFC of addicts had a lower amplitude of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo) (Liu et al. 2016c). Zhu et al. (2017) indicated the dysfunction of DMN in addicts. Using various metrics such as FC, ALFF, ReHo, graph theory and network-based statistics, a recent rs-fMRI study showed that there might be an enhanced reward system and visual-spatial processing ability in addicts (Weng et al. 2018). Using independent component analysis, we reported that for the healthy individuals, chewing BQ can immediately increase connectivity of the frontal networks (e.g., the orbital frontal and frontoparietal networks) and decrease that of DMN (Huang et al. 2017a). We also found increased FC in the networks (e.g., the orbital frontal network) related to reward sensitivity and affective decision-making and decreased FC in the parts of DMN (e.g., medial frontal/ACC network) in addicts (Huang et al. 2017b).

It is worth noting that, except Huang et al. (2017a) studying the acute effects (i.e., instantaneous changes in the functional brain after chewing BQ) of healthy individuals, the above-mentioned rs-fMRI studies only focused on the chronic effects (i.e., functional brain differences between long-term addicts and healthy controls under normal conditions). Indeed, acute drug administration may have different drug responsiveness between naïve users and habitual users because of related tolerance, while chronic effects are more related persistence consequence of acute and long-term drug use. Combining these two different research perspectives would help us develop a profound and comprehensive understanding of the neural mechanisms of BQ addiction.

It is also worth noting that the above studies on BQ addiction are based on the conventional univariate analysis, namely

region-by-region or connectivity-by-connectivity group-level statistical comparisons. Although localized to regions associated with changes caused by BQ addiction, the univariate analysis compares individual brain regions or connections in isolation, which is an overly simplistic assumption about brain function (Bullmore and Sporns 2012). Because brain functional organization is not necessarily discrete, and our goal is to understand the entire brain, not single brain regions/connections, it is also necessary to detect the correlation *between* brain regions/connections (Nicholas and Turk 2013).

Multivariate Pattern Analysis (MVPA), based on machine learning, decodes difference patterns between brain regions/connections by learning a discrimination rule from a data set, which can subsequently categorize new samples. Compared with the univariate approach, MVPA considers variables together to take better advantage of the inherent multivariate nature of high-dimensional neuroimaging data (Norman et al. 2006), and it can identify the features that contribute the most to the classifier (Meier et al. 2012). Therefore, MVPA has been widely used in neuroimaging studies (Ding et al. 2015; Guo et al. 2018; Loos et al. 2019). Among many MVPA methods, support vector machine (SVM) is widely used for its excellent classification performance and its ability to handle very high-dimensional data.

In this study, SVM was used to explore the acute effects of BQ-chewing in addicts and controls respectively and a cross-sectional comparison was conducted to explore the chronic effects. The main aims were to: (Andrews-Hanna et al. 2010a) use MVPA to obtain the corresponding predictive features of two effects (i.e., the acute effect on controls and addicts and the chronic effect); (Andrews-Hanna et al. 2010b) characterize the features of the two effects from three levels (i.e., connectivity, region, and network), and (Andrews-Hanna et al. 2014) further study the relationship between the altered circuits and BQ dependence severity measures.

Materials and methods

Participants

This study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University. Written informed consent was obtained from all 54 participants including 25 betel-quid dependence (BQD) subjects and 29 healthy controls (HC). All subjects are right-handed male, with 9 years of education or above. The severity of addiction was assessed by the Betel Quid Dependence Scale (BQDS) which follows the DSM-IV criteria (Lee et al. 2012), and duration (year) of BQ-chewing habit of BQD individuals was also gathered. In addition, 4 subjects were excluded due to excessive motion (>2.5 mm translation or $>2.5^\circ$ rotation) during the scans. The final sample was composed of 50

subjects, including 24 BQD individuals (see Table 1 for demographics and see **supplementary material** for more participants' information description).

Data acquisition and preprocessing

All subjects underwent two rs-fMRI scans. After first scanning, they were brought out of the scanner and given BQ. The participants were instructed to chew the nut and swallow the saliva as fast as possible in 3 min. The second rs-fMRI scan was started another 3 min later. Images were acquired on a Philips Gyroscan Achieva 3.0 T scanner (Best, Netherlands) at the Second Xiangya Hospital of Central South University (see **Supplementary material** for more specific acquisition methods and parameters). In this paper, the scans of HC before and after BQ-chewing are denoted as HC_B and HC_A, respectively, while the scans of BQD are denoted as BQD_B and BQD_A, respectively.

Statistical Parametric Mapping (SPM12: <http://www.fil.ion.ucl.ac.uk/spm>) and Data Processing Assistant for resting-state fMRI (DPARSF: <http://rfmri.org/dpabi>) (Yan et al. 2016) were used for preprocessing. Detailed descriptions of the data preprocessing were in the **supplementary material**. After preprocessing, blood oxygen level-dependent (BOLD) time-series were generated for 160 regions of interest (ROIs) derived from a series of meta-analyses of task-related fMRI studies that cover much of the brain (Dosenbach et al. 2010).

Analysis overview

Figure 1 illustrates the analytical pipeline of this study. Pearson correlation coefficient between the BOLD time-series of all ROI was calculated and then underwent Fisher's *r*-to-*z* transformation to improve its normality. This resulted in a 160×160 FC matrix for each of the 2 scans in every subject, whose lower triangle (12,720 elements) was taken as the features in the follow-up analysis.

Table 1 Demographics of the participants

	HC	BQD	<i>P</i> value
Number	26	24	NA
Age (Year)	25.00 (2.66)	23.50 (3.87)	0.12
Education (Year)	16.26 (1.37)	15.12 (1.72)	0.01
BDI	3.85 (4.63)	10.58 (6.69)	<0.01
BAI	23.16 (2.66)	28.30 (6.20)	<0.01
Symptom			
Duration of addiction (Year)	NA	7.12 (3.78)	NA
BQDS	NA	7.58 (2.16)	NA

Note. BQDS: the Betel Quid Dependence Scale; BDI: the Beck Depression Inventory; BAI: the Beck Anxiety Inventory; NA: not applicable

Classification analysis was performed independently for HC and BQD. First, the scans of the BQD group were divided into a training set (80% of the total samples) and an independent test set on a basis of subjects; the same applied to HCs. Then, classifiers were trained with a leave one subject out cross-validation (LOSOCV) framework on the training set and were validated against the independent testing set using majority voting. We iterated 100 times the entire process above to avoid biased selection of the independent testing set, identifying consistent features that were always selected to form part of the classifiers for the subsequent analysis: 1) Characterization of consistent features from three levels (connection, region, network); 2) Exploration of the chronic effects of chewing BQ by cross-section comparing the acute effects between two groups; 3) Examination of the relationship between consistent features of the BQD group and symptoms.

SVM classifier

SVM is a popular classifier among many MVPA technologies because of its ability to handle small samples with high dimensional features, successfully applied to many brain diseases (Ding et al. 2015; Liao et al. 2018; Zhao et al. 2019). For a detailed description of the SVM, see (Burges 1998). To alleviate the risk of over-fitting and facilitate follow-up characterization of contributing features, we chose linear-SVM as the classifier (Pereira et al. 2009) and set the hyperparameter *C* to 1 (Dosenbach et al. 2010), which is the trade-off between the marginal width and the misclassification penalty.

Based on Ding et al. (2015), the scans of each group were divided into a cross-validation set and an independent test set (i.e. 10 scans from 5 subjects). Then, LOSOCV was used in the cross-validation set: similar to leave one out cross-validation (LOOCV), two scans of each subject were designated as validation samples in turn whereas the two scans of remaining subjects were used to train SVM, which then predicted the validation samples to obtain validation accuracy. To speed up computation and improve performance (Pereira et al. 2009; Esterman et al. 2010), feature selection was conducted: 12,720 paired-sample *t*-tests comparing every feature across the classes (before or after chewing BQ) were performed separately on the training set of each LOSOCV fold, selecting significant features ($P(\text{FDR}) < 0.05$) as final training features. Finally, several SVM classifiers generated by LOSOCV were tested on the independent test set, and classes were determined by majority voting that selects the class that gets more than half of the votes of the SVM classifiers.

The above steps were iterated 100 times. To assess the statistical significance of the validation accuracy and test accuracy of each analysis in 100 repetitions, a nonparametric permutation test (1000 permutations) was conducted (Golland and Fischl 2003) (seeing **supplementary material** for detailed calculation procedure).

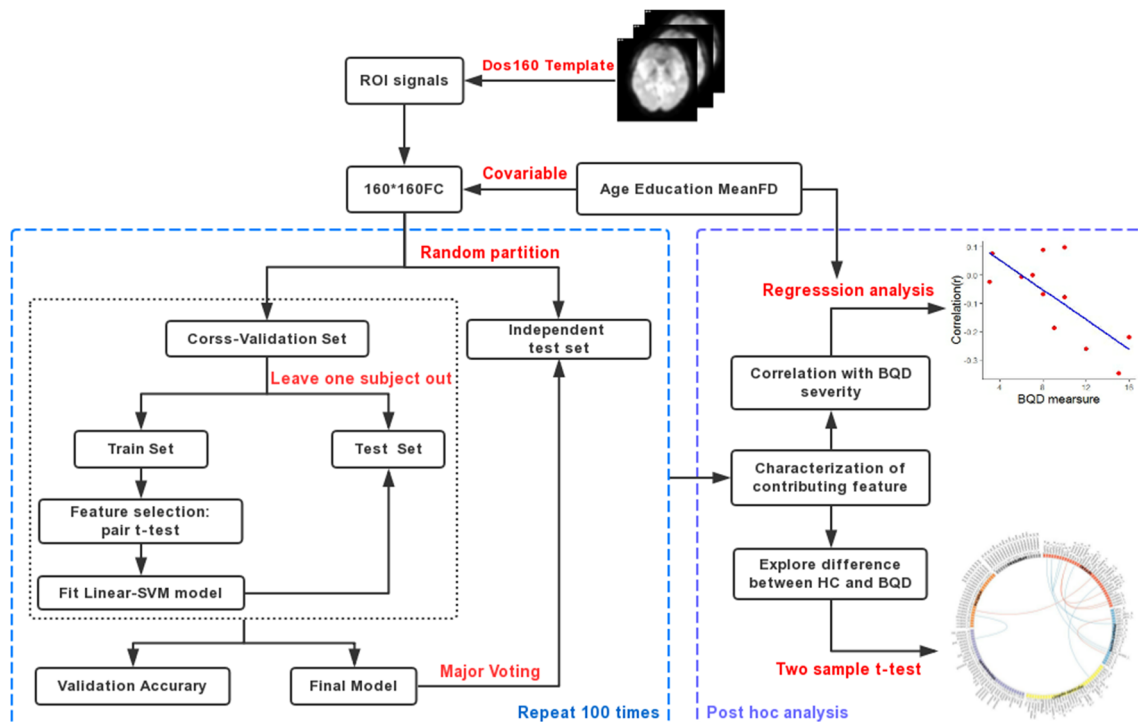


Fig. 1 Flow diagram of the analysis approach employed in the study

Connectivity-level: Exploration of consistent functional connectivity

The selected features (i.e., functional connectivity) in each fold of LOSOCV slightly differed from that of other folds because of feature selection. We selected those features that always form part of the classifier as consistent FC. Further, consistent FC with 100% overlap from the 100 iterations was selected as final consistent FC, considered for follow-up study. Feature coefficient ω of linear SVM represents the contribution of different features to the classifier, named as feature weight. If the scanned images before chewing BQ are taken as negative classes and after chewing BQ as positive classes, the positive weight features can be understood as the enhanced FC after chewing BQ while the negative weight features as weakened FC. In this study, the feature weight of consistent FC is the cumulative weight of 100 iterations.

ROI-level: Exploration of strong contributing brain regions

Different ROIs have different contributions to classifiers. Some ROIs formed many strongly weighted consistent connections with other ROIs while some did not form any. To identify the brain regions that contribute significantly to the classifier, the relative contribution (“region weight”) of each ROI in 160 ROIs was calculated by $1/2$ sum of the absolute weights of all the consistent connections to and from that ROI. In particular, an ROI was given a region weight of zero if it doesn’t form part of

any consistent FC. Then, ROI weight was scaled into $[0,1]$ and those with a scaled weight strength greater than 0.1 were visualized using BrainNet Viewer (Xia et al. 2013).

Network-level: Exploration of functional network

We partitioned 160 ROIs into six functional networks, namely default-mode, frontal-parietal, cingulo-opercular, sensorimotor, occipital, and cerebellum (Fig. S1). To assess the relative contributions of different functional networks, the consistent FC was divided into within-network or between-network connections based on whether they connected ROIs belonging to the same or different networks. If a functional connection was between two networks, half of the feature weight was assigned to each network, otherwise, the feature weight was assigned to the network to which the FC belong. Therefore, the relative contribution of within-network and between-network FC of six networks were calculated.

Chronic effects

Different parts of the consistent FC (i.e., acute effects) between HC and BQD were identified as candidate connections. Then, focusing on these candidate connections, we selected those connections with statistical significance (FDR-corrected) as aberrant circuits related to chronic effects. Specifically, we compared these candidate FCs between the HC group and the BQD group before chewing BQ via a two-

sample t-test, then identified those significantly different FCs corrected by multiple comparisons.

Correlation between consistent features and symptoms

To investigate the relationship between consistent FCs of BQD and symptoms, consistent connections (including before and after chewing BQ) separately regressed against the duration of addiction and BQDS, while controlling for age, education and mean FD.

Results

Classification performance and its statistical significance

Over the 100 random iterations, the classifiers achieved validation accuracy of $93.4\% \pm 2.8\%$ (mean $\pm$ SD) and test accuracy of $94.2\% \pm 6.2\%$ in the HC group, and validation accuracy of $96.2\% \pm 1.6\%$ and test accuracy of $95.7\% \pm 5.4\%$ in the BQD group. Permutation testing showed that the accuracies reported by real-labels samples are significantly different from that of random-labels samples (see Table 2).

Acute effects of BQ chewing in the HC group

For the HC group, an average of 130 (± 40) consistent FCs were selected in each of 100 round LOSOCV, among which 24 FCs were final to consider in follow-up analysis (Fig. 2A, Table S1). Most of these consistent FCs (23/24) were negative weight FCs, mainly including links of left precuneus—PFC [bilateral ventromedial PFC (vmPFC), medial PFC (mPFC), and orbital PFC (orbPFC)] and bilateral posterior cingulate cortex (PCC); left vmPFC—left anterior-PFC; the cerebellum—left PCC; left orbPFC—left ACC; etc. The regions that strongly contributed to the classifiers were left precuneus/PCC, occipital lobes and PFC (including orbPFC, anterior-PFC, and bilateral vmPFC) (Fig. 2B,

Table S3). From the network level, the consistent FCs were mainly the negative weight connections within DMN (Fig. 2C).

Acute effects of BQ chewing in the BQD group

For the BQD group, an average of 298 (± 79) consistent FCs were selected in each of 100 round LOSOCV, among which 77 FCs were final (Fig. 3A, Table S2). Similarly, most of these consistent FCs (73/77) were negative weight FC, mainly including links of left precuneus—PFC (including vmPFC and orbPFC), right superior frontal gyrus (SFG), PCC and right inferior parietal lobules (IPL); right precuneus—bilateral PCC and occipital lobes; right angular gyrus—bilateral ACC, dlPFC, precuneus/PCC and right SFG; etc. The powerful contribution ROIs were the SFG, angular gyrus, and bilateral precuneus/PCC, etc. (Fig. 3B, Table S4). The consistent FCs were also mainly the negative weight within DMN connections, whereas between-network FCs are mainly links between DMN and frontoparietal network (FPN) (Fig. 3C). Furthermore, positive weight connections all were between DMN and FPN.

Chronic effects of chewing BQ

There were 7 identical consistent FCs (Table S5), while 87 were different from each other in the two groups. Twelve of these 87 FCs had discrepancy (FDR-corrected) between BQD and HC, and 5 of them weakened in BQD compared to HC (Fig. 4, Table S6). Brain regions including right SFG, vmPFC, dlPFC, PCC, etc., were the core regions of the chronic effect of BQ-chewing from the perspective of ROIs. As shown in Fig. 4(B), these discrepant connections were largely within and between DMN and FPN. In addition, 11 of 12 discrepant FCs still differed between the HC group and the BQD group after chewing BQ, and the corresponding sign of the t-value is the opposite of those obtained before chewing BQ (Fig. 4(C)).

Table 2 Classification accuracy and statistical significance

	Validation		Test	
	Accuracy	$P_{\text{permutation}}$	Accuracy	$P_{\text{permutation}}$
HC_A vs. HC_B	$93.4\% \pm 2.8\%$	0 ± 0	$94.2\% \pm 6.2\%$	$7.0 \times 10^{-5} \pm 2.6 \times 10^{-4}$
BQD_A vs. BQD_B	$96.2\% \pm 1.6\%$	0 ± 0	$95.7\% \pm 5.4\%$	$6.0 \times 10^{-5} \pm 4.2 \times 10^{-4}$

Note. $P_{\text{permutation}}$ represents permutation testing p value, calculated by (number of permutation errors < observed error) / (number of permutations)

All measures are calculated as mean $\pm$ SD of 100 repetition

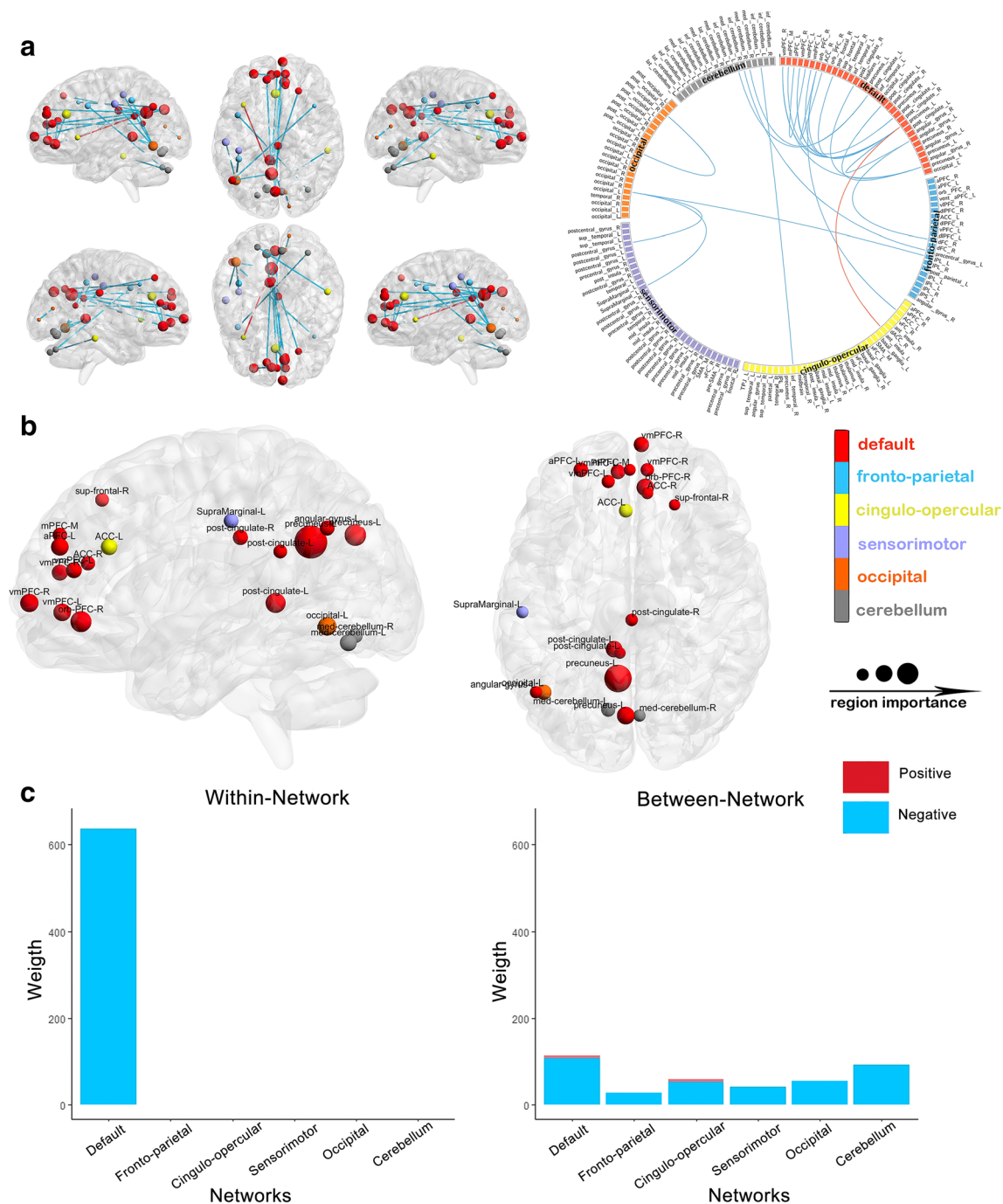


Fig. 2 Acute effects of BQ in the HC group from consistent features **(a)**, contribution ROIs **(b)** and functional network weighting **(c)**. The red line in **(a)** represents a positive weight feature (FC), while the blue line represents a negative weight feature (FC). In **(b)**, the size of ROIs

characterizes relative contribution to the classifiers, namely the greater the size, the more important it is. In the left panel of (c) shows within-network connections weighting, whereas the right panel of (C) shows between-network connections weighting

Relationship between consistent FCs and clinical characteristics

Multiple connections showed a significant regression coefficient of $P < 0.05$ (Table S7, Table S8). Before chewing BQ, connections between occipital, right

precuneus, PCC, left angular gyrus were negatively correlated with Duration, whereas the connections between occipital, right angular gyrus, left dIPFC and right IPL were negatively correlated with BQDS. After chewing BQ, connections between occipital, right precuneus, PCC and angular gyrus was negatively correlated with

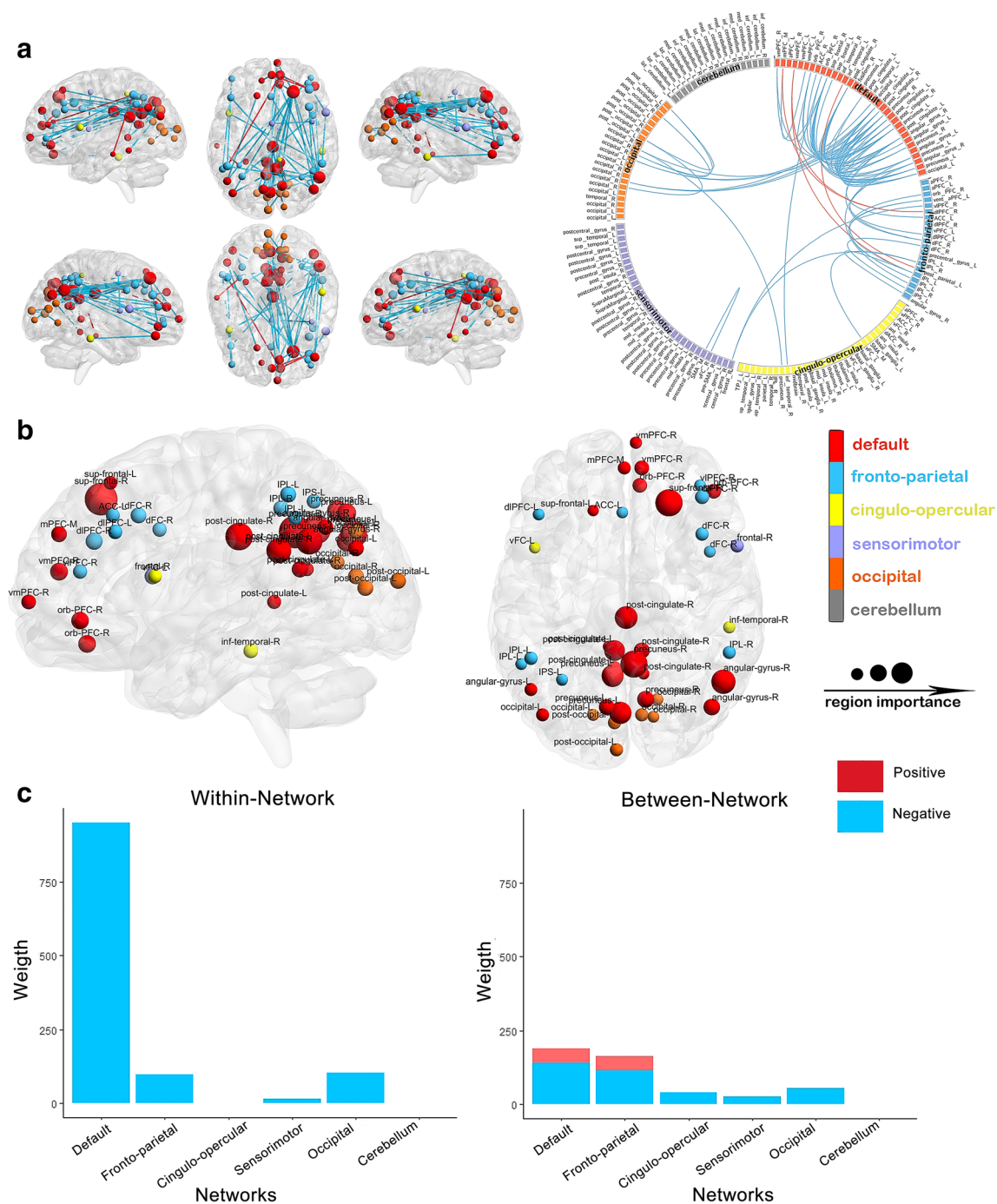


Fig. 3 Acute effects of BQ in the BQD group from consistent features (a), contribution ROIs (b) and functional network weighting (c). The red line in (a) represents a positive weight feature (FC), while the blue line represents a negative weight feature (FC). In (b), the size of ROIs

characterizes relative contribution to the classifiers, namely the greater the size, the more important it is. In the left panel of (c) shows within-network connections weighting, whereas the right panel of (c) shows between-network connections weighting

Duration, whereas connections between right SPG and left angular gyrus was negatively correlated with BQDS. However, due to a large number of connections, these results did not withstand rigorous multiple comparisons correction and should be considered exploratory.

Discussion

In this study, MVPA was used to explore two different effects on the two groups, that is, (Andrews-Hanna et al. 2010a) the acute effects of BQ in HC, (Andrews-Hanna et al. 2010b) the

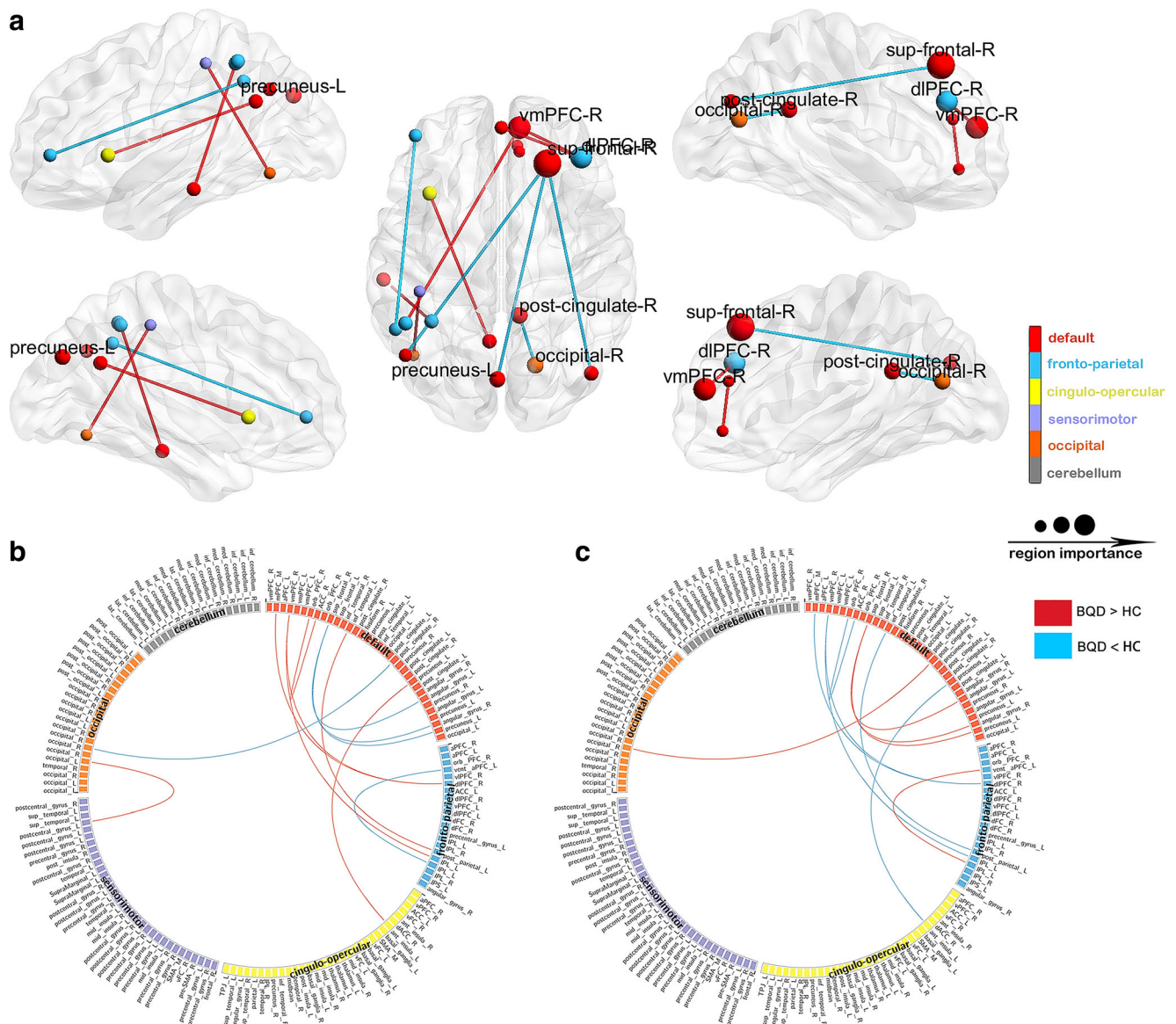


Fig. 4 Chronic effects of chewing BQ. The red lines indicate FCs for which BQD is stronger than HC, while the blue lines indicate FCs for which BQD is weaker than HC. (a) and (b) demonstrate 12 FCs discrepant between HC and BQD before chewing BQ. In (a), the size of the ROI is quantified by the t-value obtained from the two-sample t-

test, and the ROIs with an absolute t-value greater than 3 are visualized. (c) demonstrates 11 of 12 FCs with chronic effects still have group-level discrepancy after BQ-chewing and in many cases the direction changes (blue-to-red or red-to-blue)

acute effects of BQ in BQD, and (Andrews-Hanna et al. 2014) the chronic effects in BQD. To the best of our knowledge, this is the first comprehensive study on the effects of BQ-chewing on the functional brain, providing a new understanding of the neural mechanisms involved in acute and chronic BQ exposure. Consistent features were extracted as aberrant circuits and further explored from three levels of FC, ROIs, and networks to characterize the acute and chronic effects. The results showed that acute BQ-chewing would result in decreased FC predominantly in the DMN, and dysfunctional patterns were more extensive and intensive in BQD compared with HC. Furthermore, exploration of the chronic effects based on the

acute effects indicates that long-term BQ-chewing alters the connections between PFC, SFG, and parietal lobes. Simultaneously quantifying the effects of both chronic and acute BQ-chewing may contribute new neuroimaging-based insight to BQ addiction.

Methodology

During training SVM, due to the particularity of the data (two scans per subject), we developed LOOCV into LOSOCV and used paired-sample t-test for feature selection, which effectively eliminates the confounding factors caused by the

heterogeneity of the subjects and successfully decoded the acute effect (high and statistically significant accuracy). A crucial aspect of MVPA is displaying and analyzing the features that drive the multivariate classifier. Since data division occurs over 100 iterations, consistent features of each iteration may be slightly different. To reduce the bias caused by data partitioning, we used the overlapped consistent features of 100 iterations as the final, which are discriminative and robust in each analysis and are not subject to data segmentation; they are therefore considered in the follow-up analysis.

We took the scans before chewing BQ as a negative class and the scans after chewing BQ as a positive class, so positive weight features can be understood as enhanced FC after chewing BQ, while negative weight features as weakened FC. Indeed, we carried out paired-sample t-tests on those consistent features, and the sign of the t-values obtained is consistent with the weight.

Acute effects of BQ chewing

Whether HC or BQD, the predictive features for the classifiers were dominantly the diminished connectivity within DMN. The DMN consists of three parts including the midline core network, a medial temporal subsystem (MTL-DMN) and a dorsal medial prefrontal subsystem (dMPFC-DMN) (Andrews-Hanna et al. 2010b; Fox et al. 2005). For instance, the midline core of DMN—including the ventral medial prefrontal cortex, the dorsal medial prefrontal cortex, and the PCC/precuneus plus the lateral parietal cortex—plays a key role in internally directed or self-generated thought and is active when people are engaged in self decision-making processes (Andrews-Hanna et al. 2010b). The dMPFC-DMN (including the dMPFC, temporoparietal junction, and temporal pole) (Andrews-Hanna et al. 2010a) subsystem participates in facial emotion recognition and in understanding others' mental states (Andrews-Hanna et al. 2014). The medial temporal lobe (MTL)-DMN subsystem is activated by personal past and future episodic/semantic thoughts, and greater resting-state FC was observed in individuals with such thoughts (Andrews-Hanna et al. 2010b).

Both groups have shown reduced FC between anterior (vmPFC, mPFC, orbPFC) and posterior (PCC/Precuneus) DMN. The mPFC and PCC are structurally (Greicius et al. 2007) and functionally (Buckner et al. 2008) connected. Both of them are recruited for self-related thoughts. Reduced connectivity in the anterior-posterior DMN after acute BQ chewing may impair self-awareness after acute BQ chewing, which supports the uncontrolled drug-taking behavior observed in BQD individuals. Similar results regarding disruption of the DMN function stemming from acute psychoactive drug use have been found in other addiction studies (Cole et al. 2010; Tanabe et al. 2011; Lerman et al. 2014; Huang et al. 2014; Wang et al. 2014; Fedota and Stein 2015; Zhang

and Volkow 2019). For example, acute nicotine administration may improve cognitive performance by suppressing the task-negative, internally driven DMN to focus attention on external goals (Lerman et al. 2014); Tanabe et al. (2011) demonstrated decreased coupling in the DMN after nicotine administration, specifically between the PCC, precuneus, and medial cortex; Wang et al. (2014) found reduced global brain connectivity in several regions of the DMN in the smoking, as compared with smokers in the abstinence condition. Similarly, decreased FC was observed in the precuneus (a key region in the DMN) of electronic cigarette users immediately after use. The decreased FC was associated with reduced craving, decreased withdrawal symptoms and improved concentration (Hobkirk et al. 2018), presenting features that facilitate continual drug use. Further, our findings suggest that BQ may have a positive effect on treatments of some psychiatric disorders with enhanced connections or activations on DMN, such as depression (Greicius et al. 2008; Posner et al. 2013) and schizophrenia (Woodward et al. 2011; Guo et al. 2014).

Usually, the acute effects of drug administration differ between naïve users and habitual users (Zhang and Volkow 2019). In this study, BQD individuals have more extensive and intensive reduced connectivity after chewing BQ than controls similarly to a study investigating acute electronic cigarette use, indicated overall reductions in FC from abstinence to satiety via e-cigarette, which relieved withdrawal symptoms (Hobkirk et al. 2018). Long-term BQ exposure may have contributed to the anatomical or structural abnormalities in the brain regions of addicts as it has been reported in previous studies (Chen et al. 2015; Yuan et al. 2017a; Yuan et al. 2017b). Such abnormalities may cause BQ to have more dramatic psychopharmacological effects on individual brain region. Specifically, BQD individuals have more dysfunctional connections within the posterior DMN (e.g., PCC/precuneus) and with other parts of the DMN. The PCC/precuneus is the most prominent functional hub of the brain as demonstrated by previous studies involved in self-referential thoughts and strong interactivity, as well as cognitive tasks of self-processing (Fransson and Marrelec 2008; Tomasi and Volkow 2010). Hyperconnectivity of PCC/Precuneus with other parts DMN observed in other drug addicts during abstinence might present the ruminative behavior, resulting in the observed distress and unhappiness (Killingsworth and Gilbert 2010); whereas weaker connections after acute BQ chewing may produce the feelings of euphoria, relaxation and a sense of wellbeing in BQD individuals. The SFG, the most predictive ROI in the BQD group (Table S4), has excitatory and inhibitory influences on cravings and the modulations of reactivity to cravings (Rose et al. 2011), where its abnormality might be involved in drug relapses. Moreover, some altered (decreased or increased) connections were found within and between fronto-parietal network involved in various cognitive processes such as attention control (Markett et al. 2014),

inhibitory control (Dodds et al. 2011), and decision-making (Bogdanov et al. 2017). Users of BQ reported experiencing heightened alertness, euphoria, relaxation, arousal, improved motor responses, and a sense of wellbeing, suggesting that the altered connectivity (e.g. dlPFC—mPFC) may enhance cognitive abilities and thus perpetuate addictive behavior. In future studies, such findings may need to be further confirmed by cognitive and behavioral data.

Taken together, our findings suggest that acute BQ-chewing does not alter the functionality of the entire brain but does affect certain brain regions associated with advanced functions such as attention, inhibition, and self-consciousness, in line with a previous EEG study which demonstrated that BQ intoxication does not affect gross human behavior but influences the psychological features of perception including perceived increased arousal, reduced ability to think and slowing of perception of the passage of a single minute time interval (Osborne et al. 2011). In addition, our findings were reproduced in the data that removes global signals. The results showed similar patterns (including consistent FCs, contributing ROIs and network distribution) to previous studies, indicating the reliability of our findings (see **Supplementary Materials**).

Chronic effects of BQ chewing

A more intuitive understanding of the chronic effect of BQ use is a direct comparison between HC and BQD before chewing BQ (i.e., HC_B vs. BQD_B). MVPA approach was employed to explore the chronic effects, unfortunately, the classification accuracy was low and statistically insignificant (see **Supplementary Material**). Our previous study found discrepancies between HC_B and BQD_B using a two-sample t-test which were not corrected for multiple comparisons (Huang et al. 2017b).

It is also reasonable to obtain the chronic difference by cross-sectionally comparing the acute effects of the two groups because the difference may be caused by the prolonged effects of BQ on the BQD's brain. Indeed, there were as many as 87 different consistent FCs between BQD and HC, which indirectly reflects the brain dysfunction caused by long-term BQ dependence. The 12 discrepant connections identified (FDR-corrected) were predominantly across regions of DMN (PFC, SFG, precuneus/PCC, angular gyrus, etc.) and FPN (dlPFC, IPL, etc.), which are involved in higher brain functions such as reward (orbPFC), decision-making (dlPFC), and impulse control (orbPFC, ACC). These results are not surprising since multiple studies suggest that FC changes in these areas are critical to addiction (Kober et al. 2010; Lin et al. 2015; Weiland et al. 2015; Cheng et al. 2019). For example, enhanced ACC—orbPFC in BQD may be associated with inhibitory control of reward-related behavior (Goldstein and Volkow 2002), which may result in the inability of addicted individuals to control short-term and immediate gratification of habitual drug use regardless of existing or

anticipated negative consequences (Cheng et al. 2019). The DMN also interacts with the subcortex, the executive control network (ECN) and salience network (SN) (Li et al. 2018; Raichle 2015) a feature believed to influence cognitive processing, emotional regulation, impulsivity, and attention in goal-directed tasks (Fox et al. 2005). Evidence shows that abnormal DMN function and disrupted interaction with other networks impairs emotional and cognitive processing, leading to craving behavior and relapse (Zhang and Volkow 2019). For example, our study found great dysconnectivity between the DMN and the frontal-parietal network. The frontoparietal network is linked with top-down cognitive control such as working memory, attentional control, mental flexibility and decision-making (Cole et al. 2013). Our results are consistent with findings from other addiction studies. For instance, cocaine-dependent individuals had weaker connectivity between the DMN and frontoparietal ECN (Liang et al. 2015). Additionally, patients with heroin dependence had reduced connectivity between dMPFC and left dorsolateral PFC (a key node in ECN) (Li et al. 2018). We argue that reduced connectivity between the DMN and the FPN may lead to a lack of control over BQ craving and poor decision making, leading to continual use of BQ. Interestingly, most of these 12 connections (11/12) still have significant differences between the two groups after chewing BQ. Taken together, these circuits were noticeably altered by both chronic and acute BQ exposure, providing a reliable neuroimaging-based BQ addiction foci. Although it may miss some information to explore chronic effects by cross-sectional comparison, this is a practical assessment that identified several significantly different connections, providing useful information for future research.

Unlike the acute effects, the chronic effects are sparse and difficult to detect; in other words, functional brains of addicts are “similar” to the controls, with little difference variability between the two groups. Two possible speculations are proposed here. (Andrews-Hanna et al. 2010a) Exploration of chronic effects may be disturbed by various confounding factors, including individuals' differences in lifestyle and withdrawal symptoms (craving, anxiety, irritability, etc.) of BQD individuals (Brooks et al. 2017). In contrast, we used paired-sample t-tests to reduce the contribution of confounding factors due to individual heterogeneity in exploring acute BQ-chewing. (Andrews-Hanna et al. 2010b) Guo et al. (2016) found that schizophrenia patients showed a dynamic structural reorganization as the disease progressed, making the brain of patients “closer” to that of healthy people, or more difficult to distinguish from them. We suspect that the functional brain has a similar remodeling mechanism. In this study, addicts have been chewing BQ for an average of more than 7 years, and their functional brains may have been dynamically reorganized with the course of addiction to accommodate daily neural activities. Therefore, a longitudinal experimental design may be considered in the future to validate these two possible speculations.

Limitation

This study has several limitations. First, because of the particularity of the sample and experimental requirements, this study, like many other studies on drug addiction, has a relatively small sample size with only male participants from Hunan Province, China. In future studies, a larger sample size consisting of both male and female participants from other regions in China may ensure unbiased results. Second, the use of other psychoactive substances, such as cigarettes or alcohol could have influenced the results, even though all recruited participants met the inclusion and exclusion criteria. Finally, future studies using longitudinal data may reduce possible confounders and may also lead to a better understanding of the mechanisms fundamental for the neuro-transition from initial BQ use to dependence..

Conclusion

Existing fMRI studies on drug addiction focus either on chronic effects or on the acute effects, with few studies consider these two effects together (Lerman et al. 2014; Fedota and Stein 2015). Here, MVPA technology was used to comprehensively study the acute and chronic effects of BQ-chewing, which is unprecedented in previous studies on rs-fMRI of BQ dependence, and even rare in other drug addiction studies. We found that acute BQ-chewing can cause dysfunction of DMN, which is more severe and widespread in addicts than controls, while many of these acute changes in brain function are part of chronic changes of long-term BQ-chewing. Our findings provide support and supplement for previous MRI studies on BQ dependence and help us understand the neural mechanisms involved in acute BQ chewing and BQ dependence.

All measures are calculated as mean (SD); P value is obtained by a two-sample t-test. Age and education are covariables in this study.

Acknowledgements Zhening Liu is supported by the China Precision Medicine initiative grant (No. 2016YFC0906300) and the National Natural Science Foundation of China (NSFC) grant (No.81561168021). Shuixia Guo is supported by the National Natural Science Foundation of China (NSFC) grant (No.11671129, 31671134). All the work of the study was done by the authors. The authors were responsible for the authenticity of the data and related results.

Compliance with ethical standards

Conflict of interest All authors declare no competing interests.

Ethical approval All procedures performed in studies involving human participants followed the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

- Andrews-Hanna, J. R., Reidler, J. S., Huang, C., & Buckner, R. L. (2010a). Evidence for the default network's role in spontaneous cognition. *Journal of Neurophysiology*, 104(1), 322–335.
- Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010b). Functional-anatomic fractionation of the brain's default network. *Neuron*, 65(4), 550–562.
- Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, 1316, 29–52.
- Bogdanov, M., Ruff, C. C., & Schwabe, L. (2017). Transcranial stimulation over the dorsolateral prefrontal cortex increases the impact of past expenses on decision-making. *Cerebral Cortex*, 27(2), 1094–1102.
- Boucher, B. J., & Mannan, N. (2002). Metabolic effects of the consumption of Areca catechu. *Addiction Biology*, 7(1), 103–110.
- Brooks, S. J., Ipser, J., & Stein, D. J. (2017). Chronic and acute nicotine exposure versus placebo in smokers and nonsmokers: A systematic review of resting-state fMRI studies. In *Addictive Substances and Neurological Disease* (p. 319–338). Academic press.
- Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, 1124, 1–38.
- Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature reviews. Neuroscience*, 13(5), 336–349.
- Burges, C. J. C. (1998). A tutorial on support vector machines for pattern recognition. *Data Mining and Knowledge Discovery*, 2(2), 121–167.
- Chen, F., Zhong, Y., Zhang, Z., Xu, Q., Liu, T., Pan, M., Li, J., & Lu, G. (2015). Gray matter abnormalities associated with betel quid dependence: A voxel-based morphometry study. *American Journal of Translational Research*, 7(2), 364–374.
- Cheng, Wei; Rolls, Edmund T.; Robbins, Trevor W.; Gong, Weikang; Liu, Zhaowen; Lv, Wujun et al. (2019): Decreased brain connectivity in smoking contrasts with increased connectivity in drinking. *eLife* 8.
- Cole, D. M., Beckmann, C. F., Long, C. J., Matthews, P. M., Durcan, M. J., & Beaver, J. D. (2010). Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. *Neuroimage*, 52(2), 590–599.
- Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, 16(9), 1348–1355. <https://doi.org/10.1038/nn.3470>.
- Ding, X., Yang, Y., Stein, E. A., & Ross, T. J. (2015). Multivariate classification of smokers and nonsmokers using SVM-RFE on structural MRI images. *Human Brain Mapping*, 36(12), 4869–4879.
- Dodds, C. M., Zamir, M., Robbins, S., & Trevor, W. (2011). Dissociating inhibition, attention, and response control in the frontoparietal network using functional magnetic resonance imaging. *Cerebral cortex (New York, N.Y. : 1991)*, 5, 21, 1155–1165.
- Dosenbach, Nico, U. F., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., et al. (2010). Prediction of individual brain maturity using fMRI. *Science (New York, N.Y.)*, 329(5997), 1358–1361.
- Doyle, L. W., Cheong, J., Hunt, R. W., Lee, K. J., Thompson, D. K., Davis, P. G., Rees, S., Anderson, P. J., & Inder, T. E. (2010). Caffeine and brain development in very preterm infants. *Annals of Neurology*, 68(5), 734–742.
- Esterman, M., Tamber-Rosenau, B. J., Chiu, Y.-C., & Yantis, S. (2010). Avoiding non-independence in fMRI data analysis: Leave one subject out. *Neuroimage*, 50(2), 572–576.

- Fedota, J. R., & Stein, E. A. (2015). Resting-state functional connectivity and nicotine addiction: Prospects for biomarker development. *Annals of the New York Academy of Sciences*, 1349, 64–82.
- Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, 102(27), 9673–9678.
- Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage*, 42(3), 1178–1184.
- Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, 12(11), 652–669.
- Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *The American journal of psychiatry n.*, 10(159), 1642–1652.
- Golland, P., & Fischl, B. (2003). Permutation tests for classification: Towards statistical significance in image-based studies. *Information Processing in Medical Imaging*, 18, 330–341.
- Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., Reiss, A. L., & Schlagter, A. F. (2007). Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry*, 62(5), 429–437.
- Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2008). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, 1(19), 72–78.
- Guo, S., Kendrick, K. M., Yu, R., Wang, H.-L. S., & Feng, J. (2014). Key functional circuitry altered in schizophrenia involves parietal regions associated with sense of self. *Human Brain Mapping*, 35(1), 123–139.
- Guo, S., Palaniyappan, L., Liddle, P. F., & Feng, J. (2016). Dynamic cerebral reorganization in the pathophysiology of schizophrenia: A MRI-derived cortical thickness study. *Psychological Medicine*, 46(10), 2201–2214.
- Guo, S., Huang, C.-C., Zhao, W., Yang, A. C., Lin, C.-P., Nichols, T., & Tsai, S.-J. (2018). Combining multi-modality data for searching biomarkers in schizophrenia. *PLoS One*, 13(2), e0191202.
- Gupta, P. C., & Warnakulasuriya, S. (2002). Global epidemiology of areca nut usage. *Addiction Biology*, 7(1), 77–83.
- Hobkirk, A. L., Nichols, T. T., Foulds, J., Yingst, J. M., Veldheer, S., Hrabovsky, S., Richie, J., Eissenberg, T., & Wilson, S. J. (2018). Changes in resting state functional brain connectivity and withdrawal symptoms are associated with acute electronic cigarette use. *Brain Research Bulletin*, 138, 56–63.
- Huang, W., King, J. A., Ursprung, W., Sanouri, W., Zheng, S., Zhang, N., Kennedy, D. N., et al. (2014). The development and expression of physical nicotine dependence corresponds to structural and functional alterations in the anterior cingulate-precuneus pathway. *Brain and behavior*, 4(3), 408–417.
- Huang, X., Liu, Z., Mwansisya, T. E., Pu, W., Zhou, L., Liu, C., Chen, X., Rohrbaugh, R., Marienfeld, C., Xue, Z., & Liu, H. (2017a). Betel quid chewing alters functional connectivity in frontal and default networks: A resting-state fMRI study. *Journal of magnetic resonance imaging : JMIR*, 45(1), 157–166.
- Huang, X., Pu, W., Liu, H., Li, X., Greenshaw, A. J., Dursun, S. M., Xue, Z., & Liu, Z. (2017b). Altered brain functional connectivity in betel quid-dependent chewers. *Frontiers in Psychiatry*, 8, 239.
- Killingsworth, M. A., & Gilbert, D. T. (2010). A wandering mind is an unhappy mind. *Science n.*, 6006(330), 932.
- Kober, H., Mende-Siedlecki, P., Kross, E. F., Weber, J., Mischel, W., Hart, C. L., & Ochsner, K. N. (2010). Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proceedings of the National Academy of Sciences of the United States of America*, 107(33), 14811–14816.
- Lee, C.-Y., Chang, C.-S., Shieh, T.-Y., & Chang, Y.-Y. (2012). Development and validation of a self-rating scale for betel quid chewers based on a male-prisoner population in Taiwan: The betel quid dependence scale. *Drug and Alcohol Dependence*, 121(1–2), 18–22.
- Lee, C.-H., Chiang, S.-L., Ko, A. M.-S., Hua, C.-H., Tsai, M.-H., Warnakulasuriya, S., et al. (2014). Betel-quid dependence domains and syndrome associated with betel-quid ingredients among chewers: an Asian multi-country evidence. *Addiction (Abingdon, England)*, 7, 109, 1194–1204.
- Lerman, C., Gu, H., Loughhead, J., Ruparel, K., Yang, Y., & Stein, E. A. (2014). Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. *JAMA Psychiatry*, 71(5), 523–530.
- Leshner, A. I. (1997). Addiction is a brain disease, and it matters. *Science (New York, N.Y.)*, 278(5335), 45–47.
- Li, Q., Liu, J., Wang, W., Wang, Y., Li, W., Chen, J., Zhu, J., Yan, X., Li, Y., Li, Z., Ye, J., & Wang, W. (2018). Disrupted coupling of large-scale networks is associated with relapse behaviour in heroin-dependent men. *Journal of Psychiatry & Neuroscience*, 43(1), 48–57.
- Liang, X., He, Y., Salmeron, B. J., Gu, H., Stein, E. A., & Yang, Y. (2015). Interactions between the salience and default-mode networks are disrupted in cocaine addiction. *The Journal of Neuroscience*, 35(21), 8081–8090.
- Liao, W., Li, J., Duan, X., Cui, Q., Chen, H., & Chen, H. (2018). Static and dynamic connectomics differentiate between depressed patients with and without suicidal ideation. *Human Brain Mapping*, 39(10), 4105–4118.
- Lin, F., Wu, G., Zhu, L., & Lei, H. (2015). Altered brain functional networks in heavy smokers. *Addiction Biology*, 20(4), 809–819.
- Liu, T., Li, J., Zhang, Z., Xu, Q., Lu, G., Huang, S., Pan, M., & Chen, F. (2016a). Altered long-and short-range functional connectivity in patients with betel quid dependence: A resting-state functional MRI study. *Cellular Physiology and Biochemistry*, 40(6), 1626–1636.
- Liu, T., Li, J., Zhao, Z., Zhong, Y., Zhang, Z., Xu, Q., Yang, G., Lu, G., Pan, S., & Chen, F. (2016b). Betel quid dependence is associated with functional connectivity changes of the anterior cingulate cortex: A resting-state fMRI study. *Journal of Translational Medicine*, 14, 33.
- Liu, T., Li, J.-J., Zhao, Z.-Y., Yang, G.-S., Pan, M.-J., Li, C.-Q., Pan, S.-y., & Chen, F. (2016c). Altered spontaneous brain activity in betel quid dependence: A resting-state functional magnetic resonance imaging study. *Medicine*, 95(5), e2638.
- Loos, E., Egli, T., Coynel, D., Fastenrath, M., Freytag, V., Papassotiropoulos, A., de Quervain, D. J.-F., & Milnik, A. (2019). Predicting emotional arousal and emotional memory performance from an identical brain network. *Neuroimage*, 189, 459–467.
- Markett, S., Reuter, M., Montag, C., Voigt, G., Lachmann, B., Rudolf, S., et al. (2014). Assessing the function of the fronto-parietal attention network: Insights from resting-state fMRI and the attentional network test. *Human Brain Mapping*, 4(35), 1700–1709.
- Meier, T. B., Desphande, A. S., Vergun, S., Nair, V. A., Song, J., Biswal, B. B., Meyerand, M. E., Bim, R. M., & Prabhakaran, V. (2012). Support vector machine classification and characterization of age-related reorganization of functional brain networks. *Neuroimage*, 60(1), 601–613.
- Nicholas, B., & Turk, B. (2013). Functional interactions as big data in the human brain. *Science (New York, N.Y.)*, 342(6158), 580–584.
- Norman, K. A., Polyn, S. M., Detre, G. J., & Haxby, J. V. (2006). Beyond mind-reading: Multi-voxel pattern analysis of fMRI data. *Trends in Cognitive Sciences*, 10(9), 424–430.

- Osborne, P. G., Chou, T.-S., & Shen, T.-W. (2011). Characterization of the psychological, physiological and EEG profile of acute betel quid intoxication in naïve subjects. *PLoS One*, 6(8), e23874.
- Osborne, P. G., Ko, Y.-C., Wu, M.-T., & Lee, C.-H. (2017). Intoxication and substance use disorder to Areca catechu nut containing betel quid: A review of epidemiological evidence, pharmacological basis and social factors influencing quitting strategies. *Drug and Alcohol Dependence*, 179, 187–197.
- Pereira, F., Mitchell, T., & Botvinick, M. (2009). Machine learning classifiers and fMRI: A tutorial overview. *Neuroimage*, 45(1 Suppl), S199–S209.
- Posner, J., Hellerstein, D. J., Gat, I., Mechling, A., Klahr, K., Wang, Z., McGrath, P. J., Stewart, J. W., & Peterson, B. S. (2013). Antidepressants normalize the default mode network in patients with dysthymia. *JAMA Psychiatry*, 70(4), 373–382.
- Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience*, 38, 433–447.
- Rose, J. E., McClemon, F. J., Froeliger, B., Behm, F. M., Preud'homme, X., & Krystal, A. D. (2011). Repetitive transcranial magnetic stimulation of the superior frontal gyrus modulates craving for cigarettes. *Biological Psychiatry*, 70(8), 794–799.
- Sariah, A., Liu, Z., Pu, W., Liu, H., Xue, Z., & Huang, X. (2019). Structural and functional alterations in betel-quid chewers: A systematic review of neuroimaging findings. *Frontiers in Psychiatry*, 10, 16.
- Tanabe, J., Nyberg, E., Martin, L. F., Martin, J., Cordes, D., Kronberg, E., & Tregellas, J. R. (2011). Nicotine effects on default mode network during resting state. *Psychopharmacology*, 216(2), 287–295.
- Tomasi, D., & Volkow, N. D. (2010). Functional connectivity density mapping. *Proceedings of the National Academy of Sciences of the United States of America*, 107(21), 9885–9890.
- Wang, K., Yang, J., Zhang, S., Wei, D., Hao, X., Tu, S., & Qiu, J. (2014). The neural mechanisms underlying the acute effect of cigarette smoking on chronic smokers. *PLoS One*, 9(7), e102828.
- Weiland, B. J., Sabbineni, A., Calhoun, V. D., Welsh, R. C., & Hutchison, K. E. (2015). Reduced executive and default network functional connectivity in cigarette smokers. *Human Brain Mapping*, 36(3), 872–882.
- Weng, J.-C., Chou, Y.-S., Huang, G.-J., Tyan, Y.-S., & Ho, M.-C. (2018). Mapping brain functional alterations in betel-quid chewers using resting-state fMRI and network analysis. *Psychopharmacology*, 235(4), 1257–1271.
- Woodward, N. D., Rogers, B., & Heckers, S. (2011). Functional resting-state networks are differentially affected in schizophrenia. *Schizophrenia Research*, 130(1–3), 86–93.
- Xia, M., Wang, J., & He, Y. (2013). BrainNet viewer: A network visualization tool BrainNet viewer: A network visualization for human brain Connectomics. *PLoS One*, 8(7).
- Yan, C.-G., Wang, X.-D., Zuo, X.-N., & Zang, Y.-F. (2016). DPABI: Data Processing & Analysis for (resting-state) brain imaging. *Neuroinformatics*, 14(3), 339–351.
- Yuan, F., Kong, L., Zhu, X., Jiang, C., Fang, C., & Liao, W. (2017a). Altered gray-matter volumes associated with betel quid dependence. *Frontiers in Psychiatry*, 8, 139.
- Yuan, F., Zhu, X., Kong, L., Shen, H., Liao, W., & Jiang, C. (2017b). White matter integrity deficit associated with betel quid dependence. *Frontiers in Psychiatry*, 8, 201.
- Zahr, N. M., Kaufman, K. L., & Harper, C. G. (2011). Clinical and pathological features of alcohol-related brain damage. *Nature reviews. Neurology*, 7(5), 284–294.
- Zhang, R., & Volkow, N. D. (2019). Brain default-mode network dysfunction in addiction. *NeuroImage*, 200, 313–331.
- Zhao, W., Guo, S., Linli, Z., Yang, A. C., Lin, C.-P., & Tsai, S.-J. (2019). Functional, anatomical, and morphological networks highlight the role of basal ganglia-thalamus-cortex circuits in schizophrenia. *Schizophrenia bulletin*.
- Zhu, X., Zhu, Q., Jiang, C., Shen, H., Wang, F., Liao, W., & Yuan, F. (2017). Disrupted resting-state default mode network in betel quid-dependent individuals. *Frontiers in Psychology*, 8, 84.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.