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ORIGINAL RESEARCH

Neural response to betel quid cues in chewers: a functional magnetic resonance imaging study

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Abstract

The World Health Organization regards betel quid (BQ) as a human carcinogen. The current study analyzes whether the BQ cues can elicit activity in the chewers' craving-related brain areas. We adopted a cue-reactivity paradigm to examine the changes in the brain activities. The urge intensity was also included to examine whether it can moderate the brain areas stimulated by BQ cues. Sixteen male BQ chewers and 16 healthy male controls were recruited and analyzed. Four types of cues were adopted: BQ cues, matched food cues, visual control cues, and resting crosshair cued. The most direct and important comparison was between the brain activities elicited by the BQ cues versus those by the food cues. Furthermore, to test the current urge intensity effect, we compared BQ chewers with a strong urge versus those with a weak urge. All of the three-dimension anatomical and multi-slice task-based functional images were acquired using 3 T MRI. We found that (1) the BQ chewers and the healthy controls had similar brain activation patterns when comparing any two cue types, (2) the high-urge (not the low-urge) chewers showed craving-related activations (e.g., anterior cingulate cortex, medial orbitofrontal gyrus, and superior frontal gyrus) in the critical BQ cues vs. the food cue comparisons. (3) The high-urge chewers had larger contrast activations (BQ - Food) in many craving-related brain areas than low-urge chewers did (e.g., frontal gyrus). The urge states endorsed by the chewers can moderate the neural responses to BQ cues. Multisensory cues should be considered to elicit more intense and consistent cravings.

Keywords Betel quid · Craving · Cue-reactivity paradigm · Functional MRI

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Introduction

Chewing betel quid (BQ, or "bin lang" in Taiwanese Mandarin) is a common practice across various Asian-Pacific areas and among a small number of migrant communities in Western countries (Winstock et al. 2000; Winstock 2002; Gupta and Ray 2004). The World Health Organization regards BQ as a human carcinogen (IARC 2004), and DSM-IV and ICD-10 dependence symptoms may develop with heavy use (Benegal et al. 2008; Lee et al. 2014). BQ contains many neuroactive compounds (such as arecoline) that play important role in several psychological effects (such as an elevated arousal and enhanced memory) (Osborne et al. 2017).

The cue-reactivity paradigm has been among the most popular methods for exploring substance craving over the past decades (Carter and Tiffany 1999; Wilson et al. 2004). Craving for addictive substances (e.g., BQ) is a central feature

of addiction (Sayette 2016). The recent fifth edition of DSM adds craving as a diagnostic criterion for substance use disorders. Cues and contexts associated with drug use can induce craving, leading to relapse (Welberg 2013). Cue reactivity involves exposing addicted individuals to the substance-related cues to elicit craving while concurrent changes (e.g., brain regions activities) are assessed (Drummond 2000; Reynolds and Monti 2013; Rose et al. 2013). Functional neuroimaging studies have employed the cue-reactivity paradigm to illustrate the neural basis of cravings for illegal drugs (Wilson et al. 2004), cigarettes (Due et al. 2002), alcohol (Groefsema et al. 2016), food (Pelchat et al. 2004), gambling (Potenza et al. 2003), online games (Ko et al. 2009), and so on.

The urge states (e.g., strong vs. mild), which were confirmed by the participants, can moderate the brain activations elicited in the cue-reactivity paradigm (Wilson and Sayette 2015). Wilson and Sayette (2015) reviewed the functional magnetic resonance imaging (fMRI) studies of cigarette craving, comparing smokers with a larger self-reported desire to smoke (the nicotine-deprived smokers) with smokers with a lower desire to smoke (the non-deprived smokers). They found that the rostral anterior cingulate cortex (rACC) and medial/ventromedial prefrontal cortex (PFC) are reliably activated in the nicotine-derived smokers to a greater degree than among the non-deprived smokers. Wilson and Sayette suggest that this differential activation in the rACC and medial/ventromedial PFC may be partly attributed to different urge intensities in smokers.

The current study analyzed whether the BQ cues can elicit the chewers' craving-related brain areas such as the mesocorticolimbic system, including the prefrontal system and the basal forebrain system. We also included the urge intensity (Wilson and Sayette 2015) to examine whether it can moderate the brain areas elicited by the BQ cues. To the best of our knowledge, this is the first study to evaluate the brain changes of BQ chewers exposed to the BQ cues. The imbalance between these two neural systems increases the likelihood of substance use (Heatherton and Wagner 2011; Noël et al. 2013). Recent BQ imaging studies showed hypoactive prefrontal inhibitory control (e.g., decreased gray matter volume in the rACC and dorsolateral PFC (dlPFC) (Chen et al. 2015) and a hyperactive basal forebrain reward system (e.g., increased connectivity from ACC to the reward network) (Liu et al. 2016) among the BQ chewers. Recently, Weng et al. (2018) employed resting-state fMRI and reported the enhanced reward system for the BQ chewers, but it had a relatively preserved inhibitory control (Weng et al. 2018). Using generalized q-sampling imaging, Weng et al. (2018) reported increases in diffusion anisotropy in brain areas regarding the reward system and inhibitory control, showing that a facilitated reward system and attentional control were indicated (Weng et al. 2017). Taken together, given the functional and structural brain changes in the BQ chewers, the BQ cues in the cue-reactivity paradigm should be sensitive to eliciting the chewers' craving-related brain areas.

Meta-analysis and review neuroimaging studies have shown that the substance cue reactivity is associated with the orbitofrontal cortex (OFC) and the dlPFC (Wilson et al. 2004; Chase et al. 2011; Kühn and Gallinat 2011; Jasinska et al. 2014; Wilson and Sayette 2015). The OFC has been implicated in many reward-based functions (Shott et al. 2015). It integrates information from many sensory modalities and represents the reward value of a reinforcer, which may play a role in reinforcement learning (Rolls 2004). The dlPFC is believed to play a key role in the integration of cognitive functions (e.g., working memory) and motivationally relevant information (e.g., reward values) in guiding motivated behavior (Wallis and Miller 2003).

The superior frontal gyrus (SFG) and inferior frontal gyrus (IFG) are also reported in neuroimaging studies using the cue-reactivity paradigm (Chase et al. 2011; Jasinska et al. 2014). The SFG supports planning, motivation and emotional information processing (McClernon et al. 2009; Rose et al. 2011). The IFG is involved in the inhibition of a prepotent response (Aron et al. 2004; Duann et al. 2009). Greater activations of the SFG and IFG in response to smoking cues (vs. neutral cues) have been reported in smokers (McClernon et al. 2009; Rose et al. 2011; Engelmann et al. 2012).

The dorsal striatum (putamen and caudate nucleus), the ventral striatum (nucleus accumbens) and the amygdala in the basal forebrain system have also been reported to be related to substance cue reactivity (Chase et al. 2011; Kühn and Gallinat 2011; Jasinska et al. 2014). The dorsal striatum plays an important role in habitual drug seeking and reinforcing learning (Koob and Volkow 2010). The ventral striatum contributes to the increased incentive salience of addictive substances (Robinson and Berridge 2000). The amygdala mediates a cue-induced reinstatement of drug-seeking behavior (Everitt et al. 2000; See et al. 2003) and promotes the negative reinforcement associated with compulsive drug use (Koob and Volkow 2010).

The brain areas, besides the mesocorticolimbic system, are also activated in response to substance cues. For example, the visual system, including the occipital lobe and visual association cortex (e.g., fusiform gyrus) are related to identifying the salience of visual, appetitive cues (Tang et al. 2012; Gearhardt et al. 2014).

To examine the cue reactivity more comprehensively, we created four types of cues: BQ cues, matched food cues, visual control cues, and a resting crosshair cue (George et al. 2001). The most direct and important comparison performed was the one between the brain activities elicited by the BQ cues versus those by the matched food cues. In addition, to test the current urge intensity effect (Wilson and Sayette 2015), we compared BQ chewers with a strong urge versus those with a weak urge.

We hypothesized that the urge states endorsed by the BQ chewers can moderate the brain activations elicited in the cue-reactivity paradigm. Particularly, when comparing activations between the BQ and Food, the BQD-Hs (but not the BQD-Ls) may show that the brain areas related to craving (e.g., the mesocorticolimbic system) are activated.

Materials and methods

Participants

There were two groups of male participants included in this study: the dependent BQ chewers (hereafter, 'BQD'; $N = 16$) and the non-chewer healthy controls (hereafter, 'HC'; N = 16). Since there are far more male chewers than female chewers, we recruited only males. To maximize the between-group difference in BQ craving, we recruited dependent chewers and non-chewers. The participants were recruited using three methods: human resources or employment agencies, recruitment advertisements, and introduction to BQ chewers by former participants. All participants were at least 20 years of age and right-handed.

The BQDs were included if they met the following criteria: (a) current BQ chewers and (b) had dependence scores higher than the cut-off point of 24 on the Betel Nut Dependency Scale (BNDS) (Li et al. 2012). The BNDS consists of three factors: craving and desire (four items), withdrawal response (four items), and tasting habits (three items; e.g., I care about the types, textures, and feelings that come from chewing BQ). Higher scores indicate a higher level of dependence on BQ. The BQDs were asked to abstain from BQ for 24 h before visiting the laboratory. The HC had never chewed BQ in their lifetimes. Informed consent was obtained from all participants; the study was approved by the institutional review board of Chung Shan Medical University Hospital (CS13114).

Exclusion criteria for both groups were any eye diseases, such as cataract and glaucoma, a history of another primary mental disorder (e.g., schizophrenia) or alcohol/illicit-substance-use disorder during the past year, any neurological illnesses, any prescription or psychotropic medications, and metallic implants or other contraindications on the MRI. The HCs had no history of psychiatric disorders, neurological illness or substance-use disorders. Ruling out the participants with a family history of substance-use disorders was critical, particularly when comparing the HCs versus the substance-use group (Ersche et al. 2012; Ersche et al. 2013). The HCs with a family history of substance-use disorders were likely to have brain abnormalities similar to those in the substance-use groups, possibly due to genetic or epigenetic influences (Ersche et al. 2012, Ersche et al. 2013).

Materials

There were four types of cues: BQ cues, matched food cues, visual control cues, and a resting crosshair cue. For each cue type (except for the crosshair cue), there were 36 color photographs. One hundred and twenty-five BQ color photographs were collected from websites or were photographed by the experimenters. Five heavy BQ chewers (not included in the current imaging study) independently selected the BQ pictures that were most representative of the BQ. Only those pictures selected by at least four chewers were selected, which resulted in 75 BQ pictures. We randomly selected 36 BQ pictures out of these 75 pictures for use in the formal experiment. The food pictures were selected to match the BQ pictures. Each food picture was cautiously selected and edited to be as perceptually identical to the BQ picture as possible, except for the BQ content (e.g., a man pinching a betel nut toward his mouth vs. pinching a piece of chewing gum). The visual control pictures were created from the BQ pictures in Adobe Photoshop CS3 (Adobe Systems Inc., San Jose, California) by various distortion effects, such as blurring and smoothing, resulting in pictures that matched the BQ cues in physical features (e.g., color and hue) but lacked any objective recognition.

Design

A 456-s script for stimulus presentation was created by E-prime (Psychology Software Tools, Inc., Sharpsburg, Pennsylvania, USA), consisting of six 76-s epochs. Each epoch contained three 20-s blocks: 1 block for each of the BQ cues, matched food cues, and visual control cues, and one 16-s resting crosshair cue (a black crosshair against a white background). Each 20-s block consisted of five pictures, each of which was displayed for 4 s. The order of the blocks (BQ, matched food, visual control, and crosshair) and the pictures within the blocks were randomized (Fig. 1). Each picture appeared only once.

MRI data acquisition

All three-dimension anatomical and multi-slice task-based functional images were acquired using a 3.0-Tesla MRI (Magnetom Skyra, Siemens Medical Systems, Erlangen, Germany) with a 20-channel head coil. The participants were instructed to lie down, to remain with their head motionless with a cotton pad, to wear earplugs to reduce the noise generated by the MRI machine and to wear video goggles with an image display (Resonance Technology, Inc. Northridge, California, USA). The participants with myopia wore video goggle with special lenses for degree correction to ensure that each participant could clearly see the display screen. All of the participants were instructed to keep their eyes closed, relax, think of nothing in particular, remain awake, and open their

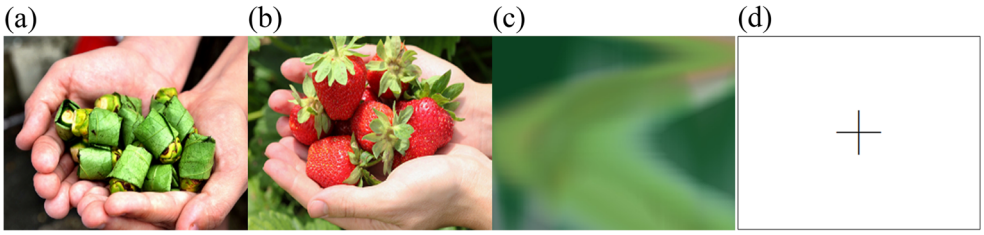

Fig. 1 Sample stimuli used in the current study. **a** BQ cue, **b** matched food cue, **c** visual control cue, and (**d**) crosshair cue

eyes to watch the display screen of the video goggles when a cue-induced task was performed.

All anatomical T1 weighted images were acquired using the three-dimension magnetization-prepared rapid gradient-echo (3D MPRAGE) sequence with repetition time (TR)/echo time (TE)/inversion time (TI) = 2500 ms/2.27 ms/902 ms, a flip angle (FA) = 8°, and 160 axial slices with a resolution (voxel size) = 1.0 × 1.0 × 1.0 mm^3. The task-based functional images were obtained using the gradient echo-echo planar image (GRE-EPI) sequence. The image parameters were as follows: TR/TE = 2000/30 ms, in-plane resolution (pixel size) = 2.7 × 2.7 mm^2, slice thickness = 4 mm, number of repetitions = 240, and 28 axial slices aligned along the anterior commissure-posterior commissure (AC-PC) lines. The fMRI scanning time was 8 min.

Functional image processing and analysis

The functional MR image processing and statistical analysis were performed using SPM8 (Statistical Parametric Mapping, The Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK). For motion correction, we calculated the center of each image and realigned the data to the first volume. After the correction was performed, the six head motion parameters of all of the participants were below ±0.04 mm for translation and ± 0.04° for rotation. Following the slice-timing correction and realignment, the data were normalized to the standard Montreal Neurological Institute (MNI) space with affine transformation and resampled to isotropic 3-mm voxels. The data were then spatially smoothed to increase the signal-to-noise ratio using a 6-mm full width at a half-maximum (FWHM) Gaussian kernel.

We then performed the 1st level t-tests (individual analysis) on the individuals. Because the presentation order of cue-induced stimulation was random in each participant, we added four stimulation conditions for each participant, respectively, according to the experimental design model, including the BQ cues, the matched food cues, the visual control cues, and a resting crosshair cue. We conducted six t-test paired comparisons for the four abovementioned conditions. We then performed 2nd level t-tests (group comparisons) to assess the critical BQ and food differences the between high-urge and low-urge BQ chewers. The age and education year were used as covariates to remove any effects caused by the differences among each group. The xjview toolbox (http://www.alivelearn.net/xjview) was used to visualize the results.

Procedure

After entering the laboratory, the participants were informed about the safety regulations and signed the informed consent. Next, the participants completed an integrative questionnaire form, which was used to collect demographic background, major medical history, betel nut usage histories, BNDS, and the current urge to chew (pre-urge). They were then escorted into the MRI suite. After exiting from the MRI suite, they were asked about their current urge to chew again (post-urge). To rate their urge to chew, we asked participants to assess "How strong is your urge to chew right now?" on an anchored rating scale that ranged from 0 (not at all) to 10 (extremely).

Results

Participants

There was no difference between the ages of the BQDs and HCs (Table 1). There was a between-group difference in education years. The BQDs with a pre-urge score ≧6 were categorized as BQD-H, and those with a pre-urge score < 6 were categorized as BQD-L (Table 2). In the subsequent analysis on imaging, age and education year served as covariates.

Urge to chew before and after the scan

The pre-urge and post-urge means and SDs in each BQ group (BQD, BQD-H, and BQD-L) are listed in Table 3. For each group, there was no difference in the urge between before and after the brain scan.

Paired comparisons of the four cue types in the BQDs and HCs

The results of the paired comparisons in each group of BQD and HC are shown in Table 4. No activated brain areas were observed when comparing the BQ cues vs. the food cues in each group. When comparing the other cue pairs, both groups had similar activated brain areas (medial occipital gyrus

Table 1 Characteristics of BQD and HC

	BQD ($n = 16$)		HC (n = 16)		*t(30)*	*p*
	Mean	(SD)	Mean	(SD)		
Age (years)	37.13	(10.44)	32.06	(3.13)	1.859	0.073
Education Years	13.63	(2.13)	15.63	(2.31)	−2.551	0.016
BNDS	28.38	(3.24)	11.00	(0)	21.431	< 0.001
Months	173.50	(151.86)	n/a			
Monthly expenses (NT dollars)	1628.13	(1517.89)	n/a			
Days per month	20.75	(26.05)	n/a			
Number per day	20.50	(9.77)	n/a			
Pre-urge	5.13	(2.09)	0		9.792	< 0.001
Post-urge	5.00	(2.50)	0		7.989	< 0.001

BNDS, Betel Nut Dependency Scale; Months, the number of months chewing BQ; Monthly expense, money expend on BQ in the recent month; Days per month, the average number of days chewing BQ in the recent month; Number per day, the number of BQ per day in the recent month

(MOG), inferior occipital gyrus (IOG), cuneus, calcarine fissure, and lingual gyrus).

Paired comparisons of the four cue types in the BQD-Hs and BQD-Ls

The results of the paired comparisons in each group of the BQD-Hs and BQD-Ls are shown in Table 4. The BQD-Hs had several activated brain areas when comparing the BQ cues vs. the food cues. When comparing the other cue pairs, both groups had similar activated brain areas (MOG, IOG, cuneus, calcarine fissure, and lingual gyrus).

Between-group (BQD-Hs and BQD-Ls) comparisons of the BQ vs. food contrasts

We compared the critical BQ cues vs. food cues contrasts between the BQD-Hs and BQD-Ls, with age and education year as covariates (Fig. 2). The BQD-Hs had larger contrast activations (BQ vs. food) than the BQD-Ls did in many brain areas, including in the SFG, IFG, middle frontal gyrus (MFG), precentral gyrus, supplementary motor area (SMA), inferior parietal gyrus (IPG), supramarginal gyrus, fusiform gyrus, calcarine fissure, superior occipital gyrus (SOG), MOG, IOG, and lingual gyrus.

Discussion

The current study adopted the cue-reactivity paradigm to investigate BQ chewers' craving-related brain areas. Moreover, we examined whether the urge states of chewers showed moderation of the brain activations elicited in the cue-reactivity paradigm (Wilson and Sayette 2015). The main conclusion from our study is that the urge states (Wilson and Sayette 2015) endorsed by the

Table 2 Characteristics of BQD with high (BQD-H) and low (BQD-L) urge to chew

	BQD-H ($n = 6$)		BQD-L ($n = 10$)		*t(14)*	*p*
	Mean	(SD)	Mean	(SD)		
Age (years)	41.83	(10.23)	34.30	(9.99)	1.448	0.170
Education Years	14.67	(1.63)	13.00	(2.21)	1.595	0.133
BNDS	30.50	(2.26)	27.10	(3.14)	2.303	0.037
Months	199.00	(164.73)	158.20	(150.60)	0.507	0.620
Monthly expenses (NT dollars)	1275.00	(1063.84)	1840.00	(1754.49)	−0.709	0.490
Days per month	21.17	(9.07)	20.10	(10.63)	0.205	0.841
Number per day	26.67	(37.61)	17.20	(17.54)	0.691	0.501
Pre-urge	7.17	(1.60)	3.90	(1.20)	4.666	< 0.001
Post-urge	5.67	(2.42)	4.60	(2.59)	0.816	0.428

BNDS, Betel Nut Dependency Scale; Months, the number of months chewing BQ; Monthly expense, money expend on BQ in the recent month; Days per month, the average number of days chewing BQ in the recent month; Number per day, the number of BQ per day in the recent month

Table 3 The average pre-urge and post-urge in each BQ group

	BQD Mean (SD)	BQD-H Mean (SD)	BQD-L Mean (SD)
Pre-urge	5.13 (2.09)	7.17 (1.6)	3.90 (1.20)
Post-urge	5.00 (2.50)	5.67 (2.42)	4.60 (2.59)
t value for comparing pre- vs. post- urge	0.255 (15)	2.236 (5)	−1.300 (9)
p	0.802	0.076	0.226

BQ chewers can moderate the brain activations elicited in the cue-reactivity paradigm.

First, when comparing activations between the BQ and food cues, there were no activated brain areas in the BQDs or HCs. When comparing any other pairs of cue types, both groups had the same activated brain areas, which were primarily involved in visual processing. Second, when comparing the activations between the BQ and food cues, the BQD-Hs (but not the BQD-Ls) showed several activated brain areas related to craving. When comparing any of the other two types of cues, both groups had the same activated brain areas, which were primarily involving visual processing. Finally, the BQD-Hs showed larger contrast activations (BQ vs. food) than the BQD-Ls did in several brain areas related to craving (e.g., the SFG and IFG).

BQDs and HCs had similar brain activation patterns

When comparing the BQ vs. non-food (visual control or crosshair) cues, food vs. non-BQ (visual control or crosshair) cues, and visual control vs. crosshair cues, both the BQDs and HCs showed activated brain areas in the occipital lobe (cuneus, calcarine fissure, lingual gyrus, MOG, and IOG), which were related primarily to visual processing. The calcarine fissure and the cuneus are important for basic visual processing (e.g., texture and orientation), and they are projected from the retinas. The lingual gyrus plays a role in the encoding of complex images and visual working memory (Machielsen et al. 2000). MOG is involved in the spatial and non-spatial processing of visual stimuli (Renier et al. 2010), and IOG is involved in the processing of non-face stimuli (e.g., rotation-invariant 2-D shapes) (Silvanto et al. 2010) and faces (Pitcher et al. 2011).

The recognizable, real objects (e.g., BQ cues and food cues in the current study) may elicit greater brain activations in many brain areas compared with the non-object textures (e.g., visual control) and simple line segments (e.g., a crosshair) (Grill-Spector 2003). Therefore, high activations of components of the occipital lobe (e.g., cuneus, calcarine fissure, lingual gyrus, MOG, and IOG) may reflect different visual processing between recognizable, real objects (BQ cues and food cues) vs. non-object (visual control cues) and simple objects (a crosshair). Additionally, high activations in the occipital lobe may also reflect different visual processing in terms of complexity (complex visual control vs. simple crosshair).

In both the BQDs and the HCs, there were no activated brain areas when comparing the BQ and food cues. The

Table 4 Brain regions activated by group (in (A) BQD and HC, and in (B) BQD-H and BQD-L) and by condition

(A) BQD and HC:		
BQ – Food		
	BQD	HC
No significant activated brain areas found.		
BQ – Visual Control, Food – Visual Control, BQ – Crosshair, Food– Crosshair, Visual Control – Crosshair		
	BQD	HC
Both groups activated the same brain areas: cuneus, calcarine fissure, lingual gyrus, MOG, and IOG		
(B) BQD-H and BQD-L:		
BQ – Food		
	BQD-H	BQD-L
Left ACC, left medial OFG, left rectus gyrus, right SFG, STG, precuneus, calcarine fissure, right lingual gyrus, MOG		none
BQ – Visual Control, Food – Visual Control, BQ – Crosshair, Food– Crosshair, Visual Control – Crosshair		
	BQD-H	BQD-L
Both groups activated the same brain areas: cuneus, calcarine fissure, lingual gyrus, MOG, and IOG		

MOG middle occipital gyrus, *IOG* inferior occipital gyrus, *ACC* anterior cingulate cortex, *OFG* orbitofrontal gyrus, *SFG* superior frontal gyrus, *STG* superior temporal gyrus

$p = .05$ and cluster size > 30.

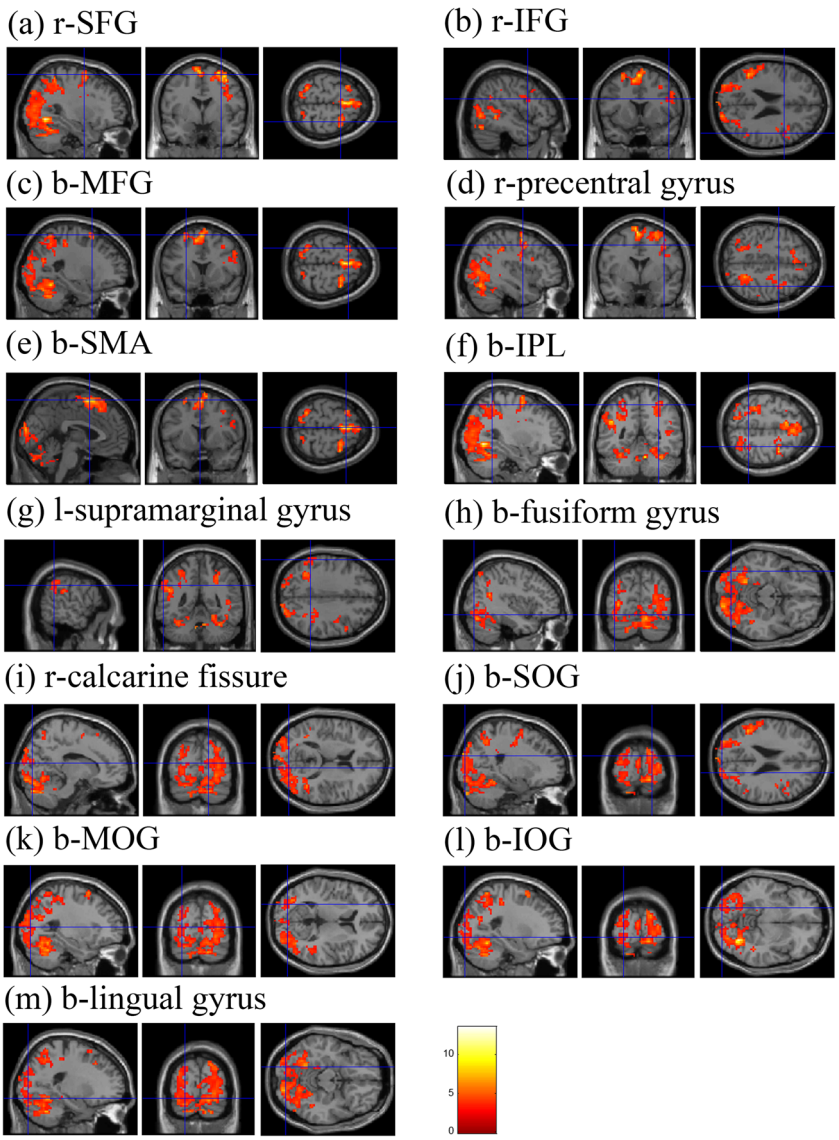

Fig. 2 BQ cue–food cue differences between the BQD-H and BQD-L (BQD-H > BQD-L only) groups were found in the (**a**) right superior frontal gyrus (SFG), **b** right inferior frontal gyrus (IFG), **c** bilateral middle frontal gyrus (MFG), **d** right precentral gyrus, **e** bilateral supplementary motor area (SMA), **f** bilateral inferior parietal lobule (IPL), **g** left supramarginal gyrus, **h** bilateral fusiform gyrus, **i** right calcarine fissure, **j** bilateral superior occipital gyrus (SOG), **k** bilateral middle occipital gyrus (MOG), **l** bilateral inferior occipital gyrus (IOG), and (**m**) bilateral lingual gyrus. Those in the BQD-L did not have brain areas that elicited larger activations than those in the BQD-H. Age and education year served as covariates. $P < 0.005$, cluster size >100 voxel. The color bar represents the t-score

heterogeneity of urge states within BQ chewers may reflect weak activation differences between BQ and food cues (Wilson and Sayette 2015). Our results show that the distinction between high-urge and low-urge chewers is critical for understanding craving-related brain areas.

BQD-Hs (but not BQD-Ls) showed craving-related activations in BQ and food contrast

The activated ACC in the BQD-Hs is consistent with Wilson and Sayette's (2015) meta-analysis study in which the ACC was more reliably activated by the cigarette cues in the high-urge smokers than it was in the low-urge smokers. The ACC plays a role in tasks involving inhibitory control, conflicts, or error monitoring (Nee et al. 2007; Volkow et al. 2012; Ersche et al. 2013). The ACC is also activated by stimuli that elicit reward anticipation (Liu et al. 2011) or pain and negative effects (Shackman et al. 2011). In the BQD-Hs, the BQ cues (in comparison to the food cues) could elicit reward anticipation and a negative effect, followed by the regulation of that effect. However, in the BQD-Ls, the BQ cues may elicit anticipation and a negative effect to the extent similar to those of the food cues, reducing the activation differences between these two types of cues.

The current result of the activated medial OFC in BQD-Hs is also consistent with that of Wilson and Sayette (2015). The medial OFC involves "hot" executive functions (Noël et al. 2013) that integrate numerous affective/emotional (somatic) responses and produce stimulus-reward associations and reward-related behavior (Walton et al. 2010). Many studies (Wilson et al. 2004; Kringelbach 2005; Bray et al. 2010; Chase et al. 2011) have suggested that medial OFC is important for appetitive behavior and decision-making, particularly in regard to the expectations of a reward.

The SFG supports higher cognitive functions such as working memory (monitoring and manipulation) and top-down attentional orientation (Hopfinger et al. 2000; Du Boisgueheneuc et al. 2006). The task-based fMRI studies have shown a greater activation in the SFG in response to smoking cues versus neutral cues, and subjective reports of craving were highly correlated with activation in response to smoking cues (McClernon et al. 2009; Rose et al. 2011; Jasinska et al. 2014). The history of the rewarding (one of the top-down factors) of BQ chewing may selectively influence the high-urge chewers' attention to the BQ cues.

The STG is involved in auditory processing (Moerel et al. 2014), facial emotion perceptions (Bigler et al. 2007), and social cognition (Jou et al. 2010). Liu, Li, Zhao, Yang et al. argued that the increased activity in the temporal regions (including that in the STG) may be a positive reinforcement factor for developing repetitive BQ chewing behavior. Some fMRI studies also reported a cue-elicited activation of STG while subjects viewed addictive substances, such as alcohol (Schacht et al. 2013) and cigarettes (Goudriaan et al. 2010). More imaging studies on BQ chewers are needed to clarify the role of the STG in the cue-reactivity paradigm.

Activations of the visual system in the occipital lobe (including in the precuneus, calcarine fissure, right lingual gyrus, and MOG) in the cue-reactivity paradigm have been reported (Engelmann et al. 2012; Schacht et al. 2013). The occipital lobe is primarily involved in visual processing. Activation of visual areas when viewing the BQ pictures may implicate the preparation of motor behaviors directed to substances (e.g., BQ) (Engelmann et al. 2012) in the high-urge BQ chewers.

BQD-Hs had larger contrast activations (BQ vs. food) in craving-related brain areas than BQD-Ls did

The frontal cortex, which includes the SFG, IFG and MFG, plays a critical role in the current cue-reactivity paradigm. The SFG supports the working memory and top-down attentional orientation (Hopfinger et al. 2000, Du Boisgueheneuc et al. 2006). The IFG is involved in the inhibition of the prepotent response (Aron et al. 2004; Duann et al. 2009). The MFG is involved in reorienting attention from stimulus-driven, exogenous attention to top-down endogenous attentional control (Chica et al. 2013; Japee et al. 2015). Both areas are a part of the ventral attentional network (VAN) (Corbetta et al. 2008). Activations of the frontal cortex have been reported in meta-analysis studies in relation to many addictive substances (e.g., alcohol) (Wilson et al. 2004; Chase et al. 2011; Kühn and Gallinat 2011). When viewing the BQ cues, the BQD-Hs may inhibit their prepotentiated behaviors to chew BQ and reorient their attention away from BQ. More imaging studies are needed to test this possibility.

The IPL (including the supramarginal gyrus) is part of the mirror neuron system (Cattaneo and Rizzolatti 2009) that can relate to addictive behavior (Pineda and Oberman 2006; Kühn and Gallinat 2011). Mirror neurons respond to self-movement, as well as to the observation of movement. Possibly, when seeing people holding or chewing a BQ, the viewers' (particularly BQD-Hs) IPL and supramarginal gyrus are activated as if they themselves are holding or chewing BQ.

Activations of the visual system in the occipital lobe (calcarine fissure, lingual gyrus, SOG, MOG, and IOG) and in the visual association cortex (e.g., fusiform gyrus) may be due to enhanced attentional allocation to the substance (e.g., BQ) cues (Engelmann et al. 2012). The fusiform gyrus in the ventral pathway (the 'what' pathway) (Goodale and Milner 1992) has been shown to respond to human faces (Kanwisher and Yovel 2006) and complex familiar objects (e.g., BQ) (Gauthier et al. 2000). The activation of the visual-related cortex (e.g., the occipital lobe and fusiform gyrus) may be due to increased attentional allocation to the BQ cues. It has been shown that dependent BQ chewers can bias their attention toward the BQ cues (Ho et al. 2013; Shen et al. 2016). Repeated use of addictive substances may result in the brain becoming hypersensitive to the substance and substance-related cues (Robinson and Berridge 2003).

Activations of the precentral gyrus and SMA in the cue-reactivity paradigm have been reported (Engelmann et al. 2012, Schacht et al. 2013). The precentral gyrus (including the SMA) contributes to voluntary movement. Liu et al. (2016) also reported higher regional homogeneity in the precentral gyrus in BQ chewers. The activation of motor areas when viewing BQ pictures may implicate the preparation of motor behaviors directed to substances (e.g., BQ) (Engelmann et al. 2012) in high-urge BQ chewers.

Urge to chew did not change after viewing the BQ cues

All of the BQ chewers did not have elevated urges to chew after viewing the BQ cues. It is possible that the unfamiliar and uncomfortable MRI environment (Wilson and Sayette 2015) affected the BQ chewers' urge to chew BQ. Additionally, in Taiwan, chewing BQ usually has a negative social image; therefore, social desirability or guilt (Fletcher et al. 2007) may make the BQ chewers underestimate their urges. Furthermore, using only the visual cues (e.g., viewing BQ pictures) may not be enough to elicit a strong urge. Multisensory BQ cues (e.g., visual, audio, tactile, haptic, olfactory, and gustatory cues, or any combinations of these) should be adopted to elicit more intense and consistent cravings (Yalachkov et al. 2012). A single-item urge rating is advantageous in situations calling for repeated and rapid reporting of craving throughout an experimental paradigm where measurement reactivity can be problematic (e.g., the cue-reactivity paradigm). Additionally, reviews suggest that single-item scales consistently support the diagnostic utility

of craving (Tiffany and Wray 2012). However, in addition to the self-reported one-item urge rating, multiple measures (e.g., multi-item craving scales, cognitive processing tasks, neurobiological responding, and so on) could be considered to obtain a broader understanding of craving (Sayette et al. 2001).

Limitations

The current study was limited in its small sample size of the high-urge BQ chewers. It is possible that BQ is a weakly addictive substance and that the current BQ chewers may not develop dependence symptoms in terms of DSM-IV or ICD-10 (Benegal et al. 2008; Lee et al. 2014). As a result, the deprivation of BQ use may not be effective to enhance the urge to chew. In the future, more effective approaches to elicit urges before performing a brain scan can be adopted, such as the abovementioned multisensory cues or mental imagery on substance use experience (Kavanagh et al. 2005; Jáuregui-Lobera et al. 2012). The advantage of the four-cue design is that we can examine the cue reactivity more comprehensively. However, since there were four types of cues, the current design had a fewer number of trials in BQ and Food. Therefore, the current design may be disadvantageous due to its low power to detect the brain activity differences between BQ and Food. The carry-over effect may reduce or even diminish brain activity differences between the conditions. The counterbalancing or randomization may not be the most powerful design due to the carry-over effect. Instead, the fixed order of the control cues (e.g., food cues) followed by the substance cues (e.g., BQ cues) is more powerful and less biased (avoiding carry-over) (Sayette et al. 2010).

Conclusions

The current study adopted the cue-reactivity paradigm to examine the neural basis of craving among BQ chewers. The BQDs and HCs had similar brain activation patterns when comparing any two cue types. The urge states supported by the chewers can moderate the neural responses to the BQ cues. Namely, the BQD-Hs, but not the BQD-Ls, showed craving-related activations in the critical BQ cue vs. food cue comparisons. Additionally, the BQD-Hs had larger contrast activations (BQ-Food) in many craving-related brain areas than the BQD-Ls did. Since craving may directly drive drug use and relapse, there is interest in developing and refining pharmacological and psychological treatments targeting drug craving. Studying brain responses during mild desires may not be the same as studying brain responses during overpowering urges. One implication is the need to create clinical settings that incorporate high craving states into their assessments and treatments.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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

Informed consent Informed consent was obtained from all of the individual participants included in the study.

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