

Cognitive Neuroscientific Approach in Betel-quid Chewers: A Systematic Review

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The World Health Organization regards betel quid (BQ) as a human carcinogen. The BQ chewers may develop dependence symptoms. Although chewing BQ is common in many Asian countries, BQ is still a “populous orphan” in the field of addictive substance. The current review paper systematically reviews the cognitive neuroscientific studies on BQ chewers to understand the chewing effect on cognitive functions and brain. This review includes 25 studies ranged from 1976 to 2019. According to the subjects and study tools, these studies are categorized into “cognitive functions” and “executive control and reward systems.” The “cognitive functions” session includes alertness, selective attention, short-term memory, and executive control. The “executive control and reward systems” session includes the studies that adopted the magnetic resonance imaging to investigate the possible imbalance between the executive control and reward systems. The current review shows that (1) the alertness studies on BQ chewers are few and inconsistent, (2) chewing BQ can affect spatial attention distribution that facilitates target identification, (3) dependent chewers can bias their attention to BQ cues, (4) dependent chewers may have impaired spatial short-term memory, (5) the behavioral studies on executive control are few and inconsistent, (6) imaging studies, in general, show deteriorated executive control in dependent chewers, but show inconsistent patterns on the reward system. The current review discusses several research limitations for future BQ studies.

Keywords: *betel quid, brain imaging, cognitive neuroscience*

Extended Abstract

The World Health Organization regards betel quid (BQ) as a human carcinogen. BQ chewers may develop dependence symptoms as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) and The International Statistical Classification of Diseases and Related Health Problems (ICD). BQ is prepared in different ways in different countries. One popular type of BQ in Taiwan is *pauhiòh* (meaning “wrapped by leaf” in Taiwanese Mandarin). To prepare *pauhiòh*, an unripe areca fruit is stuffed into a tightly rolled betel leaf with white or red slaked lime pasted on the inner sides of the leaf. Although chewing BQ is common in many Asian countries, BQ is still a “populous orphan” in the field of addictive substances.

This paper systematically reviews cognitive neuroscientific studies on BQ chewers to understand the effect of chewing BQ on cognitive functions and the brain. Previous reviews of BQ have focused on pharmacology/neurology, epidemiology/public health, cancer, and structural/resting-state brain imaging. A previous review of structural and resting-state brain imaging was limited in scope because it did not include behavioral studies on cognition, task-based functional magnetic resonance imaging (fMRI), and other tools (such as eye tracking and electroencephalography (EEG)) that are also important in cognitive neuroscience. This review provides a more complete overview of cognitive neuroscientific studies of BQ chewers.

This review was based on the preferred reporting items for systematic review and meta-analysis (PRISMA) criteria. An initial search was conducted in PubMed with no limitations on publication date or type. Various combinations of key words were used, including betel quid (OR betel nut) AND dependence (OR cognitive OR attention OR memory OR fMRI), resulting in 10 combinations ($= 2 \times 5$). Studies that (1) were in the field of cognitive neuroscience, (2) had human participants, and (3) were included in either SSCI, SCI, or TSSCI were included in the review. Studies that were (1) duplicates, (2) review papers, (3) conference abstracts, or (4) unpublished were excluded. Other articles were obtained from the reference lists of the retrieved published articles and those that cited the retrieved articles (identified via Google Scholar). This search procedure obtained 25 articles in total, published between 1976 and 2019 (Table 1).

Most early studies (1976 to 1990s) focused on manual motor response and used EEGs. A large number of articles (21 of the 25) were published between 2010 and 2019. They covered a broad range of research topics, such as spatial attention, short-term memory, inhibitory control, sustained attention, attentional bias, craving, and imbalance between the executive control system and reward system. According to the subjects and study tools, we categorized these studies as “cognitive functions” or “executive control and reward systems.” The “cognitive functions” group included measures of alertness, selective attention, short-term memory, and executive control. The “executive control and reward systems” group included studies that used magnetic resonance imaging to investigate the possible imbalance between the executive control and reward systems.

The results of the review were as follows. First, there were few alertness studies on BQ chewers and the results were inconsistent. Specifically, the results on the manual motor responses were inconsistent and the interpretations of how chewing BQ affects manual motor responses were also inconsistent. The results of the two EEG studies were also inconsistent. Second, chewing BQ can immediately affect spatial attention distribution, which facilitates target identification. Third, dependent chewers

can quickly attend to BQ-related cues and maintain their attention on these cues. Fourth, dependent chewers may have impaired spatial short-term memory. BQ chewing may not immediately or chronically affect chewers’ and non-chewers’ verbal short-term memory. BQ chewing may not affect chewers’ object short-term memory. Fifth, the behavioral studies on executive control were few and their results were inconsistent. BQ chewing may reduce inhibition, updating, and set-shifting. BQ chewing may also immediately facilitate sustained attention. Finally, imaging studies, in general, indicate deteriorated executive control in dependent chewers, but patterns in the reward system were inconsistent.

This review of research on the cognitive neuroscience of BQ chewers suggests several limitations and prospects worth exploring.

- (1) Definitions of BQ dependence are unclear and possibly inconsistent. Early studies usually did not define BQ dependence and did not report details of participants’ chewing habits. After 2010, studies began to use dependence scales to recruit participants, but they used different scales. Although these scales were developed in accordance with the DSM guidelines, there is currently no psychometric analysis of the scales and no brief form that is more suitable for clinical use.
- (2) The concurrent use of substances has not been adequately considered. BQ and tobacco are often used concurrently. Neurologically, arecoline (one of the primary chemical components of BQ) and nicotine have been shown to act on muscarinic and nicotinic acetylcholine receptors. Therefore, when studying the effects of BQ on cognition, the concurrent use of substances should be taken into account. Early studies usually did not consider the concurrent use of substances. After 2010, some studies considered and ruled out the influences of tobacco and alcohol. However, some studies did not describe the use of tobacco and alcohol by BQ chewers.
- (3) More appropriate control groups or conditions are needed. Some early studies did not include controls. Some studies did not exclude healthy controls whose family members (e.g., their siblings) had a history of substance use disorder. Although these healthy

controls did not have substance use disorder, their brain structures and executive functions may have been similar to those of addicts, which may confound interpretations of the result. Finally, when studying the acute chewing effect, some studies did not control for the chewing actions (e.g., by adding a chewing gum baseline). Therefore, it is difficult to distinguish between the pharmacological effects of BQ and the effects of chewing action on cognitive function.

- (4) Different BQ preparations should be considered. To date, cognitive neuroscience studies have not explored how different BQ preparations affect cognitive function and the brain. In Hunan, China, ripe areca fruits are made into candied fruit. In India, the large areca seeds retrieved from the ripe areca fruits are sliced and chewed with tobacco additives. In Taiwan, an unripe areca fruit is stuffed into a tightly rolled betel leaf with white or red slaked lime pasted on the inner sides of the leaf.
- (5) Cognitive neuroscientific studies on BQ are very few and the research topics are still limited. All of the studies have had small sample sizes, which may result in larger sampling errors. The majority of identified BQ studies (14 out of 25) focused on the imbalance between executive control and the reward system. Other studies covered a wide range of research topics (e.g., alertness, spatial attention, short-term memory, inhibitory control, sustained attention, attentional bias, and craving). Thus for each topic, there is only a very small number of articles.
- (6) Interpretation of structural and resting-state brain imaging results may require assistance from studies using cognitive tasks. One brain area or neural network may be involved in many functions (e.g., the ACC is involved in inhibitory control, error monitoring, awareness, and so on), which may cause difficulties when interpretating structural and resting-state brain imaging studies. Including cognitive tasks may help to clarify brain functions. For example, combining structural imaging with a task measuring inhibitory control makes it clearer that certain brain regions (such as the dlPFC) are related to inhibitory control.
- (7) There have been many BQ studies focusing on diverse topics and the results are mostly inconsistent. Researchers are encouraged to use multiple tools (e.g., clinical neuropsychological assessments) to explore a variety of research topics. Interdisciplinary studies are also encouraged to increase the depth and width of BQ research.
- (8) Understanding the changes in the chewers' cognitive functions and brains can facilitate the development of treatments and policies. BQ is an addictive substance, but compared to smoking cessation and alcohol cessation, there is still no appropriate way to quit. Looking to the future, robust research could provide the foundation to develop effective treatment methods and policies to help clinicians to implement and evaluate the effectiveness of abstinence.