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ORIGINAL INVESTIGATION

Spatial short-term memory is impaired in dependent betel quid chewers

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Abstract

Rational Betel quid is regarded as a human carcinogen by the World Health Organization. It remains unknown whether chewing betel quid has a chronic effect on healthy betel quid chewers' memory.

Objectives The present study aims to investigate whether chewing betel quid can affect short-term memory (STM).

Methods Three groups of participants (24 dependent chewers, 24 non-dependent chewers, and 24 non-chewers) were invited to carry out the matrix span task, the object span task, and the digit span task. All span tasks' results were adopted to assess spatial STM, visual STM, and verbal STM, respectively. Besides, there are three set sizes (small, medium, and large) in each span task.

Results For the matrix span task, results showed that the dependent chewers had worse performances than the non-dependent chewers and the non-chewers at medium and large set sizes. For the object span task and digit span task, there were no differences in between groups. In each group, recognition performances were worse with the increasing set size and showing successful manipulation of memory load.

Conclusions The current study provided the first evidence that dependent betel quid chewing can selectively impair spatial STM rather than visual STM and verbal STM. Theoretical and practical implications of this result are discussed.

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Chewing betel quid (known as "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 (Gupta and Ray 2004; Winstock 2002; Winstock et al. 2000). Betel products are prepared differently according to cultural practices. For example, betel products have been used as digestive agents, anti-helminths, breath fresheners, and aphrodisiacs and have been used to maintain stamina (Bales et al. 2009). Betel quid is regarded as a human carcinogen by the World Health Organization (IARC 2004), and the possible dependence symptoms may develop in terms of DSM-IV and ICD-10 criteria (Benegal et al. 2008; Lee et al. 2014).

The current study asked whether long-term betel quid chewing could affect the chewers' short-term memory (STM). This is a critical issue because deteriorated STM may lead to inappropriate actions (Vallar and Shallice 2007). Chewing betel quid remains popular among blue-collar workers in Taiwan (Chen and Shaw 1996; Chuang et al. 2007); therefore, inappropriate actions (e.g., forgot important safety instructions) in workplaces may lead to serious public safety problems.

An interaction between arecoline (one of primary ingredients in betel quid) and memory was suggested from patients with neurodegenerative disease (e.g., Alzheimer's disease, AD) and animal studies. The intake of arecoline has been shown that there is acute improving memory in patients with AD. For example, arecoline can acutely improve their verbal memory (Asthana et al. 1995; Raffaele et al. 1996), visual STM (Christie et al. 1981; Raffaele et al. 1991), and spatial STM (Raffaele et al. 1996). Patients with AD had degenerated synthesis of acetylcholine (Asthana et al. 1995), deteriorating

a variety of cognitive functions (Geula and Mesulam 1989; Roth 1986). Neurologically, arecoline acts as an agonist primarily at muscarinic acetylcholine receptors (Chu 2002; Winstock 2002), thereby improving cognitive functions (Clader and Wang 2005; Freo et al. 2002). Animal studies showed that injection of arecoline evokes activations in many cortical (Haubrich and Reid 1972) and subcortical (Molinengo et al. 1988) areas involved in attention (e.g., frontal cortex), sensory processing (e.g., visual cortex), and memory (e.g., hippocampus and limbic areas) (Freo et al. 2002).

The findings reporting acute memory improvement usually employed animals that were naïve to arecoline or patients presenting with AD and presumed degenerated synthesis of acetylcholine. In contrast, arecoline, acutely derived from chewing betel quid, did not affect naïve or habitual chewers verbal STM (Osborne et al. 2011; Wyatt 1996). A recent meta-analytic study reported structural brain abnormalities in stimulant-dependent individuals (Ersche et al. 2013). Many studies have reported impaired memory (e.g., STM) in addictive users (Abrous et al. 2002; Bolla et al. 2002; McKetin and Mattick 1998; Solowij et al. 2002). Furthermore, the impairment in STM may be selective to some types of STM but not the others. Besides, the impairment may be more profound in dependent users than in non-dependent users. For example, McKetin and Mattick (1998) reported that dependent amphetamine users had worse verbal STM than non-dependent users, who in turn were worse than the non-users. Cognitive dysfunctions associated with marijuana use (e.g., arithmetic, verbal expression, and verbal STM) are positively correlated worse with increasing dosage, increasing years of use, and more frequent use (Block and Ghoneim 1993; Bolla et al. 2002; Pope et al. 2001; Pope and Yurgelun-Todd 1996; Solowij et al. 2002). Although not yet tested, these results from other drug studies suggest that the CNS stimulant properties of betel quid consumption may detrimentally influence cognitive functions of the long-term users but not be evidenced in the performance of naïve users.

The current study measured three types of STM, respectively: verbal STM, spatial STM, and visual STM. These types of STM correspond to the conceptual framework of two subsidiary storage systems in supporting of the central executive: the phonological loop and the visuospatial sketchpad (Baddeley 2000; 2003). The sound-and-language-based phonological loop comprises a phonological store that can temporarily hold information and an articulatory rehearsal operation analogous to subvocal speech. The visuospatial sketchpad can temporally store spatial and non-spatial visual information. The current study adopted three common span tasks to measure these three types of STM. The matrix span task was adopted to measure the capacity to memorize the spatial locations (spatial STM) (Kane et al. 2004). The object span task was adopted to measure the capacity to memorize the novel objects (visual STM) (Makovski et al. 2010). The digit span task was adopted to measure the capacity to memorize the digits (verbal STM) (Kane et al. 2004). The set size (the number of to-be-remembered items) was manipulated in each task to examine the effect of memory load.

The current study asked whether chronic betel quid chewing could affect the chewers' STM. We adopted the aforementioned three span tasks to measure three different types of STM. It was hypothesized that impaired STM may be likely in the dependent chewers rather than in the non-dependent chewers and the non-chewers.

Method

Participants

There were three groups of male participants: the dependent chewers ($N=24$), the non-dependent chewers ($N=24$), and the non-chewers ($N=24$). All participants were up to and including 20 years of age, free from any psychiatric disorder, any neurological disorder, and current major medical or vision problems that could interfere with the experiment protocol. All chewers were currently betel quid chewers with concurrent use of cigarette and alcohol. All the non-chewers never smoked, but only four of them have never drunk alcohol. The dependent chewers had dependence scores higher than the cut-off point, 24, on the Betel Nut Dependency Scale (BNDS) (Li et al. 2012), and the non-dependent chewers had scores lower than the cut-off point. The BNDS consists of three factors: craving and desire, withdrawal response, and tasting habits. Higher scores indicate a higher level of dependence. In addition to BNDS, participants' smoking and alcohol drinking dependences were recorded by the Fagerstrom Test for Nicotine Dependence (FTND) (Fagerström 1978; HPA 2011) and the Alcohol Use Disorders Identification Test (AUDIT) (Chen et al. 2004; Saunders et al. 1993). Since the dependent chewers might be heavy users of tobacco or alcohol (Ho 2014; Wen et al. 2005), it was extremely difficult to screen out the heavy chewers with concurrent (possibly heavy) use of tobacco or alcohol. Instead, we took the FTND and AUDIT scores as the covariates in the subsequent analyses. The process of recruiting participants abided by the regulations set up by the Research Ethics Committee Central Regional Research Ethics Center, Taichung, Taiwan. Informed consent was obtained before the experiment.

Apparatus

All the span tasks were programmed with E-prime software and presented on a 17-in. CRT desktop monitor (refresh rate = 85 Hz). The viewing distance was 50 cm.

Design

In the matrix span task (Kane et al. 2004), participants recalled sequences of red-square locations within successive matrices. A sequence of 4 × 4 matrices (5.7° × 5.7°) was used, each presenting one of the 16 squares (each square 1.4° × 1.4°) in red. The set sizes (number of red-square locations to be recalled) were 2, 4, or 6. There were 15 practice trials, followed by 48 formal trials (16 trials for each set size). Red-square locations never repeated within a trial.

In the object span task (Alvarez and Cavanagh 2004; Makovski et al. 2010), participants determined whether the single polygon was the same as or different from the memory item previously displayed at that location. The memory items were the gray random polygons (3.4° × 3.4°) presented on an imaginary circle (radius = 4.0°) centered at fixation. The set sizes were 2, 4, or 6. When the set size was 2, the random polygons were presented 0° and 180° clockwise from 12 o'clock; when 4, 45°, 135°, 225°, and 315° clockwise; when 6, 30°, 90°, 150°, 210°, 270°, and 330° clockwise. There were 15 practice trials, followed by 72 formal trials. For each set size, there were 24 formal trials, equally distributed for the "same" and "different" responses. The random polygons never repeated within a trial.

In digit span task (Kane et al. 2004), participants recalled sequences of digits (1–9). Each digit was 2.8° in height and 1.7° in width, and each was set in Times New Roman font. The set sizes were 3, 6, or 9. There were 9 practice trials, followed by 18 formal trials (6 trials for each set size). The digits never repeated within a trial. For the formal trials, each digit appeared 12 times in total.

Procedure

Participants were required to complete a questionnaire about demographic background, major medical history, betel quid histories, and BNDS (Li et al. 2012). After completing the questionnaire, they began the span tasks. The three span tasks (Fig. 1) were completely counterbalanced across participants. The three set sizes were randomized within each span task.

In the matrix span and object span tasks, three non-repeated digits (randomly from 1–9) for 1000 ms in each trial. Participants needed to say these digits out loud repeatedly from the onset of digits until their responses were made. This verbal repetition decreased possible verbal encoding of locations and objects in both span tasks (articulatory suppression) (Logie et al. 1990). In the matrix span task, after the disappearance of the digits, a 4 × 4 matrix with blank squares appeared for 1000 ms, one of the squares became red for 650 ms with a 500-ms inter-stimulus blank matrix and repeating 2, 4, or 6 times (equal to the set size). Finally, participants reproduced the sequence of red-square locations in the correct order on a blank 4 × 4 matrix. Participants pressed "SKIP" button to skip the locations that they did not remember and pressed "OK" after they responded then for starting next trial.

In the object span task, after the disappearance of the digits, a central fixation cross appeared for 1000 ms. Then, 2, 4, or 6 memory items appeared for 1000 ms with a 1000-ms inter-stimulus fixation display. Finally, a probe item appeared at one of the locations of the memory items. Participants made a same/different judgment by pressing "s" (labeled "the same") or "d" (labeled "different").

In the verbal span task, each trial began with a central fixation for 500 ms, followed by one digit for 1000 ms with a 500-ms inter-stimulus blank display. Participants read the digit out lout when it was presented. The number of digits was equal to the set size. Finally, participants typed the digits in the correct order. Participants entered "0" to replace the digit they did not recall. They pressed "Enter" on a keyboard after they responded then for starting next trial.

Results

Participants

There was no significant age difference between the groups (Table 1). In comparison to the non-dependent chewers, the dependent chewers had higher BNDS scores, spent more money on betel quids, had more days per month chewing betel quids, and had more betel quids per day. In addition, the three groups differed significantly in the education years ($F(2, 69) = 14.192$, $p < .0001$, $\eta_p^2 = .291$), the FTND scores ($F(2, 69) = 36.225$, $p < .0001$, $\eta_p^2 = .512$), and the AUDIT scores ($F(2, 69) = 39.572$, $p < .0001$, $\eta_p^2 = .534$). This showed that the dependent chewers had lower education years, higher FTND scores, and higher AUDIT scores than the other two groups (all $ps < .0001$). The non-dependent chewers had higher FTND and AUDIT scores than the non-chewers (all $ps < .0001$), and both groups had comparable education years ($p = .738$).

Matrix span task

Only the trials with correct sequences were considered as correct trials. We conducted a 3 (group: dependent chewers, non-dependent chewers, and non-chewers) × 3 (set size: 3, 4, or 6) mixed analysis of covariance (ANCOVA) on accuracy rates, with the former as a between-group factor and the latter as a within-group factor (Table 2). The education years, the FTND scores, and the AUDIT scores were served as the covariates. The main effects of group ($F(2, 66) = 3.288$, $p < .05$, $\eta_p^2 = .091$) and set size ($F(2, 132) = 14.249$, $p < .0001$, $\eta_p^2 = .178$) were significant. All the post hoc tests in the current study were controlled by using Fisher's least significant difference (LSD) procedure. Further analysis showed that

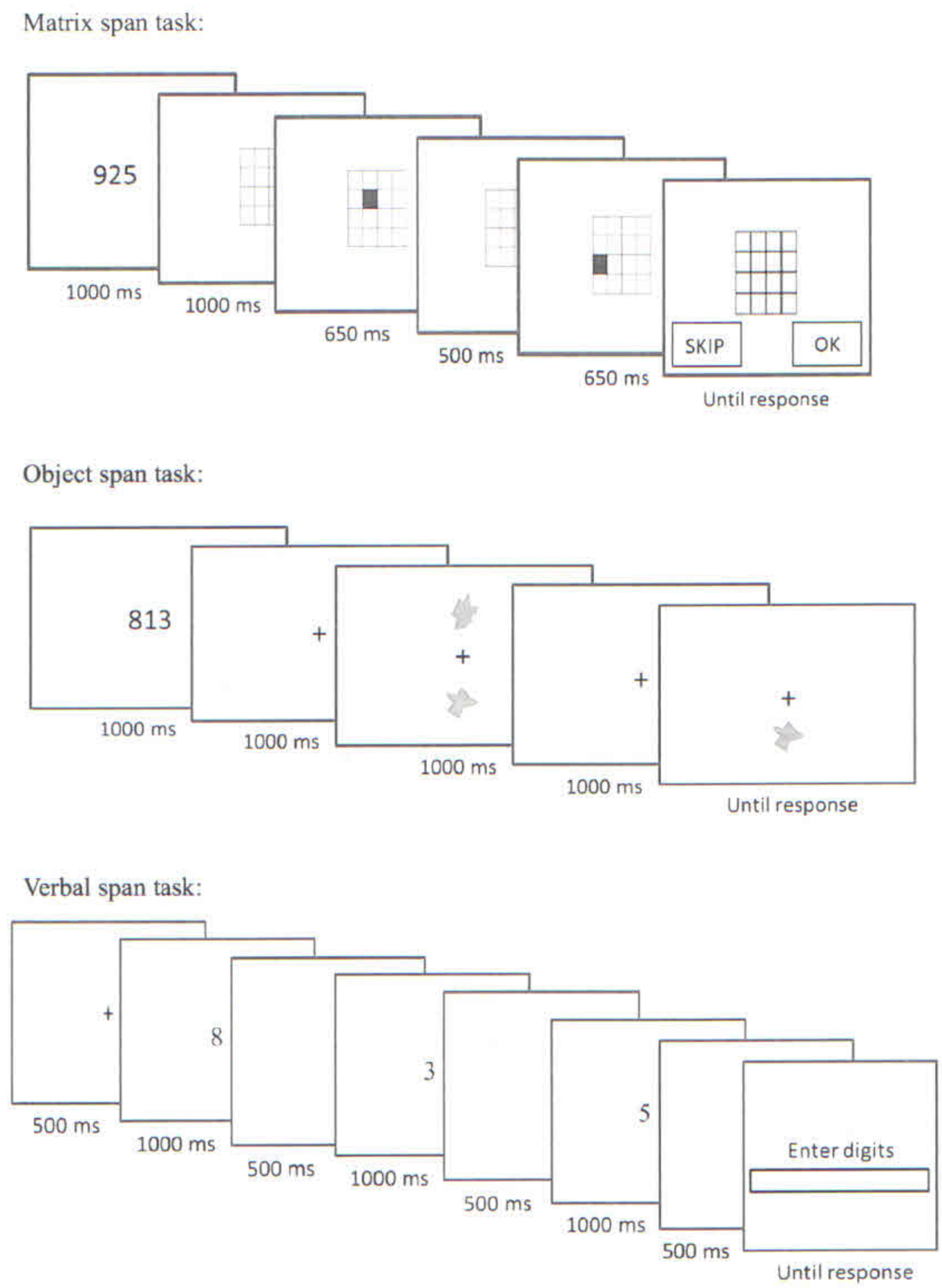

Fig. 1 Example procedures of three span tasks (the small set size)

Table 1 Characteristics of dependent chewers, non-dependent chewers, and non-chewers (standard deviations in parenthesis)

	Dependent chewers	Non-dependent chewers	Non-chewers	$F(2,69)$ or $t(46)$	p value
Age (years)	31.7 (5.5)	30.4 (5.8)	32.6 (5.8)	.92	.405
Education (years)	12.3 (2.7)	15.1 (1.9)	15.3 (1.8)	14.19	<.0001
BNDS	29.9 (4.8)	16.0 (4.0)	–	10.85	<.0001
FTND	5.0 (2.6)	4.0 (2.7)	0.0 (0.0)	36.23	<.0001
AUDIT	12.7 (5.8)	7.3 (5.2)	1.1 (1.0)	39.57	<.0001
Months	123.1 (83.3)	95.0 (79.3)	–	1.20	.238
Monthly expenses (NT dollars)	1733.3 (1670.6)	68.8 (168.6)	–	4.86	<.0001
Days per month	22.1 (10.3)	2.7 (5.2)	–	8.24	<.0001
Number per day	22.6 (23.5)	0.5 (1.2)	–	4.60	<.0001
Hours since last chew	26.1 (43.6)	4423.0 (13939.2)	–	1.55	.129

Table 2 Means and standard errors of means (in parenthesis) across three groups and set sizes after controlling for the covariates in matrix span task

Set size	Dependent	Non-dependent	Non-chewers	
2	.954 (.015)	.983 (.012)	1.000 (.017)	.983 (.006)
4	.840 (.037)	.900 (.027)	.985 (.040)	.908 (.015)
6	.436 (.074)	.660 (.055)	.678 (.080)	.591 (.029)
	.743 (.036)	.848 (.027)	.891 (.040)	

dependent chewers had lower accuracy than the non-dependent chewers ($p<.05$) and non-chewers ($p<.05$). There was no accuracy difference between the non-dependent chewers and the non-chewers ($p=.400$). Besides, a larger set size led to worse performance, showing successful manipulation of set size. Performances when set size = 6 was worse than when set size = 4 ($p<.0001$) and set size = 2 ($p<.0001$). Performances when set size = 4 were worse than when set size = 2 ($p<.0001$).

Importantly, the interaction between group and set size was significant ($F(4, 132)=2.677$, $p<.05$, $\eta_p^2=.075$). Further analysis showed that when set size = 2, there were no differences among the three groups ($F(2, 66)=2.100$, $p=.131$, $\eta_p^2=.060$). When set size = 4, there were no differences among the three groups ($F(2, 66)=2.363$, $p=.102$, $\eta_p^2=.067$). When set size = 6, at least one group was different from the others ($F(2, 66)=3.228$, $p<.05$, $\eta_p^2=.089$). Further analysis showed that the dependent chewers had worse performance than the non-dependent chewers ($p<.05$) and the non-chewers (marginal significance, $p=.077$). There was no significant difference between the non-dependent chewers and the non-chewers ($p=.863$).

Object span task

The same 3 (group) × 3 (set size) mixed ANCOVA was conducted (Table 3). The education years, the FTND scores, and the AUDIT scores were served as the covariates. Only the main effect of set size was significant ($F(2,132)=4.094$, $p<.05$, $\eta_p^2=.058$). The group main effect ($F(2,66)=.555$, $p=.577$, $\eta_p^2=.017$) and interaction effect ($F(4,132)=.423$, $p=.792$, $\eta_p^2=.013$) were not significant. Further analysis showed that performances when set size = 6 were worse than when set size = 4 and set size = 2 (all $ps<.0001$). Performances when set size = 4 were worse than when set size = 2 ($p<.0001$).

Verbal span task

Only the trials with correct sequences were considered as correct trials. The same 3 (group) × 3 (set size) mixed ANCOVA was conducted (Table 4). The education years, the FTND scores, and the AUDIT scores were served as the covariates. Only the main effect of set size was significant ($F(2, 132)=14.578$, $p<.0001$, $\eta_p^2=.181$). The group main effect ($F(2, 66)=.456$, $p=.636$, $\eta_p^2=.014$) and interaction effect ($F(4, 132)=.529$, $p=.715$, $\eta_p^2=.016$) were not significant. Further analysis showed that performances when set size = 9 were worse than when set size = 6 and set size = 3 (all $ps<.0001$). Performances when set size = 6 were worse than when set size = 3 ($p<.0001$).

General discussion

The current study asked whether chronic betel quid chewing could affect chewers' STM. We found that the dependent chewers had worse performance in spatial STM than the non-dependent chewers and the non-chewers. The impairment was profound when the memory load was large (set size = 6). The between-group differences were not found in visual STM and verbal STM. In all three span tasks, the main effect of set size was significant. It indicated the successful manipulation of memory load in these tasks.

The dependent chewers had worse performance in the matrix span task than the non-dependent chewers and the non-chewers. It indicated a selective impairment in spatial STM in the dependent chewers. Spatial memory has been consistently shown in the dorsal "where" pathway (e.g., the posterior cingulate gyrus and medial parietal lobe) (Wager and Smith

Table 3 Means and standard errors of means (in parenthesis) across three groups and set sizes after controlling for the covariates in object span task

Set size	Dependent	Non-dependent	Non-chewers	
2	.884 (.042)	.873 (.032)	.826 (.046)	.861 (.017)
4	.697 (.034)	.721 (.025)	.676 (.037)	.698 (.014)
6	.588 (.031)	.631 (.023)	.623 (.033)	.614 (.012)
	.723 (.026)	.742 (.020)	.708 (.029)	

Table 4 Means and standard errors of means (in parenthesis) across three groups and set sizes after controlling for the covariates in digit span task

Set size	Dependent	Non-dependent	Non-chewers	
3	.996 (.006)	.993 (.004)	1.000 (.007)	.998 (.002)
6	.805 (.062)	.815 (.046)	.893 (.067)	.838 (.025)
9	.437 (.101)	.321 (.075)	.360 (.110)	.379 (.040)
	.746 (.047)	.710 (.035)	.759 (.051)	

2003).[1] Moreover, the addition of executive demand (e.g., temporal order) for spatial memory (e.g., recalling spatial locations in correct sequence in the matrix span task) produced more right-hemisphere activations (e.g., anterior prefrontal cortex, ventral frontal cortex, and dorsal anterior cingulate area) (Eriksson et al. 2015; Wager and Smith 2003). Possibly, betel quid chewing could deteriorate the dependent betel quid chewers' brain areas in the dorsal ("where") pathway and in the right hemisphere, causing worse spatial STM. Notice that the brain areas (e.g., anterior intraparietal sulcus and caudal intraparietal sulcus) in the dorsal pathway can also process object features (e.g., shape, size, or orientation) (Milner 2012; Milner and Goodale 2008). The object feature processing provides unconscious bottom-up moment-to-moment sensory calibration of self-movements (Milner 2012; Milner and Goodale 2008). It is possible that these object-feature-processing brain areas (anterior intraparietal sulcus and caudal intraparietal sulcus) remained intact in the dependent chewers. Alternatively, it is also possible that these areas were disrupted but did not affect object STM. Heretofore, there are no studies examining whether or how long-term betel quid chewing affects the chewers' brain activities. In future, brain-imaging studies are required to understand betel quid chewers' possible abnormalities in brain function and structure.

Between-group performance differences were not observed in the object and digit span tasks. This suggested that betel quid chewing might not impair visual STM and verbal STM. The result that verbal STM was not affected by chronic chewing is similar to previous findings (Osborne et al. 2011; Wyatt 1996) showing no acute chewing effects on verbal STM. Wyatt reported that verbal STM was not affected after chewing one or one-half betel quids, in comparison to the no-chew baseline. Osborne et al. reported no verbal STM difference after chewing gum or betel quid. Together, chewing betel quid may not have acute or chronic effects on chewers' verbal STM.

Object memory has been consistently shown in the ventral "what" pathway (e.g., the fusiform gyrus and the inferior temporal gyrus) (Wager and Smith 2003). In addition, object memory may be lateralized in the left hemisphere (Courtney et al. 1998; d'Esposito et al. 1998). A lot of meta-analytic studies have shown that left lateralization of verbal memory in the inferior frontal cortex near Broca's area (Wager and Smith 2003). It is possible that betel quid chewing caused relatively less impairment to the brain areas in the ventral pathway and in the left hemisphere. Future studies on brain imaging in betel quid chewers are needed to examine this hypothesis.

Previous studies showed that substance use (e.g., cannabis, ecstasy, and nicotine) could impair visual STM and verbal STM. For example, cannabis-dependent adolescents had selective deficits in visual STM and verbal STM, even after 6 weeks of abstinence (Schwartz et al. 1989). Current heavy cannabis users demonstrated worse recall of word lists than the control group (Fletcher et al. 1996; Pope et al. 2001), but this impairment may be reversible after at least 28 days of abstinence (Pope et al. 2001). Recent meta-analytic papers on ecstasy and memory (Nulsen et al. 2010; Verbaten 2003) showed that ecstasy users had worse performance on visuospatial STM, verbal STM, and visuospatial working memory. Chronic nicotine use can cause disruptions in verbal memory and working memory in adolescent smokers (Jacobsen et al. 2005) and adult smokers (Richards et al. 2003).

The current study reported the comparable STM performances across three span tasks between non-dependent chewers and non-chewers. This indicated that betel quid chewing did not necessarily affect STM. Previous studies showed mixed results when comparing the cognitive performances of the non-dependent users and the non-users. For example, the moderate, recreational ecstasy users showed impaired memory in comparison to the non-users (Verkes et al. 2001). Alternatively, nicotine and marijuana studies (Block and Ghoneim 1993; Shiffman et al. 1995; Solowij et al. 2002) showed that light or short-term substance users had similar performances as the non-users in many cognitive tests (e.g., memory and learning). The non-dependent betel quid chewers may have relatively intact neural networks involving STM mentioned above, thereby leading to comparable STM performances.

The current study had at least three limitations. First, the current study was limited in distinguishing which specific stages of STM (encoding, storage, retrieval, or any combinations of these three stages) were impaired in the dependent chewers. Second, the current study was limited in assessing the acute effects of betel quid chewing on STM. Third, the limitation of the study is that the effects on spatial STM cannot be solely attributed to chronic betel quid consumption but must also be considered to possibly have a component influenced by chronic alcohol consumption or some interaction of betel quid and alcohol.[2]

[1] We adopted the papers that described the neural correlates of working memory (WM) (e.g., Eriksson et al. 2015; Wager and Smith 2003) to discuss the neural correlates of STM. In many studies, the terms of STM and WM refer to the similar concept: short-term maintenance of information. For example, Eriksson et al. defined WM as "maintains information in an easily accessible state over brief periods of time (several seconds to minutes)" (p.33), similar to the concept of STM. In Wager and Smith, they included simple storage of information in their meta-analysis. Since these papers adopted a similar concept as STM, these papers should be appropriate for discussing neural correlates of STM. Alternatively, a number of papers have highlighted the distinction between WM and STM (e.g., Kane et al. 2004). The neural correlates of STM and WM might also differ. We thank one anonymous reviewer for this comment.

[2] We thank an anonymous reviewer for this comment.

In conclusion, the current study reported that the dependent chewers had worse performance in spatial STM, particularly at large memory load. Many blue-collar workers in Taiwan are betel quid chewers (Chen and Shaw 1996; Chuang et al. 2007). These workers are likely to be employed in positions such as truck drivers, construction laborers, and porters, examples of jobs that require spatial navigation capability. Impaired spatial STM can worsen their work performance particularly in the area of higher memory load requirement such as memorizing a complex goods-delivery route. On the other hand, the relatively intact verbal and visual STM may be able to compensate for the harmful effect due to impaired spatial STM. In addition to the laboratory-based tasks, the standardized and validated neuropsychological tests are also encouraged for understanding various aspects of cognitions in betel quid chewers.

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Compliance with ethical standards The process of recruiting participants abided by the regulations set up by the Research Ethics Committee Central Regional Research Ethics Center, Taichung, Taiwan. Informed consent was obtained before the experiment.

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

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