ORIGINAL ARTICLE

Brain Magnetic Resonance Imaging of Regular Kratom (*Mitragyna speciosa* Korth.) Users: A Preliminary Study

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ABSTRACT

Introduction: *Mitragyna speciosa* (Korth.) or kratom is a native medicinal plant of Southeast Asia. Commonly used by hard labours in harsh working environment, the ingestion of brewed kratom decoction is reported to produce dose-dependent stimulant and opioid-like effects. Kratom is also regularly consumed as a pain killer and as traditional cure for common maladies such as fever and cough. However, it remains unknown whether regular consumption of kratom decoction is associated with brain abnormalities in regular users in traditional settings. **Methods:** A total of 14 subjects (7 regular kratom users and 7 non-kratom users) voluntarily participated in this cross-sectional study. Face-to-face interviews were conducted with kratom users to determine history of kratom use and later these respondents underwent brain magnetic resonance imaging (MRI). **Results:** There were no significant differences ($p>0.05$) in the intracranial volume (ICV), cortical volumes (frontal, parietal, temporal, occipital, or cingulate lobe), or subcortical volumes (striatum, hippocampus, or amygdala), as well as in the diffusion tensor imaging (DTI) metrics, fractional anisotropy (FA) and mean diffusivity (MD) between kratom users and the controls. **Conclusion:** This preliminary study showed long-term consumption of kratom decoction is not significantly associated with altered brain structures in regular kratom users in traditional settings. However, further study is needed to establish more data for kratom use and its effects.

Keywords: *Mitragyna speciose*, *mitragynine*, kratom, magnetic resonance imaging, brain, opioid.

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INTRODUCTION

Mitragyna speciosa Korth., or 'kratom' is an indigenous evergreen tropical plant native to Southeast Asia (1,2). Historically, kratom leaves have been used in parts of Southeast Asia as a folk remedy for treating common maladies, e.g. pain, fever, cough, fatigue, diarrhoea, and as a mild psychostimulant for improving laborious work under harsh seasonal conditions (3–5). In Malaysia, kratom is used mainly for stamina and endurance, especially for those working as farmers, fishermen and factory workers with odd shift hours. Kratom also used socially and recreationally as well as to improve sexual performance (4). Kratom leaves can be freshly chewed by removing the vein, dried and consumed in the form of powder with tea or coffee, or brewed and ingested as an herbal decoction (1). Due to its purported pain-relieving efficacy, kratom has begun to attract wider attention in the West as a natural remedy for improving mood (e.g. anxiety and depression), managing chronic pain, and managing withdrawal from prescription and illicit drug use (6–8).

Kratom has been classified as an atypical opioid (9), with its principal alkaloid (*mitragynine*) and one of its minor alkaloids (*7-hydroxymitragynine*) acting as a partial agonist at mu-opioid receptor and competitive

antagonist at kappa and delta-opioid receptors with limited side-effects compared to classical opioids (10). Despite kratom's purported self-reported efficacy in managing mood disorders, chronic pain, and prescription opioid dependence (11), its use in the West has also been linked to case reports of detrimental health effects such as hepatoxicity, cardiovascular and gastrointestinal complications, hypothyroidism, seizures, neonatal withdrawal and deaths (12–16). Rat studies have further linked kratom administration to impaired cognitive functioning (17,18), necrosis of neuronal cells, alterations in the white matter of the hippocampus, frontal lobe and cerebellum, as well as degenerative nerve cell damage (i.e. pyknosis of neuronal cells) after chronic (100mg/kg) *mitragynine* administration (19). In spite of such concerning evidence, understanding of the effects of kratom use is yet limited, preventing an informed discourse on its efficacy and safety.

In particular, since kratom is claimed to have opioid-like properties in the scientific literature and by the Food and Drug Administration (FDA), there is concern that its long-term use may have negative health consequences. Chronic opioid use has been associated with potential brain alterations including altered structural and functional connectivity, as well as volumetric differences across cortical and subcortical brain regions (amygdala, nucleus accumbens, hippocampus (20). The extent to which kratom affects brain morphology, if at all, have not been examined in long-term kratom users. With magnetic resonance imaging (MRI), the study of brain morphology has advanced the knowledge on how drugs such as opioids affect the brain as some study suggests presence of rapid changes of the some brain structures in opioid use (21). Accordingly, we sought to determine whether frequent consumption of kratom decoction was linked to differences in brain structure (i.e. cortical and subcortical volume, as well as diffusion tensor imaging (DTI) scalars) relative to non-kratom using controls.

MATERIALS AND METHODS

Study design and subjects

A total of 14 subjects (7 kratom users and 7 non-kratom using controls) were recruited through convenience sampling from Penang, a northern state of peninsular Malaysia for this cross-sectional study. Eligible respondents were then screened by a psychiatrist and received blood testing comprising complete blood count, comprehensive metabolic testing, and liver function testing. The subjects also underwent a face-to-face interview conducted by a trained research assistant using a semi-structured instrument that collected information related to respondent's socio-demographic characteristics, including current age, gender, ethnicity, marriage and employment status, and kratom use history, including first age of kratom use, kratom use duration, and current frequency and quantity of daily kratom use. Respondents then underwent brain MRI scans at the Imaging unit of Advanced Medical and Dental Institute, Universiti Sains Malaysia.

Study inclusion and exclusion criteria

The inclusion criteria for the study included respondents who were 18 years or older, who self-reported daily use of kratom and used kratom on a daily basis for at least one year. We only recruited those with one or more years of kratom use history since regular long-term (>1 year) kratom consumption was associated with dependence and unpleasant side effects (3,22). We excluded respondents who reported other illicit drug use such as opiates, amphetamine, methamphetamine, cannabis, methadone, ketamine, and benzodiazepine as confirmed by qualitative screens of urine for drugs of abuse; respondent who had current or previous mental health or neurological condition as well as traumatic brain injury or any medical problems requiring treatment; and respondents who had MRI contraindications such as claustrophobia or metal implants. The control subjects were also subjected to the same exclusion criteria, but did not have a kratom use history.

Ethics

This study protocol has been reviewed and approved by the Human Ethics and Research Committee of Universiti Sains Malaysia. As a token of appreciation, respondents were given financial compensation for their time as most of the respondents worked odd jobs and participation in this study for a day would cause loss of income. All respondents gave their written-informed consent.

Mitragynine analysis

To estimate the quantity of *mitragynine* consumed by the kratom users, two processed kratom juice samples were acquired from kratom traders in the community from which the respondents commonly obtained their kratom supply. On average, subjects consumed around 3 glasses of kratom decoction daily. The *mitragynine* content in the acquired kratom samples ranged from 24.06mg to 28.93mg. Thus, it is estimated that kratom users in this study ingested about 72.18mg to 86.79mg of *mitragynine* daily. For this study, the concoctions were brewed by the researchers with kratom leaves obtain from a single seller. Subjects consumed 3 glasses of kratom juice to achieve the required dosage. Procedures used to determine *mitragynine* content in the kratom juice samples are described in a previous study (23).

MRI data acquisition and processing

All subjects were imaged on a 1.5-T GE Signa HDx scanner (Milwaukee, WI, USA) with an 8-channel head coil. Structural T1 data were acquired using a 3D Fast Spoiled Gradient Echo sequence (echo time (TE) = 4.412ms, repetition time (TR) = 10.66ms, matrix size = 512x512mm, in-plane resolution = 0.47x0.47mm, slice thickness = 4mm) (Figure 1). T1-weighted images were processed using Freesurfer (24) automated pipeline. This process included automated skull-stripping, linear

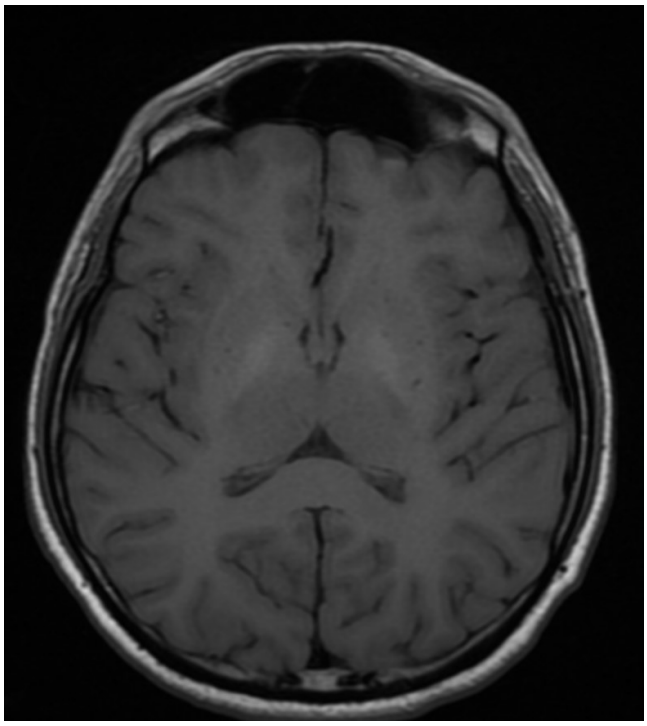

Figure 1: Axial T1 image of the brain. This image shows the brain of a subject in kratom group at the level of basal ganglia. The T1 weighted image was analysed using Freesurfer software.

Talairach registration, intensity normalization, cortical parcellation, and subcortical segmentation (24) (Figure 2).

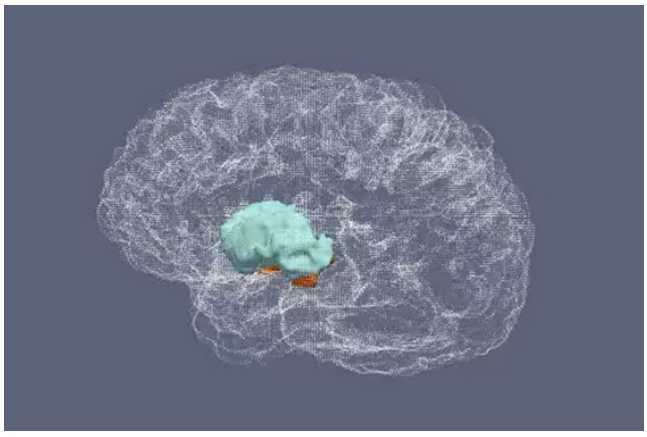

Figure 2: Reconstructed image and segmentation of basal ganglia. Automated skull-stripping, linear Talairach registration, intensity normalisation, cortical parcellation and subcortical segmentation were performed to measure the subcortical structures volume.

Volumetric measurements from the segmented cortical and subcortical regions were extracted for analysis. Diffusion-weighted images were acquired with a single-shot echo-planar imaging (SS-EPI) Stejskal-Tanner sequence (30 volumes, b-value = 1000 s/mm2, TR = 17000ms, TE = 101.1ms, field of view (FOV) = 24x24cm, matrix size = 256x256mm, in-plane resolution = 0.9375x0.9375mm, 50 axial slices of 3mm thickness). 3 sets of unweighted (b=0) images were also acquired. Diffusion MRI data were processed using FSL's (FMRIB Software Library v5.0.10, http://www.fmrib.ox.ac.uk/fsl) FDT and TBSS package (25). Mean subject fractional anisotropy (FA) and mean diffusivity (MD) values were extracted (Figure 3).

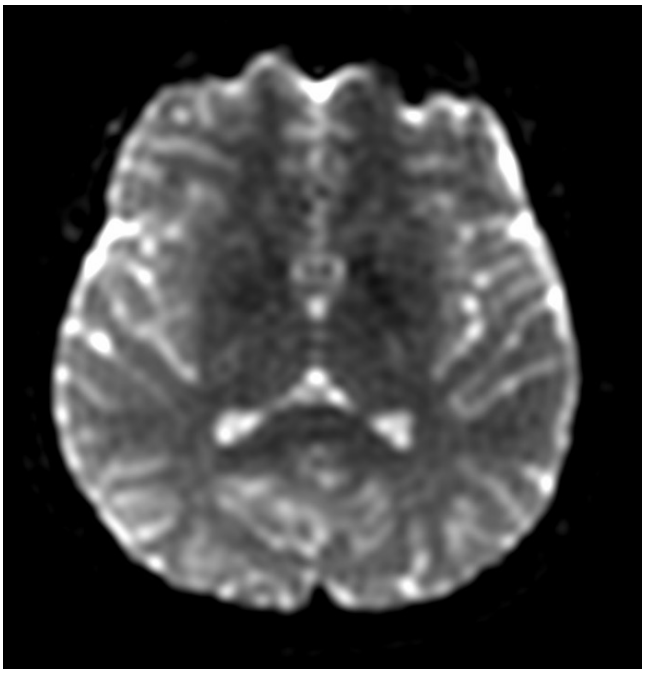

Figure 3: Diffusion tensor image at basal ganglia level. This image taken from a subject in kratom group shows diffusion tensor image and processed to extract fractional isotropy (FA) and mean diffusivity (MD) values.

Statistical analysis

Cortical and subcortical volumes were extracted for the frontal lobe, parietal lobe, temporal lobe, occipital lobe, cingulate lobe, striatum, hippocampus, and amygdala. Scalar values for average FA and MD were also extracted. Volumetric outputs were adjusted for age by residualising its influence for analysis. Subsequently, age-adjusted volumes, and FA and MD values were compared between kratom users and controls using the Mann-Whitney U test.

RESULTS

Demographic characteristics and kratom use history

The subject's demographic characteristics are presented in Table I. All subjects were male, and were of Malay ethnicity with similar education level (11 years of

Table I: Subject demographic and kratom use

	Kratom Users Mean (SD)	Non-Using Controls Mean (SD)
Gender (Male)	7	7
Age	27.1 (2.5)	20.9 (2.0)
Education Years	11.0 (0.0)	11.3 (0.8)
Kratom Use		
Age at First Use	22.7 (3.9)	-
Duration of Use	4.4 (2.4)	-
Quantity/Day (Glasses)	3.4 (1.8)	-

primary and secondary education). Kratom users were slightly older than the control group. All kratom users had consumed between 72.18mg to 86.79mg of *mitragynine* daily for up to 5 years duration.

Brain volume

On brain MRI, no significant differences were found between kratom users and the controls, in intracranial volumes (ICV), cortical volumes of the frontal-, parietal-, temporal-, occipital-, or cingulate cortex, or subcortical volumes of the striatum, hippocampus, or amygdala, after adjusting for age. Neither were there significant differences in diffusion tensor imaging (DTI) metrics, fractional anisotropy (FA) and mean diffusivity (MD), between kratom users and the controls as showed in Table II.

DISCUSSION

The current study examined brain structure associated with regular consumption of kratom decoction. The results demonstrated no significant differences in cortical (frontal, parietal, temporal, occipital, and cingulate lobes) and subcortical (striatum, hippocampus, and amygdala) volumes, or FA and MD values in regular kratom users compared to non-users. Some study involving prescription opioid users reported changes in subcortical volume especially amygdala (21). However, we were unable to measure significant changes in subcortical volume measurement. As for cortical volume measurement, some study in cocaine users did not show significant changes in these volumes which is similar to our findings (26). In chronic methamphetamine use, some study have reported significant changes in hippocampal volume reduced hippocampal volume in chronic methamphetamine users compared to control subjects (27). All of these studies showed some similarities to kratom users although some showed significant difference of brain volume.

While kratom is gaining popularity in Europe and north America as a novel recreational substance, the risk and benefits of use remain understudied (8). The findings from this study are thus timely in providing insight on morphological brain effects associated with kratom use.

Though kratom use been associated with posterior reversible leukoencephalopathy and recurrent seizures (28,29), it must be noted that the reported negative effects were likely induced by the combine use of kratom with other illicit substances as highlighted in case-studies, as well as in poison centre reports (14). Furthermore, commercially available kratom products are suspected to be adulterated (or spiked) with *7-hydroxymitragynine*, a potent kratom alkaloid which naturally only present in a very low amount in kratom leaves (30). In relation to central nervous system exposure, *mitragynine* and *7-hydroxymitragynine* are able to cross the blood-brain barrier (BBB) and interact with the efflux transporters P-glycoprotein (31–33), and breast cancer resistance protein (hBCRP) (34), which are both expressed at the BBB and function to limit permeation and to remove potentially neurotoxic endogenous and exogenous substances from the brain. Hence, it is possible that the reported detrimental effects of kratom on the brain were resulted from drug-drug interaction, where kratom alkaloids aided or increased brain permeation of other illicit substances by inhibiting function of the efflux transporters. On the other hand, kratom alkaloids were reported to increase activities of the P-glycoprotein and cytochrome P450 enzymes through modulation of pregnane X receptor expression (35). Notably, most of the reported kratom exposure cases in the West have been aggravated by the concomitant use of kratom extracts with other substances like ethanol, benzodiazepines, narcotics, and acetaminophen (14). So far, kratom consumption among users in traditional settings in Southeast Asia has not been linked to adverse health effects or toxicity (23,36). Previously reported studies on

Table II: Brain volume measurement

	Kratom Users Mean (SD)	Non-Using Controls Mean (SD)	p-value[a]
Brain Volume (mm^3)			
Intracranial Volume (ICV)	1533814 (589675)	1263670 (174579)	0.338
Frontal Lobe	156987 (9277)	163655 (15237)	0.749
Parietal Lobe	106861 (7694)	99966 (7320)	0.482
Temporal Lobe	87669 (7502)	90105 (9116)	0.749
Occipital Lobe	50506 (3458)	50358 (2639)	0.848
Cingulate Lobe	18637 (1567)	18658 (2569)	0.655
Striatum	17429 (1741)	20743 (2502)	0.949
Hippocampus	9834 (974)	9734 (895)	0.949
Amygdala	3014 (343)	3283 (308)	0.749
Fractional Anisotropy (FA)	0.263 (0.007)	0.272 (0.008)	0.085
Mean Diffusivity (MD)	0.0012 (0.00007)	0.0011 (0.00004)	0.064

[a]Mann-Whitney U test applied with brain volumes adjusted for age ($p<0.05$).

kratom's adverse effects are also mostly confined to case studies of acute toxicity or physical health effects (1). The brain morphology associated with regular kratom consumption has not been explored prior to this study.

This study has a few limitations. While we did not find any structural differences between users and controls, our sample size may have limited power to detect a significant difference. Generalisation of our finding is therefore difficult. Second, our use of self-reported data limited in our ability to validate users previous illicit drug use despite the use of confirmatory drug screens. Finally, in order to assess kratom-related effects on the brain relative to those of other opioids such as opioid dependence which have been associated with volumetric differences across brain regions including the amygdala, nucleus accumbens, hypothalamus, as well as frontal and cingulate lobes (20,21,37), it would be useful to include an opioid-using group in future studies.

CONCLUSION

In conclusion, our findings indicate that regular consumption of kratom decoction (equivalent to a daily dose of 72.18 mg to 86.79 mg of *mitragynine*) was not associated with altered brain structure relative to non-using controls. Given its limited number of harmful effects when used as a single agent, kratom and its alkaloids hold therapeutic potential as a novel medication for pain management and addiction management, since *mitragynine* is shown to have little abuse potential and can be used to reduce opioid intake (38,39). However, future studies must extend these findings to a larger sample including opioid-dependent users.

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