NEUROSCIENCE RESEARCH NOTES

OPEN ACCESS | RESEARCH NOTES ISSN: 2576-828X

Altered effective connectivity within the default mode network in kratom (*Mitragyna speciosa*) users: A resting-state fMRI study

Suzana Mat Isa [1,4], Aini Ismafairus Abd Hamid [1,5]*, Darshan Singh [2] and Muhamad Zabidi Ahmad [3,4,6]

[1] Department of Neurosciences, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[2] Centre for Drug Research, Universiti Sains Malaysia, 11800 Minden, Penang, Malaysia.
[3] Biomedical Imaging Department, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Bertam, 13200 Kepala Batas, Pulau Pinang, Malaysia.
[4] Imaging Unit, USM Bertam Medical Centre, Universiti Sains Malaysia, Bertam, 13200 Kepala Batas, Pulau Pinang, Malaysia.
[5] Brain and Behaviour Cluster, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.
[6] Diagnostic Imaging Services, KPJ Perlis Specialist Hospital, 01000 Kangar, Perlis.
* Correspondence: aini_ismafairus@usm.my; Tel.: +609-767 6348

Received: 26 December 2024; **Accepted**: 4 May 2025; **Published**: 23 September 2025
Edited by: Pike See Cheah (Universiti Putra Malaysia, Malaysia)
Reviewed by: Subapriya Suppiah (Universiti Putra Malaysia, Malaysia);
Wen Jia Chai (Universiti Teknologi MARA, Malaysia);
Muhammad Riddha Abdul Rahman (Universiti Sultan Zainal Abidin, Malaysia).
https://doi.org/10.31117/neuroscirn.v8i3.400

Abstract: Kratom (*Mitragyna speciosa*) is a Southeast Asian plant with stimulant and opioid-like properties, traditionally used for its medicinal effects. However, its increasing popularity and potential for dependence raise concerns about its impact on brain function. This study investigated alterations in effective connectivity (EC) within the default mode network (DMN), a network associated with self-related processes, in kratom users compared to healthy controls. Ten regular kratom users (mean age: 27.30 ± 3.97) and seven healthy controls (mean age: 20.72 ± 1.88) underwent resting-state functional magnetic resonance imaging (rs-fMRI). The EC analyses were performed using spectral dynamic causal modelling to examine directional influences between DMN regions. A fully connected model best represented EC in both groups; however, the control group lacked a significant connection between the right inferior parietal cortex (RIPC) and the posterior cingulate cortex (PCC). Kratom users exhibited hyperconnectivity between the medial prefrontal cortex (MPFC) and the left inferior parietal lobule (LIPL) connection compared to controls. Additionally, negative correlations were identified between the duration of kratom use and connectivity from PCC to RIPC. In contrast, positive correlations were observed between the duration of use and connectivity from RIPC to PCC. These findings suggest that kratom consumption may alter EC within the DMN, particularly the MPFC→LIPL connection, potentially due to chronic intake. This preliminary study provides neuroimaging insights into the effects of kratom on the brain and contributes to ongoing discussions regarding its potential for dependence and therapeutic applications.

Keywords: fMRI; Kratom; Resting state fMRI, Spectral DCM, Effective connectivity, Default mode network (DMN), Addiction.

1.0 INTRODUCTION

Kratom (*Mitragyna speciosa*), a Southeast Asian plant with a long history of traditional use, has gained attention for its opioid-like properties (Abdullah & Singh, 2021; Vicknasingam et al., 2010) and thus its potential in managing opioid withdrawal and pain (Singh et al., 2014; Vicknasingam et al., 2020). However, its complex pharmacology (Hossain et al., 2023) and legal status (Bergen-Cico & MacClurg, 2016; Khalil et al., 2020) in various regions necessitate a deeper understanding of its effects on the brain. While research on kratom's physiological effects is emerging (Singh et al., 2018a), investigations into its neurological impacts remain limited. Animal studies have suggested that kratom may influence memory, cognition, and brain activity (Compton et al., 2014; Ilmie et al., 2015; Suhaimi et al., 2021). Importantly, these studies indicate potential variability in effects based on dosage and use patterns.

Investigating the effects of kratom on the human brain poses unique ethical challenges. Its potentially addictive nature and varying legal status across jurisdictions raise concerns regarding participant vulnerability and the long-term implications of research findings. Acknowledging these complexities is crucial to ensure that such studies adhere to the highest ethical standards, including obtaining rigorous informed consent and respecting participant autonomy.

This study employed resting-state functional magnetic resonance imaging (rs-fMRI) to investigate the effects of long-term kratom consumption on effective connectivity (EC) in the human brain. Focusing on the default mode network (DMN), a network implicated in self-referential thinking and introspection (Greicius et al., 2003) , this study aimed to provide novel insights into the neural mechanisms potentially altered by kratom use. The DMN was of particular interest due to its involvement in processes like mind-wandering and self-awareness, which could be differentially affected by kratom's psychoactive properties. Additionally, the DMN has been implicated in various neuropsychiatric disorders, including addiction (Zhang & Volkow, 2019), making it a relevant target for investigating the potential long-term effects of kratom use and its role in disrupting the cycle of addiction (Loganathan & Ho, 2020).

The medial prefrontal cortex (MPFC) and inferior parietal lobule (IPL) are crucial nodes within the DMN, known to play significant roles in cognitive functions such as decision-making, attention, and self-referential processing (Abdul Rahman et al., 2020; Smallwood et al., 2021; Yin et al., 2016). The MPFC is involved in evaluating the value of rewards and making decisions based on potential outcomes (Jobson et al., 2021; Molnar-Szakacs & Uddin, 2013), while the IPL contributes to attentional control and the integration of sensory information with internal representations (Numssen et al., 2021). Given their involvement in these processes, alterations in the connectivity between the MPFC and the IPL could have implications for understanding the cognitive and behavioural effects of kratom, particularly concerning its potential for addiction. In this study, it was hypothesised that long-term kratom users would exhibit altered EC within the DMN compared to controls. The EC analysis was used to examine the directional influence of brain regions within the network. Findings from this study contribute to the limited literature on kratom's neurological effects and inform public health discussions regarding its potential risks and benefits.

2.0 MATERIALS AND METHODS

2.1 Study design and participants

This study employed a cross-sectional design and recruited ten kratom users (mean age: 27.30 ± 3.97 years) and seven healthy control participants (mean age: 20.72 ± 1.86 years) through convenience sampling. Participants engaged in a face-to-face interview with a trained research assistant, utilising a semi-structured questionnaire to gather their socio-demographic information (i.e., age, gender, ethnicity, marital status, and employment status) and kratom use history (i.e., age of initiation, duration, quantity, and frequency of use). Kratom users typically consumed their kratom decoction before the MRI session, which aligned with their habitual consumption patterns. The MRI session was conducted two to three hours after intake to allow

the effects of kratom to manifest. Brain MRI scans were acquired at the Imaging Unit, USM Bertam Medical Centre, Universiti Sains Malaysia.

2.2 Experimental protocol

Ethical approval for this study was granted by the Human Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/20040193). All participants provided written informed consent before participation and received a small token of appreciation for their time and travel. Study data were maintained with strict confidentiality and were accessible only to researchers. The inclusion criteria encompassed the following: (1) male participants, (2) those aged from 18 to 40 years, (3) self-reported regular kratom users consuming at least three glasses (300 mL each) of kratom solution daily for a minimum of one year, (4) completion of at least 11 years of education, and (5) absence of MRI contraindications. The exclusion criteria were as follows: (1) current or past illicit drug and alcohol use (defined as any lifetime use), (2) positive urine drug screen results for illicit substances before enrollment, and (3) self-reported current or past mental health or neurological conditions. The selection of only male participants was due to previous studies, particularly on opioids, which have shown that brain responses can differ between males and females (Sharp et al., 2022). Furthermore, the prevalence of Kratom use is significantly higher among males compared to females (Choo et al., 2022; Farris et al., 2019). Control participants, recruited from the same community as the kratom users, adhered to the same criteria except for kratom use history.

2.3 Mitragynine analysis

Mitragynine, the primary psychoactive alkaloid found in kratom, was quantified in prepared kratom samples commonly used by participants. Participants reported consuming an average of 3.8 glasses of kratom daily (**Figure 1**). Several studies (Singh et al., 2018a; Singh et al., 2018b) used the quantification method involving the same sample, whereby the mitragynine concentration per glass was estimated to be between 24.06 mg and 28.93 mg, resulting in an estimated daily intake of 91.428 mg and 109.94 mg. The limitations of this quantification method, particularly due to the variability in kratom preparation and alkaloid content, were acknowledged.

2.4 Behavioral analysis

Before scanning, cognitive function was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) Research Suite 6.0 (software key: 941863346). The test evaluated motor, memory, attention, and executive functions through tasks such as the Motor Screening Task (MOT), Delayed Matching to Sample (DMS), reaction time (RT), and attention switching task (AST). Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 26, with *t*-tests used to determine significance at $p<0.05$.

2.5 Resting-state functional magnetic resonance imaging (rs-fMRI)

2.5.1 Data acquisition

MRI scans were performed using a 1.5-T magnetic resonance imaging system (Signa HDx; GE, Milwaukee, WI, USA) with an 8-channel phased-array head coil. T1-weighted images were acquired using a volumetric 3-dimensional spoiled gradient recall (BRAVO) sequence with the following parameters: TR = 10.7 ms, TE = 4.4 ms, FA = 13°, FOV =240 x 240 mm^2, matrix size = 320 × 320, slice thickness = 4 mm, voxel size = 4 × 1 × 1 mm^3, and number of slices = 40. Resting-state functional scans were acquired using a gradient-echo-planar imaging (EPI) sequence with the following parameters: TR = 1750 ms, delay = 250 ms, TE = 30 ms, flip angle = 90°, FOV = 240 x 240 mm^2, matrix size = 64 x 64, slice thickness = 4 mm, number of axial slices = 28, and voxel size = 3.75 x 3.75 x 4 mm^3. The functional run consisted of 240 image volumes, acquired over a total duration of 11 minutes and 42 seconds. Participants were instructed to keep their eyes closed, relax, and remain awake throughout the resting-state scan.

2.5.2 Image processing

Functional image preprocessing was performed using Statistical Parametric Mapping software 12 (SPM 12; Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK; www.fil.ion.ucl.ac.uk) (Friston et al., 2007) on MATLAB 9.3 (R2017b; MathWorks Inc., MA, USA). Preprocessing steps included discarding the first five volumes to allow for signal stabilization, slice timing correction to account for differences in slice acquisition times, realignment (motion correction) to correct for head motion during the scan, co-registration of functional images to anatomical T1 images, spatial normalization to the Montreal Neurological Institute (MNI) EPI template, and spatial smoothing using an 8 mm full-width at half-maximum (FWHM) Gaussian kernel.

Four regions of interest (ROIs) within the DMN (Di & Biswal, 2014) were selected for analysis: (1) posterior cingulate cortex (PCC): 0, -52, 26 (5 mm radius); (2)

MPFC: 3, 54, -2 (5 mm radius); (3) left inferior parietal lobule (LIPL): -50, -63, 32 (5 mm radius); and (4) right IPL (RIPL): 48, -69, 35 (5 mm radius).

Spectral Dynamic Causal Modelling (DCM) was employed to investigate EC within the DMN, estimating directional influences between brain regions based on their rs-fMRI time series. Thirty models representing different connectivity patterns were constructed based on the study by Di and Biswal (2014), and Bayesian model selection (BMS) (Stephan et al., 2009) was used to identify the best-fitting model. The winning model was then used to estimate EC parameters, with endogenous connectivity at a posterior probability of 0.9 or greater considered significant (Penny et al., 2004).

2.6 Statistical analysis

Statistical analyses were conducted using SPSS software version 26. Independent *t*-tests were performed to compare EC values between groups. Effect size was calculated using the Hedges' *g* (https://www.socscistatistics.com/effectsize/default3.aspx) and classified as small (0.2-0.5), medium (0.5-0.8), or large (> 0.8) (Sullivan & Feinn, 2012).

2.7 Correlation analysis

Pearson's correlation analysis was conducted to assess the relationships between EC values and variables such as cognitive test scores (MOT, DMS, RT, and AST), duration of kratom use, quantity consumed, age, and age of kratom initiation. Bonferroni correction was applied for multiple comparisons.

3.0 RESULTS

3.1 Demographic results

The demographic characteristics of the participants are presented in **Table 1**. All participants were male and predominantly Malay, as kratom use in Malaysia is deeply rooted in Malay culture and has been used for many reasons (Grundmann et al., 2023; Singh et al., 2016, 2019). This demographic pattern is attributed to cultural normalisation rather than biological predisposition. Kratom users were significantly older than those in the control group ($p<0.05$). The average daily kratom consumption among users was 3.8 glasses, with an estimated daily mitragynine intake ranging from 91.428 mg to 109.94 mg. The mean duration of kratom use in this study was 4.2 years.

The cognitive performance of kratom users and control participants is presented in **Table 2**. No significant differences were found between the two groups in cognitive performance, as assessed by MOT, DMS, RT, and AST.

Table 1. Demographic characteristics

	Kratom [mean±SD]	Healthy [mean±SD]
Gender (Male)	N=10	N =7
Age	27.30 [3.97]	20.72 [1.88]*
Education years	11.00 [0.00]	11.43 [1.13]
Kratom use		
a) Initial age of use	23.10 [4.38]	N/A
b) Duration of use	4.20 [2.09]	N/A
c) Quantity of use per day (glasses)	3.80 [1.99]	N/A
d) Frequency of use per day	3.50 [1.65]	N/A

*Significant difference, p<0.05

Table 2. Cognitive performance of kratom users and a healthy group.

Cognitive Tests	Kratom [mean±SD]	Healthy [mean±SD]	*p*-value	Effect size (Cohen D)	95% Confidence Interval	
					Lower	Upper
Motor (MOT)						
Mean latency (speed)	184.99 [153.67]	210.66 [121.85]	0.508	-0.334	-234.011	458.339
Mean error (accuracy)	23.80 [9.79]	27.142 [3.76]	0.602	0.263	-349.405	209.578
Memory (DMS)						
Percent correct	222.27 [235.15]	165.88 [205.91]	0.617	-0.252	-291.585	178.808
Attention (RT)						
Simple accuracy score	27.14 [3.76]	23.80 [9.79]	0.407	0.420	-0.564	1.391
Mean simple reaction time	210.66 [121.85]	184.99 [153.67]	0.719	0.181	-123.287	174.611
Executive function (AST)						
Congruent cost (mean correct)	71.38 [77.82]	67.61 [76.65]	0.923	-0.049	-85.021	77.482
Switching cost (mean correct)	139.45 [91.09]	88.66 [135.66]	0.368	-0.457	-167.471	65.889

MOT: Motor Screening task; DMS: Delayed matching to sample; RT: Reaction time; AST: Attention switching task.

3.2 Bayesian model selection (BMS)

For both groups, the fully connected Model 30, in which all four DMN regions (PCC, MPFC, LIPC, and RIPC) are interconnected, provided the best fit to the data, with a posterior probability of 1 (**Figure 1**).

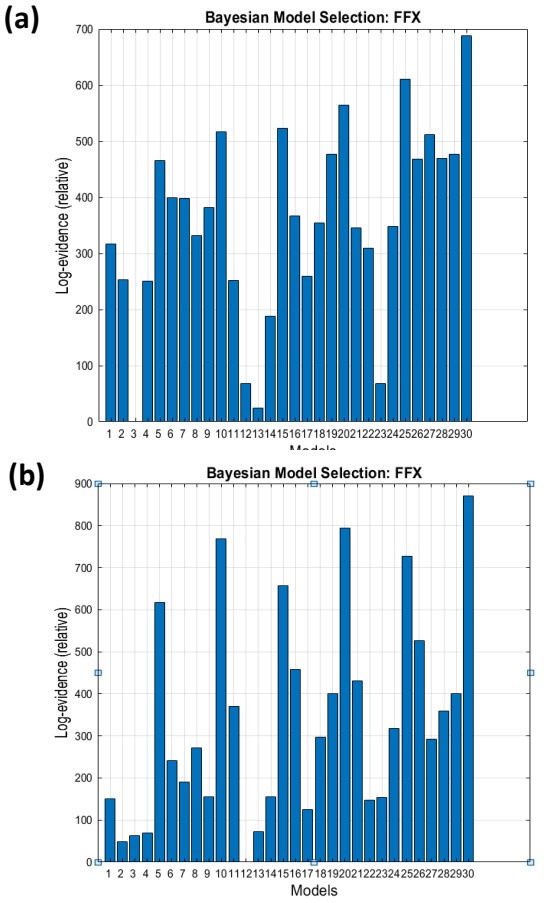

Figure 1. The Bayesian model selection results displaying models in relative log-evidence: (a) the healthy group and (b) the kratom group.

3.3 Dynamic causal modelling (DCM)

Figure 2 and **Figure 3** illustrate the mean connectivity strength of the optimal DCM model for the control and kratom groups, respectively. In the control group, all connections in the optimal DCM model were significant (posterior probability ≥ 0.9) except for the RIPC→PCC connection, which is represented by a dotted line in **Figure 2**. In contrast, the kratom group exhibited reciprocal connections in all directions. EC values included both excitatory (positive) and inhibitory (negative) connections (**Table 3**, **Figures 2-3**).

No significant differences in EC were found between groups. However, the effect size analysis indicated a large effect for MPFC→LIPC (g=1.081, p=0.293) and medium effects for LIPC→MPFC (g=0.539, p=0.891) and PCC→LIPC (g=0.618, p=0.230), with higher values observed in the kratom group.

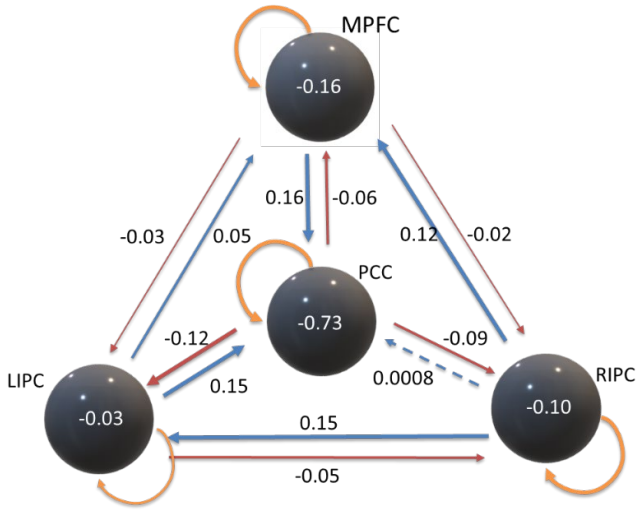

Figure 2. EC model in healthy participants. Dashed lines indicate a posterior probability of ≤ 0.9. Blue arrows depict excitatory connections, while red arrows represent inhibitory connections. The width of the arrows signifies the strength of connectivity. Orange arrows indicate self-connections.

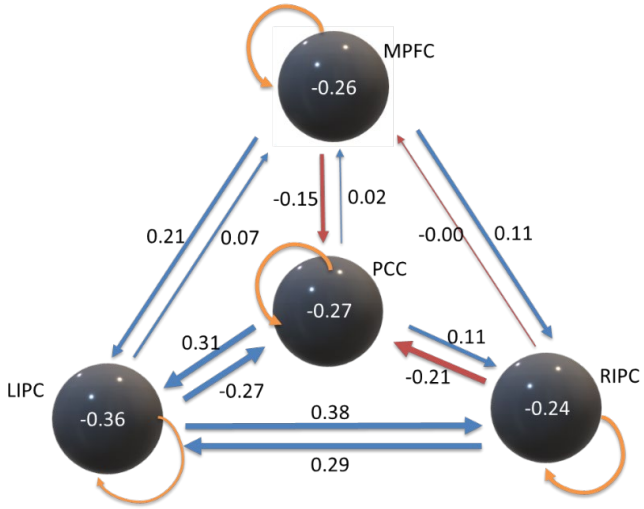

Figure 3. EC model in kratom participants. Dashed lines indicate a posterior probability of ≤ 0.9. Blue arrows depict excitatory connections, while red arrows represent inhibitory connections. The width of the arrows signifies the strength of connectivity. Orange arrows indicate self-connections.

Table 3. Endogenous connection between the four DMN regions of the best model for each group.

Brain Connectivity	Healthy Group [N=7] EC [Hz]	Kratom Group [N=10] EC [Hz]	*p*-value [a]	Effect Size [b]
MPFC→LIPC	-0.03 [1.00]	0.21 [1.00]	0.293	**1.081**
LIPC→MPFC	0.05 [1.00]	0.07 [1.00]	0.891	**0.539**
MPFC→PCC	0.16 [1.00]	-0.15 [1.00]	0.678	0.209
PCC→MPFC	-0.06 [1.00]	0.02 [0.92]	0.491	0.347
MPFC→RIPC	-0.02 [0.99]	0.11 [1.00]	0.929	0.044
RIPC→MPFC	0.12 [1.00]	-0.00 [0.92]	0.511	0.332
LIPC→RIPC	-0.05 [1.00]	0.29 [1.00]	0.501	0.340
RIPC→LIPC	0.15 [1.00]	0.38 [1.00]	0.535	0.169
LIPC→PCC	0.15 [1.00]	-0.27 [1.00]	0.447	0.362
PCC→LIPC	-0.12 [1.00]	0.31 [1.00]	0.230	**0.618**
PCC→RIPC	-0.09 [1.00]	0.11 [1.00]	0.821	0.112
RIPC→PCC	NS	-0.21 [1.00]	0.773	0.144
MPFC	-0.16 [1.00]	-0.26 [1.00]	0.695	0.196
LIPC	-0.03 [0.96]	-0.36 [1.00]	0.637	0.242
RIPC	-0.10 [1.00]	-0.24 [1.00]	0.571	0.300
PCC	-0.73 [1.00]	-0.27 [1.00]	0.339	0.485

Note. The statistical comparison results (t-test) are shown in the right column, with high and medium effect sizes in bold. A positive value indicates excitatory connectivity, while a negative value indicates inhibitory connectivity. PCC: Posterior Cingulate cortex, MPFC: Medial Prefrontal Cortex, LIPC: Left Inferior Parietal Cortex, RIPC: Right Inferior Parietal Cortex

[a] Two-tailed independent sample t-test at $p<0.05$.

[b] Cohen's corrected d (Hedge's g).

3.4 Correlation analyses between EC, cognitive scores, and kratom characteristics

A moderate negative correlation was found between the duration of kratom use and EC values in PCC→RIPC (r=-0.647, p=0.043; **Figure 4**). Conversely, a moderate positive correlation was observed between RIPC→PCC and the duration of kratom use (r=0.639, p=0.047; **Figure 5**). No significant correlations were identified between EC values and other variables, i.e., age, quantity of use, or age of initiation. Additionally, after applying the Bonferroni correction ($p<0.0071$), no significant correlations were observed between EC values and cognitive scores in either group.

4.0 DISCUSSION

This study investigated optimal brain connectivity models within the DMN in both kratom users and healthy control groups. BMS identified a fully connected model (Model 30) as the best fit for both groups, indicating that all four DMN regions (PCC, MPFC, LIPC, and RIPC) are interconnected. Notably, while the optimal model for the control group lacked a significant connection between RIPC and PCC, the kratom group exhibited a fully connected model, with all connections being significant.

The presence of a fully connected model in the kratom group is particularly noteworthy, given previous research indicating that kratom does not impair brain structural connectivity, i.e., fractional anisotropy and mean diffusion (Singh, Chye, et al., 2018), or cognitive performance(Singh et al., 2018b). This suggests that while kratom may not disrupt the physical connections between brain regions, it could potentially modulate functional connectivity within the DMN (Ma et al., 2015; Tarumov, et al., 2019; Upadhyay et al., 2010).

Despite sharing some pharmacological properties with opioids, such as partial agonist activity at opioid receptors, kratom's effects on brain networks, particularly the DMN, appear to be distinct. This difference may be attributed to kratom's complex pharmacology, which involves interactions with non-

opioid receptors, potentially leading to a unique modulation of intrinsic brain activity.

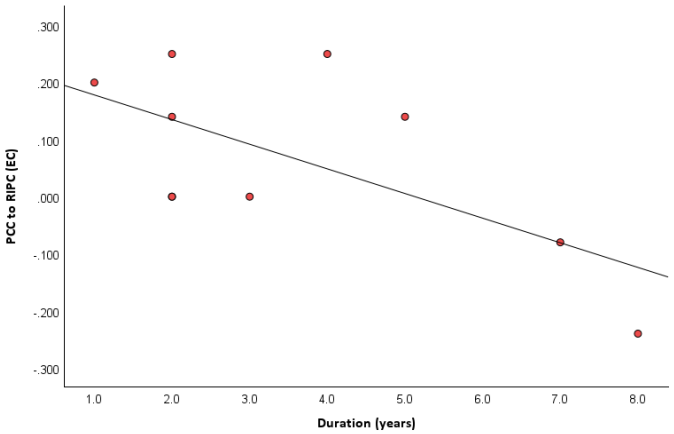

Figure 4. Correlation analysis between endogenous connectivity and duration of kratom use in PCC→RIPC.

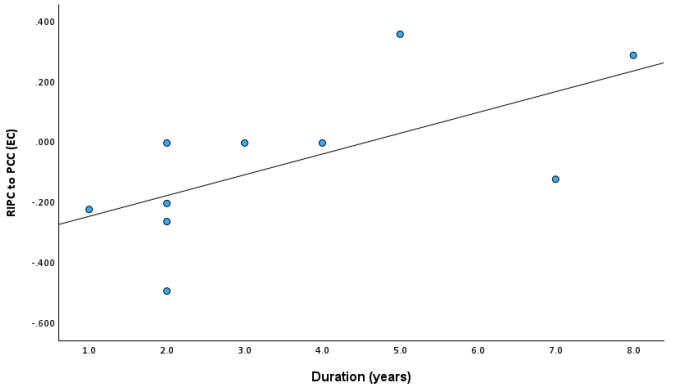

Figure 5. Correlation analysis between endogenous connectivity and duration of kratom intake in RIPC→PCC.

4.1 Effective connectivity value in kratom users and the control group

Analysis of EC values revealed the presence of both excitatory (positive) and inhibitory (negative) connections within the DMN in both groups (**Figures 2 to 3**), suggesting similar top-down and bottom-up processing. This result is consistent with previous studies that demonstrated inhibitory self-connections across all DMN regions (Nawi et al., 2020; Wahab et al., 2022), as well as a greater influence from the MPFC on the PCC (Di & Biswal, 2014).

In the control group, the strongest excitatory connections were observed from the MPFC to the PCC (at 0.16 Hz) and from the RIPC to the MPFC (at 0.12 Hz). Conversely, in the kratom group, the strongest excitatory connections were from the RIPC to the LIPC (0.38 Hz) and from the PCC to the LIPC (0.31 Hz). The strongest inhibitory connection in the control group was from the PCC to the RIPC (-0.09 Hz). The number of negative ECs was approximately the same in both groups, with 10 of 16 connections in the control group and 8 of 16 connections in the kratom group.

While no significant differences in EC values were observed between the groups, the effect size analysis revealed a large effect for MPFC→LIPC (g=1.081) and medium effects for LIPC→MPFC (g=0.539) and PCC→LIPC (g=0.618). Notably, kratom users exhibited significantly higher EC values in the MPFC→LIPC connectivity compared to controls, indicating a potential hyperconnectivity in this pathway.

These findings suggest that the altered connectivity between the MPFC and the IPL observed in addiction may also be associated with kratom addiction. Altered connectivity between these two regions could contribute to the addictive properties of kratom by impairing decision-making, impulse control, and attention (Jobson et al., 2021; Kim & Lee, 2011). These effects align with the addiction theory proposed by Koob and Volkow (2016), which emphasises the role of disrupted brain circuits in reward processing and decision-making in addiction. Repeated drug use leads to neuroadaptations in the brain, resulting in impaired self-control and increased drug-seeking behaviours. Addiction affects the mesocorticolimbic dopamine system, including the MPFC and the nucleus accumbens (NAc), as well as other brain regions such as the insula and the amygdala (Koob & Volkow, 2016). Several studies have shown that addiction is associated with decreased connectivity between the MPFC and IPL (Luijten et al., 2014; Ma et al., 2010; Zhang & Volkow, 2019), which has been observed in various types of addiction to other substances, such as heroin (Ye et al., 2018; Zilverstand et al., 2018).

Research on the effects of kratom on the human MPFC and IPL is limited, but studies in rat brains have shown that kratom alters functional connectivity in the frontal cortex (Suhaimi et al., 2021). Therefore, understanding the relationship between the MPFC→IPL connectivity and kratom addiction may provide new insights into the underlying mechanisms of addiction and aid in developing new treatments for this disorder. Although no statistically significant differences in EC were found, rsfMRI was still able to detect group differences, as indicated by the large effect size in the analysis.

4.2 Correlations of effective connectivity (EC) with duration, initial age of kratom use, and quantity consumed

No significant correlations were identified between EC values and variables such as age, age of kratom initiation, and quantity of kratom consumed. However, as illustrated in **Figure 4**, a significant moderate negative correlation was observed between the duration of kratom use and the EC value in PCC→RIPC (r=-0.647, p=0.043). Conversely, a significant moderate positive correlation was found between the duration of kratom use and the EC value in RIPC→PCC (r=0.639, p=0.047), as shown in **Figure 5**. After applying the Bonferroni correction for multiple comparisons, these correlations were no longer statistically significant (adjusted p-value threshold: p<0.0071), suggesting that the observed effects may not be robust under stricter statistical criteria. Larger sample sizes or refined methodologies may be required to establish more definitive relationships.

Previous studies have suggested that the PCC functions as the central node of the brain, connecting all major structural modules and playing a crucial role in functional-process integration (Andrews-Hanna et al., 2014; Tang et al., 2016; Zhang & Volkow, 2019). The observed decrease in the PCC→RIPC connectivity over time has led us to postulate that prolonged kratom use may disrupt the efficiency of this connection. Since PCC activation directly influences RIPC activation, longer kratom intake may weaken this connectivity. The connection between PCC and RIPC has been suggested to influence empathy (Esménio et al., 2019) and self-referential processing in humans (Zhang & Volkow, 2019). Given the PPC's central role in brain networks, further investigation is warranted to understand how chronic kratom use may impact its connectivity. Therefore, we hypothesised a potential association between the duration of kratom use and EC.

4.3 Limitations

This study had several limitations. First, the sample size was relatively small. In future research, we aim to increase the sample size and include a more balanced sample in terms of sex and ethnicity. Additionally, using a more controlled environment, such as by monitoring participants' kratom use history and intake before scanning, would enhance the reliability of the findings. This would involve recording the duration of use, quantity consumed, and preparation of the decoction by the study team. The use of comorbid substances, such as alcohol, cigarettes, and e-cigarettes, could affect the brain's connectivity patterns and should be controlled either through inclusion and exclusion criteria or as covariates in the analysis. Furthermore, studies comparing kratom to other substances, including opioids and amphetamine-type stimulants, could provide deeper insights into its effects on brain functions. Screening tools, such as relevant questionnaires like the Kratom Dependence Scale (KDS) and Clinical Opioid Withdrawal Scale (COWS), as well as blood and urine tests, should also be incorporated to control for the influence of comorbid drug use. Additionally, this study utilised a 1.5T MRI scanner, which limited the ability to obtain high-resolution images of the brain. Therefore, using higher-field-strength MRI machines in future studies would improve image quality and enable a more detailed interpretation of brain activation and connectivity. Finally, measuring blood mitragynine levels is recommended to enhance the accuracy of kratom intake assessment.

5.0 CONCLUSIONS

In conclusion, findings of this study indicate that regular consumption of kratom decoction is associated with altered connectivity within the DMN, specifically in the MPFC→IPL connection. A fully connected model best represents DMN network dynamics in kratom users. Furthermore, this study identified a potential relationship between the duration of kratom use and EC, particularly in the RIPC→PCC connection. These findings enhance our understanding of the neural changes associated with kratom use and may provide insights into the brain mechanisms underlying kratom dependence. This preliminary study offers novel information on the effects of kratom on the brain and contributes valuable perspectives for discussions on public health policies and interventions concerning kratom consumption.

Supplementary Materials: None

Acknowledgements: This work was supported by the Research University Grant of Universiti Sains Malaysia and the Higher Institution's Centre of Excellence (HICoE) Grant. We thank Muhammad Eshal Dzulkapli for assistance with field data collection and radiographers Nurul Ain Mohd Khatli and Noor Aishah Mohd Zainal.

Author Contributions: DS and ZA conceptualised the project idea; SM administered the project; SM, AI and DS planned and executed the methodology; DS acquired fundings for the project; SM and AI analysed and interpreted the data; SM wrote the original draft; AI, DS and ZA reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

Abdul Rahman, M. R., Abd Hamid, A. I., Noh, N. A., Idris, Z., & Abdullah, J. M. (2020). The effective connectivity of the default mode network following moderate traumatic brain injury. *Journal of Physics: Conference Series*, *1497*(1), 012008. https://doi.org/10.1088/1742-6596/1497/1/012008

Abdullah, M. F. I. L, & Singh, D. (2021). The adverse cardiovascular effects and cardiotoxicity of kratom (*Mitragyna speciosa* Korth.): A comprehensive review. *Frontiers in Pharmacology*, *12*, 1–12. https://doi.org/10.3389/fphar.2021.726003

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, *1316*(1), 29–52. https://doi.org/10.1111/nyas.12360

Bergen-Cico, D., & MacClurg, K. (2016). Kratom (*Mitragyna speciosa*) use, addiction potential, and legal status. In V. R. Preedy (Ed.), *Neuropathology of drug addictions and substance misuse* (Vol. 3, pp. 903–911). Academic Press. https://doi.org/10.1016/B978-0-12-800634-4.00089-5

Choo, L. L., Zahari, M. M. A., Choy, S. K., Rahim, N. A., & Rashid, R. A. (2022). The Prevalence and Psychosocial Correlates of Ketum (*Mitragyna speciosa*) use among individuals on methadone maintenance therapy programme in Hospital Taiping, Malaysia. *Healthcare*, *10*(4), 746. https://doi.org/10.3390/healthcare10040746

Compton, D. M., Garcia, C., Kamaratos, A. V, Johnson, B. G., & Wedge, T. (2014). An examination of the consequences of chronic exposure to *Mitragyna speciosa* during adolescence on learning and memory in adulthood. *The Journal of Phytopharmacology*, *3*(5), 300-309. https://doi.org/10.31254/phyto.2014.3501

Di, X., & Biswal, B. B. (2014). Identifying the default mode network structure using dynamic causal modeling on resting-state functional magnetic resonance imaging. *NeuroImage*, *86*, 53–59. https://doi.org/10.1016/j.neuroimage.2013.07.071

Esménio, S., Soares, J. M., Oliveira-Silva, P., Zeidman, P., Razi, A., Gonçalves, Ó. F., Friston, K., & Coutinho, J. (2019). Using resting-state DMN effective connectivity to characterize the neurofunctional architecture of empathy. *Scientific Reports*, *9*(1), 2603. https://doi.org/10.1038/s41598-019-38801-6

Farris, M., Leong, I., Abdullah, B., Singh, D., Narayanan, S., Rahim, A. A., & Vicknasingam, B. (2019). Socio-demographic characteristics, kratom use and quality of life (QoL) of regular kratom (*Mitragyna speciosa* Korth.) users. *Malaysian Journal of Medicine and Health Sciences*, *15*(3), 4-9.

Friston, K. J., Ashburner, J., Kiebel, S. J., Nichols, T. E., & Penny, W. D. (2007). *Statistical parametric mapping: The analysis of functional brain images*. Academic Press. https://doi.org/10.1016/B978-0-12-372560-8.X5000-1

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(1), 253–258. https://doi.org/10.1073/pnas.0135058100

Grundmann, O., Hendrickson, R. G., & Greenberg, M. I. (2023). Kratom: History, pharmacology, current user trends, adverse health effects and potential benefits. *Disease-a-Month*, *69*(6), 101442. https://doi.org/10.1016/j.disamonth.2022.101442

Hossain, R., Sultana, A., Nuinoon, M., Noonong, K., Tangpong, J., Hossain, K. H., & Rahman, M. A. (2023). a critical review of the neuropharmacological effects of kratom: An insight from the functional array of identified natural compounds. *Molecules*, *28*(21), 7372. https://doi.org/10.3390/molecules28217372

Ilmie, M. U., Mansor, S. M., & Abdullah, J. M. (2015). Behavioural and electrophysiological evidence of impaired learning and memory in male Sprague Dawley rats following subchronic exposure to standardised methanolic extract of *Mitragyna speciosa* Korth. *Malaysian Journal of Medical Sciences*, *22*(8), 45–51.

Jobson, D. D., Hase, Y., Clarkson, A. N., & Kalaria, R. N. (2021). The role of the medial prefrontal cortex in cognition, ageing and dementia. *Brain Communications*, *3*(3), fcab125. https://doi.org/10.1093/braincomms/fcab125

Khalil, S., Halim, @, Ahmad, R., Alida, S., & Abdullah, J. (2020). Enforcement status of the Poison Act 1952 against offences related to kratom (*Mitragyna speciosa* Korth) misuse in Malaysia. *UUM Journal of Legal Studies*, *11*(1), 75-93.

Kim, S., & Lee, D. (2011). Prefrontal cortex and impulsive decision making. *Biological Psychiatry*, *69*(12), 1140–1146. https://doi.org/10.1016/j.biopsych.2010.07.005

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760–773. https://doi.org/10.1016/S2215-0366(16)00104-8

Loganathan, K., & Ho, E. T. W. (2020). Neurocognitive interventions based on network neuroscience may break the cycle of drug addiction relapse. *Neuroscience Research Notes*, *3*(2), 15–22. https://doi.org/10.31117/neuroscirn.v3i2.48

Luijten, M., Machielsen, M. W. J., Veltman, D. J., Hester, R., de Haan, L., & Franken, I. H. A. (2014). Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. *Journal of Psychiatry and Neuroscience*, *39*(3), 149–169. https://doi.org/10.1503/jpn.130052

Ma, N., Liu, Y., Li, N., Wang, C. X., Zhang, H., Jiang, X. F., Xu, H. S., Fu, X. M., Hu, X., & Zhang, D. R. (2010). Addiction related alteration in resting-state brain connectivity. *NeuroImage*, *49*(1), 738–744. https://doi.org/10.1016/j.neuroimage.2009.08.037

Ma, X., Qiu, Y., Tian, J., Wang, J., Li, S., Zhan, W., Wang, T., Zeng, S., Jiang, G., & Xu, Y. (2015). Aberrant default-mode functional and structural connectivity in heroin-dependent individuals. *PLoS ONE*, *10*(4), e0120861. https://doi.org/10.1371/journal.pone.0120861

Molnar-Szakacs, I., & Uddin, L. Q. (2013). Self-processing and the default mode network: Interactions with the mirror neuron system. *Frontiers in Human Neuroscience*, *7*, 571. https://doi.org/10.3389/fnhum.2013.00571

Nawi, M., Hamid, A., & Marzuki, A. (2020). Effective connectivity of a default mode network in human brain: In search of a dominant node using spectral dynamic causal modeling. *Physics and Technology in Medicine Publisher: Malaysian Association of Medical Physics*, *1*(1), 1–14.

Numssen, O., Bzdok, D., & Hartwigsen, G. (2021). Functional specialization within the inferior parietal lobes across cognitive domains. *ELife*, *10*, e63591. https://doi.org/10.7554/eLife.63591

Penny, W. D., Stephan, K. E., Mechelli, A., & Friston, K. J. (2004). Comparing dynamic causal models. *NeuroImage*, *22*(3), 1157–1172. https://doi.org/10.1016/j.neuroimage.2004.03.026

Sharp, J. L., Pearson, T., & Smith, M. A. (2022). Sex differences in opioid receptor mediated effects: Role of androgens. *Neuroscience and Biobehavioral Reviews*, 134, 104522. https://doi.org/10.1016/j.neubiorev.2022.104522

Singh, D., Chye, Y., Suo, C., Yücel, M., Grundmann, O., Ahmad, M. Z., Ho, E. T. W., Mansor, S. M., Yusof, S. R., McCurdy, C. R., Müller, C., & Vicknassingam, B. (2018). Brain magnetic resonance imaging of regular kratom (*Mitragyna speciosa* Korth.) users: A preliminary study. *Malaysian Journal of Medicine and Health Sciences*, *14*(Sup 1), 65–70.

Singh, D., Müller, C. P., & Vicknasingam, B. K. (2014). Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. *Drug and Alcohol Dependence*, *139*, 132–137. https://doi.org/10.1016/j.drugalcdep.2014.03.017

Singh, D., Murugaiyah, V., Hamid, S. B. S., Kasinather, V., Chan, M. S. A., Ho, E. T. W., Grundmann, O., Chear, N. J. Y., & Mansor, S. M. (2018a). Assessment of gonadotropins and testosterone hormone levels in regular *Mitragyna speciosa* (Korth.) users. *Journal of Ethnopharmacology*, *221*, 30–36. https://doi.org/10.1016/j.jep.2018.04.005

Singh, D., Narayanan, S., Müller, C. P., Swogger, M. T., Chear, N. J. Y., Dzulkapli, E. B., Yusoff, N. S. M., Ramachandram, D. S., León, F., McCurdy, C. R., & Vicknasingam, B. (2019). Motives for Using Kratom (*Mitragyna speciosa* Korth.) among Regular Users in Malaysia. *Journal of Ethnopharmacology*, *233*, 34–40. https://doi.org/10.1016/j.jep.2018.12.038

Singh, D., Narayanan, S., Müller, C. P., Vicknasingam, B., Yücel, M., Ho, E. T. W., Hassan, Z., & Mansor, S. M. (2018b). Long-term cognitive effects of kratom (*Mitragyna speciosa* Korth.) use. *Journal of Psychoactive Drugs*, *51*(1), 19–27. https://doi.org/10.1080/02791072.2018.1555345

Singh, D., Narayanan, S., & Vicknasingam, B. (2016). Traditional and non-traditional uses of mitragynine (kratom): A survey of the literature. *Brain Research Bulletin*, *126*, 41–46. https://doi.org/10.1016/j.brainresbull.2016.05.004

Smallwood, J., Bernhardt, B. C., Leech, R., Bzdok, D., Jefferies, E., & Margulies, D. S. (2021). The default mode network in cognition: a topographical perspective. *Nature Reviews Neuroscience*, *22*(8), 503–513. https://doi.org/10.1038/s41583-021-00474-4

Stephan, K. E., Penny, W. D., Daunizeau, J., Moran, R. J., & Friston, K. J. (2009). Bayesian model selection for group studies. *NeuroImage*, *46*(4), 1004–1017. https://doi.org/10.1016/j.neuroimage.2009.03.025

Suhaimi, F. W., Hassan, Z., Mansor, S. M., & Müller, C. P. (2021). The effects of chronic mitragynine (kratom) exposure on the EEG in rats. *Neuroscience Letters*, *745*, 135632. https://doi.org/10.1016/j.neulet.2021.135632

Sullivan, G. M., & Feinn, R. (2012). Using Effect Size—or Why the P Value Is Not Enough. *Journal of Graduate Medical Education*, *4*(3), 279–282. https://doi.org/10.4300/jgme-d-12-00156.1

Tang, R., Razi, A., Friston, K. J., & Tang, Y. Y. (2016). Mapping smoking addiction using effective connectivity analysis. *Frontiers in Human Neuroscience*, *10*, 195. https://doi.org/10.3389/fnhum.2016.00195

Tarumov, D., Trufanov, A., Chakchir, O., Abdulaev, S. H., Partsernyak, A., Efimtsev, A., Bystrova, D., Kurasov, E., Shamrey, V., & Zhelezniak, I. (2019). Possibilities of resting state functional magnetic resonance imaging in the assessment of the functional state of the brain in patients with opioid addiction. *Journal of Psychiatry and Psychiatric Disorders*, *3*(4), 168–178. https://doi.org/10.26502/jppd.2572-519x0071

Upadhyay, J., Maleki, N., Potter, J., Elman, I., Rudrauf, D., Knudsen, J., Wallin, D., Pendse, G., McDonald, L., Griffin, M., Anderson, J., Nutile, L., Renshaw, P., Weiss, R., Becerra, L., & Borsook, D. (2010). Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain*, *133*(7), 2098–2114. https://doi.org/10.1093/brain/awq138

Vicknasingam, B., Chooi, W. T., Rahim, A. A., Ramachandram, D., Singh, D., Ramanathan, S., Yusof, S. M., Zainal, H., Murugaiyah, V., Gueorguieva, R., Mansor, M., & Chawarski, M. C. (2020). Kratom and pain tolerance: A randomized, placebo-controlled, double-blind study. *Yale Journal of Biology and Medicine*, *93*(2), 229-238.

Vicknasingam, B., Narayanan, S., Beng, G. T., & Mansor, S. M. (2010). The informal use of ketum (*Mitragyna speciosa*) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. *International Journal of Drug Policy*, *21*(4), 283–288. https://doi.org/10.1016/j.drugpo.2009.12.003

Wahab, N. S. A., Yahya, N., Yusoff, A. N., Zakaria, R., Thanabalan, J., Othman, E., Hong, S. B., Kumar, R. K. A., & Manan, H. A. (2022). Effects of different scan duration on brain effective connectivity among default mode network nodes. *Diagnostics*, *12*(5), 1277. https://doi.org/10.3390/diagnostics12051277

Ye, J. J., Li, W., Zhang, D. S., Li, Q., Zhu, J., Chen, J. J., Li, Y. Bin, Yan, X. J., Liu, J. R., Wei, X., Wang, Y. R., & Wang, W. (2018). Longitudinal behavioral and fMRI-based assessment of inhibitory control in heroin addicts on methadone maintenance treatment. *Experimental and Therapeutic Medicine*, *16*(4), 3202–3210. https://doi.org/10.3892/etm.2018.6571

Yin, Y., He, X., Xu, M., Hou, Z., Song, X., Sui, Y., Liu, Z., Jiang, W., Yue, Y., Zhang, Y., Liu, Y., & Yuan, Y. (2016). Structural and functional connectivity of default mode network underlying the cognitive impairment in late-onset depression. *Scientific Reports*, *6*, 37617. https://doi.org/10.1038/srep37617

Zhang, R., & Volkow, N. D. (2019). Brain default-mode network dysfunction in addiction. *NeuroImage*, *200*, 313–331. https://doi.org/10.1016/j.neuroimage.2019.06.036

Zilverstand, A., Huang, A. S., Alia-Klein, N., & Goldstein, R. Z. (2018). Neuroimaging impaired response inhibition and salience attribution in human drug addiction: A systematic review. *Neuron*, *98*(5), 886–903. https://doi.org/10.1016/j.neuron.2018.03.048