BRIEF REPORT

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Neural Correlates of Emotion-Cognition Interaction During Working Memory Maintenance in Obsessive-Compulsive Disorder: The Role of the Dorsolateral Prefrontal Cortex

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ABSTRACT

The neural correlates for the effect of emotional distraction on working memory (WM) function in obsessive-compulsive disorder (OCD) have not been clearly identified. This study utilized functional magnetic resonance imaging (fMRI) to investigate the effect of emotional distraction during WM maintenance in OCD patients and to determine if the frontoparietal region was involved during the task. Patients with OCD tried to maintain WM during the task-irrelevant anxiety-provoking distractions, which induced interruption and needed attention. Compared with healthy controls, the patients with OCD showed significantly increased activities in the dorsolateral prefrontal cortex (DLPFC) supplementary motor area during the delayed-response WM task with anxiety-provoking distractors. An increase in the activity of the DLPFC and SMA reflects compensatory efforts of neural circuits to perform cognitive tasks by controlling emotions and inhibiting the interference of anxiety provoking distractors during WM tasks. In addition, the brain areas showed significantly decreased activities during the delayed-response WM task with neutral distractors were superior parietal gyrus and fusiform gyrus. The parietal cortex, along with the DLPFC is the main structure for frontoparietal network and is involved in cognitive control. Therefore, parietal dysfunction in OCD patients prevents them from paying appropriate attention to visual processing for picture distractors during the WM task. Our findings might be helpful for further understanding of the neural correlates that are associated with the effects of emotional distraction on cognitive function in OCD.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is characterized by unwanted intrusive thoughts, ideas, or images (obsessions) accompanied by anxiety and repetitive behaviors or mental acts (compulsions) to reduce this anxiety. Since OCD patients generally recognize the irrationality of their symptoms, they continuously suffer from anxiety and distress related to obsession and compulsion. Obsession and related anxiety are the primary psychopathology in OCD, which might be associated with abnormal interactions between cognition and emotion.

In this study, we conducted event-related functional magnetic resonance imaging (fMRI) while the participants performed delayed-response WM tasks with emotional distractors to observe which brain regions, especially the frontoparietal area, were involved. A delayed-response WM task allows the neural correlates of WM maintenance to be investigated while task-irrelevant distractors are presented during the interval between encoding and retrieval.[7] However, only a limited number of studies have assessed neural mechanisms of the effects of emotional distraction on cognition using delayed-response WM tasks in OCD. Our study could provide novel insights into the neural mechanisms that are associated with abnormal cognitive-emotional interaction in OCD patients.

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MATERIAL AND METHODS

Subjects and Instruments

Patients with OCD were recruited for participation from the psychiatric clinic of the Jeonbuk National University Hospital. Inclusion criteria were as follows: age between 18 and 65 years, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), Text Revision OCD according to the Structured Clinical Interview for Axis I DSM-IV Disorders,[8] and right-handedness. The following were used as exclusion criteria: history of significant medical or neurological illness, current severe other mental illness, current pregnancy, or breastfeeding. Healthy controls matched on age, gender, and education period with OCD patients were recruited via advertisement. Recruiting for the participants was done through advertisements. Healthy controls were selected by the following exclusion criteria: history of significant medical or neurological illness, current severe other mental illness, current pregnancy, or breastfeeding. All participants gave written informed consent and this study was approved by the Institutional Review Board of the Jeonbuk National University Hospital (No. CBIRB0907-65).

A total of 12 patients with OCD and 12 healthy controls underwent fMRI on a 3.0 Tesla Magnetom Verio MR Scanner (Siemens Medical Solutions, Erlangen, Germany), all of whom were right-handed. The severity of symptoms was evaluated with Hamilton Rating Scale for Anxiety (HAM-A), Hamilton Rating Scale for Depression (HAM-D), Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and the Clinical Global Impression-Severity (CGI-S).[9-11] Hamilton Rating Scale for Anxiety is a psychological questionnaire used by clinicians to evaluate the severity of anxiety and consists of 14 items on a scale of 0 to 4, with 4 being the most severe. The reliability coefficient (Cronbach α) of HAM-A for 97 subjects with anxiety disorders was 0.77-0.92 depending on the raters.[12] Hamilton Rating Scale for Depression is a 17-item questionnaire used to provide an indication of depression and is used to rate the severity of depression by probing mood, feelings of guilt, suicide ideation, insomnia, weight loss, agitation, and somatic symptoms. For 2 raters, the correlation between summed scores for 10 patients with depression was 0.84.[10] Yale-Brown Obsessive Compulsive Scale is a test to rate the severity of OCD symptoms and is computed from the subscales for obsessions (items 1-5) and compulsions (items 6-10). The mean reliability coefficient (Cronbach α) of Y-BOCS for 4 raters was 0.89 (0.88-0.91).[11] Clinical Global Impression-Severity is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment. The intraclass correlation coefficient of CGI-S for 11 patients with OCD by 6 raters was 0.68.[13] A total of OCD patients (n = 12) received psychiatric medications with stable dosages. All participants practiced the task paradigm prior to MR scanning and were instructed to sustain attention during the tasks.

MAIN POINTS

- Compared with healthy controls, the patients with OCD showed significantly increased activities in the dorsolateral prefrontal cortex (DLPFC) and supplementary motor area (SMA) during the delayed-response WM task with anxiety-provoking distractors.
- An increase in the activity of the DLPFC and SMA reflects compensatory efforts of neural circuits to perform cognitive tasks by controlling emotions and inhibiting the interference of anxiety provoking distractors during WM tasks.
- The brain areas showed significantly decreased activities during the delayed-response WM task with neutral distractors were superior parietal gyrus and fusiform gyrus.
- Parietal dysfunction in OCD patients prevents them from paying appropriate attention to visual processing for picture distractors during the WM task.
- These results suggest that the frontoparietal region was involved in controlling emotional distractors and maintaining cognitive functions.

Task Paradigms

All participants underwent fMRI scanning during delayed-response WM tasks (face recognition task) with emotional distractors. The WM task paradigm consisted of sequences of trial "encoding (6 seconds), WM maintenance (4 seconds), distractor (6 seconds), button preparation (2 seconds), retrieval (2 seconds), and intertrial interval (ITI) (12 seconds)" (Figure 1).

The human faces (male and female in an equal ratio) were selected from a high school yearbook, which were converted to black-and-white pictures of an oval shape that showed only the eyes, nose, mouth, and eyebrows. The neutral and anxiety-provoking pictures were presented to induce emotional responses. A total of 50 emotional distractor picture images were collected from the International Affective Picture System[14] and a variety of Web sites. Among them, a psychiatrist selected 20 neutral and 20 anxiety-provoking pictures. All task paradigms of this fMRI paradigm were presented to the participants using the SuperLab software (Cedrus Corporation, San Pedro, Calif, USA).

Functional Magnetic Resonance Imaging Data Acquisition

Functional magnetic resonance imaging data were acquired on a 3.0 Tesla Magnetom Verio MR Scanner (Siemens Medial Solutions, Malvern, Pa, USA) with a bird-cage head coil. A total of 25 axial slices parallel to the anterior commissure-posterior commissure line were acquired using a gradient-echo planar pulse sequence with the following parameters: repetition time (TR)/echo time (TE) = 2000 ms/30 ms, flip angle = 90°, field of view (FOV) = 22 cm × 22 cm, matrix size = 64 × 64, and slice thickness = 5 mm. In addition, 2 phases of dummy scans were supplemented to circumvent unstable fMRI signals. The high resolution T1-weighted

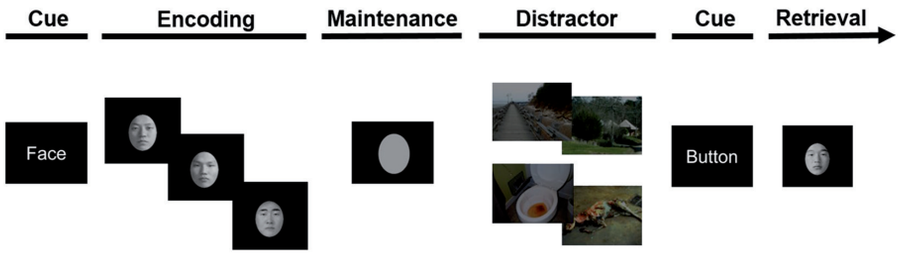

Figure 1. Diagrams for delayed-response working memory (WM) tasks with anxiety-provoking and neutral distractors*. *In the encoding task, 3 different human faces appear simultaneously and the subjects were instructed to encode and maintain the WM for the presented human faces, followed by looking at the distractors with neutral pictures (or anxiety-provoking pictures) while maintaining the WM. In the retrieval period, one of the faces presented in the encoding task or a new face was presented (50% were presented with an encoding face, and 50% were presented with a new face), and then the response to the probe for the previously presented human face or a new face was assessed.

images (TR/TE = 1900 ms/2.35 ms) were comprised with a FOV = 22 cm × 22 cm, matrix size = 256 × 256, and a slice thickness = 5 mm.

Data Preprocessing and Analysis

The fMRI data were analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, University College London, London, UK). Prior to statistical analysis, a slice-timing correction was performed on the fMRI data. Images were realigned by using the reference volume and were spatially normalized to the standard Echo-planar imaging (EPI) template in the Montreal Neurological Institute (MNI) space and resampled to a 2 × 2 × 2 mm resolution. Finally, images were smoothed with an 8-mm full-width-half-maximum Gaussian filter. Preprocessed data were analyzed using the standard general linear model approach within SPM8. We used the data from the distractor phase for imaging analysis. To analyze the individual blood-oxygen-level-dependent signal, an independent samples *t*-test was performed in the rest and activation conditions (neutral pictures and anxiety-provoking pictures).

Statistical Analysis

Demographic and Clinical Characteristics: The normality test (Kolmogorov-Smirnov and Shapiro-Wilk test) has been performed for variables such as age, education period, CGI-S, HAM-A, HAM-D, and Y-BOCS. Since all variables did not follow a normal distribution, a Mann-Whitney *U*-test (non-parametric test) was used to compare the age, education period, and scores on the symptom scales (HAM-A, HAM-D, Y-BOCS, and CGI-S) between the 2 groups, which are presented as median (min-max). Fisher's exact test (non-parametric test) was used to compare the sex distribution and handedness between the 2 groups, which are presented as n (%). The statistical analyses were performed with IBM Statistical Package for Social Sciences 26.0 program (IBM SPSS Corp., Armonk, NY, USA).

Functional Magnetic Resonance Imaging Analysis: An independent samples *t*-test (parametric test, uncorrected, $\alpha = 0.005$) was used to compare the differential brain activation patterns between the OCD patients and healthy controls. The purpose of this study was to investigate the effect of emotional distraction on the whole brain areas during WM maintenance in OCD patients. Brain activity and MNI coordinates were analyzed using the SPM8, custom-made software, and MRIcron software.[15] Statistical Parametric Mapping uses a parametric approach based on the normal distribution of the data. Statistical Parametric Mapping is image process with voxel values that are, under the null hypothesis, distributed according to a known probability density function. In the imaging analysis, we performed the statistical analysis for 510 340 brain voxels to compare 2 groups. Numerous neuroimaging studies do not use the normality test to evaluate brain activation.[6,7,16-18] Table 2 shows the MNI coordinates of the maximum peak in the activated brain areas.

RESULTS

Demographic and Clinical Characteristics

The median ages of participants were 29 (20-49) years for OCD patients and 28 (19-40) years for healthy controls, resulting from the Mann-Whitney *U*-test ($P = .468$, Table 1). Of the 12 patients with OCD, 9 (75%) were male, as was the healthy control group (Fisher's exact test, $P = 1.000$, Table 1). All 12 (100%) OCD patients and 12 (100%) healthy controls were right-handed (Table 1). The median education period was 16 (12-16) years for OCD patients and 16 (12-18) years for healthy controls (Mann=-Whitney *U*-test, $P = 1.000$, Table 1). There were no significant differences in the age, gender, and education period between the 2 groups. The clinical characteristics of the OCD patients are presented as a median as follows: duration of illness (6 (1-17) years), HAM-A (11 (2-26)), HAM-D (5.5 (2-13)), Y-BOCS (27.5 (20-34)), and CGI-S (5 (4-7)). The median scores for the facial recognition task with neutral distractors (10 trials) were 70 (30-80)% and 55 (25-80)% in the healthy controls and the patients with OCD, respectively (Mann-Whitney U-test, $P = .291$, Table 1), whereas the median scores for the anxiety-provoking distractors (10 trials) were 70 (60-90)% and 70 (33-80)% in the healthy controls

Table 1. Characteristics of Patients with OCD and Healthy Controls

	Patients with OCD "Median (Min-Max)" (n=12)	Healthy Controls "Median (Min-Max)" (n=12)	*P*
Age (years)[a]	29 (20-49)	28 (19-40)	.468
Gender (male/female)[b]	9 (75%)/3 (25%)	9 (75%)/3 (25%)	1.000
Handedness (right/left)[b]	12 (100%)/0	12 (100%)/0	-
Education period (years)[a]	16 (12-16)	16 (12-18)	1.000
Duration of illness (years)[a]	6 (1-17)	-	-
HAM-A[a]	11 (2-26)	9 (0-3)	<.001
HAM-D[a]	5.5 (2-13)	0 (0-2)	<.001
Y-BOCS[a]	27.5 (20-34)	0 (0-0)	<.001
CGI-S[a]	5 (4-7)	1 (1-1)	<.001
Accuracy of recognition task (%)			
Anxiety-inducing distractors[a]	70 (33-80)	70 (60-90)	.610
Neutral distractors[a]	55 (25-80)	70 (30-80)	.291

CGI-S, Clinical Global Impression-Severity; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
[a]Data are presented as median (min-max). Mann–Whitney U-test (non-parametric test) was used to compare the age, education period, and scores on the symptom scales (HAM-A, HAM-D, Y-BOCS, CGI-S) between the 2 groups.
[b]Data are presented as n (%). Fisher's exact test (non-parametric test) was used to compare the sex distribution and handedness between the 2 groups.

and the patients with OCD, respectively (Mann–Whitney *U*-test, $P=.610$, Table 1).

Differential Activation Patterns Associated with Anxiety-Provoking Distractors

In the patients with OCD, the brain activation area showed significantly increased activation during anxiety-provoking distractors, when compared with healthy controls (independent samples *t*-test, all brain regions $P < .005$, Table 2, Figure 2) and the differences included the DLPFC and supplementary motor area (SMA). The brain activation areas which showed significantly decreased activation during anxiety-provoking distractors (all brain regions $P < .005$, Table 2, Figure 2) were the superior parietal gyrus (SPG) and fusiform gyrus (FuG).

Differential Activation Patterns Associated with Neutral Distractors

In the patients with OCD, there was no area of increased activation during neutral distractions, when compared with healthy controls. The brain activation areas which showed significantly decreased activation during a neutral distractor (independent samples *t*-test, all brain regions $P < .005$, Table 2) were the inferior temporal gyrus, postcentral gyrus, precuneus, supramarginal gyrus, SPG, inferior parietal gyrus, calcarine gyrus, inferior frontal gyrus, thalamus, cerebellar cortex, FuG, and lingual gyrus.

DISCUSSION

Suicidal behavior is a clinical correlate of emotional dysregulation which is an underlying character trait that has been associated with susceptibility to suicide risk.[19] However, our study demonstrated neural correlates within the brain circuit that are associated with emotional regulation during delayed-response WM maintenance in OCD patients. Cognitive control is composed of 2 main processes: (1) operations which allow the mind to actively maintain goals and goal-relevant information (WM) and (2) operations which aim to keep irrelevant information out of the mind (cognitive inhibition).[20] Emotional stimuli can distract and challenge an individual's ability to maintain focus on goal-relevant information[21] and thus impair cognitive performance. The results indicated that the accuracy for the face recognition task with the anxiety-provoking distractors and neutral distractors in OCD patients was lower than healthy controls (the median scores for the anxiety-provoking distractors 70 (33-80)% vs. 70 (60-90)%; the median scores for the neutral distractors 55 (25-80)% vs. 70 (30-80)%) (Table 1). Though not significant, the results of the face recognition task might suggest difficulties in WM maintenance for anxiety-provoking distractors in OCD patients. Accordingly, our results showed that brain regions relevant to cognitive control showed increased activation. In particular, when compared with healthy controls, OCD patients showed significantly increased activities in the DLPFC and SMA during the delayed-response WM task with the anxiety-provoking distractor (Table 2).

The DLPFC involves high order information processing such as sustained attention and problem-solving allowing focus on goal-relevant information by controlling emotions and inhibiting the interference of anxiety-provoking distractors during WM tasks.[16] The SMA also inhibits undesired actions and promotes desired actions during the process of performing the tasks related to WM and response inhibition,

Table 2. Differential Brain Activities Between Patients with OCD and Healthy Controls in Working Memory Task with Neutral and Anxiety-Inducing Distractors: Independent Samples *t*-Test (Uncorrected, $\alpha = 0.005$)

Anatomical Areas	Controls > Patients with OCD				Patients with OCD > Controls			
	Maximum *t*-Value	MNI coordinates (*x*, *y*, *z*)			Maximum *t*-Value	MNI coordinates (*x*, *y*, *z*)		
Neutral distractor								
Inferior temporal gyrus	6.22	51	−54	−16	-			
Postcentral gyrus	4.53	53	−24	55	-			
Precuneus	4.49	11	−74	58	-			
Supramarginal gyrus	4.47	51	−26	40	-			
Superior parietal gyrus	4.14	27	−57	55	-			
Inferior parietal gyrus	4.10	49	−35	55	-			
Calcarine gyrus	3.87	−4	−83	11	-			
Inferior frontal gyrus	3.64	−50	9	19	-			
Thalamus	3.52	−19	−26	8	-			
Cerebellar cortex	3.45	−33	−54	−25	-			
Fusiform gyrus	3.41	42	−26	−23	-			
Lingual gyrus	3.36	−9	−54	2	-			
Anxiety-inducing distractor								
Superior parietal gyrus	3.44	26	−56	56	-			
Fusiform gyrus	3.35	40	−36	−18	-			
Dorsolateral prefrontal cortex	-				4.65	−37	16	54
Supplementary motor area	-				3.71	−11	26	61

OCD, obsessive-compulsive disorder.

and promptly resolves the situation where there is a conflict of options.[22,23] Therefore, an increase in the activity of the DLPFC and SMA reflects compensatory efforts of neural circuits to perform cognitive tasks at a high level. However, considering that performance in patients with OCD was not sufficient compared with healthy controls, it suggested that such cognitive neural recruitment was not effective. Such ineffectiveness is attributed to limbic interference in top-down inhibition and is associated with an increase in functional connectivity between the frontal and limbic regions.[22] Stern et al[24] observed that, when subjects with OCD performed decision-making tasks, task-related connectivity between the frontal region and amygdala was proportional to subjective uncertainty, and Heuvel et al[25] reported that, when planning tasks were conducted on patients with OCD, panic disorder, and hypochondriasis, task performance had a negative correlation with limbic activation. However, in this study, limbic area hyperactivation was not observed in patients with OCD, and there was no significant difference in the accuracy of task performance between patients with OCD and healthy controls, meaning that such connectivity was not strong.

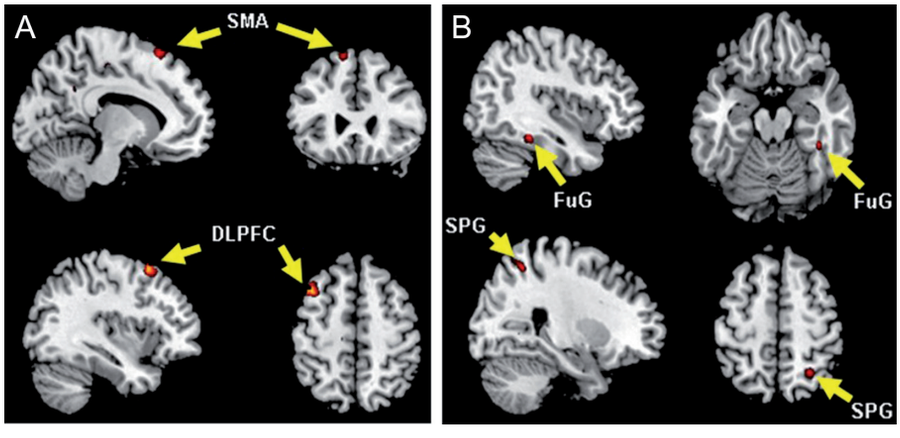

Figure 2. A, B. Brain regions that predominantly showed increased activation during anxiety-provoking distraction (all brain regions $P < .005$). (A) OCD > Controls. (B) Controls > OCD.

Our results are consistent with previous studies. Menzies et al[5] summarized the findings from various neuroimaging studies including functional, metabolic, and structural, and proposed a cognitive dorsolateral-striatal circuit along with the affected orbitofrontal-striatal circuit in OCD. Several studies have demonstrated inefficient WM-related hyperactivation of the DLPFC and SMA in OCD.[5,23,26]

In addition, OCD patients showed significant decreases in activities in the SPG during the delayed-response WM task with both neutral and anxiety-provoking distractors, compared with healthy controls. The superior and inferior parietal cortexes are associated with executive functions such as attention to the visual object, spatial perception, and WM.[27] Patients with OCD showed decreased metabolism in the parietal cortex.[28,29] Assuming that viewing the picture distractors lead to increased visual and perceptual processing, decreased activation of parietal areas could be associated with lower cognitive function. These results could suggest that parietal dysfunction in OCD patients prevents them from paying appropriate attention to visual processing for picture distractors during the WM task, compared with healthy controls. Moreover, the parietal cortex, along with the DLPFC, is the main structure for frontoparietal network and is involved in cognitive control.[30] Increased activation in the parietal cortex which is also regulated by limbic activity[21] was observed during cognitive tasks in multiple functional and structural imaging studies with subjects with OCD.[6,31,32] Therefore, a decrease in the activity of the parietal cortex can make it difficult to perform WM tasks. The FuG is associated with facial perception,[33] and if activation decreases in this region, it is hard to focus on the target face owing to goal-irrelevant distractors. Therefore, a decrease in the activity of the FuG in patients with OCD can explain the low performance of WM tasks, compared to healthy controls. There were some limitations to this study. First, the number of subjects was small, future studies with larger numbers of subjects are needed for additional assessment. Second, all OCD patients received psychotropic medications. Though the link between psychotropic medications and OCD mechanisms is not the main topic of the present paper, a study is valuable to verify the effects of various doses and types of drugs on brain activity. Additionally, although a total of OCD patients (n = 12) were receiving stable doses of psychotropic drugs, mean Y-BOCS scores indicated a clinically significant OCD population. Unfortunately, we do not know exactly why. The clinicians might be in the process of adjusting the drug dose or be trying Cognitive Behavioral Therapy (CBT) rather than increasing the drug. However, for research, it seems that prominent symptoms may be helpful. Finally, our study did not measure cognitive ability (e.g., Intelligence quotient [IQ]) of participants with standardized assessment tools. Further study is required to reflect the effect of IQ on task performance.

In summary, although only a part of the hyperactivity of the frontoparietal area observed by many previous studies was identified, this study may provide support for the hypothesis that DLPFC plays a role in controlling anxiety-provoking distractors when performing cognitive tasks in OCD patients. Therefore, the present findings could provide further evidence for frontoparietal dysfunction during cognitive-emotional interaction in OCD patients.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Jeonbuk National University Hospital (Approval No: CBIRB0907-65).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – J-C.Y.; Design – J-C.Y.; Supervision – J-C.Y.; Materials – J-C.Y.; Data Collection and/or Processing – J-C.Y., J-I.P., G-W.K., C-M.M.; Analysis and/or Interpretation – J-C.Y., S-H.N., J-I.P., G-W.K., C-M.M; Literature Review – J-C.Y, S-H.N, J-I.P.; Writing – S-H.N, J-I.P.; Critical Review – J-C.Y.

Declaration of Interests: The authors have no conflicts of interest to declare.

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