Original Article
https://doi.org/10.9758/cpn.2023.21.1.99
Clinical Psychopharmacology and Neuroscience 2023;21(1):99-107
pISSN 1738-1088 / eISSN 2093-4327

Harm Avoidance is Correlated with the Reward System in Adult Patients with Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Imaging Study

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Objective: Hypoactivity in the reward system among patients with attention deficit hyperactivity disorder (ADHD) is a well-known phenomenon. Whether the activity in the reward pathway is related to harm avoidance, such as in sensitivity to punishment, is unclear. Evidence regarding the potential difference between ADHD patients and controls in terms of this association is scarce.
Methods: Event-related functional magnetic resonance imaging was conducted on subjects performing the Iowa gambling test. Fourteen adults with ADHD and 14 controls were enrolled in the study.
Results: Harm avoidance was found to be positively correlated with the activities of the bilateral orbitofrontal cortex and right insula in individuals with ADHD. A group difference was also confirmed.
Conclusion: Understanding the roles of harm avoidance and brain activation during risk tasks is important.

KEY WORDS: ADHD; fMRI; Harm avoidance; Reward system; Iowa gambling test.

INTRODUCTION

An altered reward system is considered an important characteristic of patients with attention deficit hyperactivity disorder (ADHD) [1]. Some problematic behavioral tendencies related to the reward system have been observed among patients with ADHD, such as poor decision-making, delayed aversion, and more importantly, risk preference [2-4]. Functional magnetic resonance imaging (fMRI) studies have confirmed hypoactivation in several brain areas, such as the medial orbitofrontal cortex and ventral striatum (VS), during the performance of high-risk tasks in patients with ADHD [5-8]. This collection of evidence may imply dysfunction in the ventral frontostriatal network in individuals with ADHD, leading to poor evaluation and learning in risk-related tasks [9].

In addition, it was found that individuals with ADHD may be less sensitive to penalties during a gambling task [10]. This mechanism may be helpful in explaining the high comorbidity with substance use, gambling and gaming on the internet in patients with ADHD [11-14]. Probing traits related to brain activation during perception of the consequence (winning or losing) after decision-making in high-risk tasks (such as gambling) will be helpful in order to increase our understanding of the etiology of ADHD.

It was found that the tendency towards greater behavior inhibition is correlated with lower activation in the VS during winning [15] among healthy subjects, meaning that in healthy people, the lower activation in the reward system results in better impulsivity control. However, it was proposed that the relationships between impulsivity-related traits and VS activation during reward anticipation are not identical between healthy subjects and patients with ADHD [7]. Plichta and Scheres [7] proposed several

Received: July 28, 2021 / **Revised:** October 5, 2021
Accepted: November 25, 2021
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models to explain this controversial phenomenon. For example, the relationship between impulsivity and responsiveness in the VS could be of an inverted U shape. Patients with ADHD might have a higher level of impulsivity, and therefore the relationship could be a negative association [7]; meanwhile, normal controls may have a low to moderate level of impulsivity, and the relationship between impulsivity and responsiveness in the VS could be a positive association.

However, it is worthy of note that adults with ADHD have a higher score in terms of the level of harm avoidance [16,17]. It was found that increased harm avoidance was correlated with the inattention score and hyperactivity among adults with ADHD [18], and a higher level of harm avoidance might be a positive in terms of preventing risky behavior, such as problematic drinking [19]. The concept of harm avoidance may also be related to a lower risk-taking propensity [20], as demonstrated by Paulus *et al.* [21]. These phenomena may imply that harm avoidance is paradoxically positively correlated with ADHD severity, but negatively correlated with impulsivity. Meanwhile, in animal and human studies, using the serotonin depletion paradigm, it was confirmed that a low serotonin tone was correlated with altered sensitivity to reward and punishment [22,23]. As harm avoidance is related to a lower serotonin function [24], it may be an important factor related to brain activity during high-risk tasks.

Studies have indicated that harm avoidance may not only be related to insula activation among patients with ADHD [25], but also to activation of the medial prefrontal cortex, as confirmed by a near-infrared spectroscopy study [26]. It was found that a higher level of harm avoidance is correlated with activation of the insula during the punishment response in a gambling task among healthy subjects [21]. To the best of our knowledge, this specific effect related to a gambling task has not yet been reconfirmed. Whether this effect is present among patients with ADHD is also unclear. The higher level of harm avoidance among patients with ADHD [17], and its association with the severity [18]. Whether a higher level of harm avoidance is related to hyperactivity or hypoactivity in the reward system remains unclear.

Gambling or risky decision-making is related to the reward pathway, which is also an important biological characteristic among patients with ADHD. As several areas, and not only the insula, in this pathway may play a role, and may be correlated with harm avoidance [27,28], multiple regions of interest (ROIs) were probed in the present study [8,29]. The aim of this study was to probe the association between harm avoidance and brain activity in the reward system during winning and losing in a well-established task, the Iowa gambling task (IGT) [30], among adult patients with ADHD. A group of healthy controls was also included.

METHODS

Participants and Procedures

Fourteen adult participants (nine male and five female, mean age = 26.14 ± 4.09 years) with a clinical diagnosis of ADHD who were referred by psychiatric outpatient clinics of a university hospital from January 2012 to December 2015 were enrolled in this study. The inclusion criteria were as follows: subjects must (i) fulfill the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD; (ii) be aged over 20; (iii) have no physical disease and stable vital signs; (iv) present no evidence of substance abuse/dependence as evaluated during a clinical interview with the research psychiatrist at the time of enrollment; and (v) have never received any antipsychotics or antidepressants and be free of any psychotropic medication for more than one week before testing. The exclusion criteria were as follows: (i) other co-morbid psychiatric illnesses, substance abuse/dependence, or neurological illnesses; (ii) intellectual disability or an intelligence quotient < 70; (iii) all female participants of child-bearing age had to take an acceptable form of contraceptive throughout the duration of the study in order to be included. All female participants underwent an instant urine pregnancy test before the experiment. One participant was taking methylphenidate but stopped one week before screening; two had received methylphenidate in the past; and the other eleven patients had never been medicated with methylphenidate.

Fourteen healthy controls (five female and nine male, mean age = 28.43 ± 7.59 years) were enrolled from the community. There were no significant differences in age ($t = 0.99$, $df = 36$, $p = 0.33$) between the two groups. All participants in the control group were confirmed by a senior psychiatrist as being free of any mental disorder using the Mini International Neuropsychiatry Interview (MINI), and none had received any psychotropic medications in the

past 3 months.

The Institutional Review Board for the Protection of Human Subjects at National Cheng Kung University Hospital approved the research protocol (no. A-BR-101-118), and this protocol conformed to the provisions of the Declaration of Helsinki. All participants signed written informed consent forms after the procedures had been fully explained.

Iowa Gambling Task

The IGT was conducted on a PC using a customized program written using E-PRIME 1.1 software (Psychology Software Tools, Pittsburgh, PA, USA). In the present study, the original version of the IGT was employed [30], with modification to allow use in event-related fMRI analysis [31-33]. All participants completed 10 sessions of the IGT with 10 trials in each session, and participants could rest between sessions when lying in the scanner. Each session lasted for three and a half minutes. After some prior scans, we determined that 3.5 minutes was a long enough duration in which to complete 10 trials. This procedure was as reported in our previous study [8,29].

Functional Image Acquisition and Analysis

Magnetic resonance imaging data were acquired using a GE 3T MR750 scanner with an 8-channel brain array coil in the Mind Research and Imaging Center (MRIC) at National Cheng Kung University. Blood oxygenation level dependent (BOLD) responses and in-plane anatomical data were recorded for each participant. Anatomical images were obtained using whole-brain sagittal T1-weighted spoiled gradient-recalled scans (flip angle = 12°, field-of view [FOV] = 22.4 cm, matrix size = 256 × 256, slice thickness = 1 mm, gap = 0 mm, slices = 170). Functional images were acquired using a T2*-weighted echo-planar imaging (EPI) sequence (repetition time [TR] = 2 sec, TE = 33 ms, FOV = 24 cm, matrix size = 64 × 64, thickness = 3 mm, gap = 0, slices = 40). For each participant, 10 functional runs were performed, the experiment lasting about 40 minutes in total.

Statistical Parametric Mapping software (SPM8; Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm) was used to preprocess and analyze the data. The functional images for each participant were slice time-corrected to the middle (i.e., 39th interleaved image) slice and then spatially-realigned using a six-parameter rigid-body spatial transformation. The high-resolution structural image was then co-registered to the mean functional image generated by the realignment phase. The functional images were spatially-normalized to the Montreal Neurological Institute (MNI) template, with the resulting warping parameters generated by structural image segmentation resampled to a voxel size of 3 × 3 × 3 mm, then spatially-smoothed using a 6-mm full width at half maximum isotropic Gaussian kernel. A high-pass filter with a cutoff of 128 seconds was applied to the data.

In the first-level model, event-related responses were assessed by creating fixed-effect general linear models for each participant, produced by regressors of interest as the canonical hemodynamic response function. We used 8 regressors to create events in each trial: preparation phrase onset times; phase onset times for advantageous and disadvantageous responses; times that the 3 types of outcome (win, loss, and neutral, represented as an outcome of "0") appeared in the feedback phase; and 2 actual feedback values of win and loss. Six realignment parameters were also included as covariates in the model. Following model estimation, two contrasts were built for each participant in order to assess differences in the BOLD response under the following conditions: (i) win minus neutral in the feedback phase (win feedback); (ii) loss minus neutral in the feedback phase (loss feedback). Following model estimation, parametrical contrasts were built for each subject to assess the BOLD response during the win and loss feedback phases.

Region of Interest Analysis

We extracted parametrical estimates from parametrical modulator contrasts in each ROI obtained from three studies of the reward system of human beings [34-36]. The MNI coordinates of these ROIs were (−33, 42, −5) and (33, 41, −5) for the left and right OFC, respectively [34]; (−10, 12, −6) and (16, 12, −6) for the VS in the left and right hemispheres, respectively; (0, 46, −10) for the medial prefrontal cortex [35]; (4, 24, 30) for the anterior cingulate cortex; and (−40, 16, 4) and (40, 16, 4) for the insula in the left and right hemispheres, respectively [36]. Each ROI was a 10-mm sphere centered on the coordinates.

Harm Avoidance Using the Tridimensional Personality Questionnaire (TPQ)

Assessment of temperament traits was performed using the TPQ, a 100-item questionnaire that measures three

personality dimensions: novelty-seeking, harm avoidance, and reward dependence. Only harm avoidance was used in this analysis. Harm avoidance is defined as an inherited tendency toward the inhibition or cessation of behaviors, such as pessimistic worry in anticipation of future problems, passive avoidance behaviors such as fear of uncertainty and shyness of strangers, and rapid fatigability [37]. Two items were excluded from scoring in accordance with Cloninger *et al.* [20]. The Chinese version of the TPQ has been validated [37].

ADHD Severity

The adult ADHD Self-Report Scale-V1.1 (ASRS-V1.1) Symptoms Checklist was used to assess the severity of ADHD in this study [38].

Statistics

Independent *t* tests and chi-square tests were used to examine group differences. Correlation analysis was conducted to probe the association between brain activity and harm avoidance, and generalized linear models were employed to probe the group difference in this association. Statistical analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Significance was assumed at $p < 0.05$.

RESULTS

The demographic and clinical characteristics of the study participants are presented in Table 1. The group difference in the score of harm avoidance was not significant (ADHD: 15.50 ± 7.95, controls: 13.36 ± 5.05, $t = 0.85$, $p = 0.40$). In addition, no significant differences in brain activity related to winning ($ps > 0.26$) or losing ($ps > 0.23$) were found. Harm avoidance was not correlated with ADHD severity among the controls (Part A: r = −0.48, p=

Table 1. Demographic and clinical characteristics of the participants

Variable	ADHD (n = 14)	Controls (n = 14)	Statistic	
			t	*p* value
Sex, M/F	9/5	9/5		
Age (yr)	26.14 ± 4.09	28.43 ± 7.59	−0.99	0.33
Education (yr)	16.14 ± 1.29	15.86 ± 2.25	0.41	0.68
Duration of illness (yr)	12.71 ± 6.98			
Treated with methylphenidate	3 (21)			
ADHD severity Part A (inattention)	25.21 ± 3.85	9.21 ± 5.63	8.78	< 0.001
ADHD severity Part B (hyperactivity)	19.14 ± 5.42	3.79 ± 3.95	8.57	< 0.001
Harm avoidance	15.50 ± 7.95	13.36 ± 5.05	0.85	0.40
Brain activation				
Winning				
Anterior cingulate cortex	0.65 ± 2.86	−0.05 ± 3.33	0.60	0.56
Left orbitofrontal cortex	−1.20 ± 2.84	−0.30 ± 1.68	−1.02	0.32
Left ventral striatum	−0.15 ± 1.70	0.07 ± 1.29	−0.39	0.70
Left insula	−0.10 ± 2.09	−1.08 ± 2.38	1.15	0.26
Medial prefrontal cortex	0.13 ± 3.29	0.66 ± 2.64	−0.47	0.64
Right orbitofrontal cortex	−1.12 ± 2.08	−0.40 ± 1.79	−0.98	0.33
Right ventral striatum	−0.21 ± 0.94	0.08 ± 0.96	−0.81	0.43
Right insula	−0.65 ± 2.19	−0.42 ± 2.18	−0.28	0.78
Losing				
Anterior cingulate cortex	1.34 ± 3.88	−0.26 ± 3.77	1.10	0.28
Left orbitofrontal cortex	−1.97 ± 3.80	−1.15 ± 2.16	−0.70	0.49
Left ventral striatum	−0.10 ± 2.77	−0.72 ± 1.55	0.73	0.47
Left insula	0.80 ± 2.97	−0.80 ± 2.68	1.49	0.15
Medial prefrontal cortex	−0.78 ± 4.29	0.03 ± 3.61	−0.54	0.60
Right orbitofrontal cortex	−2.07 ± 3.41	−0.74 ± 2.09	−1.24	0.23
Right ventral striatum	−0.49 ± 1.79	−0.36 ± 1.27	−0.22	0.83
Right insula	−0.04 ± 3.36	−0.02 ± 2.46	−0.02	0.98

Values are presented as number only, mean ± standard deviation, or number (%).
ADHD, attention deficit hyperactivity disorder.

0.08; Part B: r = 0.12, $p = 0.68$) or patients with ADHD (Part A: r = −0.44, $p = 0.11$; Part B: r = 0.17, $p = 0.55$). Harm avoidance was found to be associated with brain activity in the left OFC (winning: r = 0.69, $p < 0.01$; losing: r = 0.63, $p < 0.05$), right OFC (winning: r = 0.76, $p < 0.01$; losing: r = 0.74, $p < 0.01$), and right insula (winning: r = 0.81, $p < 0.01$; losing: r = 0.66, $p < 0.01$) among the patients with ADHD; however, no associations were observed among the controls, as shown in Table 2. A generalized linear model indicated a significant group * harm avoidance interaction in the activity of the left OFC (Wald $\chi^2 = 4.05$, $p < 0.05$), right OFC (Wald $\chi^2 = 7.28$, $p <$

Table 2. Association between harm avoidance and brain activity among patients with ADHD (n = 14) and controls (n = 14)

Regions of interest	Winning				Losing			
	ADHD		Controls		ADHD		Controls	
	r	*p* value	r	*p* value	r	*p* value	r	*p* value
Anterior cingulate cortex	0.19	0.53	−0.41	0.15	0.22	0.46	−0.34	0.24
Left orbitofrontal cortex	0.69	0.007*	0.02	0.94	0.63	0.016*	0.00	0.99
Left ventral striatum	0.42	0.14	−0.32	0.27	0.37	0.19	−0.25	0.39
Left insula	0.03	0.91	−0.38	0.18	0.03	0.93	−0.25	0.40
Medial prefrontal cortex	0.51	0.06	0.09	0.75	0.52	0.06	0.28	0.33
Right orbitofrontal cortex	0.76	0.002*	−0.22	0.46	0.73	0.003*	−0.15	0.62
Right ventral striatum	0.47	0.09	−0.37	0.19	0.45	0.11	−0.16	0.58
Right insula	0.81	0.000*	−0.45	0.11	0.66	0.010*	−0.29	0.31

ADHD, attention deficit hyperactivity disorder.
*$p < 0.05$.

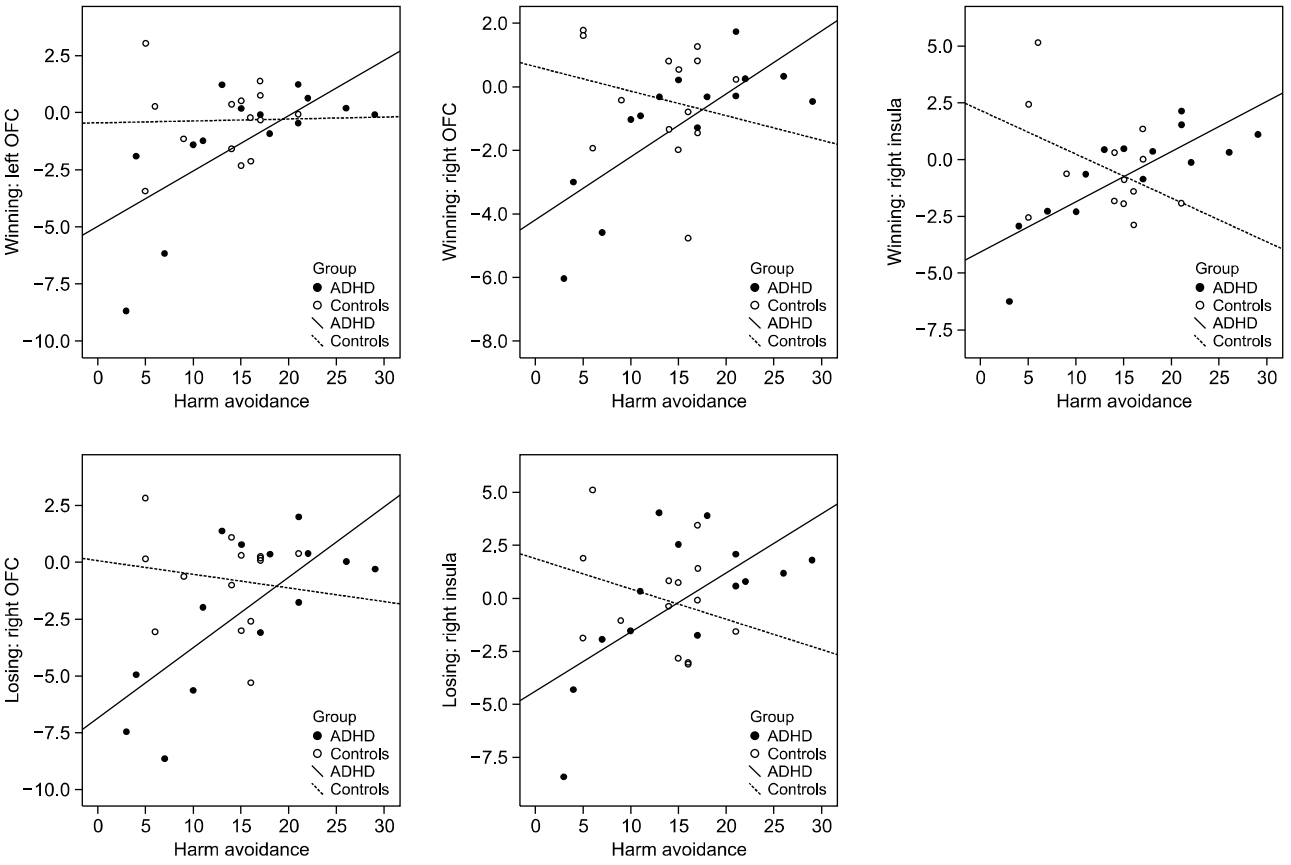

Fig. 1. Association between harm avoidance and brain activity after receiving a reward or punishment.
OFC, orbitofrontal cortex; ADHD, attention deficit hyperactivity disorder.

0.01), and right insula (Wald $\chi^2 = 16.06$, $p < 0.01$) during winning, and the right OFC (Wald $\chi^2 = 7.28$, $p < 0.01$) and right insula (Wald $\chi^2 = 7.68$, $p < 0.01$) during losing, as shown in Figure 1.

DISCUSSION

Our findings indicated that the tendency towards harm avoidance is correlated with activity in two important regions of the reward system, the insula and OFC, in patients with ADHD. Although this association in healthy controls was reconfirmed in the findings of Paulus *et al.* [21], it is stronger in patients with ADHD than in controls. This group difference may be in agreement with the models of Plichta and Scheres [7]. It has also been demonstrated that motivation deficit is correlated with dopamine receptor and transporter availabilities among patients with ADHD, whereas this effect is not significant among controls [39]. Therefore, we speculated that the link between fundamental psychological function and monoamine neurotransmitter activity would be stronger in patients with ADHD than in healthy controls. As harm avoidance could be correlated with serotonin function [24], this finding may imply that brain activity during reward in patients with ADHD is also correlated with serotonin function. Meanwhile, whether or not altered brain activation is related to losing among patients with ADHD [10] was inconclusive in this study.

Considering that ADHD could be characterized by a higher level of harm avoidance [17] and hypoactivity in the reward system [5-7], this finding is very surprising. However, this result may be in agreement with the construct of harm avoidance. Anticipatory worry and fear of uncertainty are two important domains of harm avoidance [20]. These domains might be related to the mental effort in regard to the behavior consequence after an uncertain choice. It was reported that activation in the reward system during risk-taking decision-making is related to harm avoidance and neuroticism [21]. Our results may reconfirm the finding of Paulus *et al.* [21]. Therefore, the trait of harmful avoidance would be a factor that activates the reward system more significantly in the ADHD group than in the healthy controls.

Our results indicated that the insula and OFC are regions correlated with harm avoidance. The insula was found to be related to the aversive state, which could be harmful for individuals [40]; in addition, the insula plays a pivotal role in the salience network, detecting salient stimuli and events [41]. Detection of behavior consequences could be important for individuals with a tendency towards harm avoidance. Our findings also confirmed the role of the OFC, though the mechanism is as yet unclear. It has been found that the lateral OFC is related to the process of punishment [34] and the process of the consequence after making an uncertain choice [42], which could be important for those who have a higher level of harm avoidance.

This association was only found among the patients with ADHD, and this represents a novel finding. However, little is known with regards to the mechanism of the group difference between ADHD patients and controls. The inverted U-shaped model proposed by Pilchta and Scheres [7] might be helpful in terms of understanding the group difference. Assuming that ADHD is correlated with lower activity in the reward system, the association between harm avoidance and activity in the reward system might be within the left area of the inverted U shape, which is a positive association. Meanwhile, the healthy controls might be near the top of the inverted U shape, and therefore the magnitude of the association would be much smaller than in patients with ADHD.

Harm avoidance is correlated with lower serotoninergic activity [20,24,43], which might be related to affective disorders. However, our findings may imply that a higher level of harm avoidance might be of benefit to patients with ADHD. Evidence from genetic studies may provide some hints for solving this puzzle. Individuals with the 5-HTTLPR (serotonin-transporter-linked promoter region) allele were found to exhibit biased attention to the selection of positive stimuli rather than negative stimuli [44], which may lead to risk preference. In addition, our previous findings indicated that a higher serotonin transporter availability could be related to quick relapse among heroin users [45]. Therefore, whether harm avoidance is positive or negative for patients with ADHD remains to be elucidated.

Limitations

There were several limitations of the present study. First, our sample size was not large. Second, we used the IGT as a virtual reward task with fMRI, and whether our findings can represent decision-making activity in the real world is unclear.

Conclusion

To conclude, our findings reconfirmed the positive association between harm avoidance and activation in the reward system in responding to the aversive state and punishment, particularly among patients with ADHD.

■ Funding

This study was funded by the National Science Council of Taiwan (NSC 102-2420-H-006-007-MY2), the Ministry of Science and Technology, Taiwan (MOST 104-2314-B-006-053-MY2), and National Cheng Kung University Hospital (NCKUH-10104019 and NCKUH-10603020).

■ Acknowledgments

The authors are indebted to Ms. Tsai Hua Chang and Mr. Chien Ting Lin from National Cheng Kung University Hospital. We also thank the Mind Research and Imaging Center (MRIC) at National Cheng Kung University for consultation and instrument availability. The MRIC is supported by the Ministry of Science and Technology.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

■ Author Contributions

Design the study and writing protocol: Yen Kuang Yang. Help to design the study: Dong-Yu Yang. Contribute to the statistical analyses: Shih-Hsien Lin, Ching-Lin Chu. Writing the first draft of the manuscript: Tsung-Hua Lu. Managing data collection: Mei Hung Chi, Wei Hung Chang, Po See Chen. All authors interpreted the analysis of the results and helped to revise the manuscript.

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