

The Indirect Effect of Prefrontal Gray Matter Volume on Suicide Attempts among Individuals with Major Depressive Disorder

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Trait impulsivity is a known risk factor for suicidality, and the prefrontal cortex plays a key role in impulsivity and its regulation. However, the relationship between trait impulsivity, neural basis, and suicidality has been inconsistent. Therefore, this study aimed to explore the relationship between impulsivity and its structural correlates (prefrontal gray matter volume), suicidal ideation, and actual suicide attempts. A total of 87 individuals with major depressive disorder participated in study, and the gray matter volume of the prefrontal regions was extracted from T1 images based on region of interest masks. The variables for the mediation models were selected based on correlation analysis and tested for their ability to predict suicide attempts, with impulsivity and suicidal ideation as the mediation variables and gray matter volume as the independent variable. A significant correlation was observed between suicidal ideation and the left dorsolateral prefrontal cortex and right dorsomedial prefrontal cortex. The dual-mediation model revealed a significant indirect relationship between gray matter volume in both regions and suicide attempts mediated by motor impulsivity and suicidal ideation. The counterintuitive positive relationship between gray matter volume and suicidality was also discussed.

Key words: Attempted suicide, Gray matter, Prefrontal cortex, Suicidal ideation

INTRODUCTION

Impulsivity is widely believed to be a risk factor for suicide among individuals with major depressive disorder [1, 2]. A study in both adults [3] and adolescent patients with major depressive disorder (MDD) found that those who attempted suicide showed higher impulsivity scores than those who did not attempt suicide [4]. The same tendency was observed in non-psychiatric individuals [5], and a prospective study also showed that impulsivity was one of the major predictors of suicide attempts [2]. However, other studies on patients with MDD could not find a direct relationship

between impulsivity and suicidal attempts. Previous studies on MDD found no difference in total impulsivity score between those who attempted suicide and those who did not [6, 7]. Another study conducted on men who died by suicide did not find a direct relationship between impulsivity and suicide attempts [8]. Similarly, the total impulsivity score did not show a significant relationship with the lethality of the suicide attempts [9].

The inconsistencies above might be due to the fact that impulsivity is a complex construct with multiple meanings [10], consisting of related but distinct facets [11, 12]. The Barrett Impulsiveness Scale (BIS-11), one of the most widely used measures of impulsivity, subdivides impulsivity into three subcomponents (attentional, motor, and non-planning impulsiveness) [13-15]. Attentional impulsiveness refers to the inability to focus and cognitive instability, whereas motor impulsiveness refers to rash actions and perseverance. Non-planning impulsiveness refers to the trait of not planning rationally before taking action [15]. Importantly, different areas of the frontal lobe are associated differently with each

Submitted February 24, 2022, Revised March 18, 2022,
Accepted March 25, 2022

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subcomponent of impulsivity [16], and the different subcomponents of impulsivity are related to different event-related potential components [12]. These findings indicate that the sub-traits of impulsivity are differentially related to executive processes. Therefore, a subcomponent-level approach is required to obtain novel implications regarding the relationship between suicide and impulsivity.

Previous studies have reported about the relationship between the subcomponents of impulsivity and suicide. A study conducted among psychiatric inpatients showed that motor impulsivity differentiates between psychiatric inpatients with multiple versus single lifetime suicide attempts [17]. Similarly, a high level of motor impulsivity is associated with a greater risk of planned and highly lethal suicide attempts [18].

The effect of impulsivity on suicide attempts might be indirect. Predictably, suicidal ideation precedes suicide attempts [19]. Impulsivity is strongly correlated with suicidal ideation and can predict such ideation [20]. A longitudinal study demonstrated that impulsivity is a strong indicator of suicidal ideation [21]. This study reported that impulsivity moderates the severity of depression in the relationship between hopelessness and suicidal ideation. They found that patients with greater impulsivity were more likely to develop suicidal ideations, regardless of the severity of their depression symptoms.

Several neuroimaging studies have demonstrated an association between the structure of the prefrontal cortex and impulsivity [16]. For example, the thickness of the frontal cortex has been negatively associated with impulsiveness, as measured by the BIS-11 [16]. Studies have shown positive correlations between self-reported impulsivity and the volume of the anterior cingulate gyrus and dorsolateral prefrontal cortex. Studies on healthy subjects have also reported a relationship between prefrontal structures and impulsivity. Lower prefrontal gray matter volume [22] and thinner prefrontal cortices [23] are related to higher impulsivity in healthy adults.

Functional neuroimaging studies have also supported the relationship between prefrontal cortex activity and impulsivity. For example, differential activation during wins and losses in the ventromedial prefrontal cortex (vmPFC) was significantly correlated with scores on the non-planning subscale of the BIS-11 [24]. Activation of the vmPFC has also been reported to be specifically sensitive to losses under negative expectancy.

The current study hypothesized that the decreased gray matter volume of prefrontal cortex regions would be related the increased risk of suicide attempts indirectly through impulsivity and suicidal ideation. To test this idea, we proposed and utilized multiple dual-mediation models.

MATERIALS AND METHODS

Participants

The participants included in the study were diagnosed with MDD by board-certified psychiatrists (Ham B-JH, J-WP, and H-WL) using the Structured Clinical Interview from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I Disorders. Basic demographic information, including age, sex, educational level, and clinical information was collected. The age of the participants who attempted suicide and those who did not, ranged from 19 to 56 years, with an average of 32.00 years. The severity of depressive symptoms in all participants was assessed using the 17-item Hamilton Depression Rating Scale (HDRS) [25]. All clinical scales were assessed at the time of the MRI scanning. Patients were excluded from the current study based on the following criteria: comorbidity with any other major psychiatric disorder(s); psychotic features, such as delusions or hallucinations; history of a serious or uncontrolled medical illness; any primary neurological illness; and any contraindication to MRI scanning, such as metal implants or claustrophobia. A total of 87 patients with MDD were divided into two groups: 50 as SA who had previously attempted suicide and 37 as who had no previous history of suicide attempt. Informed consent was obtained from all participants after a thorough explanation of the study was provided. This study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No: ED15006) and adhered to the principles of the Declaration of Helsinki.

Measurement of impulsivity and suicidal ideation

Self-reporting questionnaires were used, including the 19-item Beck Scale for Suicide Ideation (SSI) [26] to measure the current severity of suicidal ideation (i.e., attitudes, plans, and behaviors to commit suicide in the last 2 weeks) and BIS [27] to measure the degree of impulsivity.

Image acquisition

Three-dimensional structural MRI scans were acquired using a 3.0 Tesla Siemens Trio whole-body imaging system (Siemens Medical Systems, Iselin, NJ, USA), using a dedicated 32-channel high-resolution phased-array coil for brain imaging. T1-weighted images were acquired parallel to the anterior commissure-posterior commissure line using T1-weighted magnetization-prepared rapid gradient-echo imaging (repetition time=1,900 ms, echo time=2.6 ms, field of view=220 mm, 256×256 matrix size, 176 coronal slices without gap, 1×1×1 mm³ voxels, flip angle=16°, and number of excitations=1).

Image processing

The Computational Anatomy Toolbox (CAT12: <http://www.neuro.uni-jena.de/cat/>) for Statistical Parametric Mapping (SPM12) package was used to perform voxel-based morphometric analysis. We followed standard CAT12 preprocessing: 1) segmentation of the images into gray matter, white matter, and cerebrospinal fluid; 2) affine registration to a standard ICBM template; 3) DARTEL normalization to the MNI template; and 4) modulation by linear and nonlinear components derived from spatial normalization. The total intracranial volume for each participant was extracted. Finally, the images were smoothed using an 8 mm Gaussian filter.

Region of interest (ROI) mask generation

Areas of conventional parcellation atlases encompass a relatively large area in the frontal lobes; however, the recent parcellation atlases (Brainnetome, HCP-MMP) are subdivided in detail, and ROI masks are generated by identifying major prefrontal cortex areas as described by Carlén [28]. As shown in Fig. 1, a total of 12 bilateral regions, including the dorsomedial prefrontal cortex (dmPFC), dorsolateral prefrontal cortex (dlPFC), ventromedial prefrontal cortex (vmPFC), ventrolateral prefrontal cortex (vlPFC), orbital frontal cortex (OFC), and anterior cingulate cortex (ACC) were segmented based on the Brainnetome atlas [29].

Statistical analysis

The statistical software package R 4.12 was used for the data analysis. Descriptive analysis was conducted to examine the de-

mographic and disease characteristics of the subjects. To exclude the possible effect of total intracranial volume, the TIV difference between two groups was tested. Pearson's correlation analysis was employed to determine the relationships among suicidal ideation, the three subcomponents of impulsivity as measured by BIS-motor, non-planning, and inattentiveness, and the mean volumes of the 12 prefrontal cortex subcomponents. Serial multivariable mediation analysis was conducted to establish a mediating model of the mean volumes of the prefrontal cortex areas that showed a significant correlation with suicidal ideation. This analysis allowed for the inclusion of an independent variable, a dependent variable (DV), and two simultaneous mediator variables. In each model, the mean volume of the prefrontal ROI was determined to be the independent variable (IV), the suicide attempt was determined to be the binomial independent variable (IV), and the impulsivity subcomponent (MV_1) and suicidal ideation (MV_2) were used as pathways from cortical volume to suicidal attempt. All direct and indirect effects were estimated using the PROCESS macro in Model 6 [30]. The total effect (c) refers to the relationship between IV and DV without controlling for the MVs. A direct effect (c') refers to the relationship between IV and DV after controlling for MVs (demoralization or depression). The indirect effects of the serial multiple mediation analysis were the effects of IV on DV through MV_1 or MV_2 , or both MV_1 and MV_2 . A 95% confidence interval (CI) was calculated using 10,000 bootstrapping re-samples. If the 95% CI of the mediation path did not contain a value of 0, the indirect effect was considered statistically significant.

RESULTS

Demographics

The demographic characteristics of each participant, including age, sex, education level, and clinical characteristics, such as the self-questionnaires (SSI and BIS) are summarized in Table 1. In the present dataset, the mean age of the SA group was 31.6, the mean percentage of women was 56%. For the NS group, the mean age was 34.9, and the mean percentage of women was 45.9%.

Total intracranial volume

The TIV difference between the two groups was not significant ($p=0.684$).

Correlation analysis

The results of the Pearson's correlation analysis are presented in Table 2. It was observed that suicidal ideation was significantly correlated with motor ($r=0.330$, $p<0.01$) and non-planning ($r=0.257$, $p<0.05$) impulsivity, but not with the attention subcom-

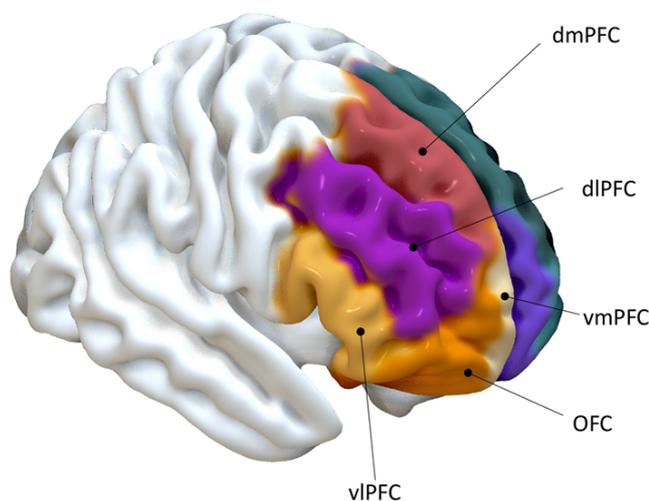


Fig. 1. The regions of interest (ROIs) of the prefrontal cortex, segmented as described by Carlén. dmPFC, dorsomedial prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; OFC, orbital frontal cortex; ACC, anterior cingulate cortex.

Table 1. The demographic and clinical characteristics of the study participants

	Total (n=87)	SA (n=50)	NS (n=37)	p-value
Demographics				
Age, years	32.00 (11.17)	31.60 (10.88)	32.54 (11.69)	0.704
Sex (female/male)	45/42	28/22	17/20	0.353
Education (years)	13.65 (2.45)	13.32 (2.49)	13.89 (2.38)	0.281
Clinical scales				
HDRS-17 score	14.09 (5.66)	14.94 (5.71)	12.95 (5.45)	0.102
SSI	17.72 (9.03)	21.30 (8.47)	12.89 (7.46)	<0.001***
BIS	54.77 (10.53)	55.66 (9.93)	53.57 (11.32)	0.373
BIS_attention	15.86 (3.32)	16.20 (2.96)	15.41 (3.76)	0.291
BIS_motor	16.61 (4.54)	17.02 (4.32)	16.05 (4.83)	0.338
BIS_non_planning	22.30 (4.17)	22.44 (4.08)	22.11 (4.33)	0.718

Standard deviation is given in parentheses. SA, MDD patients with a history of suicide attempt(s); NA, MDD patient without previous suicide attempt; HDRS, Hamilton Depression Rating Scale; SSI, Scale for Suicide Ideation; BIS, Barret Impulsiveness Scale.

Table 2. The correlation between suicidal ideation, depression, impulsivity, and the mean gray matter volume of the ROIs.

	Suicidal ideation	HDRS-17	BIS_attention	BIS_motor	BIS_non-planning
Suicidal_ideation	-				
HDRS-17	0.504***				
BIS_attention	0.209	0.208			
BIS_motor	0.330**	0.232*	0.645***		
BIS_non_planning	0.257*	0.052	0.643***	0.651***	
L_ACC	0.193	0.113	0.183	0.236*	0.192
L_dIPFC	0.237*	0.170	0.248	0.323**	0.262*
L_dmPFC	0.202	0.114	0.237	0.254*	0.171
L_oPFC	0.170	0.122	0.198	0.266*	0.141
L_vIPFC	0.203	0.170	0.243	0.248*	0.214*
L_vmPFC	0.056	0.117	0.224	0.236*	0.101
R_ACC	0.185	0.231*	0.146	0.200	0.150
R_dIPFC	0.191	0.165	0.244*	0.284**	0.220*
R_dmPFC	0.223*	0.091	0.287**	0.325**	0.290**
R_oPFC	0.151	0.105	0.212*	0.236*	0.160
R_vIPFC	0.134	0.140	0.206	0.197	0.127
R_vmPFC	0.153	0.155	0.195	0.232*	0.115

HDRS, Hamilton Depression Rating Scale; BIS, Barret Impulsiveness Scale; L_ACC, left anterior cingulate cortex; L_dIPFC, left dorsolateral prefrontal cortex; L_dmPFC, left dorsomedial prefrontal cortex; L_vIPFC, left ventrolateral prefrontal cortex; L_vmPFC, left ventromedial prefrontal cortex; R_ACC, right anterior cingulate cortex; R_dIPFC, right dorsolateral prefrontal cortex; R_dmPFC, right dorsomedial prefrontal cortex; R_vIPFC, right ventrolateral prefrontal cortex; R_vmPFC, right ventromedial prefrontal cortex. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

ponent of the BIS-11 ($r = 0.209$, $p > 0.05$). Among the ROI volumes of the prefrontal cortex, the left dlPFC ($r = 0.237$, $p < 0.05$) and right dmPFC ($r = 0.223$, $p < 0.05$) were significantly correlated with suicidal ideation. The significant correlations between ROI volumes and impulsivity measures are shown in Table 2.

Mediation analysis

Based on the correlation results, four serial multivariate mediation models were tested. The left dlPFC and right vmPFC were tested for motor and non-planning impulsivity. Among the four models, two indirect mediation effects revealed significant effects. Fig. 2 demonstrates the relationships between prefrontal volume, motor impulsivity, suicidal ideation, and suicide attempts. The left dlPFC volume had a direct effect on motor impulsiv-

ity ($\beta = 0.649$, $p = 0.002$), but the direct effect on suicide attempts was not significant ($p = 0.518$). However, the indirect effect of left dlPFC volume on suicide attempts through both motor impulsivity and suicidal ideation was significant ($\beta = 0.05$, $SE = 0.0293$, 95% $CI = 0.0087 \sim 0.1212$). Right dmPFC volume had a direct effect on motor impulsivity ($\beta = 0.941$, $p = 0.002$), but the direct effect on suicide attempts was not significant ($p = 0.647$). However, the indirect effect of left dlPFC volume on suicide attempts through both motor impulsivity and suicidal ideation was significant ($\beta = 0.07$, $SE = 0.0438$, 95% $CI = 0.0138 \sim 0.1841$).

DISCUSSION

The current study examined the association between prefrontal

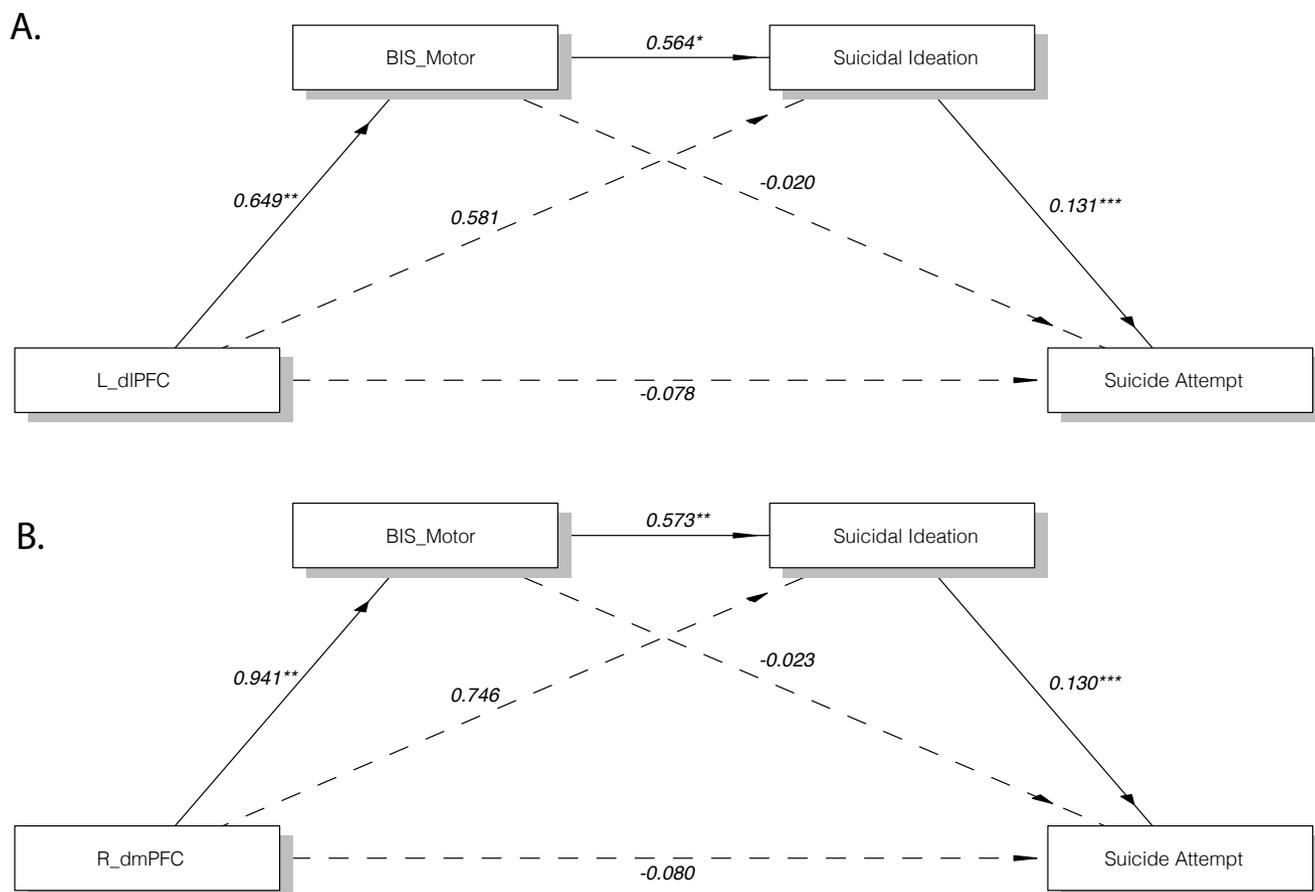


Fig. 2. The indirect effect models for serial multivariable mediation. BIS_Motor, Barrett Impulsiveness Scale (motor subcomponent); L_dIPFC, left dorsolateral prefrontal cortex; R_dmPFC, right dorsomedial prefrontal cortex.

brain regions and suicide attempts mediated by impulsivity among patients with MDD. No direct relationship between prefrontal gray matter volume and suicide attempts was identified, but the gray matter volume analysis showed that suicidal ideation was positively associated with the left dlPFC and right dmPFC. Motor impulsiveness was correlated with all prefrontal ROIs except the right ACC and vmPFC. Non-planning impulsivity was related to the left dlPFC, vlPFC, right dlPFC, and dmPFC.

Contrary to our hypothesis, positive relationships were observed between trait impulsivity components and gray matter volume. Interestingly, this finding is consistent with a study conducted on patients with MDD, which reported that greater prefrontal volume is associated with more lethal suicide attempts [31]. Increased prefrontal volume was also observed in binge drinkers [32], and people with bipolar disorder who attempted suicide had greater volumes of insula and ACC, compared to those who did not attempt suicide [33]. This counterintuitive finding might be interpreted as a compensatory mechanism in response to severe stress leading to suicide attempts [31], but it also possibly reflects the complex

mediation effect of impulsivity. A recent meta-analysis found a positive correlation between trait impulsivity and gray matter volume in the inferior frontal cortex [34]. It has also been reported that frontal gray matter volume is positively associated with motor impulsivity in psychiatric patients [35]. Several functional neuroimaging studies have also supported the paradoxical relationship between the frontal areas and impulsivity. For example, a positive correlation between motor impulsivity and ventrolateral prefrontal cortex activity during successful inhibition of a task has been reported [36].

Our findings indicate that there may be a much more complex relationship between impulsivity and suicide attempts. First, when assessing the effect of impulsivity on suicide attempts, the subcomponents of impulsivity should be considered rather than treating it as a whole. The results of previous studies underscore the significance of motor impulsivity. One study reported that people who attempted suicide showed higher motor impulsivity than individuals with suicidal ideations but no history of attempts [37]. Another study also showed that increased motor impulsivity is re-

lated to increased attempt numbers among MDD participants [17]. Along with these findings, our study suggests that distinguishing between facets of impulsivity is important for suicide risk assessment among patients with MDD [38].

Notably, several studies have reported a negative relationship between prefrontal gray matter volume and suicide attempts. For example, patients with depression who were suicidal showed lower gray matter volume in the dmPFC than non-suicidal MDD patients [39]. Similarly, patients who attempted suicide had reduced vlPFC volume compared to non-attempters [40]. The differences between these studies and the current study may be explained by the counterintuitive positive relationship between gray matter volume and impulsivity observed in healthy young adult participants [41-43] and psychiatric patients [35]. Antonucci et al. [35] reported positive correlations between left, right, and total OFC gray matter volumes and the BIS motor impulsivity scores. The prefrontal cortex plays a generative role in impulsivity [35]. Behavioral addiction, such as pathological gambling, has been linked to increased gray matter volumes in the prefrontal cortex [44], and highly impulsive individuals with psychopathic traits also have larger frontal gray matter volumes [45]. These results can be interpreted as a counter-argument against the concept “the larger the volume, the better the function” [46, 47]. Taken together with the generative role of the prefrontal cortex, one possible alternative explanation for these findings is that suicidal ideation and attempts require a certain level of impulsivity, which is likely to be absent in individuals with MDD. Indeed, a decrease in depressive symptoms is associated with an increased risk of suicide attempts [48] and suicidal ideation [49].

Understanding the complex relationship between impulsivity and suicidality is important for reducing suicide risk and lethality in individuals with major depressive disorders. The current study attempted to track the possible pathways that lead individuals with MDD to attempt suicide, and found two potential pathways that mediated the structural basis of impulsivity and suicidality. This study has several limitations, including the absence of healthy controls and the possible effect of illness duration and medication on both gray matter volume and the clinical measures. A relatively small sample size limits the generalizability of the findings and future studies to include a larger sample size and more detailed control on suicide attempt, including lethality is needed. The study only tested impulsivity, but there might be many other factors like aggression [8], that can lead to the suicide attempt. It would be beneficial to explore the possible mediation effect of those traits on the relationship between brain and suicidal behavior. Nevertheless, the study provides a potential conceptual framework for investigating the brain-behavior link in suicidality among patients

with MDD.

ACKNOWLEDGEMENTS

This work was supported by the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (NRF2020M3E5D9080792; NRF-2020R1A6A3A13069915).

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