Associations of MSK1 Methylation and Executive Function With Suicidal Ideation in Adolescents With Major Depressive Disorder:

A Prospective Cohort Study

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Abstract

Objective: Adolescent suicide is a major public health problem, and risk of suicide is higher among those with major depressive disorder (MDD), which may be linked to alterations in mitogen- and stress-activated kinase 1 (MSK1) and to defects in executive function. Here, we aimed to investigate the potential impacts of executive function and MSK1 methylation on suicidal ideation in adolescents with MDD.

Methods: The study enrolled 66 drug-naive adolescents who were experiencing their first episode of MDD from February 2019 until October 2020. After 6 weeks of receiving antidepressant treatment, 65 participants remained in the study. Suicidal ideation and depressive severity were assessed using the Hamilton Depression Rating Scale, while executive function was evaluated using the Cambridge Neuropsychological Test Automated Battery. MSK1 methylation was measured using bisulfite DNA analysis.

Results: Among the 66 adolescents with MDD, 43 (65.15%) reported suicidal ideation, while 23 (34.85%) did not. Individuals with suicidal ideation had worse executive function and higher MSK1 methylation than those without suicidal ideation. The MSK1 methylation percentage may predict suicidal ideation in adolescents with MDD (odds ratio [OR] 1.227, 95% CI [1.031 to 1.461]). Improvement in executive function was significantly associated with reduced suicidal ideation during antidepressant treatment (β = −0.200, 95% CI [−0.877 to −0.085]).

Conclusions: Our results strengthen the evidence for a link among MSK1 methylation, executive function, and suicidal ideation in adolescent MDD.

Trial Registration: Chinese Clinical Trial Registry identifier: ChiCTR2000033402.

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As a leading cause of death among young people worldwide, adolescent suicide is a concerning health issue.[1–3] In the US, lifetime prevalence of suicide ideation among adolescents appears to be around 12%, with 4% of all respondents going so far as to plan suicide and another 4% attempting it.[4] Suicidal ideation is one of the strongest predictors of suicide, and it is particularly well described in individuals with major depressive disorder (MDD).[5–7] Identifying risk factors for suicidal ideation among adolescents with MDD may guide evaluations and interventions to reduce suicide risk.

One risk factor for suicidal ideation may be executive dysfunction. *Executive function* refers to a set of cognitive processes necessary for complex, goal-directed tasks, including working memory, inhibitory control, and cognitive flexibility.[8] These skills enable individuals to establish goals, plan, and accomplish tasks, playing an integral role in daily activities such as learning, work, and the management of everyday life. Thus, disruption of executive function can affect emotional and cognitive processing, potentially contributing to an increased risk of suicide.[9,10] In fact, studies of adults have consistently indicated an association between alterations in executive function and risk of suicide, but whether the same holds among adolescents is unclear. One reason is that few relevant studies have been conducted on adolescents,[11]

Editor's Note
We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

Clinical Points

- Suicide is one of the most important issues related to adolescent mental health. Therefore, there is an urgent need to identify valuable biomarkers and therapeutic targets for early detection and treatment of suicidal ideation.
- MSK1 methylation status may be a proxy marker for suicidal ideation in depressive adolescents, and treatment targeting executive function may contribute to improvement in suicidal ideation.

and another reason is that available studies have come to divergent conclusions. For example, some surveys of adolescents in the US linked risk of suicide to worse executive function,[12,13] but a survey of adolescents in Spain found that risk of suicide was associated with deficits in complex cognition, episodic memory, and social cognition, but not in sensorimotor or executive function.[14] In fact, one survey of adolescents in the US linked suicidal ideation to *better* executive function.[15] Moreover, most investigations into the relationship between executive function and suicidal ideation in depressive patients have been cross-sectional,[16] highlighting the need for longitudinal studies.

Suicide has been linked to altered methylation of genes in the brain.[17,18] For example, altered methylation of the gene encoding brain-derived neurotrophic factor has been linked to higher risk of suicide ideation and executive dysfunction.[19–21] A downstream effector of this neurotrophic factor is mitogen- and stress-activated protein kinase 1 (MSK1), which helps regulate neuroplasticity, learning, and cognition.[22–24] Recently, a knock-in point mutation of the MSK1 gene which results in the elimination of the kinase activity of MSK1 has been shown to disrupt enrichment-dependent cognitive flexibility in mice.[25] Cognitive flexibility, a part of executive function, has long been associated with suicide in human.[26,27] This led us to wonder whether altered methylation of the gene encoding MSK1 might affect risk of suicidal ideation. Previously, our exploratory study found that MSK1 was differentially methylated in MDD adolescents,[28] but its specific role in suicide ideation has not been reported.

We explored this question in a longitudinal study of adolescents with first-episode, drug-naïve MDD. We hypothesized that (1) adolescents with suicidal ideation would show worse executive function and different MSK1 methylation than those without such ideation, (2) pretreatment executive function and/or MSK1 methylation would predict risk of suicidal ideation before treatment, and (3) changes in executive function and MSK1 methylation during treatment would be associated with changes in suicidal ideation.

MATERIALS AND METHODS

Participants and Procedures

The study involved 66 adolescents with drug-naïve, first-episode MDD who were receiving outpatient services at the Department of Psychiatry of West China Hospital, Sichuan University (Chengdu, China). This study was approved by the Ethics Committee of West China Hospital of Sichuan University, and the study was registered at Chinese Clinical Trial Registry (identifier: ChiCTR2000033402). All participants and their legal guardians signed written informed consent before entering the study.

Patients were enrolled if they were receiving services at our center between February 2019 and October 2020, if they were 12–17 years old, if they were diagnosed with MDD based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition,[29] if they scored at least 20 on the Hamilton Depression Rating Scale (HDRS),[30] if Chinese was their first language, and if they had completed at least primary education. Patients were excluded if they had other psychiatric disorders (eg, alcohol use disorder, bipolar disorder, general anxiety disorder), severe somatic conditions (eg, cancer), or a history of electroconvulsive treatment.

All enrolled patients received antidepressant treatment for 6 weeks, with the specific regimen determined by the attending physician. Dosages of antidepressants (eg, sertraline, agomelatine, escitalopram, fluoxetine, venlafaxine, paroxetine, mirtazapine, trazodone) were converted to fluoxetine equivalents for the purposes of this study.[31] Concomitant sedatives or hypnotics were permitted as prescribed by the attending physician. Efficacy of treatment was assessed in terms of the reduction in HDRS score.

Before antidepressant treatment and again after 6 weeks of treatment, all patients were subjected to clinical assessment, cognitive testing, and peripheral blood collection.

Measures

Suicidal ideation. Depressive symptoms and response to treatment were assessed by an experienced psychiatrist using the HDRS. Suicidal ideation was measured using item 3 on the HDRS, which was scored as follows: 0 = suicidal ideation absent, 1 = respondent feels life is not worth living, 2 = respondent wishes he/she were dead or has any type of thoughts about possible death, 3 = respondent has suicidal ideas or gestures, 4 = respondent attempted suicide. A score of 2 or higher was regarded as suicidal ideation, whereas a score of 0 or 1 was considered absence of such ideation. Changes in suicidal ideation were calculated by subtracting the score after treatment from the score before treatment.

Executive functioning. Executive functioning was assessed using One Touch Stockings of the Cambridge (OTS) and Spatial Span (SSP) from the Cambridge Neuropsychological Test Automated Battery (CANTAB).[32]

Table 1.

Demographic and Clinical Characteristics of Adolescents With Major Depressive Disorder, With or Without Suicidal Ideation[a]

Characteristic	All patients (n = 66)	With suicidal ideation (n = 43)	Without suicidal ideation (n = 23)	*Z*/χ2/*t*	*P*
Age, median (IQR), y	14.00 (13.00, 16.00)	14.00 (13.00, 15.00)	14.00 (13.00, 16.00)	−0.612	.541[b]
Male/female, n	11/55	8/35	3/20	0.334	.564[c]
Education, mean ± SD, y	9.18 ± 1.58	9.02 ± 1.55	9.48 ± 1.62	−1.118	.268[d]
Baseline HDRS score (without item 3 about suicide), median (IQR)	25.00 (22.00, 28.00)	25.00 (23.00, 30.00)	25.00 (22.00, 27.00)	−0.769	.442[b]
Executive function on OTS					
Number of first-choice errors, median (IQR)	5.00 (3.00, 6.00)	5.00 (3.00, 6.00)	5.00 (4.00, 6.00)	−1.007	.314[b]
Mean latency until correct response, ms, median (IQR)	25,703.63 (20,269.58, 34,380.02)	26,049.00 (20,138.73, 38,631.40)	23,733.27 (20,313.20, 29,959.60)	−0.881	.378[b]
Mean number of choices until correct response, median (IQR)	1.47 (1.27, 1.80)	1.40 (1.27, 1.80)	1.60 (1.27, 1.80)	−0.991	.322[b]
Probability of error given correct, mean ± SD	0.36 ± 0.18	0.35 ± 0.18	0.42 ± 0.23	−1.156	.252[d]
Number of problems solved on first choice, median (IQR)	10.00 (9.00, 12.00)	10.00 (9.00, 12.00)	10.00 (9.00, 11.00)	−1.007	.314[b]
Executive function on SSP					
Number of attempts, median (IQR)	9.00 (7.00, 11.00)	9.00 (7.00, 11.00)	9.00 (7.00, 11.00)	−0.279	.780[b]
Span length, median (IQR)	6.00 (5.00, 7.00)	6.00 (5.00, 8.00)	6.00 (5.00, 7.00)	−0.268	.789[b]
Mean time to first response (span length 2), ms, median (IQR)	2,526.00 (2,382.00, 2,859.20)	2,629.50 (2,420.67, 2,986.31)	2,481.22 (2,320.00, 2,634.00)	**−2.106**	**.035**[b]
Total number of errors	12.00 (8.00, 16.25)	12.00 (8.00, 17.00)	12.00 (8.00, 16.00)	−0.189	.850[b]
MSK1 methylation, %, median (IQR)	5.70 (3.69, 8.06)	6.67 (4.36, 9.18)	4.08 (3.08, 6.25)	**−2.654**	**.008**[b]

[a]Boldface indicates statistical significance.
[b]Independent-samples Mann-Whitney *U* test.
[c]χ^2 test.
[d]Independent-samples *t* test.
Abbreviations: HDRS = Hamilton Depression Rating Scale, IQR = interquartile range, OTS = One Touch Stockings of the Cambridge, SSP = Spatial Span.

The OTS is a 10-min task that is based upon the Tower of Hanoi test and measures spatial planning and working memory. The SSP is the visuospatial analog of the Digit Span Task that measures spatial short-term memory and working memory capacity. In the present study, scores for the OTS and the SSP were determined. Higher scores for number of problems solved on first choice on the OTS and span length on the SSP indicated better executive function, while lower scores on the other measures of the OTS and SSP indicated better executive function. Changes in measures of cognition were calculated by subtracting the score before treatment from the score after treatment.

MSK1 methylation. DNA samples were extracted from whole blood using a DNA extraction kit (51192, Qiagen), and the quantity and purity of DNA were determined using a spectrophotometer (NanoDrop2000c, Thermo). Then, bisulfite conversion was performed using a methylation modification kit (59104, Qiagen) according to the manufacturer's protocol, and bisulfite-converted DNA was amplified by PCR.

The PCR products were pyrosequenced on a PyroMark Q96 ID system (Qiagen). The percentage methylation was quantified with PyroMark Q CpG software (Qiagen). We analyzed the methylation status of 3 CpG sites in the MSK1 gene, using PCR primers and cycling conditions as described.[28] MSK1 methylation was expressed as the mean percentage of methylation across the 3 CpGs. Changes in MSK1 methylation were calculated by subtracting the percentage before treatment from the percentage after treatment.

Statistical Analysis

Comparisons of sociodemographic and clinical variables between adolescents with or without suicidal ideation were performed using the Mann-Whitney *U* test or independent-samples *t* test in the case of continuous variables, or the χ^2 test in the case of categorical variables. Comparisons of executive function and MSK1 methylation were also performed using the Mann-Whitney *U* test or independent-samples *t* test, depending on the normality of the data. Predictors of pretreatment suicidal ideation were identified using binary logistic regression (forward conditional procedure). Correlations between changes in executive function or MSK1 methylation and changes in suicidal ideation between baseline and after 6 weeks of treatment were tested using Spearman correlation. The observed correlations were further tested in multivariate linear models, in which the covariates were HDRS score (without item 3 about suicide) and suicidal ideation at baseline. All statistical analyses were performed using SPSS (version 26.0, IBM). Differences associated with a 2-tailed $P < .05$ were considered statistically significant.

Table 2.

Linear Regression Analyses to Identify Associations Between Changes in Executive Function and Changes in Suicidal Ideation During Antidepressant Treatment[a]

Model	*B*	β	95% CI	*P*
Model 1				
Changes in the mean number of choices until correct response on the OTS	−0.481	−0.200	−0.877 to −0.085	**.018**
Changes in score on HDRS (without item 3 about suicide)	0.058	0.322	0.028 to 0.088	**<.001**
Score for suicidal ideation at baseline	0.759	0.630	0.559 to 0.959	**<.001**
Model 2				
Changes in MSK1 methylation	−0.016	−0.062	−0.060 to 0.028	.463
Changes in score on HDRS (without item 3 about suicide)	0.057	0.316	0.027 to 0.087	**<.001**
Score for suicidal ideation at baseline	0.754	0.624	0.546 to 0.963	**<.001**

[a]Boldface indicates statistical significance.
Abbreviations: HDRS = Hamilton Depression Rating Scale, OTS = One Touch Stockings of the Cambridge.

RESULTS

Participant Characteristics

A total of 66 adolescents with MDD were enrolled, of whom 43 (65.15%) had suicidal ideation and 23 (34.85%) did not. Age, sex, education, and baseline HDRS score (without item 3 about suicide) were similar between the two groups. Compared with MDD patients without suicidal ideation, those with such ideation scored higher on mean time to first response on the SSP (span length 2) and had a higher mean percentage of MSK1 methylation. The remaining measures of cognition were similar between the two groups (Table 1).

All patients received antidepressant medication, but 1 was lost to follow-up, so the assessments after 6 weeks of treatment were carried out on 65 patients. The median dose of antidepressants was 40.61 mg/d in fluoxetine equivalents. The two groups received similar total doses during the 6 weeks ($Z = -1.518$, $P = .129$) and showed similar reductions in HDRS score, indicating similar treatment efficacy ($Z = -0.734$, $P = .463$).

MSK1 Methylation Predicts Pretreatment Risk of Suicidal Ideation

To explore the independent predictors of suicidal ideation in untreated MDD adolescents, we performed binary logistic regression analysis involving the following pretreatment covariates: age, sex, education, baseline HDRS score (without item 3 about suicide), SSP mean time to first response (span length 2), MSK1 methylation percentage, and the interaction between SSP mean time to first response and MSK1 methylation percentage. Only MSK1 methylation percentage had a significant impact on the risk of suicidal ideation (odds ratio [OR] 1.227, 95% CI [1.031 to 1.461], $P = .021$, Hosmer-Lemeshow $P = .599$).

Association Between Changes in Executive Function and Changes in Suicidal Ideation During Antidepressant Treatment

Among the 65 patients who completed the 6-week follow-up, an increase in the mean number of choices until the correct response on the OTS negatively correlated with a decrease in suicidal ideation (Spearman $\rho = -0.270$, $P = .032$). In contrast, changes in HDRS score (without item 3 about suicide) did not correlate with changes in any measures of cognitive function. This implies that the relationship of changes in executive function with changes in suicidal ideation occurred independently from changes in depression severity.

Next, we performed multiple linear regression in which the dependent variable was changes in suicidal ideation, and we adjusted for baseline suicidal ideation and changes in HDRS score (without item 3 about suicide). This regression indicated a significant association between changes in the mean number of choices until correct response on the OTS and changes in suicidal ideation ($\beta = -0.200$, 95% CI [−0.877 to −0.085], $P = .018$; Table 2).

Association Between Changes in MSK1 Methylation and Changes in Suicidal Ideation During Antidepressant Treatment

Among the 65 patients who completed the 6-week follow-up, an increase in MSK1 methylation percentage negatively correlated with a decrease in suicidal ideation (Spearman $\rho = -0.325$, $P = .008$), but changes in MSK1 methylation did not correlate with changes in HDRS score (without item 3 about suicide) (Spearman $\rho = -0.083$, $P = .510$). This implies that the relationship of changes in MSK1 methylation with changes in suicidal ideation was independent of changes in depression severity.

Next, we performed multiple linear regression in which the dependent variable was changes in suicidal ideation, and we adjusted for baseline suicidal ideation and changes in HDRS score (without item 3 about suicide). This regression did not detect a significant association between changes in MSK1 methylation percentage and changes in suicidal ideation ($\beta = -0.016$, $P = .463$; Table 2).

DISCUSSION

Our study observed differences in executive function and MSK1 methylation between adolescents with drug-naïve, first-episode MDD who experienced suicidal ideation or not. In addition, we found evidence that the MSK1 methylation percentage may be able to predict risk of suicidal ideation before treatment. In our multivariate linear regression, changes in executive function after 6

weeks of antidepressant treatment were associated with changes in suicidal ideation, but not with changes in MSK1 methylation. However, we found significant correlations between changes in MSK1 methylation and changes in suicidal ideation in a Spearman correlation analysis. To our knowledge, this is the first study to simultaneously examine cognition, DNA methylation, and suicidal ideation in MDD adolescents, and it is one of the few studies to examine this population longitudinally in order to observe directly the effects of antidepressant treatment.

Our findings support the hypothesis that among MDD adolescents, those with suicidal ideation have worse executive function than those without it, and that improvement in executive function during antidepressant treatment is associated with reduced suicidal ideation. Thus, our findings support, in adolescents with MDD, the association between executive function and suicide ideation reported for adults.[33] Our findings are also consistent with previous studies in adolescents.[34,35] Changes in executive function during treatment have been linked to changes in suicidal ideation, independently of changes in depressive symptoms. For example, effective ketamine therapy against suicidal ideation is associated with improved cognitive function,[36,37] consistent with our results here.

Several cognitive models and theories of suicide could explain these findings. Deficits in executive function may lead to inaccurate perception, interpretation, retrieval, and response to environmental information and therefore result in rigid thinking styles and pessimism.[38] These deficiencies in reasoning and problem solving, as well as negative bias toward oneself, others, and the environment, are closely related to the occurrence and development of suicidal ideation.[11] Classical psychotherapeutic approaches, such as rational emotive behavior therapy, aim to change dysfunctional beliefs in order to prevent suicide.[39] Therefore, targeting executive function may be therapeutically useful for depressive adolescents with suicidal ideation.

We found evidence that MSK1 methylation percentage may be an independent risk factor for suicidal ideation among MDD adolescents. DNA methylation, especially CpG methylation, generally represses gene expression and potentially affects protein expression as well.[40] Thus, we speculate that decreased methylation of MSK1 may decrease gene expression and impair one's ability to adapt to stress, which may in turn increase risk of suicidal ideation. This may reflect involvement of MSK1 in cognition and stress responses[25,41,42]: the protein helps regulate synaptic plasticity and glutamatergic neurotransmission to facilitate cognitive flexibility.[22,25] The determination of MSK1 levels and downstream signaling is beneficial to understanding the underlying mechanisms.

During the antidepressant treatment, decreased MSK1 methylation was observed accompanied with improvement in suicidal ideation, which also provided further support for the importance of MSK1 within the process of suicidal ideation. However, this significant association disappeared after inclusion in a multivariate model, indicating that the baseline level of suicidal ideation and improvement in depression severity had more significant association with improvement in suicidal ideation than did MSK1 methylation. In any case, the current study suggested MSK1 methylation level as a potential biomarker or therapeutic target for suicidal ideation in adolescent MDD. Previously, it has been shown that antidepressants could modify DNA methylation, which may lead to the alleviation of mood symptoms.[43] Therefore, gaining greater understanding to clarify the interaction between MSK1 methylation and antidepressants may contribute to increasing the effectiveness of treatments for suicidal ideation. Other factors that influence DNA methylation, such as genetic variants and environmental exposures, also deserve further investigation.[44]

Limitations

Our findings should be considered carefully in light of limitations. First, our study did not include healthy controls, so the conclusions apply only to adolescents with MDD. Second, patients received different antidepressant treatments, and we did not assess possible significant differences on anxiolytics/hypnotics intake between the two groups. Third, we did not measure anxiety levels, parental support levels, or level of adolescents' engagement with the school/community, which may be confounders, as they are associated with suicidal ideation and depressive severity. Fourth, follow-up lasted only 6 weeks, which may not be long enough to capture some clinically relevant outcomes. Fifth, the sample was relatively small, so our results should be verified and extended in larger populations, preferably in different ethnic groups.

Despite these limitations, our study suggests that MSK1 methylation status may be a proxy marker for suicidal ideation in depressive adolescents and that improvements in executive function may independently predict improvement in suicidal ideation. Our work provides new insights for better understanding of the pathogenesis, prevention, and treatment of suicidal ideation among young people.

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