Klotho and Matrix Metalloproteinase-9 Levels and Their Association With Inhibitory Dyscontrol in Adolescents With First-Episode Major Affective Disorders

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Abstract

Background: The roles of Klotho and matrix metalloproteinase (MMP)-9 in the pathomechanisms underlying first-episode major affective disorders as well as their impact on related inhibitory control function remain unclear.

Methods: This study included 44 adolescents with first-episode bipolar disorder, 60 with first-episode major depressive disorder, and 46 age-matched healthy controls between January 1, 2021, and August 31, 2024. *DSM-5* criteria were used to make the diagnoses of 2 major affective disorders. All the participants were assessed for levels of Klotho and MMP-9 and completed the go/no-go task. Generalized linear models (GLMs) were employed to compare Klotho and MMP-9 levels, along with inhibitory control function, between groups.

Results: After adjustments for demographic characteristics, clinical symptoms, and psychotropic medication use, the GLMs indicated that adolescents with bipolar disorder and those with major depressive disorder exhibited significantly lower Klotho levels compared with the control group ($P = .007$). Additionally, adolescents with bipolar disorder had the highest MMP-9 levels ($P = .002$), followed by those with major depressive disorder ($P = .031$), compared with healthy controls. Furthermore, lower Klotho levels and higher MMP-9 levels were associated with inhibitory control deficits.

Conclusions: Adolescents experiencing first-episode bipolar disorder and major depressive disorder exhibited decreased Klotho levels and increased MMP-9 levels, both of which were associated with deficits in inhibitory control function. Additional studies are warranted to clarify the specific pathomechanisms underlying the complex associations between major affective disorders, Klotho and MMP-9 dysregulation, and deficits in inhibitory control function.

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Major affective disorders are conceptualized along a spectrum that includes major depressive disorder and bipolar I disorder, distinguished by a range of mood states from severe melancholia to extreme mania.[1,2] Bipolar disorder affects more than 1% of the global population across all ethnicities and socioeconomic backgrounds, establishing it as a leading cause of disability among young individuals worldwide.[1] Major depressive disorder, with an estimated lifetime prevalence of 16%, occurs twice as frequently in women than in men and is associated with significant long-term impacts on individuals, their families, and society.[2] The development of vulnerability to both bipolar and major depressive disorders is influenced by a range of neurobiological and environmental factors.[1,2]

Emerging evidence indicates a relationship between Klotho, an antiaging hormone-like protein, and major affective disorders.[3–6] Pavlatou et al[4] hypothesized that Klotho dysregulation may be implicated in both major depressive disorder and bipolar disorder. Preclinical studies have demonstrated that Klotho-deficient mice exhibited reduced protection against oxidative stress in the central and peripheral nervous systems, leading to greater vulnerability to depressive behaviors and cognitive impairment.[4,7] Gao et al[3] reported significantly lower plasma Klotho levels in older patients with first-episode major depressive disorder compared with nondepressive controls and identified the rs9315202 T allele, a single-nucleotide polymorphism (SNP) in the *Klotho* gene, as a potential biomarker of depression severity. Conversely,

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Clinical Points

- The role of Klotho and matrix metalloproteinase-9 (MMP-9) in first-episode major affective disorders and related inhibitory dyscontrol remains uncertain.
- Adolescents with bipolar disorder exhibited the lowest Klotho levels and the highest MMP-9 levels.
- In the go/no-go task, Klotho levels were inversely correlated with the standard deviation of the mean reaction time, while MMP-9 levels were positively correlated with errors.

findings from the National Health and Nutrition Examination Survey indicated that serum levels of Klotho were positively associated with an increased risk of major depressive disorder among adults in the United States.[5] However, a study by Sartorius et al[8] comparing serum Klotho levels between 53 patients with depression and 39 age-matched healthy controls revealed no difference in Klotho levels between the groups. In the first comparative study of Klotho levels in patients with bipolar disorder, Barbosa et al[6] revealed that both patients with bipolar disorder in remission and those experiencing a manic episode exhibited elevated plasma Klotho levels compared with controls. Furthermore, Brunoni et al[9] demonstrated increased Klotho levels in patients with bipolar depression compared with those with major depressive disorder. However, these studies did not include adolescent patients and those with the first episode, but rather focused on adult patients and those with recurrent affective episodes.

Matrix metalloproteinase-9 (MMP-9) has also garnered scientific interest regarding its role in the pathophysiology of major affective disorders.[10–14] MMPs, particularly MMP-9, are crucial for maintaining the integrity of the basement membranes lining blood vessels and play a key role in cellular responses to environmental factors, including oxidative stress and inflammation.[12] Elevated MMP-9 levels have been associated with the disruption of the blood–brain barrier.[15] In a study by Shibasaki et al,[10] serum MMP-9 levels were positively correlated with depressive symptoms in 21 patients with treatment-resistant depression. Additionally, a cohort study of 203 adults with recurrent major depressive disorder and 99 healthy controls demonstrated that the presence of the T-1702A SNP in MMP-9 gene was associated with a higher risk of recurrent depression (odds ratio = 2.19).[14] Rybakowski et al[13] reported significantly higher MMP-9 levels in young adults with bipolar depression compared with the control group. Another cohort study of 681 adults, including 399 with bipolar disorder and 282 healthy controls, revealed that patients with bipolar disorder exhibited significantly higher MMP-9 levels compared with the control group, even after adjustment of demographic variables, tobacco use, and obesity.[11] Notably, a preclinical study on Klotho-deficient mice demonstrated that in vivo administration of a recombinant adeno-associated virus-2 carrying the mouse Klotho cDNA resulted in reduced vascular infiltration of inflammatory cells and decreased hyperexpression of collagen 1, scleraxis, and MMP-9.[16] Fan et al[16] further demonstrated that Klotho deficiency was associated with increased MMP-9 expression, which was reversed through *Klotho* gene induction. However, associations between MMP-9 levels and first-episode bipolar disorder as well as major depressive disorder remain unclear.

Previous studies have demonstrated inhibitory control dysfunction in adolescents with first-episode bipolar disorder and major depressive disorder.[17] A clinical study involving 30 adolescents with first-episode major depressive disorder in remission and 49 community controls revealed that adolescents with major depressive disorder made more errors in the go/no-go task than the controls.[17] Peters et al[18] demonstrated that adolescents with depression with histories of childhood adversity exhibited deficits in both performance-based (go/no-go task) and observer-rated (Behavior Rating Inventory of Executive Function) measures of inhibitory control compared with healthy adolescents. Additionally, a meta-analysis of inhibitory control function involving 13,807 participants suggested that inhibitory control deficits are a transdiagnostic endophenotype across various mental disorders, including bipolar disorder and major depressive disorder.[19] Breuer et al[19] reported that patients with bipolar disorder had higher error rates in the antisaccade task compared with those with major depressive disorder. Cotrena et al[20] examined the inhibitory control function by using the Hayling Sentence Completion Test Section B—Response Inhibition in 72 patients with bipolar disorder, 45 with major depressive disorder, and 89 healthy controls. Their findings indicated that patients with bipolar disorder made the most errors, followed by those with major depressive disorder, compared with the control group.[20] Notably, no study to date has investigated the associations between inhibitory control function and Klotho levels or MMP-9 levels.

In the present study, we investigated Klotho and MMP-9 levels as well as inhibitory control function among adolescents with first-episode bipolar disorder and major depressive disorder. We hypothesized that adolescents with first-episode major affective disorders would exhibit lower levels of Klotho and higher levels of MMP-9 compared with healthy controls. We further hypothesized that deficits in inhibitory control are associated with reduced Klotho levels and increased MMP-9 levels among adolescents with first-episode major affective disorders.

METHODS

Participants and Study Procedure

In this study, we recruited 44 adolescents aged 12–19 years diagnosed with first-episode bipolar disorder and 60 adolescents diagnosed with first-episode major

depressive disorder, in addition to 46 age-matched healthy adolescents, between January 1, 2021, and August 31, 2024. Diagnoses of bipolar disorder and major depressive disorder were made by board-certified senior child and adolescent psychiatrists in accordance with the criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition. The exclusion criteria for this study encompassed lifetime diagnoses of autism spectrum disorder, attention-deficit hyperactivity disorder, schizophrenia, alcohol and substance (including cigarette and e-cigarette) use disorders, eating disorders, organic mental disorders, severe autoimmune diseases, epilepsy, and cerebrovascular diseases, as well as pregnancy or breastfeeding and unstable physical illnesses. We did not enroll adolescents with a history of first (eg, parents) and second (eg, grandparents) degree relatives with major psychiatric disorders in the healthy control group. The 17-item Hamilton Depression Rating Scale (HDRS) and Young Mania Rating Scale (YMRS) were assessed for all participants.[21,22] The experience of being bullied was documented based on self-reports from the participants. This study was conducted in accordance with the Declaration of Helsinki and received approval from the Institutional Review Boards of Taipei Veterans General Hospital. Written informed consent was obtained from all participants as well as from the parents of adolescent subjects.

Measurement of Klotho and MMP-9

Serum levels of Klotho and MMP-9 were assessed using Human Klotho DuoSet enzyme-linked immunosorbent assay (ELISA) kits and Human MMP-9 Quantikine ELISA kits (DY5334-05, R&D Systems, Inc, Minneapolis, Minnesota). Fasting serum samples were collected in serum separator tubes and allowed to clot for 30 minutes. All samples were subsequently stored at −80°C until analysis. The assays were conducted following the manufacturer's instructions. The final absorbance of the mixtures was measured and analyzed at 450 nm using a Bio-Tek PowerWave XS ELISA plate reader, along with Bio-Tek's KC Junior software (Winooski, VT, USA). The detection range for the assays was 78.10–5,000 pg/mL, with a sensitivity threshold of 50 pg/mL. The standard curve fulfilled the linear regression criterion with an R^2 value of ≥0.95, confirming its reliability.

Measurement of Neurocognitive Functions

The go/no-go task was employed to assess inhibitory control function. Participants in the go/no-go task were instructed to respond immediately upon the appearance of the "×" symbol, while refraining from pressing the key when the "+" symbol appeared. After completing a pretest in which they provided all correct answers, participants underwent the formal test. We recorded their errors and the standard deviation (SD) of the mean reaction time for the further analyses. The go/no-go task has been utilized frequently in our previous studies.[23,24]

Statistical Analysis

For between-group comparisons, the F test was applied to continuous variables, while Pearson χ^2 test was used for categorical variables. Kolmogorov-Smirnov tests indicated that the levels of Klotho and MMP-9 were not normally distributed; consequently, a logarithmic transformation was performed on the data. Generalized linear models (GLMs) were employed to compare the levels of Klotho and MMP-9, as well as inhibitory control function, between groups. These models were adjusted for age, sex, body mass index (BMI), history of being bullied, clinical symptoms (total HDRS and YMRS scores), and the use of psychotropic medications. Additionally, GLMs were utilized to investigate the associations between levels of Klotho and MMP-9 and inhibitory control function, while adjusting for group, age, sex, BMI, history of being bullied, clinical symptoms, and psychotropic medication use. Finally, we examined an association between Klotho and MMP-9 levels using the GLM with adjustments of demographic characteristics, history of being bullied, clinical symptoms, and psychotropic medication use. A 2-tailed P value of less than .05 was deemed statistically significant. All data processing and statistical analyses were performed using SPSS software, version 17 (SPSS Inc).

RESULTS

In the present study, we enrolled 44 adolescents with first-episode bipolar disorder, 60 with first-episode major depressive disorder, and 46 healthy adolescents, with an average age of approximately 16 years (Table 1). Adolescents with bipolar disorder were more obese (P = .013) than those with major depressive disorder and healthy adolescents (Table 1). Family income did not differ between groups (P = .838) (Table 1). The total HDRS (P < .001) and YMRS (P < .001) scores were higher in the disease groups than in the control group; there was no difference in the HDRS scores between the 2 disease groups, while the total YMRS scores were slightly higher in the bipolar disorder group than in the major depressive disorder group (Table 1). In the bipolar disorder group, 10 (22.7%) patients were in remission, and 34 (77.3%) were in the depressive state, while none were in the manic state. In the major depressive disorder group, 9 (15.0%) patients were in remission, and 51 (85.0%) were in the depressive state (Table 1). The prevalence of a history of being bullied was highest (P < .001) among adolescents with bipolar disorder (45.2%), followed by adolescents with major depressive disorder (38.3%), compared with healthy adolescents (8.7%) (Table 1). Use of the antidepressants was highest among adolescents with major depressive disorder (73.3%), while use of the mood stabilizers (29.5%) and

Table 1.

Demographic and Clinical Characteristics Between Groups

	Adolescents with first-episode major affective disorder (n = 104)				
	A. Bipolar disorder (n = 44)	B. Major depressive disorder (n = 60)	C. Healthy adolescents (n = 46)	*P* value	Post hoc
Age, mean (SD), y	16.32 (1.36)	15.85 (1.78)	16.13 (1.38)	.302	
Sex, n (%)				.101	
Female	33 (75.0)	44 (73.3)	26 (56.5)		
Male	11 (25.0)	16 (26.7)	20 (43.5)		
BMI, mean (SD)	24.02 (5.97)	21.59 (4.01)	21.54 (3.63)	.013	A > B ~ C
History of being bullied, n (%)	19 (45.2)	23 (38.3)	4 (8.7)	<.001	A > B > C
Clinical symptoms, mean (SD)					
HDRS scores	11.91 (6.00)	13.46 (4.89)	0.46 (0.86)	<.001	A ~ B > C
YMRS scores	3.41 (1.82)	2.58 (0.93)	0.07 (0.25)	<.001	A > B > C
Current mood state, n (%)					
Remitted state	10 (22.7)	9 (15.0)	–		
Manic state	0 (0.0)	–	–		
Depressive state	34 (77.3)	51 (85.0)	–		
Psychotropic medications, n (%)					
Antidepressants	22 (50.0)	44 (73.3)	0 (0.0)	<.001	B > A > C
Mood stabilizers	13 (29.5)	1 (1.7)	0 (0.0)	<.001	A > B > C
Atypical antipsychotics	31 (70.5)	27 (45.0)	0 (0.0)	<.001	A > B > C
Benzodiazepines/Z-drugs	21 (47.7)	29 (48.3)	0 (0.0)	<.001	A ~ B > C
Family income (USD[a]/month), mean (SD)	3,794.85 (7,229.75)	3,547.08 (3,897.73)	3,104.08 (2,107.71)	.838	

[a]1 USD = 32.87 New Taiwan dollars.
Abbreviations: BMI = body mass index; HDRS = 17-item Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

atypical antipsychotics (70.5%) was highest among adolescents with bipolar disorder (Table 1). Use of benzodiazepines/Z-drugs did not differ between 2 disease groups (Table 1).

After adjusting for age, sex, BMI, history of being bullied, clinical symptoms (total HDRS and YMRS scores), and the use of psychotropic medications, GLMs revealed that adolescents with first-episode bipolar disorder ($P = .002$) and those with first-episode major depressive disorder ($P = .004$) exhibited significantly lower levels of Klotho compared with the control group, with no significant difference in Klotho levels between the 2 diagnostic groups (Figure 1). In addition, adolescents with first-episode bipolar disorder exhibited the highest levels of MMP-9 ($P = .002$), followed by those with first-episode major depressive disorder ($P = .031$), compared with healthy adolescents (Figure 1). Figure 2 showed that adolescents with first-episode bipolar disorder had the largest SD of the mean reaction time in the go/no-go task ($P = .014$) compared with those with first-episode major depressive disorder and healthy adolescents after adjusting for demographic data, history of being bullied, clinical symptoms, and medication use.

Finally, GLMs adjusted for group, age, sex, BMI, history of bullying, clinical symptoms, and use of psychotropic medications found a negative association ($B = -6.18$, $P = .021$) between Klotho levels and the SD of the mean reaction time in the go/no-go task and a positive association ($B = 0.71$, $P = .035$) between MMP-9 levels and errors in the go/no-go task (Table 2). We found no association between Klotho levels and MMP-9 levels ($P = .852$).

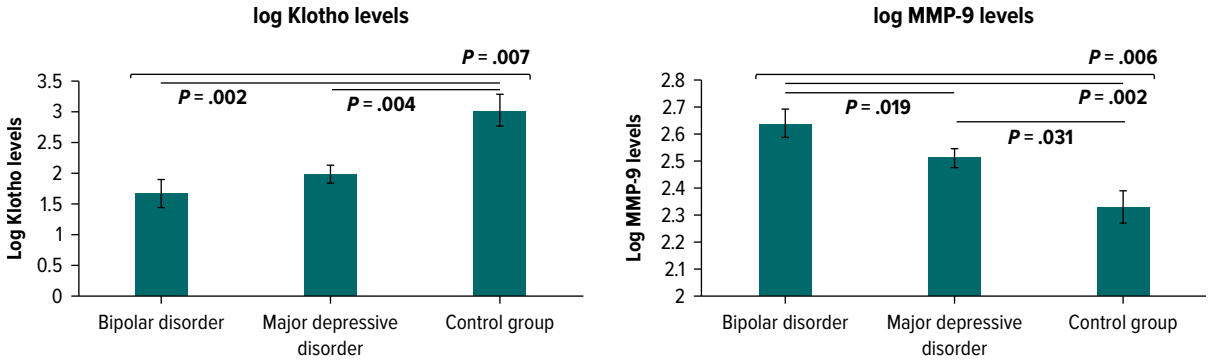
DISCUSSION

Our findings supported the study hypotheses, indicating that both adolescents with first-episode bipolar disorder and those with first-episode major depressive disorder exhibited reduced Klotho levels and elevated MMP-9 levels compared with healthy controls, independent of clinical symptoms, history of being bullied, and use of psychotropic medications. Moreover, adolescents with first-episode bipolar disorder performed worse in the go/no-go task than those with first-episode major depressive disorder. Furthermore, deficits in inhibitory control function were associated with decreased Klotho levels and increased MMP-9 levels.

Increasing evidence has underscored the crucial role of Klotho in the neurodevelopment and the pathomechanisms underlying major affective disorders.[4,6] As mentioned, Klotho deficiency was associated with an increased susceptibility to oxidative stress and systemic and neural inflammation,[16] which may lead to the development of major affective disorders such as bipolar disorder and major depressive disorder.[4,6] Through in situ hybridization, Clinton et al[25] mapped Klotho mRNA expression in both developing and adult rat brains and observed that Klotho mRNA expression levels in regions such as the cortex, hippocampus, and

Figure 1.

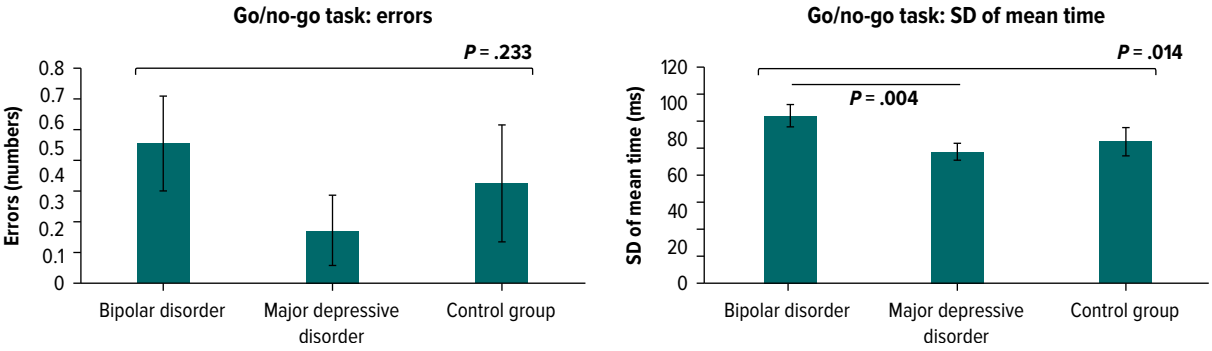
Estimated Klotho and MMP-9 Levels Based on the Generalized Linear Model After Adjusting for Age, Sex, BMI, History of Being Bullied, Clinical Symptoms, and the Use of Psychotropic Medications[a]



[a]The units for Klotho are pg/mL and ng/mL, respectively. Kolmogorov–Smirnov tests indicated that the levels of Klotho and MMP-9 were not normally distributed; consequently, a logarithmic transformation was performed on the data.
Abbreviations: BMI = body mass index, MMP-9 = matrix metalloproteinase-9.

Figure 2.

Estimated Inhibitory Control Function Based on the Generalized Linear Model After Adjusting for Age, Sex, BMI, History of Being Bullied, Clinical Symptoms, and the Use of Psychotropic Medications



Abbreviation: BMI = body mass index.

Table 2.

Associations Between Klotho and MMP-9 Levels and Inhibitory Control Function Using the Generalized Linear Model After Adjusting for Age, Sex, BMI, History of Being Bullied, Clinical Symptoms, and Psychotropic Medication Use[a]

	Errors			SD of the mean reaction time		
	B	SE	*P* value	B	SE	*P* value
Log Klotho levels	0.03	0.08	.669	−6.18	2.68	**.021**
Log MMP-9 levels	0.71	0.34	**.035**	−18.02	11.70	.124

[a]Boldface indicates significance.
Abbreviations: BMI = body mass index; MMP-9 = matrix metalloproteinase-9.

amygdala gradually increased, reaching adult levels by postnatal day 21. In a preclinical study involving both young and aging mice, Klotho was demonstrated to enhance cognitive function in young mice and mitigate cognitive deficits in older mice.[26] Furthermore, previous research has identified an association between heterozygosity for Klotho-rs9536314 and rs9527025 SNPs and elevated blood Klotho levels and enhanced cognitive function throughout adulthood,[26,27] supporting our finding of an association between reduced Klotho levels and deficits in inhibitory control function.

The findings of Clinton et al[25] and de Vries et al[26] may help explain the reduced Klotho levels observed in first-episode bipolar disorder and major depressive disorder observed in both our study and that of Gao et al,[3] whereas Zhang et al[5] and Brunoni et al[9] reported increased Klotho levels in cases of recurrent major affective disorders. The reduction in Klotho levels during the first episode of major affective disorders may indicate increased vulnerability to oxidative stress and

inflammation, which could contribute to the development of major affective disorders and related cognitive dysfunction.[3,6,25,26] Conversely, the elevated Klotho levels observed after recurrent major affective episodes might reflect a compensatory, self-rescue mechanism by which Klotho acts to mitigate brain dysfunction and related pathologies, such as systemic inflammation.[4,6] In addition, the long-term treatment of antidepressants may possibly explain this compensatory hypothesis.[28,29] Paroni et al[28] identified that the presence of a T allele in the Klotho SNPs of both rs1207568 and rs9536314 was associated with the treatment response to selective serotonin reuptake inhibitors. Our previous clinical trial involving 48 patients with treatment-resistant depression found that add-on low-dose ketamine infusion combined with antidepressants resulted in an increase in Klotho levels compared to add-on low-dose midazolam combined with antidepressants.[29] However, a prospective study design is required to confirm these potential associations between Klotho levels and first-episode vs recurrent major affective disorders. In addition, a clinical trial on healthy adults has shown a beneficial effect of exercise on the Klotho levels and further indicated an association between increased Klotho levels and improvement in cognitive function.[30] The exercise-induced increase in Klotho levels may reflect the therapeutic and procognitive effects of exercise for patients with major affective disorders.[31] The intervention targeted at Klotho may be a potential strategy for major affective disorder treatment.

The second major finding of our study revealed that adolescents with first-episode bipolar disorder exhibited the highest MMP-9 levels, followed by those with first-episode major depressive disorder, compared with healthy controls. This result suggests that blood–brain barrier dysfunction occurs at an early stage (first episode) of both bipolar disorder and major depressive disorder.[15,32,33] A clinical study involving 21 patients with treatment-resistant depression revealed a positive correlation between depressive symptoms and MMP-9 levels.[10] In a cohort study, Dickerson et al[11] reported significantly elevated MMP-9 levels in 399 adults with bipolar disorder compared with 282 age-matched controls. Furthermore, Seitz-Holland et al[33] demonstrated that increased MMP-9 levels were associated with slower processing speed, poorer working memory, and reduced hippocampal volume among young adults with severe mental disorders, including bipolar disorder and major depressive disorder. Our findings also demonstrated a link between elevated MMP-9 levels and an increased number of errors in the go/no-go task among adolescents with first-episode major affective disorders, underscoring the significant role of MMP-9 in the pathomechanisms underlying major affective disorders and associated impairments in inhibitory control.

Finally, our study findings indicated that only adolescents with first-episode bipolar disorder and not those with major depressive disorder exhibited deficits in inhibitory control, as indicated by the standard deviation of the mean reaction time in the go/no-go task, even after adjustment of clinical symptoms, a history of being bullied, and the use of psychotropic medications. This finding aligns with evidence suggesting that inhibitory dyscontrol served as an endophenotype for bipolar disorder, independent of disease severity or treatment.[19,34,35] A preliminary study of 27 patients with bipolar disorder, 15 healthy siblings, and 23 healthy controls revealed that patients with bipolar disorder and their healthy siblings displayed similar impairment in the affective go/no-go task compared with healthy controls.[34] Lombardo et al,[35] who evaluated inhibitory control function by using the self-reported Barratt Impulsiveness Scale, version 11 (BIS-11), reported that among 54 euthymic patients with bipolar disorder, 57 healthy siblings, and 49 healthy controls, the patients with bipolar disorder had the highest BIS-11 scores, followed by their healthy siblings, compared with the control group.

Several limitations of this study warrant consideration. First, we evaluated inhibitory control function solely through performance in the go/no-go task. Future studies should explore the associations between various aspects of cognitive function, such as executive function and working memory, and levels of Klotho and MMP-9. Second, adolescents continued their psychotropic medications during cognitive evaluations. Although Klotho and MMP-9 levels were measured to prevent exacerbation of their affective symptoms—a decision grounded in ethical considerations—further research using a drug-free design is necessary to validate our findings. Third, information, such as exercise and daily diet, was not available in the present study. Therefore, we could not comprehensively investigate the contributions of these factors to Klotho levels.

In conclusion, the present study demonstrated that adolescents with first-episode bipolar disorder and major depressive disorder exhibited decreased levels of Klotho and elevated levels of MMP-9, which were associated with deficits in inhibitory control function, independent of clinical symptoms, history of being bullied, and the use of psychotropic medications. These findings suggest that reduced Klotho levels and increased MMP-9 levels may serve as trait markers for bipolar disorder and major depressive disorder, as well as indicators of disease-related inhibitory dyscontrol. Further research is required to elucidate the specific pathomechanisms underlying the complex associations between major affective disorders, dysregulation of Klotho and MMP-9, and deficits in inhibitory control function. Whether Klotho and MMP-9 may serve as potential biomarkers for

adolescent-onset major affective disorders and whether they can predict treatment response in adolescents with these disorders warrant further investigation.

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Data Availability: The data supporting the findings of this study are available from the corresponding author upon request. However, these data are not publicly accessible due to ethical regulations in Taiwan.

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