Greater Monoamine Oxidase A Binding in Perimenopausal Age as Measured With Carbon 11–Labeled Harmine Positron Emission Tomography

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Abstract

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IMPORTANCE—Perimenopause is a period of high risk for mood disorders, and it has been proposed that perimenopause is also a window of risk for processes linked to later dementia. However, in human perimenopause, the neurobiological changes implicated in the genesis of mood disorders or dementia have not been identified. Monoamine oxidase A (MAO-A) is an important brain enzyme that creates oxidative stress, influences apoptosis, and metabolizes monoamines. After declines in estrogen level, MAO-A density may be elevated for a month or longer, and repeated declines in estrogen level occur with greater magnitude during perimenopause.

OBJECTIVE—To investigate whether MAO-A total distribution volume (V_T), an index of MAO-A density, is elevated in women of perimenopausal age (41–51 years).

DESIGN, SETTING, AND PARTICIPANTS—In a cross-sectional study at a tertiary care psychiatric hospital, 58 women underwent carbon 11–labeled harmine positron emission tomography. These included 19 young women of reproductive age (mean [SD], 28.26 [5.05] years), 27 women of perimenopausal age (mean [SD] age, 45.21 [3.41] years; including 14 women with change in menstrual cycle length with a mean [SD] age of 45.50 [4.00] years and 13 women with no change in menstrual cycle length with a mean [SD] age of 44.92 [2.81] years), and 12 women in menopause (mean [SD] age, 56.25 [3.19] years).

MAIN OUTCOMES AND MEASURES—Values of MAO-A V_T in the prefrontal cortex, anterior cingulate cortex, dorsal striatum, ventral striatum, thalamus, hippocampus, and midbrain.

RESULTS—On average, MAO-A V_T in perimenopausal age was elevated by 34% compared with reproductive age and by 16% compared with menopause (multivariate analysis of variance, group effect, $F_{16,94} = 3.03$; $P < .001$). Within the perimenopausal age group, meeting Stages of Reproductive Aging Workshop criteria for perimenopause, which is mainly based on menstrual cycle length, was not associated with MAO-A V_T ($F_{8,18} = 0.548$; $P = .81$) but tendency to cry was positively correlated with MAO-A V_T in the prefrontal cortex ($r = 0.54$; $P = .008$).

CONCLUSIONS AND RELEVANCE—To our knowledge, this is the first report of a change in a central biomarker during perimenopausal age that is also present during major depressive episodes and high-risk states for major depressive episodes. The functions of MAO-A influence oxidative stress and apoptosis, 2 processes implicated as excessive in both mood disorders and dementia. Hence, greater MAO-A V_T during perimenopause may represent a new target for assessing novel interventions to prevent mood disorders and reduce longer-term risk of neurodegenerative disease.

The transition of perimenopause has an important influence on the long-term health of women.[1] Most health investigations of perimenopause focus on physical symptoms and the influence of hormone replacement therapy (HRT) on risk for dementia. However, recent studies[2,3] demonstrate a high rate of new-onset major depressive episodes (MDEs) and minor depression (sustained depressed mood and anhedonia for several weeks) during perimenopause, with respective rates of 17% and 16%.[2] Unfortunately, the neurobiological changes in perimenopause that explain the predisposition to mood disorders and/or dementia are not established in humans.

Menstrual cycles continue for most of perimenopause, although cycles are less regular, with peaks and declines that are substantially greater and more erratic than those in the main reproductive years; plasma estrogen levels reach a stable but lower plateau in the last year of perimenopause (eAppendix in Supplement).[1] It has been suggested that estrogen fluctuations in perimenopause influence cognition and mood through several processes, including neuronal survival in the dentate gyrus,[4] changes in signal transduction factors regulating synaptic plasticity and connectivity,[5] clearance of extracellular serotonin,[6] and altered levels of proteins that influence cell survival such as Bcl2[7] and monoamine oxidase A (MAO-A). [8–14] To our knowledge, none of these markers have been examined in perimenopause in any species. Our study focuses on the latter marker, MAO-A, an important brain enzyme that creates oxidative stress, influences apoptosis, and metabolizes monoamines. In regions with high MAO-A density in animal models and in cell lines, changes in 17β-estradiol levels typically have an inverse influence on later MAO-A levels, messenger RNA (mRNA), and activity[10–14] (ie, reduced estrogen agonism or effect is associated with higher MAO-A levels, mRNA, and activity, which may be sustained even longer than a month past the initial shift in estrogen level[13]).

In this study, carbon 11 ($[^{11}C]$)–labeled harmine positron emission tomography (PET) is applied to investigate MAO-A total distribution volume (V_T), an index of MAO-A density in the brain, in women of perimenopausal age, young reproductive age, and menopausal age. In brain tissue during health, MAO-A levels are highly correlated with MAO-A activity, and hormonal influences on MAO-A level parallel changes in MAO-A activity.[10–14] Harmine itself binds to the center of the functional cavity in MAO-A.[15] Thus, $[^{11}C]$harmine is an excellent PET radiotracer with high affinity and selectivity for the MAO-A enzyme as well as reversible kinetics, and it has been modeled in humans.[16,17] The resulting MAO-A V_T values are highly correlated with known MAO-A density.[16–18] Given that the strong fluctuations in estrogen level during perimenopause include episodes of large declines and given that large declines in estrogen level are associated with elevations in MAO-A density, mRNA, and activity,[10–14] our main hypothesis is that women of perimenopausal age have increased MAO-A V_T throughout the brain. Our second hypothesis is that this increase normalizes during menopause as episodic estrogen declines no longer occur. Although we hypothesize global changes in MAO-A V_T during perimenopause, our third hypothesis is that elevated MAO-A V_T in specific regions becomes more functionally relevant and that mood-associated symptoms, such as the psychological symptom of crying, are positively correlated with prefrontal and anterior cingulate cortices. Crying is a frequent symptom of perimenopause,[19,20] and elevated MAO-A V_T has been reported during postpartum blues,[21] which is strongly associated with increased crying.[22]

Methods

Participants

Fifty-eight women underwent $[^{11}C]$harmine PET imaging (Table 1). Twenty-seven women were in the perimenopausal age range (41–51 years); among these 27 women, 14 were experiencing clinical symptoms of perimenopause (mean [SD] age, 45.50 [4.00] years) as per the Stages of Reproductive Aging Workshop (STRAW) criteria,[23] while 13 were not

experiencing a change in cycle length (mean [SD] age, 44.92 [2.81] years). Women in the perimenopausal age range were scanned within the follicular phase of their menstrual cycle. Nineteen younger women were of reproductive age (mean [SD] age, 28.26 [5.05] years), and 12 women were in menopause (mean [SD] age, 56.25 [3.19] years; mean [SD] time since last menstrual period, 9.00 [3.95] years). The mean age at onset of perimenopause is known to be 46 years,[1] with 95% entering perimenopause between 39 and 51 years; thus, the age range in this study is inclusive of most women.

For all participants, exclusion criteria included recent pregnancy (within 6 months), recent abortion (within 6 months), oral contraceptive use within 2 years, HRT, treatment with bioidentical hormones, and hysterectomy. Other exclusion criteria included cigarette smoking, herbal, drug, or medication use within 8 weeks, history of psychiatric or medical illness, suicide attempts, and substance abuse. Participants received a pregnancy test to ensure they were not pregnant at the time of testing, and they had a urine drug screen. Screening instruments to confirm the absence of past or current mental disorders included a score higher than 7 on the 17-item Hamilton Depression Rating Scale,[24] the Structured Clinical Interview for *DSM-IV* for Axis I disorders[25] and Axis II disorders,[26] and the Adult Crying Inventory.[27] The Adult Crying Inventory is a 54-item self-report with excellent internal consistency (Cronbach $\alpha = 0.87–0.95$),[28,29] and scores are highly correlated with crying frequency and proneness to crying.[29,30]

Women of perimenopausal age kept a 4-month diary to rate heaviness of bleeding and length of cycles. In addition, women of perimenopausal age completed the Menstrual Cycle Questionnaire[31] and Greene Climacteric Scale.[20] Onset of perimenopause (with physical symptoms) within the perimenopausal age group was based on the STRAW criteria,[23] with a main weighting of a change in cycle length of 7 days or greater for consecutive cycles and a lesser weighting that is given to other criteria such as vasomotor symptoms and follicle-stimulating hormone levels.

This study was reviewed and approved by the Research Ethics Board for Human Subjects at the Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada. Written informed consent was obtained from each participant prior to participation in the study.

Image Acquisition and Analysis

Each participant underwent 1 [^{11}C]harmine PET scan to determine regional MAO-A V_T. For each PET scan, 370 MBq of [^{11}C]harmine was administered as a bolus intravenously. An automatic blood sampling system was used to measure arterial blood radioactivity during the first 10 minutes of the scan. Manual samples were obtained at 2.5, 7.5, 15, 20, 30, 45, 60, and 90 minutes after injection. The method of measuring radioactivity in whole blood and parent compound in plasma has been previously described[17] (eAppendix in Supplement).

Each participant also underwent magnetic resonance imaging (MRI) (Signa 1.5-T scanner; fast spoiled gradient-echo, T1-weighted image; voxel dimensions, x = 0.78, y = 0.78, and z = 1.5 mm; GE Medical Systems) for the region-of-interest (ROI) delineation. The ROIs were determined using a semiautomated method in which regions of a template MRI are

transformed onto the individual MRI based on a series of transformations and deformations that match the template image to the individual coregistered MRI as well as segmentation of the individual MRI to select the gray matter voxels as previously described.[32,33] Each participant's MRI was coregistered to the summed PET image, and the resulting transformation was applied to the ROIs to create a mask for time activity curve extraction.

For the first 2 hypotheses, ROIs sampled were implicated in affect regulation and MDEs or have moderate to high MAO-A density and included the prefrontal cortex, anterior cingulate cortex, midbrain, thalamus, putamen, striatum, and hippocampus.[18,33–38] For [^{11}C]harmine PET, V_T may be validly and reliably measured with either an unconstrained 2-tissue compartment model or with the Logan model with arterial sampling (for which the underestimate of V_T is negligible at the noise level of time activity curves from the ROIs),[17] and the latter was applied in this study.

Statistical Analysis

The main analysis consisted of a multivariate analysis of variance (MANOVA) investigating the effect of group (young reproductive age, perimenopausal age, menopause) on global regional MAO-A V_T. To specifically assess whether regional MAO-A V_T was elevated in the perimenopausal age group compared with the young reproductive age group and whether MAO-A V_T was lower in the menopause group compared with the perimenopausal age group, additional comparisons were carried out using the protected least significant difference procedure.

To assess the relationship of MAO-A V_T to physical symptoms in perimenopause, MANOVA was applied with MAO-A V_T as the dependent variable and presence of menstrual cycle change as a predictor variable. Pearson correlation coefficients were applied to assess the correlation between the Adult Crying Inventory score and MAO-A V_T in the prefrontal cortex and anterior cingulate cortex, 2 regions implicated in the generation of cognitive mood symptoms. These are also regions for which MAO-A V_T has been associated with level of depressive symptoms in MDEs.[33]

Results

As shown in Figure 1, MAO-A V_T was strongly elevated during perimenopausal age across all regions assessed, on average by 34% compared with reproductive age and 16% compared with menopause (MANOVA, group effect, $F_{16,94} = 3.03$; $P < .001$; regional comparisons, P .05, Fisher least significant difference test). Significant univariate effects were also found in all brain regions ($F_{2,58} = 7.63–16.49$; P .001). Additional comparisons (based on least significant difference test) showed greater MAO-A V_T in women in the perimenopausal age group relative to the young reproductive age group in all regions ($P < .001$) and in the perimenopausal age group relative to the menopause group in all regions (P .05). In addition, MAO-A V_T in menopausal women was significantly higher than in young reproductive age women in the putamen, anterior cingulate, and striatum ($P < .05$). Consistent with the overall results, independent samples t test comparing mean MAO-A V_T showed significant whole-brain differences between groups (young reproductive vs perimenopausal age range, $t_{44} = −4.7$, $P < .001$; perimenopausal age range vs menopause,

t_{37} = 2.1, P = .04; reproductive age vs menopause, t_{29} = −2.4, P = .02). Furthermore, MANOVA to assess group effect on regional MAO-A V_T was rerun across the 3 groups, including only women in the reproductive age group within the follicular phase (n = 13) because all the women in perimenopause were in the follicular phase. Results were similar with a strong group effect ($F_{16,82}$ = 2.073; P < .02) and similar significant univariate effects within each brain region (P = .01 to P < .001).

Within the perimenopausal age group, MAO-A V_T levels were not associated with meeting STRAW criteria[23] for perimenopause ($F_{8,18}$ = 0.548; P = .81) (Figure 2). Comparisons of the demographic and clinical characteristics of the women who did or did not meet STRAW criteria are shown in Table 2 (for additional comparisons of supportive STRAW criteria with MAO-A V_T, see eAppendix in Supplement). Within the perimenopausal age group, a significant positive correlation was found between tendency to cry, as measured with the Adult Crying Inventory, and MAO-A V_T in the prefrontal cortex (r = 0.54; P = .008) (Figure 3). The correlation with crying was not significant in the anterior cingulate cortex (r = 0.35; P = .10), although it was in the same direction.

Discussion

Our main findings are that MAO-A V_T is strongly elevated throughout the brain during the typical age of perimenopause (41–51 years) compared with younger age and that MAO-A V_T is lower in menopause than in perimenopause. This suggests a new mechanism for the exceptionally high prevalence of MDEs during perimenopause, has potential implications for the timing and approach of HRT, and raises new considerations for defining changes in the brain relative to other physical changes during perimenopause.

Given the high prevalence of depressive symptoms during perimenopause, it would be expected that some central biomarkers of MDE would be present during perimenopause; however, to our knowledge, this is the first demonstration of a change in a central biomarker during perimenopausal age that is similarly changed during MDEs. Elevated MAO-A levels, demonstrated most frequently in the prefrontal cortex, occur during MDEs in humans, [33,36–38] and greater MAO-A activity and mRNA have also been demonstrated in cortical and subcortical regions in animal models of depression.[39–41] To date, no other markers of change in major depressive disorder, including glial cell loss, lower γ-aminobutyric acid levels, abnormal glutamate/ glutamine levels, reduced *N*-acetyl aspartate levels, deficiencies in functional brain-derived neurotrophic factor and cyclic adenosine monophosphate response element–binding protein in hippocampus, and hippocampal volume loss, have been reported as abnormal during perimenopausal age. It is possible that this reflects a lack of focused investigation, although some markers such as volumetric MRI measurement of the hippocampus have been assessed in relation to age. One partial exception is the finding by Moses-Kolko et al[42] of relatively increased serotonin 1A receptor binding in the prefrontal cortex as women age, which was interpreted as protective against MDEs beyond age 65 years. From the perspective that major depressive disorder is a complex psychiatric illness with multiple abnormalities, our study suggests that markers related to excessive MAO-A activity, such as indices of greater oxidative stress, or markers of greater predisposition toward intrinsic apoptosis may also be more likely to change during perimenopausal age.

Also, given that an emerging strategy in complex illnesses with multiple phenotypes is to develop methods of prevention through reducing risk of individual phenotypes, we suggest that MAO-A V_T might be a useful target for assessing the impact of novel strategies to prevent MDEs in perimenopause.

Our results suggest that the optimal timing for strategies to maintain neuropsychiatric health during perimenopause is between ages 41 and 51 years because oxidative stress and apoptosis are processes influenced by MAO-A that are enhanced in dementia,[43,44] and it has also been proposed that greater activity of MAO-A itself may predispose to neurotoxic effects in Alzheimer disease.[45] A recent concept in HRT for preventing cognitive aging and dementia is that HRT should be investigated for benefit prior to neurobiological changes that accompany menopause[46,47] because late HRT increases likelihood of dementia, possibly due to strokes and brain atrophy.[48,49] Our study suggests that late HRT overlaps poorly with the elevation in MAO-A V_T but early HRT in a window of ages 41 to 51 years would overlap much more closely. Given that strong estrogen declines are implicated in elevating MAO-A levels, an interesting future direction would be to assess whether HRT, which should dampen estrogen fluctuation, specifically targets the increase in MAO-A V_T observed in perimenopause.

Recent advances have been made in understanding the role of MAO-A in neurodegenerative disease,[43] neurodevelopment,[50,51] and mood disorders.[33,36–38,52] However, MAO-A was identified more than 30 years ago, raising the question as to why a change in MAO-A levels or activity has not previously been reported in perimenopause. Based on the sex ratio and age distribution presented in previous studies, no study individually sampled more than 3 women aged 41 to 51 years.[18,53–55] For example, within the 2 studies providing precise details of age and sex, among 87 participants aged 21 hours to 99 years, the number of women between ages 41 and 51 years sampled in each study was 1 and 0.[18,53]

Presently, the criteria for perimenopause, such as the STRAW classification,[23] emphasize physical criteria such as menstrual cycle length, vasomotor symptoms, and plasma follicle-stimulating hormone levels. However, given the lack of correlation between these measures and brain MAO-A V_T, this indicates that measures reflective of the state of other organs cannot be assumed to be optimally representative of changes in the brain. Our study suggests there is additional value for including psychological measures such as tendency to cry, which did relate to the brain measure of MAO-A V_T, to gauge some aspects of perimenopause in addition to the main STRAW criteria.[23]

Our study has the advantage of measuring an index of MAO-A density in vivo but has disadvantages associated with PET imaging. The resolution of PET does not allow us to determine the cellular specificity of the changes in MAO-A V_T, and MAO-A can be present in glia and neurons. A second limitation is that we selected MAO-A V_T as a marker. The advantage of this marker is that it is robustly measured with [^{11}C]harmine PET, but the disadvantage is that it represents both specific binding and free and nonspecific binding. Even so, the free and nonspecific binding for [^{11}C]harmine represents only 15% of MAO-A V_T, so the differences in this measure primarily reflect a change in specific MAO-A binding. [17,56] A third limitation is that the prefrontal and anterior cingulate cortices were prioritized

for the third hypothesis of a correlation between greater MAO-A V_T with the psychological measurement of crying, but MAO-A V_T is highly intercorrelated among different brain regions within individuals; hence, it cannot be concluded that MAO-A V_T in the prefrontal cortex is preferentially related to crying vs the other regions assayed. In addition, the cross-sectional design is a limitation. However, the magnitude of change across the groups is quite substantive, particularly between women of reproductive age and women of perimenopausal age, so it is extremely unlikely that a bias in sampling could explain this difference.

Conclusions

To our knowledge, this is the first report of a change in a central biomarker during perimenopausal age that is also present during MDEs. The functions of MAO-A influence processes implicated in both mood disorders and dementia, and greater levels of MAO-A itself (particularly in the prefrontal cortex) are associated with MDEs and depressive symptoms.[33,36–38,43] Hence, greater MAO-A levels during perimenopause may represent a new target for assessing novel interventions to prevent mood disorders and reduce longer-term risk of neurodegenerative disease, and the optimal timing of such interventions should be early. Finally, our study found that change in MAO-A V_T during perimenopausal age was associated with crying, a psychological symptom, rather than the change in menstrual cycle length. This demonstrates that staging of perimenopause may not be uniform between the brain and the rest of the body and that future definitions of perimenopause should consider staging brain changes in perimenopause differently from alterations in menstrual cycle length.

Acknowledgments

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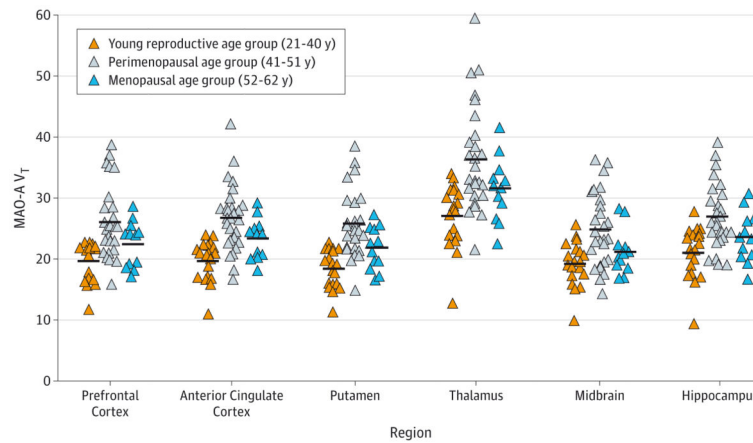
Figure 1. Monoamine Oxidase A (MAO-A) Total Distribution Volume (V_T) in Women of Young Reproductive Age, Women of Perimenopausal Age (All Women Regardless of Cycle Length), and Older Women in Menopause

On average, MAO-A V_T in perimenopausal age was 34% greater compared with reproductive age and 16% greater compared with menopause (multivariate analysis of variance, group effect, $F_{16,94} = 3.03$; $P < .001$). Horizontal lines indicate mean MAO-A V_T.
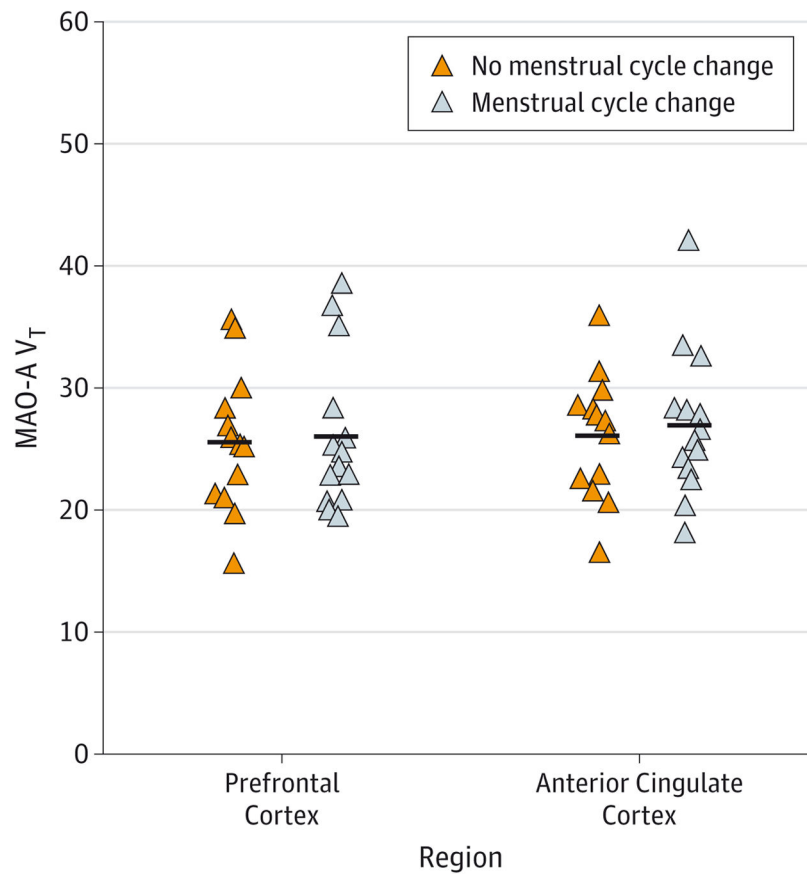
Figure 2. Comparison of Monoamine Oxidase A (MAO-A) Total Distribution Volume (V_T) in the Prefrontal Cortex and Anterior Cingulate Cortex in Women in the Perimenopausal Age Group With No Change in Menstrual Cycle Length vs Those With a Significant Change in Menstrual Cycle Length

Within the perimenopausal age group, MAO-A V_T was not associated with meeting Stages of Reproductive Aging Workshop criteria for perimenopause ($F_{8,18} = 0.548$; $P = .81$). Horizontal lines indicate mean MAO-A V_T.
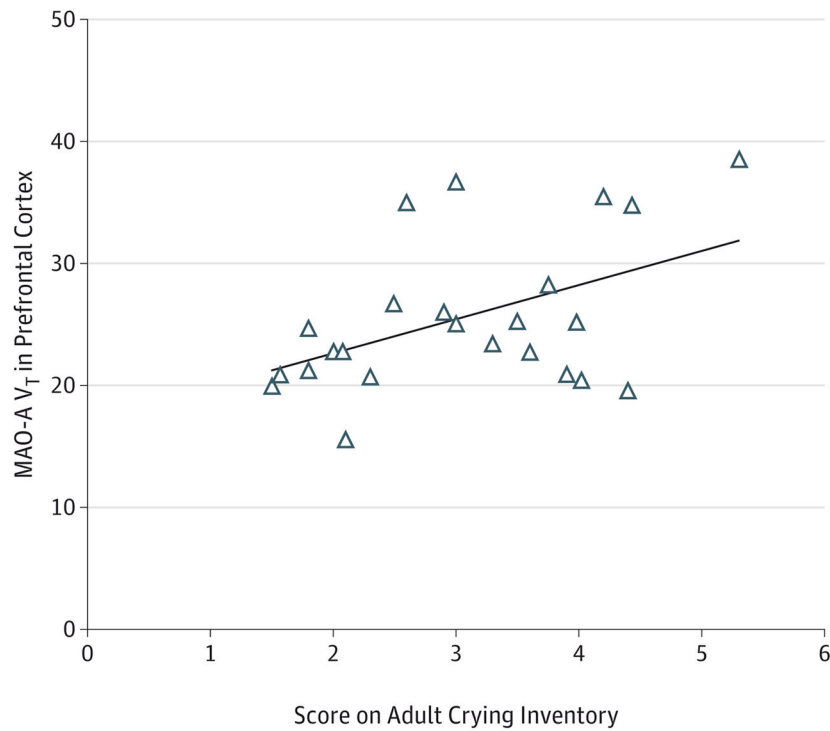
Figure 3. Positive Correlation Between Monoamine Oxidase A (MAO-A) Total Distribution Volume (V_T) in the Prefrontal Cortex and Scores on the Adult Crying Inventory in the Perimenopausal Age Group

For the correlation between MAO-A V_T in the prefrontal cortex and scores on the Adult Crying Inventory, $r = 0.54$ (2-tailed $P = .008$).

Table 1

Demographic Characteristics and 17-Item Hamilton Depression Rating Scale Scores of Study Participants

Characteristic	Mean (SD)		
	Young Reproductive Age (n = 19)	Perimenopausal Age (n = 27)	Older Menopausal Age (n = 12)
Age, y	28.26 (5.05)	45.21 (3.41)	56.25 (3.19)
Education, y	16.00 (2.94)	16.31 (2.43)	15.86 (1.13)
17-Item Hamilton Depression Rating Scale score[a]	0.50 (0.83)	1.12 (1.92)	0.31 (0.61)

[a]Scores derived on the day of scanning.

Table 2

Demographic and Clinical Characteristics of Subgroups in the Perimenopausal Age Group

Characteristic	Mean (SD)	
	No Change in Menstrual Cycle Length (n = 13)	**Significant Change in Menstrual Cycle Length[a] (n = 14)**
Age, y	44.92 (2.81)	45.50 (4.00)
Education, y	16.54 (2.74)	16.07 (2.13)
17-Item Hamilton Depression Rating Scale score[b]	1.46 (2.57)	1.07 (1.53)
Adult Crying Inventory score	3.24 (0.93)	2.81 (1.17)
Climacteric measure		
Menopause Rating Scale score		
Psychological symptoms	1.41 (1.50)	2.79 (2.61)
Somatovegetative symptoms	1.50 (1.57)	2.50 (2.14)
Urogenital symptoms	0.33 (0.65)	1.82 (2.02)[c]
Total	3.25 (3.17)	7.11 (5.52)[c]
Greene Climacteric Scale score		
Psychological	4.08 (3.40)	5.87 (2.81)
Anxiety	2.17 (1.91)	2.74 (1.64)
Depression	1.92 (1.89)	3.27 (1.42)[c]
Somatic	2.33 (1.84)	2.91 (1.93)
Vasomotor	0.50 (0.76)	1.55 (1.50)[c]
Sexual dysfunction	0.25 (0.60)	0.82 (0.94)
Hormonal measure		
Estradiol, pg/mL	150.9 (102.8)	150.6 (221.2)
Progesterone, ng/mL	0.85 (1.13)	0.31 (0.19)
Follicle-stimulating hormone, mIU/mL	7.6 (4.9)	21.5 (24.5)[d]

SI conversion factors: To convert estradiol to picomoles per liter, multiply by 3.671; to convert progesterone to nanomoles per liter, multiply by 3.18; and to convert follicle-stimulating hormone to international units per liter, multiply by 1.0.

[a] As defined by Stages of Reproductive Aging Workshop criteria.[23]

[b] Scores derived on the day of scanning.

[c] $P < .05$, 2-tailed t test with Welch correction for unequal variances.

[d] $P < .05$, 1-tailed t test with Welch correction for unequal variances.