


## RESEARCH ARTICLE

# The relationships between brain structural changes and perceived loneliness in older adults suffering from late-life depression

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**Objective:** Late-life depression is a significant health risk factor for older adults, part of which is perceived loneliness. In this voxel-based morphometry study, we examined the relationships between perceived loneliness and depression recurrence.

**Methods:** Fifty-two older adults were recruited, and they were split into 3 groups: single episode, multiple episodes, or normal control groups, according to their clinical histories.

**Results:** This result suggests the level of functioning regarding the reward system may be negatively related to the number of depressive episodes. Taken together, the findings of this study offer important insight into the neural underpinnings of the course and chronicity of late-life depression.

## KEYWORDS

late-life depression, MRI, perceived loneliness, voxel-based morphometry

## 1 | INTRODUCTION

Late-life depression (LLD) is a significant health risk factor for older adults because of its association with physical impairments and decline in cognitive functioning<sup>1</sup> and has an incidence rate as high as 15%.<sup>2</sup> Findings

from neuroimaging studies have revealed that neural correlations of emotional regulation have structural abnormalities in people with depression.<sup>3</sup> Furthermore, among these depressed subjects, the medial prefrontal cortex (mPFC), hippocampus, and structures related to coping with stress are different from the healthy controls (HC).<sup>4,5</sup> Other studies have

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also shown reduced gray matter (GM) volume in the mPFC, subdivisions of the anterior cingulate cortex, the subgenual and subcallosal cortex, and the limbic regions, such as the hippocampus and amygdala.<sup>5</sup>

There are multiple factors that may predispose older adults to LLD. According to the “vascular depression” hypothesis, the onset of LLD could be due to neurobiological changes resulting from vascular disease such as hypertension within the brain. It is suggested that the clinical expression of LLD is mediated by the hypermetabolism of dorsal cortical regions and hypermetabolism of ventral limbic structures.<sup>6,7</sup> Moreover, endocrine disturbances, such as diabetes and depression, were found to be highly related. The presence of diabetes, for instance, almost doubles the risk for depression through the role of hormones in relation to the control and feedback mechanisms in neural structures.<sup>8</sup> In terms of psychosocial factors, perceived loneliness is one of the most prominent contributors.<sup>4,9-11</sup> Perceived loneliness refers to the perception of being socially isolated, resulting from a discrepancy between one's social needs and real-life social relationships.<sup>12</sup> Lonely people see stressors as threats rather than challenges and cope with stressors in a passive, isolative way.<sup>13</sup>

Perceived loneliness is associated with changes in both brain structure and function. Previous literature has suggested that brain structures implicated in social cognition are associated with an individual's online social network.<sup>14</sup> The neural basis of perceived loneliness may have multiple folds. It may relate to one's sensitivity to social cues and reward, which is governed by the dopaminergic reward circuit (i.e., the ventral striatum [VS]), which is activated when understanding basic rewards. Ventral striatum activity is highly related to the expectation of the desired outcome; higher expectation will lead to a higher magnitude of the activity.<sup>15</sup> Indeed, lonely persons showed weaker activation in the VS when viewing pictures of pleasant social events than when viewing pleasant social pictures of nonsocial objects.<sup>16</sup> The regional white matter (WM) column in the left posterior superior temporal sulcus, the bilateral inferior parietal lobule, the right anterior insula, the posterior temporoparietal junction, the rostralateral, and the dorsomedial prefrontal cortex have been shown to be reduced in people with high levels of perceived loneliness.<sup>17</sup> It is speculated that changes in the WM volume reported above may relate to impaired empathy and low self-efficacy.

Although perceived loneliness is a major maintenance factor of depression,<sup>9-11</sup> little is known about how the brain changes in relation to the recurrence of depression and how this recurrence is related to perceived loneliness. Treadway et al<sup>5</sup> studied the differences in the hippocampal subfields and the mPFC in the progression of depression associated with stress and found that the number of recurrent episodes is positively related to the hippocampal subfields, especially the dentate gyrus and striatum. They then suggested that volumetric changes associated with depression may fluctuate with the levels of the illness's severity, as well as the frequency of relapse. Indeed, people with depression have different levels of perceived loneliness throughout the progression of their illness, and this perceived loneliness alters the brain structures differently at different periods of the illness.

Taking the reviewed literature into consideration, this study examined the relationships between perceived loneliness and depression recurrence, specifically the relationships between the neural effects of varying degrees of perceived loneliness and relapse frequency. Perceived loneliness is a variable that can be manipulated through therapeutic

## Key points

- The gray matter volume in the striatum will be affected by the perceived loneliness level and the recurrence of depressive episodes
- The level of functioning regarding the reward system may be negatively related to the number of depressive episodes
- Perceived loneliness level is positively correlated to the number of depressive episodes

intervention. Attaining a greater understanding of the neurobehavioral relationships underlying perceived loneliness and depression relapse will provide significant insight for applied research on treatment and prevention strategies for LLD. We hypothesized that (1) the perceived loneliness levels would be higher in individuals with multiple recurrent episodes than in people experiencing single depressive episode or the controls and (2) the group differences in perceived loneliness might be reflected in the structure of the brain regions associated with social rewards.

## 2 | METHODS

### 2.1 | Participants

This study was approved by the Institutional Review Board in the Chang Gung Memorial Hospital. Fifty-two right-handed participants aged more than 60 years (19 males and 33 females, age  $67.92 \pm 5.0$  y) were recruited from a psychiatric outpatient clinic of the Chang Gung Memorial Hospital. Informed consents were obtained from all participants. Participants belonged to one of the following 3 groups: (1) single episode (SE), (2) multiple episode (ME), and (3) Healthy Control (HC). Participants in the SE and ME groups all had their onset of their first depressive episode after age 60 and were diagnosed by 2 geriatric psychiatrists based on the diagnostic interview of unipolar major depressive disorder according to the Structured Clinical Interview of *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*.<sup>18</sup> Participants were excluded if there were other histories of major psychiatric and/or neurological disorders or cognitive impairment.

Antidepressants were maintained during the scan due to ethical reasons, but the prescription was not changed for  $\geq 2$  weeks prior the scan. The duration of participants' use of hypnotics was recorded as well. Participants were included only if they did not have any other histories of major psychiatric illness. Those with a score  $< 24$  in the Mini-Mental State Examination and a history of other neurological diseases were excluded to ensure no confounding effect from cognitive impairment or other neurological changes.

### 2.2 | Psychological measures

The Chinese version of 17-item Hamilton Rating Scale for Depression (HAM-D) was used to measure the severity of depression in the subjects.<sup>19,20</sup> The HAM-D is a widely used scale in measuring the severity of depression and depressive symptoms in both psychological and

neuropsychiatric studies. It has good interrater reliability ( $K > 0.92$ ) for most of the items and the total score (Cronbach  $\alpha > 0.7$ ).<sup>20</sup>

Subjects' perceived loneliness was measured by using the 20-item UCLA Loneliness Scale (LS).<sup>21</sup> It has good sensitivity to perceived loneliness with high internal consistency (coefficient alpha ranging from 0.89 to 0.94), test-retest reliability ( $r = 0.73$ ), and is suitable for both adults and older adults.<sup>22,23</sup> Internal consistencies of the Chinese LS scores were 0.85 for a sample of 153 Chinese undergraduate participants.<sup>24</sup> The construct validity of the Chinese LS was supported by a positive correlation with another scale of social loneliness. The Chinese translation of the LS used in this study was back translated by individuals experienced in English-to-Chinese translations.

The physical functioning of the subjects was measured by the Chinese version of Short-Form Health Survey (SF-36).<sup>25</sup> It is a brief self-administered questionnaire, which measures 8 health dimensions: physical functioning, role limitation due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, mental health, and one single item scale on health transition. SF-36 has proved useful in monitoring population health. The Chinese version used has good test-retest reliability with coefficients ranged from 0.66 to 0.94 and the Cronbach  $\alpha$  of 0.65 to 0.87.

### 2.3 | Magnetic resonance imaging data acquisition

The structural brain measure included acquisition, preprocessing, and whole brain voxel-based morphometry (VBM) analysis. T1-weighted structural images were acquired using a 3.0T MR 750 scanner (GE Healthcare Systems, USA) with an 8-channel head coil. High-resolution, whole-brain volume T1-weighted structural images were acquired using an inversion recovery-prepared 3D fast spoiled gradient-echo sequence with the following parameters: TR = 8 milliseconds,

TE = 3 milliseconds; TI = 450 milliseconds; FOV =  $250 \times 250 \text{ mm}^2$ ; and voxel size =  $0.98 \times 0.98 \times 1 \text{ mm}^3$ .

## 2.4 | Statistical analysis

### 2.4.1 | Behavioral findings

One-way analysis of variance was conducted in Statistical Package for the Social Sciences 23.0 (SPSS; IBM) to examine the gender, age, and physical functioning difference between groups. One-way analysis of covariance was then conducted to examine the Group effect on scores on LS and HAMD with gender and age as the covariate. Pairwise comparisons were conducted to further test the between-group differences in the scores on each of the 2 scales. Partial correlation, controlling for gender and age, was then performed to explore the relationships between progression of illness and LS scores.

### 2.4.2 | Structural brain image preprocessing and analysis

The acquired structural brain images were preprocessed using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) implemented in SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK). The East Asian template was used for affine registration. GM, WM, and cerebrospinal fluid were categorized from the images. High-dimensional DARTEL was used for spatial normalization, as it was sensitive enough to examine small brain structures and was the optimal approach for whole-brain alignment. Normalized, unsegmented images were visually inspected for gross artifacts resulting from normalization. Finally, both GM and WM segments were smoothed with an 8-mm, full-width half-maximum Gaussian kernel by SPM8.

Whole-brain analyses were conducted on the smoothed T1 images using a general linear model that involved permutation test (5000 iterations) through the FMRIB Software Library (FSL)-randomize approach. The interaction model was Group (categorical variable)  $\times$  LS

**TABLE 1** Mean comparison among 3 groups

	Single Episode (n = 19)	Multiple Episode (n = 10)	Healthy Control (n = 23)	Statistical Analysis	Comparison Group	Post hoc P value
Gender	5 males, 14 females	5 males, 5 females	9 males, 14 females	$F = 0.83$ $P = .442$	SE vs ME SE vs HC ME vs HC	.220 .401 .559
Age (y)	$67.1 \pm 5.5$	$71.4 \pm 2.6$	$67.1 \pm 4.8$	$F = 3.27$ $P = .046^*$	SE vs ME SE vs HC ME vs HC	.024* .958 .023
Number of episode	1	$2.7 \pm 1.9$	0	...	...	
SF-36	$73.1 \pm 25.2$	$67.8 \pm 30.9$	$85.0 \pm 23.0$	$F = 1.95$ $P = .154$		
LS <sup>a</sup> (scores)	$41.4 \pm 12.5$	$41 \pm 10.2$	$33.2 \pm 8.3$	$F = 3.96$ $P = .026^*$	SE vs ME SE vs HC ME vs HC	.918 .013* .052
HAMD (scores) <sup>a</sup>	$12.4 \pm 6.5$	$8.9 \pm 6.2$	$5.7 \pm 4.13$	$F = 8.034$ $P = .001^{**}$	SE vs ME SE vs HC ME vs HC	.108 .000** .126

Abbreviations: HAMD, Hamilton Rating Scale for Depression; HC, healthy control; LS, Loneliness Scale; ME, multiple episode; SE, single episode; SF-36, Short-Form Health Survey.

Data are expressed as mean  $\pm$  standard deviation.

<sup>a</sup>Gender and age were added as covariate in the analysis.

\*indicates a significant statistical different with  $P < .05$ .

\*\*indicated a significant statistical different with  $P \leq .001$ .

(continuous variable). A contrast between the 3 groups would be considered significant when a significant difference between GM volume and the LS scores was found. For each significant cluster, average GM volume was extracted and then correlated with LS scores for each of the 3 groups.  $P < .01$  was set as the threshold for the analyses.

### 3 | RESULTS

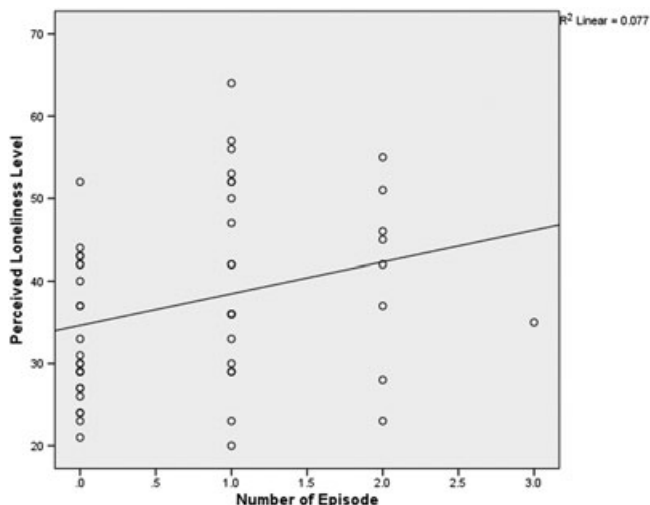
Demographics of the participants in the 3 groups are presented in Table 1. Both SE and ME groups had significantly higher LS and HAMD scores when compared to the HC group. It was observed that among the 3 groups, the gender composition in ME group is slightly different from the other 2 groups while the mean age in ME group is older than the other 2 groups.

#### 3.1 | Behavioral findings

There were significant differences between the 3 groups in age but not in gender and their physical functioning (Table 1). Post hoc test Least Significant Difference (LSD) showed a significant age difference between the SE and ME groups ( $P = .024$ ). The analysis of covariance revealed there were significant differences between the 3 groups in both LS and HAMD (Table 1). Post hoc test LSD showed significant differences between SE and HC in LS ( $P = .026$ ) and HAMD ( $P = .001$ ). Partial correlation showed a positive trend between the episode number and the perceived loneliness scores ( $P = .044$ ). That is, individuals with multiple depressive episodes scored higher on the LS than those experiencing their first depressive episode or those in the HC group (Figure 1).

#### 3.2 | Neuroimaging findings: brain structural analyses

Findings of the VBM analysis did not show significant group differences in the whole-brain GM volume.



**FIGURE 1** Relationship between perceived loneliness and number of episodes

#### 3.2.1 | Interaction between groups and score on the Loneliness Scale

After controlling for gender and age, significant Group  $\times$  LS interactions were revealed in the correlated clusters. A large significant cluster in the left putamen, left caudate, and left pallidum in which the regional GM volume positively correlated with LS scores of patients in SE, but negatively correlated in LS scores of patients in ME (cluster size = 81,  $P[\text{corr}] < .05$ ). The peak voxel was situated within MNI coordinate  $x = -16.5$ ,  $y = 1.5$ ,  $z = 9$  (Figure 2). Concurring with previous findings,<sup>13,15</sup> those peak clusters formed the reward-related brain regions. This interaction suggested that increasing depressive episodes may compromise the reward learning system.

### 4 | DISCUSSION

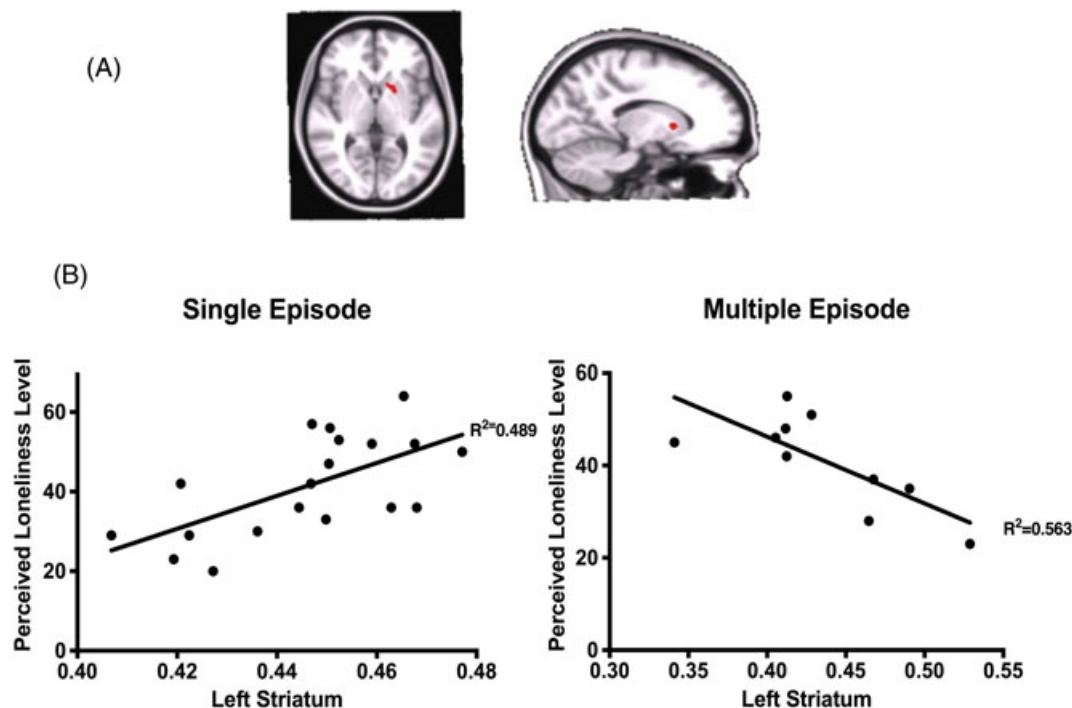
Our behavioral results support our first hypothesis that perceived loneliness levels would be higher in individuals with more recurrent episodes than in people who have only experienced a single depressive episode or controls. Our neuroimaging results provide support for our second hypothesis that the group differences in perceived loneliness levels would be reflected in the brain regions related to social rewards. These findings have important implications both in terms of LLD prognosis and treatment development.

#### 4.1 | Perceived loneliness and relapse of LLD

We observed a positive relationship between the number of depressive episodes and the levels of perceived loneliness, as reflected by the scores on the LS, which supported our first hypothesis that the perceived loneliness levels would be higher in individuals with multiple recurrent episodes than the other 2 groups. We speculated that this positive correlation may be explained by the varying levels of attentional control in people suffering from LLD. According to cognitive theories of depression, the overall negative mood state and negative social interactions may relate to deficits in processing social stimuli in emotion recognition, specifically happiness expression.<sup>26,27</sup> This social processing ability requires attentional control for engagement and disengagement of attention to emotional stimuli.<sup>28</sup> Indeed, previous studies have shown that depressed patients were selective in attending to negative cues and furthermore have difficulties with disengaging the attention from these negative stimuli.<sup>3,29</sup> In the initial episode of depression, patients may be capable of successfully regulating their emotions by recruiting additional resources from different brain regions, such as the medial frontal and ventral anterior cingulate cortex.<sup>3</sup> However, during recurrence, the ability for compensatory strategies may be weakened and therefore hamper their ability to accurately appreciate social rewarding cues in social environments. This blunted reward system is typical of people suffering from depression. In other words, the higher the number of relapses, the worse their perceived loneliness level.

#### 4.2 | Gray matter volume

Our findings regarding the absence of significant differences in whole-brain GM volume among the 3 groups differ somewhat from that of



**FIGURE 2** A, The cluster showing significant LS  $\times$  Group effects, ie, left putamen, left caudate, and left pallidum (cluster size = 81,  $P[\text{corr}] < .05$ ). The peak voxel was situated within MNI coordinate  $x = -16.5$ ,  $y = 1.5$ ,  $z = 9$ . B, The correlation between LS and the regional gray matter volume for patients with single episode (left panel) and those with multiple episode (right panel) [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

previous studies. For example, reduced GM volumes in the prefrontal cortex and the hippocampal region in depressed adults have been reported.<sup>30,31</sup> Methodological differences may help explain these discrepancies. As both the clinical and healthy participants of this study were older adults, the already existing age-related change of GM volume may have masked structural differences amongst the 3 groups in this study. The different levels of illness severity between our study and previous studies may also explain the discrepant findings observed. We only studied older adults who developed late onset depression, meaning the duration of the illness should be shorter compared to that of adults who have experienced multiple depressive episodes. This proposal is in line with Bremner et al<sup>31</sup> observation that the hippocampal volume reduction correlated with the total duration of major depression.

#### 4.3 | Caudate, putamen, and pallidum

Given the known functions of the striatum in appreciating social rewards,<sup>15,32</sup> the volume of the VS may modulate subjective experiences of loneliness in depressed patients, which concurred with our second hypothesis. People with higher levels of perceived loneliness may be more active in searching for social cues, which are essential in forming social connections with others.<sup>33</sup> Hence, when searching for social rewards, the striatum could be significantly activated to serve the need of understanding those rewards. The negative relationship between the GM volume of the striatum and the number of depressive episodes seems to suggest a trend of illness progression as the reward-learning network becomes increasingly compromised.

Previous reports have suggested a blunted processing of incentive salience, incentive motivation, and reinforcement learning in people with depression. Furthermore, recurrences of the illness worsen the abnormalities mentioned and affect the presentation of the depressive symptoms.<sup>34</sup> This line of thought may explain the decrease in the GM volume while the number of episodes increased, which may relate to the blunted processing happening within the reward-related striatal circuit.

Previous studies have suggested the pallidum plays an important role in depression symptom presentation<sup>35</sup>; pallidum lesions were associated with psychic akinesia presented as apathy, anhedonia, and reduced affects, a symptomatic presentation similar to that observed in people with depression.<sup>36</sup> In this study, we observed a negative relationship between the number of relapse episodes and the GM volume of the left pallidum. This finding is consistent with the observations reported above.

#### 4.4 | Gender and age

In our study, there are more female subjects than males. This gender composition is in line with previous literature showing the prevalence rate of depression to be higher in females compared to males.<sup>37</sup> Moreover, it is noted that the mean age in the ME group is greater than the other 2 groups and statistical analysis showed the significant differences lies between the SE and ME group. This age difference may be due to the year of their onset. In our samples, the mean onset age for the SE and ME group is  $64.42 \pm 4.36$  and  $63.80 \pm 2.30$ , respectively. It is thus logical to speculate that the older the subjects become, the higher chance they will suffer from depressive recurrence than

their younger counterparts. Even though there is a gender imbalance between the 3 groups and there is a significant age difference between SE and ME groups, we have controlled for the 2 factors in our analysis, and the same pattern of results remained. Therefore, it is believed that our results are not due to age and gender effects.

#### 4.5 | Limitations

The results of this study should be considered in light of a number of limitations. Firstly, we did not acquire the baseline GM volume when the patients were first diagnosed with depression and were consequently unable to examine changes in GM volume during the course of their illness. Future longitudinal studies may wish to consider monitoring the abovementioned changes so as to understand the effects on the brain as the depression progresses. A second limitation of our study was that the gender ratio of our sample was biased towards female participants, as well as the age differences between the 3 groups. While our sample may reflect the actual gender distribution in LLD, we were unable to establish any gender-related or age-related effects on the neurobehavioral relationship of perceived loneliness in older adults suffering from LLD. Thirdly, it is noted that our study had a limited sample size. The results generated should thus be interpreted with caution, and further validation on the results should be performed with more data points. Fourthly, we did not include the history of any physical diseases of our participants even though we controlled their physical functioning for comparison. It would be worthwhile to include details of physical diseases in future studies to have a better picture of how physical diseases may affect the neurobehavioral relationship of perceived loneliness in elderly with LLD. Finally, future studies may wish to include participants with varying degrees of depression severity to further our understanding of the course of LLD. This insight is critical to the development of comprehensive intervention programs.

#### 5 | CONCLUSIONS

This study provides important evidence that perceived loneliness is associated with changes in the neural presentation of people with LLD in the left putamen, left caudate, and left pallidum. These areas are related to the reward circuit, which helps individuals understand social rewarding cues. These results suggest that the perceived loneliness levels in single and recurrent LLD patients may have different neural pathways in affecting the depressive symptoms and that knowing the perceived loneliness level will help to understand the progression of their illness. These results also have potential implications for treatment outcome in depression. In particular, they contribute to the literature suggesting that the activity in the striatum could be a potential neural marker and intervention target for depression,<sup>38</sup> therefore bringing clinical value in preventing as well as treating affective disorder.

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#### CONFLICT OF INTEREST

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a conflict of interest.

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