Gray Matter Changes in Late Life Depression—a Structural MRI Analysis

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Multiple brain morphometric changes have been reported in late-life depression (LLD), mostly in studies comparing volumes of circumscribed brain areas. The aim of our study is to characterize the volumetric changes of multiple gray matter regions in relation to age of onset/duration of illness. We predicted that the association of gray matter volumes with total duration of illness and age of onset would differ depending on whether the region was susceptible to the toxic effects of chronic exposure to cortisol or to the vascular/neurodegenerative changes accompanying prodromal dementia. Seventy-one elderly depressed subjects were studied along with thirty-two comparison subjects. High-resolution T1-weighted brain MRIs were processed using an automated labeling pathway technique. To protect against type-I error, we combined the right and left hemisphere volume data. We sampled 24 regions of interest (ROIs). We used the primary visual cortex volume to normalize for individual variations in brain size. LLD Subjects had smaller volumes than non-depressed subjects in 17 of the 24 examined ROIs. Shorter duration of illness and later age of onset was correlated with smaller volumes of parahippocampal area and parietal inferior area. A later age of onset was also correlated with smaller volumes of several frontal and temporal areas, cingulum, and putamen. Our findings support a dementia prodrome model more strongly than a toxic stress model in this group of subjects. However, it remains likely that both processes as well as other factors contribute to the heterogeneity of volumetric brain changes in LLD.
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INTRODUCTION

Brain morphometric changes reported in late-life depression (LLD) have included significant bilateral volume reductions in gray matter in anterior cingulate, gyrus rectus, and orbitofrontal cortex (Ballmaier *et al*, 2004; Lai *et al*, 2000), as well as smaller hippocampal (Steffens *et al*, 2000) and frontal lobe volumes (Kumar *et al*, 2000). Several studies have reported smaller left medial temporal and left caudate volumes (Greenwald *et al*, 1997), and right hemisphere frontal atrophy more prominent in late-onset depression, when compared with early-onset depression (Almeida *et al*, 2003). White matter lesions in the medial orbital region also correlate with depression severity (MacFall *et al*, 2001). Using voxel-based morphometry, (Bell-McGinty *et al*, 2002) found that elderly depressed subjects had lower right hippocampal volume than comparison subjects and that the volume of the hippocampal-entorhinal cortex was inversely associated with the number of years since the first episode of depression.

These varied changes have been interpreted primarily, albeit not exclusively, by two different hypotheses (1) toxic stress and (2) dementia prodrome (Sheline *et al*, 1996; Steffens *et al*, 2000). The toxic-stress hypothesis predicts that smaller volumes of specific brain regions are correlated with earlier age of onset and longer duration of illness (Sheline *et al*, 1996). The dementia prodrome hypothesis predicts that volumetric reduction will correlate with later age of illness onset and/or shorter duration of illness, reflecting an underlying vascular or neurodegenerative process (Steffens *et al*, 2000).

A key challenge presented by this literature is that most studies have compared volumetric changes in circumscribed areas of brain. Very few studies have evaluated multiple brain regions in the same subjects

(Ballmaier et al, 2004). Since the literature presents varied findings, we conducted an expanded analysis of the volumetric changes of multiple gray matter regions implicated variously by the toxic stress hypothesis (hippocampus, amygdala, frontal areas, cingulate) and by the prodromal dementia hypothesis (limbic structures as well as temporo-parietal areas and subcortical gray matter, including caudate, putamen, pallidum, and thalamus). We hypothesized that LLD subjects would have smaller volumes relative to non-depressed comparison subjects in regions identified as being susceptible to either the potential toxic effect of cortisol or to the prodromal chances accompanying a vascular/neurodegenerative process. We predicted that the association of gray matter volumes with total duration of illness and age of onset would differ depending on whether the region was susceptible to the effects of toxic stress or neurodegeneration. We hypothesized that volumes of gray matter in the medial temporal and prefrontal regions would be inversely correlated with illness duration (reflecting the cumulative effects of toxic stress), whereas limbic and temporo-parietal gray matter volumes would be inversely correlated with age of onset (reflecting neurodegeneration risk).

MATERIALS AND METHODS

Data for this study were provided by the second and third maintenance therapies in late life depression studies (MTLD-II and MTLD-III) conducted at the University of Pittsburgh Advanced Center for Intervention and Services Research for late-life mood disorders between 1999 and 2004 (MTLD-II) and between 2004 and 2006 (MTLD-III). Details of the MTLD studies' protocols are described elsewhere (Reynolds et al, 2006). In brief, participants were 70 and older, diagnosed via Structured Clinical Interview for DSM-IV (First et al, 1995) with current non-psychotic, non-bipolar major depressive disorder (single-episode or recurrent), a 17-item Hamilton Depression Rating Scale (Hamilton, 1960) of 15 or higher, and a Mini Mental State Examination (MMSE)(Folstein et al, 1975) score of 17 or higher. Cognitive function was assessed with the Dementia Rating Scale (Mattis, 2004) and the Executive Interview (Royall et al, 1992). Subjects included in this study had a Mini Mental State Examination of 24 or above.

Seventy-one subjects with LLD were included in this study along with thirty-two non-depressed, non-demented comparison subjects equated for age, sex, and education. The comparison subjects had no history of documented psychiatric illness. MRI was performed as part of each study's baseline evaluation. The MR images were acquired using a GE Signa 1.5 Tesla scanner. A volumetric spoiled gradient recalled (SPGR) sequence was used to acquire high-resolution T1-weighted images. Images were acquired in the coronal plane, with 1×1 mm in plane resolution, and 1.5 mm slice thickness. One hundred and twenty continuous slices were acquired.

T1-weighted brain MRIs were processed using the automated labeling pathway (ALP) technique (Wu et al, 2006). ALP Technique relies on atlas-based segmentation (in deformable registration approach) to measure regional volumetric differences between groups in a number of pre-defined regions of interest. The pathway combines a series of publicly available software packages (AFNI, BET, FLIRT, and ITK) and some locally developed programs to implement atlas-based segmentation of MRIs (Wu et al, 2005). Using ALP, anatomic areas of interest defined on the reference brain (MNI colin27) were transformed to fit each individual's anatomic image, and were then segmented into gray, white, and CSF tissue types. The anatomic regions of interest are 90 manually traced regions from the AAL atlas (Tzourio-Mazoyer et al, 2002).

In ALP image registration is used to coregister the 3D SPGR image of each subject and the template colin27. Prior to the registration the skull and scalp is stripped from both colin27 and the subject's 3D SPGR using the Brain Extraction Tool—BET (Smith, 2002), and followed by erosion and dilation to remove additional skull and scalp (Wu et al, 2005). The fully deformable registration model we use is similar to models described previously (Chen, 1999). We have implemented this using the registration library in Insight Segmentation and Registration Toolkit (Yoo, 2004). This method starts with a grid-based piecewise linear registration and then uses a demons registration algorithm as a fine-tuning procedure for a voxel-level spatial deformation. The fully deformable registration allows for a high degree of spatial deformation, which seems to give it a particular advantage over other standard registration packages, such as AIR and SPM (Woods et al, 1998). Images were visually evaluated by an operator to check for inaccuracies of misalignment, a procedure that requires less than 1 min per brain. No misalignment was detected in this study. Voxel counts of total brain volume, gray matter in the whole brain, and gray matter for each ROI (right and left hemisphere) were then automatically obtained.

We selected 24 ROIs that we predicted would be smaller in LLD subjects. Some of these regions were obtained through combining adjacent structures: for example, anterior and middle cingulate were combined in one ROI (cingulum), frontal inferior orbital, frontal middle orbital, and frontal superior orbital were combined into one region (frontal orbital). To further protect against type I error, we limited the number of regions we examined by combining right and left hemisphere data.

Several methods are used in the literature to control for regional brain volumes variability, as height, body mass index, whole brain volume, intracranial volume or specific brain areas that have minimal age-related variations. Manual measurements of intracranial volume or the use of height/body mass index as a proxy for the intracranial volume can be unreliable for the elderly population (Rosano et al, 2007). Moreover, different gray matter structures (frontal areas, medial temporal areas) have a non-linear age-related variability, rendering the use of the whole gray matter volume as control less accurate (Raz et al, 2005). Also—in this specific sample—the whole brain was larger in the depressed subjects than in the comparison subjects. Thus, we chose to use the volume of the primary visual cortex (the calcarine area) to control for individual variations in brain size, as this is one of the regions with minimal inter-subject variation as well as with minimal age-related variation (Raz and Rodrigue, 2006).

We divided our analysis into two phases. In the first phase, we analyzed the volumetric differences between

controls and LLD subjects in the 24 ROIs. In the second phase, we analyzed the correlation between the volumes of the 24 ROIs and the total duration of the depressive illness/ the age of onset of first depressive episode. The total duration of illness was defined as the amount of time that has passed since the onset of the first depressive episode.

Statistical Analysis

We compared demographic and baseline clinical measure between LLD subjects and comparison subjects with two sample t-tests for continuous data. Fisher's Exact tests were used for categorical data.

T-tests were used to compare MRI volumes between comparison subjects and LLD subjects. Then, the P-values were adjusted using False Discovery Rate control to correct for multiple comparisons. This procedure was performed using SAS PROC MULTTEST (SAS Institute I, 2000). False Discovery Rate controls the expected proportion Type I errors among the rejected hypotheses. It is a less conservative comparison procedure with greater power than Family Wise Error Rate Control (Dudoit, 2003).

Pearson Product Moment Correlation was used to evaluate the association between duration of illness/the age of onset of first depressive episode and MRI volumes among LLD subjects. A square root transformation was used on the total duration of the depressive illness since it was not normally distributed.

RESULTS

The clinical and demographic characteristics are presented in Table 1.

After controlling for multiple comparisons, subjects with LLD had significantly smaller volumes than non-depressed subjects in 17 of the 24 areas: frontal superior orbital, frontal orbital, frontal inferior, frontal superior medial, gyrus rectus, insula, hippocampus, parahippocampal area, amygdala, parietal inferior, putamen, pallidum, thalamus, temporal superior, temporal pole, temporal middle, and temporal inferior (see Table 2).

Among subjects with LLD, we found that the duration of illness was positively correlated with tissue volume in the parahippocampal area and parietal inferior area (see Table 3). The same areas had smaller volumes correlated with an older age at onset (see Table 3). In addition, four frontal areas (frontal superior, frontal orbital, frontal middle, and frontal medial superior), three temporal areas (temporal pole, temporal middle, and temporal inferior), cingulum and putamen had smaller volumes that were significantly correlated with an older age at onset. (see Table 3).

DISCUSSION

Our study shows that, when compared with non-depressed, non-demented elderly, subjects with LLD have significantly reduced volumes of multiple areas of the brain, predominantly in the frontal orbital and medial regions, as well as in the entire temporal lobe and the limbic system (hippocampus, amygdala, parahippocampal area). The parietal area

adjacent to the temporal cortex is also significantly smaller in subjects with LLD. These results are congruent with previous reports from the literature (Bremner, 2005), describing changes in orbito-frontal cortex (Ballmaier et al, 2004; Coffey et al, 1993), inferior parietal (Ballmaier et al, 2004), hippocampus (Bell-McGinty et al, 2002; Sheline et al, 1996; Videbech and Ravnkilde, 2004), amygdala (Sheline et al, 1998) and putamen (Husain et al, 1991).

The distribution of changes is concordant with a recent hypothesis implicating a limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuit described in association with early-onset recurrent depression (Sheline, 2003). Similarly, a functional circuit involving these limbic-cortical regions has also been described (Mayberg, 2007). Our study suggests that these circuits, documented through the convergent findings of functional and structural imaging approaches, are also involved in LLD (Mayberg, 2007).

Our findings indicate an extensive neuroanatomical substrate, with multiple areas involved in the morphologic changes associated with LLD. These results can be interpreted according to the two most prevalent hypotheses, the toxic stress, and the dementia prodrome. According to the toxic-stress hypothesis of depression, high levels of glucocorticoids (McEwen, 1997; Sapolsky, 1993) induce shrinking of the highly sensitive hippocampal gray matter (Sapolsky et al, 1985; Sheline et al, 1999; Steffens et al, 2000; Videbech and Ravnkilde, 2004). According to the prodromal dementia hypothesis of LLD, a subgroup of subjects develops LLD as a very early clinical presentation of dementia (Alexopoulos et al, 1993; O'Brien et al, 2004; Steffens et al, 2000). In this case, lower volumes would be interpreted as a marker of neuronal loss related to an as yet undeclared neurodegenerative or vascular process (Alexopoulos et al, 1993; Greenwald et al, 1997). Most findings supporting this theory have been described in left medial temporal lobe (Greenwald et al, 1997), left caudate (Greenwald et al, 1997; Krishnan et al, 1992), anterior cingulate (Drevets et al, 1997), and putamen (Husain et al, 1991).

Both hypotheses predict smaller hippocampal volumes, but diverge when predicting the relationship between hippocampus and age of onset/duration of illness. According to the toxic-stress hypothesis, a younger age of onset and a longer duration of illness would be associated with smaller hippocampal volume due to longer exposure to toxic levels of cortisol (Sheline et al, 1996). By contrast, according to the dementia prodrome hypothesis, an older age of onset and a shorter duration of illness would be associated with smaller hippocampal volumes due to atrophy related to neurodegeneration or vascular lesions (Steffens et al, 2000).

While the differences in our sample between LLD subjects and comparison subjects do not conclusively demonstrate the validity of either the toxic or the prodromal theory of depression, the correlation with the total shorter duration of illness/later age of onset of depression would be more consistent with the prodromal dementia hypothesis of depression rather than the toxic-stress hypothesis in this group of subjects.

Our findings regarding the correlation with age of onset/ duration of illness contrast with previous reports from our group (Bell-McGinty et al, 2002). These differences may be related to several factors including our 2.3 times larger

Table 1 Demographic and Clinical Characteristics of the Sample

Demographic and clinical characteristics	Comparison subjects (N = 32), Mean (SD); (Range) or N (%)	Depressed subjects (N = 71), Mean (SD); (Range) or N (%)	Testing differences between groups
Current age (years)	71.0 (6.7); [56.3–89.5]	72.2 (6.2); [60.3–91.7]	t-value = −0.93, DF = 101 P-value = 0.36
Men, N (%)	15 (46.9%)	22 (31.0%)	Fisher's exact test, P-value = 0.13
Caucasian, N (%)	28 (87.5%)	65 (91.6%)	Fisher's exact test P-value = 0.50
Education, years	14.9 (2.4); [12–20]	14.0 (2.7); [8–20]	t-value = 1.50, DF = 101 P-value = 0.14
Folstein mini mental state examination	29.0 (1.0); [26–30]	28.7 (1.5); [24–30]	t-value[a] = 1.27, DF[a] = 86.2 P-value = 0.21
Hamilton Rating Scale for depression, 17 item	2.4 (1.8), (N = 31); [0–6]	18.3 (3.0); [15–25]	t-value[a] = −32.59, DF[a] = 89.4 P-value < 0.0001
Mattis Dementia Rating Scale	139.6 (2.9); [133–144]	137.4 (4.4); [125–144]	t-value[a] = 3.01, DF[a] = 88 P-value = 0.003
EXIT	6.7 (3.6), (N = 31); [0–14]	7.9 (3.5); [0–17]	t-value = −1.55, DF = 100 P-value = 0.12
Total duration of depression (years)		19.9 (19.2)	
Duration of current episode of depression (weeks)	—	120.4 (173.7), (N = 70); [3–1040]	—
Proportion of subjects with early onset depression (age of onset < 60)	—	38 (53.5%)	
Proportion of subjects with recurrent depression (number of episodes of depression ⩾2)	—	43 (60.6%)	
Age of onset of first episode of depression	—	52.3 (20.1); [10–87]	—
Proportion of subjects receiving antidepressants at baseline	—	12 (17.1%)	—
Proportion of subjects receiving antipsychotics at baseline	—	1 (1.4%)	—
Proportion of subjects receiving benzodiazepines at baseline	1 (3.1%)	19 (27.1%)	Fisher exact P-value = 0.003

[a]Satterthwaite method for unequal variance.

sample and the different sample profile. Our sample has a different gender ratio (more women) and contains older subjects with a slightly worse cognitive performance. Also, we used a different MR analytic paradigm—ALP, while the previous report used voxel-based morphometry. Nevertheless, the volumetric differences between LLD subjects and comparison subjects confirm the previous report (Bell-McGinty et al, 2002).

For this group of LLD subjects, these findings do not support toxic stress as the predominant mechanism of volumetric changes because the reduced volumes of ROIs were correlated with a shorter duration of the total illness and/or a later age of onset. This pattern is the opposite expected as a result of chronic exposure to high levels of cortisol. In other words, subjects who develop depression *de novo* at an older age seem to be more likely to have an underlying process, either vascular or degenerative or both,

that may trigger the onset of depression through affecting one or several stations on the limbic–cortical–striatal–pallidal–thalamic circuit.

It is important to emphasize that we do not consider these two models as the only two compelling etiopathogenic hypotheses for LLD. Biological pathways of LLD occur in the specific psychosocial context of old age (including increased medical burden and social support network diminution). Our intention was to characterize brain volumetric changes in relation to these two hypotheses regarding the neurobiological substrate of LLD. Also, the toxic stress hypothesis and the dementia prodrome hypothesis are not mutually exclusive, as these two phenomena can operate in parallel and/or in sequence. Our study's design did not allow us to identify the cases with both toxic stress and vascular/neurodegenerative changes.

Table 2 Volumetric Characteristics of the 24 ROIs, Whole Brain and Calcarine Area in the LLD Subjects ($N = 71$) and the Comparison Subjects ($N = 32$)

Region of interest	Comparison group mean (SD)	LLD subjects mean (SD)	P-Value FDR adjusted
Whole brain[a]	515438.44 (61121.12)	518236.03 (63063.89)	0.834
Calcarine area[a]	13170.53 (2480.30)	14289.28 (2317.03)	0.044
Frontal superior area	1.43 (0.32)	1.32 (0.24)	0.082
Frontal superior orbital area	0.59 (0.11)	0.54 (0.09)	0.029
Frontal middle area	2.11 (0.43)	1.95 (0.34)	0.066
Frontal orbital area[b]	2.08 (0.38)	1.89 (0.27)	0.012
Frontal inferior area[c]	1.59 (0.29)	1.47 (0.24)	0.044
Frontal superior medial area	1.06 (0.28)	0.92 (0.18)	0.011
Rectus	0.50 (0.11)	0.45 (0.08)	0.029
Insula	1.22 (0.26)	1.06 (0.18)	0.006
Cingulum area[d]	1.97 (0.34)	1.85 (0.27)	0.066
Cingulum posterior	0.21 (0.06)	0.20 (0.03)	0.417
Hippocampus	0.83 (0.13)	0.75 (0.11)	0.007
Parahippocampal area	0.84 (0.16)	0.78 (0.11)	0.044
Amygdala	0.26 (0.04)	0.22 (0.04)	0.003
Parietal superior area	0.86 (0.20)	0.83 (0.15)	0.477
Parietal inferior area	0.97 (0.22)	0.89 (0.15)	0.044
Precuneus	1.62 (0.29)	1.59 (0.21)	0.557
Caudate	0.93 (0.19)	0.89 (0.18)	0.457
Putamen	1.24 (0.23)	1.11 (0.18)	0.007
Pallidum	0.44 (0.09)	0.40 (0.07)	0.047
Thalamus	1.00 (0.20)	0.88 (0.15)	0.006
Temporal superior area	1.47 (0.31)	1.29 (0.21)	0.006
Temporal pole[e]	1.44 (0.34)	1.30 (0.21)	0.026
Temporal middle area	2.56 (0.45)	2.31 (0.33)	0.011
Temporal inferior area	1.93 (0.37)	1.78 (0.25)	0.029

[a]For whole brain and calcarine area measured in mm^3.
[b]Frontal lateral orbital+frontal inferior orbital+frontal middle orbital.
[c]Frontal inferior operculum+frontal inferior_Tri.
[d]Cingulum anterior+cingulum middle.
[e]Temporal pole superior+temporal pole middle.

Our study has several strengths, including a relatively large group of participants compared with other structural MRI analyses in late life depression, which typically have samples of 20–50 participants (Ballmaier *et al*, 2004; Lavretsky *et al*, 2007). This allowed us to control for age-related structural changes of the gray matter. We used a phenotypically homogenous sample (subjects were all selected by strictly defined inclusion and exclusion criteria), which reduced the variance due to differences in clinical presentations. We used the ALP volumetric method, which is ideal for assessing neuroanatomical correlates of dementia risk in large epidemiological studies, because of its fully automated design. We have recently shown that ALP can detect significantly smaller global and focal gray matter volumes in demented compared to cognitively normal, even in small study groups (Rosano *et al*, 2005). The ALP technique has several advantages: (1) it can analyze the entire brain, utilizing previously published, and validated neuroanatomical boundaries; (2) the fully automated design allows for quality control interventions in extreme cases,

such as massive brain atrophy or focal brain tumors; (3) ALP provides individual volumetric measures of single ROI's, as well as group differences for either single or multiple ROI's.

Our study, however, has some limitations. We did not compare gender-related volumetric changes and there is variability in time between study entry and the MRI scanning. It is highly unlikely that significant changes in the volumes would emerge during the several weeks between enrolment and scanning. Some patients were receiving psychotropic medications at baseline, including benzodiazepines (see Table 1). However, we have no data regarding the chronicity of benzodiazepine use or the compliance with treatment. Moreover, neuroimaging studies failed to report any brain abnormalities in subjects treated long term with benzodiazepines (Busto *et al*, 2000). Also, at this time, we chose not to analyze the laterality of the changes, mainly to protect against Type I Error inflation, but also because most studies do not report lateralized findings (Ballmaier *et al*, 2004) or they suggest an

Table 3 Correlation of ROIs Volumes with Age of Onset and Total Duration of Depressive Illness

ROI	Correlation with age of onset		Correlation with duration of depression	
	Pearson correlation coefficient	P-value	Pearson correlation coefficient	P-value
Frontal superior area	−0.27	0.023	0.16	0.196
Frontal superior orbital area	−0.22	0.060	0.16	0.173
Frontal middle area	−0.24	0.047	0.15	0.201
Frontal orbital area[a]	−0.27	0.022	0.17	0.151
Frontal inferior area[b]	−0.18	0.129	0.06	0.593
Frontal medial superior area	−0.33	0.005	0.19	0.104
Rectus	−0.08	0.519	−0.02	0.868
Insula	−0.16	0.172	0.07	0.588
Cingulum[c]	−0.27	0.023	0.19	0.115
Cingulum Posterior Area	0.12	0.310	−0.11	0.371
Hippocampus	−0.17	0.169	0.07	0.549
Parahippocampal area	−0.31	0.010	0.25	0.038
Amygdala	−0.16	0.189	0.08	0.524
Parietal superior area	−0.12	0.320	0.04	0.763
Parietal inferior area	−0.37	0.001	0.26	0.030
Precuneus	−0.22	0.069	0.16	0.179
caudate	−0.15	0.224	0.23	0.056
Putamen	−0.24	0.044	0.19	0.116
Pallidum	−0.14	0.243	0.10	0.393
Thalamus	−0.23	0.057	0.13	0.293
Temporal superior area	−0.19	0.112	0.01	0.916
Temporal pole[d]	−0.24	0.042	0.09	0.457
Temporal middle area	−0.28	0.018	0.12	0.337
Temporal inferior area	−0.24	0.048	0.08	0.513

[a]Frontal lateral orbital+frontal inferior orbital+frontal middle orbital.
[b]Frontal inferior operculum+frontal inferior_Tri.
[c]Cingulum anterior+cingulum middle.
[d]Temporal pole superior+temporal pole middle.

attenuation of the 'normal' volumetric asymmetry (Kumar et al, 2000). Also, albeit significantly statistic, some of the correlations we report are not very strong—the only regions that have correlations >0.3 with age of onset are frontal superior, parahippocampal, and parietal inferior. Overall, the variable strength of these correlations might suggest rather subtle and uneven changes of volumetric gray matter in LLD. Another possible limitation concerns the reliability of determining the actual age of lifetime onset of major depression in 70- and 80-year-old subjects, who are prone to errors of recall and suggestions. To overcome this we used structured interviews and we corroborated information from family members and past medical record, when available. However, given this limitation, our findings should be regarded with caution.

Further research is needed with large groups of depressed subjects using a lifespan approach to identify characteristics that may confer individual vulnerability to toxic stress, and/or a vascular or degenerative process. Further, research is also needed to obtain more precise associations between clinical presentation, longitudinal evolution of LLD, and mapping of the specific volumetric changes in different areas of the brain.

CONFLICT OF INTEREST

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