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Modeling the brain morphology distribution in the general aging population

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ABSTRACT

Both normal aging and neurodegenerative diseases such as Alzheimer's disease cause morphological changes of the brain. To better distinguish between normal and abnormal cases, it is necessary to model changes in brain morphology owing to normal aging. To this end, we developed a method for analyzing and visualizing these changes for the entire brain morphology distribution in the general aging population. The method is applied to 1000 subjects from a large population imaging study in the elderly, from which 900 were used to train the model and 100 were used for testing. The results of the 100 test subjects show that the model generalizes to subjects outside the model population. Smooth percentile curves showing the brain morphology changes as a function of age and spatiotemporal atlases derived from the model population are publicly available via an interactive web application at `agingbrain.bigr.nl`.

Keywords: statistical modeling, non-rigid groupwise registration, partial least squares regression, spatiotemporal atlas, LMS method

1. INTRODUCTION

Both normal aging and neurodegenerative diseases such as Alzheimer's disease cause morphological changes of the brain. To better distinguish between normal and abnormal brain morphology, it is necessary to model changes in brain morphology owing to normal aging. These changes can be quantified with magnetic resonance (MR) imaging. In this paper we propose a method to analyze the morphological brain changes in the general aging population.

Previously, methods for estimating growth models and spatiotemporal atlases have been proposed.[1–5] Davis *et al.* proposed a kernel regression on image dissimilarities to estimate a brain image representative for each age.[1] Niethammer *et al.* proposed a generative model using geodesic regression, in which subject-specific trajectories can be estimated from a set of initial momenta.[2] Both Serag *et al.* and Dittrich *et al.* proposed a method to build a spatiotemporal atlas for neonatal and fetal brain development respectively, using kernel based local averaging.[3,4] These methods estimate how the mean morphology of the population changes with age but do not estimate the entire distribution of the morphology in the population. Durrlemann *et al.* proposed a framework for spatiotemporal analysis of longitudinal imaging data, estimating both the mean and variance of the changes in brain morphology over time across the population.[5]

We propose a method for modeling the brain morphology distribution in the general aging population. With this method one is able to:

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1. visualize the distribution of the brain morphology in the population as a function of age;
2. compare individual brain scans with an atlas at the same age, and examine to which extent these individuals deviate from the healthy population.

Figure 1 shows an example of how the brain morphology of an individual is compared to the morphology distribution of the population in our framework. In contrast to Durrleman *et al.*, the proposed method does not require longitudinal data.[5] A novel groupwise registration method is used to register all images to a template space. As the resulting transformations have many parameters, we use partial least squares regression (PLSR) to obtain low-dimensional scores that represent the high-dimensional deformation. Singh *et al.* also used PLSR to relate anatomical shape changes to a covariate, but they mainly focus on analyzing the regression coefficient,[6] whereas we are mainly interested in the resulting scores. Furthermore, we use Cole's LMS method[7] for regression of percentile curves on the obtained scores to estimate smooth deformation curves modeling the morphology distribution. The LMS method estimates a median, coefficient of variation and the skewness of the distribution at each age. To visualize the percentiles as actual deformations, we create spatiotemporal atlases.

We evaluate the method using data of healthy individuals, acquired in the Rotterdam Scan Study (RSS). The RSS is a local prospective large population-based cohort study, in which multi-spectral MR imaging data of over 5000 individuals are collected at multiple time points.[8] We apply our method to a subset of 1000 T1-weighted (T1w) scans, uniformly distributed over an age range of 46 - 92 years.

Both the percentile curves and the spatiotemporal atlases can be used for the two applications mentioned above. A publicly available interactive web application was made and can be viewed at `agingbrain.bigr.nl`.

2. METHODS

In our method, brain shape is described by the deformation from a population template space. The deformations from template space are estimated with a groupwise image registration method. The groupwise registration method is not biased to any of the images that are used in the analysis. The computed non-rigid deformations consist of many parameters, i.e. are high-dimensional. To reduce this dimension, we use partial least squares regression (PLSR), which uses both the deformation parameters and their corresponding ages to find main modes

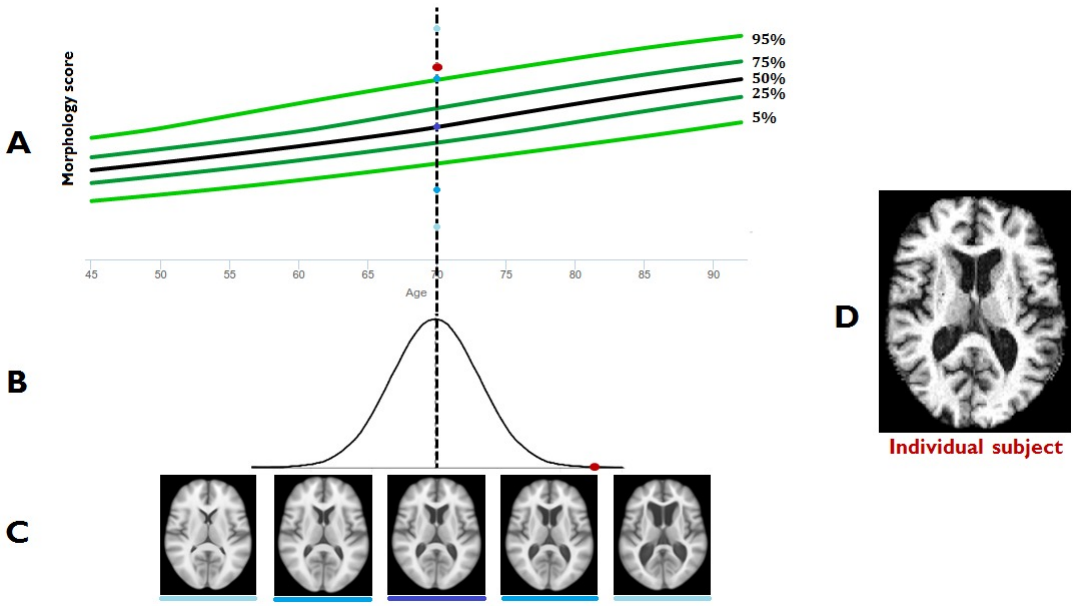


Figure 1: Illustration of the proposed framework, showing how brain morphology of an individual is compared to the morphology distribution of the population. Panel A shows how the morphology distribution of the entire population changes as a function of age. Panel B shows the morphology distribution at the specific age of 70 years. Panel C represents the distribution of panel B graphically. The deformation associated with the morphology scores indicated by the colored dots in the graph of panel A are applied to an average brain image. Panel D shows an individual subject at the age of 70 years. This individual is indicated with a red dot in the graphs of panel A and B. Please note that this individual is similar in morphology to the fourth image in panel C and its morphology score lies close to the score of the fourth image in panel C (best seen in color).

of deformation that explain the variability in age. The sections below describe all steps of the method in more detail. Figure 2 shows a flowchart of the method.

2.1 Pre-processing

The T1w scans were non-uniformity corrected using the N3 algorithm.[9] We performed multi-atlas brain extraction using the method described in Bron *et al.*,[10] with a set of 30 atlases.[11,12] The extracted atlas masks were transformed to subject space and the atlas labels were fused, resulting in a brain mask for each subject.

As an initialization, we registered all images to MNI space with an affine transformation. MNI space is a commonly used space for brain imaging analysis.[13] An affine transformation was used to decrease variation in brain size between the subjects. The affine transformation is obtained by performing a registration of the brain mask of each subject to the MNI brain mask.

2.2 Non-rigid groupwise image registration

Subsequently all images are non-rigidly registered to a common template space, using a groupwise registration approach.[14] This method was originally proposed for intra-subject registration of MRI images with different contrast, and in this work we investigate if the method is applicable to inter-subject registration as well. Let M_n be the image of subject $n \in [1, N]$ of which the transformation is parametrized by a vector $\boldsymbol{x}_n \in \mathbb{R}^P$ with P the number of transform parameters. To model the transformation from the template space to each subject we used cubic B-splines.[15] The groupwise approach assumes that, when images are registered, the intensities can be mapped to a low-dimensional ($L < N$) subspace. In this specific case, the registered images are assumed to have equal intensities, apart from a scaling factor. Therefore, the dimension of this subspace equals one: $L = 1$. The method of Huizinga *et al.*[14] with $L = 1$ could be considered as an extension of normalized cross-correlation from pairwise ($N = 2$) to groupwise ($N > 2$) settings. The images M_n for all n were registered simultaneously to a common template space, by maximizing (with respect to $\boldsymbol{x}_n$) the variance explained by a single principal component in the N-dimensional space. To ensure that the template space is located in the geometrical center of the population the constraint $\sum_n \boldsymbol{x}_n = \mathbf{0}$ was enforced during optimization.

2.3 Partial least squares regression

A statistical model of brain morphology is built by approximating the transform parameter vectors $\boldsymbol{x}_n \approx \boldsymbol{W}\boldsymbol{s}_n$, where $\mathbf{W} = [\boldsymbol{w}^1, \boldsymbol{w}^2, \ldots, \boldsymbol{w}^\gamma]$ are γ deformation modes that have the highest covariance with age and $\boldsymbol{s}_n = [s_n^1, s_n^2, \ldots, s_n^\gamma]^{\mathrm{T}}$ is the vector with scores for these modes of subject n. The loadings $\boldsymbol{W}$ and the scores $\boldsymbol{s}$ are determined with partial least squares regression (PLSR). Note that each $\boldsymbol{x}_n$ contains $P \gg N \geq \gamma$ transform parameters. With PLSR we reduced the dimension of the transform parameter space and obtained a γ-dimensional

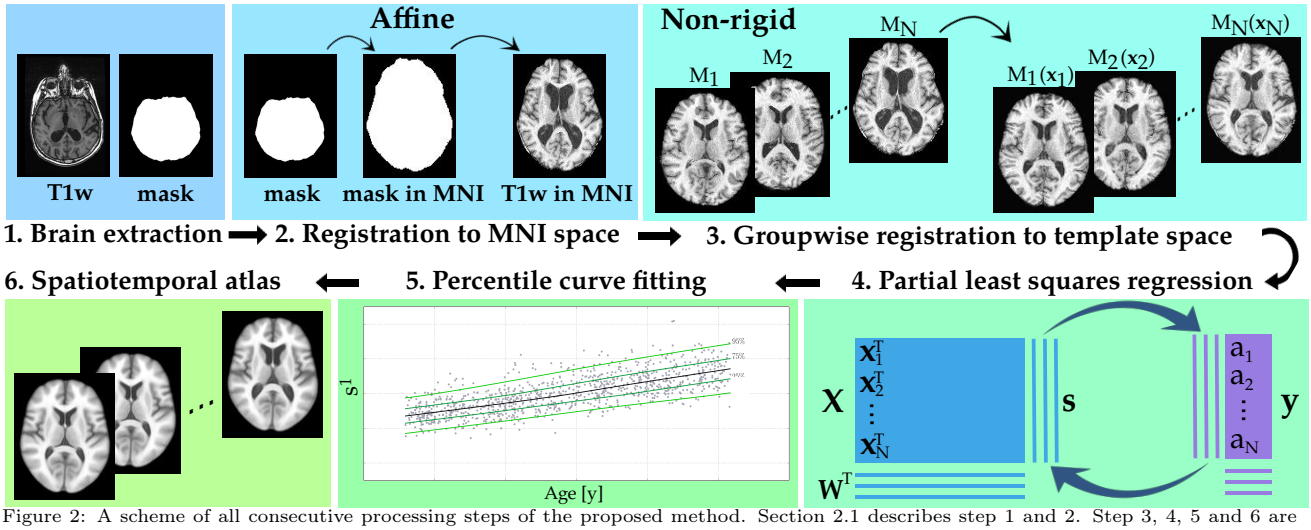


Figure 2: A scheme of all consecutive processing steps of the proposed method. Section 2.1 describes step 1 and 2. Step 3, 4, 5 and 6 are explained in Sections 2.2, 2.3, 2.4 and 2.5, respectively.

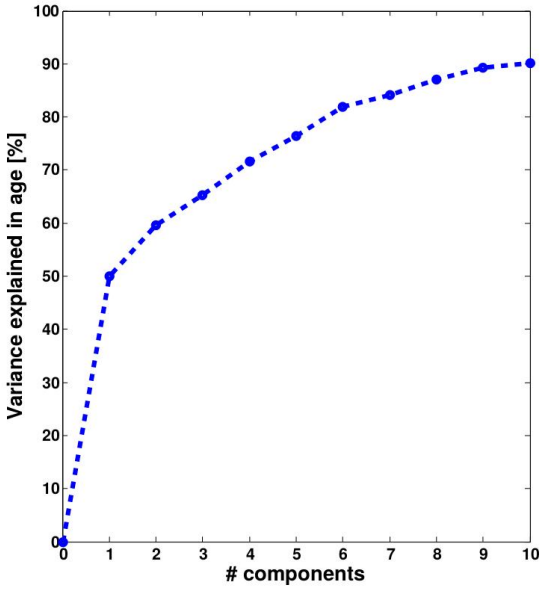


Figure 3: The cumulative percentage of explained variance in age over the population, as function of the number of PLS components.

score-vector $\boldsymbol{s}$. The number of components, γ, is a trade-off between the ability of the model to explain the observed deformation fields and over-fitting. The selected number of components is determined by inspecting the cumulated variance explained in the covariate age.

2.4 Percentile curve fitting

A population aging brain morphology model should describe the mean morphology as well as variability, and changes of mean and variability as functions of age. Percentile curves are an effective way to represent a changing distribution as a function of age. We estimated percentile curves for each PLSR score and hence obtained estimates of brain morphology trajectories for each percentile of the population.

The LMS method[7] estimates the skewness of a normal distribution (L) expressed by the power of the Yeo-Johnson transformation,[16] median (M) and coefficient of variation (S) for the appropriate score at each age. These three parameters completely describe the measurement's distribution over the age range. The complexity of the fitted curves is influenced by the degrees of freedom δ, a user-defined parameter. For the percentile curve fitting we employed the R-library VGAM.[17] Confidence intervals for the percentile curves are estimated by bootstrapping the PLSR scores.

2.5 Atlas generation

We visualized the deformations represented by each loading $\boldsymbol{w}^j$, $j \in [1, \gamma]$, as a function of age using the smooth percentile curves. Let $s^j(a,p)$ be the $p^{\text{th}}\%$ percentile curve at age a of loading j. If $s^j(a,p)$ is used to approximate $\boldsymbol{x}_n$, instead of the actual scores s_n^j, one obtains a smooth transformation as a function of age:

$$\tilde{\boldsymbol{x}}^j(a,p) = \boldsymbol{w}^j s^j(a,p). \tag{1}$$

The transform parameters $\tilde{\boldsymbol{x}}^j(a,p)$ can be applied to the mean template image to visualize the morphology changes captured by PLSR loading $\boldsymbol{w}^j$.

3. EXPERIMENTS AND RESULTS

We performed a proof-of-concept study on 1000 T1w brain scans from the Rotterdam Scan Study.[8] The ages of these subjects are uniformly distributed over a range of 46 - 92 years. They were registered in a groupwise fashion with the method explained in Section 2.2. After visual inspection two scans were removed after registration, but before proceding with the statistical analysis, due to brain extraction failure or extreme imaging artifacts. For

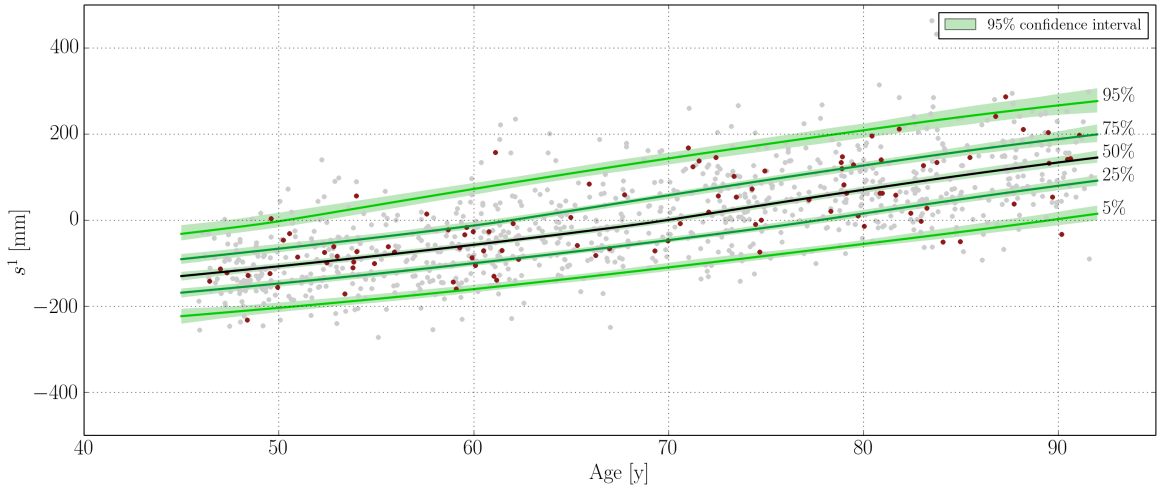
the groupwise registration we used a multi-resolution strategy with four resolutions in which the control point spacing of the B-spline transformation model is halved with each resolution step, until a final spacing of 10 mm was reached. The registration resulted in 1000 transformations of which 900 randomly selected transformations were used in the PLSR to model the population. To evaluate the generalizability outside the model population the remaining 100 scores were calculated by projecting the 100 transform parameter vectors on the PLSR loadings $\mathbf{W}$.

The plots in Figure 3 show that the explained variance in age only slightly increases after adding more than one component, indicating that the first main deformation mode $\boldsymbol{w}^1$ describes most of the variance due to age and adding more components adds little information to the age-related deformation.

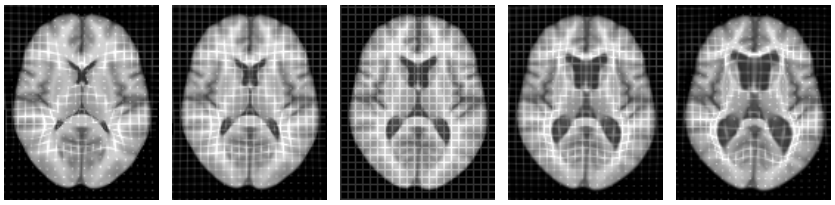
Figure 4(a) shows the 900 scores s_n^1 for $n \in [1, 900]$, the 100 scores s_i^1 of the test subjects for $i \in [1, 100]$ and the percentile curves $s^1(a, p)$ for $p \in [5, 25, 50, 75, 95]\%$. Figures 4(b) - 4(e) show the loading $\boldsymbol{w}^1$. $\boldsymbol{w}^1$ clearly shows an increase in ventricle size for increasing s^1. This indicates that the deformation causing an increase in ventricle size is the deformation that is most correlated with age. The scores of the 100 test subjects map onto the distribution of the model population. This suggests that this method can be used to compare individual brain morphology to that of the population. Figure 5(a) shows the 900 scores s_n^2 for $n \in [1, 900]$, the 100 scores s_i^2 of the test subjects for $i \in [1, 100]$ and the percentile curves $s^2(a, p)$ for $p \in [5, 25, 50, 75, 95]\%$. Figures 5(b) - 5(e) show the loading $\boldsymbol{w}^2$. $\boldsymbol{w}^2$ is best viewed saggitally. Figure 5 shows that the variation of $\boldsymbol{w}^2$ with age is small in comparison to the variance within the population.

4. DISCUSSION AND CONCLUSION

We proposed a method for estimating a brain morphology distribution from a cross-sectional population. Since longitudinal data is often not available this is an advantage of the proposed method. However, a limitation of cross-sectional analysis over such an age span is that it contains brain scans from multiple generations. Brains

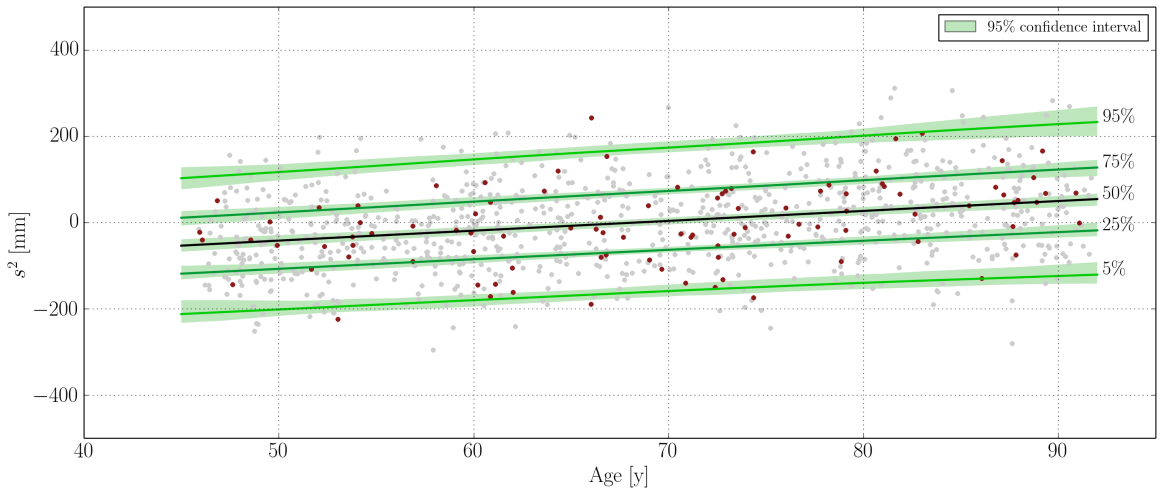


(a) scores s and fitted curves of $\boldsymbol{w}^1$

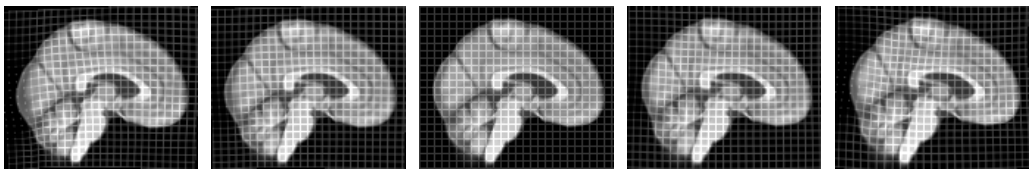


(b) s = -300 (c) s = -150 (d) s = 0 (e) s = 150 (f) s = 300

Figure 4: (a) The scores of the 900 training subjects as light dots, the scores of test subjects as dark dots, and the fitted percentile curves of 5%, 25%, 50%, 75% and 95% for $\boldsymbol{w}^1$. (b)-(f) $\boldsymbol{w}^1$ applied to the mean of all images in the template space, for scores -300, -150, 0, 150 and 300 mm.



(a) scores s and fitted curves of $\boldsymbol{w}^1$



(b) s = -300 (c) s = -150 (d) $s = 0$ (e) $s = 150$ (f) $s = 300$

Figure 5: (a) The scores of the 900 training subjects as light dots, the scores of test subjects as dark dots, and the fitted percentile curves of 5%, 25%, 50%, 75% and 95% for $\boldsymbol{w}^2$. (b)-(f) $\boldsymbol{w}^2$ applied to the mean of all images in the template space, for scores -300, -150, 0, 150 and 300 mm.

of different generations may age at different rates, due to a difference in prosperity when these generations lived.

Several limitations of the current version of this method should be mentioned; Firstly, due to the affine registration as an initialization, the age-related effect of global brain shrinkage is removed, however, by using a different initial transformation model or by extracting the scaling and shear components of the initial transformation to MNI space, this can be solved. Secondly, the method is purely deformation-based and it is likely that the B-spline transformation model cannot capture all possible morphology changes. Possibly the model can be extended with non-deformation-based quantitative imaging biomarkers, such as tissue- and region volumes, diffusion-, and perfusion-based measures. Finally, besides aging, other factors cause the brain morphology to change, which is currently not taken into account in the model. Extending the number of covariates could remedy this.

The brain morphology of a new individual, which was not part of the groupwise registration, can be compared to the morphology of the population by computing the PLSR score of this individual subject. To achieve this an unbiased transformation from the atlas to the individual subject is necessary. A registration method to obtain this transformation will be part of future work.

To conclude, we developed a new method for analyzing and visualizing the changes of the brain morphology distribution in the general aging population. We analyzed the morphology using deformations obtained with image registration of a cross-section of the population. Besides a distribution plot of brain scores we visualize the morphology by creating spatiotemporal atlases. Both the plot and the atlases can be used to compare an individual brain scan with the population. The spatiotemporal atlases as well as the percentile curves are made publicly available via an interactive web application at `agingbrain.bigr.nl`.

5. ACKNOWLEDGEMENTS

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