GROUP LEVEL COMPARISON OF NORMALIZATION TEMPLATES IN CHILDREN'S FMRI STUDY

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Purpose: Spatial normalization is essential for most functional MRI studies[1]. Individual brain is spatially normalized to a standard coordinate space prior to voxel-based statistics[2]. However, such a transformation could introduce unexpected registration error in practice and increase individual variations[3]. The registration to a template is more difficult for brains of specific populations such as children, senior adults and patients. Optimization normalization methods and templates have been proposed. In this study, we adopted three different templates for spatial normalization in a children's study. The templates include a children's template (CT) [4], an average template (AT) generated by SPM with our study group's data and the widely used western adult MNI template (MNI). Our hypothesis is the individual difference will be smaller when a proper template is used, and then the statistical power will be increased as a result. We compared the functional activation difference between two children's groups, in conditions of the three templates for spatial normalization. Our result supports the hypothesis, and shows decreased individual differences when CT was used for registration. We also found scaling parameter from linear spatial transformation could be an important factor of individual differences.

Method: Twenty-nine healthy children (8.01±0.59 years) participated in this study, and sixteen of them were trained for mental abacus calculation (MA). The control group (CN) had no experience of this training at all. MR images were scanned on a Philips Achieva 1.5T MRI machine. The anatomical images were acquired using a 3D-FFE sequence, 150 slices in sagittal plane (TR/TE = 25/4.6ms, flip angle 15o, FOV = 256×256mm, matrix=256×256). All subjects also underwent a blocked design working-memory task scan. The functional images were collected by a single-shot EPI sequence with following parameters: TR/TE=2000/50ms, slice thickness 5mm, flip angle=90o, FOV=230×230mm, matrix=64×63.

Imaging processing was performed using SPM8 on Matlab platform. Data pre-processing included realign, spatial normalization and spatial smooth. During normalization, transformation matrix was computed between the individual's T1-weighted image and templates, and applied to EPI images. As mentioned above, the three different templates (CT/AT/MNI) were utilized respectively. In order to generate an AT, we first randomly picked a subject's image as a target, and all subjects' images were registered to the target. These registered images were then averaged and generated an average image, which was aligned to the MNI coordinate space and utilized as an AT. The rotation, scaling and shearing parameter matrix of linear transformation were produced during spatial normalization. For each transformation matrix, its singular value was computed. The sum square of three singular values was treated as a synthesized index of normalization scaling parameters. Big difference between individual brain and template in shape or size usually resulted in a large scaling parameter as defined.

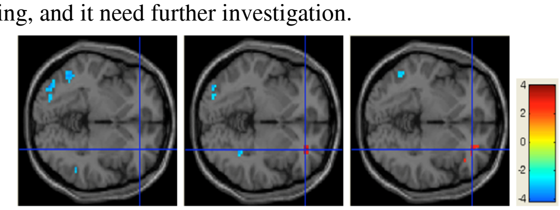
RESULTS: Group-level statistics shows significant differences between the children with and without training. However, activation difference is found not consistent across the usage of three different templates in the right frontal inferior orbital region (rFIO) (Fig. 1). This group difference could not be detected when MNI template was used for spatial normalization. Furthermore, scaling parameters of normalization from native space to each template are also compared. It is found significant differences between any pair of templates (P<0.001), but no difference between the two groups of children (Fig 2). Thereafter, these scaling parameters were used as individual index to simply characterize registration difference. With inclusion of them as covariates during group student's t-test, between-group difference in rFIO was detectable in all the three templates case (Fig.3).

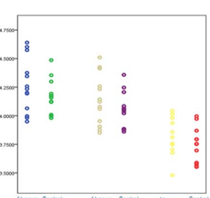
Furthermore, the averaged BOLD contrast within rFIO is found negatively correlated with behavior response time across subjects. This correlation is also different among the three normalization processes, CT (P=0.019) and AT (P=0.023) reaches significance of 0.05, but only the MNI (P=0.192) case is not. No significant correlation is found in the same region for control group using any kind of template. After corrected with individual scaling parameters, these negative correlations all reaches significance level: P=0.016 for CT, P=0.041 for AT and P=0.017 for MNI.

DISCUSSION: The affine transformation during normalization is usually different across subjects due to brain size and shape variation. An imperfect normalization process thus would cause unexpected individual variability. Our results clearly show the importance of a proper brain template. Since our children subjects are from one city of China, their developing brains in anatomy are different from western brain samples used for MNI template. Therefore, group difference are more robustly detected with CT and AT for normalization. Furthermore, result in figure 3 shows the defined scaling parameters could be good index of transformation errors, and can be used as covariates for across-subject correction.

BOLD signal in frontal orbital region is usually thought to be sensitive to artifacts in functional studies, and we also found BOLD signal in a sub-region of rFIO is quite vulnerable to normalization strategy in this study. However, the negative correlation between activation size and behavior performance across subjects in trained group indicates that importance of the function in the region of rFIO. Thereafter, the activation and group differences in this region shouldn't be simply artifacts in this study.

CONCLUSION: Normalization to a default template, such as MNI in SPM, is a common process for many group studies. However, we have shown such a not optimized procedure could introduce individual variability related with registration error, and cause losing detection power in some brain region, such as the frontal orbital area. A better-matched brain template or an easier obtained group-averaged template may improve the result, and the usage of transformation parameters as individual indices could also help to some extend as we shown. Finally, the negative correlation between brain activity in rFIO and behavior performance in the MA trained group indicates an importance role of frontal orbital region during mental abacus training, and it need further investigation.





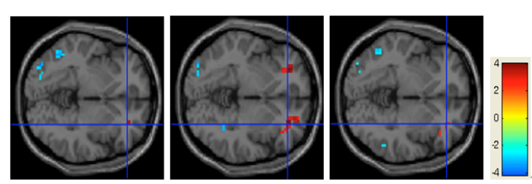


Fig. 1 (Left), Group difference in right FIO region (labeled) is inconsistent across the usages of three templates (P<0.05, alphasim corrected).

Fig. 2 (Middle), Scaling parameters were significantly different from each pair of brain templates (P<0.001).

Fig. 3 (Right), Group difference in right FIO region is consistently detected in all three conditions with inclusion of the scaling parameters as covariates (P<0.05, alphasim corrected).

REFERENCES: **[1].** Friston KJ et al., Hum Brain Mapp 1995;3:165–89; **[2].** Friston KJ et al., NeuroImage 1999;10:385–96. **[3].** Brett M, et al., Nat Rev Neurosci 2002;3:243–9. **[4].** Luo YS et al.,. Unpublished.