Quantitative and local mouse brain morphometry in longitudinal MRI studies

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Introduction Brain morphometry is defined as studying the variations and changes of brain shape, which is key step in monitoring diseases. Brain morphometry is often performed by group-wise comparison between populations of diseased subjects and healthy controls. In earlier work, we presented the Moore-Rayleigh statistical test to quantify local shape differences between groups of transgenic mice[1]. In this work we show that this nonparametric test can be applied to quantify local shape changes over time in a longitudinal study of a single group of mice.

Methods One group of male C57BL/6J mice (n=10) was exposed to stress by administering the hormone corticosterone for 2 weeks. Brain T2 MR scans (Bruker BioSpin 9.4T) were acquired at three different time points: baseline (7 days before corticosterone exposure), exposure (after 2 weeks exposure to corticosterone) and recovery (7 days after 2 week exposure has ended). The MRI scans were all normalized and an average was created from the baseline scans. The individual scans from baseline, exposure and recovery were registered by nonlinear registration to the baseline average, resulting in three groups of deformation fields (n=10 per group) indicating the local changes in the brain (direction and magnitude) between two time points. In this study, the exposure and recovery time point are both compared to the baseline time point. The 3D Moore-Rayleigh test [2] is applied separately for both time point comparisons: First, for each voxel the difference of the deformation vectors of the two time points to be compared is taken, resulting in set of 3D real-valued vectors $X=(X_1,\ldots,X_n)$. Next, these vectors are scaled by the rank of their lengths, where X(N) is the longest vector: The summation of the ranked vectors is considered a Rayleigh random flight with increasing steps (eq 1). The probability distribution function of R_N can be determined by (eq 2) and be evaluated by way of a combinatorial expansion[2], resulting in a *p*-value per voxel.

$$R_N = \sum_{n=1}^{N} \frac{nX_{(n)}}{\left\|X_{(n)}\right\|} \qquad \text{(Eq 1)}$$

$$p(R_N = r) = \frac{2r}{\pi} \int_0^{\infty} t \frac{\sin \frac{rt}{N\sqrt{N}}}{r} \prod_{n=1}^{N} \frac{\sin nt}{nt} dt \qquad \text{(Eq 2)}$$

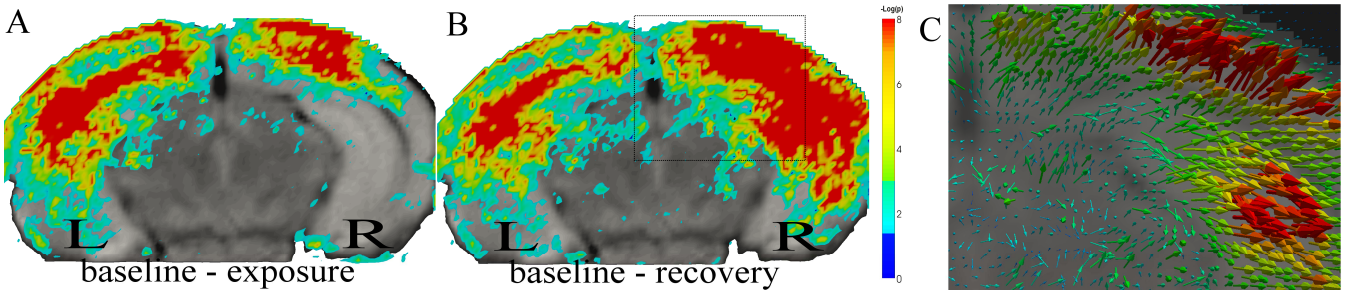

Figure 1. The significant differences between the baseline and respectively exposure (A) and recovery (B) as given by the Moore-Rayleigh test. Red shows the areas which remain significant after Bonferroni correction. The black square shows the location of (C), a part of the average deformation field created from recovery scans.

Results The results of the Moore-Rayleigh test show that corticosterone effects the hippocampal areas (figure 1A and 1B). This is confirmed by manual delineations of the hippocampus (figure 2), which shows a decrease in hippocampal volume after 2 weeks of stress and a recovery of the volume afterwards. A t-test shows only a significant difference ($p<0.05$) for the right hippocampus in the baseline-recovery comparison. The MR test confirms this effect: A large part of the right hippocampus is found significantly different from the baseline (figure 1B). But, the Moore-Rayleigh test also shows small local hippocampal areas of significant differences at the comparison of the baseline to exposure (figure 1A), which are too small to give a significant result in the volumetric measurements. Information whether these local differences are due to a decrease or an increase of hippocampal volume can be retrieved from the original deformation fields (figure 1C): Each arrow indicates how a voxel in the recovery scan needs to be warped to fit the baseline scan.

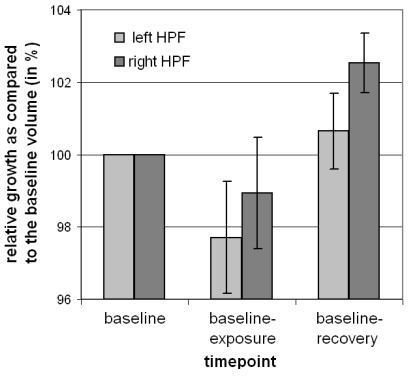

Figure 2. The relative growth of the hippocampus indicated as percentage of the volume at baseline (average and standard error).

Conclusion The Moore-Rayleigh test is a nonparametric test that can be used in longitudinal studies to detect significant different areas, which are still significant under Bonferroni correction without computational expensive algorithms like permutation tests.

References

1. Scheenstra AE et al. Inf Process Med Imaging. 2009;21:564-75.
2. M. Muskulus et al, A generalization of the Moore-Rayleigh test for testing symmetry of vector data and two-sample problems. Technical Report, MI-2009-05, Mathematical Institute, Leiden University, The Netherlands.