The similarity of the brain in healthy monozygotic twins: a voxel based analysis of volume, T2 and DTI

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Introduction: The voxel-based (VB) approach has become a popular method for the objective analysis of various parameters such as volume, T2 and DTI parameters. The technique depends on the baseline variability in the control group and hence, any means of reducing this variability is highly desirable. A common approach to achieve this is by matching the control subjects to the patients according to characteristics such as age and gender. However, this has been shown to be largely ineffectual (1). Monozygotic (MZ) twins represent "perfectly" matched pairs sharing not only age and gender but also an identical genetic background. Structural differences between twin pairs are minimized and believed to reflect only environmental factors. Here, we investigate the potential benefits of using MZ twins in VB studies of volume, T2 and DTI parameters.

Methods: *Subjects*: Twins pairs: 23 pairs of healthy MZ twins recruited through the Australian Twin Registry (8 male twins pairs, mean age: 30±5 years). Control pairs: corresponding age- and gender-matched but unrelated pairs slected from our MR database (mean age: 30±5 years).

Imaging: MRI performed on a 3 T GE scanner. T1-weighted structural imaging performed with an inversion-recovery prepared FSPGR sequence (voxel size: 0.5×0.5×2mm). T2 mapping was performed with a CPMG sequence (0.9×0.9×5mm, 8 echoes, TE=29-231ms). DTI was performed using spin echo (SE) EPI with the following parameters: b=1200 s/mm^2, Twins: 56 directions, 1.6×1.6×3mm; Control pairs: 28 directions, 2.5×2.5×2.5mm. The influence of the difference in DTI acquisition parameters is explored below.

Voxel-based analyses: Spatial normalization of the images were performed using the pre-processing steps for volume (VBM (2)), T2 (VBR (3)), and DTI parameters (VBD). Both grey matter (GM) and white matter (WM) segments were analysed for volume changes; preprocessing of fractional anisotropy (FA) and mean diffusivity (MD) images followed an optimized pathway (4). The statistical threshold for voxel-based comparisons was p<0.00005 (uncorrected).

Analysis of intra-pair structural similarity: The spatially normalized images of each pair were subtracted from each other. The structural similarities were then assessed in the following manner:

Global analysis: The variance of the absolute intra-pair difference images was calculated over the twin and control-pair groups and the mean variance obtained over the appropriate global mask (GM mask for GM-VBM, WM mask for WM-VBM and FA-VBD).

Voxel-based focal analysis: The absolute intra-pair difference image was calculated, i.e. $|$(twin-pair difference)-(control-pair difference)$|$. These images were smoothed (10 mm kernel) and compared between corresponding twin and control pairs using a paired t-test. Simple contrasts were used to assess the "difference-of-differences" between the control-pairs and the twins since absolute difference images were used.

Results: Table 1 displays the global measures of variance between the intra-pair difference images. The consistent reduced variance in the twin-pairs in all the analyses reflects a greater degree of global structural similarity. Figure 1 shows the calculated variance maps for the VBD(FA) analysis and a clear reduction of variance is observed in the twin pairs. Figure 2 shows the results of the voxel-based analyses. The absolute difference images were consistently less for twins than for the control-pairs as indicated by the focal areas in the contrast: twin pair > control-pair. The focal differences were largely symmetrical and most widespread for the VBD(MD) analysis. No areas of of increased difference in twins, as compared to controls were observed (opposite contrast) at the chosen statistical threshold. Since the DTI acquisition parameters differed between the two groups, the difference analysis for this case was repeated with the "control-pair" group substituted by randomized pairings of the twins. Five such control groups were thereby obtained. The global variance in these groups was 0.026±0.001 (cf. 0.025 in Table 1 for the true control-pairs) and the spatial distribution of similarity was unchanged to that shown in Fig. 2.

Discussion & Conclusions: Recruitment of twin pairs requires considerable effort and time so the resulting benefits must be fully demonstrated and justified. This study has indicated the potential benefits of using twin pairs for voxel-based analyses of volume, T2 and DTI. Using images that had undergone the typical preprocessing steps of VB analysis, a greater degree of structural similarity was demonstrated among the twin pairs. Many studies have shown that MZ twins have considerable structural similarities when compared to dizygotic twins or unrelated pairs. However, twin brains are not "identical" (5) and inter-twin differences lie on a continuum with some features under tight genetic control and others having a greater potential for environmental influences. VB preprocessing was nevertheless shown in this study to retain a considerable degree of structural similarity and this extends to T2 and DTI parameters. Therefore, twins discordant for diseases associated with abnormalities in these parameters may provide an ideal opportunity to probe the genetic and environmental determinants of the condition.

References: (1) Pell GS et al., ISMRM 2007 (submitted); (2) Ashburner J et al, NI, 11:805 (2000); (3) Pell G.S. et al, NI 21:707 (2004) (4) Pell GS et al., ISMRM 2006, #1062; (5) Bartley AJ et al., Brain 120:257 (1997)

	control	twins	% diff
VBM (GM)	0.114	0.100	-11.9
VBM (WM)	0.076	0.069	-8.5
VBR (T2)	0.425	0.351	-17.4
VBD (FA)	0.025	0.017	-32.7
VBD (MD)	0.081	0.052	-36.1

Table 1 Global measures of the variance of the intra-pair differences between in the control- and twin- pairs. The % difference is also shown ((twin-control)/control).

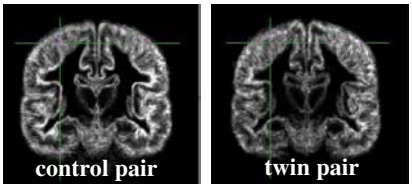

Fig. 1 Variance maps calculated from the intra-pair difference for the control- and twin pairs in the analysis of FA

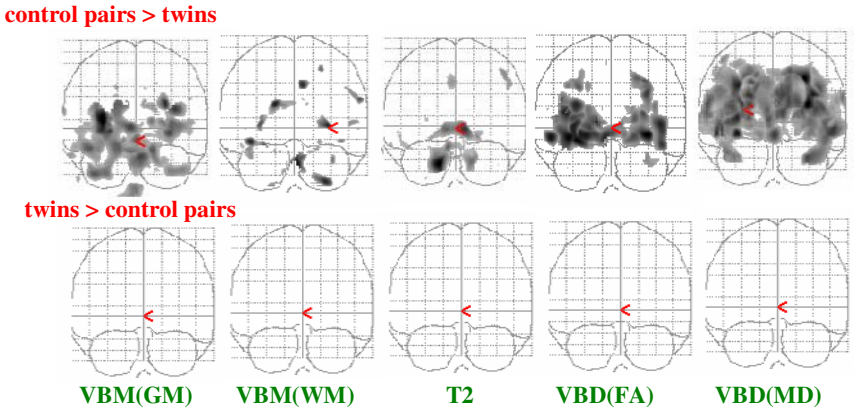

Fig. 2 VB analysis of the degree of similarity between twin and control pairs. The absolute intra-pair difference images are compared using paired t-test analysis (p<0.00005 uncorrected). The control>twin contrast, for example, shows areas in which the twin pairs are more similar than the control pairs. Glass brain results are shown for the analyses of volume, T2 and DTI parameters.