

Testing the sensitivity of Tract-Based Spatial Statistics to simulated treatment effects in preterm neonates

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Background

Preterm infants carry a profound risk of developing a spectrum of major disabilities and deficits in cognition, coordination and behaviour¹ and microstructural alterations in the developing preterm white matter may underlie some of these deficits². Neuroprotective strategies for the preterm infant have been proposed, however it is difficult to evaluate the potential of therapeutic intervention during early development without appropriate biomarkers. Tract-based spatial statistics (TBSS; www.fmrib.ox.ac.uk/fsl/)³ has been shown to provide a powerful biomarker for neonatal neuroprotection in small groups of patients with severe brain injury⁴ and therefore may represent an ideal method for assessing the efficacy of future therapeutic strategies in preterm infants. Here, we simulate global treatment effects, represented by increased FA, across different group sizes to test the sensitivity of TBSS to FA differences in neonates. As proof of concept we compare these simulations to a real 'effect' of increasing age at scan.

Methods

Fractional anisotropy (FA) maps constructed from 3-Tesla, 15 direction DTI acquired from 90 preterm infants at term-equivalent age were used for the study. Datasets were randomly split into 'treated' and 'untreated' groups of increasing size (from 5 to 45 per group) and each FA map was co-registered to a common template using a TBSS pipeline optimized for neonates⁵. For each group size, all 'treated' infants' FA map values were artificially increased voxelwise by between 1 and 20% to simulate a global treatment effect before transformation to the common space. FSL's Randomise (v2.5; www.fmrib.ox.ac.uk/fsl/) was used to perform statistical comparison of 'treated' and 'untreated' FA maps and the number of voxels where a significant difference ($p < 0.05$ corrected) could be detected was calculated as a percentage of the total number of voxels in the TBSS skeleton. As proof of concept the FA maps were split into two groups of 45 according to each infant's postmenstrual age at scan ('old' infants scanned after 41+3 weeks and 'young' infants scanned before 41+3 weeks). The % of voxels where a significant difference could be detected between the two groups was compared to that predicted by the simulated data.

Results

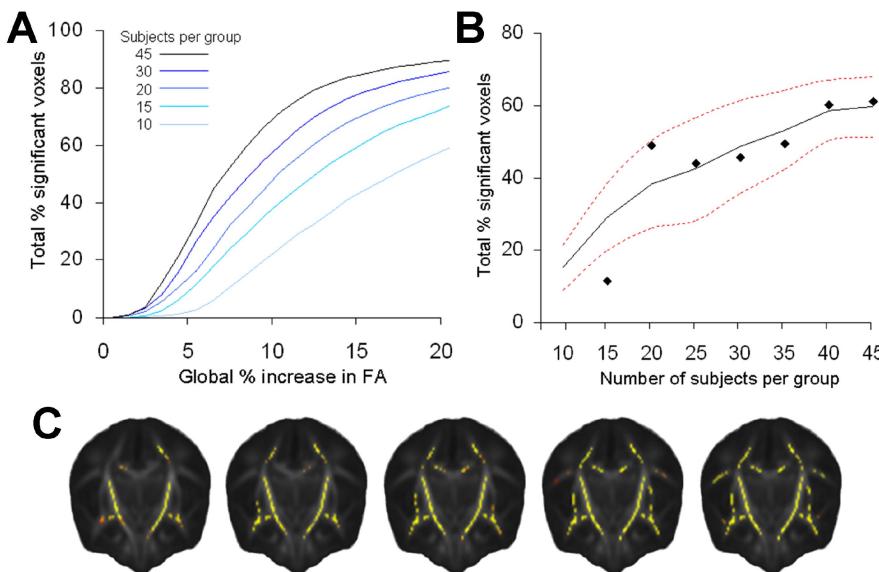


Figure 1: Simulating treatment effects using TBSS

Conclusion

TBSS can readily be used in neonates to detect global differences in FA even in relatively small group sizes. These preliminary data indicate that using TBSS as a biomarker may allow trials of potential neuroprotective strategies to measure outcome earlier in development and with fewer subjects.

References

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3. Smith et al. *Neuroimage* **31**, 1487-1505 (2006).
4. Porter et al. *Pediatr. Res.* **68**, 205-209 (2010).
5. Ball et al. *Neuroimage* **53**, 94-102 (2010).

Figure 1 shows the % of voxels across the TBSS skeleton where significant differences ($p < 0.05$, corrected) could be detected after artificially increasing FA in 'treated' maps by up to 20%. Data from comparisons between group sizes of 10, 15, 20, 30 and 45 are shown in (A). In (C), voxels where a 10% increase in FA was detected in groups sizes of 10 (left), 15, 20, 30 and 45 (right) are shown. Simulated data were compared to the global effect of increasing age at scan in (B). Infants scanned after 41+3 weeks had a mean 8% increase in FA across the whole TBSS skeleton. The line shows the % of voxels expected to detect an 8% increase in FA for each group size (\pm SD in dotted red lines). Each point marks the % voxels where a significant increase was detected between 'old' and 'young' groups of increasing size.