The number of subjects needed to detect a change in white matter microstructure depends on the pathway in question

Sonya Bells[1], C John Evans[1], and Derek K Jones[1]
[1]*School of Psychology, CUBRIC, Cardiff, Wales, United Kingdom*

Introduction:

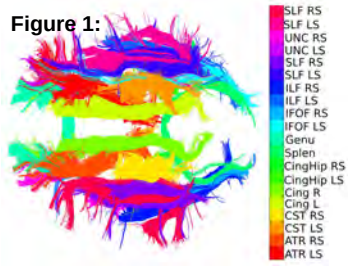
The ability to evaluate differences in white matter (WM) across time plays an important role in noninvasive -MRI research from clinical studies to brain training studies. Whilst these types of studies are important it is also critical to determine the number of subjects needed for statistical power when planning and designing a project. The purpose of this study was to do just that in a number of different WM acquisitions (diffusion weighted, multi-component relaxometry and combined hindered and restricted model of diffusion (CHARMED)) at a single imaging center for a repeated measures design in eighteen of the most common white matter tracts (Figure 1).

Methods:

Five healthy males (mean age= 37.1 ± 4.9 y) underwent a battery of white matter imaging at 3 T (GE HDx scanner). Participants attended five sessions on separate days at least 1 week apart where 3 different white matter MRI measurements were acquired: (1) cardiac-gated diffusion-weighted images (single-shot spin-echo EPI sequence, b-value = 1200 s/mm^2; 60 gradient directions; six non-DW images; 60 axial slices; TR = 20 R-R intervals[1]), (2) multi-component (mc) relaxometry images based on mcDESPOT (SPGRs were: TE/TR = 2.1/4.7 ms, flip angle (α) = 3,4,5,6,7,9,13,18; mcDESPOT-bSSFPs were: TE/TR = 1.6/3.2 ms, α = [10.6,14.1,18.5,23.8,29.1,35.3,45,60][2]) were fit according to the mcDESPOT model[2] to get myelin water fraction (MWF) and T1 and (3) combined hindered and restricted model of diffusion (CHARMED) images (spin-echo EPI sequence, TR/TE=17000/114 ms, Δ/δ= 50/43 ms, 13- noncollinear directions at 8 b-values 937,1875,2812,3750,4687.5,5625,6562.5,7500 s/mm^2)[3] providing information on the restricted compartment (Fr) as a proxy estimate of 'axon density'

Fiber tracking based on damped Richardson-Lucy (dRL) deconvolution extracted the fiber orientation density function (fODF) to reconstruct 18 white matter fasciculi, using a modified version of ExploreDTI[4]. Non-linear registration to DW-images was performed on each metric and sampled at each vertex of reconstructed tracts. For each WM tract, the mean, variance, coefficient of variation (CV) and reliability (intraclass correlation coefficient [ICC]) between subjects were computed and applied to power calculations to determine the number of subjects required to detect a given effect size (or % change).

Figure 1:

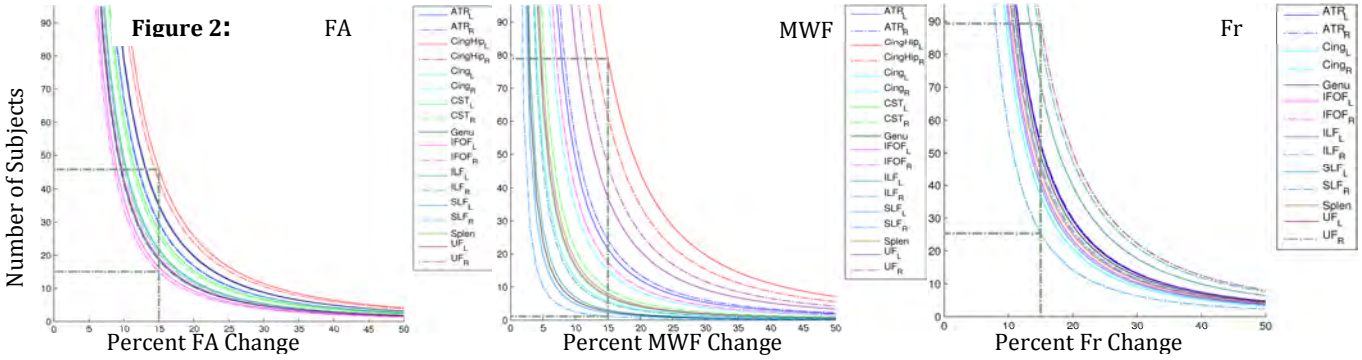


Results & Discussion:

Power calculations based on variation estimates (see table for Genu and Cingulum) were made for the white matter metrics for all 18 tracts. Figure 2 shows the number of subjects required to detect a given effect size in FA, MWF and Fr across all 18 tracts, demonstrating the number of subjects needed to detect a specific percent change in FA, MWF or Fr depends on the tract of interest. For example, to detect a 15% change (indicated by vertical and horizontal dashed lines) in FA about 45 subjects are needed in the parahippocampal cingulum, while only a third of this number (i.e. 15) are needed for uncinate fasciculus (UF). On the other hand to detect the same effect in MWF in the UF, around 40 subjects are needed. These findings have implications for the sensitivity to detect an effect in response to an intervention, or in monitoring disease progression, and equally importantly, the relative cost of running a suitably powered study on different WM systems.

Regions		FA	RD (mm^2/s)	MWF	T1	Fr
Genu	Median	0.48±0.11	(0.71±0.41)x10^{-3}	0.23±0.03	963.88±107.93 ms	0.29± 0.09
	CV_{BS}	25.52	28.03	12.94	13.50	31.45
	ICC [CI]	0.94 [0.80-0.99]	0.90 [0.69-0.98]	0.75 [0.11-0.97]	0.96 [0.87-0.99]	0.96 [0.87-0.96]
Cing	Median	0.61±0.16	(0.71±0.84)x10^{-3}	0.24±0.02	892.85±60.38 ms	0.27± 0.09
	CV_{BS}	22.00	14.90	23.29	17.62	31.15
	ICC [CI]	0.96 [0.88-0.99]	0.95 [0.83-0.99]	0.93 [0.74-0.99]	0.99 [0.97-0.99]	0.75 [0.14-0.97]

Figure 2:



Conclusion: This study demonstrates that the power to detect a change in a metric is not uniform throughout the brain or between metrics and as a consequence, in some underpowered studies, certain pathways are more likely to reveal a change than others. Furthermore, this study provides critical information for the design of future studies to ensure that they are sufficiently powered to detect an effect.

References:[1]Whittall et al. (1997) MRM.37:34;[2]Deoni et. al. (2008)MRM.60:137;[3]De Santis et al. (2012) MRM.70:490 ;[4]Leemans A et al. (2009) Proc. ISMRM 17th Annual Meeting, Honolulu, Hawaii.p.3537.