Gene hunting in DTI: Boosting Power to Detect Genes that Influence Fiber Tracts

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Introduction: Little is known about the impact of single-nucleotide polymorphisms (SNPs) on the white matter of the brain. Localization of SNPs associated with individual differences in white matter integrity [1] and connectivity [2] may shed light on the molecular mechanisms of individual differences in cognition. To study SNP effects, large populations are needed; even so, anisotropy values derived from DTI may be corrupted by local partial-volume effects and inconsistent registration across a population. We set out to alleviate the effect of intra-voxel heterogeneity, fiber mixing and non-homology of registered tracts to better localize genetic variants that influence fiber integrity. We examined factors that affect the power to detect effects of the SNP in the brain-derived neurotrophic factor (BDNF) gene. BDNF plays a key role in axonal growth, neurotransmitter release, and long-term potentiation associated-learning [1,3]. However, the impact of its polymorphism is not yet fully understood.

Methods: High magnetic field (4T) diffusion tensor MR images were acquired from 288 genotyped healthy young adult twins and siblings (mean age: 23.4+/-1.9; 57 MZ pairs, 75 DZ pairs, and 24 non-twin siblings; 183 female). Fractional anisotropy (FA) maps for each individual were elastically registered to a common study-specific high FA template to ensure optimal registration of white matter tracts. The JHU-DTI-MNI atlas [4,5] was also registered to our target for accurate ROI analysis. Most DTI-derived measures, like FA, do not take into account fiber crossings; FA estimates from a single-tensor model can be incorrectly reduced due to fiber mixing and partial volume effects. To suppress this effect, a voxel-wise map of local signal-to-noise (SNR) in the FA value was obtained by calculating the mean FA from 30 (15M, 15F) randomly selected registered subjects at each voxel and its surrounding 26 voxel neighborhood, and dividing by the standard deviation of the FA value in the same voxels. Individual FA maps were then weighted by the template SNR map on a voxel-wise level to incorporate neighboring FA values: $FA^*(x,y,z) = \sqrt{\overline{neigh}(x,y,z)'^* SNR(x,y,z) * \overline{neigh}(x,y,z)}$ where *neigh*(x,y,z) is a vector consisting of the FA values of the voxel of interest and its 26 neighboring voxels. ROI analysis was performed to study the effect of the BDNF (rs6265) polymorphism on the mean FA and FA* values of 20 common tracts. A mixed model regression analysis incorporating the genetic relatedness of the subjects was used for this association [6].

Results: When the population mean FA* value was lower than the mean FA value, fiber crossing or non-homology of anisotropy maps across subjects may be falsely contributing to the population variance, and voxelwise genetic association tests performed in these regions may be unreliable and were therefore not calculated (N/A in the following tables), reducing the number of statistical tests performed. Regions where the mean FA value showed trends towards significance, including the forceps major and the left inferior fronto-occipital fasciculus (IFOF), were re-evaluated with FA*. A higher association of BDNF with the IFOF was found with the SNR-adjusted measure, FA* (**Table 1**), confirming previous studies where the BDNF polymorphism was found to show similar effects [1]. In this region, FA was generally higher in the val/val carriers of the gene (67.7% of the total) versus those with a met66 variant in an allele (32.3%). 4600 permutations of the polymorphism labels were assessed with the mixed model regression; permutation corrected p-values are reported in **Table 1**. Similar analysis was performed with a SNP of the catechol-*O*-methyltransferase (COMT) gene at the rs4680 SNP. (**Table 2**). Although no tracts showed associations significant at the 5% level, there were trend-level associations with the anisotropy level of

the left corticospinal tract; further investigation is needed in a larger population. Inconsistent findings between FA and FA* in the hippocampal cingulum also suggest that care should be taken when drawing conclusions from an ROI based approach, and replication studies are essential.

Conclusions: This study shows the potential value of incorporating *a priori* information on the population signal-to-noise for DTI measures, and provides an alternative to homogeneous filtering approaches that ignore the signal-to-noise of the empirical data. Tractography approaches may also be used, but an ROI method, used with high-dimensional elastic registration, can take into account structural variations in the tracts. These analyses could be also extended to voxelwise analysis, including voxelwise genome-wide association scanning (vGWAS)[7].

References:

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BDNF	Anterior thalamic radiation - L	Anterior thalamic radiation - R	Corticospinal - L	Corticospinal - R	Cingulate gyrus cingulum - L	Cingulate gyrus cingulum - R	Hippocampal cingulum - L	Hippocampal cingulum - R	Forceps Major	Forceps Minor
FA	0.4233	0.3918	0.5416	0.5431	0.4701	0.4264	0.2967	0.2807	0.5673	0.4404
p-value	0.6277	0.7152	0.8369	0.797	0.4978	0.2047	0.5863	0.6779	0.0935	0.4811
FA*	0.5098	0.4598	0.8154	0.7518	0.4225	0.3291	0.1574	0.1415	0.5786	0.4380
p-value	0.3013	0.8912	0.6889	0.8846	N/A	N/A	N/A	N/A	0.076	N/A

	Inferior fronto-occipital fasciculus - L	Inferior fronto-occipital fasciculus - R	Inferior longitudinal fasciculus - L	Inferior longitudinal fasciculus - R	Superior longitudinal fasciculus - L	Superior longitudinal fasciculus - R	Uncinate fasciculus - L	Uncinate fasciculus - R	Temporal SLF - L	Temporal SLF - R
FA	0.4310	0.4033	0.3693	0.4433	0.4219	0.4208	0.3789	0.3712	0.4685	0.4743
p-value	0.0478	0.5165	0.7903	0.3211	0.9314	0.9849	0.1057	0.2499	0.8527	0.7733
FA*	0.4959	0.4749	0.4089	0.5182	0.4740	0.5114	0.3461	0.2819	0.5901	0.6365
p-value	0.0216	0.4309	0.5128	0.1515	0.9634	0.9137	N/A	N/A	0.9979	0.8199

Table 1: Significance of BDNF associations with mean anisotropy values in white matter tracts shown for FA and FA* where FA*≥ FA. P-values shown are corrected after 4600 permutations of the data.

COMT	Anterior thalamic radiation - L	Anterior thalamic radiation - R	Corticospinal - L	Corticospinal - R	Cingulate gyrus cingulum - L	Cingulate gyrus cingulum - R	Hippocampal cingulum - L	Hippocampal cingulum - R	Forceps Major
FA	0.4233	0.3918	0.5416	0.5431	0.4701	0.4264	0.2967	0.2807	0.5673
z-score	0.4879	0.3408	0.2157	0.1959	1.6786	1.9103	0.6420	0.2942	0.3757
FA*	0.5098	0.4598	0.8154	0.7518	0.4225	0.3291	0.1574	0.1415	0.5786
z-score	0.3363	0.1736	0.0726	0.0948	N/A	N/A	N/A	N/A	0.1563
z*-z	-0.1516	-0.1672	-0.1431	-0.1011	N/A	N/A	N/A	N/A	-0.2194

	Inferior fronto-occipital fasciculus - L	Inferior fronto-occipital fasciculus - R	Inferior longitudinal fasciculus - L	Inferior longitudinal fasciculus - R	Superior longitudinal fasciculus - L	Superior longitudinal fasciculus - R	Uncinate fasciculus - L	Uncinate fasciculus - R	Forceps Minor
FA	0.4310	0.4033	0.3693	0.4433	0.4219	0.4208	0.3789	0.3712	0.4404
z-score	0.4237	0.8464	1.2891	0.5089	0.9418	1.4941	0.0532	0.2577	0.2217
FA*	0.4959	0.4749	0.4089	0.5182	0.4740	0.5114	0.3461	0.2819	0.4380
z-score	1.1401	0.5173	0.7546	0.3882	0.7612	0.1719	N/A	N/A	N/A
z*-z	0.7164	-0.3291	-0.5345	-0.1207	-0.1806	-1.3222	N/A	N/A	N/A

Table 2: COMT associations, as z-score differences between FA and FA*, with mean anisotropy values in white matter tracts shown for FA and FA* where FA*≥FA

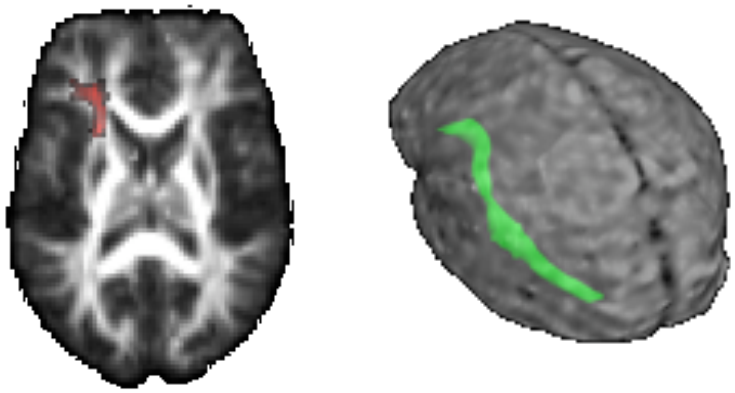

Figure 1: Left inferior fronto-occipital fasciculus tract where carriers of a BDNF met66 allele tend to show a significantly lower FA.