WHITE MATTER CEREBRAL BLOOD FLOW IS INVERSELY CORRELATED WITH STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN THE HUMAN BRAIN

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INTRODUCTION: In recent years, there has been a growing interest to understand functional connectivity among distinctive brain regions (1,2). Some evidence has suggested that such a functional connectivity is supported by structural connections via white matter fiber tracts (3,4). We therefore further hypothesized that functional measures of the white matter, e.g. perfusion, may have a more direct link to gray matter connectivity, compared to simple structural measures. Previous neuroimaging studies have demonstrated the presence of cerebral blood flow (CBF) in the white matter, but have not studied its spatial distribution. With recent advances in Arterial-Spin-Labeling (ASL) methodology, it is now possible to determine white matter CBF with sufficient accuracy (5). In the present study, a quantitative pseudo-continuous ASL (PCASL) MRI was used to obtain maps of absolute CBF. DTI was used to delineate ten major fiber tracts in the brain. The resulting voxel masks served as the regions-of-interest (ROIs) and were applied to the CBF maps to calculate the tract-specific CBF in the white matter. Across fiber tracts, CBF showed a paradoxically inverse correlation with fractional anisotropy (FA) obtained from DTI. Functional connectivity MRI (fcMRI) was performed to allow the assessment of resting-state neural activity in the gray matters connected by each tract. An inverse correlation was again observed between tract-specific CBF and the functional connectivity.

METHODS: *Experiments* were performed on ten healthy subjects (age 25-23 years, 6M/4F) on a 3T scanner (Philips). The imaging protocol consisted of five MR techniques: Quantitative PCASL, DTI, fcMRI, T2-weighted EPI, and T1-weighted anatomic scan. The PCASL protocol was based our previous study (6) with the exception that spin-echo EPI acquisition was used instead of the more widely used gradient-echo so that the EPI distortions in ASL image match that of DTI. The choice of spin-echo would allow for more precise image registration between DTI and ASL, which is critical for the tract-specific CBF estimation. The duration of PCASL was 18 min. DTI used 30 gradient-encoding directions with a b value of 1000 s/mm^2 and a scan duration of 3.5 min. FcMRI used TR/TE/flip angle=1500ms/30ms/60° with a scan duration of 10 min. PCASL, DTI and fcMRI had the same geometric parameters: FOV = 200x200 mm^2, matrix = 80x80, no gap between slices, voxel size = 2.5x2.5 mm^3. T2 EPI was acquired to provide a template to which all other modalities were registered. MPRAGE T1 image was acquired for anatomic reference and for estimation of brain volume.

Data Processing: All images were co-registered to T2 EPI and the following parametric maps were obtained from respective data: CBF, FA, ADC, radial and axial diffusivity. Fiber-tracking was performed on the DTI data and, to avoid potential controversies on the validity of the small fibers, the tract-specific CBF investigation was limited to ten major fiber tracts that have been previously shown to be highly reproducible across raters and across data sets (7): forceps major of the corpus callosum, forceps minor of the corpus callosum, cingulum-in-the-cingulate-cortex, cingulum-to-hippocampus, anterior thalamic radiation, uncinate fasciculus, corticospinal tract, arcuate fasciculus, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus. The masks of the fiber tracts were applied to the aforementioned maps to obtain tract-specific parametric values. To ensure that our ROI included predominantly white matter and to minimize gray matter partial volume effect, two procedures were undertaken. First, only voxels that have white matter probability of >50% were included in the final ROI (the averaged white matter probability in the final tract mask was >90% for all tracts). Second, the resulting spatially averaged CBF value was further divided by a correction factor, $P_{wm}+2.5xP_{gm}$, where the gray/white matter CBF ratio was assumed to be 2.5 (8). Using the fcMRI data, we calculated the cross-correlation coefficient (cc) between gray matter regions at the two ends of the fiber tracts, which were defined by expanding the fiber terminals spherically by three voxels. For statistical analysis, we calculated partial correlations among white matter CBF, FA and fcMRI cc, after factoring out the contributions from white matter probability and a layer index indicating the distance to the cortical surface (to account for confounding effect of arterial transit time which may affect CBF values derived from ASL).

RESULTS and DISCUSSION: *CBF vs. FA:* Fig. 1a shows the locations of the major fiber tracts in a representative subject. Averaged CBF across the ten white matter tracts were 16.1±3.1 ml/100g/min with forceps minor having a lowest CBF (9.7±3.9 ml/100g/min) and cingulum-to-hippocampus having a highest value (25.7±7.8 ml/100g/min). Significant differences in CBF were observed across fiber tracts (omnibus F test, P<0.001), suggesting that CBF across white matter fiber tracts is highly heterogeneous. The differences were not due to variations in white matter probability or distance to cortical surface (P>0.1). Instead, the fiber-specific CBF was found to be highly correlated with FA. As shown in Fig. 1b, an inverse correlation was observed between CBF and FA (partial r=-0.66±0.18, multiple-comparison-corrected P<0.001). CBF was also positively correlated with radial diffusivity (P=0.001) and negatively correlated with axial diffusivity (P=0.003). *CBF vs. fcMRI:* Fig. 2a shows an example of the relative locations of fiber tract and gray matter nodes. Fig. 2b shows a scatter plot between white matter CBF and gray matter fcMRI cc, demonstrating a significant inverse correlation (partial r=-0.52±0.20, multiple-comparison-corrected P<0.001). That is, a fiber tract that has a higher CBF value tends to have a lower cc between the two terminal gray matter regions connected by this tract, and vice versa. Comparing FA and fcMRI cc values, a positive correlation was observed (partial r=0.76±0.09, P<0.001), in agreement with previous reports (4). Fig. 2c shows the scatter plot between FA and cc for the group-averaged data.

In summary, our results revealed a significant relationship between white matter CBF and the degree of gray matter functional connectivity. These findings support the notion that white matter connections are important for gray matter activity coherence. We also found a significant correlation between anatomic (i.e. FA) and functional (i.e. CBF) measures of white matter fiber tract. The signs of the correlations were, however, negative. Therefore, the mechanism underlying these correlations requires further investigation. We propose that the findings may be due to one or more of the following mechanisms 1) white matter CBF may be inversely related to axonal density (positively related to axonal diameter of the tract); 2) white matter CBF may reflect the efficiency of action potential propagation; 3) white matter CBF may be affected by the mechanical tightness of the fiber bundle.

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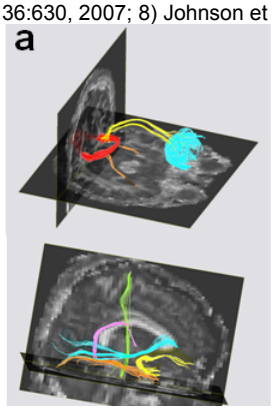

Fig. 1: (a) Illustration of major white mater fiber tracts in a representative subject. (b) Scatter plot between tract-specific CBF and FA, showing a significant correlation between these two parameters.

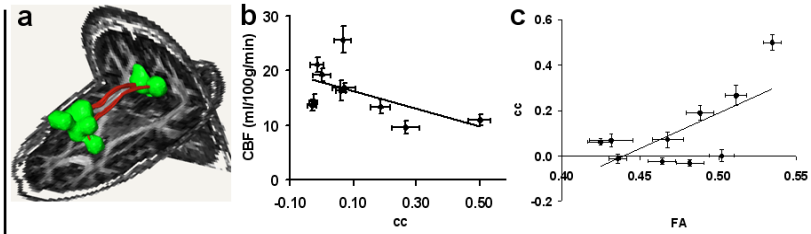

Fig. 2: Relationship between gray matter connectivity and white matter functional and structural parameters. (a) Illustration of the relative locations of gray matter nodes and white matter fiber tracts. An example for cingulum-in-the-cingulate-cortex is shown. The gray matter nodes were defined by expanding the fiber terminals by 3 voxels spherically. (b) Scatter plot between tract-specific CBF and fcMRI cc values between gray matter nodes. (c) Scatter plot between tract-specific FA and fcMRI cc values.