Direct coupling of brain structural and functional information within white matter: a unified framework

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Abstract

One of the ultimate goals of neuroscience is to decipher the elusive relationship between brain structure and function. However, current research on brain structure-function coupling remains incomplete due to the lack of depiction of this relationship within white matter. Additionally, macro-scale network-based analyses lack effective, direct approaches to bridge two distinct data modalities, as the structural and functional characteristics were separately obtained from white matter and gray matter. Here, we propose an innovative, unified framework where structure and function are directly and hierarchically integrated. By applying it to the HCP U100data, a reliable and heterogeneous pattern of structure-function coupling was observed in the deep white matter, characterized by higher coupling strength within commissural tracts, such as the corpus callosum, and associational tracts, including the cingulum and superior longitudinal fasciculus. Four white matter functional networks exhibited strong and robust structure-function coupling. Moreover, white matter primarily exhibits decoupling characteristics as age increases and a significant association between white matter structure-function coupling and behavioral measures has been established. This work represents the first quantification of structure-function coupling within the white matter, revealing its considerable repeatability and significant physiological relevance. The findings advance our understanding of the relationship between brain anatomical structure and physiology, offering a novel perspective for future investigations.

Introduction

Integrative pattern of anatomy and physiology is crucial for understanding brain operational mechanisms. Precisely how the anatomical structure of the brain shape and constrains a repertoire of complex functions remains incompletely understood. Neuroimaging studies have been keen to elucidate this relation in humans. Currently, macroscale human brain networks serve as the primary approach for investigating brain structure-function coupling (SFC) and have achieved remarkable milestones. From simple correlations to harmonic analysis and modelling, various methods and findings have been employed to uncover the subtle relationships between anatomical structural connectome (SC) and physiological functional connectome (FC). To some degree, alignments exist between these two types of network connectivity. Nevertheless, studying structure-function coupling from a network perspective (node-edge) is indirect, overlooking the procedural nature of interregional functional information transmission.

Biologically, the primary components of gray matter are neuronal somas, while white matter is mainly composed of axons. White matter anatomy scaffolds signal conduction within axons. The procedural nature of structure-function coupling involves two main steps: 1. ‘Gray-white matter physiological connection’: physiological activity initiated by somas in gray matter modulates the physiological processes occurring within white matter. 2. ‘Structural-functional coupling within white matter’: anatomic wiring of white matter sculpts axonal signal propagation, thereby regulating the intrinsic functional synchronization between gray matter regions. A two-step analysis of structure-function coupling has long been hindered by the gap in a pivotal link - assessment of physiological activity within white matter (Fig. 1a).

In the past decade, Ding and his colleagues have concentrated on the functional activity of white matter, undertaking substantial efforts to clarify its properties. Convergent evidences have expounded that bold signal observed in white matter is of physiological relevance. White matter fMRI facilitates refined and direct investigation of structure-function coupling. The first stage of the two-step analysis - ‘gray-white matter physiological connection’ has been explored by gray-white matter functional covariance connectivity, functional signal clustering et al, unveiling compelling results. However, the second step - ‘structural-functional coupling within white matter’ remains elusive.

Here we originally proposed a unified framework for direct coupling of brain structural and functional information within white matter. The framework was tensor FA-based - The structural FA is the classical diffusion tensor FA while we also introduced a novel functional tensor based on signal co-fluctuation. Meanwhile, it was hierarchical - structure-function coupling patterns have been uncovered at the level of voxels, tracts and networks. Using this framework, differential distributions of structural-functional coupling within white matter, pronounced heterogeneity in the corpus callosum and four functional networks with high SFC were found. What’s more, repeatability of regions (voxels-tracts-networks) with high structural-functional coupling were validated using ICC. Age effects, the relationship between coupling and behavioral measurements were also examined. Several regions significantly decouple with age increasing. Significant CCA brain-behavior correspondence was presented.

Our research offers a novel neuroimaging perspective on the direct relationship between physiology and anatomy. For the first time, the pattern of structure-function coupling within the white matter has been characterized, addressing a gap in our understanding of brain structure-function relationships.

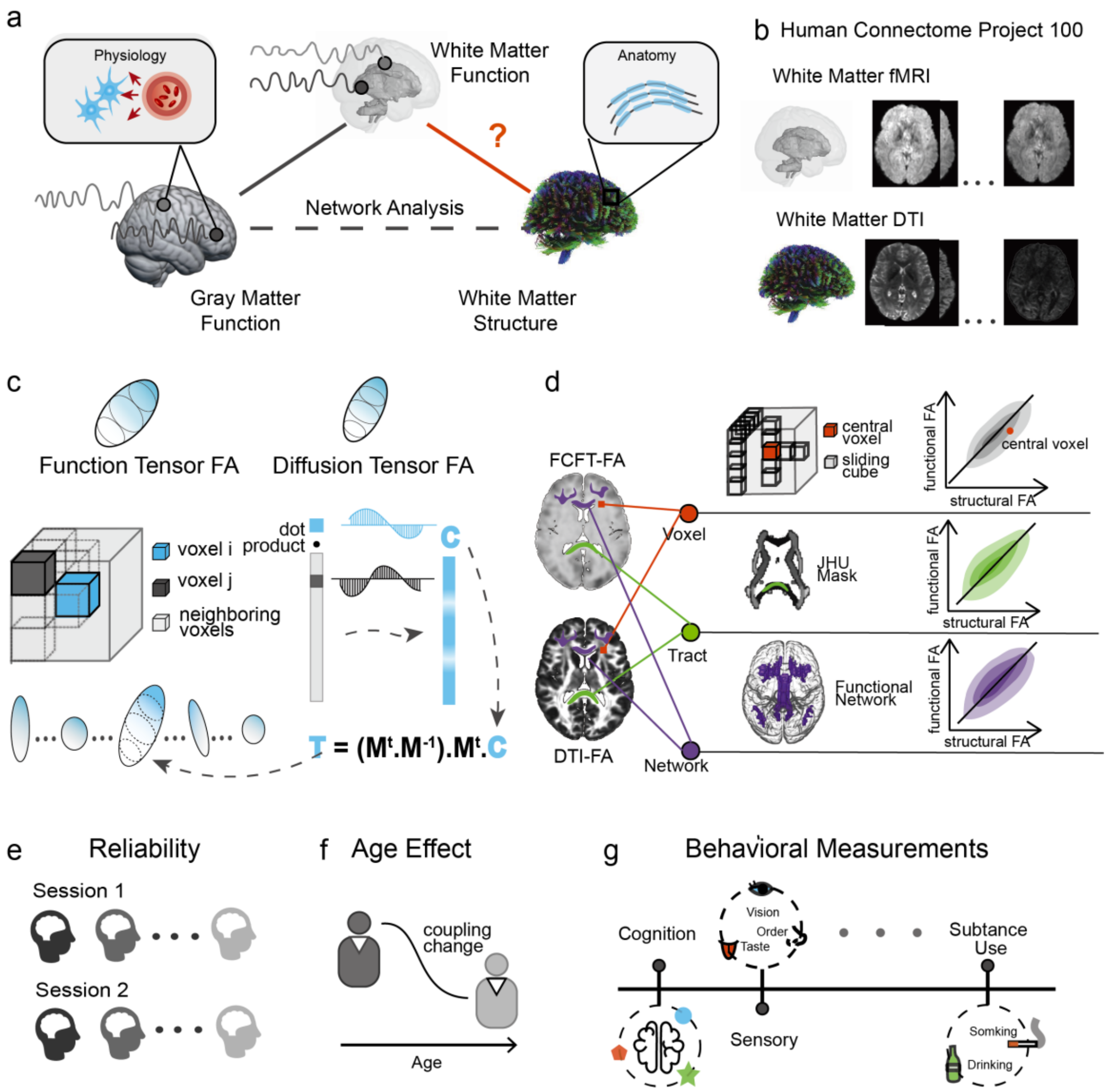

Figure 1. Illustration of study design. a. The main focus of the study is the structural-functional coupling in white matter, which directly fills the gap in understanding the relationship between brain structure and function. **b.** HCP U100 cohort. **c.** Constructing functional co-fluctuation tensors. Specifically, time series of each voxel were first z-scored and the estimated correlation C_{ij} in FCT was replaced by dot-product $[z_i(t) \cdot z_j(t)]$ between adjacent voxels within a 3x3x3 cube. Functional co-fluctuation tensors were then averaged temporally. **d.** Calculating voxel-wise, tract-wise and network-wise structural-functional coupling. Pearson correlation was used to calculate the spatial linear relationship between structural FA and functional FA across voxels at different scales. Statistical analysis**(e-g)** verified repeatability**(e)** and explored the effect of age**(f)** and the relationship with behavioral measurements**(g)**.