Multimodal Connectomics in Traumatic Brain Injury
Exploring TBI Effects: Integrating Brain Structure and Function

Abigail LIVNY[1,2], Anat Leibovivi[1,2], Galia TSARFATY[1,2], Reut RAIZMAN[1]
1. *C.BIRD -Clinical brain Imaging R&D Center, Sheba Medical Center, Israel.* ***2.*** *Gray Faculty of Medicine, and Sagol School of Neuroscience, Tel-Aviv University, Israel.*

E-mail: *Abigail.livnyezer@gmail.com*

Abstract: Complementary structural and functional neuroimaging provides insights into brain disorder mechanisms, prognosis, and treatment personalization, with mild TBI as a prime example. This researc details structural and functional alterations. An integrative framework captured abnormal network dynamics undetectable through single modalities, advancing AI-driven precision medicine.

Keywords: Neuroimaging, Connectivity, Brain-Injury, Artificial-Intelligence

Introduction

The complexity of the human brain stems from the intricate interplay between structural architecture and functional dynamics. While function is constrained by structure, their relationship is complex; functional connections can exist without direct structural links. Capturing these rich, dynamic structure-function relationships requires a comprehensive perspective. Understanding neuropathology requires an integrated approach combining both structural connectivity (the physical white matter pathways), and functional connectivity (the dynamic patterns of neural communication) that give rise to cognition and behavior. Thus, studying neuropathology through a single imaging modality provides only a partial account of disease effects, making comprehensive approaches crucial for uncovering pathological mechanisms and guiding effective treatment.

Mild traumatic brain injury (mTBI) and concussion exemplify this complexity, representing how neuropathology disrupts the delicate balance between brain structure and function. As a leading cause of mortality and morbidity, particularly among young populations, mTBI presents a critical diagnostic challenge due to its high prevalence yet elusive objective assessment. Current approaches to mTBI diagnosis predominantly rely on subjective clinical assessments, behavioral symptom estimation, and neuropsychological testing, leading to prolonged diagnostic periods and trial-and-error treatment approaches that significantly impact patient well-being. Conventional anatomical imaging techniques frequently fail to detect the subtle alterations characteristic of mTBI, exacerbating the diagnostic challenge due to inconsistent injury definitions and the inadequacy of classification systems like the Glasgow Coma Scale.

Mild TBI is fundamentally characterized by widespread alterations in brain connectivity, often stemming from diffuse axonal injury that damages white matter connections and disrupts the overall brain network architecture. This growing recognition of mTBI as a disorder of disrupted connectivity underscores the need for analytical frameworks, such as graph theory, that can capture the subtle, network-level alterations often missed by conventional imaging. While studies in moderate-to-severe TBI have shown alterations in global efficiency, hub centrality, and their associations with clinical and cognitive outcome, there remains a critical gap in understanding how structural network organization is affected across the spectrum of injury severity, particularly in mTBI. Complementing these structural insights, functional alterations in mTBI manifest as both widespread disruptions and adaptive compensatory mechanisms. Functional connectivity within key brain networks, particularly affecting hub regions that facilitate efficient information transfer across the brain, are disrupted. Hypoconnectivity in the default mode network (DMN) is apparent post-injury, impairing cognitive processing and memory, while hyperconnectivity within the DMN is linked with acute symptom severity. Patients also demonstrate widespread decreases in homotopic functional connectivity (the synchrony between homologous brain regions across hemispheres), particularly affecting the DMN, executive control network, fronto-parietal network, and dorsal attention network.

This complex interplay between structural damage and functional reorganization creates a decoupling phenomenon where the normal structure-function interaction is disrupted. The connectome, defined as the comprehensive map of all neural connections within the brain, offers a unique neural-print that not only captures individual connectivity variations but also correlates strongly with clinical symptoms and behavioral phenotypes. This network-centric perspective is essential for understanding how distributed damage or dysfunction, as seen in mTBI, can propagate throughout the brain, initiating pathological cascades that affect large-scale neural systems and their phenotype.

Advanced neuroimaging techniques, especially connectomics, combined with powerful Artificial Intelligence (AI) algorithms represent a significant advancement in bridging the diagnostic gap in mTBI. The ability of AI to identify subtle patterns within large, complex datasets transforms connectomic biomarkers into objective, predictive decision support tools for precision medicine. Our overarching aim is to explore how structural, functional, and cross-modal (structure-function coupling) brain connectivity disruptions contribute to clinical and cognitive outcomes. By integrating multimodal neuroimaging, graph theory, and AI-driven analytics, we aim to identify sensitive biomarkers that capture the acute and long-term effects of mTBI.

Methods

This research is based on multiple ethically approved studies of diverse cohorts across the spectrum of TBI severity and recovery stages. Participants underwent a multimodal MRI protocol, detailed symptom assessments, and cognitive testing at acute, subacute, and chronic time points post-injury. Across studies, rigorous screening excluded individuals with confounding neurological or psychiatric conditions. Healthy age and gender matched participants were also recruited.

MRI scans were acquired using 3T Philips Ingenia and Siemens Prisma scanners at Sheba Medical Center, employing standardized protocols across studies to capture high-quality structural and functional brain data. The imaging protocol included high-resolution T1-weighted, T2-FLAIR, Task fMRI, resting-state fMRI, and diffusion-weighted sequences, with minor variations in acquisition parameters. This multimodal approach enabled detailed assessment of brain anatomy, connectivity, and spontaneous activity, forming a robust foundation for advanced connectomics analyses. Anatomical, functional and diffusion MRI data were processed with established pipelines (VBM-SPM for anatomical, CONN for fMRI, ExploreDTI and MRtrix3 for DWI). Individual connectomes were constructed with Brainnetome or AAL atlases.

Cognitive function was assessed using a range of validated neuropsychological tools targeting domains such as executive function, memory, attention, and abstract reasoning. Assessments included both standardized computerized batteries (e.g., CANTAB) and custom tasks (e.g., abstract reasoning), with performance quantified through accuracy and reaction time. In one study, access to objective pre-injury cognitive scores from a national database allowed for direct comparison of post-injury decline, offering a rare and precise baseline. Clinical outcomes were evaluated using a range of standardized questionnaires that assessed global functioning, symptom severity, and quality of life following injury. Common tools included the Glasgow Outcome Scale–Extended (GOSE) to rate overall functional recovery, the Rivermead Post-Concussion Symptoms Questionnaire to quantify post-concussion symptom burden, and additional self-report measures assessing emotional well-being and health-related quality of life.

Rigorous statistics (t-tests, ANCOVA, Pearson correlations) and strict false-discovery-rate and cluster-level corrections ensured control over multiple-comparison error. Connectivity matrices provided inputs for machine-learning models such as multivariate logistic regression, XGBoost, and convolutional neural networks to classify groups and predict cognitive outcome.

Results

Our results reveal widespread and severity-dependent disruptions in brain structure and function following TBI, with distinct cognitive findings. Objectively measured cognitive decline, especially in non-verbal abstract reasoning, associated with bilateral insula volume loss, was observed in TBI patients[1]. A consistent "dose-response" pattern in both global and local graph theory structural connectivity measures, with reduced strength, efficiency, and hub integrity correlating with greater injury severity. The right thalamus, a prominent hub in healthy individuals, no longer served as a central hub in TBI patients, indicating its particular vulnerability to brain injury. Similarly, precuneus no longer linked network efficiency to reasoning performance[2]. Functional imaging revealed diminished homotopic connectivity and widespread interhemispheric disconnection in TBI patients, particularly in the cingulate cortex, thalamus, superior temporal pole, and cerebellum III[3]. Anterior cerebellar (Vermis III–V, left lobule IV–V) overactivation was observed during an fMRI abstract reasoning task, accompanied by altered connectivity with frontoparietal regions, signaling compensatory recruitment. Finally, multimodal integration of structural and functional metrics, improved group classification, beyond a single connectivity modality. In particular, combining thalamic homotopic connectivity with corpus callosum integrity significantly enhanced diagnostic accuracy. Finally, AI models achieved <95% accuracy in distinguishing TBI patients from controls while integrating structural and functional connectomics features from well-known TBI related regions.

Discussion

Our multimodal, connectomics-driven framework provides a robust approach for characterizing TBI, while capturing complementary aspects of network integrity. It effectively integrates structural and functional MRI with graph-theoretical metrics, further associated with clinical and cognitive outcomes. This integrative approach, together with advanced AI, yields high diagnostic accuracy in detecting subtle injury signatures and cognitive decline. However, limitations include modest sub-analysis sample sizes, and TBI injury heterogeneity. Future work should focus on expanding to multi-center longitudinal cohorts and integrating metabolic or blood-based biomarkers for enhanced prognostication.

Conclusions

Together, these results demonstrate that multimodal connectomics can capture the hidden network pathology of TBI and predict cognitive outcome with high precision. Clinically, such biomarkers could improve diagnosis, trajectory monitoring, and personalized intervention for patients across the TBI spectrum.

References

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