Transdiagnostic Analysis of White Matter Injury: Pediatric Demyelinating Disorders and a Brain Tumor Injury Model

Julia Bérubé Boutin[1,2], Noor Al Dahhan[1], Donald Mabbott[1,2]
[1]Neurosciences & Mental Health, The Hospital for Sick Children
[2]University of Toronto

SickKids MABBOTT LAB brain plasticity & repair

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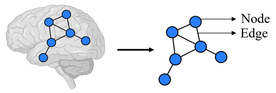
Introduction

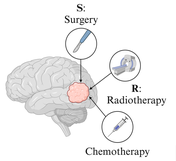
- Structural connectivity, defined by the network of white matter tracts interconnecting regions of the brain, evolves throughout development and is vulnerable to white matter injury
- **Graph theory:** a mathematical model that conceptualizes structural connectomes as a graph



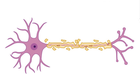
Examine the extent to which brain regions are connected (**integration**), distinguishable (**segregation**), and the importance of a given region to the network (**centrality**)

- In several clinical populations, greater segregation and reduced integration correlate with poorer cognitive outcomes

Pediatric Brain Tumor Survivors (PBTS)



Treatments for a brain tumor



Global diffuse white matter injury

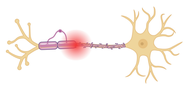
+ Disrupted brain connectivity [1,2,3,4,5,6]

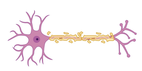
↑ Segregation ↓ Integration

Cognitive Dysfunction: ~40-100%[7], progressive and lasting cognitive decline[8]

Children with a Demyelinating Disorder

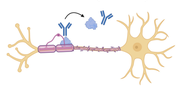
Multiple Sclerosis (MS)





Less diffuse white matter injury

Myelin Oligodendrocyte Glycoprotein Antibody Disease (MOG)



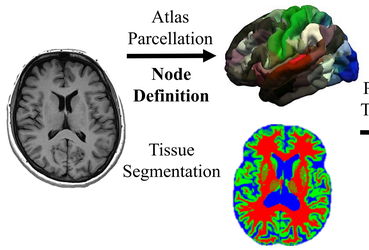
Cognitive Dysfunction: ~33%[9] and ~10-50%[10], evidence of initial compensation/recovery

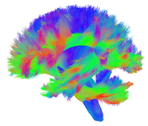
- Variations in white matter injury and severity of cognitive dysfunction between patient groups suggest that structural connectivity may be differentially impacted

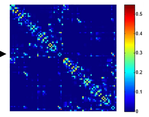
What is the impact of different types of white matter injury in pediatric brain tumor survivors and children with a demyelinating disorder on whole-brain structural connectivity?

Methods

1. Network Construction: completed for a previous study



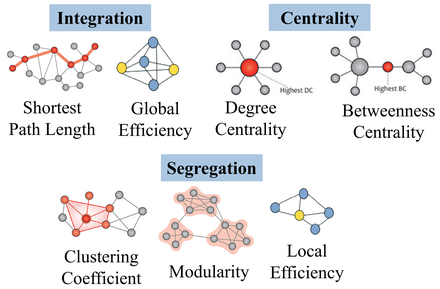




2. Graph Theory Analysis of Structural Connectivity

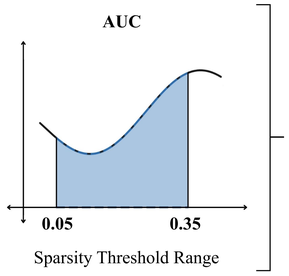
GRETNA

Sparsity thresholded (0.05-0.35) and binarized networks



3. Statistical Analysis

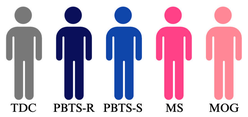
Robust regressions and post-hoc tests were used to compare **area under the curve (AUC)** measures for each graph theory metric between participant groups



Our Robust Regressions: modelled the relationship between each graph theory metric and several predictors while handling the presence of outliers and non-normally distributed data

- **Predictors:** Study ID (dataset 1 vs dataset 2), Group ID (TDC vs PBTS-R vs PBTS-S vs MS vs MOG), Intracranial Volume, Age, Age at diagnosis

Post-hoc contrasts:



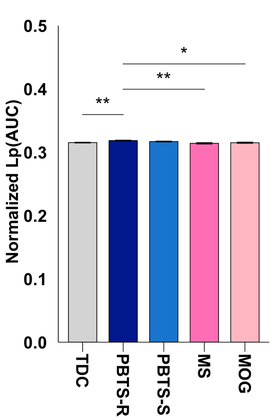
Clinical and Demographic Characteristics

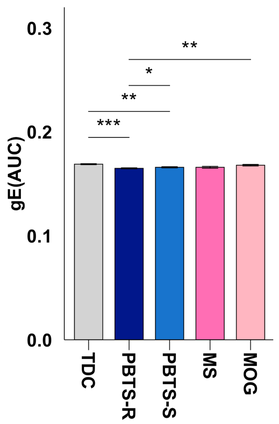
Parameter	TDC (n = 64)	PBTS-R (n = 26)	PBTS-S (n = 14)	MS (n = 19)	MOG (n = 13)
Sex (Male) (n)	29	16	8	6	3
Age (M(SD))	13.94(2.91)	14.73(2.54)	12.56(2.76)	16.64(1.07)	11.75(2.85)
Age at Diagnosis (M(SD))	-	7.04(2.42)	5.62(2.90)	13.93(2.50)	9.71(3.42)
Time Since Diagnosis (Years) (M (SD))	-	6.81(3.83)	6.39(3.13)	2.94(2.65)	2.37(2.09)
EDSS Score (M (SD))	-	-	-	1.61(0.91)	1.08(0.40)
Number of Clinical Events (M(SD))	-	-	-	2.05(1.43)	2.85(2.41)

Results

Comparing Network Integration Between Groups

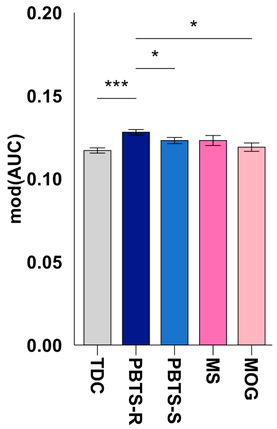
PBTS treated with radiation demonstrated reduced network integration compared to TDC and demyelinating disorder patients.

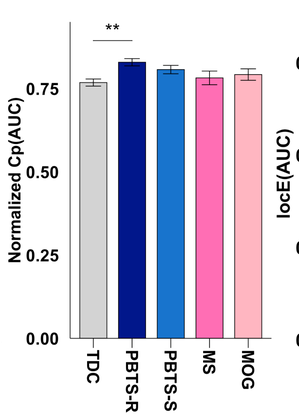


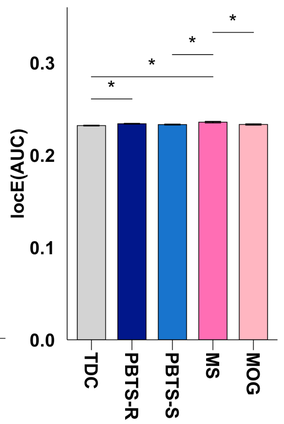


Comparing Network Segregation Between Groups

PBTS treated with radiation and children with MS demonstrated increased network segregation compared to TDC, but PBTS demonstrated greater disruptions.

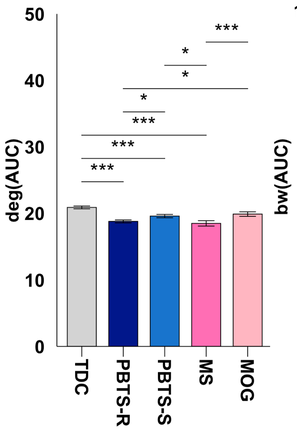


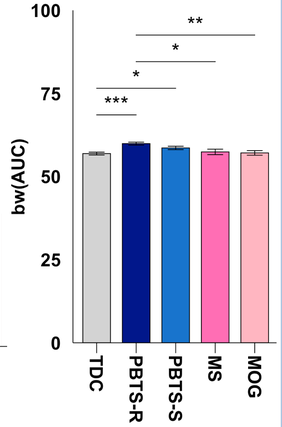




Comparing Network-Averaged Centrality

PBTS and children with MS demonstrated reduced network centrality compared to TDC and children with MOG.



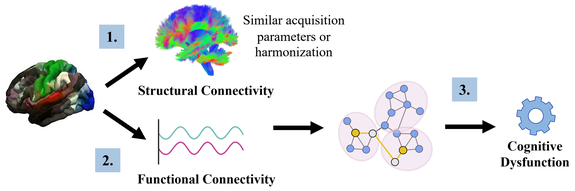


TDC= typically developing children, **PBTS** = pediatric brain tumor survivors; **R** = treated with radiation, **S** = treated with surgery, **MS** = multiple sclerosis, **MOG** = myelin oligodendrocyte glycoprotein antibody disease

p > 0.05 *, p > 0.01**, p > 0.001***

Conclusions

- First study to compare whole-brain structural connectivity in PBTS and children with a demyelinating disorder
- Findings indicate greater segregation of WM networks for PBTS and MS patients, and reduced integration only for PBTS
  - Suggests an impairment in the structural network's ability to integrate information across distinct regions
- Widespread versus localized white matter injury in PBTS and demyelinating disorders respectively, differentially impact structural connectivity
  - Intensive treatment for a brain tumor may result in more severe disruptions to structural connectivity
  - Focal white matter lesions may result in relatively more preserved structural connectivity, especially in patients with few clinical events

Future Directions

- Limitation: brain imaging acquisition parameters were different between patient groups which may have contributed to the observed results
- Future studies should examine the relationship between structural and functional connectivity and how this relates to cognitive functioning
  - Reduced network integration and increased segregation are associated with reduced cognitive flexibility and general intelligence in PBTS[2,11]
  - Differences in network integration and segregation may underlie the variations in the severity of cognitive dysfunction between patient groups