ABNORMAL SPINAL CORD MYELINATION DUE TO OLIGODENDROCYTE DYSFUNCTION IN A MODEL OF HUNTINGTON DISEASE

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INTRODUCTION

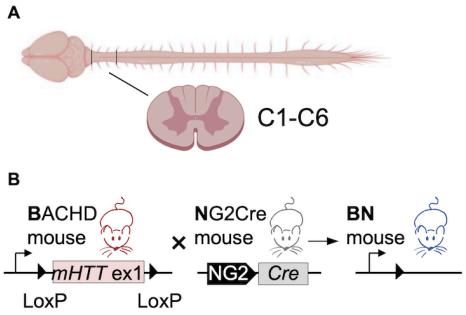
The contribution of grey matter (GM) and white matter (WM) degeneration to the progressive brain atrophy in Huntington Disease (HD) has been well studied. Comparatively, the pathological features of the second major part of the central nervous system (CNS), namely the spinal cord, in HD are less well characterised. In particular, it still remains unclear whether the WM area of the spinal cord is affected in HD. Here, using the BACHD mouse model of HD, we first show that spinal GM and WM areas are significantly atrophied in BACHD mice compared to wild-type (WT) controls. Secondly, we genetically reduced mHTT expression in oligodendroglia by crossing BACHD mice to NG2-Cre mice and show that this rescues myelin abnormalities in HD mice.

OBJECTIVE

The aim of this study is to investigate spinal cord pathology in HD. The specific objectives are:

A. To evaluate WM and myelination abnormalities, using histological and electron microscopy analysis of myelinated fibers

B. To evaluate the impact of the inactivation of mHTT in oligodendroglia on these measures using the full-length BACHD mouse model of HD



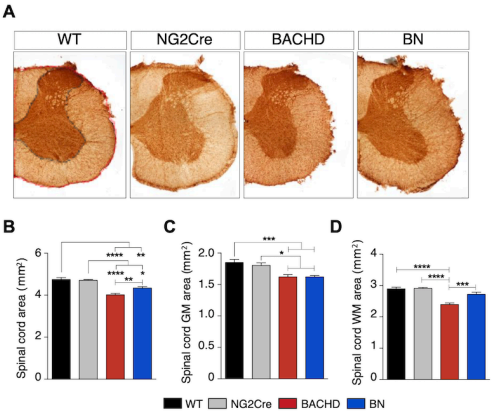
RESULTS

1 Spinal WM atrophy is rescued by inactivation of mHTT in oligodendroglia

To determine whether GM and WM regions are atrophied in the spinal cord of 12 months old BACHD mice, we measured the area of GM and WM in the cervical (C1-C6) regions of the spinal cord by histological assessment using the oligodendroglia marker Olig2 (**A**).

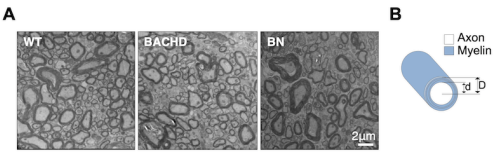
RESULTS

- The spinal total area, GM, and WM area were significantly lower in BACHD mice compared to WT controls (**B**)
- White, but not grey, matter atrophy in the spinal cord of BACHD mice was rescued in BN mice (**C,D**)
- Significant atrophy of the spinal GM region in BN mice compared to WT mice was reported (**C**), but no differences in spinal WM area were found between WT and BN mice (**D**)

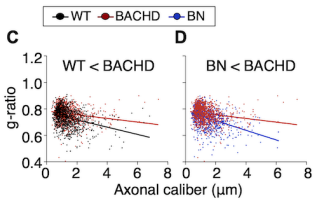


2 Oligodendroglia-intrinsic effects of mHTT cause myelin deficits in HD mice spinal cord

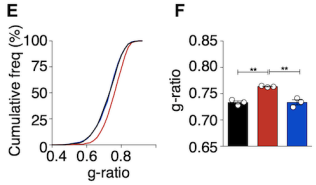
We used electron microscopy to visualize myelinated fibers of the spinal cord at 12 months of age (**A**). G-ratio was used as measure of myelin thickness (**B**).



BACHD mice showed increased g-ratio compared to WT (**C,E,F**), indicating that their myelin sheaths were thinner.

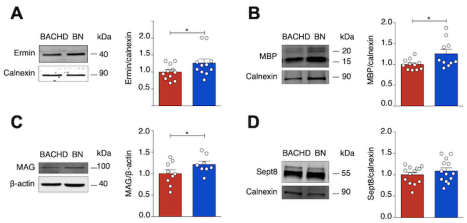


This phenotype was rescued in BN mice, where g-ratio is comparable to WT (**C,E,F**).



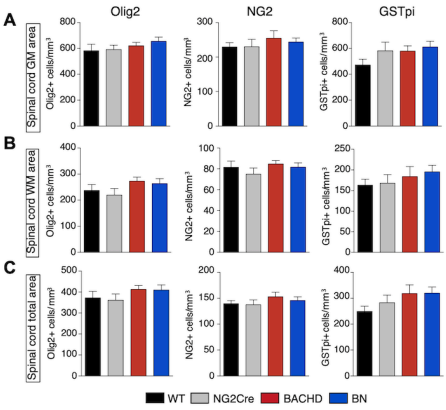
3 mHTT inactivation in oligodendroglia increases levels of myelin proteins

We show that Ermin, myelin basic protein (MBP) and myelin-associated glycoprotein (MAG) were significantly increased in the spinal cord of BN versus BACHD mice (**A-C**), whereas Sept8 did not show any significant changes (**D**).



4 Inactivation of mHTT in oligodendroglia has no effect on oligodendroglial density

Using different oligodendroglia lineage markers, namely Olig2, GST-pi, and NG2, no changes in oligodendroglia density were observed in the spinal GM (**A**), WM (**B**), and total area (**C**) of BACHD and BN mice at 12 months of age.



SUMMARY

- Our findings firstly demonstrate that the myelination abnormalities observed in brain WM structures in HD extend to the spinal cord.
- Secondly, they suggest that myelin deficits are primarily driven by cell-intrinsic, mHTT induced defects in oligodendroglia.

ACKNOWLEDGEMENT

The work was partly funded by grants from the Agency for Science Technology and Research (Singapore) and the National University of Singapore to M.A.P.

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