Neural mechanisms of nucleus accumbens deep brain stimulation for self-injurious behaviours in Autism Spectrum Disorder

Kristina Zhang (kristina.zhang@sickkids.ca)[1,2], Rafi Matin[1,2], Mark Ebden[2], Karim Mithani[2,4], Jacob Ellegood[3], Jason P. Lerch[3], Flavia Venetucci Gouveia[2], George M. Ibrahim[1, 2, 4]
[1]Institute of Medical Science, University of Toronto; [2]Program in Neuroscience & Mental Health, Hospital for Sick Children; [3]Mouse Imaging Centre, Hospital for Sick Children, [4]Division of Neurosurgery, Hospital for Sick Children

Introduction

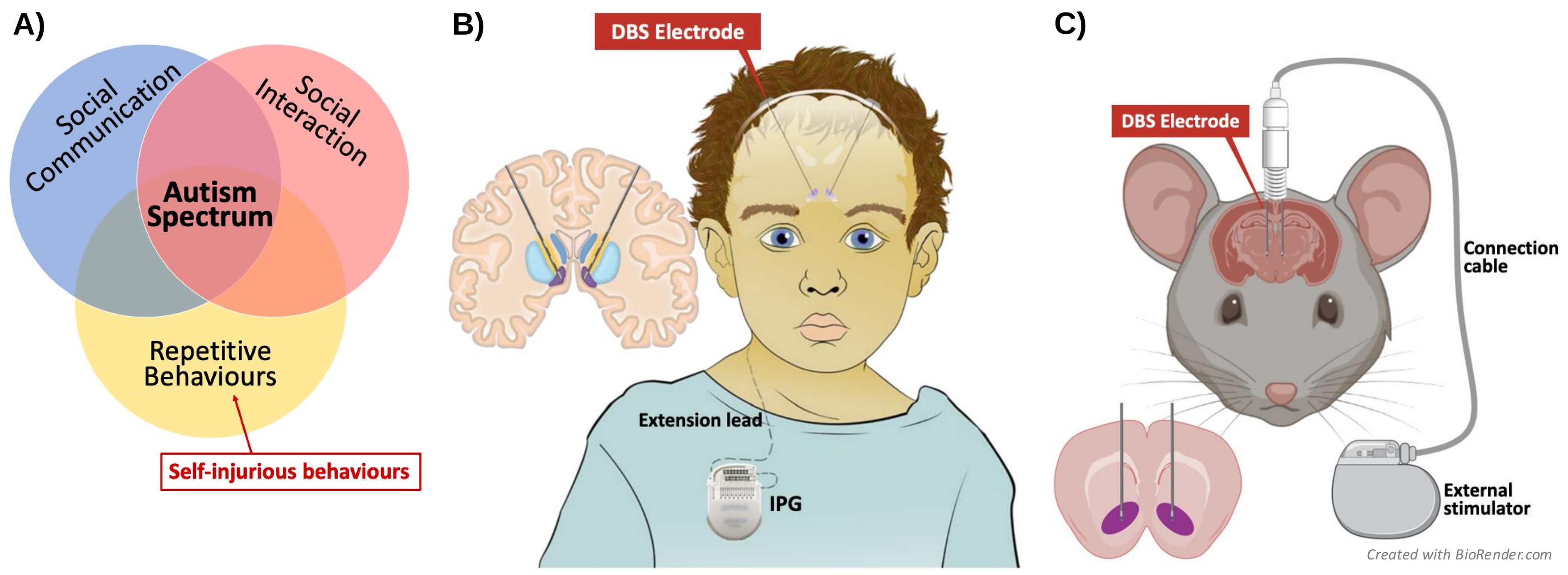


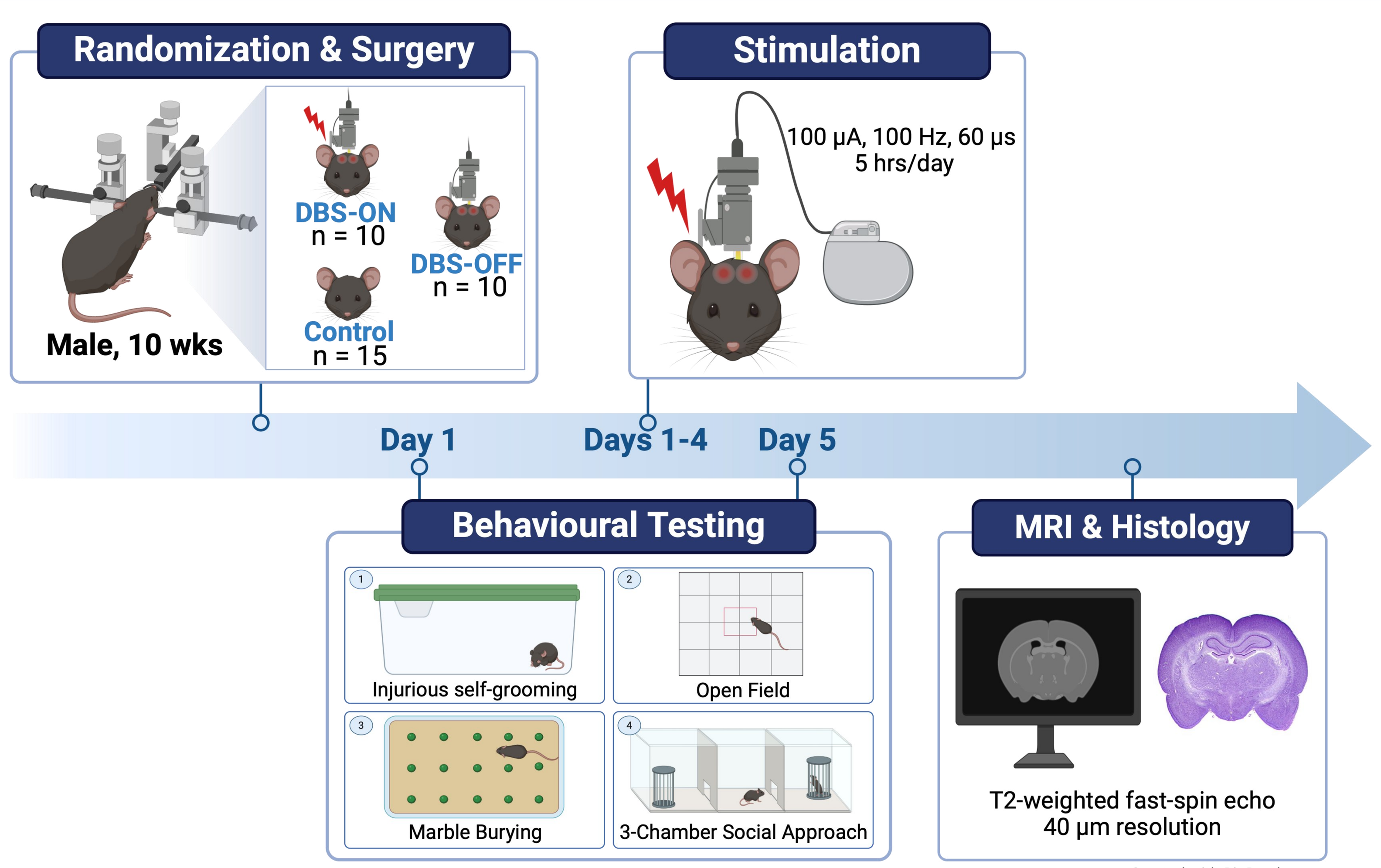
Figure 1. (A) Autism Spectrum Disorder is characterized by a triad of impairments. Deep brain stimulation is used for both (B) clinical applications and (C) pre-clinical studies using animal models. Electrodes are implanted to specific brain targets and receive electrical current from an internal pulse generator (IPG) or external stimulator.

- Self-injurious behaviours (SIB) are exhibited by >50% of patients with Autism Spectrum Disorder (ASD) or developmental delay.[1]
- The nucleus accumbens (NAcc) is critically involved in the neurocircuitry regulating SIB.[2]
- Deep brain stimulation (DBS) is a precise neuromodulation strategy for targeting pathological brain circuitry, with promising applications in neurological and psychiatric disorders.[3]
- The BTBR T^{+} *Itpr3*^{tf}/J (BTBR) inbred mouse is an established model of ASD that exhibits several ASD-relevant phenotypes including excessive injurious self-grooming, impaired social behaviour, and high anxiety.[4,5]

Hypotheses

NAcc-DBS in BTBR mice will:
- Reduce the severity and/or frequency of SIB and ASD-related behaviours
- Induce morphological changes in brain regions that regulate SIB

Methods



Results

NAcc-DBS improves SIB and select ASD-related behaviours

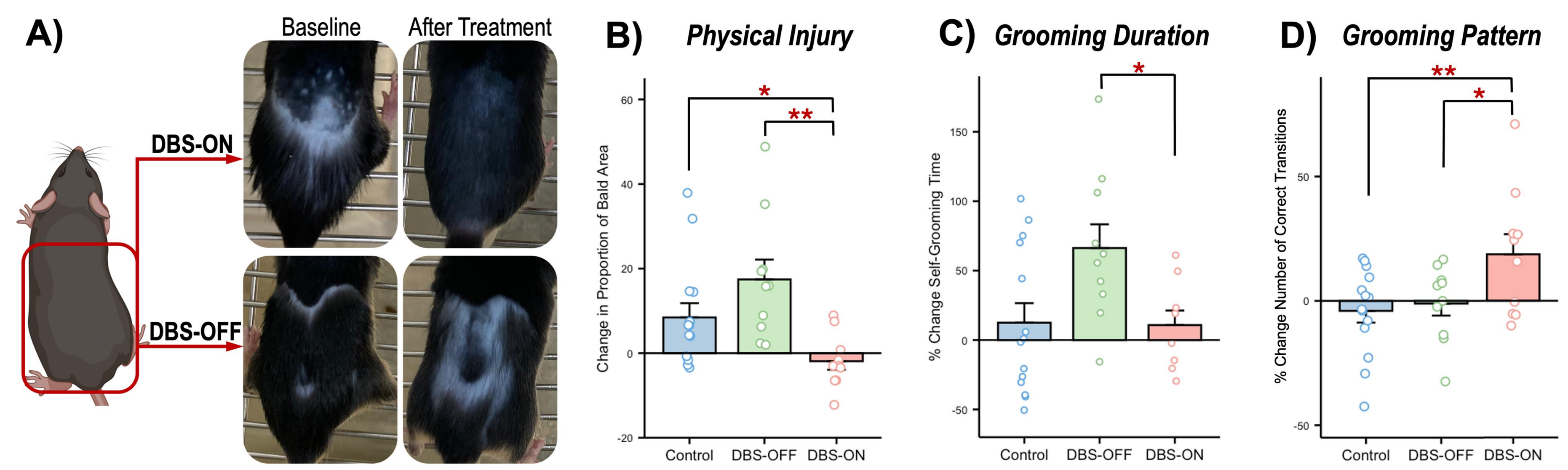


Figure 2. Injurious self-grooming in BTBR mice. (A) Representative images of a DBS-ON (top row) and DBS-OFF (bottom row) mouse before and after chronic NAcc-DBS. Percent change in (B) physically injured area, (C) time spent self-grooming, and (D) correct grooming transitions after chronic NAcc-DBS treatment. Values are mean ± SEM; * $p < 0.05$; ** $p < 0.01$.

NAcc-DBS reduced SIB as demonstrated by the healing of skin and fur growth (Fig 2A & B). Animals treated with chronic NAcc-DBS also exhibited significant improvements in total self-grooming duration (Fig 2C) and pattern (Fig 2D).

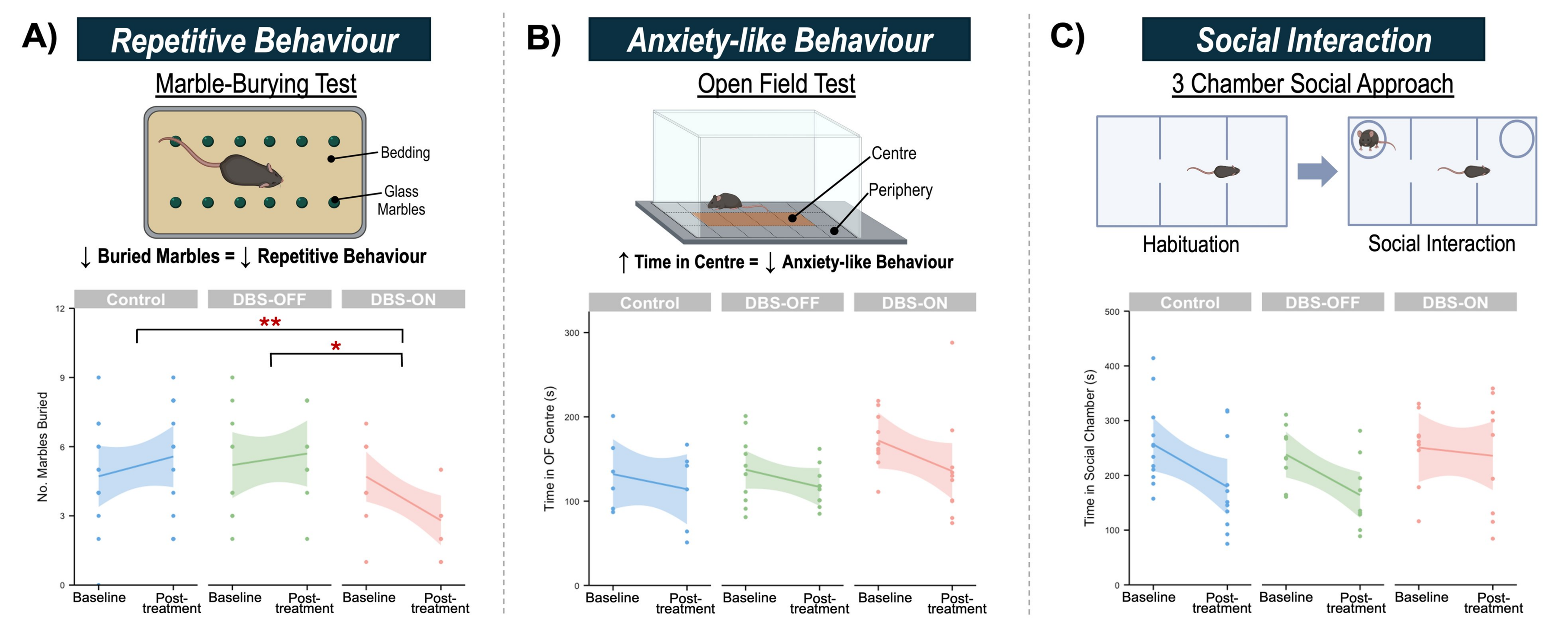


Figure 3. Evaluation of ASD-relevant behavioural phenotypes including (A) repetitive behaviour, (B) anxiety-like behaviour, and (C) social interaction. Abbreviations: DBS: deep brain stimulation; OF, open field. Values are mean ± SEM; * $p < 0.05$; ** $p < 0.01$.

NAcc-DBS reduced repetitive behaviour and had no significant effect on anxiety-like behaviour or sociability in BTBR mice (Fig 3).

NAcc-DBS induces volumetric brain changes

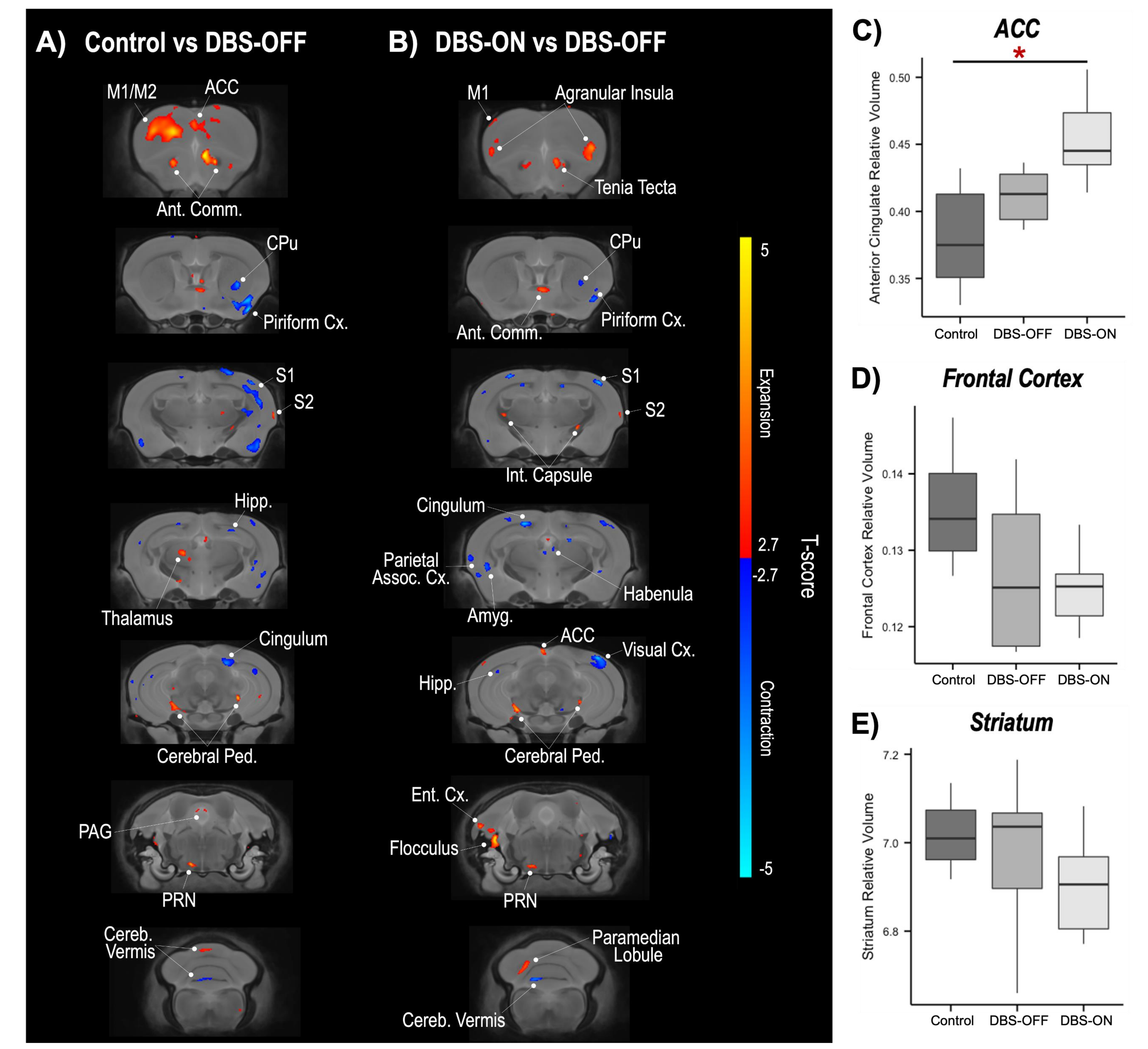
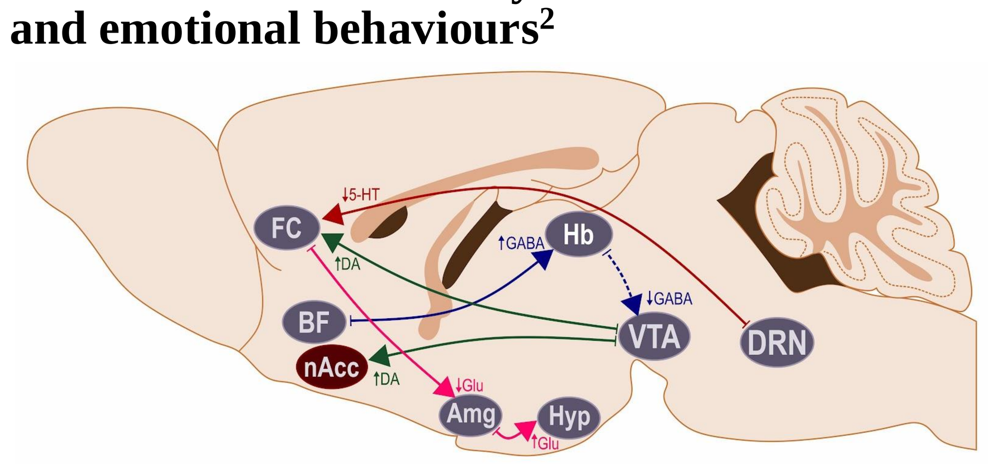


Figure 4. Voxel-wise relative brain volume differences between (A) Control and DBS-OFF, or (B) DBS-ON and DBS-OFF. Boxplot of voxel-wise differences of the (C) ACC, (D) frontal cortex, and (E) striatum in BTBR mice. Abbreviations: ACC, anterior cingulate cortex; Amyg., amygdala; Ant. Comm., anterior commissure; Cereb., cerebellar; CPu, caudate putamen; Cx., cortex; Ent., entorhinal; Hipp., hippocampus; Int., internal; M1/M2, primary/secondary motor area; PAG, periaqueductal grey; Ped., peduncle; PRN, pontine reticular nucleus; S1/S2, primary/supplemental somatosensory area.

Chronic NAcc-DBS altered the volume of several brain regions critically involved in SIB (Fig 4A & B) such as the anterior cingulate area, frontal cortex, and striatum (Fig 4C-E), as detected by deformation-based morphometry analysis using T2-weighted magnetic resonance imaging (MRI) scans.[6]

Discussion & Conclusions

Nucleus accumbens: Key structure for reward and emotional behaviours[2]



- Fronto-limbic-striatal network is key in regulating SIB
- Major afferent dopamine (DA) & glutamate (Glu) projections
- NAcc-DBS may induce behaviour changes by modulating DA input to NAcc

5-HT, serotonin; Amg, amygdala; BF, basal forebrain; DRN, dorsal raphe nucleus; FC, frontal cortex; Hb, habenula; Hyp, hypothalamus

Chronic NAcc-DBS treatment:

- Behaviour Improvements
  - ↓ SIB
  - ↓ Repetitive behaviour
- Neuroanatomical Changes
  - Volume changes in structures along SIB brain circuitry:
    - ↑ Anterior Cingulate
    - ↓ Frontal Cortex
    - ↓ Striatum

Future Directions:

Neurochemical effects of NAcc-DBS	NAcc-DBS in children with SIB & ASD	Brain networks involved in treatment response

References & Acknowledgements

1. Arron K., Oliver C., Moss J., et al. (2011) *J. Intellect. Disabil. Res.*, 55: 109-120.
2. Yan H., Shlobin N.A., Jung Y., et al. (2022) *J. Neurosurg.*, Jul 22: 1-10.
3. Lee D.J., Lozano C.S., Dallapiazza R.F., et al. (2019) *J. Neurosurg.*, 131: 333-342.
4. McFarlane H.G., Kusek G.K., Yang M., et al. (2008) *Genes Brain Behav.*, 7(2):152-63.
5. Kalueff A.V., Stewart A.M., Song C., et al. (2016) *Nat. Rev. Neurosci.*, 17(2): 45-59.
6. Nieman B.J., van Eede M.C., Spring S., et al (2018) *Curr Protoc Mouse Biol.*, 8(2): e44.

CIHR IRSC
TCP The Centre for Phenogenomics
research training centre | Restracomp