Neural circuitry underlying DBS treatment for self-injurious behaviours in Autism Spectrum Disorder

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Introduction:

Children with Autism Spectrum Disorder (ASD) often manifest self-injurious behaviours (SIB) that may become severe and refractory with limited treatment options (Arron et al. 2011). These SIBs may lead to disability or death and deprive children and their families of quality of life. Deep brain stimulation (DBS) has recently been developed in a world-first phase I clinical trial at the Hospital for Sick Children as a potential treatment for affected children (NCT03982888; Yan et al. 2022). The nucleus accumbens (NAcc) is thought to be a relevant target because of its key role in the neurocircuitry regulating SIB. However, the neural underpinnings of NAcc stimulation for SIBs are poorly understood, and multi-disciplinary translational studies using both pre-clinical animal models and clinical data are necessary to explore the mechanisms of disease and treatment. Here, we evaluated the behavioural and neuroanatomical changes induced by NAcc-DBS in a mouse model of SIB and ASD to provide insights into the pathophysiology underlying the treatment being offered in the phase I clinical trial at the Hospital for Sick Children.

Methods:

BTBR T+ Itpr3tf/J (BTBR) mouse models of SIB and ASD received chronic DBS or sham stimulation to the bilateral NAcc (100 μA, 100 Hz, 60 μs). Treatment was followed with a series of behavioural tests evaluating ASD-related phenotypes (self-injurious, repetitive, anxiety-like, and social behaviours) and structural MRI. Deformation-based morphometry (Lerch, Sled, and Henkelman 2011) and MAGeTbrain (Multiple Automatically Generated Templates Brain Segmentation Algorithm; Chakravarty et al. 2013) pipelines were applied to identify distinct volumetric changes along the NAcc neurocircuitry and correlated with SIB improvement in BTBR mice.

Results:

Chronic, high-frequency NAcc-DBS reduced repetitive and SIBs, as well as improved sociability among BTBR mice. These behavioural improvements were correlated with reduced volume in several brain areas thought to be critical for the regulation of SIB, such as the frontal cortex, habenula, amygdala, and hypothalamus (Figure 1).

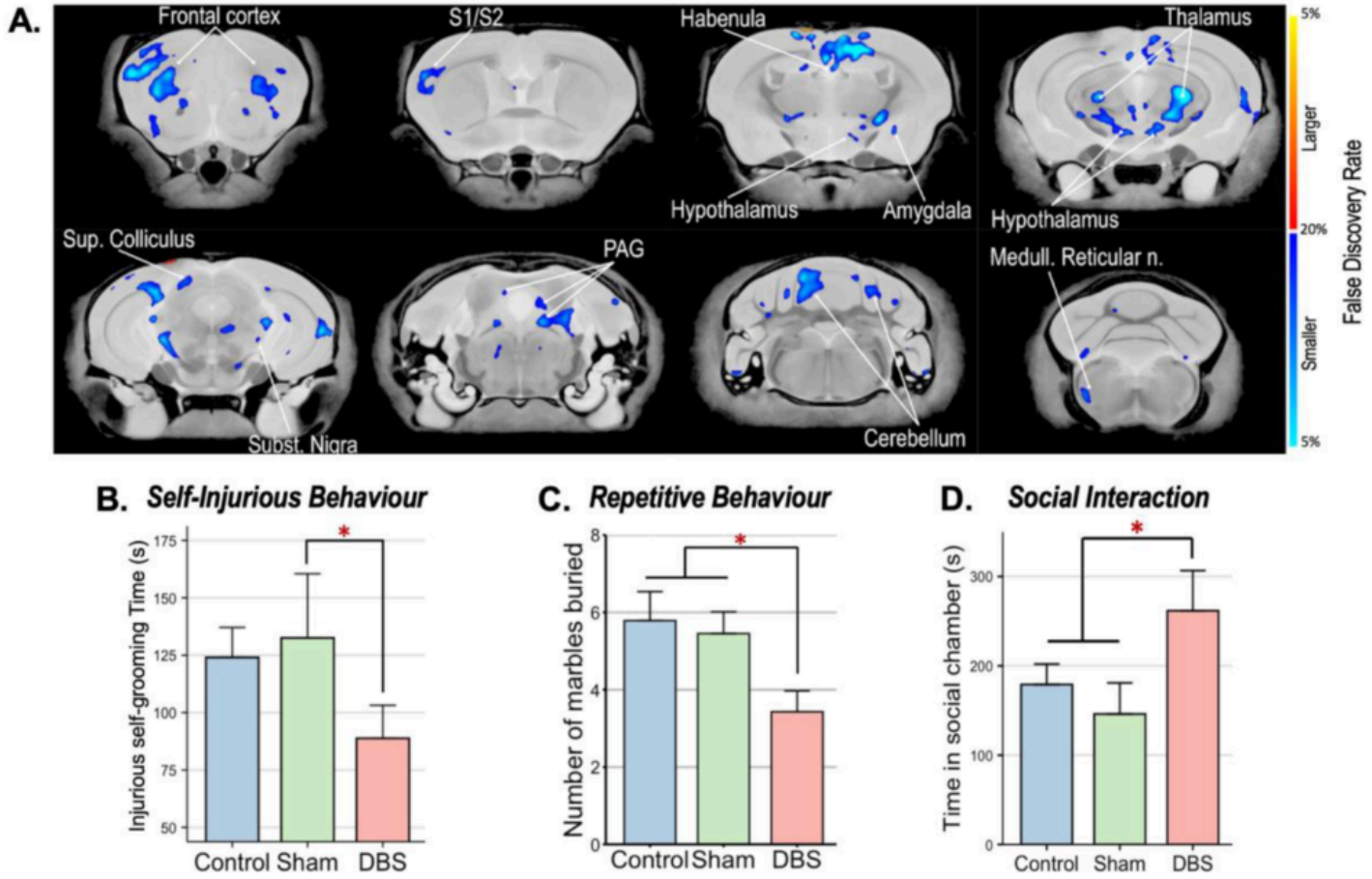

Figure 1. Neuroanatomical and behavioural changes induced by NAcc-DBS in BTBR mice. **(A)** Fly-through of coronal slices in the brain highlighting the volume changes exhibited by BTBR mice treated with NAcc-DBS. Animals treated with NAcc-DBS exhibited reduced **(B)** self-injurious behaviour (as evaluated by a 10-minute grooming assay), **(C)** repetitive behaviour (as evaluated by the marble burying test), and **(D)** improved social interaction (as evaluated by the three-chamber social approach test) relative to animals that did not receive active stimulation. Abbreviations: PAG, periaqueductal gray; S1/S2, primary and secondary somatosensory cortices.

Conclusions:

We demonstrate that NAcc-DBS improves SIB outcomes in BTBR mice through induction of volumetric changes to diverse brain structures involved in SIB regulation. These findings will provide mechanistic insight to the world-first pilot trial of NAcc-DBS in children with severe SIB and ASD. Results from this study will advance our understanding of the neural circuitry subserving SIB, mechanisms underlying symptom improvement following treatment, and provide foundational evidence to establish NAcc-DBS as a therapy for affected children.

Brain Stimulation:

Deep Brain Stimulation [1]

Disorders of the Nervous System:

Neurodevelopmental/ Early Life (eg. ADHD, autism) [2]

Emotion, Motivation and Social Neuroscience:

Emotion and Motivation Other

Modeling and Analysis Methods:

Segmentation and Parcellation

Neuroanatomy, Physiology, Metabolism and Neurotransmission:

Subcortical Structures

Keywords:

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Treatment

[1|2]Indicates the priority used for review

Provide references using author date format

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