Progress Report

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Title of Project: **Brain structural and motor function correlations in childhood arterial ischaemic stroke using multimodal magnetic resonance imaging**

**Summary:**
Stroke is among the top ten causes of death in children. Contrary to popular belief, children do not recover better than adults because more than half of childhood stroke survivors have long term disabilities, which may include physical, learning, behavioural or social problems and seizures. Weakness or paralysis down one side of the body is the most common problem following stroke but the reasons why some children recover better than others is not understood. The underlying mechanism by which the brain reorganises and rewires itself following stroke is largely unknown.

Recent advances in brain magnetic resonance imaging (MRI) technology have the potential to provide answers about how childrens’ brains change following stroke. Our team aims to understand differences in brain structure and function following childhood stroke by comparing children who have made a good physical recovery to those who have not. The study will use three specific MRI techniques. The first technique, called diffusion imaging, allows us to investigate changes in brain wiring (nerve fibre tracts). These tracts are the information highways, which transmit electrical information from one region of the brain to another and to the muscles via the spinal cord and nerves. Functioning of a nerve fibre tract is affected by the integrity of its myelin sheath – a lipid and protein substance coats the nerve fibre and speeds up the transmission of electrical signal along the nerve fibre. To further understand the structure-functional relationship of the nerve fibre tract, a second MRI technique, called magnetisation transfer ratio (MTR) imaging, allows us to measure and quantify the amount of myelin - an indirect MRI biomarker reflecting the degree of nerve fibre recovery following stroke. We expect to find differences in the structure of these fibre tracts, and amount of their myelin sheaths between the two groups of children with good and poorer motor outcomes.

The third technique, functional MRI (fMRI), uses subtle changes in blood oxygen level to determine which groups of activated brain cells in the cortex are controlling body movements. We expect to see differences in the areas brain activating movement between the two groups of children, which will help us understand changes in the functional networks controlling movements.

We believe this work is an important first step in understanding how childrens’ brain recover following stroke. This research will inform future studies to map structural and functional changes with time, from when the stroke occurs. This
is important because identifying early brain imaging predictors of poorer outcome may influence the early approach of doctors and therapists to rehabilitation following childhood stroke.

**Objectives:** To identify MRI biomarkers that characterise differences in recovery in children with and without unilateral motor deficit (hemiparesis) following childhood arterial ischaemic stroke.

**Progress:**

**Ethics and Recruitment**

An ethics application for this study was prepared and submitted to the Royal Children’s Hospital Human Research Ethics Committee (HREC). The protocol was subsequently approved in December 2016. We have begun recruitment of participants and have obtained formal consent from three participants and their parents. Participant recruitment has been delayed for reasons detailed below.

**MRI Scanner upgrade**

There has been an unexpected delay in our plans for data collection. The initial piloting of the MRI sequences and analyses were successful, however in early 2017 our site secured funds to perform a major hardware and software upgrade of the research MRI scanner (From a TIM-Trio to a Prisma Siemens system). The upgrade was initially planned for June 2017 but was delayed till September 2017. This was then followed by a short period of internal hardware calibration and QA testing in October 2017. **The improvements in scanning will be significant so the decision was made to delay data acquisition until after the upgrade as the images before and after the upgrade would not be comparable.** It is anticipated that there will be significant improvements in data quality following the upgrade however, with enhanced structural resolution, fMRI signal-to-noise profile. We have scheduled patients from the first available research bookings, starting from November 2017.

**MRI Pilot**

We undertook a series of pilot tests of the MRI scanning protocol and subsequent analyses. We aimed to: 1) examine the feasibility of collecting “more demanding” functional MRI data (i.e. In motor fMRI, the child was asked to perform a motor task during the scan); 2) examine the feasibility of processing and analysing the MTR sequence, which was not used previously in childhood stroke imaging. We elected not to pilot the diffusion imaging sequence because our team already have considerable experience acquiring and processing diffusion MRI data in clinical paediatric groups. Two healthy adult volunteers and three study participants participated in MRI scans. Pertinent findings from the MRI pilot are described below.
Findings so far:

Case 1
This is a 12 year old girl with persistent right hand and wrist weakness, four years following a left-sided middle cerebral artery (MCA) stroke, participated in the motor fMRI pilot. It highlighted the need to flexibly adapt the motor paradigm to select a movement within the capabilities of the child. This participant had limited hand movement and could not complete a finger tapping motion, so completed an elbow flexion motion on the left and right instead. Figure 1 summarises the difference in brain areas activating the same movements between two sides of the body. While the right elbow flexion task elicited activation in the expected left-sided brain motor regions (Fig 1, upper row), the left elbow flexion task elicited activations of the same motor regions, but on both sides of the brain (Fig1 lower row). This pattern of brain activation differed from those observed in adult patients who had slow or no recovery of motor function.8, 9 Our preliminary findings suggest stroke also affects brain wiring, controlling movement of the non-stroke affected arm in children, and the possible mechanistic differences underlying brain rewiring and reorganisation in childhood stroke compared to their adult counterparts. More works need to be done to further substantiate these preliminary findings.

Figure 1. Motor fMRI of a 12 year old girl with left MCA stroke and right-sided hand weakness, showing the differences of brain activation when performing a right elbow flexion task (upper row) and a left elbow flexion task (lower row). Abbreviations: L: left; R: right.
Case 2
This is an 18 year old male with persistent right hand weakness, four years following a left MCA territory ischemic stroke (Fig 3A), underwent an quantitative MTR image pilot. We were able to demonstrate reduced MTR value within the infarct (Fig 3C; dotted circle), suggesting low myelin content/degeneration of the involved motor nerve fibre bundles. This finding supports current literature evidence showing reduced MTR parameters are associated with worsen functional recovery following stroke.

Figure 3. Multimodal structural MRI images of an 18 years-old male with persistent right sided hemiparesis, four years following a left MCA territory ischaemic stroke (dotted circles). A) Acute diffusion trace image, showing diffusion restriction in the posterior limb of the internal capsule. B) Chronic FLAIR image showing the gliotic final infarct extending into the left basal ganglia. C) Whole brain myelination map based on magnetisation transfer ratio (MTR) images, showing decreased myelin content within the final infarct. Abbreviations: L: left; R: right.
Findings summary:

As can be seen, we have successfully collected sophisticated MRI data on selected children with slow/poor motor recovery from stroke. Our preliminary findings suggested children's brain might rewire differently following arterial ischaemic stroke compared to their adult counterparts (Case 1 and Figure 1). Quantitative MTR provides useful biomarkers of nerve fibre myelin content. Low myelin content is associated with poor stroke recovery in children (Case 2 and Figure 2). While this is a work in progress, our findings are novel and provide insights into the neuropathological mechanisms of childhood stroke recovery and potential clinically relevant MRI biomarkers associated with poor stroke outcome in children.

References

9. Dancause N, Touvykine B, Mansoori BK. Inhibition of the contralesional hemisphere after stroke: Reviewing a few of the building blocks with a focus on animal models. Prog Brain Res. 2015;218:361-387