Supplementary online content

Contents

eTable 1. MRI Scan Protocol THIN-study 2

DTI analysis and reading 3

eFigure 1. Region of interest location 4

eFigure 2. Rectal temperature profile for each group during intervention 5

References 6

Aker K, *et al. Arch Dis Child Fetal Neonatal Ed* 2020; 105:405–411. doi: 10.1136/archdischild-2019-317311

eTable 1. MRI Scan Protocol THIN-study

Parameter	**DTI**	**DWI**	**3D T1**	**T1 IR**	**T2**	**SWI**	**MRS[a]**
b-value, s/mm^2	b = 0 and b = 600	b = 0 and b = 700	n/a	n/a	n/a	n/a	n/a
Orientation	Axial	Axial	Sagittal	Axial	Axial	Axial	Axial
Fold-over Direction	AP	AP	AP	RL	RL	RL	RL
TR, ms	3670 (shortest)	2400	9.9 (shortest)	5000	7700	16 (shortest)	2000 (long)
TE, ms	52 (shortest)	105 (shortest)	4.6	15	140	23 (shortest)	144
TI, ms	n/a	n/a	n/a	900	n/a	n/a	n/a
No. of Slices	45	35	120	35	35	110	25 voxels
Slice Thickness, mm	2.5	3.0	1.0	3.0	3.0	1.0	1.5
Slice Gap, mm	0	0	0	0	0	0	
FOV, mm	200x200	180x180	192x192	170x170	170x170	180x180	
Matrix (resolution)	80x80	192x192	192x192	256x256	256x256	448x448	
Voxel Size, mm	2.5x2.5x2.5	1.0x1.0x3.0	1.0x1.0x1.0	0.7x0.7x3.0	0.7x0.7x3.0	0.4x0.4x1.0	1.0x1.0x1.5
k-space Coverage	Halfscan, factor 0.68	Halfscan, factor 0.72	Full	Full	Full	Elliptical	
Parallel Imaging	SENSE (p = 2)	SENSE (p = 1.5)	SENSE (p = 1)	SENSE (p = 1.4)	no	SENSE (p = 2.4)	No
Flip Angle	90°	90°	8°	90°	90° (120° refocusing)	15°	90°
Scan Technique	DTI. SS-EPI SPIR fat saturation	DWI. SS-EPI SPIR fat saturation	3D T1 TFE	TSE IR	TSE	T1 FFE	
Turbo Factor (ETL)	n/a	n/a	n/a	5	11	n/a	n/a
Diffusion Tensor Directions	High (32)	3	n/a	n/a	n/a	n/a	n/a

Abbreviations: DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; IR, inversion recovery; SWI, susceptibility weighted imaging; MRS, MR spectroscopy; AP, anterior-to-posterior; RL, right-to-left; TR, repetition time; TE, echo time; TI, inversion time; FOV, field of view; SENSE, sensitivity encoding; SS-EPI, single-shot echo planar imaging; SPIR, spectral presaturation inversion recovery; TFE, turbo field echo; TSE, turbo spin echo; FFE, fast field echo; ETL, echo train length.

[a] Multi voxel spectroscopy (25 voxels cover basal ganglia)

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DTI analysis and reading

The diffusion tensor imaging (DTI) analyses were performed with the tools of the FMRIB Software Library (FSL; Oxford Centre for Functional MRI of the Brain, UK; www.fmrib.ox.ac.uk/fsl). Image artefacts due to motion and eddy current distortions were minimised by registration of all DTI acquisitions to the mean b=0 image using affine registration. The brain was extracted using Brain Extraction Tool (part of FSL). FMRIB's Diffusion Toolbox was used to fit a diffusion tensor model to the raw diffusion data in each voxel. Voxel-wise maps of fractional anisotropy (FA) and mean diffusivity (MD) were calculated for the TH- and SC-groups.

Voxel-wise statistical analysis of the DTI data was performed using Tract-Based Spatial Statistics (TBSS, FSL).[1 2] Voxel-wise statistics of the skeletonised FA and MD were carried out on the WM skeleton using Randomise (FSL) to test for group differences between the TH- and SC-groups. Randomise performs non-parametric permutation-based testing of inference using Threshold-Free Cluster Enhancement[3] with a correction for multiple comparisons ($p<0.05$, corrected for sex, birth weight and gestational age).

A region-of-interest (ROI) approach was also applied to extract FA and MD from posterior limb of the internal capsule (PLIC), thalami, lentiform nuclei, midbrain, and genu and splenium of the corpus callosum, as defined by the JHU Neonate Brain Atlas (eFigure 1).[4] Each participant's individual FA image was registered to the JHU Neonate Brain Atlas using linear and non-linear registration (FSL). Manual adjustments of the ROIs were performed to ensure that the ROIs were placed anatomically correct in each participant, and mean FA and MD were calculated for all participants and ROIs.

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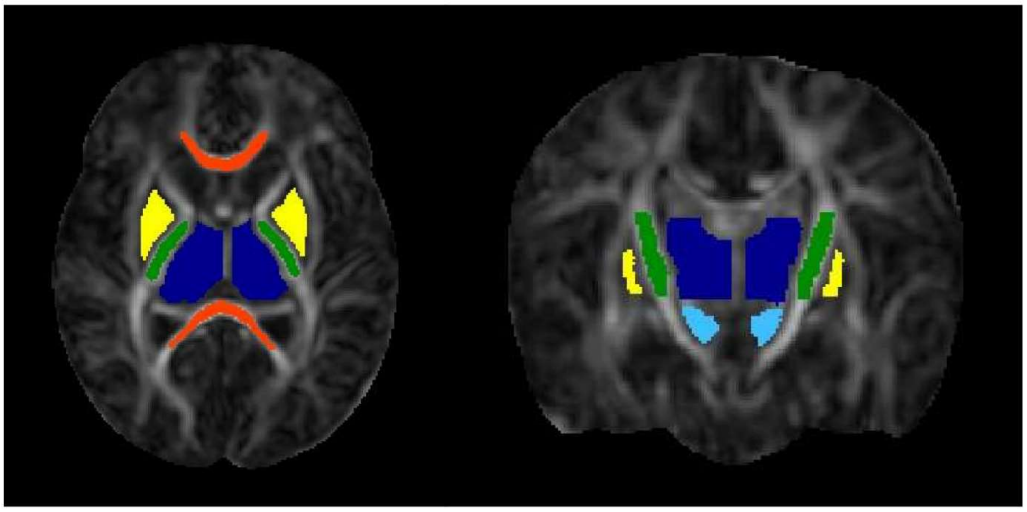
eFigure 1. Region of interest location



Posterior limb of the internal capsule (green), thalami (dark blue), lentiform nuclei (yellow), midbrain (light blue), and genu and splenium of the corpus callosum (red) overlaid on JHU Neonate Brain Atlas fractional anisotropy template.

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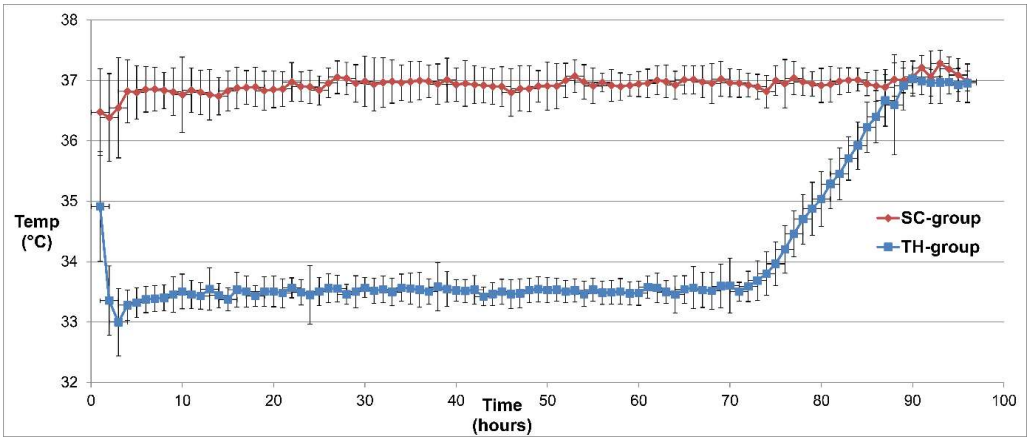
eFigure 2. Rectal temperature profile during intervention



SC, standard care; TH, therapeutic hypothermia.
The vertical bars indicate mean±2 SD. Time 0 is the first temperature taken after randomization.

Mean age of starting therapeutic hypothermia (TH) was 3.75 hours (SD 1.44) and mean rectal temperature on admission to NICU was 35.8°C (SD 0.80) in TH-group and 36.2°C (SD 0.63) in standard care (SC) group. Rectal temperature dropped to target range within the first hour after initiation of cooling in 22 infants (88%). Sixty-four temperature measurements (3.6%) during TH were outside the target range. There were no temperatures ≥38°C during rewarming or 12 hours thereafter. In the SC-group, 175 temperature measurements (10%) were outside the target range. No measurements were above 38°C, but 32 measurements (2%) were between 37.5°C and 38.0°C during the first 72 hours.

References

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