Harmonization recommendations for Neuroimaging data

Appendix 1 of LifeCycle report D6.3

Report on the relationship of early-life stressors with fetal and childhood brain developmental outcomes and the extent to which these mediate associations of early-life exposures with mental health and psychopathology life course trajectories

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Appendix 1

Harmonization recommendations for Neuroimaging data

1. Aim of task WP 6.3

The aim of Work Package 6, Task 3 of LifeCycle is to 'Identify early brain development that mediates the relationships between early-life stressors and later mental health and disease'. For this purpose, it is important to harmonize the neuroimaging data that has been collected and potential future neuroimaging data collection within the EU Child Cohort Network.

The aim of this specific neuroimaging protocol is to guide the cohorts in the harmonization process to generate variables that will be comparable across cohorts and measurements. The harmonization strategy is based on an adaptation of the DataSHaPER guidelines [1], aimed to facilitate a rigorous, transparent and effective harmonization, made in the framework of the MeDALL project [2], like in the complete work package (WP 6), as well as neuroimaging networks that are existing (e.g ENIGMA, http://enigma.ini.usc.edu).

2. Neuroimaging domains

The following table provides a short description of the neuroimaging outcome domains. We have not assigned any priority yet, because there are only a few cohorts that have neuroimaging data. In addition, the neuroimaging data was assessed at very different ages ranges. Because it is very hard to share surface-based data and MRI images (need for large storage), the first step is to harmonize summary variables in the LifeCycle project.

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Neuroimaging domains	Dimensions	Definitions (different levels of complexity depending on age)
Structural neuroimaging	Volumetric data in mm^3	Preferably processed through Freesurfer v 6.0
	Cortical surface area in mm^2	Preferably processed through Freesurfer v 6.0
	Cortical thickness in mm	Preferably processed through Freesurfer v 6.0
	Gyrification Index	Preferably processed through Freesurfer v 6.0
	Surface-based data	Preferably processed through Freesurfer v 6.0
Diffusion weighted neuroimaging	Fractional anisotropy	Mean FA values per tract; preferably processed using standard tools in combination with the AutoPtx software [1-5] https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/AutoPtx
	Diffusivity measures	Mean MD. RD and AD values per tract; preferably processed using standard tools in combination with the AutoPtx software MD: mean diffusivity AD: axial diffusivity RD: radial diffusivity
Resting-state functional neuroimaging	Summary measures quantifying fluctuations in the connectivity time courses	*Ongoing process in Generation R* Whole brain dynamic functional network connectivity (DFNC)
	Summary stats based on graph theory	Global efficiency, shortest path length, number of nodes and edges
Task-related functional neuroimaging	Dependent on tasks and specific cohorts	

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3. Time periods variables

Neuroimaging data has only been collected in a few cohorts, namely ALSPAC, the Generation R Study, Norwegian Mother and Child Cohort Study (MOBA), Northern Finnish Birth Cohort (NFBC1966 and. NFBC1986). In Generation R Next, neuroimaging data will be collected in new-borns (planned assessment). We may need to adjust the inventory for this cohort in a later phase of the study. However, age range goes beyond 18 years, while in Lifecycle the focus is on children up to 18 years.

Table 1: Cohorts with neuroimaging information

Cohort	0-5 yrs.	5-10 yrs.	10-13 yrs.	13-15 yrs.	15-20 yrs.	20-25 yrs.	25-30 yrs.	30+ yrs.
ALSPAC						X		
The Generation R Study		X	X	X	(X)			
NFBC1966								X
MOBA	X	X	X					
NFBC1986						X	X	
Generation R Next	(X)							

X: data available
(X): planned data collection
Age range after 18 years

Based on group consensus in WP6 (June/July 2020), the harmonization of the neuroimaging data will be similar to the harmonization of the behavioural outcomes, and will be on a yearly basis up to 30 years. Cohorts will only make the variables in the ages where data if is available. If no MRI data is available, e.g. at 4 years in the Generation R or ALSPAC cohort, then this variable will not be constructed.

4. Technical details neuroimaging

For now, technical information is only partly available. See tables below.

Table 2: Technical parameters of the acquired structural magnetic resonance imaging (T1)

	MOBA	MOBA	Generation R	Generation R	Generation R	ALSPAC	NFBC1986	NFBC1966
Age range	4-10 years	4-10 years	6-9 years	9-12 years	13-14 years	20-25	20-30 years	33-44 years
Number of	¿?	¿?	1070	3992	On-going	800 **	329/471***	188/285***
Scanner	¿?	¿?	3T GE	3T GE	3T GE	3T GE HDx	1.5 T	1.5 TGE
Head coil	¿?	¿?	8	8	8	8	8	8
Sequence type	¿?	¿?	IR-FSPGR	IR-FSPGR	IR-FSPGR			3D-SPGR
TR (ms)	¿?	¿?	10.3	877	877	7.8		35
TE (ms)	¿?	¿?	4.2	3.4	3.4	3.0		5.0
TI (ms)	¿?	¿?	350	600	600			
NEX	¿?	¿?	1					
Flip angle (°)	¿?	¿?	16	10	10			35
FOV	¿?	¿?		220 x 220	220 x 220			
Matrix	¿?	¿?	256 x 256	220 X220	220 X220			
Voxel size (mm^3)	¿?	¿?	0.9 x 0.9 x	1.0 x 1.0 x	1.0 x 1.0 x 1.0	1.0 x 1.0 x	1.0 x 1.0 x	1.0 x 1.0 x
Accelerating factor	¿?	¿?	2	2	2			
Acquisition time	¿?	¿?	5 min 40 s	5 min 40 s	5 min 40			
Post-processing	¿?	¿?	Freesurfer	Freesurfer v	Freesurfer v			Freesurfer

IR-FSPGR: Intense Inversion Recovery Fast Spoiled Gradient Recalled, T1 weighted image; TR, Repetition Time; TE, Echo Time; TI, Inversion Time

3D fast spoiled gradient echo sequence - ALSPAC;

3D SPGR : three dimensional spoiled gradient echo;

Table 3: Technical parameters of the acquired diffusion weighted images (DTI)

	MOBA	MOBA	Generation R	Generation R	Generation R	ALSPAC	NFBC1986	NFBC1966
Age range	4-10 years	4-10 years	6-9 years	9-12 years	13-14 years	20-25 years	20-30	33-44 years
Number of	¿?	¿?	1070	3777	On-going		329/471	188/285
Scanner	¿?	¿?	3T GE	3T GE	3T GE	3T GE HDx	1.5 T	
Sequence type	¿?	¿?	EPI					
Head coil	¿?	¿?	8	8	8	8	8	
TR (ms)	¿?	¿?	11000	12500	12500		9000	
TE (ms)	¿?	¿?	8	72	72	87	102	
FOV (mm)	¿?	¿?	256 x 256	240 x 240	240 x 240	230 x 230	192 x 192	
Matrix size	¿?	¿?	128 x 128	120 x120	120 x120	96 x96	104 x 104	
Number of slices	¿?	¿?	77	65	65		61	
Voxel size	¿?	¿?	2 x 2 x 2	2 x 2 x 2	2 x 2 x 2	2.4 x 2.4 2.4	2.3 x 2.3 x	
Directions	¿?	¿?	35	35	35	60	64/32?	64/32?
b-value	¿?	¿?	0 s/mm^2	900	900	1200 s/mm^2	1000	1000
Acquisition time	¿?	¿?	7 min 40 s	7 min 40 s	7 min 40 s		8 min 25 s	
Pre-processing	¿?	¿?	FSL, FMRIB,	FSL, FMRIB,	FSL, FMRIB,	Explore DTI		
Post-processing	¿?	¿?	Tractography	Tractography	Tractography	Tractography,		

EPI: echo planar imaging

5. Instructions to harmonize variables

- Identify the cohort-specific instruments that measure the main neuroimaging domains. We advise to all use the same software and the same pipeline to produce the variables when possible. Generation R has been using FreeSurfer version 6.0 for structural processing (**see Annex I**) and for diffusion weighted image processing the Generation R study used Autoptx (**see Annex II**). For functional MRI (task-related and resting-state), quality assessment is also important, but currently there are no recommendations for specific ways to process the data. In Generation R standard tools have been used from the FSL-package.
- In order to be as consistent as possible, it is important to more or less perform the quality assessment in similar ways. In the Generation R, there is some information on how the quality assessment was done for the T1 and DTI images and this can be shared upon request. There are also several automated QA tools available online, that we might consider to start using in the cohorts.
- For each harmonized assessment, it is important to provide the exact age in years of when the assessment took place.; this will facilitate developing trajectories.
- For volumetric measures make sure we keep the original data of Freesurfer; volumes in mm3, surface are in mm2 and thickness in mm. Do not convert the volumes in other scales (e.g. cm3 or cm2). For diffusion weighted measures, also keep the same scales, (e.g. FA ranges from 0 to 1). In this case standardization of the measures is not needed, and outcomes remain interpretable.
- Provide a description of the harmonized variables, including: cohort name, domain, dimension, harmonized variable, description, source variables, data type, interpretation original score, evaluator, number of subjects, syntax, and date of update (See Annex II. Example: Description of harmonized variables). You will find attached the template file to provide this information.
- Future actions related to harmonization process: if there are cohorts that are going to collect neuroimaging it is good to use similar sequences when possible and the same software packages for processing.
- For the analyses, batch effects can be considered with the COMBAT tools; this tool has been used in structural MRI data, as well as diffusion MRI data [6-7], and is freely available on GitHub: https://github.com/Jfortin1/ComBatHarmonization
- The focus will be on the core neuromaging outcome, which are key volumetric measures: estimated intracranial volume, total gray matter, total white matter, cerebellum, amygdala and hippocampal volume.
- For instructions on quality control after the harmonization, use the instructions that were used for the variables harmonized previously in WP6 starting on page 36 in the WP6 harmonization protocol. Step 1 verify list of variables and formats, step 2 check univariate distributions, step 3 check internal validation, step 4 check quality for repeated measures, step 5 complete the online catalogue.

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6. References

[1] De Groot M, Vernooij MW, Klein S, Ikram MA, Vos FM, Smith SM, Niessen WJ, Andersson JLR, 2013. Improving alignment in Tract-based spatial statistics: Evaluation and optimization of image registration. NeuroImage, 76, 400-411.

[2] Mori S, Kaufmann WE, Davatzikos C, Stieltjes B, Amodei L, Fredericksen K, Pearlson GD, Melhem ER, Solaiyappan M, Raymond GV, Moser HW, Van Zijl PCM, 2002. Imaging cortical association tracts in the human brain using diffusion-tensor-based axonal tracking. Magnetic Resonance in Medicine 47, 215–223.

[3] Stieltjes B, Kaufmann WE, Van Zijl PC, Fredericksen K, Pearlson GD, Solaiyappan M, Mori S, 2001. Diffusion tensor imaging and axonal tracking in the human brainstem. NeuroImage 14, 723–735.

[4] Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, Hua K, Zhang J, Jiang H, Dubey P, Blitz A, Van Zijl P, Mori S, 2007. Reproducibility of quantitative tractography methods applied to cerebral white matter. NeuroImage 36, 630–644.

[5] Wakana S, Jiang H, Nagae-Poetscher LM, Van Zijl PCM, Mori, S, 2004. Fiber Tract–based Atlas of human white matter anatomy. Radiology 230, 77–87

[6] Fortin JP, Parker D, Tunc B, Watanabe T, Elliott MA, Ruparel K, Roalf DR, Satterthwaite TD, Gur RC, Gur RE, Schultz RT, Verma R, Shinohara RT, 2017. Harmonization Of Multi-Site Diffusion Tensor Imaging Data. NeuroImage, 161, 149-170.

[7] Fortin JP, Cullen N, Sheline YI, Taylor WD, Aselcioglu I, Cook PA, Adams P, Cooper C, Fava M, McGrath PJ, McInnis M, Phillips ML, Trivedi MH, Weissman MM, Shinohara RT, 2018. Harmonization of cortical thickness measurements across scanners and sites. NeuroImage, 167, 104-120.

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Annex I Freesurfer information

General

FreeSurfer is a software package for the analysis and visualization of structural and functional neuroimaging data from cross-sectional or longitudinal studies. General information about the software can be found on the FreeSurfer Wikipage:
https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki

Download and installation

Information about downloading and installing FreeSurfer:
https://surfer.nmr.mgh.harvard.edu/fswiki/DownloadAndInstall

Steps to run FreeSurfer on your data:

1. Refer to your subject in your data folder

```
SUBJECT="R112594"
EVENT="100015"
```

2. make the directory that FreeSurfer will look in for the MGZ file, and

```
mkdir -p ${MRDATA}/structural/${SUBJECT}/mri/orig
```

3. convert from DICOM to MGZ

```
mri_convert -it dicom -ot mgz
${MRDATA}/dicom/${SUBJECT}/${EVENT}/IRFSPGR*/*0001.dcm
${MRDATA}/structural/${SUBJECT}/mri/orig/001.mgz
```

4. kick-off FreeSurfer on the subject

```
recon-all -s ${SUBJECT} -autorecon-all
```

Depending on the hardware running FreeSurfer takes about 20-24 hours per subject. Depending on the quality data, it may be necessary to add flags to the command (https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all) or to manually correct topologies.

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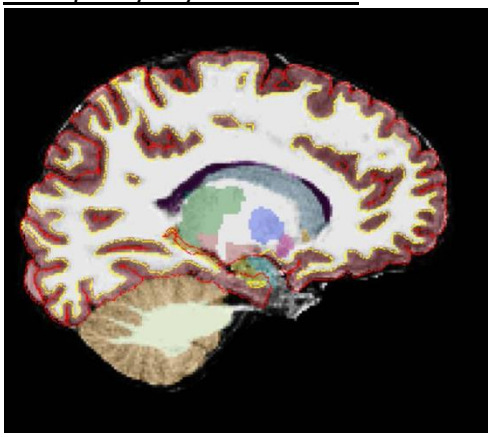
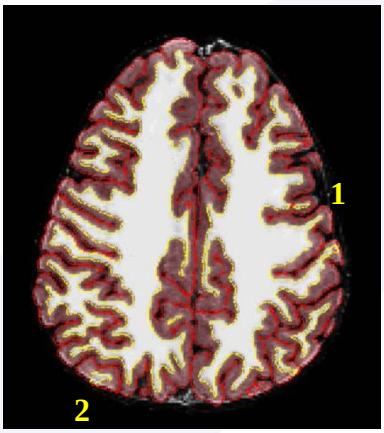
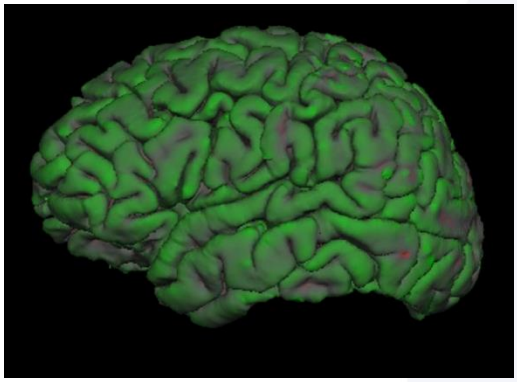
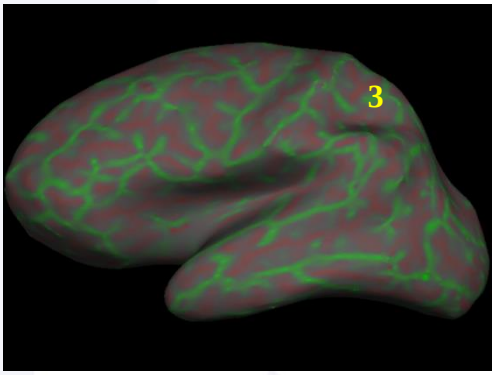
Freesurfer output checking
Example of a good dataset:









Why this is a *good quality* Freesurfer output:

In this example, you see that that the white matter and the grey matter lining follows the image correctly. Little mistakes in the 2D image are visible (1 and 2), but if this in a few slices, then this is not a problem. The 3D pial image looks smooth and there are little intense colored areas visible on both the 3D pial image as well as the 3D inflated image looks smooth.

Note that there is a difference in the shape of the inflated surface when comparing it to the adult inflated surface (bert). The inflated surface of pediatric data does have a bump in the occipital area (3), which looks off, but as long the surface is smooth this should not be a problem. Data with good quality will be used in the analyses.

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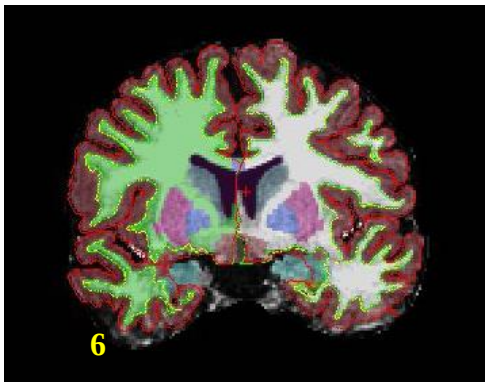

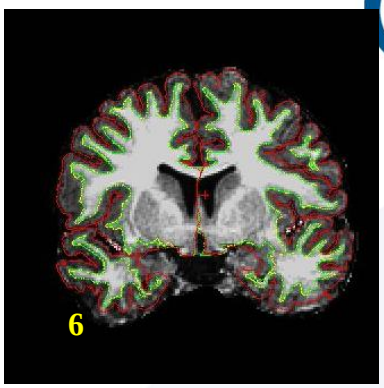

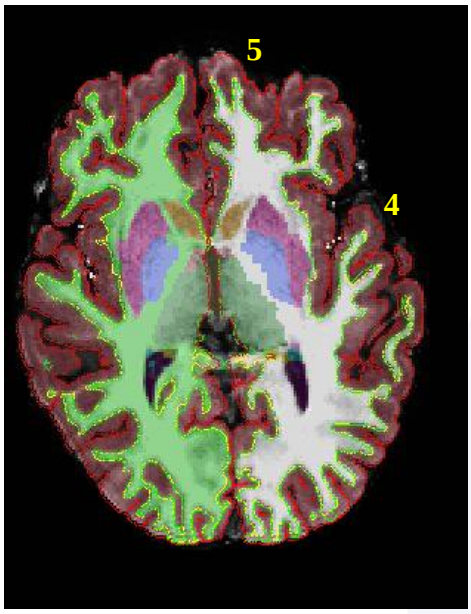

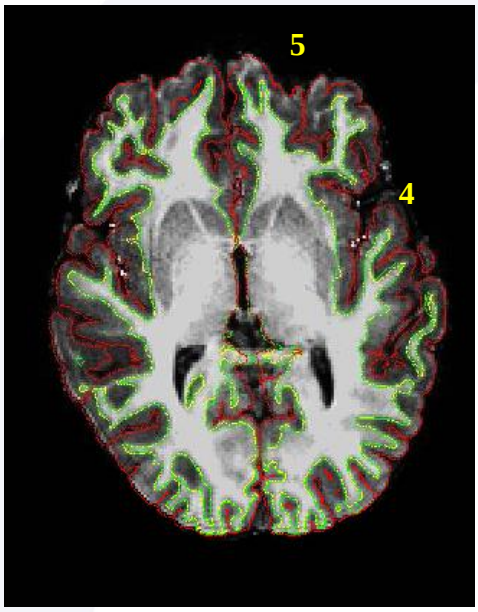

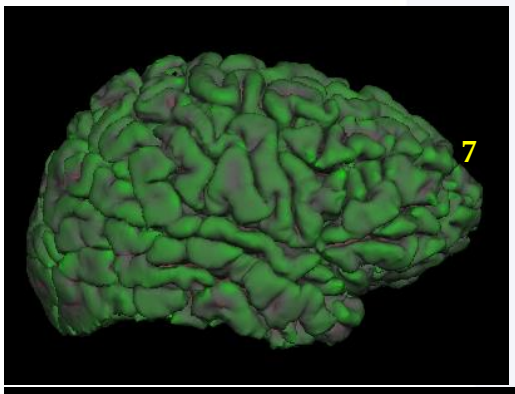

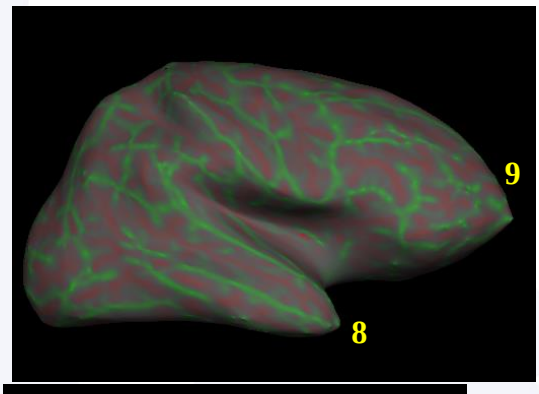

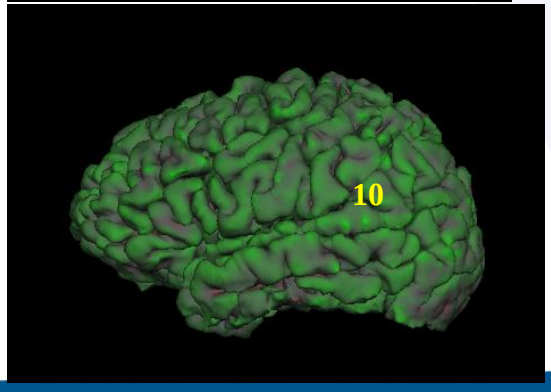

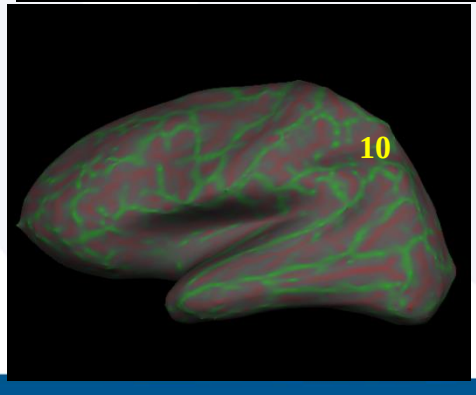

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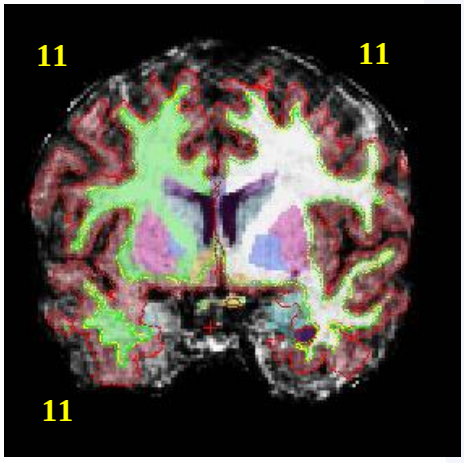
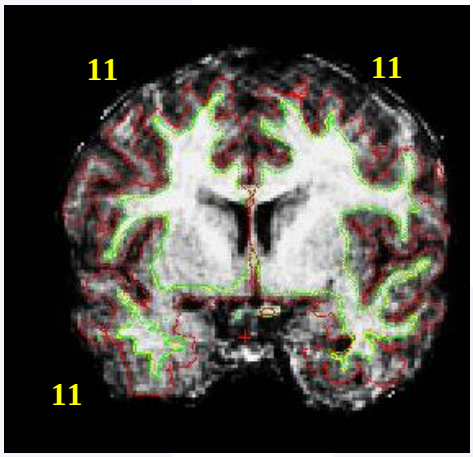
Why this is a *questionable quality* Freesurfer output:

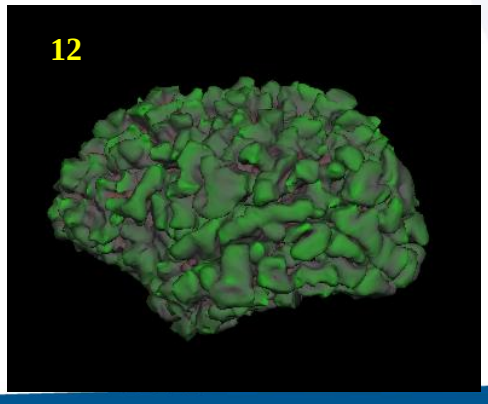
In this example, you see that that overall the white matter and the grey matter lining follow the image. However, there are some areas where the lining could be better, sometimes the grey matter does not follow the surface correctly (4) and you can also see this in the white matter lining (5). When you see this in one or two slices that should not be a problem, but when you see this at multiple slices then this means you miss a significant proportion of the grey and white matter.

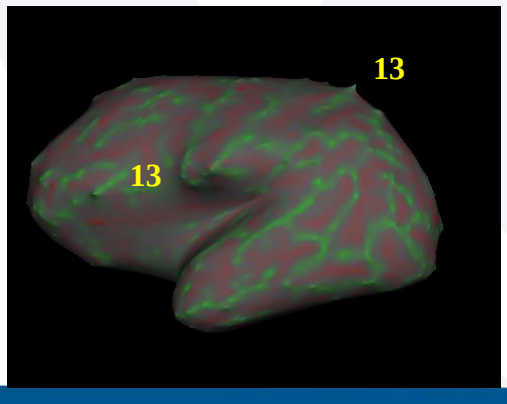
Specifically, the temporal lobe has this problem more often and is therefore separately rated (6).

In this case, the accumulation of the little mistakes can be seen in the 3D pial surface image, where little chunks of gyri (7) are missing. In particular, the frontal area does not look smooth like the good quality image, but the surface looks chunky, rocky or bumpy. Although the 3D inflated surface looks smooth, you do see some spikes (the frontal area and the temporal area looks spiky, 8,9) and intense colored spots are visible on the pial and the inflated surface (10) as well. Although the data is not perfect (questionable) it is of *sufficient* quality to be used in the analyses. It is expected that a large proportion of the pediatric data will be of this quality.









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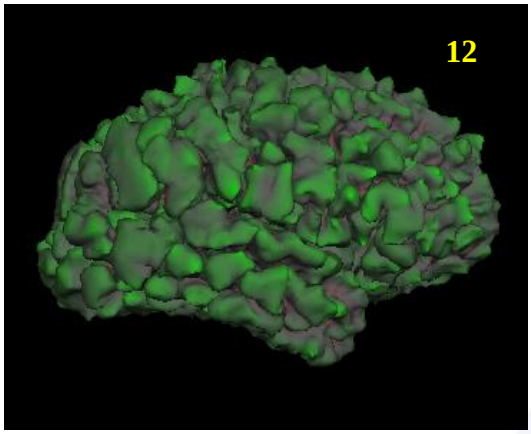

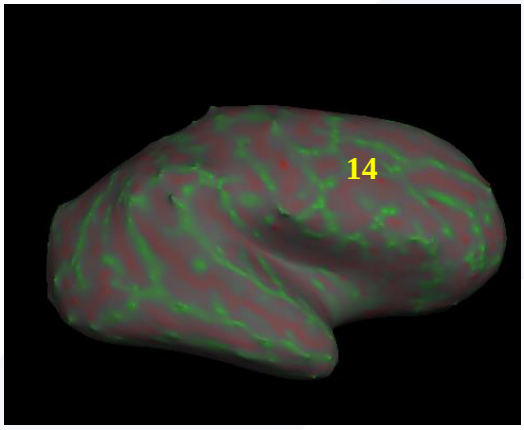

Why this is a *poor quality* Freesurfer output:
In this example, you see that that overall the white matter and the grey matter lining do not follow the image (11). Actually, the quality of the input image is very blurry and even a manual segmentation would have been impossible. The rings that you see are due to movement. It is very clear that the red line does not follow the grey matter at all.
Again, you can see the accumulation of all the mistakes the 3D pial surface image, where the surface looks completely chunky or rocky (12). You do not recognize a brain in this image. Further, the 3D inflated surface does not look smooth and there is a lot of spiking (13) and intense colored spots (14) on the inflated surface are clearly visible as well. We will not use data with poor quality output in the analyses.

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Annex II AutoPtx

Information on the AutoPtx package can be found:
https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/AutoPtx

AutoPtx v0.1.1 is a set of simple scripts and mask images to run probabilistic tractography in subject-native space using pre-defined protocols. AutoPtx requires a working version of FSL and has been tested on Linux and Mac.

To run this package, FSL should be working. If the FSL package is not installed; one can find this here: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki

The AutoPtx software package can calculate average FA, MD, RD and AD for the main white matter tracts. These include: brain stem tracts, projection fibers, association fibers, limbic system fibers and callosal fibers.

Diffusion image processing was conducted using DTIPrep tool (https://www.nitrc.org/projects/dtiprep/) by inspecting a combination of manual and automated checks, including examining slice wise variation in the diffusion signal, examining the sum-of-squares error of the tensor calculation, and inspecting intersubject registration accuracy.

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Annex III Harmonization table variables

For cerebellum volume, first compute sum of cerebellar cortex and white matter volume for left and right hemisphere.

- ***List of yearly intervals variables***

	Variable name	Label description	Values	Unit	Datatype	comments
META-VARIABLES						
Child identifier	Child_id	Unique identifier number for the index child				Either the original id or a new id generated by the cohort; Should already be created for the core variable list, please add here to make it possible to combine data
BRAIN VOLUMES						
Estimated intracranial volume	etiv_0 etiv_1 etiv_2 etiv_3 etiv_4 etiv_5 etiv_6 etiv_7 etiv_8 etiv_9 etiv_10 etiv_11 etiv_12 etiv_13	Estimated intracranial volume at age 0-1 years Estimated intracranial volume at age 1-2 years Estimated intracranial volume at age 2-3 years Estimated intracranial volume at age 3-4 years Estimated intracranial volume at age 4-5 years Estimated intracranial volume at age 5-6 years Etc..		mm^3	Continuous, rounded without decimals	Based on freesurfer v 6.0 output data (aseg file)

	etiv_14 etiv_15 etiv_16 etiv_17 …. etiv_30					
Total gray matter	TotalGrayVol_0 TotalGrayVol_1 TotalGrayVol_2 TotalGrayVol_3 TotalGrayVol_4 TotalGrayVol_5 TotalGrayVol_6 TotalGrayVol_7 TotalGrayVol_8 TotalGrayVol_9 TotalGrayVol_10 TotalGrayVol_11 TotalGrayVol_12 TotalGrayVol_13 TotalGrayVol_14 TotalGrayVol_15 TotalGrayVol_16 TotalGrayVol_17 … TotalGrayVol_30	Total gray matter volume at age 0-1 years Total gray matter volume at age 1-2 years Total gray matter volume at age 2-3 years Total gray matter volume at age 3-4 years Total gray matter volume at age 4-5 years Total gray matter volume at age 5-6 years Etc..		mm^3	Continuous, rounded without decimals	Based on freesurfer v 6.0 output data (aseg file)
Total white matter	CerebralWhiteMatterVol_0 CerebralWhiteMatterVol_1	Cerebral white matter volume at age 0-1 years Cerebral white matter volume at age 1-2 years		mm^3	Continuous, rounded without decimals	Based on freesurfer v 6.0 output data (aseg file)

	CerebralWhiteMatterVol_2 CerebralWhiteMatterVol_3 CerebralWhiteMatterVol_4 CerebralWhiteMatterVol_5 CerebralWhiteMatterVol_6 CerebralWhiteMatterVol_7 CerebralWhiteMatterVol_8 CerebralWhiteMatterVol_9 CerebralWhiteMatterVol_10 CerebralWhiteMatterVol_11 CerebralWhiteMatterVol_12 CerebralWhiteMatterVol_13 CerebralWhiteMatterVol_14 CerebralWhiteMatterVol_15 CerebralWhiteMatterVol_16	Cerebral white matter volume at age 2-3 years Cerebral white matter volume at age 3-4 years Cerebral white matter volume at age 4-5 years Cerebral white matter volume at age 5-6 years Etc..				

	CerebralWhiteMatterVol_17 … CerebralWhiteMatterVol_30					
Amygdala	Right-amygdala_0 Right-amygdala_1 Right-amygdala_2 Right-amygdala_3 Right-amygdala_4 Right-amygdala_5 Right-amygdala_6 Right-amygdala_7 Right-amygdala_8 Right-amygdala_9 Right-amygdala_10 Right-amygdala_11 Right-amygdala_12 Right-amygdala_13 Right-amygdala_14 Right-amygdala_15 Right-amygdala_16 Right-amygdala_17 … Right-amygdala_30	Right amygdala volume at age 0-1 years Right amygdala volume at age 1-2 years Right amygdala volume at age 2-3 years Right amygdala volume at age 3-4 years Right amygdala volume at age 4-5 years Right amygdala volume at age 5-6 years Etc..		mm^3	Continuous, rounded without decimals	Based on freesurfer v 6.0 output data (aseg file)
	Left-amygdala_0 Left-amygdala_1 Left-amygdala_2 Left-amygdala_3 Left-amygdala_4	Left amygdala volume at age 0-1 years Left amygdala volume at age 1-2 years Left amygdala volume at age 2-3 years Left amygdala volume at age 3-4 years Left amygdala volume at age 4-5 years		mm^3	Continuous, rounded without decimals	Based on freesurfer v 6.0 output data (aseg file)

	Left-amygdala_5 Left-amygdala_6 Left-amygdala_7 Left-amygdala_8 Left-amygdala_9 Left-amygdala_10 Left-amygdala_11 Left-amygdala_12 Left-amygdala_13 Left-amygdala_14 Left-amygdala_15 Left-amygdala_16 Left-amygdala_17 … Left-amygdala_30	Left amygdala volume at age 5-6 years Etc..				
hippocampus	Right-hippocampus_1 Right-hippocampus_2 Right-hippocampus_3 Right-hippocampus_4 Right-hippocampus_5 Right-hippocampus_6 Right-hippocampus_7 Right-hippocampus_8 Right-hippocampus_9 Right-hippocampus_10 Right-hippocampus_11 Right-hippocampus_12 Right-hippocampus_13 Right-hippocampus_14 Right-hippocampus_15	Right hippocampus volume at age 0-1 years Right hippocampus volume at age 1-2 years Right hippocampus volume at age 2-3 years Right hippocampus volume at age 3-4 years Right hippocampus volume at age 4-5 years Right hippocampus volume at age 5-6 years Etc..		mm^3	Continuous, rounded without decimals	Based on freesurfer v 6.0 output data (aseg file)

	Right-hippocampus_16 Right-hippocampus_17 ... Right-hippocampus_30					
	Left-hippocampus_0 Left-hippocampus_1 Left-hippocampus_2 Left-hippocampus_3 Left-hippocampus_4 Left-hippocampus_5 Left-hippocampus_6 Left-hippocampus_7 Left-hippocampus_8 Left-hippocampus_9 Left-hippocampus_10 Left-hippocampus_11 Left-hippocampus_12 Left-hippocampus_13 Left-hippocampus_14 Left-hippocampus_15 Left-hippocampus_16 Left-hippocampus_17 .... Left-hippocampus_30	Left hippocampus volume at age 0-1 years Left hippocampus volume at age 1-2 years Left hippocampus volume at age 2-3 years Left hippocampus volume at age 3-4 years Left hippocampus volume at age 4-5 years Left hippocampus volume at age 5-6 years Etc..		mm^3	Continuous, rounded without decimals	Based on freesurfer v 6.0 output data (aseg file)
Age at neuroimaging	sMRI_age_0 sMRI_age_1 sMRI_age_2 sMRI_age_3 sMRI_age_4	Exact neuroimaging age 0-1 years Exact neuroimaging age 1-2 years Exact neuroimaging age 2-3 years Exact neuroimaging age 3-4 years Exact neuroimaging age 4-5 years		years	Continuous, decimals	

	sMRI_age_5 sMRI_age_6 sMRI_age_7 sMRI_age_8 sMRI_age_9 sMRI_age_10 sMRI_age_11 sMRI_age_12 sMRI_age_13 sMRI_age_14 sMRI_age_15 sMRI_age_16 sMRI_age_17 … sMRI_age_30	Exact neuroimaging age 5-6 years Etc..				

Annex IV Example description harmonized variables

- ***Example: Description of harmonized variables for excel sheets***

cohort	domain	dimension	harmonized variable	description	source variables	data type
GenR	Neuroimaging	Structural MRI	etiv_0_5	Estimated intracranial volume at age 0-5 years	TBV_GENR_F@5	continuous

interpretation original score	evaluator	number of subjects	Recoding syntax	Software for recoding	Date of harmonization
Number represents volume in mm3	MRI machine	2299	***copy new variable with correct name depending on exact age at assessment***. IF (agechild_MRI<12 AND agechild_MRI >=11) etiv_11=etiv. VARIABLE LABELS etiv_11 'estimated intrcranial volume assessed at between ≥11 year and < 12 years'. *** define level of variable ***. *** remove decimals ***. VARIABLE LEVEL etiv_11 (SCALE). FORMATS etiv_11 (f8.0).	IBM SPSS statistics v.25	20/12/2018