Best Practices in Structural Neuroimaging of Neurodevelopmental Disorders

Lea L. Backhausen[1], Megan M. Herting[2], Christian K. Tamnes[3,4,5], Nora C. Vetter[1]

1. Department of Child and Adolescent Psychiatry, Faculty of Medicine of the Technische Universität Dresden, Dresden, Germany
2. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
3. PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway
4. NORMENT, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
5. Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway

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Summary

Cohort of interest

Brain morphological metrics in Freesurfer

Presentation of the brain morphological metrics

Differences in brain developmental trajectories between control group and ADHD, ODD and CD patients

Challenges and good practises with quality control

Study design

Image acquisition

Image processing

Quality control

Statistical analysis

Cohort of interest

Age: **5-24 yo** (no younger, because of methodological challenges)

Selected neurodevelopmental disorders:

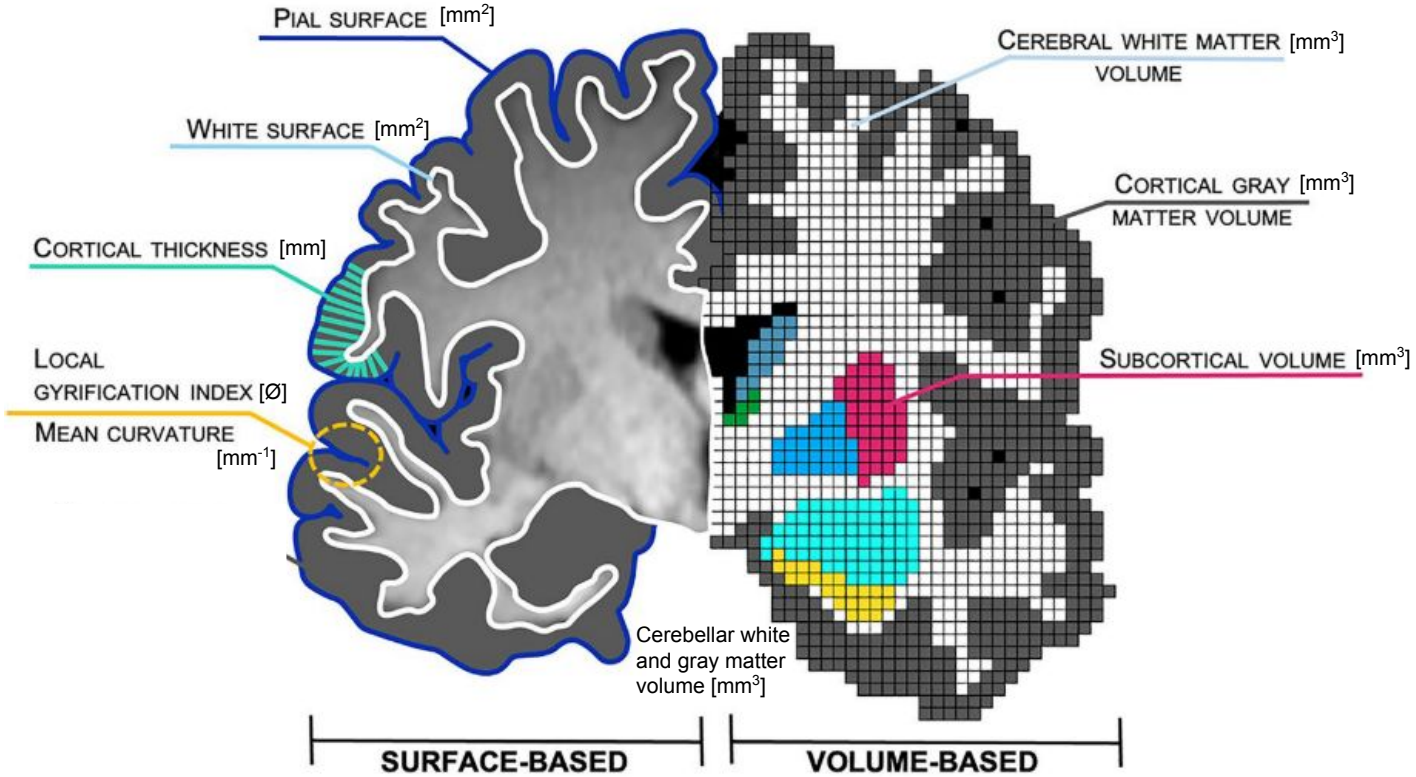
- Attention Deficit Hyperactivity Disorder (**ADHD**) *(prevalence approx. 6 %; Barkley, 2014)*,
- Conduct Disorder (**CD**) *(prevalence approx. 3 %; Canino et al., 2010)*,
- Oppositional Defiant Disorder (**ODD**) *(prevalence approx. 3 %; Canino et al., 2010)*.

Imaging tool: **Structural Magnetic Resonance Imaging (sMRI)**
MRI modality: **T1-weighted sequence**

Morphological metrics computation process: **Freesurfer (v7.1)**

Goal of this review: Improve protocols for study design, image acquisition and analysis, quality control, and statistical analysis, in the end goal of **identifying neurobiological markers for neurodevelopmental disorders**.

Main brain morphological metrics in Freesurfer



Color	Subcortical structure
Black	Cerebrospinal fluid
Blue-gray	Nucleus caudatus
Green	Thalamus
Magenta	Putamen
Deep sky blue	Globus pallidus
Cyan	Amygdala
Yellow	Hippocampus

Fig. 1 Overview of structural brain metrics in Freesurfer on a coronal slice of an MRI T1w image in ATLAS space

Differences in brain developmental trajectories between control group and ADHD, ODD and CD patients

Morphological metric	Typical developmental trajectories throughout adolescence	Atypical trajectories in ADHD, CD and ODD
Whole brain volume [mm^3]	Gradually decreases starting age 13 and stabilizes in the early twenties *(Mills et al., 2016)*	2.5% reduction for ADHD *(Greven et al., 2015)*
Estimated Total Intracranial Volume (eTIV or ICV) [mm^3]	Increases annually of around one percent between late childhood and mid-adolescence and stabilizes in late adolescence *(Mills et al., 2016)*	5% reduction for ADHD *(Vetter et al., 2020)*
Cortical gray matter volume [mm^3]	Gradually decreases starting age 8 and stabilizes in third decade *(Mills et al., 2016; Tamnes et al., 2013; Wierenga et al., 2014)* Mostly driven by cortical thickness	CD+ODD: reductions in the bilateral insula and the left middle/superior frontal gyrus *(Noordermeer et al., 2016)* → empathy and introspection ADHD: mitigated results *(Ambrosino et al., 2017; Semrud-Clikeman et al., 2014)*
↳Cortical thickness [mm]	Decreases linearly from childhood up to early adulthood *(Tamnes et al., 2017; Walhovd et al., 2017)*	ADHD: delayed cortical thinning in prefrontal areas *(Shaw et al., 2007)* → attention, motor planning CD: reduced thickness of parietal lobe, paracentral lobule, precuneus *(Hyatt et al., 2012)* and superior temporal cortex *(Wallace et al., 2014)* (correlated with callous unemotional traits)
↳Cortical gray area [mm^2]	Stays stable or decreases very little starting age 9 *(Amlien et al., 2016; Tamnes et al., 2017; Vijayakumar et al., 2016; Wierenga et al., 2014)*	ADHD: reduced total, frontal, temporal, and parietal area *(Noordermeer et al., 2017)* CD+ODD: mitigated results *(Fairchild et al., 2015; Sarkar et al., 2015; Wallace et al., 2014)*

Differences in brain developmental trajectories between control group and ADHD, ODD and CD patients

Morphological metric	Typical developmental trajectories throughout adolescence	Atypical trajectories in ADHD, CD and ODD
Local gyrification index	Decreases from childhood to adulthood *(Mutlu et al., 2013; Raznahan et al., 2011).*	ADHD from 10 to 18 yo: no alteration in baseline gyrification nor in developmental trajectories *(Shaw et al., 2012; Forde et al., 2017)* CD: widespread folding deficits *(Hyatt et al.,2012)*
Subcortical volumes	Decrease for the most part during the adolescence	**Overall reduction of specific regions underlying the symptomatology of each disorder** (attention processes, motor planning, and emotional regulation in ADHD, as well as empathy, introspection, and emotion processing in CD and ODD)
↳basal ganglia (i.e. nucleus caudatus, putamen, and globus pallidus), nucleus accumbens, and cerebellar gray matter	Volume decreases from ages 8 to 22	ADHD: volume reductions in the amygdala, nucleus accum- bens, hippocampus, and putamen *(1713 patients 4-63 yo, Hoogman et al., 2017)*
↳amygdala and hippocampus	Increase with age during adolescence *(Durston et al., 2001; Giedd et al., 1996)* or stay stable *(Tamnes et al., 2013).* Seem to increase slightly from age 10 to 22 *(Herting et al., 2018)*.	CD+ODD: reductions in the striatum, amygdala, and hippocampus *(Noordermeer et al., 2017; Rogers & Brito, 2016)*
Cerebral white matter volume	Increases throughout childhood and adolescence *(Mills et al., 2016; Westlye et al., 2010).*	ADHD+CD: no alteration *(Greven et al., 2015; Stevens & Haney-Caron, 2012)*

Differences in brain developmental trajectories between control group and ADHD, ODD and CD patients

Source of inconclusiveness in findings: *(Vijaya- kumar et al., 2018)*

- Different age range between studies
- Number of assessments
- Sample characteristics
- Image acquisition setup
- Image processing techniques
- Longitudinal statistical analytic methods
- Challenges to do longitudinal studies (development) with patient groups
  - **Longitudinal studies** on ADHD, CD and ODD are rare *(Shaw et al., 2012, 2013, 2014)*
  - Replaced by **cross-sectional studies** focused on age-related or age-independant differences between several patients and control groups

Challenges and good practises with quality control: Study design

- Start by fixing a **clear goal** for the clinical developmental sMRI study
- Consider **generalizability of sample** during recruitment and report details (i.e. age, IQ, socio- economic status, pubertal status, and ethnicity)
- Report **physical and psychiatric comorbidities** (diseases association)
- For the patient group:
  - Report characteristics for (previous) **medication and therapy, age of onset and duration of illness** for neurodevelopmental disorder
  - Report **diagnostic procedure** • confirmed by whom and how (e.g. through questionnaires and clinical interviews by registered psychologist or study staff) • **cut-offs** to define clinical psychopathology • specify **subtypes and severity**
  - Challenge: **recruit enough patients** to compare effects of confounding variables such as disorder subtypes comorbidities, medication and other treatments.
  - Add a control group *(Bednarz & Kana, 2018; Greene et al., 2016)*
- **Match groups** according to e.g. sex and age; provide information on matching strategy
- Provide **information on missing data** (e.g. questionnaires, medication status, IQ)

Challenges and good practises with quality control:

Image acquisition

- Reduce and compensate motion (big issue with children and/or neurodevelopmental disorders):
  - Implement and report protocols to **improve comfort and get compliance to stay still**
  - Report on **participants' motion**
  - Consider acquisition techniques (e.g. fMRI as proxy, PROMO) for **motion-correction** *(Tisdall et al., 2016)*
- **Avoid change in scanner hardware, sequences and protocols** across sites and participants
  - If not possible, account for differences in all analyses
- Preferably, follow **T1-weighted sequence acquisition protocols** recommended by Freesurfer (MPRAGE, FLASH or Bandwith matched imaging)
- **Repeat the acquisition** if data quality is not satisfactory (5-10 min for 1 mm^3 resolution)
  - Technical artifacts: head coverage, radiofrequency noise, signal inhomogeneity, and susceptibility *(Costa et al., 2009; Reuter et al., 2015; Wood & Hen- kelman, 1985)*.
  - Motion artifacts: swallowing, blinking, chewing, turning, fidgeting or repositioning a limb *(Bellon et al., 1986; Zaitsev et al., 2015)*.
- Manual or automatic pre-treatment and quality control

Challenges and good practises with quality control:

Image processing and quality control

- Employ **same software (and version) across all participants** within a study and report details
- Give preference to software that covers brain metrics and regions of interest, chose these a priori **based on literature and hypotheses**, and report details
- Report on **quality control procedure**
  - Inspection of the quality of raw and processed images with specification of exclusion criteria
  - Tools or algorithms used during quality control procedure
  - Manual changes/troubleshooting techniques
- **Freesurfer** provides cortical measurements registered onto **two standard atlases** : Destrieux atlas *(Destrieux et al., 2010)* and the Desikan-Killiany atlas *(Desikan et al., 2006)*
- For more than one data set per participant, use **Freesurfer longitudinal stream** :
  1. Cross-sectional pipeline
  2. Template creation
  3. New analysis based on template
- Transparent and detailed report on quality control:

Challenges and good practises with quality control:

Quality control

- Need of **transparent and detailed reports on quality control and rejected data**
- Combine visual inspection (time consuming) and automatically computed metrics:

Table 1 Quality control approaches for sMRI data

Method	QC input metrics	Visual QC/ classifier categories	Technique	QC output	Performance
FD (Savalia et al., 2017) **(frame-by-frame displacement)**	FD from functional MRI scan of the same session as proxy for motion in T1-weighted images	Three categories: pass, warn, fail	Flagging procedure; combining visual QC and estimates of head motion from functional MRI scans	FD estimates and visual QC ratings	FD estimates complement visual QC rating
Euler number (Rosen et al., 2018)	Euler number outputted by FreeSurfer	Three categories: 0 (gross artifacts/fail), 1 (some artifacts but usable), 2 (no artifacts)	/	Euler number, no specific recommendations	Euler number as most accurate quality measure/highest correlation with visual QC
MRI-QC (Esteban et al., 2017)	Raw T1-weighted images, 64 IQMs per input image **(image quality metrics)**	Binary classifier: include, exclude	random forests classifier trained on a publicly available, multi-site data set (17 sites, $N = 1102$)	individual anatomical reports (calculated IQMs and metadata in the summary, as well as a series of image mosaics and plots designed for the visual assessment of images)	Intra-site prediction: high accuracy; Unseen site prediction: leaves space for improvement (76 % ± 13 % accuracy)
Qoala-T (Klapwijk et al., 2019a, 2019b)	Metrics form the FreeSurfer output files aseg.txt, aparc_area.txt and aparc_thickness.txt (all for both hemispheres) including the variable surface holes	Four categories: 1 (excellent), 2 (good), 3 (poor), 4 (failed)	supervised-learning model, random forests classifier trained on the BrainTime data	Qoala-T score (ranging from 0 to 100), recommendation whether to visually check and whether to include or exclude each data set from further analyses	Intra-site prediction: high accuracy (mean AUC = 0.98); Unseen site prediction: similar accuracy (mean AUC = 0.95)

AUC area under the curve, *QC* quality control, *FD* frame-by-frame displacements, *IQM* image quality metrics, *MRI* magnetic resonance imaging

Challenges and good practises with quality control:
Statistical analysis

- Consider e.g. **sex, age, and global brain size** as covariates (not for cortical thickness)
  - If correcting for global brain size:
    - Report the brain metric and correction method used
    - Report results from both raw and corrected regional brain measures
    - Take into account relationships between sex, age, and global brain size
- Appropriately account for the multivariate nature of the data by:
  - Correcting for multiple comparisons applying suggested thresholds for different brain metrics
  - Conducting multivariate analysis

Conclusion

- We review the different steps of clinical developmental sMRI research:
  - study design
  - image acquisition
  - image processing
  - quality control at different stages
  - statistical analysis and interpretation
- Each step requires a choice between different approaches in literature
- Overall, researchers are encouraged to provide more information on data acquisition and manipulation in order to provide robust and comparative results

Bonus: Mental disorders pathologies

- mix of factors ranging from **genetics** *(Blesson & Cohen, 2020)* **to epigenetics and environmental influences** *(Nigg, 2012)*.

- classification into clinical categories may not match **individual circumstances, problems, and needs** (psychopharmacological and psychotherapeutic treatments) *(Hyman, 2010)*

Bonus: List of semi-automated segmentation tools

- Freesurfer (v7.4.1)
- AFNI
- Brain Visa
- Brain Voyager
- CARET
- CAT12
- FSL
- MindBoogle
- Human Connectome Project (HPC) pipeline (modified version of Freesurfer 5.3.0)