

MIDUS 3 Project 5 Instruments (December, 2023)

Eyeblink Startle Reflex (EBR)

1. **Type of instrument:** A pair of Ag-AgCl 4mm Touchproof shielded electrodes were placed below one eye on the inferior orbicularis oculi muscle to measure blink magnitude in response to acoustic startle probes (50ms duration at 105 dB) presented 2.9 seconds after picture onset, 0.4 s after picture offset or 1.9 s after picture offset (pictures are presented for 4 seconds). The non-disposable Ag-AgCl 4mm Touchproof electrodes were used on participants run before the March 2020 COVID-19 pandemic. For participants run in October 2020 and beyond, a pair of disposable cloth facial electrodes Biopac EL513 with a 10 mm contact area on 2 cm x 2 cm backing were used. The front had standard snap for unshielded Biopac LEAD110 1m TP snap connection. The back had conductive adhesive solid gel. Variables C5PDATE_YR and C5PDATE_MO can be used to differentiate when a participant had the disposable sensors applied. Data quality was not affected by this sensor change. For an introduction to EBR methods, please see Blumenthal and colleagues (2005) guidelines paper and/or Tassinari and Cacioppo's "The Skeletal Motor System - Surface Electromyography" chapter in *The Handbook of Psychophysiology*.
2. **Mode of administration:** Participants had the electrodes placed on their face and were then escorted into an electrically shielded booth where they were seated in front of a computer screen. Participants run in October 2020 and beyond may have had a disposable face mask on depending on comfort-level within the data collection booth. Wearing a face mask did not affect data quality. A computer located outside the booth recorded the data. This portion of the study took place in the Waisman Brain Imaging Core, located in the Waisman Center on the UW-Madison campus.
3. **Method by which respondent will receive and return instrument:** All startle recording was done in the lab.
4. **Other information:**
 - a. **BIOPAC recording:** Raw EMG signals were amplified 5,000 times (using ERS100C amplifiers) prior to digitization at 1000 Hz with 16-bit precision using Acknowledge software and BIOPAC hardware MP150 system from April 2017-October 2017, and BIOPAC hardware MP160 system from November 2017-May 2022 (BIOPAC systems, Inc., Goleta, CA). Subsequent processing with Matlab included 30 Hz highpass filtering, rectification and integration with a time constant of 20 ms.
 - b. **Startle scoring:** Eyeblink reflex magnitudes (in microvolts) were calculated by subtracting the amount of integrated EMG at reflex onset from that at peak amplitude (maximum amount of integrated EMG between 20 and 120 ms following probe onset). Trials with no perceptible eyeblink reflex were assigned a magnitude of zero and included in analysis. Eyeblink reflex magnitudes were log-transformed to normalize the data, then z-scored to range-correct the data separately for each participant. Eyeblink reflex amplitudes were calculated similarly, except trials with no perceptible eyeblink reflex were excluded from the analysis.
 - c. **Data quality filter variable:** A filter variable is provided including the number of valid eyeblink responses across the entire session [C5B]. There were a total possible of 81 eyeblinks across the session (3 valences x 3 probe times x 9 trials for each valence/probe time; 3 trials/valence were non-probed). Therefore, it is recommended that those participants who did not provide at

least 10 or more valid eyeblinks across the session be dropped from analyses.

- d. **Differences in timing of startle probe between waves:** For the MIDUS Refresher sample, there was a variable timing delay (mean ~62 ms) between when the startle probe was intended to be presented and when it was actually presented due to computer software/hardware changes. Data processing procedures were adapted to account for this timing delay when processing EBR data from the MIDUS Refresher sample. No such delay existed for data collected in the MIDUS 2 sample nor the MIDUS 3 sample.

Corrugator supercilii (COR)

1. **Type of instrument:** A pair of Ag-AgCl 4mm Touchproof shielded electrodes were placed above one brow line on the corrugator supercilii muscle to measure “frowning of the brow” responses to positive, neutral, and negative pictures. The non-disposable Ag-AgCl 4mm Touchproof electrodes were used on participants run before the March 2020 COVID-19 pandemic. For participants run in October 2020 and beyond, a pair of disposable cloth facial electrodes Biopac EL513 with a 10 mm contact area on 2 cm x 2 cm backing were used. The front had standard snap for unshielded Biopac LEAD110 1m TP snap connection. The back had conductive adhesive solid gel. Variables C5PDATE_YR and C5PDATE_MO can be used to differentiate when a participant had the disposable sensors applied. Data quality was not affected by this sensor change. For an introduction to COR methods, please see Tassinari and Cacioppo’s “The Skeletal Motor System - Surface Electromyography” chapter in *The Handbook of Psychophysiology*.
2. **Mode of administration:** Participants had the electrodes placed on their face and then were escorted into an electrically shielded booth where they were seated in front of a computer screen. Participants run in October 2020 and beyond may have had a disposable face mask on depending on comfort-level within the data collection booth. Wearing a face mask did not affect data quality. A computer located outside the booth recorded data. This portion of the study took place in the Waisman Brain Imaging Core, located in the Waisman Center on the UW-Madison campus.
3. **Method by which respondent will receive and return instrument:** All corrugator recording and data collection was done in the lab.
4. **Other information:**
 - a. **BIOPAC recording:** Raw EMG signals were amplified 5,000 times (using ERS100C amplifiers) prior to digitization at 1000 Hz with 16-bit precision using Acknowledge software and BIOPAC hardware MP150 system from April 2017-October 2017, and BIOPAC hardware MP160 system from November 2017-May 2022 (BIOPAC systems, Inc., Goleta, CA).
 - b. **Processing:** After 60 Hz notch filtering, the data were visually inspected and artifacts were removed from the corrugator data. A Fast Fourier Transform (FFT) was performed on all artifact-free 1 s chunks of data (extracted through Hanning windows with 50% overlap) to derive estimates of spectral power density ($\mu V^2/Hz$) in the 30 – 200 Hz frequency band. These values were log-transformed to normalize the data. Corrugator activity was computed for 13 distinct epochs for each of the image valences (positive, neutral, negative). The first epoch covers a 1 s pre-picture epoch that served as a baseline recording and was subtracted from corrugator activity in the subsequent 12 epochs. The baseline-corrected epoch data were then Z-scored within subject and averaged across 4-seconds creating 3 distinct blocks, in order to

create a summary score of corrugator activity during the picture presentation (1-4 seconds~EARLY corrugator activity), immediately following picture offset (5-8 seconds~MIDDLE corrugator activity), and later after offset (9-12 seconds~LATE corrugator activity).

- c. **Data quality filter variable:** A filter variable is provided indicating the quality of the corrugator measures [C5C]. Poor quality corrugator data may include significant noise and artifact, so it is recommended to exclude the poor quality data if at all possible given the sample.

Zygomaticus major (ZYGO)

1. **Type of instrument:** A pair of Ag-AgCl 4mm Touchproof shielded electrodes were placed on one cheek along the zygomaticus major muscle to measure “smiling” responses to positive, neutral, and negative pictures. The non-disposable Ag-AgCl 4mm Touchproof electrodes were used on participants run before the March 2020 COVID-19 pandemic. For participants run in October 2020 and beyond, a pair of disposable cloth facial electrodes Biopac EL513 with a 10 mm contact area on 2 cm x 2 cm backing were used. The front had standard snap for unshielded Biopac LEAD110 1m TP snap connection. The back had conductive adhesive solid gel. Variables C5PDATE_YR and C5PDATE_MO can be used to differentiate the when a participant had the disposable sensors applied. Data quality was not affected by this sensor change. For an introduction to ZYG methods, please see Tassinary and Cacioppo’s “The Skeletal Motor System - Surface Electromyography” chapter in *The Handbook of Psychophysiology*.
2. **Mode of administration:** Participants had the electrodes placed on their face and then were escorted into an electrically shielded booth where they were seated in front of a computer screen. A computer located outside the booth recorded data. This portion of the study took place in Waisman Brain Imaging Core, located in the Waisman Center on the UW-Madison campus.
3. **Method by which respondent will receive and return instrument:** All zygomaticus recording and data collection was done in the lab.
4. **Other information:**
 - a. **BIOPAC recording:** Raw EMG signals were amplified 5,000 times (using ERS100C amplifiers) prior to digitization at 1000 Hz with 16-bit precision using Acknowledge software and BIOPAC hardware MP150 system from April 2017-October 2017, and BIOPAC hardware MP160 system from November 2017-May 2022 (BIOPAC systems, Inc., Goleta, CA).
 - b. **Processing:** After 60 Hz notch filtering, the data were visually inspected and artifacts were removed from the zygomaticus data. A Fast Fourier Transform (FFT) was performed on all artifact-free 1 s chunks of data (extracted through Hanning windows with 50% overlap) to derive estimates of spectral power density ($\mu V^2/Hz$) in the 30 – 200 Hz frequency band. These values were log-transformed to normalize the data. Zygomaticus activity was computed for 13 distinct epochs for each of the image valences (positive, neutral, negative). The first epoch covers a 1 s pre-picture epoch that served as a baseline recording and was subtracted from zygomaticus activity in the subsequent 12 epochs. The baseline-corrected epoch data were then Z-scored within subject and averaged across 4-seconds creating 3 distinct blocks, in order to create a summary score of zygomaticus activity during the picture presentation (1-4 seconds~EARLY zygomaticus activity), immediately following picture offset (5-8 seconds~MIDDLE zygomaticus activity), and later after offset (9-12 seconds~LATE zygomaticus activity).

- c. **Data quality filter variable:** A filter variable is provided indicating the quality of the zygomaticus measures [C5L]. Poor quality zygomaticus data may include significant noise and artifact, so it is recommended to exclude the poor quality data if at all possible given the sample.

Reaction Times (RT) and Accuracy

1. **Type of instrument:** Behavioral observations recorded during the performance of the emotional response task during which psychophysiology was collected.
2. **Mode of administration:** The task was comprised of a decision of the color of the border (purple or yellow) that surrounded the positive, negative, or neutral image for a duration of 500 ms. (The image remained 3500 ms after the border offset.) The participant pressed the left key with their index finger when the color was purple, and the right key with their middle finger when the color was yellow.
3. **Method by which respondent will receive and return instrument:** The task was programmed in E-Prime (Psychology Software Tools, Inc, Pittsburgh, PA) and ran on a PC outside the psychophysiology booth in the Waisman Brain Imaging Core, located in the Waisman Center on the UW-Madison campus. Data were recorded on this PC using E-Prime software while the participant was performing the task.
4. **Other information:**
 - a. **Quantification:** Reaction times were recorded as the difference between the time of the onset of the image and the onset of the button press. Accuracy is scored by summing the number of correct identifications of the border color and expressed as a proportion of the total number of trials presented to the participant.

Self-Report

1. **Type of instrument:** Paper and pencil report.
2. **Mode of administration:** Given to participants on paper to complete during the lab visit.
3. **Method by which respondent will receive and return instrument:** Completed and returned during the lab visit.
4. **Other information:**
 - a. Both the Positive and Negative Affect Schedule, “now” form (PANAS-NOW) and the Spielberger State-Trait Anxiety Inventory, “State” form (STAI-X1) were administered at four different time points.
 - i. **Time 1:** Self-reports are first administered immediately after we obtain informed consent at the psychophysiology session
 - ii. **Time 2:** Immediately after completing the emotional response picture-viewing task
 - iii. **Time 3:** Upon their arrival on the day of the MRI session
 - iv. **Time 4:** Immediately after finishing the MRI scan
 - b. The other questionnaires were not administered at a specific time.
 - i. Positive and Negative Affect Schedule, “general” form (PANAS-GEN)
 - ii. Spielberger State-Trait Anxiety Inventory, “Trait” form (STAI-X2)
 - iii. Dispositional Positive Emotion Scale (DPES)
 - iv. Emotion Regulation Questionnaire (ERQ)
 - v. Interpersonal Reactivity Index (IRI)
 - c. **Scoring:**

- i. **Reverse-coding:** STAI-X1, STAI-X2, and IRI are the only measures that included reverse coding. Items were reverse coded as necessary and as indicated by published guidelines for scale use.
- ii. **Average:** A score for each scale/subscale was determined by taking an average of all unambiguously completed items (i.e., skipped items and questions for which more than one response was indicated were dropped). An average was taken instead of a sum to simplify problems of missing items (a sum would be affected by missing items; an average is not). Scales for which fewer than 50% of items were completed were excluded.

Cube and Paper Test

1. **Type of instrument:** Paper and pencil report.
2. **Mode of administration:** Given to participants on paper to complete during the lab visit during the psychophysiology session.
3. **Method by which respondent will receive and return instrument:** Completed and returned during the lab visit.
4. **Other information:**
Scoring: Total number of responses and number of correct responses were calculated for both the cube and paper subsets (10 questions each), as well as the total score combining both subsets (20 questions).

CANTAB Cognitive Assessments

1. **Type of instrument:** Welo R10 tablets or Microsoft Surface touchscreen tablets and presspad. CANTABeclipse 6.0. Refer to <http://www.cambridgecognition.com/>
2. **Mode of administration:** Participants completed multiple tasks during the lab visit. Instructions given to participants prior to each task.
3. **Method by which respondent will receive and return instrument:** Completed during lab visit. Data downloaded from tablet after participant finishes session.
4. **Other information:** Participants typically completed tasks in the order listed after psychophysiology emotional response task during first day of visit, with the exception of CGT (which was typically administered following MRI scan on second day of visit). Measures are listed below; for more detailed descriptions of tasks, see *M3_P5_DOCUMENTATION_OF_CANTAB_20231219*. Tasks included:
 - a. **MOT (Motor Screening Task)**
 - i. **Measures:**
 1. Mean error
 2. Mean latency
 - b. **IED (Intra-Extra Dimensional Set Shift)**
 - i. **Measures:**
 1. Stages completed
 2. Completed stage trials
 3. Completed stage errors
 4. EDS errors
 5. Pre-ED errors
 6. Total errors
 7. Total trials
 8. Total errors (adjusted)
 9. Total trials (adjusted)
 10. Reversal Learning

11. Reversal Learning Scaled by Trials
12. Attentional Flexibility
13. Attentional Flexibility Scaled by Trials
- c. **AGN (Affective Go/No-Go)**
 - i. **Measures:**
 1. Mean correct latency (separately by valence and shift, non-shift blocks)
 2. Total commissions (separately by valence and shift, non-shift blocks)
 3. Total omissions (separately by valence and shift, non-shift blocks)
 4. Mean affective response bias
- d. **IST (Information Sampling Task)**
 - i. **Measures:**
 1. Discrimination errors
 2. Sampling errors
 3. Mean opening box latency
 4. Mean number of boxes opened
 5. Mean P(Correct)
- e. **AST (Attention Switching Task)**
 - i. **Measures:**
 1. Total correct trials
 2. Total incorrect trials
 3. Total commission errors
 4. Total omission errors
 5. Congruency cost (Mean)
 6. Percent commission trials
 7. Percent correct trials
 8. Percent incorrect trials
 9. Percent omission trials
 10. Mean latency
 11. Switch cost (Mean)
- f. **ERT (Emotion Recognition Task)**
 - i. **Measures:**
 1. Percent correct
 2. Total number correct
 3. Total number incorrect
 4. Mean overall response latency
- g. **CGT (Cambridge Gambling Task)**
 - i. **Measures:**
 1. Quality of decision-making
 2. Deliberation time
 3. Risk taking
 4. Risk adjustment
 5. Delay aversion
 6. Overall proportion bet

FreeSurfer-Extracted Structural Brain Measurements

1. **Type of instrument:** 3T MR750 GE Healthcare MRI Scanner (Waukesha, WI) using a 32-channel NOVA head coil.

2. **Mode of administration:** MRI scans typically took place during the morning of the second day of data collection (see *M3_P5_DOCUMENTATION_OF_BRAIN_MEASURES_20231219* for details on study timing/procedures).
3. **Method by which respondent will receive and return instrument:** All scans were performed at the Waisman Brain Imaging Laboratory on the UW-Madison campus.
4. **Other information:**
 - a. **Scanning parameters:** These data were derived from BRAVO T1-weighted structural images (TR = 8.2 ms, TE = 3.2 ms, flip angle = 12°, FOV = 256 mm, 256 x 256 matrix, 160 axial slices, inversion time = 450 ms) with 1-mm isotropic voxels.
 - b. **Scan processing:** Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite (v. 6.0.0), which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in prior publications (Dale *et al.*, 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl *et al.*, 2001; Fischl *et al.*, 2002; Fischl *et al.*, 2004a; Fischl *et al.*, 1999a; Fischl *et al.*, 1999b; Fischl *et al.*, 2004b; Han *et al.*, 2006; Jovicich *et al.*, 2006; Segonne *et al.*, 2004, Reuter *et al.* 2010, Reuter *et al.* 2012). Briefly, this processing includes motion correction and removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne *et al.*, 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl *et al.*, 2002; Fischl *et al.*, 2004a) intensity normalization (Sled *et al.*, 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl *et al.*, 2001; Segonne *et al.*, 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale *et al.*, 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl *et al.*, 1999a), registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across subjects (Fischl *et al.*, 1999b), parcellation of the cerebral cortex into units with respect to gyral and sulcal structure (Desikan *et al.*, 2006; Fischl *et al.*, 2004b; Klein & Tourville, 2012), and creation of a variety of surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas *et al.*, 2002) and manual measurements (Kuperberg *et al.*, 2003; Salat *et al.*, 2004). FreeSurfer morphometric procedures have been demonstrated to

show good test-retest reliability across scanner manufacturers and across field strengths (Han *et al.*, 2006; Reuter *et al.*, 2012). Segmentation quality was visually assessed and manually edited as necessary (<http://freesurfer.net/fswiki/Edits>).

- c. **Hippocampal Module (Hippocampal subfield and amygdala nuclei segmentations):** Segmentation of the hippocampal subfields and amygdala nuclei was performed using FreeSurfer version 7.1.0. Description of these segmentations can be found in Iglesias *et al.*, 2015 for the hippocampus and Saygin & Kliemann *et al.* 2017 for the amygdala.
- d. **MRI Filter variables:**
 - i. A filter variable is provided, indicating whether or not participants completed at least part of the MRI protocol [C5IC].
 - ii. A filter variable is provided, indicating whether or not a radiologist flagged the scan for an abnormality during review [C5IF]. Flags are commonly indicating small vessel ischemic disease, presence of meningiomas or other masses, and/or referrals to specialists.
- e. **Differences in Freesurfer naming conventions between waves:** For the MIDUS Refresher wave, there are aseg variables labeled as 'CorticalWhiteMatter' which were extracted using Freesurfer 5.3.0 . For MIDUS 3, Freesurfer 6.0 labeled that same aseg variable as 'CerebralWhiteMatter'. Freesurfer creators thought 'CerebralWhiteMatter' was the better naming convention, but these variables are the same measure across waves.

Brain-Predicted Age

1. **Type of instrument:** 3T MR750 GE Healthcare MRI Scanner (Waukesha, WI) using a 32-channel NOVA head coil.
2. **Mode of administration:** MRI scans typically took place during the morning of the second day of data collection (see *M3_P5_DOCUMENTATION_OF_BRAIN_MEASURES_20231219* for details on study timing/procedures).
3. **Method by which respondent will receive and return instrument:** All scans were performed at the Waisman Brain Imaging Laboratory on the UW-Madison campus.
4. **Other information:**
 - a. **Scanning parameters:** These data were derived from BRAVO T1-weighted structural images (TR = 8.2 ms, TE = 3.2 ms, flip angle = 12°, FOV = 256 mm, 256 x 256 matrix, 160 axial slices, inversion time = 450 ms) with 1 mm isotropic voxels.
 - b. **MRI Filter variables:**
 - i. A filter variable is provided, indicating whether or not participants completed at least part of the MRI protocol [C5IC].
 - ii. A filter variable is provided, indicating whether or not a radiologist flagged the scan for an abnormality during review [C5IF]. Flags are commonly indicating small vessel ischemic disease, presence of meningiomas or other masses, and/or referrals to specialists.
5. **Cole brain age estimates**
 - a. **Scan Processing:** Brain-predicted age was calculated using (1) the BrainAgeR model developed by Cole and colleagues (<https://github.com/james-cole/brainager>; similar in methods to Cole *et al.*, 2015) but described in exact detail on GitHub: The software takes raw T1-

weighted MRI scans, then uses SPM12 for segmentation and normalisation. A slightly customised version of FSL's `slicedir*` is then used to generate a directory of PNGs and corresponding `index.html` file for quality controlling in a web browser. Finally, the normalised images are loaded into R using the `RNfity` package, vectorised and grey matter, white matter, and CSF vectors masked (using 0.3 in the average image from the `brainageR`-specific template, derived from $n=200$ scans, $n=20$ from each of the $n=10$ scanners) and combined.

(2) In version 2.0 of Cole's software, Principal Components Analysis was run (using R's `prcomp`), and the top 80% of variance retained. This meant 435 PCs were included. The rotation matrix of the PCA is applied to any new data and these 435 variables are then used to predict an age value with the trained model with `**kernlab**`. The entailed using a GPR with RBF kernel and default hyperparameters.

GitHub links:

BrainAgeR v1.0: <https://github.com/james-cole/brainageR/tree/1.0>

BrainAgeR v2.0: <https://github.com/james-cole/brainageR/tree/2.0>

The GitHub details for Cole v1.0 and v2.0 include a request for R citation.

"Since `kernlab` does most of the heavy lifting, please consider citing this excellent package: <https://cran.r-project.org/web/packages/kernlab/citation.html>"

"This model has yet to be used in a publication as of 30/09/2019, however some of the training dataset and general approach have been used before. So if you use this software, please consider citing one or more of the following papers:

* Cole JH, Ritchie SJ, Bastin ME, Valdes Hernandez MC, Munoz Maniega S, Royle N et al. Brain age predicts mortality. *Molecular psychiatry* 2018; 23: 1385-1392.

* Cole JH, Poudel RPK, Tsagkrasoulis D, Caan MWA, Steves C, Spector TD et al. Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. *NeuroImage* 2017; 163C: 115-124.

* Cole JH, Leech R, Sharp DJ, for the Alzheimer's Disease Neuroimaging Initiative. Prediction of brain age suggests accelerated atrophy after traumatic brain injury. *Ann Neurol* 2015; 77(4): 571-581."

However, it is important to note that none of these papers' methods exactly match the GitHub description, so they provide the gist but not exact details of the methods.

6. TSAN brain age estimates

Raw T1-weighted MRI scans were preprocessed following the guidelines presented in the GitHub repository for TSAN. The data were reoriented to the standard MNI orientation. The images were skullstripped, and corrected for B1 bias using the N4 algorithm implemented in ANTs. The data were then non-linearly registered to MNI 2 mm x 2 mm x 2 mm MNI skull stripped template. These preprocessed images were fed as input to the trained deep learning model described in these papers:

Cheng, J., Liu, Z., Guan, H., Wu, Z., Zhu, H., Jiang, J., Wen, W., Tao, D., & Liu, T. (2021). Brain Age Estimation From MRI Using Cascade

Networks With Ranking Loss. *IEEE transactions on medical imaging*, 40(12), 3400–3412. <https://doi.org/10.1109/TMI.2021.3085948>
PMID: 34086565

Liu, Z., Cheng, J., Zhu, H., Zhang, J., & Liu, T. (2020). Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part VII. *Lecture Notes in Computer Science*, 198–207.
https://doi.org/10.1007/978-3-030-59728-3_20

GitHub link: TSAN-brain-age-estimation: TSAN: Two-Stage-Age-Net, for brain age estimation from T1-weighted MRI data <https://github.com/Milan-BUAA/TSAN-brain-age-estimation>

7. PNAS CNN brain age estimates

Raw T1-weighted MRI scans were preprocessed with the FreeSurfer image analysis suite (v. 6.0.0), and the brain.mgz file output from FreeSurfer were used as input to the trained deep learning model as described in this paper:

Yin, C., Imms, P., Cheng, M., Amgalan, A., Chowdhury, N. F., Massett, R. J., Chaudhari, N. N., Chen, X., Thompson, P. M., Bogdan, P., Irimia, A., & Alzheimer's Disease Neuroimaging Initiative (2023). Anatomically interpretable deep learning of brain age captures domain-specific cognitive impairment. *Proceedings of the National Academy of Sciences of the United States of America*, 120(2), e2214634120
<https://doi.org/10.1073/pnas.2214634120>

PMID: 36595679

GitHub link: https://github.com/irimia-laboratory/USC_BA_estimator

Diffusion Weighted Imaging (DWI)-based measurements

1. **Type of Instrument:** 3T MR750 GE Healthcare MRI Scanner (Waukesha, WI) using a 32-channel NOVA head coil.
2. **Mode of administration:** Scans typically took place during the morning of the second day of data collection (see *M3_P5_DOCUMENTATION_OF_BRAIN_MEASURES_20231219* for details on study timing/procedures).
3. **Method by which respondent will receive and return instrument:** All scans were performed at the Waisman Brain Imaging Laboratory on the UW-Madison campus.
4. **Other information:**
 - a. **Scanning parameters:** A Stejskal-Tanner [J. Chem. Phys. 42, 288 (1965)] diffusion prepared spin echo EPI sequence was used with the following parameters: 74-75 x 2 mm axial slices within plane field of view = 256mm x 256 mm, acquisition matrix 128 x 128 (readout R/L), partial Fourier encoding 62.5% and ASSET (SENSE) x 2. Additional parameters TR/TE = 8575ms/Minimum. Six reference scans ($b=0$ s/mm²) and three concentric shells ($b=500$ s/mm², $b=800$ s/mm², and $b=2000$ s/mm²) were acquired with 9, 18, and 36 directions respectively.
 - b. **Scan Processing (DWI):** Preprocessing of the multi-shell diffusion weighted imaging (DWI) data was performed using the DESIGNER (Ades-Aron et al., 2018) pipeline which included the removal or mitigation of artifacts such as thermal noise, Gibb's ringing, distortion due to eddy currents, EPI distortion

due to field inhomogeneities, and B1 and Rician bias correction using tools in FSL (Jenkinson et al., 2012), ANTs (Avants et al., 2009; Avants et al., 2011), and MRtrix3 (Tournier et al., 2019). The curated DWI data were used to estimate the diffusion kurtosis imaging (DKI) (Fieremans et al., 2011) model which was then used to extract the diffusion tensor imaging (DTI) (Alexander et al., 2011; Jones & Leemans, 2011; Le Bihan et al., 2001) as well as the white matter tract integrity (WMTI) (Fieremans et al., 2013; Jelescu et al., 2015) metrics. The DKI and WMTI measures were smoothed to address spatial discontinuities ('black holes') and underestimation bias in the kurtosis estimates. Similar to the tissue specific, smoothing-compensated (T-SPOON, Lee et al., 2009) approach used in DTI analysis, spatially adaptive smoothing was performed using a mask where mean kurtosis > 0.3. The DWI data were also used to fit the multi-tissue neurite orientation dispersion and density imaging (NODDI) (Adluru et al., 2014; Fick et al., 2019; Guerrero et al., 2019; H. Zhang et al., 2012) model and derive the corresponding metrics. The resulting DWI metrics are listed below: (see

M3_P5_DOCUMENTATION_OF_BRAIN_MEASURES_20231219 for additional information on the extracted DWI metrics)

DTI metrics - fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD)

DKI metrics - mean kurtosis (MK), radial kurtosis (RK), and axial kurtosis (AK)

WMTI metrics - axonal water fraction (AWF), intra-axonal diffusivity (ias_Da), extra-axonal radial diffusivity (eas_de_perp), and extra-axonal tortuosity (eas_tort)

NODDI metrics - neurite density index (NDI), orientation dispersion index (ODI), and fraction of isotropic diffusion (FISO or CSF)

- c. These measures were spatially normalized to an iteratively estimated population specific coordinate system using ANTs. The population template was using a multi-variate approach using FA and MD measures. The JHU (FSL v6.0.4) and IIT (v5.0) (Qi & Arfanakis, 2021) atlases were warped to the population specific coordinate system and subsequently to the participant specific (native) coordinate system. Median values for the 48 JHU binary regions and weighted median (Cormen et al., 2022; Guerrero-Gonzalez et al., 2022; Surgent et al., 2022) values were computed for the 42 IIT probabilistic regions, both in the native coordinate system. Similarly, the Harvard-Oxford subcortical atlas (Frazier et al., 2005) regions with a 50% probability threshold from FSL v6.0.4 were warped to the population specific coordinate system and subsequently to the participant specific (native) coordinate system. Median values were then computed in the native coordinate system.
- d. Global summary measures in the brain were also computed using weighted median for each of the major tissue types (white matter, gray matter, and cerebro-spinal fluid) generated in the native coordinate system using the FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001) in FSL.
- e. **MRI Filter variables:**
 - i. A filter variable is provided, indicating whether or not participants completed at least part of the MRI protocol [C5IC]. NOTE: This filter does not specifically indicate whether participants completed the diffusion weighted scan.

- ii. A filter variable is provided, indicating whether or not a radiologist flagged the scan for an abnormality during review [C5IF]. Flags are commonly indicating small vessel ischemic disease, presence of meningiomas or other masses, and/or referrals to specialists.

References

- Ades-Aron, B., Veraart, J., Kochunov, P., McGuire, S., Sherman, P., Kellner, E., Novikov, D. S., & Fieremans, E. (2018). Evaluation of the accuracy and precision of the diffusion parameter Estimation with Gibbs and Noise removal pipeline. *NeuroImage*, 183, 532–543. <https://doi.org/10.1016/j.neuroimage.2018.07.066>
- Adluru, G., Gur, Y., Anderson, J. S., Richards, L. G., Adluru, N., & DiBella, E. V. (2014). Assessment of white matter microstructure in stroke patients using NODDI. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference*, 2014, 742–745. <https://doi.org/10.1109/EMBC.2014.6943697>
- Alexander, A. L., Hurley, S. A., Samsonov, A. A., Adluru, N., Hosseinbor, A. P., Mossahebi, P., Tromp, doP. M., Zakszewski, E., & Field, A. S. (2011). Characterization of cerebral white matter properties using quantitative magnetic resonance imaging stains. *Brain connectivity*, 1(6), 423–446. <https://doi.org/10.1089/brain.2011.0071>
- Avants, B. B., Tustison, N. J., Song, G. (2009). Advanced Normalization Tools (ANTs). *Insight Journal*. <https://doi.org/10.54294/uvnhin>
- Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*, 54(3), 2033–2044. <https://doi.org/10.1016/j.neuroimage.2010.09.025>
- Blumenthal, T.D., Cuthbert, B.N., Filion, D.L., Hackley, S., Lipp, O.V., & Van Boxtel, A. (2005). Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology*, 42, 1-15.
- Cacioppo, J.T., Petty, R.E., Losch, M.E., Kim, H.S. (1986). Electromyographic activity over facial muscle regions can differentiate the valence and intensity of affective reactions. *Journal of Personality and Social Psychology*, 50(2), 260–8.
- Cacioppo, J.T., Tassinary, L.G., & Berntson, G.G. (2007). *Handbook of Psychophysiology*, Cambridge University Press, 3rd edition.
- Cacioppo, J.T., Tassinary, L.G., & Berntson, G.G. (2000). *Handbook of Psychophysiology*, Cambridge University Press, 2nd edition.
- Cheng, J., Liu, Z., Guan, H., Wu, Z., Zhu, H., Jiang, J., Wen, W., Tao, D., & Liu, T. (2021). Brain Age Estimation From MRI Using Cascade Networks With Ranking Loss. *IEEE transactions on medical imaging*, 40(12), 3400–3412. <https://doi.org/10.1109/TMI.2021.3085948>
- Cole JH, Ritchie SJ, Bastin ME, Valdes Hernandez MC, Munoz Maniega S, Royle N et al. (2018). Brain age predicts mortality. *Molecular psychiatry*, 23: 1385-1392.
- Cole, J. H., & Franke, K. (2017). Predicting Age Using Neuroimaging: Innovative Brain Ageing Biomarkers. *Trends in Neurosciences*, 40(12), 681–690. <http://doi.org/10.1016/j.tins.2017.10.001>
- Cole JH, Poudel RPK, Tsagkrasoulis D, Caan MWA, Steves C, Spector TD et al. (2017). Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. *NeuroImage*, 163C: 115-124.
- Cole JH, Leech R, Sharp DJ, for the Alzheimer's Disease Neuroimaging Initiative (2015). Prediction of brain age suggests accelerated atrophy after traumatic brain injury. *Ann Neurol* 77(4): 571-581.
- Cormen, T. H., Leiserson, C. E., Rivest, R. L., & Stein, C. (2022). *Introduction to algorithms* (4th ed.). MIT Press.
- Davis, M. H. (1980). A multidimensional approach to individual differences in empathy. *JSAS Catalog of Selected Documents in Psychology*, 10, 85.
- Davis, M. H. (1983). Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology*, 44, 113-126.

- Desikan R.S., Ségonne F., Fischl B., Quinn B.T., Dickerson B.C., Blacker D., Buckner R.L., Dale A.M., Maguire R.P., Hyman B.T., Albert M.S., & Killiany R.J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, 31(3), 968-980.
- Fick, R. H. J., Wassermann, D., & Deriche, R. (2019). The Dmipy Toolbox: Diffusion MRI Multi-Compartment Modeling and Microstructure Recovery Made Easy. *Frontiers in neuroinformatics*, 13, 64. <https://doi.org/10.3389/fninf.2019.00064>
- Fieremans, E., Benitez, A., Jensen, J. H., Falangola, M. F., Tabesh, A., Deardorff, R. L., Spampinato, M. V., Babb, J. S., Novikov, D. S., Ferris, S. H., & Helpert, J. A. (2013). Novel white matter tract integrity metrics sensitive to Alzheimer disease progression. *AJNR. American journal of neuroradiology*, 34(11), 2105–2112. <https://doi.org/10.3174/ajnr.A3553>
- Fieremans, E., Jensen, J. H., & Helpert, J. A. (2011). White matter characterization with diffusional kurtosis imaging. *NeuroImage*, 58(1), 177–188. <https://doi.org/10.1016/j.neuroimage.2011.06.006>
- Fischl B., Salat D.H., Busa E., Albert M., Dieterich M., Haselgrove C., van der Kouwe A., Killiany R., Kennedy D., Klaveness S., Montillo A., Makris N., Rosen B., & Anders M. Dale A.M. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*, 33, 341-355.
- Fischl B., van der Kouwe A., Destrieux C., Halgren E., Ségonne F., Salat D.H., Busa E., Seidman L.J., Goldstein J., Kennedy D., Caviness V., Makris N., Rosen B., & Dale A.M. (2004). Automatically parcellating the human cerebral cortex. *Cereb Cortex*, 14(1), 11-22.
- Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., Herbert, M. R., Bent, E. K., Koneru, V. K., Dieterich, M. E., Hodge, S. M., Rauch, S. L., Grant, P. E., Cohen, B. M., Seidman, L. J., Caviness, V. S., & Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *The American journal of psychiatry*, 162(7), 1256–1265. <https://doi.org/10.1176/appi.ajp.162.7.1256>
- Gilbertson, M.W., Williston S.K., Paulus, L.A., Lasko, N.B., Gurvits, T.V, Shenton, M.E., Pitman, R.K., Orr, S.P. (2007). Configural cue performance in identical twins discordant for posttraumatic stress disorder: Theoretical implications for the role of hippocampal function. *Biol Psychiatry*, 62(5), 513-520.
- Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness, V. S., Jr, Kennedy, D. N., Faraone, S. V., & Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biological psychiatry*, 61(8), 935–945. <https://doi.org/10.1016/j.biopsych.2006.06.027>
- Gross, J.J., & John, O.P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology*, 85, 348-362.
- Guerrero, J. M., Adluru, N., Bendlin, B. B., Goldsmith, H. H., Schaefer, S. M., Davidson, R. J., Kecskemeti, S. R., Zhang, H., & Alexander, A. L. (2019). Optimizing the intrinsic parallel diffusivity in NODDI: An extensive empirical evaluation. *PloS one*, 14(9), e0217118. <https://doi.org/10.1371/journal.pone.0217118>
- Guerrero-Gonzalez, J., Sargent, O., Adluru, N., Kirk, G. R., Dean Iii, D. C., Kecskemeti, S. R., Alexander, A. L., & Travers, B. G. (2022). Improving Imaging of the Brainstem and Cerebellum in Autistic Children: Transformation-Based High-Resolution Diffusion MRI (TiDi-Fused) in the Human Brainstem. *Frontiers in integrative neuroscience*, 16, 804743. <https://doi.org/10.3389/fnint.2022.804743>
- Iglesias, J.E., Augustinack, J.C., Nguyen, K., Player, C.M., Player, A., Wright, M., Roy, N., Frosch, M.P., Mc Kee, A.C., Wald, L.L., Fischl, B., and Van Leemput, K.(2015). A

- computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. *Neuroimage*, 115, 117-137.
- Jelescu, I. O., Veraart, J., Adisetiyo, V., Milla, S. S., Novikov, D. S., & Fieremans, E. (2015). One diffusion acquisition and different white matter models: how does microstructure change in human early development based on WMTI and NODDI?. *NeuroImage*, 107, 242–256. <https://doi.org/10.1016/j.neuroimage.2014.12.009>
- Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, 62(2), 782–790. <https://doi.org/10.1016/j.neuroimage.2011.09.015>
- Jones, D. K., & Leemans, A. (2011). Diffusion tensor imaging. *Methods in molecular biology (Clifton, N.J.)*, 711, 127–144. https://doi.org/10.1007/978-1-61737-992-5_6
- Klein, A., & Tourville, J. (2012). 101 labeled brain images and a consistent human cortical labeling protocol. *Frontiers in neuroscience*, 6, 171. <https://doi.org/10.3389/fnins.2012.00171>
- Lang, P.J., Bradley, M.M., Cuthbert, B.N. (1990). Emotion, attention, and the startle reflex. *Psychological Review*, 97(3), 377-95.
- Lang, P.J., Bradley, M.M., Cuthbert, B.N. (2005). *International Affective Picture System (IAPS): Digitized Photographs, Instruction Manual and Affective Ratings*. Gainesville, FL: University of Florida.
- Larson, C. L., Irwin, W., Navin, S. D., Nitschke, J. B., Ruffalo, D., Shackman, A. J., & Davidson, R. J., (2000). Self-report correlates of reactivity to visual affective stimuli indexed with affect- modulated startle: specificity of a new measure. *Psychophysiology*, 37, S62.
- Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: concepts and applications. *Journal of magnetic resonance imaging : JMIR*, 13(4), 534–546. <https://doi.org/10.1002/jmri.1076>
- Lee, J. E., Chung, M. K., Lazar, M., DuBray, M. B., Kim, J., Bigler, E. D., Lainhart, J. E., & Alexander, A. L. (2009). A study of diffusion tensor imaging by tissue-specific, smoothing-compensated voxel-based analysis. *NeuroImage*, 44(3), 870–883. <https://doi.org/10.1016/j.neuroimage.2008.09.041>
- Liu, Z., Cheng, J., Zhu, H., Zhang, J., & Liu, T. (2020). Medical Image Computing and Computer Assisted Intervention – MICCAI 2020, 23rd International Conference, Lima, Peru, October 4–8, 2020, Proceedings, Part VII. *Lecture Notes in Computer Science*, 198–207. doi: 10.1007/978-3-030-59728-3_20
- Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., Tsuang, M. T., & Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophrenia research*, 83(2-3), 155–171. <https://doi.org/10.1016/j.schres.2005.11.020>
- Matlab and Statistics Toolbox [Computer software]. (Release 2018a). Natick, MA: The MathWorks.
- Mori S, Oishi K, Jiang H, et al. (2007) Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage*, 40(2), 570–582. doi:10.1016/j.neuroimage.2007.12.035
- Pedersen, W. S., Dean, D. C., Adluru, N., Gresham, L. K., Lee, S. D., Kelly, M. P., Mumford, J. A., Davidson, R. J., & Schaefer, S. M. (2022). Individual variation in white matter microstructure is related to better recovery from negative stimuli. *Emotion (Washington, D.C.)*, 22(2), 244–257. <https://doi.org/10.1037/emo0000996>
- Qi, X., & Arfanakis, K. (2021). Regionconnect: Rapidly extracting standardized brain connectivity information in voxel-wise neuroimaging studies. *NeuroImage*, 225, 117462. <https://doi.org/10.1016/j.neuroimage.2020.117462>
- Saygin ZM & Kliemann D (joint 1st authors), Iglesias JE, van der Kouwe AJW, Boyd E, Reuter M, Stevens A, Van Leemput K, Mc Kee A, Frosch MP, Fischl B, Augustinack JC. (2017).

- High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. *Neuroimage*, 155, 370-382.
- Shiota, M. N., Keltner, D., & John O. P. (2006). Positive emotion dispositions differentially associated with Big Five personality and attachment style. *Journal of Positive Psychology*, 1, 61-71.
- Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA (1983): *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.
- Stejskal E.O., & Tanner, J.E. (1965) Spin diffusion measurements: Spin echoes in the presence of a time-dependent field gradient. *J. Chem. Phys.*, 42, 288.
- Surgent, O., Riaz, A., Ausderau, K. K., Adluru, N., Kirk, G. R., Guerrero-Gonzalez, J., Skaletski, E. C., Kecskemeti, S. R., Dean Iii, D. C., Weismer, S. E., Alexander, A. L., & Travers, B. G. (2022). Brainstem white matter microstructure is associated with hyporesponsiveness and overall sensory features in autistic children. *Molecular autism*, 13(1), 48. <https://doi.org/10.1186/s13229-022-00524-3>
- Tournier, J. D., Smith, R., Raffelt, D., Tabbara, R., Dhollander, T., Pietsch, M., Christiaens, D., Jeurissen, B., Yeh, C. H., & Connelly, A. (2019). MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. *NeuroImage*, 202, 116137. <https://doi.org/10.1016/j.neuroimage.2019.116137>
- Watson, D., & Clark, L.A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, 54(6), 1063-70.
- Yin, C., Imms, P., Cheng, M., Amgalan, A., Chowdhury, N. F., Massett, R. J., Chaudhari, N. N., Chen, X., Thompson, P. M., Bogdan, P., Irimia, A., & Alzheimer's Disease Neuroimaging Initiative (2023). Anatomically interpretable deep learning of brain age captures domain-specific cognitive impairment. *Proceedings of the National Academy of Sciences of the United States of America*, 120(2), e2214634120. <https://doi.org/10.1073/pnas.2214634120>
- Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., & Alexander, D. C. (2012). NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *NeuroImage*, 61(4), 1000–1016. <https://doi.org/10.1016/j.neuroimage.2012.03.072>
- Zhang S, Arfanakis K. (2018) Evaluation of standardized and study-specific diffusion tensor imaging templates of the adult human brain: Template characteristics, spatial normalization accuracy, and detection of small inter-group FA differences. *Neuroimage*, 172, 40-50.
- Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE transactions on medical imaging*, 20(1), 45–57. <https://doi.org/10.1109/42.906424>