MIDUS Refresher 1 Project 5 Instruments (October, 2024)

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) ideally 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). For an introduction to EBR methods, please see Blumenthal and colleagues (2005) guidelines paper and/or 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 were then escorted into an electrically shielded booth where they were seated in front of a computer screen. 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 (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 [RA5B]. 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 1 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 1 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 "furrowing of the brow" responses to positive, neutral, and negative pictures. For an introduction to COR 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 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 (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 [RA5C]. 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. 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 (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 [RA5L]. 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.

Heart rate variability (HRV) – Psychophysiology

1. **Type of instrument:** An EL503 electrode was placed 2 inches below the right collarbone with BIOPAC GEL100 applied to the electrode. A second electrode with gel was placed between the hip and rib cage on the participant's left side. These electrodes measure the electrical activity of the participant's heart during a five-minute baseline recording. During the recording, participants were instructed to remain seated and relaxed while facing forward. They were instructed to avoid large body and head movements.
2. **Mode of administration:** Participants had the electrodes placed below their collarbone and above their hip 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 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 heart rate recordings and data collection were completed in the lab.
4. **Other information:**
    a. **BIOPAC recording:** Raw EKG signals were amplified 1000x using the BIOPAC ECG100C amplifiers set to "normal" mode. The signals were acquired and recorded using Acknowledge software and BIOPAC hardware (BIOPAC Systems, Inc., Goleta, CA).

b. **Processing:** After passing the data through a low-pass 35 Hz filter and a high-pass 0.05 Hz filter, the data was visually inspected with in-house graphical user interface written for use with Matlab (The Mathworks, 2018). Heart rate variability was extracted in the high frequency band (0.14-0.5) according to guidelines for adult participants from the Task Force of the European Society of Cardiology and North American Society of Pacing and Electophysiology (1996) (as cited in Allen, Chambers, and Towers, 2011). Artifacts were identified and corrected when possible with interpolation. Ectopic beats were identified and corrected using guidelines outlined by Allen, Chambers, and Towers (2011). Data files that contained other non-correctable beats or artifacts were either excluded, or only the data before or after the ectopic beat or artifact was used in analysis.
c. **Data quality:** Poor quality heart rate data included significant clipping and/or noise throughout the entire recording. This should be excluded from analysis if possible. Data that required a significant amount of editing, especially throughout the entire recording, was also excluded in accordance with recommendations from Malik and Camm (1995) (as cited in Peltola, 2012).
d. **Analysis:** Interbeat interval text files were generated by Matlab (The Mathworks, 2018) after cleaning the data. These files were stripped of their time stamps then processed with CMetX (Allen, Chambers, & Towers, 2007) as a batch. All files were sampled at a rate of 10 Hz with the artifact threshold set at the default of 300ms between beats (Allen, Chambers, & Towers, 2007). CMetX took the interbeat interval text files and output comma-separated values files with various HRV metrics for the data collected during the baseline recording (see Allen, Chambers, & Towers, 2007 for more details on CMetX and its output metrics).

Heart rate variability (HRV) – Scan

1. **Type of instrument:** A BIOPAC TSD123A transducer was placed on the end of the participant's left index finger. This transducer would connect to the BIOPAC OXY100C pulse oximeter module. The module uses red and infrared light to measure the participant's pulse and blood oxygenation during the eight minute resting state scan. Participants were instructed to remain still and relaxed while looking at a fixation cross.
2. **Mode of administration:** Participants had the oximeter placed on their left index finger just before entering the scanner bore. A computer located in a booth outside the scanner room 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 heart rate recordings and data collection were completed in the lab.
4. **Other information:**
    a. **BIOPAC recording:** The light signals were transmitted and filtered through the BIOPAC OXY100C module. The signals were then recorded using Acknowledge software and BIOPAC hardware (BIOPAC Systems, Inc., Goleta, CA).
    b. **Processing:** The data was visually inspected with in-house graphical user interface written for use with Matlab (The Mathworks, 2018). Heart rate variability was extracted in the high frequency band (0.14-0.5) according to guidelines for adult participants from the Task Force of the ESC and NASPE (1996) (as cited in Allen, Chambers, and Towers, 2011). Artifacts were identified and corrected when possible with interpolation. Ectopic beats were identified and corrected using guidelines outlined by Allen, Chambers, and Towers (2011). Data files that

contained other non-correctable beats or artifacts were either excluded, or, only the data before or after the ectopic beat or artifact was used in analysis.

c. **Data quality:** Poor quality heart rate data included significant clipping and/or noise throughout the entire recording. This should be excluded from analysis if possible. Data that required a significant amount of editing, especially throughout the entire recording, was also excluded in accordance with recommendations from Malik and Camm (1995) (as cited in Peltola, 2012).
d. **Analysis:** Interbeat interval text files were generated by Matlab (The Mathworks, 2018) after cleaning the data. These files were stripped of their time stamps then processed with CMetX (Allen, Chambers, & Towers, 2007) as a batch. All files were sampled at a rate of 10 Hz with the artifact threshold set at the default of 300ms between beats (Allen, Chambers, & Towers, 2007). CMetX took the interbeat interval text files and output comma-separated values files with various HRV metrics for the resting state recording (see Allen, Chambers, & Towers, 2007 for more details on CMetX and its output metrics).

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. **Time 1**: Self-reports are first administered immediately after we obtain informed consent at the psychophysiology session. At that time, participants complete:
        i. Positive and Negative Affect Schedule, “general” form (PANAS-GEN)
        ii. Positive and Negative Affect Schedule, “now” form (PANAS-NOW)

iii. Spielberger State-Trait Anxiety Inventory, “Trait” form (STAI-X2)
iv. Spielberger State-Trait Anxiety Inventory, “State” form (STAI-X1)
v. Dispositional Positive Emotion Scale (DPES)

b. **Time 2**: Immediately after completing the emotional response picture-viewing task, participants complete:
   i. Positive and Negative Affect Schedule, “now” form (PANAS-NOW)
   ii. Spielberger State-Trait Anxiety Inventory, “State” form (STAI-X1)
   iii. Emotion Regulation Questionnaire (ERQ)
   iv. Interpersonal Reactivity Index (IRI)
c. **Time 3**: Upon their arrival on the day of the MRI session, participants complete:
   i. Positive and Negative Affect Schedule, “now” form (PANAS-NOW)
   ii. Spielberger State-Trait Anxiety Inventory, “State” form (STAI-X1)
d. **Time 4**: Immediately after finishing the MRI scan, participants complete:
   i. Positive and Negative Affect Schedule, “now” form (PANAS-NOW)
   ii. Spielberger State-Trait Anxiety Inventory, “State” form (STAI-X1)
e. **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.
f. For more details, see *MR1_P5_DOCUMENTATION_OF_SCALES_20241015.*

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:**
   a. **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).
   b. For more details, see *MR1_P5_DOCUMENTATION_OF_SCALES_20241015.*

CANTAB Cognitive Assessments

1. **Type of instrument:** Portable SlimBook Panel Touchscreen PC and presspad. CANTAB software version 5.0. 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 *MR1_P5_DOCUMENTATION_OF_CANTAB_20241015.* 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 an 8-channel head coil.
2. **Mode of administration:** MRI scans took place during the morning of the second day of data collection (see *MR1_P5_DOCUMENTATION_OF_BRAIN_MEASURES_20241015* 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:** For participants with two artifact-free T1-weighted scans, the data from both were averaged during processing with FreeSurfer (v5.3.0). In cases where one of the two scans contained significant artifact or noise, the best available scan was used. Likewise, only one scan was used in processing data from participants for whom a second T1-weighted scan was not collected. Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite (v5.3.0), 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 averaging (Reuter *et al*. 2010) of multiple volumetric T1-weighted images (when more than one is available), 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 developmental version in FreeSurfer v6.0. 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. **Differences in Freesurfer naming conventions between waves**: For the MIDUS Refresher 1 wave, there are aseg variables labeled as ‘CorticalWhiteMatter’ which were extracted using Freesurfer v5.3.0 . For MIDUS 3, Freesurfer v6.0 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 an 8-channel head coil.
2. **Mode of administration:** MRI scans took place during the morning of the second day of data collection (see *MR1_P5_DOCUMENTATION_OF_BRAIN_MEASURES_20241015* 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.
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 slicesdir* 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 RNfiti 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 (v6.0.0), 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 an 8-channel head coil.
2. **Mode of administration:** Scans took place during the morning of the second day of data collection (see *MR1_P5_DOCUMENTATION_OF_BRAIN_MEASURES_20241015* 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: 65 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 = 7000ms/68.7ms. Four reference scans (b=0 s/mm^2) and two concentric shells (b=400 s/mm^2 and b=1200s/mm^2) were acquired with 6 and 70 directions respectively.
    b. **Scan Processing (DWI):** The DWI data were used to extract the diffusion tensor imaging (DTI) (Alexander et al., 2011; Jones & Leemans, 2011; Le Bihan et al., 2001) metrics. The data were denoised using the "dwidenoise" function in MRtrix3 (v. 3.0_RC2, using Eigen 3.2.5). MRtrix3's "mrdegibbs" function was then applied to the data in order to remove Gibbs ringing artifacts from the images. Next, the "eddy" function in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki; v5.0.11) was applied to the data to correct for eddy current-induced distortions and subject movements. Images were then skull-stripped using FSL's "bet" function and a binary brain mask was created using the skull-stripped data. Using DIPY (https://nipy.org/dipy/; v0.14.0), DTI tensors were fit at each voxel using a weighted least squares optimization. After tensors were fitted to the data, each participant's data was visually inspected for quality assurance purposes. A study-specific population Fractional Anisotropy (FA) template was then created using ANTS (http://picsl.upenn.edu/software/ants/; v2.2.0) and visually inspected for quality. Next, ANTS was used to spatially normalize individual data to the population template. Individual FA maps were again visually inspected to assure successful registration to the population FA template. Spatial transformations were subsequently applied to other DTI parameters, including mean, radial, and axial diffusivities (MD, RD, AD, respectively), as well as the map of diffusion tensors. Tensors were reoriented to adjust for this spatial transformation. A population-averaged tensor template was generated using the reoriented tensor maps and the TVMean tool as part of the DTI-TK software package (v2.3.3). Next, a white-matter mask was generated from the population-averaged FA template by thresholding at a value of 0.2 using fslmaths. Whole-brain tractography was performed using camino's deterministic tractography tool and the white matter mask as a seed. These tracts were then converted to a .trk file to allow viewing and further analyses in TrackVis (http://www.trackvis.org/; v0.6.1). From the whole-brain tractogram, the left and right uncinate fasciculi (UF) were manually delineated in TrackVis. Additional tracts and regions of interest from the IIT (Zhang & Arfanakis, 2018) and JHU (Mori et al., 2008) atlases were identified and

warped into alignment of the population FA template by coregistering each atlas to the population template. IIT and JHU atlases were then resampled into the population template space through the application of these transforms, using nearest neighbor interpolation. Next, all tracts of interest (i.e. IIT, JHU, manually defined UF) were warped into each participant's native space, using the inverse of the population spatial normalization transformations. Lastly, using AFNI "3dROIstat" (https://afni.nimh.nih.gov/) and native space images, average measures for FA, MD, RD, and AD were extracted for each tract in each subject, as well as for all voxels within the white-matter mask, providing both tract-specific and global values for the measures.

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