Supplemental Material I: Sample Characteristics

This document contains supplementary information about the samples used in the article "Meta-Analysis of Generalized Additive Models in Neuroimaging Studies" by Sørensen et al.

Lifebrain Sample

The Lifebrain sample refers to the sample used in the Case Study of Section 5, as well as the example on knot placement in Section 2.4.

General Descriptions

The Lifebrain sample was derived from major European brain studies. The main features of each samples, as well as key references, are provided below.

LCBC

Sample source

Center for Lifespan Changes in Brain and Cognition

General description of study/ procedures

Cognitively normal participants were drawn from studies coordinated by the Research Group for Lifespan Changes in Brain and Cognition (LCBC www.oslobrains.no), approved by a Norwegian Regional Committee for Medical and Health Research Ethics. Written informed consent was obtained from all participants.

Recruitment

Newspaper adds, web page adds

Population

The major part of the sample (n=810) consisted of normal, cognitively healthy participants across the lifespan. One sub-population (n = 103) consisted of patients scheduled for elective gynecological (genital prolapse), urological (benign prostate hyperplasia, prostate cancer, or bladder tumor/cancer) or orthopedic (knee or hip replacement) surgery in spinal anesthesia, turning 65 years or older the year of inclusion.

Inclusion/ exclusion criteria, screening

Adult participants were screened using a standardized health interview prior to inclusion in the study. Participants with a history of self- or parent-reported neurological or psychiatric conditions, including clinically significant stroke, serious head injury, untreated hypertension, diabetes, and use of psychoactive drugs within the last two years, were excluded. Further, participants reporting worries concerning their cognitive status, including memory function, were excluded. All participants 40-80 years of age were required to score $\geq$26 and participants > 80 years $\geq$ 25 on the

Mini Mental State Examination [1] according to population norms [2]. From the sub-population of elective surgery patients, dementia, previous stroke with sequela, Parkinson's disease, and other neurodegenerative diseases likely to affect cognitive function were initial exclusion criteria. From this pool of participants, we further selected only cognitively healthy participants based on clinical examinations at Department of Geriatric Medicine at Oslo University Hospital.

Key references

Langnes, E, Sneve, MH, Sederevicius, D, Amlien, IK, Walhovd, KB, Fjell, AM. Anterior and posterior hippocampus macro- and microstructure across the lifespan in relation to memory—A longitudinal study. *Hippocampus*. 2020; 1– 15. https://doi.org/10.1002/hipo.23189

Fjell AM, Idland AV, Sala-Llonch R, Watne LO, Borza T, Brækhus A, Lona T, Zeterberg H, Blennow K, Wyller TB, Walhovd KB. Neuroinflammation and Tau interact with amyloid in predicting sleep problems in aging independently of atrophy. Cerebral Cortex, 2018, 28, 2775-2785.

BASE-II

Sample source

Berlin Study of Aging-II

General description of study/ procedures

The medical exam consisted of a 2-day protocol including a comprehensive anamnesis performed by a physician and involving a wide array of laboratory and functional tests (including PSQI questionnaire). Medical variables were collected about 1 year prior to cognitive testing (mean time difference in years = 1.2 years; SD = 0.80). After completion of the medical examination, participants were invited to two cognitive testing sessions scheduled 1 week apart, and were tested in small groups (e.g. about 6 participants per group) on a comprehensive cognitive battery that covers key cognitive abilities measured by 21 tasks. Each session lasted about 3.5 h. From one session to the next, participants were asked to fill out psychosocial questionnaires related to subjective health and well-being. The different elements of the study were approved by the ethics committees of the Max Planck Institute for Human Development, the Charité University ethics committee and by the ethics committees of DGPs. Participants signed written informed consent and received monetary compensation for their participation in BASE-II and the MRI study. All experiments were performed in accordance with relevant guidelines and regulations.

On average the participants had 14.01 years of education (SD = 2.89) and a body mass index of 26.70 (SD = 3.51). Most of the participants were married and still living together (63%), while 14% were divorced, 4.4% single and 4.1% widowed. None of the participants took any medication that may have affected memory function or had a history of head injuries, medical (e.g., heart attack), neurological (e.g., epilepsy), or psychiatric disorders (e.g., depression).

Recruitment

Baseline Sample (TP1):

Participants were community-dwelling older adults recruited from the greater Berlin

metropolitan area through advertisements in newspapers and public areas. Participants were recruited within the Berlin Aging Study II (BASE-II) (for cohort characteristics and additional details, see Bertram et al., 2014; Gerstorf et al., 2016). The baseline sample comprised 1979

participants (the original sample consists of 2200 subjects, but we reduced the sample to those of which we have sleep and/or cognitive information). Of these, 1519 were older adults aged 61–88 years (mean age 71.5, SD 3.89; 793 female), and 460 were younger adults aged 24–40years (mean age 31.1, SD 3.38; 247 female). On average, older participants had 14.59 years of education (SD 3.03), and younger participants 15.53 years (SD 2.47).

MR Sample: After completion the comprehensive cognitive examination of BASE-II, eligible participants were invited to take part in one MRI session within a time window of 2–4 weeks after cognitive testing, consisting of 341 older adults aged 61–82 years (mean age 70.1, SD = 3.89; 131 female) and 103 younger adults (mean age 31.4, SD = 3.7; 39 female).

Longitudinal data: MR scans and cognitive scores were obtained two times (a baseline (TP1): 2012-2013; and follow-up(TP2): 2015/2016).The follow-up sample (TP2) consisted of 325 participants (247 older adults, 68 younger adults) that were re-invited from the MR-subsample only. They were invited to one cognitive session, lasting 3,5 hours and another separate MR session consisting of identical measures of the baseline study.

Population

Community-dwelling older adults recruited from the greater Berlin metropolitan area

Inclusion/ exclusion criteria, screening

None of the participants took medication that might affect memory function, and none had neurological disorders, psychiatric disorders, or a history of head injuries. All participants reported normal or corrected to normal vision, were right-handed, and scored over 27 on the Mini-Mental Status Examination.

Key references

Bertram, L., Böckenhoff, A., Demuth, I., Düzel, S., Eckardt, R., Li, S.-C. C., … Steinhagen-Thiessen, E. (2014). Cohort profile: The Berlin Aging Study II (BASE-II). International journal of epidemiology,43(3), 703–12. doi:10.1093/ije/dyt018

Gerstorf, D., Bertram, L., Lindenberger, U., Pawelec, G., Demuth, I., Steinhagen-Thiessen, E., & Wagner, G. G. (2016). Editorial. Gerontology,62(3), 311–5. doi:10.1159/000441495

Betula

Sample source

The Betula longitudinal study on aging, memory and dementia

General description of study/ procedures

A subset of 376 participants from the longitudinal Betula study (Nilsson et al., 1997) underwent structural and functional MRI in 2009-2010 and 232 returned for a follow-up scan in 2013-2014. The parent samples from which the scanned participants were derived from were originally recruited to the study in 1988, 1993, and 2008 respectively. The study is approved by the relevant ethical review board.

Recruitment

Population-based sampling was used for recruitment, detailed recruitment procedures are found in Nilsson et al., 1997. Participation in the neuroimaging study was offered to all participants who had remained in the study and completed cognitive testing at the 5th Betula test wave in 2008-2009.

Population

Population-based, healthy middle-aged and older adults

Inclusion/ exclusion criteria, screening

Severe visual or auditory handicaps, intellectual or developmental disabilities, suspected dementia, having a mother tongue other than Swedish, MRI contraindications, neurological disorders, or visual/motor deficits that could interfere with fMRI data collection, MMSE <24, brain or head surgery, substantial brain anatomical deviations.

Key references

Nilsson, L.-G., Bäckman, L., Erngrund, K., Nyberg, L., Adolfsson, R., Bucht, G., Karlsson, S., Widing, M., Winblad, B., 1997. The Betula prospective cohort study: Memory, health, and aging. Aging, Neuropsychol. Cogn. 4, 1–32. doi:10.1080/13825589708256633

Whitehall-II

Sample source

The Whitehall II imaging sub-study

General description of study/ procedures

The Whitehall II study, starting in 1985, includes 10.308 British civil servants followed over time, which allows exploring factors hypothesized to affect brain health and cognitive aging. MRI was done in Phase 11 of this study, at which time the total number participants was 6035. A random sample willing and able to give informed consent to participant in the imaging sub-study of Whitehall II was included. Ethical approval was granted generically for the "Protocol for non-invasive magnetic resonance investigations in healthy volunteers" (MSD/IDREC/2010/P17.2) by the University of Oxford Central University/ Medical Science Division Interdisciplinary Research Ethics Committee (CUREC/MSD-IDREC), who also approved the specific protocol: "Predicting MRI abnormalities with longitudinal data of the Whitehall II sub-study" (MSD-IDREC-C1-2011-71).

Recruitment

Random selection from the Whitehall II study

Population

Population-representative older adults (60-85 years)

Inclusion/ exclusion criteria, screening

MRI contraindications, unable to travel to Oxford without assistance

Key references

Filippini et al., Study protocol: the Whitehall II imaging sub-study. BMC Psychiatry, 2014, 14:159. Doi:10.1186/1471-244X-14-159

Cam-CAN

Sample source

The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study

General description of study/ procedures

A population-based cohort of 3000 adults aged 18 was recruited to Stage 1 of the project, where they completed an interview including health and lifestyle questions, a core cognitive assessment, and a self-completed questionnaire of lifetime experiences and physical activity. Of those interviewed, ~700 participants aged 18-87 (100 per age decile) continued to Stage 2 where they undergo cognitive testing and provide measures of brain structure and function. A subset of ~250 adults returned for longitudinal follow-up data. The study is conducted in compliance with the Helsinki Declaration, and has been approved by the local ethics committee, Cambridgeshire 2 Research Ethics Committee (reference: 10/H0308/50).

Recruitment

Invitation letters based on the patient lists of general practitioners within the Cambridge City area

Population

Population-based, adult lifespan (18 years and up), cognitively healthy

Inclusion/ exclusion criteria, screening

General exclusion criteria: Term-time residents of colleges and universities, and participants whose Primary Care Physician feel are inappropriate to include.

Exclusion criteria for the MRI part of the study: Not cognitively normal (MMSE $\leq$ 24, memory defect, consent difficulties), communication difficulties (hearing problems [35db at 1000 Hz], insufficient English language, vision difficulties), medical problems by self-report of diagnosis (dementia diagnosis /Alzheimer's Disease, Parkinson's Disease, Motor Neurone disease, Multiple sclerosis, cancer, stroke, encephalitis, meningitis, epilepsy, head injury with serious results [coma, unconscious for >2 hours, skull fracture], recently diagnosed or uncontrolled high blood pressure, possible pregnancy, current psychiatric conditions [bipolar disorder, schizophrenia, psychosis]), mobility problems (restricted mobility which could prevent further participation, inability to walk 10 metres), substance abuse (past or current treatment for drug abuse, current drug usage), MRI/ MEG safety and comfort exclusions.

Key references

Shafto et al. The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study protocol: a cross-sectional, lifespan, multidisciplinary examination of healthy cognitive ageing. BMC Neurology, 2014, 14:204. doi: 10.1186/s12883-014-0204-1

University of Barcelona

Sample source

Different brain aging studies from the University of Barcelona; the WAHA cohort, CR/ iTBS cohorts, GABA cohort

General description of study/ procedures

Healthy middle-aged/ older adults, all gave informed consent, in accordance with the Declaration of Helsinki (1964, last revision 2013). All study procedures were approved by the local Institutional Review Board).

Recruitment

WAHA cohort: Eligible participants were recruited via mailing study brochures (LLU) or through the non-profit organization Institute of Aging (BCN), advertisements in the study centers, and word of mouth. Interested individuals attended an informational group meeting, completed a short medical questionnaire and signed the informed consent.

CR/ iTBS cohorts: Healthy volunteers were recruited via the Institute of Aging, Barcelona. Individuals willing to participate were gathered in an informal meeting to tell them about the investigation, which included repetitive transcranial magnetic stimulation (TMS).

GABA cohort: Participants were recruited from the Institute of Aging (Barcelona) and the University of Experience, an initiative by the University of Barcelona for students aged 55 and older, offering special one and two-year degrees.

Population

Middle-aged and older, cognitively normal

Inclusion/ exclusion criteria, screening

WAHA cohort: Participants were healthy elderly men and women with normal cognitive and visual function at the time of recruitment. Inclusion criteria were age between 63 and 79 years, apparently healthy, and equally willing to be in either of the two groups. Exclusion criteria included inability to undergo neuropsychological testing; morbid obesity (BMI ≥ 40 kg/m2); uncontrolled diabetes (HbA1c > 8%); uncontrolled hypertension (on-treatment blood pressure ≥ 150/100 mmHg); prior stroke, significant head trauma or brain surgery; relevant psychiatric illness; major depression; cognitive deterioration or dementia with a score < 24 on the Mini-Mental State Examination; other neurodegenerative disorders like Parkinson's disease; advanced AMD or eye-related conditions precluding ophthalmological evaluation; prior chemotherapy; chronic illness with projected shortened lifespan; allergy to walnuts; customary use of fish oil and/or tree nuts (> 2 servings/week) and/or other relevant sources of ALA, such as flaxseed oil or soy lecithin.

CR/iTBS cohort: Eligible participants had a normal cognitive profile with MMSE scores≥24 and performances not below 1.5SD according to normative scores (adjusted for age and education (Peña-Casanova et al., 2009)) on a neuropsychological evaluation that covered the major cognitive domains (including: Verbal memory: Rey auditory verbal learning test; visual memory: Rey-Osterrieth complex figure; Language: Benton naming test; semantic and phonetic fluencies; Frontal/Executive functions: direct and inverse digits, symbol digits modalities test, trail making

test, Stroop test, London tower test; Visuospatial: line orientation, and visuoperceptive: Popplereuter's embedded figures test).

GABA cohort: None of the participants reported a diagnosis of a neurological or psychiatric disorder or any TMS contraindication (Rossi et al., 2009). Inclusion criteria for the older subjects included a normal cognitive profile with mini-mental state examination (MMSE; Folstein et al., 1975) scores of ≥24 and performance scores not more than 1.5 standard deviation (SD) below normative data (adjusted for age and years of education) on any of the administered neuropsychological tests (i.e., they did not fulfill the criteria for mild cognitive impairment (MCI); Petersen and Morris, 2005. The neuropsychological battery included (1) a screening test for dementia, using the MMSE, and an evaluation of: (2) premorbid cognition and intelligence quotient (IQ), using the vocabulary subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) and National Adult Reading Test (NART); (3) verbal memory, using the Free and Cued Selective Reminding Test (SRT); (4) executive functions, using the phonemic fluency task and Trail Making Test B (TMTB); (5) language, using the semantic fluency task and Boston Naming Test (BNT); and (6) speed of processing, using the Symbol Digit Modalities Test (SDMT).

Key references

WAHA cohort: Rajaram S, Valls-Pedret C, Cofán M, Sabaté J, Serra-Mir M, Pérez-Heras AM, Arechiga A, Casaroli-Marano RP, Alforja S, Sala-Vila A, Doménech M, Roth I, Freitas-Simoes TM, Calvo C, López-Illamola A, Haddad E, Bitok E, Kazzi N, Huey L, Fan J, Ros E. The Walnuts and Healthy Aging Study (WAHA): Protocol for a Nutritional Intervention Trial with Walnuts on Brain Aging. Front Aging Neurosci. 2017 Jan 10;8:333.

CR/ iTBS cohorts: Vidal-Piñeiro D, Martin-Trias P, Arenaza-Urquijo EM, Sala-Llonch R, Clemente IC, Mena-Sánchez I, Bargalló N, Falcón C, Pascual-Leone Á, Bartrés-Faz D. Task-dependent activity and connectivity predict episodic memory network-based responses to brain stimulation in healthy aging. Brain Stimul. 2014 Mar-Apr;7(2):287-96.

GABA cohort: Abellaneda-Pérez K, Vaqué-Alcázar L, Vidal-Piñeiro D, Jannati A, Solana E, Bargalló N, Santarnecchi E, Pascual-Leone A, Bartrés-Faz D. Age-related differences in default-mode network connectivity in response to intermitent theta-burst stimulation and its relationships with maintained cognition and brain integrity in healthy aging. Neuroimage. 2018 Nov 22.

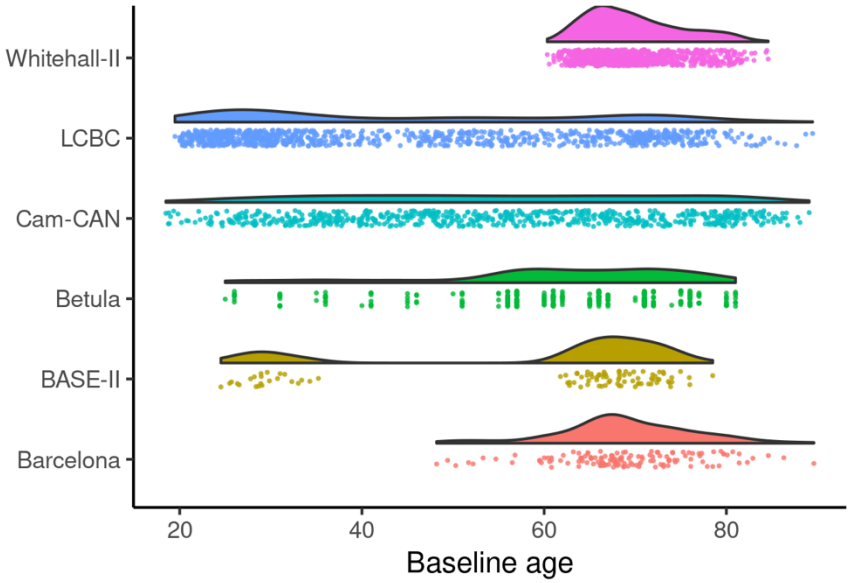
Descriptive statistics

Number of Observations

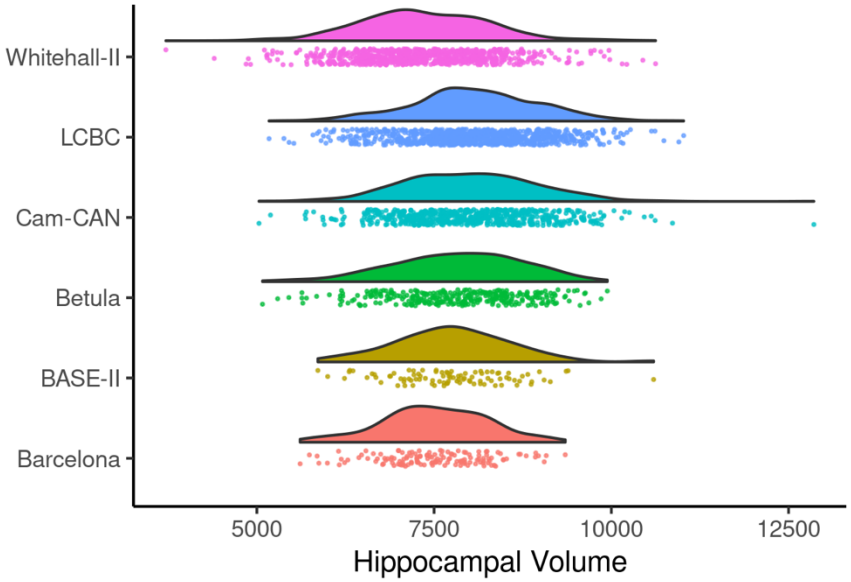
Number of participants with varying number of repeated MRI measurements, per study.

n	Barcelona	BASE-II	Betula	Cam-CAN	LCBC	Whitehall-II
1	98	1	121	366	419	773
2	1	93	189	250	172	0
3	38	0	0	0	165	0
4	0	0	0	0	43	0
5	0	0	0	0	33	0
6	0	0	0	0	80	0
7	0	0	0	0	1	0

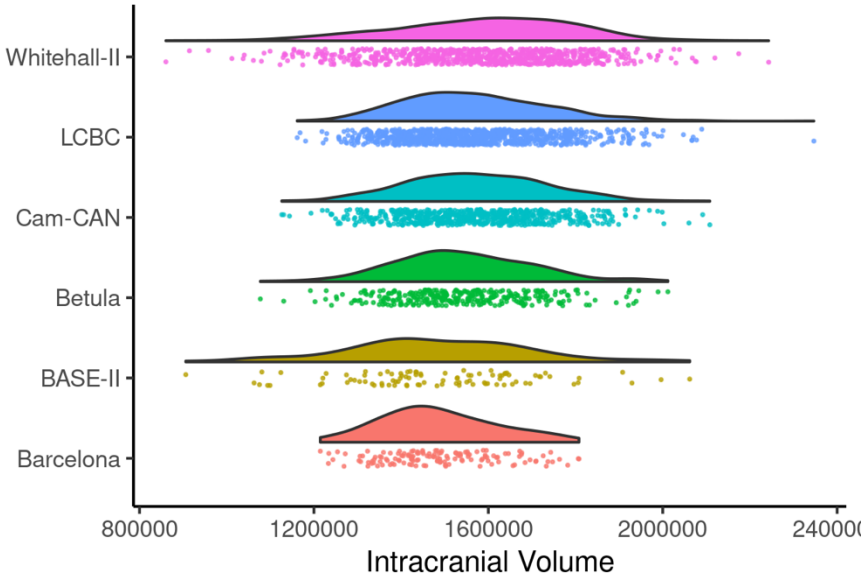
Age Distribution



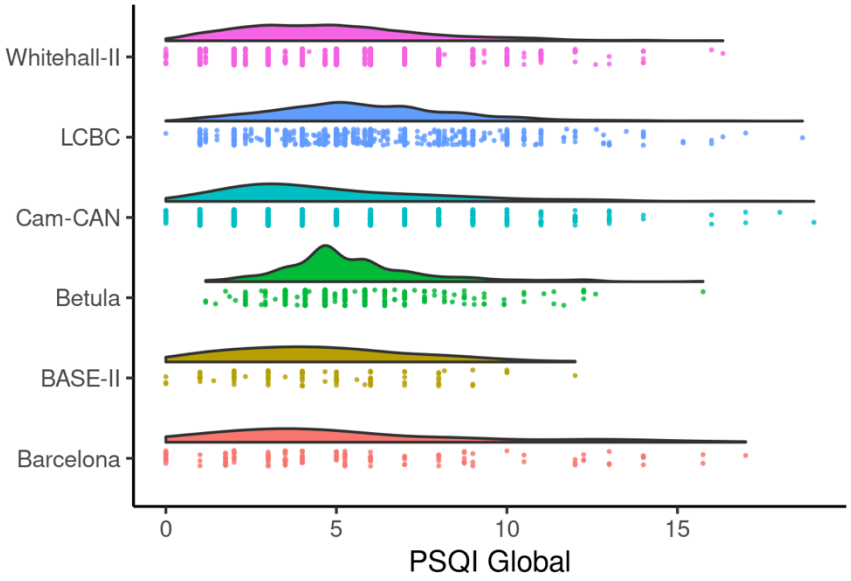
Distribution of Hippocampal Volumes



Distribution of Intracranial Volumes



Distribution of Sleep Scores



Sample Characteristics

Study	Unique Participants	Observations	Mean follow-up Interval (sd)	Max follow-up interval (range)	Age (range)	Sex (female/male)
Barcelona	137	214	3.1 (1.2)	4.9 (3.7-4.9)	69 (48-90)	145/69
BASE-II	94	187	1.6 (0.5)	2.5 (0.6-2.5)	59 (25-78)	56/131
Betula	310	499	4.0 (0.3)	5.0 (3.0-5.0)	61 (25-81)	251/248
Cam-CAN	616	866	1.4 (0.7)	3.5 (0.2-3.5)	55 (18-89)	441/425
LCBC	913	2082	3.0 (2.7)	11.0 (0.8-11.0)	52 (19-89)	1307/775
Whitehall-II	773	773	NA	NA	70 (60-85)	150/623
Total Lifebrain	2843	4621	2.8 (2.4)	11.0 (0.2-11.0)	58 (18-90)	2350/2271

LCBC Sample

The LCBC sample refers to the sample used in Figure 1 and Figure 3, and contains observations partly overlapping with the data from LCBC which is a subset of the Lifebrain sample. It differs from the LCBC sample used in the Lifebrain data in the following ways:

- The sub-population (n=103) of patients was not included.
- Participants without sleep quality scores were included.

General Description

Sample source

Center for Lifespan Changes in Brain and Cognition

General description of study/ procedures

Cognitively normal participants were drawn from studies coordinated by the Research Group for Lifespan Changes in Brain and Cognition (LCBC www.oslobrains.no), approved by a Norwegian Regional Committee for Medical and Health Research Ethics. Written informed consent was obtained from all participants.

Recruitment

Newspaper adds, web page adds

Population

The sample (n=2043) consisted of normal, cognitively healthy participants across the lifespan.

Inclusion/ exclusion criteria, screening

Adult participants were screened using a standardized health interview prior to inclusion in the study. Participants with a history of self- or parent-reported neurological or psychiatric conditions, including clinically significant stroke, serious head injury, untreated hypertension, diabetes, and use of psychoactive drugs within the last two years, were excluded. Further, participants reporting worries concerning their cognitive status, including memory function, were excluded. All participants 40-80 years of age were required to score $\geq$26 and participants > 80 years $\geq$ 25 on the Mini Mental State Examination [1] according to population norms [2]. From this pool of participants, we further selected only cognitively healthy participants based on clinical examinations at Department of Geriatric Medicine at Oslo University Hospital.

Key references

Langnes, E, Sneve, MH, Sederevicius, D, Amlien, IK, Walhovd, KB, Fjell, AM. Anterior and posterior hippocampus macro- and microstructure across the lifespan in relation to memory—A longitudinal study. *Hippocampus*. 2020; 1– 15. https://doi.org/10.1002/hipo.23189

Fjell AM, Idland AV, Sala-Llonch R, Watne LO, Borza T, Brækhus A, Lona T, Zeterberg H, Blennow K, Wyller TB, Walhovd KB. Neuroinflammation and Tau interact with amyloid in predicting sleep problems in aging independently of atrophy. Cerebral Cortex, 2018, 28, 2775-2785.

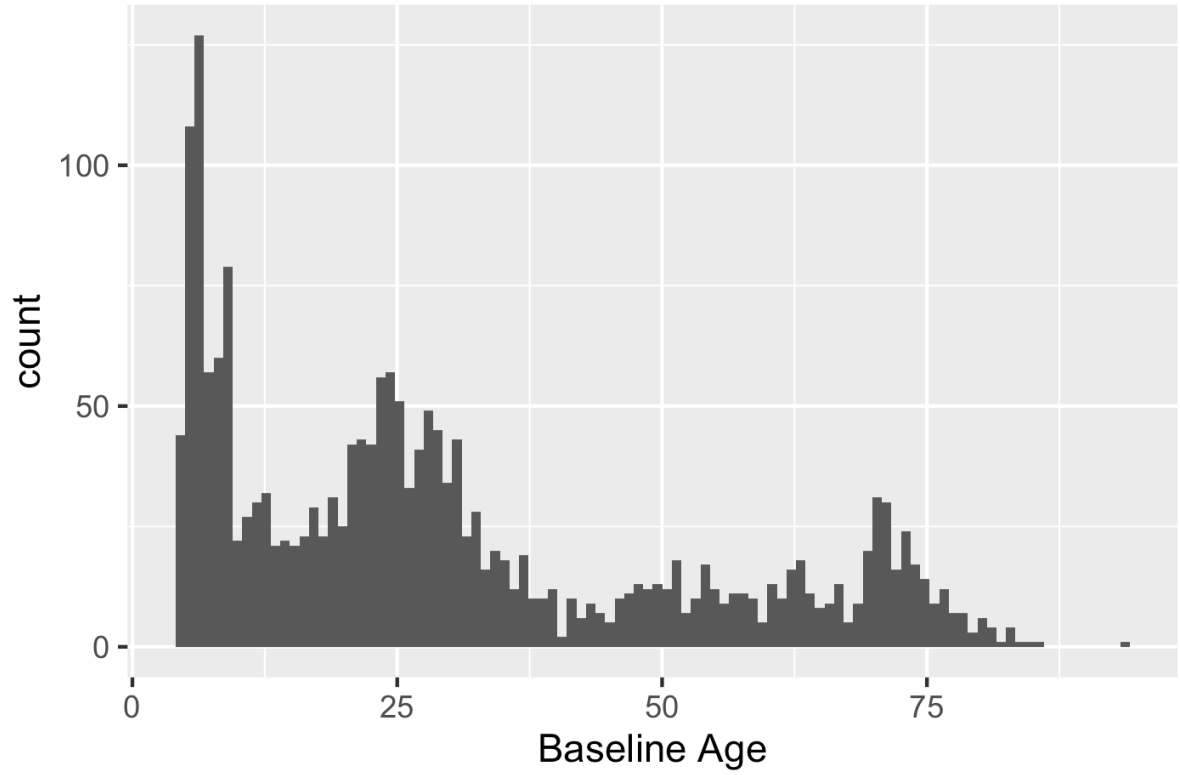
Descriptive statistics

Number of Observations

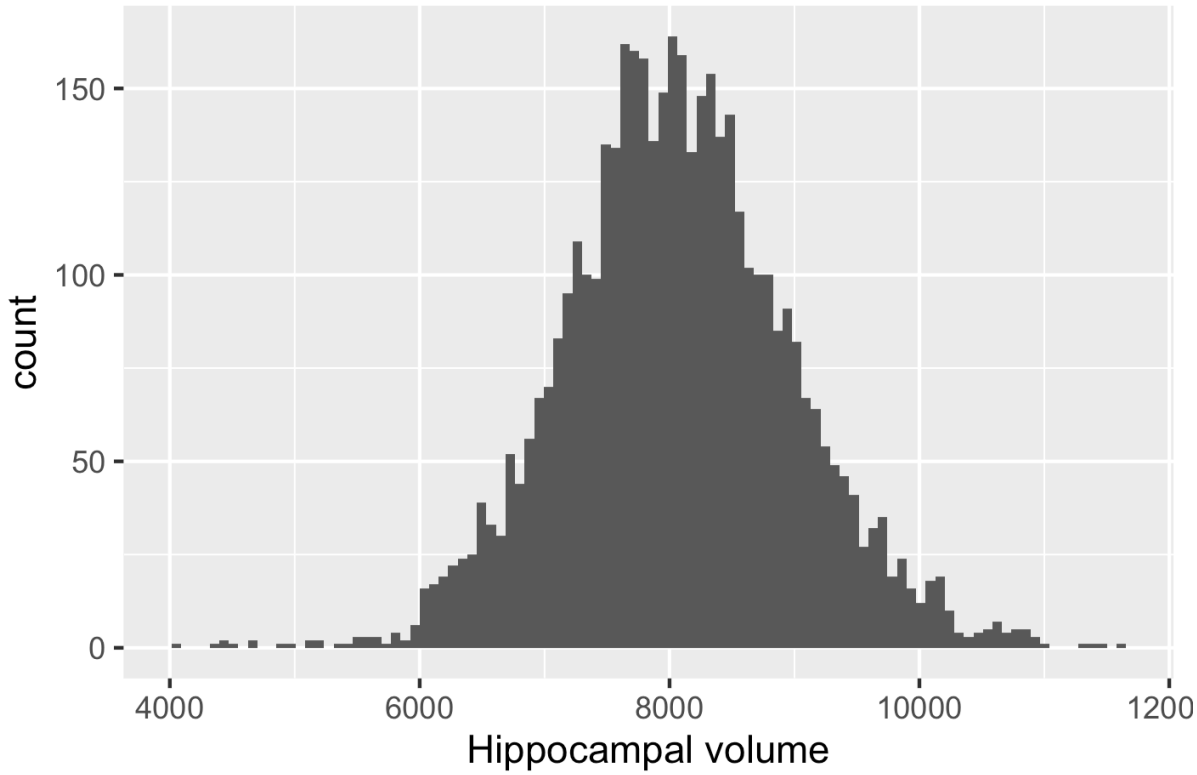
Number of participants with varying number of repeated MRI measurements.

n=1	n=2	n=3	n=4	n=5	n=6	n=7	n=8
937	473	250	189	78	88	7	1

Age Distribution



Distribution of Hippocampal Volumes



Sample Characteristics

Unique Participants	2023
Observations	4364
Mean follow-up Interval (sd)	2.0 (1.9)
Max follow-up interval (range)	3.7 (0.2 - 11.0)
Age (range)	34 (4 - 93)
Sex (female/male)	1220/803

References

1. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res, 1975. **12**(3): p. 189-98.
2. Crum, R.M., et al., *Population-based norms for the Mini-Mental State Examination by age and educational level.* JAMA, 1993. **269**(18): p. 2386-91.