



## Review

## Healthy minds from 0–100 years: Optimising the use of European brain imaging cohorts (“Lifebrain”)

K.B. Walhovd<sup>a</sup>, A.M. Fjell<sup>a</sup>, R. Westerhausen<sup>a</sup>, L. Nyberg<sup>b</sup>, K.P. Ebmeier<sup>c,\*</sup>, U. Lindenberger<sup>d</sup>, D. Bartrés-Faz<sup>e</sup>, W.F.C. Baaré<sup>f</sup>, H.R. Siebner<sup>f</sup>, R. Henson<sup>g</sup>, C.A. Drevon<sup>h</sup>, G.P. Knudsen<sup>i</sup>, I. Budin-Ljøsne<sup>i</sup>, B.W.J.H. Penninx<sup>j</sup>, P. Ghisletta<sup>k,l</sup>, O. Rogeberg<sup>m</sup>, L. Tyler<sup>n</sup>, L. Bertram<sup>o</sup>, for Lifebrain Consortium<sup>1</sup>

<sup>a</sup> Department of Psychology, University of Oslo Centre for Lifespan Changes in Brain and Cognition (UiO), Harald Schelderups Hus, Forskningsveien 3A, N-0373 Oslo, Norway

<sup>b</sup> Centre for Functional Brain Imaging (Umeå), Umeå Universitet, SE-90187 Umeå, Sweden

<sup>c</sup> Department of Psychiatry (UOXF), University of Oxford Wellcome Centre for Integrative Neuroimaging, Warneford Hospital, University of Oxford, OX37JX Oxford, UK

<sup>d</sup> Centre for Lifespan Psychology (MPIB), Max-Planck Institute for Human Development, Lentzeallee 94, D-14195 Berlin, Germany

<sup>e</sup> Facultat de Medicina, Campus Clínic, C/ Casanova, University of Barcelona Brain Stimulation Lab (UB), 143, Ala Nord, 5a planta, S-08036 Barcelona, Spain

<sup>f</sup> Region Hovedstaden (RegionH), Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Section 714, Kettegaard Allé 30, DK-2650 Hvidovre, Denmark

<sup>g</sup> Medical Research Council Cognition and Brain Science Unit (MRC), University of Cambridge, 15, Chaucer Road, CB2 7EF Cambridge, UK

<sup>h</sup> Vitas AS (Analytical Services), Gaustadalléen 21, N-0349 Oslo, Norway

<sup>i</sup> Norwegian Institute of Public Health Oslo (NIPH), PO Box 4404 Nydalen, N-0403 Oslo, Norway

<sup>j</sup> VU University Medical Centre (VUmc), PO Box 7057, NL-1007 Amsterdam, MB, USA

<sup>k</sup> Research Group: Methodology and Data Analysis, Faculty of Psychology and Educational Sciences, University of Geneva (UNIGE), Sandrine Amstutz, Uni Mail, 4<sup>e</sup> étage, boulevard du Pont-d'Arve 40, 1205 Geneva, Switzerland

<sup>l</sup> Swiss Distance Learning University, Überlandstrasse 12, Postfach 689 CH-3900 Brig, Switzerland

<sup>m</sup> Ragnar Frisch Centre for Economic Research (Frisch), Gaustadalleen 21, N-0349 Oslo, Norway

<sup>n</sup> University of Cambridge Department of Psychology (UCAM), Downing Street, CB2 3EB Cambridge, UK

<sup>o</sup> University of Lübeck Interdisciplinary Platform for Genome Analytics (LIGA-UzL), University of Lübeck, Maria-Goeppert-Str. 1 (MFCl), 23562 D-Lübeck, Germany

## ARTICLE INFO

## Article history:

Received 27 August 2017

Received in revised form 4 October 2017

Accepted 5 October 2017

Available online 8 November 2017

## Keywords:

Psychiatric disorder

Dementia

Economics and psychiatry

Epidemiology

MRI

Neurodevelopment

## ABSTRACT

The main objective of “Lifebrain” is to identify the determinants of brain, cognitive and mental (BCM) health at different stages of life. By integrating, harmonising and enriching major European neuroimaging studies across the life span, we will merge fine-grained BCM health measures of more than 5,000 individuals. Longitudinal brain imaging, genetic and health data are available for a major part, as well as cognitive and mental health measures for the broader cohorts, exceeding 27,000 examinations in total. By linking these data to other databases and biobanks, including birth registries, national and regional archives, and by enriching them with a new online data collection and novel measures, we will address the risk factors and protective factors of BCM health. We will identify pathways through which risk and protective factors work and their moderators. Exploiting existing European infrastructures and initiatives, we hope to make major conceptual, methodological and analytical contributions towards large integrative cohorts and their efficient exploitation. We will thus provide novel information on BCM health maintenance, as well as the onset and course of BCM disorders. This will lay a foundation for earlier diagnosis of brain disorders, aberrant development and decline of BCM health, and translate into future preventive and therapeutic strategies. Aiming to improve clinical practice and public health we will work with stakeholders and health authorities, and thus provide the evidence base for prevention and intervention.

© 2017 The Authors. Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

\* Corresponding author.

E-mail addresses: [k.b.walhovd@psykologi.uio.no](mailto:k.b.walhovd@psykologi.uio.no) (K.B. Walhovd), [lars.nyberg@umu.se](mailto:lars.nyberg@umu.se) (L. Nyberg), [klaus.ebmeier@psych.ox.ac.uk](mailto:klaus.ebmeier@psych.ox.ac.uk) (K.P. Ebmeier), [seklindenberger@mpib-berlin.mpg.de](mailto:seklindenberger@mpib-berlin.mpg.de) (U. Lindenberger), [dbartres@ub.edu](mailto:dbartres@ub.edu) (D. Bartrés-Faz), [wimb@drcmr.dk](mailto:wimb@drcmr.dk) (W.F.C. Baaré), [Rik.Henson@mrc-cbu.cam.ac.uk](mailto:Rik.Henson@mrc-cbu.cam.ac.uk) (R. Henson), [c.a.drevon@medisin.uio.no](mailto:c.a.drevon@medisin.uio.no) (C.A. Drevon), [GunPeggy.Knudsen@fhi.no](mailto:GunPeggy.Knudsen@fhi.no) (G.P. Knudsen), [B.Penninx@vumc.nl](mailto:B.Penninx@vumc.nl) (B.W.J.H. Penninx), [Paolo.Ghisletta@unige.ch](mailto:Paolo.Ghisletta@unige.ch) (P. Ghisletta), [ole.rogeberg@frisch.uio.no](mailto:ole.rogeberg@frisch.uio.no) (O. Rogeberg), [lktyler@csl.psychol.cam.ac.uk](mailto:lktyler@csl.psychol.cam.ac.uk) (L. Tyler), [lars.bertram@uni-luebeck.de](mailto:lars.bertram@uni-luebeck.de) (L. Bertram).

<sup>1</sup> See 4. Lifebrain Consortium.

## 1. Background

Neurodevelopmental and degenerative changes, addiction disorders and other psychiatric problems are both influenced by and mirrored in brain changes that occur throughout life. A major challenge is to determine which age-related changes are detrimental and which enhance cognitive and mental health. The potential economic benefits of an improved understanding are large, with total costs of brain disorders in Europe in 2010 estimated at € 798 billion [1]. Throughout life, our genetic dispositions interact continuously with environmental, societal, occupational and lifestyle factors to influence brain structure and function. Such changes, from the earliest stages of life to oldest age, are mapped in detail in European longitudinal studies, utilizing Magnetic Resonance Imaging (MRI). MRI yields high-resolution images of variations in brain macrostructure, microstructure and function, which can be compared with measurable changes in cognitive function and mental health. However, since MRI is expensive and time-consuming, the number of participants included in such studies tends to be low. This makes it hard to disentangle the role of the many factors that can influence brain, cognition and mental health at different stages of life. While forming a precondition for a possible personalised medicine approach, such individual variations need first to be established. For instance, age-specific mechanisms necessitate a large number of participants at all stages of life, and sex-specific effects further halve the sample sizes, thus narrowing degrees of freedom available for analyses.

### 1.1. Overall aim and objectives

This EU Horizon 2020 project “Lifebrain” aims to maximise the exploitation of brain imaging cohorts by bringing together studies on how differences and changes in brain age relate to cognitive function and mental health. This will be done by integrating and standardizing data and results from 11 large predominantly longitudinal European samples from 7 countries [2–12] (Table 1).

This will yield a database of fine-grained BCM health measures for more than 5,000 individual participants. Longitudinal brain imaging data are available for a major portion, as well as cognitive and mental health measures for broader cohorts, exceeding 27,000 examinations. The project is a collaborative initiative involving a small and medium-sized enterprise (SME), several of Europe's major brain research Centres, as well as stakeholders for efficient exploitation of results (Fig. 1).

Lifebrain includes four sub-objectives:

- Integration of data across existing major longitudinal European neuroimaging studies of age changes in brain, cognition and mental health, including genetic, epigenetic, lifestyle, and medical registry information for thousands of individuals, further enriched with health outcomes and biomarkers;
- Development and standardization of measures and methods across these major European studies of age changes in brain, cognition and mental health;
- Provision of novel information on brain, cognition and mental health maintenance, onset and course of diseases and health inequalities, to yield the evidence base for development of policy strategies for prevention and intervention, thereby addressing health inequalities;
- Communication and implementation of new knowledge, exploiting the integrative cohorts in age-specific prevention and treatment to optimize brain, cognition and mental health, improving clinical practice and health policy.

### 1.2. Vision

Personalized health care requires fundamental knowledge of risk factors and protective factors, as well as the pathways through which they work at different ages. Extrapolating from known effects of certain risks and interventions [13,14], a multifactorial and personalized approach could identify modifiable environmental factors that promote cognitive development in childhood and adolescence, foster maintenance of cognitive functions into late adulthood, delay onset of dementia, reduce need for care, and improve working ability through prevention and intervention programs. Cognitive and mental health disorders are a serious burden for individuals as well as societies [15,16]. Within 5 to 10 years, we hope knowledge established in Lifebrain will enable policy makers and health care systems to implement low-threshold strategies for individual prevention by modifiable lifestyle factors, as well as non-pharmacological interventions. In a European perspective, these could have enormous consequences for individual well-being, work abilities, and for the total costs related to increased health care needs and reduced working capabilities in older adults during the coming decades.

## 2. Methods

### 2.1. Concept

A new approach to model brain, cognitive and mental health is needed that differs in fundamental ways from previous approaches: it should be dimensional, focused on lifespan rather than specific phases of development or age, and based on systems-vulnerability and resilience, rather than simple cause-effect relationships. We argue, (1) factors that affect cognitive and mental health will often vary along a continuum across the population, (2) risks and benefits accumulate over time, and will not be coincident with the age at which their effects become apparent, and (3) the effects of these factors will vary across individuals as a function of their genotype. We aim to identify important causal factors, to improve our understanding of how these affect brain health at different ages and in different people, and to identify beneficial and cost-effective interventions. The project will proceed through distinct but tightly interacting phases (Fig. 2).

We will further combine a large population-based approach with an in-depth neurocognitive approach in order to clarify mechanisms, and how these translate into specific cognitive functions. For instance, functional variation with age and sex across countries may be due to individuals in some regions of the world having experienced better conditions in childhood and adulthood, relating to nutrition, education, disease exposure and physical and social activity patterns [17,18]. However, the pathways and mechanisms by which these broad factors work remain unknown. This knowledge is pivotal for development of efficient health policies and targeted prevention.

### 2.2. Identifying risk and protective factors

To identify risk factors for cognitive and mental disorders, we will use approaches previously developed to group participants according to their trajectories of change [19,20]. Factors such as higher education, physical activity, female sex, carrying the met-allele of the COMT gene, and not living alone were associated with maintenance of memory function; lower education, unemployment, being male, and carrying a APOE ε4 allele were risk factors for decline [20]. We have recently employed structural equation modelling (SEM) trees as a method to uncover heterogeneity in empirical data, together with predictors and potential interactions

**Table 1**

Central features of the studies that will feed into the Lifebrain database.

Cohort	Description	<i>n</i>	Obs.	MRI/Obs. <sup>a</sup>	CM	DNA <sup>b</sup>
Barcelona Spain (UB)	Collection of cross sectional and longitudinal studies (three time points) in cognitively normal adults (38–90 yrs.), MRI, lifestyle activities and cognitive reserve measured	261	467	261/415	All	x
BASE-I Germany MPIB, UzL	The Berlin Aging Study (BASE I) is an extensive multidisciplinary investigation (70–100+ yrs.) with 14 test sessions on mental and physical health, psychological functioning, and SES, with eight time points	516	1402		All	x
BASE-II Germany MPIB,UzL	BASE-II investigates the physical, cognitive, and social conditions that lead to successful ageing in a population-based longitudinal study (1,600 participants 60–80 yrs., 600 participants 20–35 yrs.), with a thorough physical health examination, multiple tests of cognitive abilities, and complete questionnaires. Two time points	2,200	2527	415/772	All	x
Betula Sweden UmU	Population based (25–100 yrs.), started in 1988, the seventh wave is ongoing. 10,400 test sessions, with ≈ 5,850 longitudinal observations. All were healthy and non-demented at baseline, but more than 400 have developed some form of dementia. Very comprehensive examinations on health, biomarkers, genotyping, neuropsychology and brain imaging. Time points five and six are part of Lifebrain	376	707	376/707	All	x
Cognition and plasticity through the lifespan (LCBC), Norway – UiO	Collection of studies by LCBC as well as collaborations, well-screened (4–90+ yrs.), comprehensive neuropsychology, MRI, lifestyle, health, biomarkers, and other measures. Some participants present with AD or other dementias or decline. Three time points	1,677	2,533	1,638/2,494	All	x
Whitehall II MRI-substudy UK UOXF	Non-industrial civil servants from London (35–55 yrs. at inclusion), cognitive and health data back to 1985, with clinical examination every 5 years, yielding a comprehensive database of information through the multiple follow ups, including a range of health and life-style related parameters, biomarkers, early predictors and genetics	800	800	775	All	x
Cambridge Centre for Ageing and Neuroscience (Cam-CAN), UK – MRC	Cambridge Centre for Ageing and Neuroscience, epidemiological, behavioural, and neuroimaging, population representative sample (18–88 yrs.), measure health, lifestyle, SES, and psychiatry. Three time points	2,690	2927	633/870	All	x
Cambridge Centre for Attention, Learning and Memory (CALM), UK – MRC	Children (5–16) referred for difficulties with attention, learning, and memory. Comprehensive neuropsychological assessment, incl. personality and executive difficulties, and MRI according to CamCAN protocols. Follow-up planned	482	482	227	All	x
Danish Developmental studies (HUBU), Denmark – REGIONH	Brain and behavioural development in children and adolescents, with up to 12 time points. MRI, cognition, Socioemotional functioning, personality, life events, lifestyle, biomarkers. First 10 assessments were performed with 6 months intervals	94	817	94/817	All	x
Danish aging studies (LISA) Denmark – REGIONH	Live Active Successful Ageing, physical activity and intervention and aging study, community-based. Three time points. Initially, only baseline data will be part of Lifebrain	450	450	390	All	x
Netherlands Study of Depression and Anxiety (NESDA), Netherlands – VUMC	Netherlands Study of Depression and Anxiety, participants (age range 18–65 at inclusion) with and without symptoms, measure psychopathology, health, demographics and SES, psychosocial function, cognition. Six time points. MRI obtained on time points one, three and six	2,981	14,860	301/632	All	x
Total		12,527	27,972	5,140/8,099	All	1,800

*n*: Number of unique individuals; Obs: total number of observations (one for every individual for each time point in longitudinal studies; CM: cognitive tests and mental health measures. MRI includes, T1, T2, DTI, RSI, resting-state fMRI, task-related fMRI. Proportion of participants with neurodegenerative disease varies.

<sup>a</sup> Number of unique subjects with MRI/total number of MRI sessions e.g. including follow-up.

<sup>b</sup> DNA: the genotyping varies some across studies. Many have GWAS, including all in NESDA, all in Base I and 300 in BASE II, ≈ 200 in LCBC, ≈ 2,200 in Betula, and GWAS for 2,000 will be performed as part of Lifebrain. Cam-CAN has collected saliva samples and DNA extraction and GWAS is a part of Lifebrain. All research participants described in Table 1 will be included in statistical analyses based on existing data. All participants that (a) can be reached, (b) are from samples where relevant ethical approval is given, (c) for whom relevant data do not already exist, and (d) are able to give full informed consent, will be asked for dried blood spot samples, buccal swab samples and online testing.

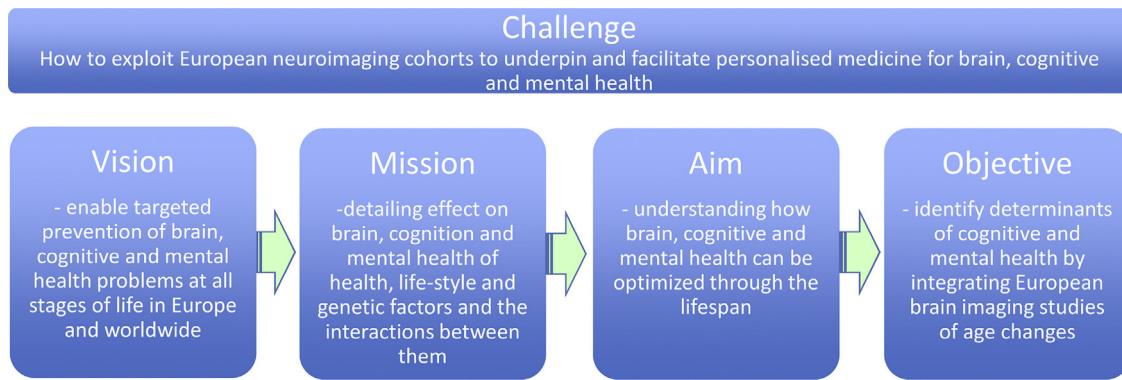


Fig. 1. Lifebrain’s vision, mission, overall aim and main objectives, and their relationships.

among them, explaining this heterogeneity [19]. We will use similar approaches to stratify larger numbers of participants according to important cognitive, psychiatric and brain health measures, and test the effects of a range of risk and protective factors, including genetics, epigenetics, socio-demographic, environmental, and lifestyle. This part of the project will allow identification of general risk factors for cognitive and mental health. Some of the relations will be correlational in nature; others can be modelled longitudinally to shed light on cause and effect. Pathways for the observed relations, and how they are moderated by a number of other factors, will be specifically targeted (see below).

We will also assess long-term effects of candidate variables from early life. The earliest of these are markers of pre- and neonatal health. Abnormal cognitive and behavioural outcomes, such as in ADHD and schizophrenia, have been linked to early development, including factors related to foetal growth and adversity [21,22]. Low birth weight, as a marker of adverse intrauterine circumstances, has been associated with a range of diseases and reduced function in daily life [23,24]. Some factors are associated with cognitive decline and increased Alzheimer’s disease (AD) risk, e.g. coronary heart disease, hypertension, and type 2 diabetes [25]. Anatomical studies show that low birth weight, premature birth, and prenatal substance exposure can affect cortical and specifically fronto-striatal development, impacting attention and executive function [26–28]. These findings underscore the importance of neonatal characteristics for brain development and individual functional differences along a continuum from normality to pathology [26].

Adding to this picture, a number of common variants in risk genes for psychiatric disorders were recently found predictive of

brain structure at birth [29]. For instance, neonates carrying APOE ε4, the major genetic risk factor for AD, were reported to have reduced volumes of temporal cortex, similar to that reported in older adults [29]. For variants of the fat mass and obesity-associated gene (FTO), which has been related to reduced brain volumes in healthy ageing and risk of AD [30,31] and depression [32], smaller brain volumes were recently shown also in adolescents [33]. Such findings should increase our attention to researching and optimizing early influences to provide resources and knowledge on health and disease determinants, onset and course of diseases and public health. Efforts to postpone decline or disease may be futile if they are only targeted at old age. By including the full lifespan, we will investigate how early life variables, including genetic and epigenetic variants, exert their effects.

In addition to the very early predictors related to pre- and perinatal conditions, we will also focus on indicators in childhood and young adulthood. For instance, intelligence scores at age 11 are remarkably good predictors for cognitive performance at age 90 years [34], and neuroticism and introversion predict development of depression later in life [35]. Furthermore, cardiovascular fitness and cognitive performance in early adulthood increased the risk of early-onset dementia and mild cognitive impairment (MCI) more than four decades later [36]. Current levels of self-reported physical activity have been related to less cortical atrophy in the prefrontal cortex across a 3.5-year period in the adult lifespan [37]. This may suggest that older adults should exercise more to prevent cortical atrophy. Alternatively, the more physically active older adults may also have been the more physically active and fit younger adults. Conversely, certain brain characteristics or changes may affect people’s physical activity [38].

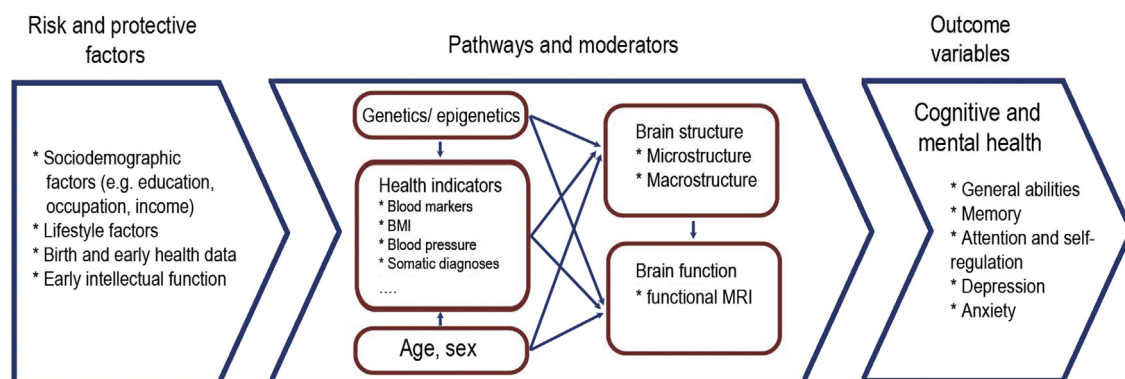
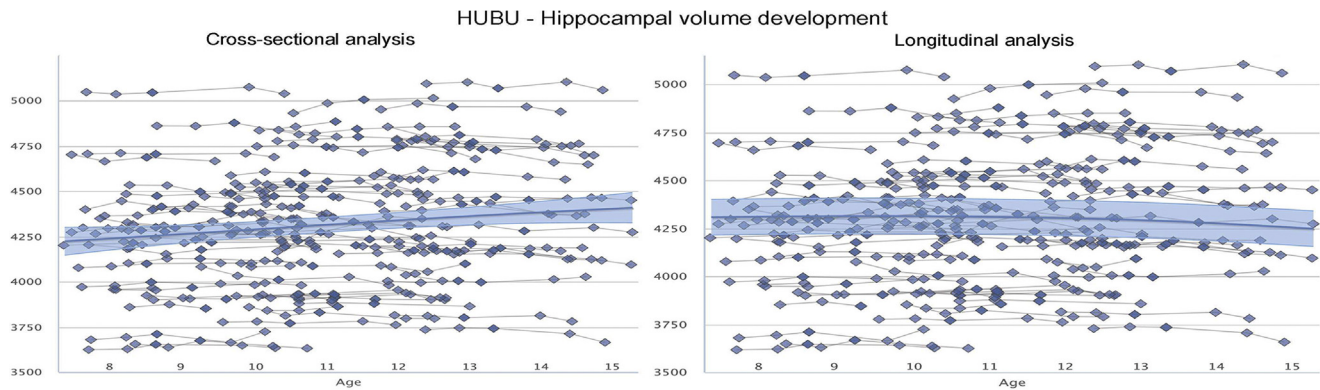


Fig. 2. Variable and analysis structure within Lifebrain.



**Fig. 3.** Developmental trajectories for hippocampal volume are very different when estimated from cross-sectional observations only by a generalized additive model (left panel of figure below) compared with a generalized additive MIXED model (right panel) taking actual change into account [10,11]. Hippocampal volume ( $\text{mm}^3$ ) was measured from T1-weighted MRI images, segmented by FreeSurfer from the left hemisphere. The fit curves were based on 510 scans from 94 participants (mean age 11.2 years, 7.5–15.4 years).

It is pivotal to examine to what extent the late-life association can be explained by early physical fitness, current physical activity, and their relationship, or if both exert unique influences. People with body mass index (BMI) > 25, showed a relationship between BMI and brain atrophy [37]. However, for older adults, higher BMI may not confer the same risk as for younger or middle-aged adults, and may even be protective, conferring a smaller risk of cardiovascular complications [39]. Similarly, certain genetic variations, such as the APOE  $\epsilon 4$  allele, reduce brain plasticity and increase brain vulnerability [40]. Thus, we might expect less stability of cognitive function [20] and a higher vulnerability to decline in the face of other risk factors for those with the risk allele. Equally, brain-derived neurotrophic factor (BDNF) is linked to neuronal growth and differentiation, and thus contributes to memory and learning, leading to differential cognitive trajectories [41] and to mental health differences [42]. These findings are in line with the broader “resource modulation” hypothesis [43], according to which the effects of common genetic variation on cognitive performance increase from early to late adulthood, reflecting the non-linear association between brain resources and performance (for review, see [44]).

In Lifebrain, using integrated cohorts representing diverse European social models over a large age range, and with the additional use of US databases, we will test national differences in risk and protective factors in BCM health.

A critical aspect of Lifebrain is the unique longitudinal neuroimaging design in some of its cohorts. Data from the first six time-points of the HUBU-project, for example, show that the developmental trajectories in hippocampal volume are not well predicted from only cross-sectional observations using a generalized additive model (left panel of Fig. 3), compared to when estimated from longitudinal information (with a generalized additive MIXED model, right panel), which takes actual change into account. The same phenomenon is frequently observed in aging, where unavoidable recruitment bias may lead to underestimation of true age effects.

In summary, we will analyze the entire lifespan, including early life characteristics, and individual factors, as well as the level of the individual and broader society, and identify risk and protective factors for brain, cognition and mental health. We will achieve this by combining population-based, cross-sectional and longitudinal cohorts with general indicators of health, together with in-depth detailed and targeted cognitive analyses across European and US studies.

### 2.3. Identifying pathways and moderators

Our longitudinal design permits identification of pathways from risk and protective factors to cognitive and mental health problems and their moderators that affect the strength or direction of relationships. We will examine how broader risk factors work at a biological and behavioural level (pathways), and evaluate interactions between identified risk factors, intermediate variables as part of pathways, and along with other important variables, e.g. sex [45,46]. Sex has been associated with differences in the risk for developing several disorders [45–48]. Observed sex differences in behaviour, cognition, emotions, and measures of brain structure and function, and their development [45,49,50] are often subtle and inconsistent, as many studies investigate limited age ranges or lack longitudinal observations [51]. Moreover, the effect of sex may differ across the lifespan [20,37,52,53]. Improved living conditions in Europe and less gender-restricted education are associated with increased sex differences in some cognitive functions, such as episodic memory, favouring women, and also decreases of others, such as numeracy [18]. It is interesting whether pathways at the level of brain and other biomarkers can be identified for sex as a moderator of cognitive and mental health over time, and across physical and social environments, including countries. Variables of interest include fatty acids, BMI, vitamins, cholesterol, blood pressure, genetic and epigenetic factors, and MRI measures of the brain. Outcome measures in Lifebrain will include many objective health variables, and refined cognitive and brain imaging assessments, mental health measures, as well as social and mental factors. This will be used to address the pathways and mechanisms for identified risk and protective factors. Essential fatty acids are important for development of cognitive function in normal pregnancies [54], as well as for severely premature infants [55]. BMI and certain blood markers are, for example, related to less (e.g. DHA, vitamin D) or more (e.g. cholesterol) brain atrophy [37]. Vitamin D has received much attention lately, as the link between vitamin D deficiency and risk of mental and neurodegenerative diseases has been established [32,56], and insufficiency or deficiency of vitamin D is common in older clinical samples. Little is known about the direction of the relationship, and whether similar relationships can be found among groups of non-demented elderly [57]. Higher levels of vitamin D appear to be related to less degeneration of major white matter tracts in the brain, even in cognitively healthy elderly participants. Vitamin D may stimulate production of neurotrophic, antioxidative and anti-inflammatory factors reduce risk for cardiovascular and cerebrovascular disease

and even influence amyloid phagocytosis and clearance [56]. If these relationships between brain change and nutrients like vitamin D can be replicated across larger and international samples, such mechanisms will provide a foundation for targeted interventions and randomized controlled trials also in normal ageing.

We do not know how potentially modifiable behaviours, e.g. eating habits and physical activity, affect blood nutrient and vitamin levels. Also unknown are effects of modifying medical factors such as BMI and hypertension, how genetic factors interact, and the impact of early-life cognitive function. There is reason to expect that established genetic variants, e.g. FTO [58], may influence the relation between food intake and blood nutrient and cardiovascular markers, and also the relation of such markers with brain atrophy. Furthermore, APOE  $\epsilon$ 4 may reduce brain plasticity, and increase vulnerability to negative impact on cognitive function [40], as well as mental health [59]. APOE  $\epsilon$ 4 carriers also have more pronounced sleep disturbances [60] and poor sleep habits have been related to brain atrophy [61], poor white matter integrity [62] and amyloid beta deposition [63] in aged individuals. Positive lifestyle factors such as physical activity [64], healthy diet [65] and high education levels [66] may be beneficial for APOE  $\epsilon$ 4 carriers, by lowering amyloid deposition [67] or promoting “maintenance” of brain metabolism [68]. Such observations are examples of considering distinct lifestyles in the context of a single or combination of genetic variant(s), in order to develop tailored strategies for intervention in subgroups of older adults. We will measure blood-based nutritional factors, food intake, genetics, and epigenetics, and relate them with measures of brain and cognitive function. Our combination of samples is vital to obtain sufficient statistical power.

The rich information in our large longitudinal databases will allow us to examine individual differences in the onset and magnitude of cognitive change, and identify genetic and lifestyle factors that predict preserved or declining cognition. In the Betula study [20], there were three distinct ageing trajectories for episodic memory (Fig. 4).

Good episodic memory in old age was also associated with preserved hippocampal function [69]. Parkinson’s disease patients with MCI have reduced fronto-striatal performance of working memory [70]. It is likely that those older participants displaying fronto-striatal/working memory impairment will be distinct from those showing hippocampus/episodic memory impairment, and that distinct genetic and lifestyle predictors are relevant for each phenotype. The same may apply to the separation of verbal and visuo-spatial memory [71]. Identification of specific cognitive phenotypes may suggest that different kinds of interventions will be effective. In addition to the broad set of existing genetic, epigenetic, health, demographic and lifestyle variables available in the Lifebrain database, we will conduct additional analyses to enrich the database with, e.g. telomere length [72] and longitudinal brain imaging [73].

In summary, we will identify variables and pathways with impact on neurocognitive function and mental health throughout life to be used in targeted intervention and prevention.

#### 2.4. Standardization and harmonization

Standardization of measures across sites post-hoc, as well as through enrichment of existing cohorts, is enacted in two separate work packages (WP). Partners have experience with multi-site neuroimaging, cognition and mental health studies. We will utilize procedures developed and described by the BioSHaRE project for data harmonization, integration and federated data analyses [74]. Measures can also be harmonized across latent variables: Since existing data have not been collected with identical scales and measures (e.g. different versions of neuropsychological tests

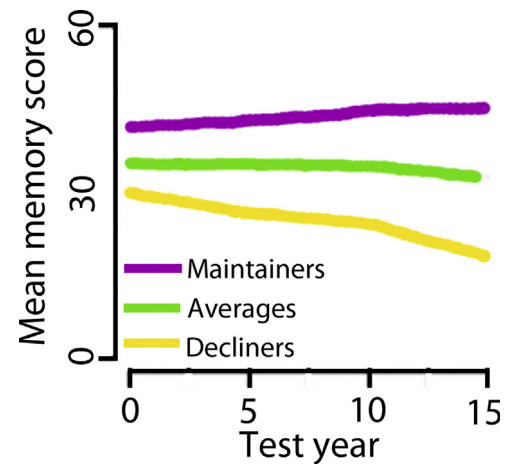


Fig. 4. By tracking memory performance over 15 years, factoring in attrition, we were able to show that 18% of 1558 participants upheld good memory function in ageing, while 13% declined [20]. The memory score was a composite based on 5 episodic-memory tasks (max score = 76).

and different MRI scanners), site-specific differences are expected for some measures. To allow measurements to be made more resistant to measurement error, and to abstract from individual scales to underlying constructs, our analyses will therefore be based also to some degree on latent factor models. We will employ standard psychometric approaches to determine construct validity across sites. We will rely on the standardized items of the new data collection phase. If standardized items are collected as a partial reassessment of site-specific items from the original data collection, this allows for the evaluation of convergent and divergent construct validity. We will test the convergence of latent factors from site-specific and standardized instruments to determine statistical overlap of hypothetical constructs across sites. This is also an effective means of dealing with missing data. Such an approach will allow merging of data across sites, and will probably be beneficial in multi-site studies outside the collaboration.

#### 2.5. Linkage with registry data

For some of the Lifebrain data, linkage to registry data may be possible. Indeed, some have already been linked by individual consent – e.g. the MRI cohorts from the Norwegian Mother and Child Study (MoBa) are linked, and Norwegian adult cohorts also have consented to link their MRI, cognitive, mental health and genetic data with the Medical Birth registry, as well as Army conscription data. Further consent for individualized linkage with population registries will be pursued especially for some Scandinavian samples.

#### 2.6. Critical measures

##### 2.6.1. Magnetic resonance imaging (MRI)

MRI at all sites includes T1-weighted scans for morphometric analyses. In addition, many cohorts have diffusion-weighted scans for structural connectivity and resting-state BOLD-weighted scans for functional connectivity analyses. Diffusion tensor imaging (DTI) in particular is sensitive to microstructural brain tissue properties, and is a promising biomarker related to development, ageing, disease, and cognition [75].

##### 2.6.2. Neuropsychology

Extensive cognitive tests are available for all cohorts, with validated and reliable measures. We focus especially on general cognitive abilities and episodic memory, in addition to cognitive

rating scales and measures of daily life function. With some variation across cohorts, cognitive measures will also include working memory, executive function and processing speed.

### 2.6.3. Genetics and epigenetics

Saliva or blood for extraction of DNA has been collected for all but two of the samples included in Lifebrain. In addition, we will examine about 2,000 further individuals.

### 2.6.4. Dried blood spots (DBS)

DBS will be collected at most sites and analyzed by Vitas (WP2 and WP3). Priority will be given to nutrients, such as essential fatty acids, cholesterol, and vitamins. Vitas will develop and validate new biomarkers on DBS tailored for Lifebrain. Candidates for new biomarkers are specific proteins, and from the Vitas comprehensive UPLC-HR-TOF-MS lipidomics platform, a panel of lipid markers with potential to predict preclinical transition to clinical stages of Alzheimer's disease.

### 2.6.5. Lifestyle and health measures

For most participants, information about lifestyle and general health is available, such as blood pressure, recordings of medication and other indices of cardiovascular disease and BMI, and will be enriched in a harmonized way through online data collection. Data on sleeping problems exist for most subjects and will be enriched through online data collection.

### 2.6.6. Mental health

Standardized measures of symptoms of depression and anxiety exist for most participants and will be enriched in a harmonized way through online data collection.

## 2.7. Investigations

Our approach calls for sophisticated modelling, and experts in longitudinal statistical modelling, bioinformatics, and genetics are included in the core group, as well as renowned neuroimaging experts. A specific task is dedicated to build an integrated multi-modal processing stream for Lifebrain, based on combining existing tools (FreeSurfer and FSL) with custom made procedures and new developments.

### 2.7.1. Neuroimaging preprocessing and statistics

FreeSurfer (FS) will be used for quantification of cortical thickness, volume and local arealization continuously across the brain surface, and volumes of a range of subcortical structures, including hippocampus. FS segments images at sub-voxel resolution and detects fine-graded effects, validated by manual segmentations and histology. All cortical metrics will be sampled in the same surface-based template, yielding unique possibilities for multi-modal integration by combining a range of different metrics while ensuring spatial coherence.

For DTI we will combine two approaches. We will use tract-based spatial statistics (TBSS) developed in the FMRIB Centre at Oxford for whole-WM comparisons. This allows voxel-based comparisons that are robust to anatomical differences and partial volume effects. For quantification of changes in major WM tracts, we use a newly developed automated and robust probabilistic reconstruction scheme – Tracula (TRActs Constrained by Underlying Anatomy) [76]. It is especially suited for longitudinal analyses, with high sensitivity and no bias in change estimates.

### 2.7.2. Cross-site standardization of neuroimaging data

The MRIs come from different scanners, which will affect the absolute measurement values. The applicants have extensive experience with large multi-centre neuroimaging, including

ENIGMA [77], ADNI, e.g. [78,79], PING [27,28], and the Oslo Multi-Sample Aging Study [80]. The segmentation procedures used in this project are not biased by scanner platform and seem not to affect the strength of relationships to neuropsychological scores [81]. Atlas-based normalization to increase robustness and accuracy of the segmentations across scanner platforms [82], and normalizing analyses for differences in grey matter–white matter contrast will increase sensitivity in multi-site studies [83]. Also, the size of each subsample will be large enough to allow statistical adjustment by scanner. Internal validation in the Oslo Multi-Sample Aging Study, showed a minor decrease in sensitivity by pooling together data from six different samples and scanners was accompanied by a large increase in power. In summary, we are well suited to tackle the challenges inherent in any multi-site study, and benefit from the manifold increases in sample size. As a feasibility check, we compared the age-trajectories of hippocampal volume from the Cam-CAN sample ( $n = 651$ ) and an LCBC subsample ( $n = 1100$ ) and observed highly comparable trajectories.

### 2.7.3. Genetic and epigenetic analyses

Data generation for genome- and epigenome-wide association study (GWAS and EWAS) analyses will be coordinated by University of Lübeck, using state-of-the-art high-throughput genome technologies for microarray-based profiling of DNA sequence (for GWAS) and methylation states (for EWAS). Several datasets have genome-wide SNP data available, and in addition we will select 2,000 individuals from at least four different datasets for de novo collection of buccal swabs, allowing us to determine both genome-wide SNP genotype and DNA methylation profiles using the “Global Screening Array” and “Infinium Methylation EPIC” array, respectively (both Illumina Inc.). Buccal swabs will be collected by participants at home using the Catch-All Sample Collection Swabs (Epibio, Inc.) following standardized collection protocols. Genome-wide data will serve several purposes in Lifebrain: First, the existing genotype and newly generated DNA methylation data can be used in the context of GWAS and EWAS analyses, to identify novel (and confirm previously reported) genetic/epigenetic determinants – and their interaction – of the cognitive and imaging traits of interest. Second, the genome-wide genotype data allow to precisely assess and correct for subtle differences in population substructure within and across cohorts, allowing to optimize data analysis procedures and inferences of non-genetic variables.

## 2.8. Data integration and statistical considerations

### 2.8.1. Statistical modelling of change

The complex longitudinal nature of the data poses significant statistical challenges in order to fully exploit the potential of combined data. To this end, Lifebrain has dedicated a task to development of new statistical tools. The consortium will address statistical challenges in three steps: (1) comparative analysis of data sets and research designs; (2) development and application of statistical tools; (3) tool refinement and model selection: For Step 1, the different research designs represented in Lifebrain will be compared to obtain an overview of their relative strengths, including differences in statistical power to detect effects of interest. Comparative analysis will inform data analysis strategies and future expansion of data sets. We will introduce a statistical tool that permits researchers to compute effect sizes that allow for unequal and person-specific measurement intervals, non-linear change, and selective attrition. For Step 2, we will promote the application of three interrelated sets of statistical tools: multivariate and dynamic variants of longitudinal structural equation modelling (SEM); classification and regression trees (CART);

generalized additive mixed modelling (GAMM). Multivariate dynamic SEM is well suited to identify lead-lag relations among constructs representing brain functions and structures, cognitive performance, and health outcomes. CART and related data mining techniques help to uncover classes of individuals with similar profiles and identify relevant predictors of class membership even with very large numbers of interacting predictors. GAMM offers powerful tests of non-linear effects on univariate criterion variables, including interactions with other covariates. We will introduce two new tools that combine the benefits of SEM and CART: (i) SEM trees [19] for discovering formerly undetected subgroups that differ in SEM parameters; (ii) SEM forests [84] for identifying variables that excel in predicting individual differences in such parameters across many predictors. We will also combine the benefits of each of the three approaches by proposing simultaneous estimation techniques for generalized multi-level models and evaluate the conditions under which they surpass existing stepwise procedures. In Step 3, we will refine the tools made available in Steps 1 and 2 based on feedback from research throughout the project. Furthermore, we will tackle the important problem of identifying and selecting those models that best summarize data across sites. We will adapt split-sample schemes and information-theoretic measures to control for multiple testing and avoid overoptimistic inferences due to double-dipping. The goal is to identify models that optimally represent the consolidated findings of the consortium, and hence contribute to theory development and generalizability. Members of the group have developed statistical tools for estimating the statistical power to detect individual differences in change in the context of longitudinal studies analysed with structural equation or multi-level models, such as latent growth curve models [85–89]. Use of these tools will permit group members to check whether the power to detect moderators of change with a given data set is adequate, and inform future design decisions, such as the spacing of measurements, or recruitment of new cohorts. In general, we expect the large databases of high-quality, well-validated and in-depth measures included in Lifebrain to yield excellent statistical power.

### 2.8.2. BIG Data – storage, transfer and processing system

Sharing of brain imaging data between large cohort studies across Europe for integrative and comparative analyses is a core of Lifebrain research. Lifebrain will establish an international brain image sharing and analysis platform. For this, we will build on expertise gained through existing collaborative data platforms among the participants (i.e., the Dementias Platform UK Imaging Informatics, DPUK-II; UOXF; UK Biobank, MRC; and the Max Planck Brain Imaging Library, OpenBILD, MPIB).

Integrated analyses of the data are envisioned in two forms: (a) fully integrated pre-processing and analysis of raw imaging data (mega-analysis); (b) statistical integration of local pre-processing and analysis (meta-analysis). A fully integrated analysis of raw data would probably achieve the best possible integration. However, formal and technical constraints might prevent sharing raw data from some sites, so the integration of locally processed data (e.g., shared in tabulated form) will be considered.

At least for the moment, the ethical permission of the different participating Centres is restricted to sharing within the Lifebrain consortium. As these permissions require to be specific and are slightly different for different countries, some data sets will be available to external applicants as a condition of funding (e.g. UK MRC), while for others a post hoc ethical approval for sharing is required and will be tied to specific conditions.

### 2.9. Uptake of research outputs

Lifebrain will develop mechanisms and tools to engage various stakeholders and bring their views and priorities to the project. Scientific exchange will take place with relevant policy makers, national decision makers, healthcare providers, patient organizations, cohort participants and researchers to support the uptake of project outputs. These outputs will be translated into specific guidelines and recommendations that will be actively disseminated according to the consortium's dissemination, exploitation and communication plan.

### 3. Conclusions

By integrating and standardizing major longitudinal studies of brain, cognition and mental health, Lifebrain aims to maximize the potential of European brain imaging cohorts. This will facilitate identification of the key determinants of cognitive and mental health across all ages, from birth to old age. Our lifespan focus fits with the novel life-course model of risk recently published by the Lancet Commission on Dementia prevention, intervention and care [90]. While we do not specifically target old age and dementia, identification of the risk factors and protective factors at all stages of life will be critical to enable future prevention of cognitive and mental disorders.

### Disclosure of interest

CAD, TEG and TF are stock-owners of Vitas AS (<http://vitas.no>), and BP has received unrestricted research funding from Jansen Research and Boehringer Ingelheim. No other competing interests have been declared.

### Acknowledgements

The project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 732592:

'Healthy minds from 0–100 years: optimizing the use of European brain imaging cohorts ("Lifebrain")'.

### Appendix A

#### 4. Lifebrain Consortium (<http://www.lifebrain.uio.no/about/>)

Pls: Kristine Walhovd (**UiO** – <https://www.oslobrains.no/>), Lars Nyberg (**Umeå** – <http://www.ufbi.umu.se/english>), Klaus Ebmeier (**UOXF** – <https://www.psych.ox.ac.uk/research/neurobiology-of-ageing>), Ulman Lindenberger (**MPIB** – <https://www.mpib-berlin.mpg.de/en/research/lifespan-psychology>), David Bartrés-Faz (**UB** – <http://www.ub.edu/bbslab/>), William Baaré (**RegionH** – <http://www.drcmr.dk/>), Richard Henson (**MRC** – <http://www.mrc-cbu.cam.ac.uk/>), Christian Drevon (**Vitas** – <http://www.vitas.no/>), Gun Peggy Knudsen (**NIPH** – <https://www.fhi.no/>), Brenda Penninx (**VUmc** – <https://www.vumc.com/>), Paolo Ghisletta (**UNIGE** – <http://www.unige.ch/fapse/mad/>), Ole Rogeberg (**Frisch** – <http://www.frisch.uio.no/>), Lorraine Tyler (**UCAM** – <http://www.psychol.cam.ac.uk/>), Lars Bertram (**LIGA UZL** – <http://www.liga.uni-luebeck.de/>).

Research Associates: Anders M. Fjell, René Westerhausen, Athanasia Monika Mowinckel, Inge Amlien (**UiO**), Micael Andersson, Sara Pudas, Mikael Stiernstedt (**Umeå**), Heidi Johansen-Berg, Enikő Zsoldos, Sana Suri, Claire E. Sexton (**UOXF**), Simone Kühn, Andreas Brandmaier, Ylva Köhncke, Sandra Düzel (**MPIB**), Cristina Solé-Padullés, Barbara Segura Fabregas (**UB**), Kathrine Skak Madsen, Louise Barué Johansen, Olga Rigina, Hartwig Siebner,



Michael Kjør, Ellen Garde, Erik Lykke Mortensen (**RegionH**), Rogier Kievit (**MRC**), Thomas E. Gundersen, Tonje Fosshem (**Vitas**), Isabelle Budin-Ljøsne (**NIPH**), Laura Nawijn (**VUmc**), Sezen Cekic (**UNIGE**), Christina M. Lill (LIGA **UzL**).

Project Administration: Barbara Bodorkos Friedman (**UiO**).

## References

- [1] Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011;21(10):718–79.
- [2] Habib R, Nyberg L, Nilsson LG. Cognitive and non-cognitive factors contributing to the longitudinal identification of successful older adults in the betula study. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2007;14(3):257–73.
- [3] Nevalainen N, Riklund K, Andersson M, Axelsson J, Ogren M, Lovden M, et al. COBRA: a prospective multimodal imaging study of dopamine, brain structure and function, and cognition. *Brain Res* 2015;1612:83–103.
- [4] Filippini N, Zsoldos E, Haapakoski R, Sexton CE, Mahmood A, Allan CL, et al. Study protocol: the Whitehall II imaging sub-study. *BMC Psychiatry* 2014;14:159.
- [5] Gathercole SE, Woolgar F, Team C, Kievit RA, Astle D, Manly T, et al. How common are WM deficits in children with difficulties in reading and mathematics? *J Appl Res Mem Cogn* 2016;5(4):384–94.
- [6] Taylor JR, Williams N, Cusack R, Auer T, Shafto MA, Dixon M, et al. The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) data repository: Structural and functional MRI, MEG, and cognitive data from a cross-sectional adult lifespan sample. *Neuroimage* 2017;144(Pt B):262–9.
- [7] Hult G, Drewelies J, Eibich P, Duzel S, Demuth I, Ghisletta P, et al. Cohort differences in psychosocial function over 20 years: current older adults feel less lonely and less dependent on external circumstances. *Gerontology* 2016;62(3):354–61.
- [8] Fjell AM, Sneve MH, Grydeland H, Storsve AB, Amlien IK, Yendiki A, et al. Relationship between structural and functional connectivity change across the adult lifespan: a longitudinal investigation. *Hum Brain Mapp* 2017;38(1):561–73.
- [9] Dijkstra-Kersten SMA, Sitnikova K, Terluin B, Penninx B, Twisk JWR, van Marwijk HWJ, et al. Longitudinal associations of multiple physical symptoms with recurrence of depressive and anxiety disorders. *J Psychosom Res* 2017;97:96–101.
- [10] Madsen KS, Baare WF, Skimminge A, Vestergaard M, Siebner HR, Jernigan TL. Brain microstructural correlates of visuospatial choice reaction time in children. *Neuroimage* 2011;58(4):1090–100.
- [11] Ramsøy TZ, Liptrot MG, Skimminge A, Lund TE, Sidaros K, Christensen MS, et al. Healthy aging attenuates task-related specialization in the human medial temporal lobe. *Neurobiol Aging* 2012;33(9):1874–89.
- [12] Maneru C, Junque C, Salgado-Pineda P, Serra-Grabulosa JM, Bartres-Faz D, Ramirez-Ruiz B, et al. Corpus callosum atrophy in adolescents with antecedents of moderate perinatal asphyxia. *Brain Inj* 2003;17(11):1003–9.
- [13] Engvig A, Fjell AM, Westlye LT, Moberget T, Sundseth O, Larsen VA, et al. Effects of memory training on cortical thickness in the elderly. *Neuroimage* 2010;52(4):1667–76.
- [14] Ngandu T, Lehtisalo J, Solomon A, Levalhti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015;385(9984):2255–63.
- [15] Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry* 1999;174:307–11.
- [16] Schweizer S, Kievit RA, Emery T, Cam CAN, Henson RN. Symptoms of depression in a large healthy population cohort are related to subjective memory complaints and memory performance in negative contexts. *Psychol Med* 2017;1–11.
- [17] Skirbekk V, Loichinger E, Weber D. Variation in cognitive functioning as a refined approach to comparing aging across countries. *Proc Natl Acad Sci USA* 2012;109(3):770–4.
- [18] Weber D, Skirbekk V, Freund I, Herlitz A. The changing face of cognitive gender differences in Europe. *Proc Natl Acad Sci USA* 2014;111(32):11673–8.
- [19] Brandmaier AM, von Oertzen T, McArdle JJ, Lindenberger U. Structural equation model trees. *Psychol Methods* 2013;18(1):71–86.
- [20] Josefsson M, de Luna X, Pudas S, Nilsson LG, Nyberg L. Genetic and lifestyle predictors of 15-year longitudinal change in episodic memory. *J Am Geriatr Soc* 2012;60(12):2308–12.
- [21] Abel KM, Wicks S, Susser ES, Dalman C, Pedersen MG, Mortensen PB, et al. Birth weight, schizophrenia, and adult mental disorder: is risk confined to the smallest babies? *Arch Gen Psychiatry* 2010;67(9):923–30.
- [22] Tuovinen S, Eriksson JG, Kajantie E, Lahti J, Pesonen AK, Heinonen K, et al. Maternal hypertensive disorders in pregnancy and self-reported cognitive impairment of the offspring 70 years later: the Helsinki Birth Cohort Study. *Am J Obstet Gynecol* 2013;208(3):e1–9.
- [23] Aizer A, Currie J. The intergenerational transmission of inequality: maternal disadvantage and health at birth. *Science* 2014;344(6186):856–61.
- [24] Ross MG, Desai M, Khorram O, McKnight RA, Lane RH, Torday J. Gestational programming of offspring obesity: a potential contributor to Alzheimer's disease. *Curr Alzheimer Res* 2007;4(2):213–7.
- [25] Syddall HE, Sayer AA, Simmonds SJ, Osmond C, Cox V, Dennison EM, et al. Birth weight, infant weight gain, and cause-specific mortality: the Hertfordshire Cohort Study. *Am J Epidemiol* 2005;161(11):1074–80.
- [26] Walhovd KB, Tamnes CK, Fjell AM. Brain structural maturation and the foundations of cognitive behavioral development. *Curr Opin Neurol* 2014;27(2):176–84.
- [27] Walhovd KB, Fjell AM, Brown TT, Kuperman JM, Chung Y, Hagler Jr DJ, et al. Long-term influence of normal variation in neonatal characteristics on human brain development. *Proc Natl Acad Sci USA* 2012;109(49):20089–94.
- [28] Fjell AM, Walhovd KB, Brown TT, Kuperman JM, Chung Y, Hagler Jr DJ, et al. Multimodal imaging of the self-regulating developing brain. *Proc Natl Acad Sci USA* 2012;109(48):19620–5.
- [29] Knickmeyer RC, Wang J, Zhu H, Geng X, Woolson S, Hamer RM, et al. Common variants in psychiatric risk genes predict brain structure at birth. *Cereb Cortex* 2014;24(5):1230–46.
- [30] Ho AJ, Stein JL, Hua X, Lee S, Hibar DP, Leow AD, et al. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. *Proc Natl Acad Sci USA* 2010;107(18):8404–9.
- [31] Reitz C, Tosto G, Mayeux R, Luchsinger JA, Group N-LNFS. Alzheimer's Disease Neuroimaging I. Genetic variants in the Fat and Obesity Associated (FTO) gene and risk of Alzheimer's disease. *PLoS One* 2012;7(12):e50354.
- [32] Milanesechi Y, Lamers F, Mbarek H, Hottenga JJ, Boomsma DI, Penninx BW. The effect of FTO rs939609 on major depression differs across MDD subtypes. *Mol Psychiatry* 2014;19(9):960–2.
- [33] Melka MG, Gillis J, Bernard M, Abrahamowicz M, Chakravarty MM, Leonard GT, et al. FTO, obesity and the adolescent brain. *Hum Mol Genet* 2013;22(5):1050–8.
- [34] Deary IJ, Pattie A, Starr JM. The stability of intelligence from age 11 to age 90 years: the Lothian birth cohort of 1921. *Psychol Sci* 2013;24(12):2361–8.
- [35] Hakulinen C, Elovainio M, Pulkki-Raback L, Virtanen M, Kivimaki M, Jokela M. Personality and depressive symptoms: individual participant meta-analysis of 10 cohort studies. *Depress Anxiety* 2015;32(7):461–70.
- [36] Nyberg J, Aberg MA, Schioler L, Nilsson M, Wallin A, Toren K, et al. Cardiovascular and cognitive fitness at age 18 and risk of early-onset dementia. *Brain* 2014;137(Pt 5):1514–23.
- [37] Walhovd KB, Storsve AB, Westlye LT, Drevon CA, Fjell AM. Blood markers of fatty acids and vitamin D, cardiovascular measures, body mass index, and physical activity relate to longitudinal cortical thinning in normal aging. *Neurobiol Aging* 2014;35(5):1055–64.
- [38] Sabia S, Dugravot A, Dartigues JF, Abell J, Elbaz A, Kivimaki M, et al. Physical activity, cognitive decline, and risk of dementia: 28-year follow-up of Whitehall II cohort study. *BMJ* 2017;357:j2709.
- [39] Batsis JA, Singh S, Lopez-Jimenez F. Anthropometric measurements and survival in older Americans: results from the third National Health and Nutrition Examination Survey. *J Nutr Health Aging* 2014;18(2):123–30.
- [40] Sundstrom A, Marklund P, Nilsson LG, Cruts M, Adolfsson R, Van Broeckhoven C, et al. APOE influences on neuropsychological function after mild head injury: within-person comparisons. *Neurology* 2004;62(11):1963–6.
- [41] Ghisletta P, Backman L, Bertram L, Brandmaier AM, Gerstorff D, Liu T, et al. The Val/Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene predicts decline in perceptual speed in older adults. *Psychol Aging* 2014;29(2):384–92.
- [42] Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. *BMC Med* 2014;12:7.
- [43] Lindenberger U, Nagel IE, Chicherio C, Li SC, Heekeren HR, Backman L. Age-related decline in brain resources modulates genetic effects on cognitive functioning. *Front Neurosci* 2008;2(2):234–44.
- [44] Papenberg G, Lindenberger U, Backman L. Aging-related magnification of genetic effects on cognitive and brain integrity. *Trends Cogn Sci* 2015;19(9):506–14.
- [45] Hanamsagar R, Bilbo SD. Sex differences in neurodevelopmental and neurodegenerative disorders: focus on microglial function and neuroinflammation during development. *J Steroid Biochem Mol Biol* 2016;160:127–33.
- [46] Loke H, Harley V, Lee J. Biological factors underlying sex differences in neurological disorders. *Int J Biochem Cell Biol* 2015;65:139–50.
- [47] Solomon MB, Herman JP. Sex differences in psychopathology: of gonads, adrenals and mental illness. *Physiol Behav* 2009;97(2):250–8.
- [48] Riedel BC, Thompson PM, Brinton RD. Age, APOE and sex: triad of risk of Alzheimer's disease. *J Steroid Biochem Mol Biol* 2016;160:134–47.
- [49] Ingallhalikar M, Smith A, Parker D, Satterthwaite TD, Elliott MA, Ruparel K, et al. Sex differences in the structural connectome of the human brain. *Proc Natl Acad Sci USA* 2014;111(2):823–8.
- [50] Joel D, Berman Z, Tavor I, Wexler N, Gaber O, Stein Y, et al. Sex beyond the genitalia: the human brain mosaic. *Proc Natl Acad Sci USA* 2015;112(50):15468–73.
- [51] Mendrek A. Is it important to consider sex and gender in neurocognitive studies? *Front Psychiatry* 2015;6:83.
- [52] Bale TL, Epperson CN. Sex differences and stress across the lifespan. *Nat Neurosci* 2015;18(10):1413–20.
- [53] Kendler KS, Edwards AC, Gardner CO. Sex differences in the pathways to symptoms of alcohol use disorder: a study of opposite-sex twin pairs. *Alcohol Clin Exp Res* 2015;39(6):998–1007.
- [54] Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* 2003;111(1):e39–44.
- [55] Henriksen C, Haugholt K, Lindgren M, Aurvåg AK, Ronnestad A, Gronn M, et al. Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid. *Pediatrics* 2008;121(6):1137–45.

- [56] Etgen T, Sander D, Bickel H, Sander K, Forstl H. Vitamin D deficiency, cognitive impairment and dementia: a systematic review and meta-analysis. *Dement Geriatr Cogn Disord* 2012;33(5):297–305.
- [57] de Koning EJ, van Schoor NM, Penninx BW, Elders PJ, Heijboer AC, Smit JH, et al. Vitamin D supplementation to prevent depression and poor physical function in older adults: Study protocol of the D-Vitaal study, a randomized placebo-controlled clinical trial. *BMC Geriatr* 2015;15:151.
- [58] de Luis DA, Aller R, Conde R, Izaola O, Gonzalez Sagrado M, Castrodeza Sanz J. The rs9939609 gene variant in FTO modified the metabolic response of weight loss after a 3-month intervention with a hypocaloric diet. *J Investig Med* 2013;61(1):22–6.
- [59] Skoog I, Waern M, Duberstein P, Blennow K, Zetterberg H, Borjesson-Hanson A, et al. A 9-year prospective population-based study on the association between the APOE\*E4 allele and late-life depression in Sweden. *Biol Psychiatry* 2015;78(10):730–6.
- [60] Hita-Yanez E, Atienza M, Gil-Neciga E, Cantero JL. Disturbed sleep patterns in elders with mild cognitive impairment: the role of memory decline and ApoE epsilon4 genotype. *Curr Alzheimer Res* 2012;9(3):290–7.
- [61] Sexton CE, Storsve AB, Walhovd KB, Johansen-Berg H, Fjell AM. Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology* 2014;83(11):967–73.
- [62] Sexton CE, Zsoldos E, Filippini N, Griffanti L, Winkler A, Mahmood A, et al. Associations between self-reported sleep quality and white matter in community-dwelling older adults: a prospective cohort study. *Hum Brain Mapp* 2017.
- [63] Branger P, Arenaza-Urquijo EM, Tomadesso C, Mezenge F, Andre C, de Flores R, et al. Relationships between sleep quality and brain volume, metabolism, and amyloid deposition in late adulthood. *Neurobiol Aging* 2016;41:107–14.
- [64] Brown BM, Peiffer JJ, Taddei K, Lui JK, Laws SM, Gupta VB, et al. Physical activity and amyloid-beta plasma and brain levels: results from the Australian imaging, biomarkers and lifestyle study of ageing. *Mol Psychiatry* 2013;18(8):875–81.
- [65] Gardener SL, Rainey-Smith SR, Barnes MB, Sohrabi HR, Weinborn M, Lim YY, et al. Dietary patterns and cognitive decline in an Australian study of ageing. *Mol Psychiatry* 2015;20(7):860–6.
- [66] Wang HX, Gustafson DR, Kivipelto M, Pedersen NL, Skoog I, Windblad B, et al. Education halves the risk of dementia due to apolipoprotein epsilon4 allele: a collaborative study from the Swedish brain power initiative. *Neurobiol Aging* 2012;33(5):e1–7 [1007].
- [67] Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Machulda M, Lowe VJ, et al. Effect of intellectual enrichment on AD biomarker trajectories: Longitudinal imaging study. *Neurology* 2016;86(12):1128–35.
- [68] Arenaza-Urquijo EM, Gonneaud J, Fouquet M, Perrotin A, Mezenge F, Landeau B, et al. Interaction between years of education and APOE epsilon4 status on frontal and temporal metabolism. *Neurology* 2015;85(16):1392–9.
- [69] Pudas S, Persson J, Josefsson M, de Luna X, Nilsson LG, Nyberg L. Brain characteristics of individuals resisting age-related cognitive decline over two decades. *J Neurosci* 2013;33(20):8668–77.
- [70] Ekman U, Eriksson J, Forsgren L, Mo SJ, Riklund K, Nyberg L. Functional brain activity and presynaptic dopamine uptake in patients with Parkinson's disease and mild cognitive impairment: a cross-sectional study. *Lancet Neurol* 2012;11(8):679–87.
- [71] Suri S, Topiwala A, Filippini N, Zsoldos E, Mahmood A, Sexton CE, et al. Distinct resting-state functional connections associated with episodic and visuospatial memory in older adults. *Neuroimage* 2017;159:122–30.
- [72] Wikgren M, Karlsson T, Nilbrink T, Nordfjall K, Hultdin J, Slegers K, et al. APOE epsilon4 is associated with longer telomeres, and longer telomeres among epsilon4 carriers predicts worse episodic memory. *Neurobiol Aging* 2012;33(2):335–44.
- [73] Nyberg L, Salami A, Andersson M, Eriksson J, Kalpouzos G, Kauppi K, et al. Longitudinal evidence for diminished frontal cortex function in aging. *Proc Natl Acad Sci USA* 2010;107(52):22682–6.
- [74] Doiron D, Burton P, Marcon Y, Gaye A, Wolfenbutter BHR, Perola M, et al. Data harmonization and federated analysis of population-based studies: the BioS-HaRE project. *Emerg Themes Epidemiol* 2013;10(1):12.
- [75] Amlien IK, Fjell AM. Diffusion tensor imaging of white matter degeneration in Alzheimer's disease and mild cognitive impairment. *Neuroscience* 2014;276:206–15.
- [76] Yendiki A, Reuter M, Wilkens P, Rosas HD, Fischl B. Joint reconstruction of white-matter pathways from longitudinal diffusion MRI data with anatomical priors. *Neuroimage* 2016;127:277–86.
- [77] Hibar DP, Stein JL, Rentneria ME, Arias-Vasquez A, Desrivieres S, Jahanshad N, et al. Common genetic variants influence human subcortical brain structures. *Nature* 2015;520(7546):224–9.
- [78] Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, et al. Brain atrophy in healthy aging is related to CSF levels of Abeta1–42. *Cereb Cortex* 2010;20(9):2069–79.
- [79] Walhovd KB, Fjell AM, Brewer J, McEvoy LK, Fennema-Notestine C, Hagler Jr DJ, et al. Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer disease. *AJNR Am J Neuroradiol* 2010;31(2):347–54.
- [80] Fjell AM, Westlye LT, Amlien I, Espeseth T, Reinvang I, Raz N, et al. High consistency of regional cortical thinning in aging across multiple samples. *Cereb Cortex* 2009;19(9):2001–12.
- [81] Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, et al. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. *Neuroimage* 2006;32(1):180–94.
- [82] Han X, Fischl B. Atlas renormalization for improved brain MR image segmentation across scanner platforms. *IEEE Trans Med Imaging* 2007;26(4):479–86.
- [83] Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols TE, Smith SM, et al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. *Proc Natl Acad Sci USA* 2013;110(23):9523–8.
- [84] Brandmaier AM, Prindle JJ, McArdle JJ, Lindenberger U. Theory-guided exploration with structural equation model forests. *Psychol Methods* 2016;21(4):566–82.
- [85] Hertzog C, Lindenberger U, Ghisletta P, Oertzen T. On the power of multivariate latent growth curve models to detect correlated change. *Psychol Methods* 2006;11(3):244–52.
- [86] von Oertzen T. Power equivalence in structural equation modelling. *Br J Math Stat Psychol* 2010;63(Pt 2):257–72.
- [87] von Oertzen T, Hertzog C, Lindenberger U, Ghisletta P. The effect of multiple indicators on the power to detect inter-individual differences in change. *Br J Math Stat Psychol* 2010;63(Pt 3):627–46.
- [88] von Oertzen T, Brandmaier AM. Optimal study design with identical power: an application of power equivalence to latent growth curve models. *Psychol Aging* 2013;28(2):414–28.
- [89] Brandmaier AM, von Oertzen T, Ghisletta P, Hertzog C, Lindenberger U. LIFESPAN: a tool for the computer-aided design of longitudinal studies. *Front Psychol* 2015;6:272.
- [90] Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet* 2017.



Kristine Walhovd

[Professor of neuropsychology, University of Oslo, the Centre for Lifespan Changes in Brain and Cognition. Has worked and published on risk and protective factors for neurocognitive function using multiple cognitive measures and imaging modalities].



Anders Fjell

[Professor of cognitive psychology, University of Oslo, the Centre for Lifespan Changes in Brain and Cognition. Has published on brain development and aging, with a special focus on memory].



René Westerhausen

[Professor of Cognitive Neuroscience, University of Oslo, the Centre for Lifespan Changes in Brain and Cognition. Has worked on structure-function associations in healthy and clinical samples with focus on inter-hemispheric integration in the asymmetrical brain].



Lars Nyberg

[Professor of Neuroscience, PI of Betula and co-PI of Cobra. Has published on neurocognitive aging, with particular focus on brain maintenance].



**Klaus Ebmeier**  
[Professor of Old Age Psychiatry University of Oxford. Has published on biological psychiatry, especially neuroimaging of major psychiatric disorders. PI of Whitehall II MRI Substudy].



**Christian A. Drevon**  
[Professor emeritus of Medicine (nutrition) of University of Oslo, and consultant in the analytical contract laboratory Vitas Ltd in Oslo Science Park. Has studied effects of nutrients and physical activity on health, with special focus on molecular nutrition and biomarkers. PI of several Norwegian and EU-financed studies. One interest has been premature infants, essential nutrients and cognitive function].



**Ulman Lindenberger**  
[Director of the Centre for Lifespan Psychology, Max Planck Institute for Human Development Berlin, and Co-Director of the Max Planck UCL Centre for Computational Psychiatry and Ageing Research based in Berlin and London. Primary research interests include behavioural and neural plasticity and brain-behaviour relations across the lifespan, multivariate developmental methodology, and formal models of behavioural change].



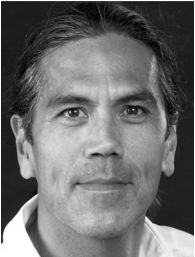
**Gun Peggy Knudsen**  
[Executive Director of Health data and digitalisation, Norwegian Institute of Public Health, PhD in medical genetics. Research focus is on psychiatric genetics, genetic epidemiology and registry based research].



**David Bartrés-Faz**  
[Professor of Medical Psychology, Faculty of Medicine and Health Sciences, University of Barcelona. Performs research within the field of brain reserve and resilience factors and mechanisms in aging. Also uses non-invasive brain stimulation techniques to modulate brain plasticity responses linked to cognitive performance.



**Isabelle Budin-Ljøsne**  
[Senior Adviser, Cohort Studies, Norwegian Institute of public Health, MA in Research Ethics. Research focus is on informed consent, international data sharing, and stakeholder engagement].



**William FC Baaré**  
[Senior Researcher, Neuroscience, Danish Research Centre for Magnetic Resonance. Uses multimodal imaging to investigate the link between brain, cognition, behaviour, and intrinsic and extrinsic variable in healthy and psychiatric populations of children and adolescents, and adults].



**Brenda Penninx**  
[Professor of psychiatric epidemiology, VU University Medical Centre, Amsterdam. Research focus is on etiology, course and consequences of major psychiatric disorders. PI of Netherlands Study of Depression and Anxiety, NESDA].



**Hartwig Siebener**  
[Professor in Precision Medicine, Director of the Danish Research Centre for Magnetic Resonance. Combines functional and structural brain imaging with interventional protocols such as transcranial brain stimulation, pharmacological challenges, or training and to gain insights into the plasticity of the human brain as well as the pathophysiology of brain diseases].



**Paolo Ghisletta**  
[Professor of Psychology, University of Geneva; Multivariate methodology and analysis applied to the study of life-long change processes].



**Rik Henson**  
[Professor of Cognitive Neuroscience, MRC Cognition & Brain Sciences Unit. Has worked on brain bases of memory and how they change with age. Expert in multimodal neuroimaging].



**Ole Rogeberg**  
[Senior Research Fellow, The Ragnar Frisch Centre for Economic Research; statistical inference, cognitive epidemiology, policy analysis].



Lorraine Tyler  
[Professor of Cognitive Neuroscience, Department of Psychology, Cambridge, is an expert in cognitive neuroscience of language and semantics, and cognitive ageing.



Lars Bertram  
[Professor of Genome Analytics, University of Lübeck; focuses on deciphering the genetic and epigenetic foundations of genetically complex human traits and diseases, in particular those related to aging and neurodegenerative diseases. Co-PI of Berlin Aging Study II (BASE-II)].