Lifebrain

D4.4 Distinguishing lifespan-applicable and age-specific risk and protective factors

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Executive Summary

This deliverable describes the published and ongoing work in Lifebrain Task 4.4 “Distinguishing lifespan-applicable and age-specific risk and protective factors”.

In line with the Lifebrain strategy of providing an evidence-based knowledgebase for more personalized medicine, the main objective of this task was to distinguish lifespan-applicable versus age-specific risk and protective factors. The current task is intertwined with specifically Tasks 4.2 “Individual pathways and mediator variables in relation to risk for mental health problems and resilience” and 4.3 “Analysis of individual pathways/mediator variables in relation to risk for poor cognitive function and decline versus resilience”. So this deliverable includes by necessity an overlap with all the other deliverables in WP4. To make coherent reading of each deliverable possible, a degree of redundancy has been included. We present relevant research results of published articles. Furthermore, we update descriptions of papers in submission, revision or in preparation and present preliminary findings were possible.

The brain changes at all times through life, in health and disease. A major challenge is to determine which changes are detrimental and which are facilitating to cognitive and mental health, and the factors causing them. Through life, our genetic dispositions interact continuously with environmental, societal, occupational and lifestyle factors to influence brain changes. These changes, from the earliest stages to oldest ages, are mapped in detail in various longitudinal studies through Europe utilizing Magnetic Resonance Imaging (MRI). Analysis of age-specificity of mechanisms to begin with necessitates a vast number of participants at all stages of life, and analysis of sex-specific effects essentially serves to halve the samples. Our studies have benefited greatly from the larger sample sizes gained from pooling multiple European neuroimaging datasets and cohorts. Particularly novel features of the integrated Lifebrain cohort are the longitudinal design, which allowed more sensitive within-person measurement of true changes over time, and the very rich genotypic and phenotypic characterization of the participating individuals. As such, the described studies have contributed to the overarching goal of better utilization of existing European neuroimaging datasets to aid the development of personalized medicine and the enhancement of cognitive and mental health throughout the lifespan. The work described in D4.4 has contributed to establish a solid foundation of knowledge for understanding how brain, cognitive and mental health can be optimized through the lifespan. We have identified determinants of brain, cognitive and mental health at different stages of life through the creation of a large database of detailed information about brain imaging relating to cognitive function, mental health, and genetics.

List of acronyms / abbreviations

BASE II	Berlin Aging Study II
Cam-CAN	Cambridge Centre for Ageing and Neuroscience, University of Cambridge
DBS	Dried blood spot
GWA	Genome-wide association study
HUBU	Hjernens Udvikling hos Børn og Unge/Brain Development of Children and Adolescents (RegionH)
ICV	Intracranial volume
IL	Interleukin
LTL	Leukocyte telomere length
MCI	Mild cognitive impairment
MPIB	Max Planck Institute for Human Development Berlin
MRI	Magnetic resonance imaging
PI	Principal Investigator
REGIONH	Region Hovedstaden/Capital region of Copenhagen, Denmark
SEM	Structural Equation Modeling
SES	Socio-economic Status
SHARE	the Survey of Health, Ageing and Retirement in Europe
UB	University of Barcelona
UCAM	University of Cambridge
UiO	University of Oslo
UOXF	University of Oxford
VUmc	VU University Medical Center Amsterdam

1. Introduction

Our brain, cognitive functions and mental health tend to change continuously across life and are affected by a number of environmental and genetic variables. These influences, however, might differ in when they influence of neurocognitive and mental health. Some factors of influences are prenatal but may still have lifelong impacts. Others may excerpt continuous effects through life, while some may be important at some life-stages. The work described in deliverable D4.4 addresses such factors of continuous vs. age-specific influences. We have focused on lifespan risk factors and their interactions and identified subgroups with differential susceptibility. This is crucial both to understand the mechanisms at work at any one specific stage, e.g. in early development, and to identify what and how residual variance is affected by factors specific to later stages in life. This has contributed solid knowledge about risk and protective factors and the pathways by which they work at different ages. This knowledge is necessary for the possible to personalize health care when it comes to the brain. Based on previous effects of select risks and interventions, a multifactorial and personalized approach make it realistic to identify modifiable environmental factors that promote cognitive development in childhood and adolescence, foster maintenance of cognitive functions into late adulthood, delay onset of dementia on a population level, reduce the need for care, and improve working ability through prevention and intervention programs. Due to the accelerated accumulation of brain disorders and cognitive decline with increasing age, even small improvements of cognitive trajectories during earlier periods of the lifespan, and reductions in rates of brain atrophy with advancing adult age, will have the potential to postpone impairment and neurodegenerative disorders and thereby substantially increase the amount of well-functioning years in the population.

Cognitive and mental health disorders are a serious threat to functioning of individuals. The World Health Organization estimates that in 2020 depression will top the list of burden of disease because of its high prevalence, chronic nature and huge adverse impact on functioning. The prevalence of depressive and anxiety disorders is rather stable over the lifespan, but subthreshold symptomatology shows an increasing prevalence with older age. This is likely due to a combination of cumulative risk factors such as important life events, somatic conditions or unhealthy lifestyle as well as structural and functional brain abnormalities that could increase vulnerability for mental problems.

The present work has contributed to a knowledge base which will be important for targeted prevention of brain, cognitive and mental health problems at all stages in life by describing the effect on brain, cognition and mental health of a range of health, life-style related, genetic, and epigenetic factors and theinteractions between them. Understanding the impact of the combination of risk and protective factors within any given person – where age may be the most critical aspect - is the key to personalize health care and design preventive strategies.

Efforts to identify and/or intervene with single genetic and environmental mechanisms to optimize cognitive function and mental health at any given age have largely failed. Lifebrain has taken a new approach to model brain, cognitive and mental health that differs in fundamental ways from previous approaches: it is dimensional, not only categorical, lifespan rather than only development or old-age-focused, and based on systems-vulnerability and resilience rather than simple cause-effect relationships.

This approach reflects a different view on lifespan changes in brain, cognitive function and mental health, and on how we can study, prevent, diagnose and treat cognitive and mental health problems. The research was based on three fundamental assumptions: (1) factors affecting cognitive and mental health often represent quantitative rather than qualitative differences in characteristics that commonly exist in the population, (2) factors known to affect cognitive and mental health at specific ages will often do so through accumulation of risks and benefits over time that are often not specific to any given age, and (3) a wealth of environmental and genetic factors and their interplay – often with an impact on the individual`s epigenetic makeup – determine optimal cognitive and mental functioning. We have worked to identify such factors and the ages at which they have their influence through the lifespan, which we believe yields potential for personalized interventions. The project has proceeded through distinct but tightly interacting parts, related to identification of risk and protective factors, identification of pathways and moderators of these broader factors, and determining conditions for optimal cognitive and mental health.

An important aspect of the study has been to assess continuous influences of candidate variables from early life. Cognitive function and behavioural problems with an established neural basis, such as in ADHD and schizophrenia, have been linked to early developmental. For instance, from epidemiological studies, it is established that low birth weight, regarded a marker of adverse intrauterine circumstances, is associated with a range of diseases and reduced function in daily life. Some of these are known to be associated with cognitive decline and increase AD risk, e.g. coronary heart disease, hypertension, and type 2 diabetes. The mechanisms for these effects are not known, however, and this hinder possible interventions and targeted lifestyle-related prevention programs.

Adding to the picture, a number of common variants in risk genes for psychiatric disorders are predictive of brain structure even at birth. For instance, neonates carrying APOE ε4, the major genetic risk factor for AD, were recently reported to have reduced volumes of temporal cortex like that reported in older adults. In Lifebrain, we have studied relationships between APOE ε4, brain structure and cognitive function across the lifespan and in different age groups. This work has demonstrated the need to widen this perspective to also comprise disorders typically associated with ageing. This does not imply that commonly occurring genetic variants doom newborns to develop AD 80 years later, but that the contribution to brain characteristics associated with AD risk may represent a stable risk factor. Consequently, our research suggests that efforts to postpone decline or disease may be futile if they are only targeted at old age. By including the full lifespan in our studies, we have been able to investigate at which ages and how the early life variables, including genetic variance, exert their effects.

1.1. Task description

Analysis to distinguish which risk and protective factors work when. For example, some characteristics present early in life (e.g. APOE genotype, birth weight) may exert lifelong influence on cognitive function and mental health, via persistent influences on the brain, while others, such as cholesterol, may rather be a risk factor if heightened in mid-life. Likewise, lifestyle factors such as physical activity level may reflect lifelong accumulation of protective effect, or may still yield positive effects if heightened only in older age.

Distinguishing age-specificity versus lifespan-applicability is pivotal to personalised medicine and targeted prevention.

1.2. Objectives

As stated in the original application, analyses in the integrated Lifebrain cohort would be aimed at identifying whether individual differences in cognitive functioning are mediated by variations in factors such as lifestyle, body mass index, blood pressure, cholesterol and other blood markers (vitamins, fatty acids, proteins), genetics/epigenetics, and different brain-integrity factors. Cognition and brain structure across the lifespan would be related to interindividual differences in lifestyle factors such as physical activity or engagement in cognitively stimulating activities. The increased statistical power gained from pooling across cohorts, and especially the availability of unique longitudinal data, along with the statistical tools developed in T3.7 was expected to significantly contribute to the identification of previously undiscovered relations or gene-by-environment effects.

1.3. Collaboration among partners

This task has been led by the University of Oslo, in cooperation with the Max Planck Institute in Berlin (MPIB), University of Barcelona (UB), University of Cambridge (UCAM), Region Hovedstaden (REGIONH) University of Oxford (UOXF), University Medical Center Amsterdam (VUmc) and Universität zu Lübeck (UzL) as main collaborators.

Collaborations among sites have been ubiquitous in all finalized and ongoing studies, with most studies listing co-authors from multiple and sometimes all participating Lifebrain sites. Consortium members from all sites have provided essential feedback at all stages of each Lifebrain study, starting with a review process in the Lifebrain Knowledge Management Committee (KMC), through consortium meeting presentations and discussions, as well as discussions on the collaborative online platform Slack, thus encompassing study conceptualization, analyses, interpretation, and paper drafting.

2. Results

At the time of writing (August 2022), T4.4 has resulted in ten published papers on the integrated Lifebrain cohort, 2 submitted manuscripts, while multiple papers are being prepared.
The sections below provide an overview of published and preliminary findings, focusing mainly on studies on the integrated Lifebrain cohort, as well as a description of current research activities that have been approved by the KMC. The studies are organized under descriptive headings below, but it should be stressed that several studies address multiple interacting factors. In total, 36 sub-studies are listed.

Title of project proposals
From demographics to cognitive neuroscience of memory – integration of SHARE and Lifebrain- in process
Education and income show heterogeneous relationships to lifespan brain and cognitive differences across European and US cohorts*
The relation of depressed mood, sleep quality and lifestyle to brain and cognitive performance
The relation of depression onset with lifestyle, chronic stress and brain and cognitive outcome
Hippocampus structural integrity in older adults with well-preserved episodic memory*
White matter microstructural correlates of aging-related change in cognition (change-change associations)
Asymmetric thinning of the cerebral cortex across the adult lifespan is accelerated in Alzheimer's disease*
Brain morphology and age (A replication study)
Do cortical thickness, volume and surface area mediate the relationship between cardio-vascular health and cognitive abilities?
Identification of the mode of covariation between vascular risk factors and cognitive decline in European and Australasian healthy aging populations
Mapping cognitive developmental trajectories and differentiation throughout childhood
Decision-tree testing cognition-MRI associations to define and differentiate cognitive reserve and brain maintenance
Intra-individual variability within episodic memory: dispersion as a sensitive marker of hippocampal volume loss among healthy old adults
Brain structural mediation of the effects of lifestyle on cognition
No association between loneliness, episodic memory and hippocampal volume change in young and healthy older adults: a longitudinal European multicenter study*
Modes of cortical brain ageing
Individual variations in 'brain age' relate to early-life factors more than to longitudinal brain change*
Leukocyte telomere length and brain aging
Self-reported sleep relates to hippocampal atrophy across the adult lifespan – results from the Lifebrain consortium*
Does education influence brain aging?*
Multiple biological pathways for resilience and resistance to memory decline in older age
Individual-specific change rates in AD-vulnerable brain regions predict genetic AD risk across the entire adult lifespan
Cannabis use and brain health: Lifebrain cohorts study
Sleep duration and brain atrophy – phenotypic associations and genotypic covariance**
Education and neurocognitive aging: a local structural equation modelling (SEM) approach
Brain aging differs with cognitive ability regardless of education*
Comparison of blood biomarkers among subjects related to brain maintenance and compensation in ageing
Biomarkers in Dried Blood Spots (DBS) and brain structural change
Poor self-reported sleep is related to regional cortical thinning in aging but not memory decline - results from the Lifebrain consortium*
Longitudinal and cross-sectional associations between BMI, diet, and brain structure
Associations of circulating C-reactive proteins, APOE ε4, and brain markers for Alzheimer's disease in healthy samples across the lifespan*

Structural brain fingerprints of personality traits: effects of sex and gender Sex and genetic interactions in physical exercise
Identifying genetic determinants of resilience to decline in memory performance with respect to genetic risk for Alzheimer's disease
GWAS meta-analysis on memory performance in Lifebrain cohorts
EWAS meta-analysis on memory performance in Lifebrain cohorts

*Published papers

** Papers being under evaluation/in print

2.1.1 Sleep

A published study by Fjell et al., (2020) targeted the important lifestyle factor sleep, and its potential impact on atrophy in the hippocampus, an important brain structure for our long-term memory abilities. The study combined data from six Lifebrain cohorts where the 1,299 participants, aged 18-90 years, had provided both self-reported assessments of various aspects of their sleeping habits and structural MRIs on one or multiple occasions. The results showed that accelerated hippocampus volume loss over time was related to several aspects of sleep, particularly to worse sleep quality and efficiency, and more self-reported sleep problems, and to a lesser extent to daytime tiredness. While significant, the effect of sleep was relatively modest in magnitude, and did not differ across different parts of the lifespan, hence it was not differentially associated with brain aging per se.

2.1.2 Socioeconomic status and societal differences

A study by Walhovd et al. (2020) tested the idea that higher socio-economic status may have facilitating and protective effects on brain and cognition. The study tested whether relationships between SES, brain volumes and cognitive ability differ across cohorts, by age and national origin. European and US cohorts covering the lifespan were studied (4-97 years, N = 500 000; 54 000 w/brain imaging). There was substantial heterogeneity across cohorts for all associations. Education was positively related to intracranial (ICV) and total gray matter (GM) volume. Income was related to ICV, but not GM. We did not observe reliable differences in associations as a function of age. SES was more strongly related to brain and cognition in US than European cohorts. Sample representativity varies, and this study cannot identify mechanisms underlying differences in associations across cohorts. Differences in neuroanatomical volumes partially explained SES-cognition relationships. SES was more strongly related to ICV than to GM, implying that SES-cognition relations in adulthood are less likely grounded in neuroprotective effects on GM volume in aging. The relatively stronger SES-ICV associations rather are compatible with SES-brain volume relationships being established early in life, as ICV stabilizes in childhood. The findings underscore that SES has no uniform association with, or impact on, brain and cognition.

A study by Nyberg et al. further tested the associations between education and brain change using longitudinal brain imaging data. Education has been related to various advantageous lifetime outcomes in previous studies. Here, using longitudinal structural MRI data (4,422 observations), Nyberg et al. tested the influential hypothesis that higher education translates into slower rates of brain aging. Cross-sectionally, education was modestly associated with regional cortical volume. However, despite marked mean atrophy in the cortex and hippocampus, education did not influence rates of change. The results were replicated

across two independent samples. These findings challenge the view that higher education slows brain aging.

An upcoming study by Fjell et al. will combine large-scale epidemiological data from SHARE (the Survey of Health, Ageing and Retirement in Europe) with cognitive and neuroimaging data in Lifebrain, to form a neuroscience-informed epidemiology, or an epidemiology-informed neuroscience. First, associations between predictors of memory performance level as well as memory change will be identified in SHARE. Thereafter, the observed associations will be tested for replication and further analysed with the more detailed cognitive and neuroimaging data available in Lifebrain. The main research questions that will be targeted are: *(1)* What are the associations between the predictor variables sex, SES, education, income, country, and initial memory function; and memory change (the memory-age-trajectory) in SHARE and Lifebrain? *(2)* What are the brain correlates of the associations observed in 1? *(3)* What are the non-memory cognitive correlates of the effects observed in 1? *(4)* How is the variance shared between the variables identified in 1-3?

2.1.3 Loneliness

Solé-Padullés et al., (2022) reported no consistent association between loneliness (measured longitudinally) and memory trajectories on the one hand and no associations between loneliness and hippocampal volume or cortical thickness across the lifespan. Specifically, higher loneliness ratings were associated with faster memory decline in one Swedish older adult Lifebrain cohort (Betula), but not in another similar German cohort of older adults (Berlin Ageing Study II; BASE-II), nor among younger Danish individuals (HUBU cohort). The associations between loneliness and memory were not seen for the Swedish cohort of older adults (BETULA). This might be partially explained by the fact that the German cohort included more than one thousand participants at baseline examination, compared to the 143 volunteers for the BETULA cohort. It was concluded that the association between loneliness and worsening of episodic memory with aging in only one cohort suggests that this emotion-cognition relation might be independent of any detectable association between loneliness and brain structure change, and that other factors, such as psychological, genetic, cultural, and socioeconomic not considered in the present study, might moderate the complex relationship between loneliness and brain health.

2.1.4 Depression

Binnewies et al. (Submitted) examined 3447 participants (18-89 years) from six population-based Lifebrain cohorts and two clinical patient-control cohorts. In the patient-control cohorts, symptom severity and presence of mild-to-severe depression (vs no depression) were associated with lower medial orbitofrontal cortex (mOFC) and rostral anterior cingulate cortical (rACC) thickness, lower hippocampal and total grey matter volume, as predicted by previous large studies, such as the ENIGMA consortium (Schmaal et al., 2020). The general population-based cohorts showed no significant association of symptom severity or presence of mild-to-severe depression (compared with no depression) with the relevant brain structures. In line with a dose-response relationship, comparing moderate-to-severe versus no depression resulted in slightly larger effect sizes in the patient-control cohorts.

One of the unique advantages of the Lifebrain consortium is the broad age-range of participants. We continued analyses to investigate if these associations change across the adult lifespan, but no consistent age effects were observed. Within the NESDA cohort, Binnewies et al (2021) already observed negative cross-sectional associations between depression and cortical thickness in the rostral ACC, independent of several lifestyle variables. However, baseline depressive symptoms and longitudinal changes in depressive symptoms were not associated with longitudinal changes in medial PFC thickness across 9-year follow-up, suggesting a lack of progressive associations between depression and rostral ACC brain structure in the adult lifespan.

Zsoldos et al., are investigating the differences in exposures, characteristics, and outcome of depression with onset before 50 and after 60 years, i.e., late onset vs. early onset depression. Based on the Demnitz, Anaturk, et al. (2020) findings, they hypothesise that onset in old age is associated with higher vascular risk in mid-life compared with early onset depression and normal controls. Early onset depression, in contrast, is more likely to be associated with life events. Data from around 1000 participants of five Lifebrain cohorts will be included, and outcomes of depression, cognitive and brain changes examined, with age as both a within- and between-subject factor.

2.1.5 Emotionality-related personality traits

We have also investigated the relation between positive and negative emotionality-related personality traits and brain structure, using the enriched Lifebrain dataset. Plachti et al, (in preparation) aim to identify multivariate structural patterns (e.g., cortical thickness, surface area, and volume) underlying different personality traits and elucidate how these may differ across the lifespan, using all 11 Lifebrain cohorts with > 1500 participants (10-85 years old) and a data-driven multivariate approach.

2.1.6 Lifestyle choices and leisure activities

Borgeest et al., (2020) examined the relationship between modifiable lifestyle factors, such as engagement in leisure activities, and age-related decline of cognitive functions in the Cam-CAN cohort. Using data-driven exploratory structural equation modelling (SEM), confirmatory factor analyses, and age-residualized measures of cognitive differences across the lifespan they found that higher education, better physical and mental health, more social engagement, and a greater degree of intellectual engagement were each individually correlated with better fluid and crystallized cognitive age-adjusted abilities. A joint path model of all lifestyle factors on crystallized and fluid abilities showed that physical health, social and intellectual engagement, and education/SES explained unique, complementary variance, but mental health did not make significant contributions above and beyond the other four lifestyle factors and age. Furthermore, these relationships were robust across age and comparable in females and males, and highly similar for fluid and crystallized domains, suggesting general effects, rather than effects specific to cognitive domain. Overall, their findings suggest that intellectually and physically challenging as well as socially engaging activities are associated with better crystallized and fluid performance across the lifespan, and that these beneficial associations between lifestyle and cognitive health are similar across age.

2.1.7 Physical activity

Observational and randomised-controlled studies have shown that physical activity is associated with measures of white and grey matter structures in the brain (Demnitz et al., 2017; Dunås et al., 2021; Jonasson et al., 2016). While promising, the benefits of exercise vary greatly across individuals. Identifying factors behind this individual variability is key to advancing the understanding of the effects of physical activity and ultimately maximize the effectiveness of interventions that promote healthy brain ageing. Further, given the wide age range available in Lifebrain, the team will test whether observed brain-physical activity associations change across the adult lifespan.

2.1.8 Diet and BMI

Nawijn et al. (in preparation) are investigating associations between BMI and brain structure across the adult lifespan both cross-sectionally and longitudinally. We will also investigate whether observed associations are moderated by sex or age. The study will also account for socioeconomic status as potential moderator. Within the NESDA cohort, Binnewies et al (2021) already observed negative cross-sectional associations between BMI and cortical thickness in the medial OFC, yet baseline BMI and longitudinal changes in BMI were not associated with longitudinal changes in medial OFC thickness across 9-year follow-up, suggesting a lack of progressive associations between BMI and medial OFC brain structure in the adult lifespan. Within the project by Nawijn et al, this will be further investigated in the Lifebrain data, holding a much larger sample and broader age range. Furthermore, Binnewies et al (in preparation) are currently investigating cross-sectional associations between brain structure and several lifestyle factors (alcohol use, smoking, physical activity, BMI and sleep) across eight Lifebrain cohorts, in which effects of age and sex on associations between lifestyle and brain structure will also be inspected.

2.2 Aging-related structural brain changes, and structure – cognition associations

2.2.1 General cognitive ability

Walhovd et al. tested the relationship between general cognitive ability and structural features of the brain, as well as changes in those features over time. Higher general cognitive ability is associated with lower risk of neurodegenerative disorders, but neural mechanisms are unknown. General cognitive ability could be associated with more cortical tissue, from young age, i.e. brain reserve, or less cortical atrophy in adulthood, i.e. brain maintenance. Controlling for education, we investigated the relative association of general cognitive ability with reserve and maintenance of cortical volume, -area and -thickness through the adult lifespan, using multiple longitudinal brain imaging cohorts (n = 3327, 7002 MRI scans, baseline age 20-88 years, followed-up up to 11 years). There were widespread positive relationships between general cognitive ability and cortical characteristics (level-level associations). In select regions, higher baseline general cognitive ability was associated with less atrophy over time (level-change associations). Relationships remained when controlling for polygenic scores for both general cognitive ability and education. Our findings suggest that higher general cognitive ability is associated with cortical volumes by both brain reserve and -maintenance mechanisms through the adult lifespan. Hence, these results points to early life factors being important in establishing a stable brain-cognition relationship which last throughout

life, while at the same time demonstrating that general cognitive ability levels are related to actual brain change also in adulthood and aging.

2.2.2 Modes of brain aging

Nyberg et al (in preparation) are testing the hypothesis of spatially distributed atrophy patterns ("modes") of brain aging. It is well documented that brain regions such as the caudate, hippocampus, and association cortices are prone to age-related atrophy, but it has been hypothesized that there exist individual differences in atrophy profiles. Here they explored individual differences in regional-atrophy patterns using latent-profile analysis of longitudinal MRI data (N=741). The results supported a two-class solution reflecting group differences in atrophy rates in several cortical regions and hippocampus but not in the caudate. The first group included about two thirds of the sample and had a fairly uniform pattern of atrophy across all six examined cortical and subcortical ROIs, with an annual shrinkage rate of about 0.5%, which is comparable with previous estimates of mean atrophy rates across individuals (Fjell et al., 2009). The second subgroup showed higher atrophy rates in the cortex and hippocampus. The higher-atrophy group was slightly older and included more males relative to females, but group differences in atrophy rates remained after controlling for age and sex. The groups were comparable regarding APOE-distribution, epigenetic age and education, but the higher-atrophy group had lower episodic memory, which is consistent with prior reports of a link between poorer memory and cortical (Cox et al., 2021) and hippocampal (Gorbach et al., 2020) atrophy, and also with findings that males are over-represented among individuals with accelerated episodic memory decline (Josefsson et al., 2012). Overall, the findings support different modes of brain aging, possibly reflecting distinct mechanisms underlying age-related atrophy in striatal versus hippocampal-cortical systems.

2.2.3 Longitudinal white matter microstructural correlates of aging-related changes in cognition

Köhncke et al., are studying longitudinal white matter microstructural correlates of aging-related changes in cognition, by using a multivariate structural equation modelling latent change score or growth curve model approach. The cognitive domains that will be considered are episodic memory, working memory, processing speed, and reasoning/fluid intelligence, and in addition to participant age the models will describe differences between sexes, account for sex in the models, as well as for education, blood pressure, diet and plasma cholesterol, fatty acid profile, 25-hydroxy-vitamin D3 as covariates, where possible.

2.3 Biomarkers, predictors, and health-related factors

2.3.1 Leukocyte telomere length

A study lead by Pudas et al. investigates the association between a putative blood-based aging biomarker, leukocyte telomere length (LTL), and longitudinal aging-related changes in structural brain imaging measures. Preliminary findings in one of the Lifebrain cohorts, the Betula study, indicate that longer baseline LTL is associated with larger baseline hippocampal volume, but not volumetric decline. In addition, longer baseline LTL is associated with total grey and posterior cingulate grey matter decline across time, in an age-dependent manner (strongest effects for the oldest and youngest participants). Ongoing analyses will attempt to replicate these findings in the BASE II cohort and investigate the influence of several

commonly available health- and lifestyle related markers on potential associations. These upcoming analyses are expected to provide information on the value of LTL over and above other health makers, as well as potentially shedding light on mechanistic routes through which telomere associations with brain may arise. Finally, polygenic scores (PGS) for LTL have been computed for a large number Lifebrain cohort participants, including for cohorts where LTL measurements are not available. PGSs will be associated to brain outcomes to assess potential genetic influences on LTL-brain associations in aging.

2.3.1 Inflammatory markers

Within Lifebrain we recently reported overall lifespan associations between increased CRP and smaller hippocampal (HPC) volumes, albeit these could not be observed in one subsample of middle-aged individuals (Wang et al., 2022). Bartrés-Faz et al. (2022) hypothesized that functional brain integrity measures would be sensitive to predict CRP levels in this group. They focused on global system segregation (SyS), a graph theory-based metric capturing the balance between within-network functional connectivity (rs-FC). 336 cognitively normal volunteers (mean age 53.8; SD: 7.1; 47.9% women) were included from the Barcelona Brain Health Initiative (Cattaneo et al., 2018). High-sensitive CRP (hsCRP) concentrations were determined through dry blood samples and log10 transformed (Wang et al., 2022). Adjusted HPC volumes were estimated from T1-wheigthed 3T magnetic resonance imaging (MRI) acquisitions (Raz et al., 2005). SyS values were calculated (Ewers et al., 2021) from 100 nodes defined by the Schaefer-Yeo atlas. Multiple linear regression investigated the associations between age, gender, cognitive function (MMSE and episodic memory), HPC volumes, APOE status, and SyS as predictor variables and hsCRP as the dependent measure. In the adjusted model only SyS and APOE predicted hsCRP concentrations (e.g., sex was not a predictor of hsCRP). Global SyS was negatively related to hsCRP. As in Wang et al., (2022), APOE E4 carriers exhibited lower CRP circulating levels than non-E4 bearers. However, there were no significant differences in SyS according to APOE genotypes. In conclusion, hsCRP blood concentrations were predicted by global segregation status of functional networks in absence of HPC volume or cognitive status effects. As such, blood-derived hsCRP levels may represent an early indicator of middle-age individual variations in a measure recently reported to predict future cognitive decline (Chan et al., 2021) and represent a cognitive resilience mechanism in the face of AD pathology (Ewers et al., 2021).

Furthermore, Bartrés-Faz et al. are investigating the associations between dried blood spot (DBS) biomarker panel used in Lifebrain, in particular inflammatory markers (i.e., interleukins (IL) IL-Ib, IL-Ira, IL-6, IL-8, IL-10, IL17-a, TNFa, MCP-1, as well as high sensitivity C-reactive protein) and memory status and hippocampal volumes. The main objective is to investigate if individual or combined composite scores of such inflammatory markers can distinguish between those subjects that show stable memory performance as well as hippocampal volumes at follow-up assessments (i.e., termed ‘maintainers’), vs. those exhibiting stable memory but progressive HPC atrophy (i.e., termed ‘compensators’). Cross-sectional, age and gender adjusted analyses, including data from N=466 individuals from the Oslo and Barcelona Lifebrain cohorts show that a ‘low grade inflammation’ composite associated with HPC volumes (the higher the composite estimation the lower the HPC volumes, b: -.17, $p<0.001$). However, preliminary analyses in an available sample of N=107 subjects with longitudinal cognitive and MRI measurements revealed no significant

associations so far. Further analyses including data from younger individuals in Lifebrain will provide a baseline for "optimal" values. It is hypothesized that the older "Maintainers" will show a DBS profile more similar to young, and that more age-related differences, positive or negative depending on type of biomarker, may be observed in the "compensators". Possible effects of sex will be investigated.

2.3.2 Vascular health and neurocognitive characteristics

Lam et al. are using Lifebrain data in a cross-cultural study attempting to identify covariation modes linking vascular risk factors and cognitive decline in European and Australasian healthy aging populations. This cross-cultural study aims to identify the factor or combination of factors, among the traditional vascular risk factors, that contribute most to cognitive decline; whether brain changes or gait measures are mediators of the above association; and whether the association is consistent across cultural, geographical, and ethnical variations. Lam et al. expect to observe both culturally invariant, as well culturally-, geographically-, and ethnically specific associations between different vascular risk factors and cognitive decline.

2.4 Differentiating theoretical accounts of neurocognitive aging

Vaqué-Alcázar et al. are using Lifebrain data to better define and differentiate between two prominent theoretical accounts proposed to explain individual differences in neurocognitive aging: brain maintenance and cognitive reserve. Whereas brain maintenance is thought to underlay maintained cognitive function in aging through relative preservation of brain integrity, cognitive reserve is proposed to operate through compensation in the form of increased functional connectivity within task-related areas and/or the recruitment of additional non-task-related regions. Vaqué-Alcázar et al., are using a decision tree process combined with structural, functional, and cognitive data from Lifebrain cohorts to identify categories of individuals best explained by each theoretical construct. Further, the role of education and other lifestyle factors, as well as sex, as possible mediators of the categorizations identified will also be investigated. We predict that this unified approach including longitudinal and multimodal neuroimaging data will better define cognitive reserve longitudinally in the context of atrophy, by identifying different pathways within this construct. Moreover, our results could allow us to establish a new categorization within the concept of brain maintenance, discerning between structural and functional components.

3. Conclusion

In the spirit of the Lifebrain project's emphasis on a lifespan perspective of heterogeneity in mental health and cognitive and brain aging, the empirical studies in this task, summarized above, described how some important influences or predictors of brain and cognitive function, such as genetic make-up and education, represent life-long and stable influences. The results further point to many effects and relationships observed in adulthood arising from earlier life-stages, childhood development or before. Still, some variables were related to ongoing changes in the brain also at later stages in life. For instance, general cognitive ability was related not only to stable differences in brain structure, but also to rate of brain change. Such analyses of large samples with wide age-ranges as crucial, since they allow us to disentangle stable and early influences from later and continuous factors affecting brain aging. Generally, the

integrated project cohort has offered, and will continue to offer, a unique foundation for examining factors that contribute to marked individual differences in mental health and cognitive functioning across the lifespan. Particularly novel features of the integrated cohort include the longitudinal design, which allows actual measurement of true changes, and the very rich genotypic and phenotypic characterization of the participant individuals. It should finally be mentioned that the Lifebrain cohort can in some studies be combined with additional cohorts from the UK and the USA, resulting in sample sizes exceeding 50,000, which is well in line with the current call of optimizing the use of existing brain-imaging cohorts.

This will ultimately provide important fundamental knowledge and new avenues for optimizing personalised prevention strategies. We believe the results described in D4.4 has taken us further in this direction, buy providing a knowledge foundation on which further research on prevention and treatment can be based.

4. References

Papers on the integrated Lifebrain cohort relevant to D.4.4, are marked by two asterisks **
Papers related to the objectives of T4.4, published by Lifebrain researchers, are marked by one asterisk *

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