Lifebrain

D4.5 Distinguishing general and gender-specific risk and protective factors

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PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services	

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Executive Summary

This deliverable describes the published and ongoing work in Lifebrain Task 4.5 “Distinguishing general and gender-specific risk and protective factors.”

In line with the Lifebrain strategy of providing an evidence-based knowledgebase for more personalized medicine, we see the sex-gender dimension as an important moderator that requires to be investigated. Sex-gender differences have been described in e.g., disease prevalence, age of disease onset. However. Only recently, there is an increased focus on incorporating sex-gender in (health) research. Sex is conceptualized as a biological construct while gender is thought of as a multifaceted and dynamic construct, influenced by social, economic, educational, cultural, and religious factors. Gender related constructs include gender equity/equality, gender roles, gender identity, gender relations, institutionalized gender. However, sex and gender are interdependent and difficult to separate. Indeed, uncritical dichotomization in “biological” (sex) and “social” (gender) should be prevented as this may lead to unfunded a priori assignment of causality and thereby hamper a deeper understanding of underlying mechanisms.

The main objective of this task was to characterize the possible role of sex-gender in relation to risk for mental health problems and poor cognitive function and decline, and resilience. 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”. Here we describe those studies that explicitly investigated and reported on sex-gender effects. This deliverable includes by necessity an overlap with D4.2 and D4.3, and 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.

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

1.1. Background

Cognitive and mental health are pivotal to productive human life, and critically depend on brain health (i.e., the preservation of brain structure and function in older age) (Walhovd et al., 2018). Neurodevelopmental, age-related neurodegenerative changes, and psychiatric problems are all 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 (Olesen et al., 2012). 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 the most advanced age, are mapped in detail in several existing 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 relatively 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 this calls for a personalised medicine approach, individual variations in these factors need to be established first. For instance, age-specific mechanisms necessitate many participants at all stages of life, and sex-specific effects further halve the sample sizes, thus narrowing degrees of freedom available for analyses. **One main objective of the Lifebrain consortium is to integrate existing cross-sectional and especially longitudinal European MRI datasets to increase statistical power to generate novel knowledge about how to improve brain, cognitive-, and mental health throughout life.**

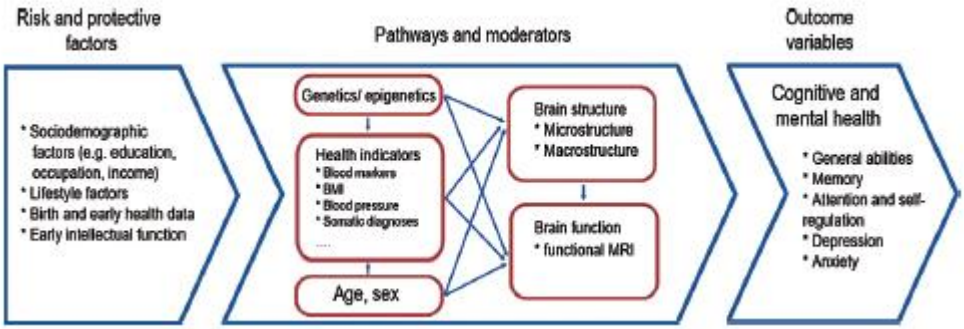

FIGURE 1 CONCETPUAL OVERVIEW OF LIFEBRAIN OBJECTIVES

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Previous reports have detailed the Lifebrain findings of Task 4.2 "Individual pathways and mediator variables in relation to risk for mental health problems and resilience" and Task 4.3 "Analysis of individual pathways/mediator variables in relation to risk for poor cognitive function and decline versus resilience". The main objective of this task (4.5) was to investigate and characterize the possible role of sex-gender in relation to risk for mental health problems and poor cognitive function and decline, and resilience.
Human cortical development is a protracted, heterogeneous, and continuous process from the embryonic stage throughout life (Fjell et al., 2019; Walhovd et al., 2017). Neuroimaging studies have identified normative differences in brain structure between males and females that may be exacerbated in psychiatric and neurological conditions (Karalija et al., 2021; Salminen et al., 2022).

Sex-gender differences have been described in e.g., the prevalence of neurological and psychiatric disorders, age of disease onset, and mortality (Almeida & Fletcher, 2022; Brugulat-Serrat et al., 2022; Mauvais-Jarvis et al., 2020; Salminen et al., 2022; Tokatli et al., 2022; Zagni et al., 2016). Females have a higher prevalence of Alzheimer's disease (AD) at higher ages, while men may present with a more aggressive course of the disease and early mortality (Dubal, 2020; Udeh-Momoh et al., 2021). In the presence of AD risk biomarkers, females, as compared to males, displayed greater hippocampal atrophy and longitudinal cognitive decline, which were most pronounced in those of lower education level and appeared to vary by APOE ε4 genotype (Koran et al., 2017). Anxiety and mood disorders are also more prevalent in women than in men, with the prevalence of major depression being twice as high in women (Almeida & Fletcher, 2022). Negative emotionality-related traits, such as neuroticism, harm avoidance, behavioural inhibition, and trait anxiety, are known risk factors for anxiety and mood disorders (Kendler et al., 2006; Nemes & Cozman, 2016; Tully et al., 2015). Females generally score higher on neuroticism than males (Schmitt et al., 2017) and this sex difference becomes apparent around puberty (De Bolle et al., 2015). While personality traits are thought to be stable, personality trait scores do show consistent changes over the lifespan (Costa et al., 2019).

Lifestyle factors, such as sleep, social connectedness, alcohol consumption, physical activity, and diet can influence brain structure and function throughout life, with possible different effects in males and females (Dunås et al., 2021; Mintzer et al., 2019; Song et al., 2022; Subramaniapillai et al., 2022; Udeh-Momoh et al., 2021). For example, poor glucose regulation (higher insulin resistance) was consistently associated with declines in well-being among older men but not women (Mantantzis et al., 2020). Furthermore, loneliness, which has been associated with depression and neuroticism as well as cognitive decline and AD (Solé-Padullés et al., 2022; de Lange et al., 2021). Loneliness seems most prevalent in adolescence and young adulthood (especially in females), and late adulthood (Lasgaard et al., 2016). Older women usually report increased loneliness (Beal, 2006; Jarach et al., 2021). Recently, de Lange et al., 2021 (de Lange et al., 2021) observed that individuals reporting both loneliness and social isolation showed higher brain age relative to controls – as part of a prominent risk profile with elevated scores on socioeconomic deprivation and unhealthy lifestyle behaviours, in addition to neuroticism and depression. It has been recently argued that loneliness maybe more associated with health, functional limitations, and depression (Jarach et al., 2021) than with social isolation.

Understanding associations between loneliness and adverse health outcomes requires elucidating the complex interaction between e.g., genetic, sex-gender as well as physical, behavioural, socioeconomic, and sociocultural factors (de Lange et al., 2021).

Despite the unequivocal role of sex-gender in disease risk, prevalence, progression, treatment, and outcome, only recently there has been an increased focus on incorporating sex-gender in (health) research (Tannenbaum et al., 2016). Sex is conceptualized as a biological construct while gender is thought of as a multifaceted and dynamic construct, influenced by social, economic, educational, cultural, and religious factors. Gender related constructs include gender equity/equality, gender roles, gender identity, gender relations, institutionalized gender (Barbieri et al., 2021). However, sex and gender are interdependent and difficult to separate (Mauvais-Jarvis et al., 2020; Polderman et al., 2018). Uncritical dichotomization in "biological" (sex) and "social" (gender) should be prevented as this may lead to unfunded a priori assignment of causality and thus hamper a deeper understanding of underlying mechanisms (Holmes & Monks, 2019). At best, sex should be seen as an imperfect proxy for hidden but more biological (e.g., hormones or sex-linked genes), environmental and sociocultural factors that covary with sex (Maney, 2016; Springer et al., 2012).

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 T3.4 was expected to significantly contribute to the identification of previously undiscovered relations or gene-by-environment effects. Previous reports have detailed the Lifebrain findings of Task 4.2 "Individual pathways and mediator variables in relation to risk for mental health problems and resilience" and Task 4.3 "Analysis of individual pathways/mediator variables in relation to risk for poor cognitive function and decline versus resilience". The main objective of this task was to investigate and characterize the possible role of sex-gender in relation to risk for mental health problems and poor cognitive function and decline, and resilience.

1.3. Collaboration among partners

This task has been led by Region Hovedstaden (REGIONH), with University of Oxford (UOXF), and University Medical Center Amsterdam (VUmc) and Universität zu Lübeck (UzL) as main collaborators. In addition, Lifebrain researchers from the University of Oslo (UiO), the Max Planck Institute in Berlin (MPIB), the University of Barcelona (UB) and University of Cambridge (UCAM), have also led studies contributing to this task, and made substantial contributions to studies led by other sites. 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 (June 2022), T4.5 has resulted in three published papers on the integrated Lifebrain cohort, some submitted manuscripts, while multiple papers are being prepared. Ongoing research activity in Lifebrain is high, with 32 studies that have been approved by the Knowledge Management Committee (KMC) and with preliminary results presented at Lifebrain meetings for most. In addition, during the project time, Lifebrain researchers have published 10 papers related to the objectives of T4.5. 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.

2.1. The role of sex/gender with respect to lifestyle, mental and physical health, and neurocognitive aging

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. Main effects of sex, and interactions between sex and age were also assessed. It has been suggested that some sleep mechanisms are differentially affected by age in men and women whereas others may remain equivalent (Mander et al., 2017; Redline et al., 2004). For instance, sex- specific changes in the circadian alerting signal have been proposed to account for greater daytime nap propensity in older men (Mander et al., 2017). It was found that although women in general reported worse sleep than men did, in line with previous studies (Smagula et al., 2016), there were no sex-specific age-effects. This lack of sex-by-age interactions suggests that self-reported sleep may be associated with similar age-trajectories for men and women.

2.1.2 Socioeconomic status and societal differences

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? Sex will be used as a predictor and interaction variable, and we will test whether there are effects of sex on memory performance, both in terms of level and in change. Preliminary results suggest that women score higher on memory tests, but do not decline less over time.

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. This larger statistical power may have favoured the emergence of significant loneliness-age and loneliness-sex associations within BASE-II. It was somehow unexpected to find more feelings of loneliness among German men, as compared to their female counterparts, because older women usually report increased loneliness (Beal, 2006; Jarach et al., 2021). Despite this, it has been recently argued that loneliness is more associated with health, functional limitations, and depression (Jarach et al., 2021) than with social isolation itself, and in the present study there was not controlled for physical health variables. Neither were other generational factors accounted for, which may have contributed to the abovementioned associations found in BASE-II. In this line, these participants were born between 1927 and 1953, a generation of working men and ‘stay-at-home’ women. Therefore, men were more likely to experience the life-changing event of retiring from work, and this may have intensified their feelings of loneliness, as compared to women. On the other hand, in the younger cohort, females reported feeling lonelier than males, a finding that is in line with a recent study, also with Danish adolescents (Eccles et al., 2020). 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. Sex did not moderate associations between depression and brain structure in the mOFC, rACC, hippocampus or total grey matter volume within population-based cohorts nor in patient-control cohorts, and the negative associations between depression and brain structure observed across patient-control cohorts were present in both men and women, fitting with previous observations in the ENIGMA consortium. 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. Possible effects of sex will be investigated and reported.

2.1.5 Emotionality-related personality traits

We have also investigated the relation between positive and negative emotionality-related personality traits and brain structure, with the possibility of elucidating the potential role of sex and gender roles (Kachel et al., 2016), 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. We expect that negative emotionality-related traits as well as extraversion are associated with measures of structural brain asymmetry and that these associations differ between sexes. Previously, in baseline analyses of the HUBU cohort, we observed sex differences in the brain structural correlates of neuroticism with higher neuroticism scores being associated with diminished cingulum FA asymmetry in boys, but with increased cingulum FA asymmetry in girls (Madsen et al., 2018). Subsequent, longitudinal analyses, including up to 11 MRI scans, showed that the relationship between neuroticism and cingulum FA asymmetry appeared to be stable in females, suggesting that it might be innate, while in males this relationship appeared to be stronger in the older part of the investigated age range (Plachti A et al., 2022).

Preliminary results in the Lifebrain sample suggest sex-specific personality-brain associations at the meta-analytical analysis level. In females, neuroticism and extraversion showed positive associations with an extended network including anterior (i.e., left medial orbitofrontal surface area and caudal anterior cingulate), parietal and occipitotemporal (i.e., fusiform) brain regions. In males, predominantly negative associations were found between neuroticism and extraversion and posterior brain regions such as left inferior temporal, bilateral lingual, but also frontal brain regions, e.g., left medial orbitofrontal and left precentral gyrus. While our findings support sex-specific differences in how personality may be associated with brain characteristics, observed associations did not survive false discovery rate (FDR) correction for multiple comparisons, suggesting considerable heterogeneity. More in-depth analyses accounting for several know confounders are in progress.

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 and for both sexes.

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. Sex has been put forward as potential moderator of the beneficial effects of exercise (Barha et al., 2019). To test this hypothesis, Demnitz, Boraxbekk et al. are using Lifebrain data to investigate whether sex is a moderator of the association between physical activity and brain structure, with a focus on volumetric measures of the hippocampus and the posterior cingulate cortex. 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 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.

2.2.2 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. As LTL is generally longer in women, possible effects of sex will also be reported.

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). We included 336 cognitively normal volunteers (mean age 53.8; SD: 7.1; 47.9% women) 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. Possible effects of sex will be reported.

2.3.3 Glucose regulation and well-being

Mantantzis et al (2020) report a sex-specific effect of glucose regulation on well-being, which was only observable in men. Glucose regulation is a key aspect of healthy aging and has been linked to brain functioning and cognition. They examined the role of glucose regulation for within-person longitudinal trajectories of well-being. In data from the Berlin Aging Study II (N = 955), they used insulin resistance as an index of glucoregulatory capacity and found that poor glucose regulation (higher insulin resistance) was consistently associated with declines in well-being among older men but not women.

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 the possible influence of sex-gender on both early- and later-life contributions to such heterogeneity. Using mainly general population samples, the Lifebrain project had limited access to mental health clinical data. Nevertheless, data from depression rating scales, about self-rated loneliness, sleep and negative personality traits were available and make it possible to report on the effects of various exposures on mood and behaviour, as well as brain health associated with these issues.

Sex did not moderate associations between depression and brain structure within population-based cohorts nor in patient-control cohorts, and the negative associations between depression and brain structure observed across patient-control cohorts were present in both men and women. Unexpected sex differences observed in the effect of loneliness in older adults needs further scrutiny by including physical health variables. Although preliminary results, uncorrected for multiple comparisons, suggest sex-specific differences in how personality maybe be represented in the brain, there seem to be considerable heterogeneity across cohorts. Poor self-reported sleep was modestly associated with faster hippocampal atrophy, and the lack of sex-by-age interactions suggest that sleep may be associated with similar age-trajectories of hippocampal atrophy for men and women. On the other hand, males were overrepresented in a subgroup that expressed a mode of brain aging characterized by accelerated cortical and hippocampal atrophy, which was also linked to poorer memory outcomes. Concentrations of blood inflammatory markers were predicted by global segregation status of functional networks in absence of hippocampal volume or cognitive status effects but not e.g., age or sex. Several studies investigating the role of sex-gender effects are ongoing. Our findings underline the complexity of unravelling the intricate web of biological, physical, behavioural, socioeconomic, and sociocultural factors that influence brain, cognitive-, and mental health throughout life.

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. More specifically, in ongoing analyses we have shown and will continue to investigate the how sex-gender influence associations between mental health, lifestyle behaviour and cardiovascular health, and brain structure and cognitive health across the lifespan. This will ultimately provide important fundamental knowledge and new avenues for optimizing personalised prevention strategies.

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Papers on the integrated Lifebrain cohort relevant to D.4.5, are marked by three asterisks *** (N=3)
Papers related to the objectives of T4.5, published by Lifebrain researchers, are marked by two asterisks ** (N = 10)
Relevant papers published by Lifebrain researchers, in which sex was modelled as a covariate, are marked with one asterisk * (N = 8)

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