Lifebrain

D4.3 Analysis of individual pathways/mediator variables in relation to risk for poor cognitive function and decline versus resilience

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Executive Summary

This deliverable describes the published and ongoing work in Lifebrain Task 4.3 "Analysis of individual pathways/mediator variables in relation to risk for poor cognitive function and decline versus resilience". The main objectives of this task were to: 1) identify combinations of life-style patterns, biomarkers, and health indicators typical for individuals with poor cognitive function or clear age-associated decline and compare these with protective factors. (2) examine how such associations are influenced by the genetic background of individuals, that is which particular lifestyles have greater impact on risk of cognitive decline or resilience for specific genetic subtypes, (3) identify age-related brain variations (i.e. atrophy in particular vulnerable systems, functional stability or compensatory reorganization of brain networks) associated with (1) and (2), and associated with neurocognitive trajectories of change or stability.

The work described in this current report targets several lifestyle factors, including sleep, physical activity, leisure activities, and diet, as well as socioeconomic status and environmental influences such as living environment and exposure to heavy metals. Genetic and epigenetic factors have been investigated in the form of genome and epigenome-wide association studies, candidate genes such as APOE, as well as polygenetic risk scores. Importantly, Lifebrain studies have shown that brain-cognition associations in aging are moderated by the genetic background of individuals. We will investigate how genetics interact with lifestyle factors such as physical activity. Furthermore, several studies have characterized individual differences in age-related structural brain factors, such as machine-learning derived 'brain age' estimates, cortical asymmetries, and systematic individual differences in "modes" of brain aging. Finally, studies are also being conducted on health-related factors such as vascular health, BMI and inflammation, as well as biomarker studies using established and more novel markers to predict cognitive and brain changes. Collectively the findings provide large-scale support for certain pathways and variables, but also challenge the relevance of others (e.g., see findings on education and sleep). In addition, the studies have contributed to the topic of how we best can estimate variation in brain integrity in aging and link such variation to the aging process per se or to more stable individual differences (e.g., see work on brain age).

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.

List of acronyms / abbreviations

BASE II	Berlin Aging Study II
BDNF	Brain derived neurotropic factor
Cam-CAN	Cambridge Centre for Ageing and Neuroscience, University of Cambridge
CFA	Confirmatory factor analysis
DBS	Dried blood spot
EWAS	Epigenome-wide association study
GWA	Genome-wide association study
HUBU	Danish Developmental studies
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
PGS	Polygenic score
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

As emphasized in the Lifebrain application, and in Walhovd et al., (2018), 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). 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 (Gustavsson et al., 2011). 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 life 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.**

Personalized health care requires fundamental knowledge of risk factors and protective factors, as well as of the pathways through which they work at different ages. Extrapolating from known effects of certain risks and interventions (Engvig et al., 2010; Ngandu et al., 2015), a multifactorial and personalised approach could potentially identify modifiable environmental factors that promote resilience, cognitive development in childhood and adolescence, foster maintenance of cognitive functions into late adulthood, delay onset of dementia, reduce need for care, and improve general wellbeing and working ability through education, prevention and intervention programmes.

In addition to the very early predictors related to pre- and perinatal conditions, Lifebrain will also focus on indicators in childhood and young adulthood. For instance, intelligence scores at age 11 years are remarkably good predictors for cognitive performance at age 90 (Deary, Pattie, & Starr, 2013), and neuroticism and introversion predict development of depression later in life (Hakulinen et al., 2016). Furthermore, higher cardiovascular fitness and cognitive performance in early adulthood decreased the risk of early-onset dementia and mild cognitive impairment (MCI) more than four decades later (J. Nyberg et al., 2014).

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 (Walhovd, Storsve, Westlye, Drevon, & Fjell, 2014). This finding suggest that exercise prevents cortical atrophy in older adults. Alternatively, it may be that the more physically active older adults were already more physically active and fit at younger ages, suggesting that certain brain characteristics or changes may affect people's level of physical activity (Sabia et al., 2017).

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 (Walhovd et al., 2014). 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 and dementia (Batsis, Singh, & Lopez-Jimenez, 2014). Similarly, certain genetic variations, such as the APOE e4 allele, reduce brain plasticity and increase brain vulnerability (Sundström et al., 2004). Thus, we might expect less stability of cognitive function (Josefsson, de Luna, Pudas, Nilsson, & Nyberg, 2012) and a higher vulnerability to decline in the face of other risk factors for those with the risk allele. Equally, brain-derived neurotrophic factor (BNDF) is linked to neuronal growth and differentiation, and thus contributes to memory and learning, leading to differential cognitive trajectories (Ghisletta et al., 2014) and to mental health differences (Hosang, Shiles, Tansey, Mcguffin, & Uher, 2014). These findings are in line with the broader "resource modulation" hypothesis (Lindenberger et al., 2008), 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.

The rich information in our large longitudinal Lifebrain database allows 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 (Josefsson et al., 2012), there were three distinct ageing trajectories for episodic memory (Fig. 1). Good episodic memory in old age was also associated with preserved hippocampal function (Pudas et al., 2013). Parkinson's disease patients with mild cognitive impairment (MCI) have reduced fronto-striatal performance of working memory (Ekman et al., 2012). 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 (Suri et al., 2017). Identification of specific cognitive phenotypes may suggest that different kinds of interventions will be effective.

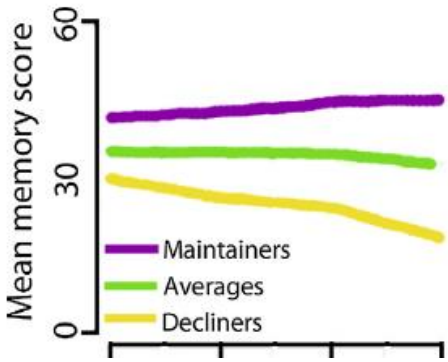

FIGURE 1

Different trajectories of age-related memory change across 15 years in the Betula study, reported in Josefsson et al., 2012, where 18% of 1558 participants upheld good memory function, while 13% declined. Figure reproduced from Walhovd et al., 2018, *European Psychiatry*, under the Creative Commons CC BY-NC-ND 4.0 licence.

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., inflammatory markers based on dried blood spot kits.

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. Also, genetic/ epigenetic factors would be considered, along with other biological markers (e.g., vitamin and protein status). The increased statistical power gained from pooling across cohorts along with the statistical tools developed in T3.4 was expected to significantly contribute to the identification of previously undiscovered relations or gene x environment effects. Hence the main actions to be undertaken under this task were stated as: (1) To identify combinations/interactions of life-style patterns and biomarker/health indicators characteristic of individuals exhibiting poor cognitive function and/or clear age-associated decline vs those acting as protective factors, related to cognitive resilience. (2) To examine how previous associations are influenced by the genetic background of individuals, i.e., identifying if and which particular lifestyles have greater impact on risk of cognitive decline vs resilience for particular genetic subtypes, providing grounds for more personalized preventive strategies in particular segments of the population. (3) Identify age-related variations in brain changes (i.e. atrophy in particular vulnerable systems, functional stability vs compensatory reorganization of brain networks) associated with (1) and (2) and linked to trajectories of neurocognitive change or stability.

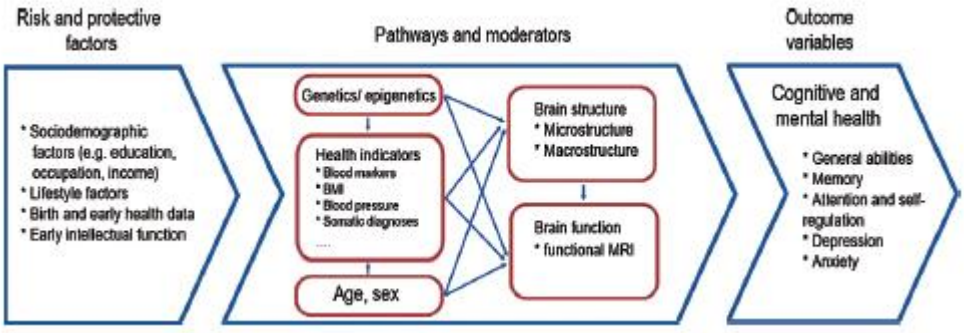

FIGURE 2 CONCETPUAL OVERVIEW OF LIFEBRAIN OBJECTIVES

1.3 Collaboration among partners

This task has been led by Umeå University (UmU), with University of Oslo (UiO), Max Planck Institute in Berlin (MPIB), the University of Barcelona (UB), Region Hovedstaden (REGIONH), and Universität zu Lübeck (UzL) as main collaborators. In addition, Lifebrain researchers from University of Cambridge (UCAM), University of Oxford (UOXF), and University Medical Center Amsterdam (VUmc VU) 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 (November 2021), T4.3 has resulted in seven published papers on the integrated Lifebrain cohort, as well as several submitted manuscripts. Ongoing research activity is high, with 26 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 31 papers related to the objectives of T4.3. These include both review papers and original research papers, and they are listed in a separate section of the reference list. 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 Lifestyle and genetic factors in relation to neurocognitive aging

Sleep

A published study by Fjell et al., (2019) 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. Another published Lifebrain study, Fjell et al., (2021), investigated self-reported sleep parameters in relation to cortical thinning across the brain.

An association between self-reported sleep disturbances and thinning of the right lateral temporal cortex was observed after age 60, and thus appeared specifically related to brain aging. The same study did not observe a significant association between aspects of self-reported sleep and longitudinal memory change. Furthermore, the small effect sizes indicate that self-reported sleep may not be an optimal biomarker of general cortical degeneration in healthy older adults. Ongoing analyses focuse specifically on sleep duration, as this is the most common index of sleep on a societal level, with two manuscripts in preparation.

Education

Nyberg et al., (2021) investigated the prominent hypothesis that the amount of education attained in childhood or youth slows the rate of brain aging. Critically, longitudinal brain imaging data from Lifebrain (1,844 scans) and the UK Biobank (2,578 scans) revealed similar patterns of brain aging for individuals with higher and lower levels of education (Figure 3). Modest cross-sectional associations were found between level of education and brain volume in the left central sulcus, such that individuals with more education had larger volumes. The latter associations likely reflect stable individual differences from youth, as no associations were detected between education and age-related volumetric decline even in this region. Thus, the findings of Nyberg et al. (2021) challenge theoretical and empirical claims that higher education slows brain aging. Instead, education was to some degree related to the size of brain volumes, which suggests that education could be related to what has been labelled a passive "brain reserve". In a recently approved upcoming Lifebrain study led by Nyberg, Lövdén et al, a local structural equation modelling (SEM) approach will be used to examine the existence of a non-linear brain-cognition relation as a function of level of education. The core hypothesis examined is that given similar levels of structural brain alterations, the cognitive performance should be more negatively impacted in individuals with lower levels of education. Support for this hypothesis would be consistent with predictions from the theory of education contributing to a more active "cognitive reserve" (Stern, 2009).

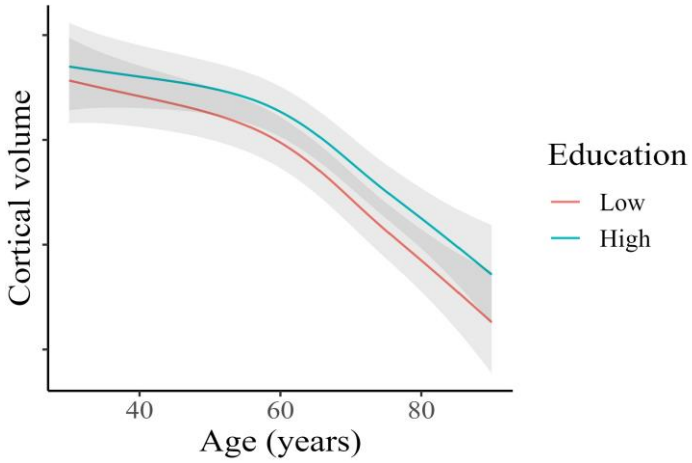

FIGURE 3

Trajectories of brain aging for individuals with high and low education from Nyberg et al. 2021, PNAS.

Socioeconomic status and societal differences

Walhovd et al., (2021) reported heterogeneous relationships between education and income as indexes of socioeconomic status on the one hand, and brain and cognitive outcomes on the other. Analyses were conducted on lifespan samples (4-97 years 54,000 with brain imaging) from both Lifebrain and cohorts from the US. The main take-home messages were that education was positively related to intracranial (ICV) and total brain gray matter (GM) volume, whereas income was related to ICV but not GM. The relationships varied substantially across samples and were generally stronger in US than European cohorts. Further, brain volumes explained part of the SES-cognition relationships. Although causal interpretations are not possible from these data, the observation that SES was more strongly related to ICV than to GM indicates that SES-cognition relations in adulthood are less likely to be grounded in neuroprotective effects on GM volume in aging. Instead, a relationship may be established early in life as ICV stabilizes already in childhood.

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?

Loneliness

Solé-Padullés et al., 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 older adult Lifebrain cohort (Betula), but not in another similar cohort of older adults (Berlin Ageing Study II; BASE-II), nor among younger individuals (HUBU cohort). Furthermore, no significant associations were observed between loneliness and cortical thickness or hippocampus volume (cf. de Lange, Kaufmann et al., 2021) . We 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. The study has been recently submitted as an original research paper to Frontiers in Aging Neuroscience (October 2021).

Living environment and environmental exposures

Kühn et al. are studying the association living environment and brain and cognition across different ages. One's living environment may affect brain structure either through enrichment, i.e., providing more complexity and novelty that boosts positive brain plasticity, or by adverse psychosocial influences that facilitate chronic stress. The hypothesis is that living in areas closer to forests and urban green (parks etc.) is associated with more brain volume in the amygdala, and that living closer to dense urban fabric is associated with less brain volume in anterior cingulate cortex. It is further hypothesized that the effects get stronger with older age, since older participants will have spent more time in and around their home address.

Another study by Kühn et al. is investigating associations between heavy metal exposure and brain volumes and cognition across different ages. Heavy metal exposure is analysed from the dried blood spot (DBS) biomarker panel used in Lifebrain. Although associations will be investigated across the whole lifespan, older adults are expected to be one of the most vulnerable populations to environmental contaminants given the longer exposure to these substances compared to younger populations and because of their lower functional reserve, allowing for less compensatory potential in the face of toxic damage.

Lifestyle choices and leisure activities

Borgeest, Henson, Shafto, Samu, & Kievit (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. 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.

Knights et al. investigated whether many lifestyle-related decisions (e.g., smoking, playing instruments, physical exercise, social interactions) were associated with cognitive performance (i.e., fluid, crystallised memory and processing abilities) and, crucially, if these effects were mediated by changes in brain structure. Confirmatory factor analysis (CFA) mapped the lifestyle variables on to three high-level latent factors (physical, environmental, and social), with each being found to predict performance for all of the individual cognitive measures (after controlling for age). Multi-age-group (young vs. midlife vs. older adults) structural equation models (SEMs) showed that, regardless of age, these lifestyle-cognitive relationships were not, however, mediated by total grey matter size (adjusted for total intracranial volume). Future aims of this project include extending analyses to white (rather than grey) matter because these brain structural measures are likely to be more sensitive to lifestyle-cognitive relationships.

Henson et al. also preregistered a project (https://osf.io/bq3a7/) to identify a functional brain correlate of cognitive reserve. In a previous study, Chan et al. (2018) showed that higher levels of mid-life activities reduce the relationship between total grey-matter volume and cognition in late-life (i.e., midlife activities functions as a form of "cognitive reserve"). The new project hypothesises that mid-life activities affect the functional system segregation of resting-state networks. Using fMRI datasets from retired participants, this project will calculate system segregation in order to repeat the moderation analyses from Chan et al. (2018) with system segregation acting as the moderator (rather than midlife activities). If it is found that higher levels of system segregation reduce the relationship between brain structure and cognition, then this project will have provided a functional brain correlate of cognitive reserve.

Physical activity

Observational and randomised-controlled studies have shown that physical activity is associated with measures of white and gray matter structures in the brain (Demnitz et al., 2017; Dunås, Wåhlin, Nyberg, & Boraxbekk, 2021; Jonasson et al., 2017).

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 and genetic profiles have been put forward as potential moderators of the beneficial effects of exercise (Barha, Hsu, ten Brinke, & Liu-Ambrose, 2019). To test this hypothesis, Demnitz, Boraxbekk et al. are using Lifebrain data to investigate whether genetic profiles (e.g., APOE e4) and sex are moderators of the association between physical activity and brain structure, and whether (or how) such associations change across the adult lifespan.

Diet and BMI

Nawijn, Jensen et al. are investigating associations between BMI and diet and brain structure across the whole lifespan both cross-sectionally and longitudinally, and whether observed associations are moderated by age. The study will also account for demographic factors such as sex and socioeconomic status as potential moderators. Within the NESDA cohort, Binnewies et al (2020) already observed negative cross-sectional associations between BMI and cortical thickness in the medial PFC, yet baseline BMI and changes in BMI were not associated with longitudinal changes in medial PFC thickness across 9-year follow-up, suggesting a lack of progressive associations between BMI and medial PFC 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.

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

Nyberg et al are testing the hypothesis of spatially distributed atrophy patterns ("modes") of brain aging, following previous findings of three major dimensions of human cortical aging (Cox et al., 2021). Specifically, this Lifebrain project investigates whether the entorhinal cortex and precuneus are age-sensitive markers of two separate modes, with the specific hypothesis that some older individuals show more marked cortical changes in the entorhinal cortex whereas others in the precuneus. Preliminary analyses provide evidence for such different modes, with some individuals having relative sparing of entorhinal cortex atrophy and instead elevated atrophy in midline parietal cortex, whereas other show the opposite direction of change patterns. These findings are well aligned with the Lifebrain focus on heterogeneity within the older population. In subsequent analytic steps, the different modes will be characterized in terms of factors such as episodic memory performance and carriage of the ε4 allele of the Alzheimer's disease risk gene *APOE*. The latter analyses may contribute evidence that one of the modes is indicative of upcoming pathological aging, whereas the other is more reflecting "normal" non-pathological neurocognitive aging.

Roe et al., (2021) investigated how an important global organizing principle of the brain, namely cortical asymmetry, is affected by aging. In the healthy young adult brain, an asymmetry in cortical thickness across hemispheres is an adaptive feature thought to underlie hemispheric specialization, and to give rise to efficient functional brain network organization. Roe et al. showed that age-related thinning of the cortex resulted in a loss of asymmetry, through accelerated thinning of the previously thicker hemisphere – a result that was highly consistent across Lifebrain cohorts. No associations were observed with asymmetry change over time and longitudinal changes in verbal memory and fluid reasoning ability in the healthy older adults. The loss of asymmetry was further accelerated in frontal and temporal brain regions of a separate sample comprised of individuals with Alzheimer's disease, which underscores its relevance for aging-related outcomes.

A study by Vidal-Pineiro et al., (2021) targeted a widely-used putative biomarker of brain aging; the brain age delta. This measure is estimated by applying machine learning to neuroimaging data to predict the chronological age of individuals and is calculated as the difference between predicted brain age and an individual's actual chronological age. A higher predicted than actual brain age is taken to reflect accelerated age-related neurodegenerative changes. Using Lifebrain data, Vidal-Piñeiro et al., showed that there was no association between cross-sectionally measured brain age and later trajectories of longitudinally measured within-person brain declines. Instead, the adulthood brain age measure was associated with early-life influences, as indexed by birth weight and polygenic scores for brain age. Vidal-Piñeiro et al. argued that these results call for more nuanced interpretations of cross-sectional indices of the aging brain, such as the brain age delta, and question their validity as markers of ongoing within-person changes of the aging brain.

Köhncke et al., is 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 account for sex, education, blood pressure, diet and plasma cholesterol, fatty acid profile, 25-hydroxy-vitamin D3 as covariates, where possible.

Borgeest et al., (2021) are using longitudinal Lifebrain brain imaging data to investigate differences between two morphological brain features, cortical thickness and surface area in terms of their sensitivity to individual differences in cognitive ability and developmental changes or declines over age. The authors found that cortical thickness was the metric most strongly associated with age cross-sectionally, as well as exhibiting the steepest longitudinal change over time (subsample N=261, aged 25-84). In contrast, surface area was the best single predictor of age-residualized cognitive abilities (fluid intelligence), and changes in surface area were most strongly associated with cognitive change over time. These findings were replicated in an independent dataset (N=1345, aged 18-93). These results suggest that cortical thickness and surface area make complementary contributions to the age-brain-cognition triangle, and highlight the importance of considering these volumetric components separately. These results inform future decisions regarding the optimal selection of morphological brain measures to best tease apart aging-related vs cognition-related individual differences.

Biological pathways for memory decline and resilience

Vidal Pineiro et al., are working on a study investigating how multiple biological pathways can contribute to resilience and resistance to memory decline in older age. The study aims to model multimodal longitudinal imaging (structural and diffusion-weighted MRI) as a set of different patterns of brain aging (independent components of longitudinal brain change), so-called *ageotypes*. These then be paired with memory test scores and genetic data. Pathway-specific polygenic risk scores (PGS) indexing genetic liability to neurodegeneration will be computed for this aim, capturing for instance genetic pathways related to metabolism or immune responses. Specifically, Vidal Pineiro et al hypothesize that: 1) Change in the aging brain will be captured by a set of distinct, reproducible patterns of brain aging. 2) Change in the different patterns of brain aging will relate to memory preservation or decline in older adults (e.g. an "all-in-one" model including all the different patterns of brain aging will explain most of the variance associated with memory change; individuals can be grouped according to their brain-aging profile). 3) The different patterns of brain aging will be associated with candidate biological mechanisms so that the different patterns of brain aging will be differently associated with biological pathways as quantified by pathway-specific PGS of Alzheimer's disease.

Genetic and epigenetic factors

Gorbach et al., (2020) examined how the main genetic risk factor for Alzheimer's disease, the ε4 allele of the *APOE* gene, moderated the relationship between aging-related decline in hippocampus volume and aging-related changes in episodic memory performance in healthy older adults from six Lifebrain cohorts. The results showed that the association between aging-related volume of the hippocampus, a key episodic-memory related brain structure, and memory changes, was only present among individuals carrying at least one ε4 allele and thereby at increased risk for Alzheimer's disease. These results demonstrate how genetic factors explain individual differences in how Alzheimer's disease-related pathophysiological brain changes translate into cognitive impairment in older adults.

The Lifebrain team in Lübeck team ascertained and harmonized genome-wide SNP genotyping data and genome-wide DNA methylation (DNAm) profiles for the majority of datasets contributing to the Lifebrain consortium. Overall, there is now more than 5,200 individuals with genome-wide genotyping data and more than 3,600 with DNAm profiles available for analysis in the context of genome-wide association studies (GWAS) or epigenome-wide association studies (EWAS). The first use of these data related to GWAS and EWAS of cross-sectional and longitudinal measures of episodic memory in Lifebrain samples with available phenotype data: The GWAS on episodic memory allowed to include n=4,054 individuals for the cross-sectional and n=1,609 for the longitudinal analyses. Especially the latter constitutes one of the world-wide largest samples assembled for this purpose. The SNP-based cross-sectional results revealed one genome-wide suggestive (P<1E-07) association with episodic memory near the non-coding RNA gene RNA5SP56 on chromosome 1. The SNP-based analyses for the longitudinal (here quantified as annual percent change) revealed genome-wide significant (P<5E-08) evidence for association with a SNP near the CCDC6 gene on chromosome 10. Interestingly, this latter gene had recently been implicated as a novel Alzheimer's disease risk locus in a GWAS by Schwartzentruber et al. 2021 . Interestingly, none of the episodic memory-based analyses yielded any noteworthy results near the APOE locus on chromosome 19.
In the EWAS analyses on the same episodic memory traits we had a total of n=1,657 and n=688 individuals available for the cross-sectional and longitudinal outcomes, respectively. While neither analysis revealed any signals that were significant on an epigenome-wide level (i.e. no association crossed a threshold of P<9E-08), we did identify several noteworthy associations significant on a suggestive level (i.e. P<10-5). These included associations near GAS7 on chromosome 17 and near CBFA2T3/PABPN1L on chromosome 16. Interestingly, both regions showed at least nominal evidence of association in both analysis arm, possibly indicated a role in both determining both cross-sectional as well as longitudinal episodic memory outcomes. Furthermore, both signals were independently observed in previous EWAS on cognitive abilities (i.e. GAS7 in Marioni et al, 2018 and CBFA2T3 in Zhang et al, 2020). To assess the potential functional basis of these associations, we are currently aligning the implicated differentially methylated DNAm sites in other work recently completed by the Lübeck group where DNAm patterns were correlated in matched buccal and brain samples of the same individuals (Sommerer et al. 2021).

Bertram, Fjell et al. intend to investigate genetic factors behind resilience to age-related decline in episodic memory performance. They will quantify, in each individual, the degree of "resilience to memory decline" with respect to individual genetic risk for Alzheimer's disease (AD; including APOE ε4 and all other currently known genetic risk variants, as polygenic risk scores). The portion of phenotypic variance in memory performance not explained by AD genetic risk will be used as outcome measure in a genome-wide association study (GWAS).

2.2 Biomarkers, predictors and health-related factors

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 gray and posterior cingulate gray 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 a number of 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.

Inflammatory markers

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 are able to 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 is 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 associations significant associations so far. Further analyses including data from younger individuals in Lifebrain will to provide a baseline for "optimal" values. It is hypothesized that the older "Maintainers" will be have 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".

Memory dispersion

Solé-Padullés et al. are testing whether episodic memory *dispersion,* defined as intra-individual variability of performance across neuropsychological tests, is a marker for ageing-related volume loss in the hippocampus. They further test whether dispersion predicts hippocampal volume loss better than standard composite scores of episodic memory function, and whether the relationship is moderated by memory complaints.

Vascular health and neurocognitive characteristics

Borgeest et al. are addressing the question of how grey matter mediates the relationship between cardio-vascular health and cognitive abilities. In these analyses, cardiovascular health is indexed by systolic blood pressure and assessed in two Lifebrain cohorts (Cam-CAN, N=708 and LCBC, N=1,345). While whole brain grey matter volume mediates the relationship between baseline systolic blood pressure and cognitive abilities measured at time point 2, further modelling showed that this mediation is comprised of two separable components: the a-paths of the mediation (blood pressure – brain) were best explained by cortical thickness, while the b-paths (brain – cognition) were mediated by surface area. Mediations investigating grey matter volume (which is a product of cortical thickness and surface area) capture both effects simultaneously but, in doing so, miss this differentiable mediating pattern.

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.

2.3 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/additional task-related activation. Vaqué-Alcázar et al., will use 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 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.

2.4 General cognitive ability - associations with brain characteristics

Walhovd et al. is investigating the associations between individual differences in general cognitive ability (GCA) and brain change throughout the lifespan. Specifically, what the relationships are between GCA as a trait, and brain changes, and whether GCA is more strongly linked to individual differences in baseline brain characteristics, rather than changes in these characteristics. Further, Walhovd et al are also testing whether there are residual effects of GCA on brain offset/ change when accounting for genetic (polygenic scores) and environmental (education) variables; whether the effects vary across generations (ages and times); and what the relationship is between change in GCA and brain changes across the lifespan.

3. Conclusion

In the spirit of the Lifebrain project's emphasis on a lifespan perspective of heterogeneity in cognitive aging, the empirical studies in this task (summarized above) have focused on both early- and later-life contributions to such heterogeneity. Genetic factors have been shown to; (i) influence structural and functional brain organization and (ii) thereby variability in general cognitive intelligence and specific cognitive abilities, and (iii) in turn contribute to educational and professional choices which (iv) may influence an individual's life-time exposure to protective (e.g., physical exercise habits) as well as harmful (e.g., smoking) environmental factors. The empirical findings also achieved the goal of showing how the genetic background of individuals can influence core associations, for example the finding of a stronger brain-cognition association in individuals at genetic risk for sporadic Alzheimer's disease.

More 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 cognitive functioning in adulthood and aging. Particularly novel features of the integrated cohort include the longitudinal design, which allowed actual measurement of true changes, and the very rich genotypic and phenotypic characterization of the participating individuals. It should finally be mentioned that the Lifebrain cohort in some studies could be combined with additional cohorts from the UK and the USA, resulting in sample sizes exceeding 50,000. In that way, the project has been well suited to confirm hypothesized relations, refute other hypothetical relations (e.g., educational attainment does not influence rate of brain aging), and explore novel associations. Thus, the conducted research is well in line with the current call of optimizing the use of existing brain-imaging cohorts

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5. Additional Lifebrain-related studies

Studies relevant for the objectives of T4.3 that Lifebrain researchers have produced during the project period, up to November 2021. These include studies on cohorts included in Lifebrain, but not necessarily the integrated Lifebrain database. A complete and updated list can also be found on the Lifebrain website (https://www.lifebrain.uio.no/publications/scientific%20articles).

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