Lifebrain

Deliverable 4.2

Individual pathways and mediator variables in relation to risk for mental health problems and resilience

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Executive Summary

Mental health is pivotal to a productive human life. It critically depends on brain health. Depressive disorders are not only amongst the most common psychiatric and neurological disorders, but also amongst all health disorders worldwide. In older age groups, depression is affected by the multi-morbidity common to advanced age, as a result, but also as a cause of morbidity. There is an obvious interaction between age and depression, in that genetic and early life factors are most important in early life depression, while for late onset depression the implication is that a healthy constitution and favourable early life conditions have protected the person from depressive symptoms, until some event later in life have generated a specific vulnerability. This generates the paradox that a typical human brain- and behavioural response (i.e. depressive symptoms) can be the outcome of very diverse exposures to noxious factors ranging from genetics, early life experiences to lifestyle and later life degenerative or allostatic changes. We have harnessed the wide age range and large numbers of participants to examine associations of depressive symptoms with brain measures and their association with age and symptom trajectories over time. In teasing apart different aspects of depression, i.e. disturbed sleep, the feeling of loneliness, and negative personality traits and their overlap and interaction with depressive symptoms, age, and sex we have managed to discover several associations of interest:

- There seems to be a sensitive period in later life, when depression is associated with mid-life vascular risk (which would include smoking, alcohol, body mass index, blood pressure, cholesterol and other blood markers), white matter changes, cognitive impairment and an increased risk of subsequent dementia.
- Mild depressive symptoms and reported loneliness by themselves showed few brain correlates in general population samples, but when they were asociated with *objective social isolation* they showed a major effect on brain age. Furthermore, moderate-to-severe depressive symptoms showed associations with reduced grey matter, stable across the adult lifespan.
- Sleep plays a special complex role as a correlate and marker, as well as potential a causal factor influencing brain health. We were able to identify hippocampal age-independent associations between poor sleep, structure and function, while (neo-)cortical associations could be found in older, but not younger participants.
- Finally, personality traits associated with negative mood appear to show an age by sex interaction, in that men diverge from women after puberty in terms of cingulate microstructure.

List of acronyms / abbreviations

BASE-II Berlin Aging Study II (MPIB)

BMI Body Mass Index

ENIGMA Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium

FA Fractional Anisotropy (Diffusion MRI measure)

HUBU Hjernens Udvikling hos Børn og Unge/Brain Development of Children and Adolescents (RegionH)

KMC Knowledge Management Committee

mOFC medial orbitofrontal cortex

MPIB Max Planck Institute for Human Development Berlin

MRI Magnetic resonance imaging

PI Principal Investigator

rACC Rostral Anterior Cingulate Cortex

REGOINH Region Hovedstaden

SES Socio-Economic Status

T Task

UB University of Barcelona

UCAM University of Cambridge

UiO University of Oslo

UOXF University of Oxford

UmU Umeå University

VUMC University Medical Center Amsterdam

WMH White Matter Hyperintensities

WP Work Package

1. Introduction

1.1 Background

Mental health is pivotal to productive human life. It critically depends on brain health. The separation of cognitive health and mental health is somewhat artificial. It is defined by the instruments that measure behaviour, rather than by any diagnosis or the brain systems involved. In fact, the presence of a 'primarily' cognitive disorder, such as dementia, often involves emotional (depression) and behavioural (apathy) disturbances. Typically, mental disorders, such as depression or psychoses, are often associated with cognitive disturbances. Moreover, the comorbidity of mental and cognitive disorders is extensive, with one often being a risk factor for the other. All this implies a certain degree of overlap between risk factors or even a 'pleiotropy' of underlying causes. Examples are the similar effect of certain lifestyle and health-related factors increasing risks for cardiovascular, mental health (late onset depression), and cognitive disorders (dementias). This deliverable includes by necessity an overlap with D4.3, and to make coherent reading of each deliverable possible, a degree of redundancy has been included.

Psychiatric problems are influenced and mirrored by age-related neurodevelopmental and neurode-generative brain changes that occur throughout life. A major challenge is to determine which age-related changes are detrimental and which enhance mental health. The potential economic benefits of such an improved understanding are large, with total costs of brain disorders in Europe in 2010 estimated to be 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 stages of life to oldest age, are mapped in detail in several existing European longitudinal studies using 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, because MRI is expensive and time-consuming, the number of participants included in such studies tends to be low. **One main objective of the Lifebrain consortium is to integrate existing European MRI datasets to increase statistical power to uncover novel knowledge about how to optimize brain, cognitive-, and mental health throughout life.**

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

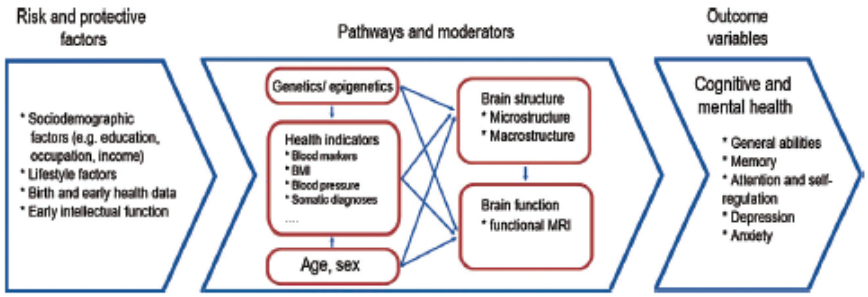

FIGURE 1 CONCETPUAL OVERVIEW

Depression is associated with structural brain changes (Schmaal et al. 2017; Schmaal et al. 2016; Sexton et al. 2012; Frodl et al. 2008), with less consistent findings for subthreshold depressive symptoms (Webb et al. 2014; Allan et al. 2016). Depressive symptoms emerging in mid- and later life have been associated with decreases in cognitive function. However, there does not only appear to be straightforward 'dose effect' of depressive symptoms in increasing the risk of dementia. Rather, it is found that a dementia diagnosis is often presaged by depressive symptoms the more frequently, the closer to the time of the dementia diagnosis they are measured (Singh-Manoux et al. 2017). This suggests that there is probably a shared mechanism underlying both late onset depression and (age-related) cognitive decline. Brain areas associated with depressive symptoms may also overlap with those implicated with relevant cognitive domains (Buckner 2004; Steele and Lawrie 2004).

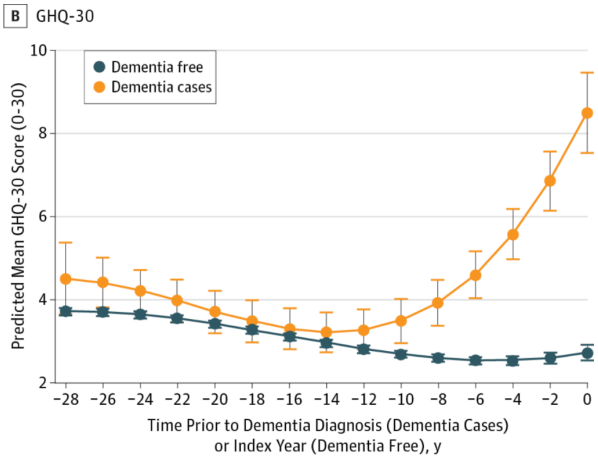

FIGURE 2 GHQ Depression Subscores increase closer to the time of dementia diagnosis

People with **late onset depressive symptoms**, but not consistently high scorers over 20 years, showed higher mean diffusivity, larger volumes of WMH and impaired executive function. In addition, the late onset group had higher Framingham Stroke Risk scores throughout the follow-up period, indicating a higher load of vascular risk factors (Demnitz, Anaturk, et al. 2020). These findings suggest that tracking depressive symptoms in the community over time may be a useful tool to identify phenotypes that show different aetiologies and cognitive and brain outcomes (Allan et al. 2016; Demnitz, Topiwala, et al. 2020; Herrmann, Goodwin, and Ebmeier 2007; Herrmann, Le Masurier, and Ebmeier 2008; Singh-Manoux et al. 2017; Valkanova, Ebmeier, and Allan 2013).

The nature of the effect of lifestyle on the relation between depression, cognition and brain structure is still unknown. Studies to date have had relatively small sample-sizes, which may have limited the ability to investigate the association between depressed mood, sleep quality, cognition, lifestyle and brain structure, and their interactions. **Within Lifebrain we have sufficient power to properly assess these associations properly.** The rich information in our large longitudinal Lifebrain database will allow us to examine individual differences in the onset and magnitude of brain change in relation to depression and identify genetic and lifestyle factors that predict preserved or declining brain structure and function.

Disturbed sleep has also often been associated with depression, even in remission (van Mill et al. 2010; Mendlewicz 2009) and at subclinical levels of depression (Gould et al. 2018). Studies have related self-reported sleep to decreases in cognitive function (Brewster, Varrasse, and Rowe 2015; Yaffe, Falvey, and Hoang 2014; Mellor et al. 2018; Waters and Bucks 2011), and proposed depression to play a critical role in the relationship between sleep and cognition in healthy individuals (Mellor et al. 2018). Sleep has been associated with changes in brain structure in young and older adults (Liu et al. 2018; Baillet et al. 2017; Sexton et al. 2017), albeit with some mixed results.

A significant association is more often reported with current measures of sleep near or at the time of cognitive assessment and MRI scans (Brewster, Varrasse, and Rowe 2015; Sexton et al. 2017). Taken together, sleep may be a promising modifiable factor that can maintain or even improve cognitive performance and brain structure across the lifespan.

Depression has often been associated with an unhealthy lifestyle. Lower physical activity and increased BMI were associated with depression (Hiles et al. 2017; Vancampfort et al. 2015), as was smoking (Fluharty et al. 2017) and alcohol (Boden and Fergusson 2011; Boschloo et al. 2011; Boschloo et al. 2014). Lifestyle has been related to (change in) brain structures and cognition. Grey matter reductions and cognitive deterioration were related to an unhealthy lifestyle, such as higher levels of alcohol consumption (Topiwala et al. 2017; Anstey et al. 2006), smoking (Vnukova et al. 2017), BMI (Bischof and Park 2015; Veit et al. 2014) and lower levels of physical activity (Erickson et al. 2019; Bherer, Erickson, and Liu-Ambrose 2013; Walhovd et al. 2014). Increased physical activity was even found to decrease cognitive decline and reductions of brain structure over time (Voelcker-Rehage and Niemann 2013).

1.2 Objectives

As stated in the application, analyses in the integrated project cohort are to identify whether individual differences in mental health and resilience are mediated via variations in lifestyle (smoking, alcohol, drugs), body mass index, blood pressure, cholesterol and other blood markers (vitamins, fatty acid, protein status, metals), genetic/ epigenetic factors and brain structure and function. Through the harmonised and coordinated use of observations of risk factors and predictors of resilience for mental disease (primarily anxiety and depression) obtained through WP2 and WP3 across more than 6000 participants who also have received MRI scans, T4.2 will (1) Examine the associations of these risk and resilience factors with objective brain measures, (2) identify particular brain measures as mechanistic mediators of risk (e.g. hippocampal atrophy) or resilience (e.g. white matter tract fractional anisotropy), (3) identify confounding factors, such as sex, social class, etc. that may have an influence on the pathways leading to promoting mental disorders via brain mediators. Specifically, we will test the effects of the following risk factors: (a) antecedent vascular and metabolic risk trajectories and morbidity, (b) low antecedent levels of physical and mental activity (measured by questionnaires), (c) baseline cognitive performance levels and up to 15-year gradients of memory decrement, (d) history of depressed mood and genetics/epigenetics.

1.3 Collaboration among partners

This task has been led by the University of Oxford (UOXF) and Vrije University Medical Center Amsterdam (VUMC), Region Hovedstaden (REGIONH), with Umeå University (UmU), Max Planck Institute in Berlin (MPIB), University of Cambridge (UCAM) and University of Barcelona (UB) as main collaborators. In addition, mental health is the focus of several main projects in Lifebrain. Lifebrain researchers from Umeå University (UmU) 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 the majority of studies listing co-authors from multiple and sometimes all participating Lifebrain sites. Through consortium meeting presentations and discussions, as well as discussions on the collaborative platform Slack, Lifebrain researchers from multiple sites have provided essential feedback to all stages of each study, including conceptualization, analyses, interpretation, and paper drafting. In order to prevent duplication and redundancy, projects are formally assessed and passed by the Knowledge Management Committee (KMC) before being opened to all collaborators within the consortium.

2. Results

At the time of writing (December 2021), T4.2 has resulted in eleven published papers on the integrated Lifebrain cohorts, as well as one submitted manuscripts. Ongoing research activity is high, with 8 studies that have been approved by the knowledge management committee (KMC) and with preliminary results presented at Lifebrain meetings for most of them. In addition, during the project time, Lifebrain researchers have published 11 papers related to the objectives of T4.2. 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 from studies on the integrated Lifebrain cohort.

2.1 Lifestyle and genetic factors in relation to mental health

Depression

We examined 3447 participants (18-89 years) from six population-based Lifebrain cohorts and two clinical patient-control cohorts (preliminary results in (Binnewies, Nawijn, Walhovd, et al. 2021; Binnewies, Nawijn, and Penninx 2021)). In the patient-control cohorts, symptom severity and presence of mild-to-severe depression (vs no depression) were associated with lower medial orbito-frontal 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. However, 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 (i.e., if there are potential moderating effects of age or sex). Yet, no consistent age-by-depression or sex-by-depression interactions were observed.

In a paper using a clinical case-control cohort, we compared brain aging, based on machine-learning analysis algorithm using whole brain information, between persons with and without a depressive and/or anxiety disorder. We confirmed that depressed cases had a more advanced brain aging as compared to healthy controls, however antidepressant use seemed to have a significant reversing effect as brain age was less advanced among antidepressant users as compared to non-users. Results were similar for persons with anxiety disorders, and could not be explained by underlying biological stress system dysfunctions (Han et al. 2021).

In another paper using the same clinical case-control cohort, we investigated the relation between depression, lifestyle and brain structure cross-sectionally and longitudinally over up to 9 years. Cross-sectionally, measured across three time-points, higher severity of depressive symptoms as well as current depression diagnosis were associated with a thinner rACC. Higher BMI was associated with thinner mOFC, and moderate alcohol consumption compared to no alcohol consumption with thicker mOFC. All of these associations were independent of each other. Longitudinally, no convincing associations between (change in) depression or lifestyle and brain change were found over up to 9 years (Binnewies, Nawijn, van Tol, et al. 2021).

Our analyses on trajectories of depressive symptoms suggest that tracking depressive symptoms over time may be a useful tool for identifying phenotypes that show different cognitive and brain outcomes (Demnitz, Anaturk, et al. 2020). We compared indices of white matter microstructure and cognitive characteristics of groups with different trajectories of depressive symptoms up to nine times over 25 years. 27 years after the first examination, participants underwent MRI to characterize white matter hyperintensities (WMH) and microstructure, and completed neuropsychological tests to assess cognition. Twenty-nine years after the first examination, participants completed a further cognitive screening test. The late, but not the consistently high scorers on depressive symptoms, showed higher mean diffusivity, larger volumes of WMH and impaired executive function. In addition, the late subgroup had higher Framingham Stroke Risk scores throughout the follow-up period, indicating a higher load of vascular risk factors (Demnitz, Anaturk, et al. 2020).

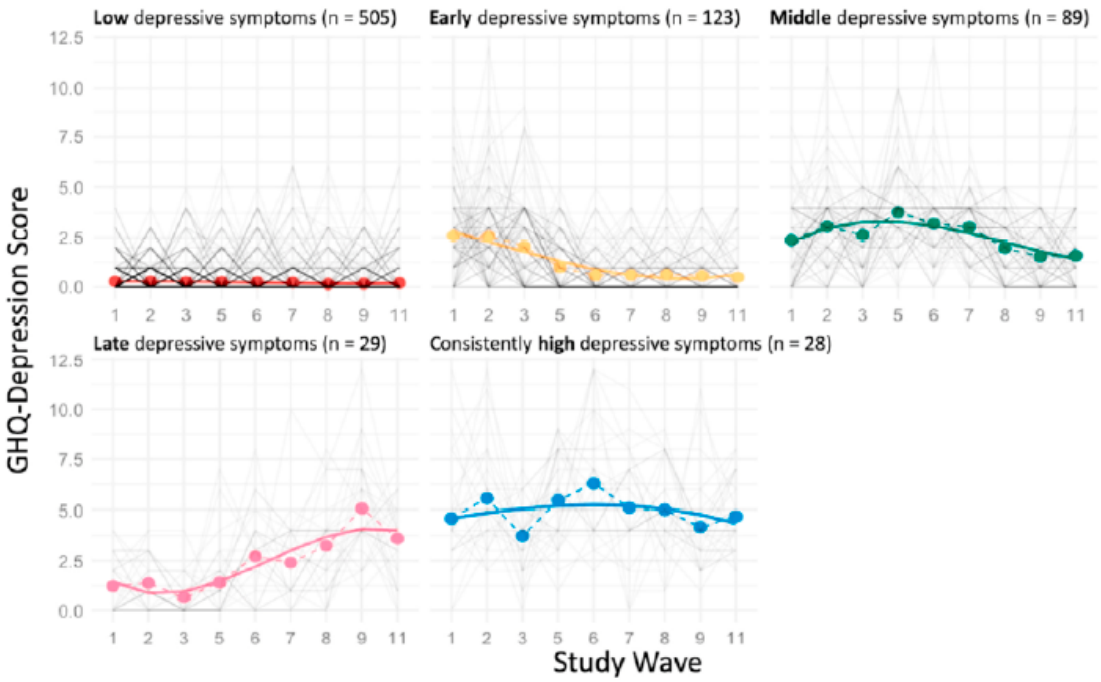

FIGURE 3 GHQ Depression Subscore Trajectories (Demnitz et al. 2020)

Finally, we 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, we 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 (Zsoldos, Vidal Pineiro, Ebmeier et al. 2022 in preparation).

Loneliness

We used data from 24,867 UK Biobank participants to investigate risk factors related to loneliness and estimate brain age based on neuroimaging data (de Lange et al. 2021). The results showed that on average, individuals who self-reported loneliness on a single yes/no item scored higher on neuroticism, depression, social isolation, and socioeconomic deprivation, performed less physical activity, and had higher BMI compared to individuals who did not report loneliness. In line with studies pointing to a genetic overlap of loneliness with neuroticism and depression, permutation feature importance ranked these factors as the most important for classifying lonely vs. not lonely individuals. While strongly linked to loneliness, neuroticism and depression were not associated with brain age estimates. Conversely, objective social isolation showed a major effect on brain age, and 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.

Whereas longitudinal studies are required to determine causality, this finding may indicate that the combination of social isolation and a genetic predisposition for loneliness involves a risk for adverse brain health. Importantly, the results underline the complexity in associations between loneliness and adverse health outcomes, where observed risks probably depend on a combination of interlinked variables including genetic as well as social, behavioural, physical, and socioeconomic factors.

In addition, Solé-Padullés et al. have recently submitted our new results to Frontiers in Aging Neuroscience, showing weak to non-existent associations between the adverse lifestyle factor loneliness and memory and hippocampal volume change across the lifespan. Higher loneliness ratings were associated with faster memory decline only in one older adult Lifebrain cohort (Betula), but not in another similar cohort of older adults (BASE-II), nor among younger individuals (HUBU cohort). Furthermore, significant associations with the Betula cohort disappeared after having ruled out eight cases of developing dementia along the fifteen-year period of evaluation, which reinforces previous findings associating loneliness with cognitive impairment and dementia. No significant associations were observed between loneliness and hippocampus volume change. There was no significant change in cortical thickness either, which was included as an exploratory analysis. Based on our results, it may be possible that the emotion-cognition link is independent of any detectable association between loneliness and brain structure change, and that other variables, such as psychological, genetic, cultural, and socioeconomic factors not considered in the present study, might moderate the complex relationship between loneliness and brain health (Solé-Padullés et al. 2022).

Sleep

We have performed extensive analyses on the associations of different sleep parameters in relation to brain structure and volumetric changes. The first paper focused on hippocampal volume and atrophy in six Lifebrain cohorts (N = 1299, 18-90 years). We found evidence for age-independent relationships between hippocampal atrophy and self-reported sleep measures, where worse sleep was related to higher hippocampal atrophy across adult and later life, although the effect sizes were moderate (Fjell et al. 2020). In a second paper, we investigated the relationship between sleep parameters and change in cortical thickness over time. Like for hippocampus, modest relationships were discovered. In contrast to the hippocampal findings, however, these relationships were age-dependent, and were seen after 60 years of age only. Thus, in younger participants, no relationship between sleep and cortical change was seen (Fjell et al. 2021). In a third paper, we found that sleep was related to changes in hippocampal integrity as measured by mean water diffusion, and a weak relationship to memory function was seen (Grydeland et al. 2021). In general, our findings so far suggest that sleep quality might be a moderately efficient biomarker of brain changes as indicated by the relatively small effect sizes.

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, using the enriched Lifebrain dataset (Kachel, Steffens, and Niedlich 2016). Negative emotionality-related traits, such as neuroticism, harm avoidance, behavioural inhibition, and trait anxiety, are known risk factors for anxiety and mood disorders (Belcher et al. 2014; Bienvenu et al. 2001; Kendler et al. 2006; Sutin, Evans, and Zonderman 2013; Nemes and Cozman 2016; Klein, Kotov, and Bufferd 2011; Tully, Wardenaar, and Penninx 2015). Whereas personality traits are thought to be stable, personality trait *scores* do show consistent changes over the lifespan (Costa, McCrae, and Lockenhoff 2019) Moreover, 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). 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. In our baseline analysis in the HUBU cohort (N = 72, age range = 10-15 years), 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) In our longitudinal analysis of the HUBU cohort (N = 76, age range = 7-19 years) including up to 11 MRI scans, we assessed if this relationship might change with age across late childhood and adolescence. This is an important question, as adolescence is associated with an increased incidence of neuropsychiatric disorders, such as anxiety, mood and substance use disorders (Paus, Keshavan, and Giedd 2008), for which neuroticism is a known risk factor. 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 et al. 2021). In addition, we aim to identify multivariate structural patterns (e.g., cortical thickness, area, gyrification, white matter fibre tract, and subcortical grey matter microstructure, and possible structural connectivity measures) underlying different personality traits, and elucidate how these relationships may change across the life span. Furthermore, we will investigate how brain structure-personality relationships are modulated by e.g., mental health, stress full live events, SES, sex/gender (Plachti et al. 2022; Madsen et al. 2022).

3. Conclusion

In the spirit of the Lifebrain project's emphasis on a lifespan perspective on heterogeneity in mental health and cognitive and brain aging, the empirical studies in this task (summarized above) have put a focus 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. We can report that depressive symptoms and depression are mainly reflected in participants recruited as patients, in whom dose-effect relationships with brain outcomes were observed, but not in unselected members of the general population. There seems to be a sensitive period in later life, when depression is associated with mid-life vascular risk (which would include smoking, alcohol, body mass index, blood pressure, cholesterol and other blood markers), white matter changes, cognitive impairment and an increased risk of subsequent dementia. Depression and reported loneliness by themselves showed few brain correlates in general population samples, but when they were asociated with *objective social isolation* they showed a major effect on brain age. Sleep plays a special complex role as a correlate and marker, as well as potential a causal factor influencing brain health. We were able to identify hippocampal age-independent associations between poor sleep, structure and function, while (neo-)cortical associations could be found in older, but not younger participants. Finally, personality traits associated with negative mood appear to show an age by sex interaction, in that men diverge from women after puberty in terms of cingulate microstructure.

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 & cognitive functioning in adulthood and aging. 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, how individual differences in mental health (depression), lifestyle behaviour & cardiovascular health are associated with brain structure and cognitive health across the lifespan. This will ultimately provide important fundamental knowledge and new avenues for optimal prevention strategies.

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