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Review

Healthy minds 0–100 years: Optimising the use of European brain imaging cohorts ("Lifebrain")

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ABSTRACT

The main objective of "Lifebrain" is to identify the determinants of brain, cognitive and mental (BCM) health at different stages of life. By integrating, harmonising and enriching major European neuroimaging studies across the life span, we will merge fine-grained BCM health measures of more than 5000 individuals. Longitudinal brain imaging, genetic and health data are available for a major part, as well as cognitive and mental health measures for the broader cohorts, exceeding 27,000 examinations in total. By linking these data to other databases and biobanks, including birth registries, national and regional archives, and by enriching them with a new online data collection and novel measures, we will address the risk factors and protective factors of BCM health. We will identify pathways through which risk and protective factors work and their moderators. Exploiting existing European infrastructures and initiatives, we hope to make major conceptual, methodological and analytical contributions towards large integrative cohorts and their efficient exploitation. We will thus provide novel information on BCM health maintenance, as well as the onset and course of BCM disorders. This will lay a foundation for earlier diagnosis of brain disorders, aberrant development and decline of BCM health, and translate into

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future preventive and therapeutic strategies. Aiming to improve clinical practice and public health we will work with stakeholders and health authorities, and thus provide the evidence base for prevention and intervention.

1. Background

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

1.1. Overall aim and objectives

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

This will yield a database of fine-grained BCM health measures for more than 5.000 individual participants. Longitudinal brain imaging data are available for a major portion, as well as cognitive and mental health measures for broader cohorts, exceeding 27.000 examinations. The project is a collaborative initiative involving a small and medium-sized enterprise (SME), several of Europe's major brain research centres, as well as stakeholders for efficient exploitation of results (Fig. 1).

Lifebrain includes four sub-objectives:

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

1.2. Vision

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

2. Methods

2.1. Concept

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

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

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