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Brain age as an imaging-based diagnostic and treatment biomarker of neurodegenerative disorders

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Brain age as an imaging-based diagnostic and treatment biomarker of neurodegenerative disorders

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Reviewable v 1

Abstract

In the proposed project we expect to improve diagnosis and treatment for patients suffering from neurodegenerative diseases by establishing a new biomarker based on deep learning and big data outputs. We will use brain age, a neuroinaging-derived marker of brain health which has previously rarely been tested longitudinally, but not in neurodegenerative disorders. The analyses will help to assess treatment response as well as stratifying and sub-typing neurodegenerative disease based on brain structural characteristics in addition to multiple other markers of disease expression.

Keywords

magnetic resonance imaging, neurodegenerative disorders, brain age

Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson disease (PD), and multiple sclerosis (MS) (Chaudhuri 2013), represent a significant challenge to national and global healthcare systems and the individuals affected (Livingston et al. 2020, Deuschl et al. 2020). The incidence of neurodegenerative disorders is expected to multiply over the next decades (Nichols et al. 2022, Huang et al. 2023). Estimates include an increase from 57 million dementia cases globally in 2019 to 152 million cases in 2050 (Nichols et al. 2022). Such upwards trends could also be observed historically from 1990 to 2021, showing a 161% increase in the prevalence of Alzheimer's and other dementias (resulting in a rate of 694 per 100,000 in 2021), and a 88% increase in MS prevalence (22 per 100,000 in 2021), respectively (Huang et al. 2023).

Neurodegenerative diseases, characterised by the progressive degeneration of the nervous system, lead to a substantial burden due to their debilitating nature and the

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complex care requirements they necessitate. Due to their progressive nature and problems of late-stage treatment, the outlined **neurodegenerative diseases require early treatment**. The main route of treatment is medication, **specific to** the **disease subtype,** and **adjusted** according **to treatment response and disease progression**. Treatment **outcomes** are, however, **challenging to measure** and visualise, resulting in a **lack of verified markers**, partly due to the large variability in both disease trajectories as well as treatment protocols (Young et al. 2018, Mekkes et al. 2024). Inaccurate diagnoses, for example, in the case of dementia (Mekkes et al. 2024), exacerbate this problem. **To establish an optimal management for this group of patients, it is hence vital to find robust imaging biomarkers allowing one to control disease progression and predict treatment success.**

What unites neurodegenerative diseases is their manifestation in the brain tissue, making the identification of brain biomarkers a critical area of ongoing research. Indeed, several neuroimaging biomarkers have been suggested to be diagnostic or even prognostic (Dubois et al. 2023, Tondo and De Marchi 2022), and brain imaging is frequently considered when evaluating neurodegenerative disorders clinically. Unfortunately, the extent to which brain biomarkers for neurodegenerative disorders can be used diagnostically and prognostically is still limited (Dubois et al. 2023, Tondo and De Marchi 2022), and biomarkers which can be used to evaluate treatment do, to our knowledge, not exist in AD and PD. Although such markers are available in MS, further development and improvements is still needed, especially for treatment response and evaluation of the neurodegenerative component of the disease. The lack of effective biomarkers to determine treatment success is a significant hurdle restricting the management of neurodegenerative disorder. Without the ability to measure clear biological outcomes, healthcare providers must rely on qualitative and partly subjective measures and decisions. This reliance does not aid the treatment process for diseases that are already inherently difficult to manage. Therefore, the development of proper brain biomarkers to evaluate treatment response is crucial.

Recent advancements in neuroscientific research have introduced the concept of **brain age as** a potential **holistic marker of brain health**. Brain age refers to the predicted age from machine or deep learning models which were trained on large-scale data of healthy participants. This provides an approximation of how a healthy brain looks throughout the lifespan (considering a range of covariates such as sex or genetic variations). Now, brain age can be predicted in neurodegenerative disease cohorts taking into account different manifestations of neurodegeneration. The predicted **brain age** of an individual person can be **contrasted with** their **chronological age, resulting in the brain age gap**. Such a brain age gap **presents associations with multiple diseases and health outcomes (** Kaufmann et al. 2019, Høgestøl et al. 2019, Korbmacher et al. 2023b). Importantly, brain age is **particularly sensitive to neurodegenerative diseases** (Høgestøl et al. 2019, Korbmacher et al. 2023b), presenting an opportunity to utilise this marker in clinical practice to detect treatment responses with high sensitivity to individual variability.

There are various biological and morphological changes which can be observed during senescence, also called ageing. Moreover, ageing is characterised by significant

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morphological heterogeneity, which increases later in life. Diseases add to that heterogeneity. Simple comparisons of morphological features between healthy and diseased groups will, therefore, lead to unspecific differences which are widely distributed across the brain.

More specifically, on a group level, it is known that ageing-related cellular atrophy affects brain grey and white matter organisation, and neurodegenerative disorders are closely age-related (Huang et al. 2023). For example, grey matter volume, surface area, and thickness decrease, and the share of free water increases in the white matter. While such phenomena can be observed on a larger scale across the brain, these patterns are highly individual considering single patients. Here, brain age can be used to conserve individual variability by comparing imaging data to an age-reference which is based on a large cohort. In contrast to direct estimates of brain morphology, brain age has the advantage of providing simple and individual-specific estimates of the state of an individual's brain by comparing the individual's multimodal magnetic resonance imaging (MRI) data to normative values.

We aim to establish a brain age biomarker which can stratify disease trajectories, indicate whether a treatment works, and we will provide imaging-derived and other phenotype-based explanations for these evaluations.

In turn, the potential of brain age as an early diagnostic tool might provide a helpful source of information about potential treatment strategies for the clinical practitioners. We will use **explainable artificial intelligence and feature importance estimation methods** to provide **region-specificity and biophysical origins of the brain tissue response**. Examples of other phenotypes which will additionally help explain brain age differences are symptom scores, medication, and demographics.

The extent to which a medication works can directly inform further clinical decisions such as changes to the treatment plan, for example, by dose-adjustment or switching to alternative medications. The newly identified biomarkers can be combined with other routine markers and be implemented in the follow-up schedule accompanying the treatment.

This project will be executed in national and international collaborations, with the core collaborative institutions being located in Norway, including the Department of Health and Functioning at the Western Norway University of Applied Sciences; the Neuro-SysMed group at Haukeland University Hospital, Bergen and the University of Bergen; and the MS group at the Oslo University Hospital, as well as the Faculties of Psychology and Medicine at the University of Oslo. The **multiple and large datasets** have **already** been **collected** in the context of previous clinical trials using different medications for the mentioned disorders.

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Objectives

The main objective of this project is to develop the brain age concept towards a treatment response biomarker in neurodegenerative disorders. Based on these findings, we will create easy-use automatic software which can be used by clinicians to assess the treatment strategy and predict the treatment response. In this context, we formulated four work packages (WP; for a graphical overview see Fig. 1).

1. Assess spatial and temporal patterns in the brain associated with ageing for healthy and patient groups.
2. Assess how brain age reflects treatment response of different medications used for the different neurodegenerative disorders. This central step includes creating predictive models for patient-specific treatment response. The evidence will additionally be examined using mega- and meta-analyses of brain age as a biomarker of neurodegenerative disease treatment success across the examined data.
3. Evaluate additional factors which can be used to enhance evaluations of treatment success.
4. Establish a readily usable toolbox for direct implementation into clinical workflows.

Figure 1. Graphical overview of the four work packages (WP) of the project.

Connected to the outlined work packages, we developed some general hypotheses for the research process:

1. We hypothesise that brain age corresponds with chronological age during healthy ageing but accelerates in the presence of disease.
2. We hypothesise that brain age associates negatively with treatment success. That will say that successful treatment is expected to change the pace of neurodegeneration towards normal degeneration which can be expected during healthy ageing.
3. We hypothesise that it is possible to reveal personalised ageing profiles which can be established by mapping the individual brain age assessment spatially and by assessing additional covariates. These profiles will add information towards more personalised treatment.

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Design and Methods

In this project, we will use various data sets collected from both previous and ongoing multi-center clinical trials for brain age predictions (Table 1). Taken together these data are a **unique collection of longitudinal multimodal MRI and clinical data of more than 2,000 patients**. The data serve to predict the participants' region-specific brain ages and connect them to relevant outcomes, such as clinical assessments, symptoms, and treatments. **In addition to healthy controls in each clinical dataset**, we have data of **more than 60,000 health controls** available which can serve to train machine and deep learning models. These models can then be applied to the patient cohort(s). In contrast to previous studies (Franke and Gaser 2019), we will validate several brain age models against each other, to reduce the influence of model-specific bias, and, instead, draw robust inferences. We will use data from the two sequences which were outlined to result in most accurate brain age predictions, as well as being commonly available clinical sequences: T_1-weighted MRI (T_1w) and diffusion-weighted MRI (dMRI).

For T_1-weighted data, which is particularly useful to characterise the brain's grey matter morphology, we will use an established deep learning brain age model, trained and validated on about 60,000 participants (Leonardsen et al. 2022), and establish additional models based on UK Biobank data (Alfaro-Almagro et al. 2018b) (N > 60,000). The established deep learning model has been shown to outperform other trained models (Dörfel et al. 2023, Hanson et al. 2024). The additional models, which will be trained in this project, will be used to validate voxel-level findings by using region-level features and provide additional biophysical information. Our new models will add detail in terms of thickness, volume and surface area estimates, the pre-trained deep learning model focuses on signal intensity values.

For dMRI data, which is particularly useful to characterise the brain's white matter, we will also use an established machine learning model, trained on about 40,000 participants (Korbmacher et al. 2023a). The assessments of these different MRI data allow for differential inference, giving more biological detail than when relying on a single sequence. However, the acquisitions depend on the different study protocols, with not all studies providing all sequences, varying disorder groups and medication administration schemes (Table 1). For the data processing, we will apply stringent quality control procedures to minimise the influence of unwanted technical artefact sand motion effects (Huang et al. 2023, Young et al. 2018), and we will harmonise data across sites to reduce the influence of random noise in the data. Machine learning models will use either three- or two-dimensional MRI data representing signal contrasts or specific bio-physically derived features, such as cortical thickness (T_1w) or diffusivity (dMRI) estimates. A brief overview of the WPs and their timeline, see Fig. 2.

WP 1: Mapping differences in ageing trajectories

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To examine the first objective, using each trained model on the respective available modality-specific data, we estimate the brain age for all participants, including both neurodegenerative disorder cases in addition to healthy controls. Across the healthy participants, we will then delineate whether the brain age gap increases naturally as participants age or whether it is relatively stable across adulthood. In a next step, such slopes can then be compared between healthy controls and different disorder groups. These analyses will help to **disentangle the extent to which brain age is sensitive to normal compared to abnormal ageing effects** (see Fig. 1, WP1). We expect to find differences between normal and abnormal ageing expressed by brain age (Hypothesis 1).

By assessing the **brain ages of individuals at different neurodegenerative disease stages**, we will be able to **better define brain age as a biomarker**. For example, one might expect that individuals with a neurodegenerative disease but without apparent neurodegeneration (neurodegeneration negative cases) might also not show abnormal brain age increases. Such specifications of the biomarker are necessary to accurately predict treatment success across patient groups, including the small portion of neurodegeneration negative patients.

WP 2: Evaluation of treatment success

As a next step, we will assess how brain age reflects the effect of treatment. Treatment effects are measured differentially, based on the study, for example with clinical scales indicating the severity of the disorder expression. However, such '**treatment success scores'** can be **standardised** and thereby **generalised across studies**, **enabling mega-analytic effect size estimates** from linear mixed effects meta regression models across sites, disorders, and studies. In the case of problems with establishing comparable treatment success scores, studies or disease and treatment clusters will be analysed one-by-one, and effects will be meta-analysed afterwards. We will delineate whether treatment in general can slow increases in brain age and thereby determine the utility of brain age as a biomarker of treatment success. Moreover, we will **stratify** the **effect for diseases and** potentially different **treatments**, dependent on statistical power estimates based on the remaining samples after quality control exclusions.

WP 3: Covariates of brain age predicting treatment success

Due to the heterogeneity of disorders, one can expect differential influences of covariates in the relationship of brain age and treatment success for the different disorders and treatments. These covariates might be crucial to add accuracy to brain age-guided estimations of treatment effects. We will first **identify relevant covariates** for which data is available across studies, in addition to the classical control variables sex and age, such as standardised cognitive test or other batteries, or different biological measures. If sufficient data are available, we will use **structural equation models to estimate mediation effects** while giving an adequate representation of the data's latent structures. These findings will inform about crucial covariates which need to be controlled for and implemented in the software pipeline which will be provided in WP4.

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WP 4: Establishing a fully automated brain age prediction pipeline

To increase the clinical transferability of this projects' findings, we will implement **a fully automated "no-code" pipeline**, which can be used by clinicians to both **estimate a patient's brain age and evaluate treatment outcomes** based on these estimates. This step is particularly important, as brain age prediction models are usually not embedded in automated clinical pipelines. Moreover, model-specific feature engineering is required, which we will also automatise. The pipeline will give different options for input data and various outputs including detailed descriptions which will help the interpretation and evaluation of the outputs. The pipeline will consider the findings from WP 1-3, informing suggestions about disease- and treatment-specific effects, and the possibility to input covariates to provide additional output and explanations for more robust inference. We will **test the pipeline together with clinicians**, and implement improvements based on collected feedback.

The final work package of the project (WP4) focusses on the translation of the findings into clinical practice. This step is important to let other researchers and clinicians validate our method. In the long run, the method can be used to directly inform clinical decision making, without the need for further technical resources (software, hardware, expertise), as the software will be fully automated. Moreover, descriptions will be provided in the outputs, and a manual will be made available to guide through the software. Moreover, all code and trained models will be made openly available to the community to also be able to use parts of the code separately, adapt or change code according to individual needs.

Organization and Collaboration

The project will be executed from Bergen at the Neuro-SysMed group at Haukeland Hospital / University of Bergen and the Western Norway University of Applied Sciences. The postdoctoral candidate will work across institutions, with short stays planned in Oslo and potentially other cities to foster knowledge exchange. However, the main project location will be in Bergen. For an overview of the collaborators (not including the postdoctoral candidate) and their contributions see Table 2.

Our collaborators from the University of Oslo grant us access to the national high performance computational cluster Sigma2 and the services for sensitive data (tjenester for sensitive data – TSD). TSD provides a platform for researchers at public research institutions to collect, store and analyse research data in a secure environment. The cluster can be accessed from anywhere in the world, including the project collaborators' locations. No additional resources are required.

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Budget

To carry out the project, we seek funding for a three-year full-time postdoc position. The other participants in the project group will contribute their own time—whether personal or research time—to this project, but they possess significant expertise either within the different data sets, cohorts or methods. The Neuro-SysMed will cover additionally needed running costs not covered by the post doc funding.

User involvement

User representatives participate in all included studies. We will invite at least one user representative for each of the examined disease groups (Amyotrophic lateral sclerosis, Alzheimer's disease, Multiple Sclerosis, Parkinson's disease). For that, where possible, we will contact the original study participants to become user representatives in our project. The users will be presented with the project before the project starts. Later, they will participate in meetings for the project throughout the study period and contribute their insights into the relevant research questions. In a follow-up meeting, the results will be reviewed. The users will then have the opportunity to participate in the interpretation of the findings, influence how the results can best be presented, and provide their opinion on how the findings might potentially impact current patient follow-ups.

Value for Patients

Better characterisations of neurodegenerative diseases and their progression are key to establish prognostics, diagnostics and treatment. Hence, the findings of this project are directly aimed at increasing the life expectancy and quality among patients with neurodegenerative diseases by contributing crucial knowledge to each of the arenas of prognostics, diagnostics and treatment. Practically, added expertise in these domains can translate to earlier and better person-centred treatment, with the potential to increase life quality and expectancy of patients living with a neurodegenerative disease.

Ethical Considerations

The data collection is ongoing or concluded, and the data are open to be reanalysed. However, necessary prolonged data access across the project period and sharing of data within the collaborator network may require additional cohort-specific REK (regional ethics committee) approvals. All such approvals will be obtained – based on consultations with the Regional committee for medical and healthcare research ethics, Western Norway, and the Data Protection Officer at Haukeland University Hospital.

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Hosting institution

Haukeland University Hospital, Bergen, Norway

Conflicts of interest

The authors have declared that no competing interests exist.

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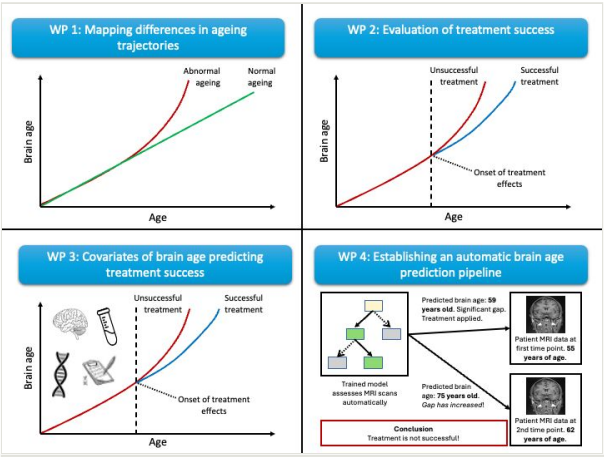

Figure 1.

Graphical overview of the four work packages (WP) of the project.

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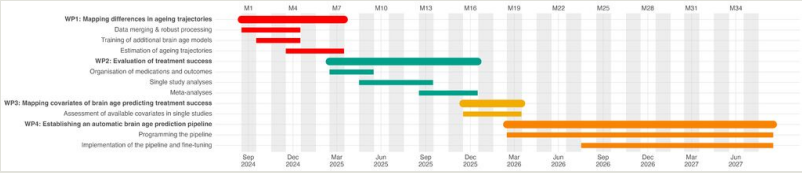

Figure 2.

Timeline of the project. The four main work packages and the according tasks are detailed by month.

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Table 1.

Overview of the available test samples. T_1w/T_2w = T_1/T_2-weighted MRI, dMRI = diffusion weighted MRI. MRS = magnetic resonance spectroscopy. fMRI = functional magnetic resonance imaging. ASL = arterial spin labelling. AD = Alzheimer's disease. MS = Multiple Sclerosis. ALS = Amyotrophic lateral sclerosis.NAD = Nicotinamide Adenine Dinucleotide.

Data set	Description	Sample Size	# of MRI assessments	MRI data
STRAT-PARK	Prospective Parkinson's disease cohort	230 patients, 70 healthy control	3	T_1w, T_2w, SWI, fMRI
Park West	Prospective Parkinson's disease cohort	200 patients, 200 healthy control	5	T_1w, T_2w
STRAT-COG	Prospective AD cohort's	100 patients, 50 controls	2	T_1w
PPMI	Parkinson's cohort followed for 10 years	450 patients, 200 healthy controls	5	T_1w
NAD-PARK	Clinical trial testing NAD in Parkinson's	15 patients and 15 healthy controls	2	T_1w, T_2w, dMRI
NO-PARK	Clinical trial testing NAD in Parkinson's	400 patients	2	T_1w
N-DOSE	Clinical trial testing NAD supplementation in Alzheimer's dementia and Parkinson's	80 patients	2	MRS
NO-ALS	Clinical trial testing NAD in ALS	180 patients	1	T_1w, T_2w, dMRI
OVERLORD-MS	Prospective, newly diagnosed MS patients treated with B-cell depletion therapies	214 patients followed for 2.5 years	5	T_1w, T_2w, dMRI, QSM, ASL, SWI, MRS
OFAMS-MS	Prospective, MS patients with established disease, received Omega3 supplement added to interferon-beta 1a	92 patients followed for more than 12 years	13 (baseline, monthly for 9 months, 12, 24, 120 months)	T_1w, T_2w, dMRI
BICAMS	Newly diagnosed MS patients on routine therapy	50-60	several scans over a 2-years period	T_1w, T_2w, dMRI, SWI, ASL
NORSEMAN	Routine MRI in a clinical trial testing NAD in progressive MS	50	3 (baseline, 12, 24 months)	T_1w, dMRI
NOR-MS	MS patient cohort treated with cladribine or rituximab	264	0 (baseline), 3 (re-baseline, 12, 24 months)	T_1w, T_2w FLAIR, QSM dMRI, ASL, perfusion

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Table 2.

Collaborators and their contributions. WP = Work Packages.

Collaborator	ORCID	Affiliation	WP	Contribution
Ivan I. Maximov	0000-0003-0367-1654	Western Norway University of Applied Sciences	1-4	MRI data processing and analysis. Development, testing and implementation of machine learning software developed in this project.
Eli Eikefjord	0000-0003-0067-8180	Western Norway University of Applied Sciences	1-3	MRI data processing and analysis, project coordination.
Frank Riemer	0000-0002-3805-5221	Haukeland University Hospital (HUH)	1-4	MRI data processing and analysis, project coordination. Testing and implementation of machine learning software developed in this project.
Kjell-Morten Myhr	0000-0002-0980-510X	HUH/Faculty of Medicine, University of Bergen	2-3	Clinical expertise and access to clinical trials.
Øivind F. G. Torkildsen	0000-0001-5294-2866	HUH/Faculty of Medicine, University of Bergen	2-3	Clinical expertise and access to clinical trials.
Charalampos Tzoulis	0000-0003-0341-5191	HUH/Faculty of Medicine, University of Bergen	2-3	Clinical expertise and access to clinical trials.
Lars T. Westlye	0000-0001-8644-956X	Faculty of Psychology, University of Oslo	1-3	Magnetic Resonance Imaging data processing and analysis. Explainable AI expertise.
Einar August Høgestøl	0000-0001-8446-2111	Faculty of Medicine, University of Oslo	2-4	Magnetic Resonance Imaging data processing and analysis. Clinical expertise and access to clinical trials.