Decoding the functional reorganization of the aging brain using machine learning applied to electroencephalography

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Abstract

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List of Abbreviations

AI	artificial intelligence
BCI	brain computer interface
CRUNCH	compensation-related utilization of neural circuits hypothesis
CSP	common spatial patterns
DMD	dynamic mode decomposition
EEG	electroencephalography
ERM	empirical risk minimization
ERP	event related potential
fMRI	functional magnetic resonance imaging
HAROLD	hemispheric asymmetry reduction in older adults
ICA	independent component analysis
LDA	linear discriminant analysis
MLE	maximum likelihood estimation
MRI	magnet resonance imaging
MVPA	multivariate pattern analysis
PASA	posterior–anterior shift in aging
PCA	principal component analysis
RF	random forest
STAC	scaffolding theory of cognitive aging
SVM	support vector machine
t-SNE	t-distributed stochastic neighbor embedding
UMAP	uniform manifold approximation and projection for dimension reduction
WHO	World Health Organization

Publications and other scientific contributions

Chapter 1

General Introduction

1.1 Motivation

> "Humans now live longer than at any time in history. But adding more years to life can be a mixed blessing if it is not accompanied by adding more life to years."
>
> Dr Tedros Adhanom Ghebreyesus, WHO Director-General"

One of the greatest societal challenges is the demographic shift towards an older population which poses enormous demands for society as a whole raising issues for the healthcare system, infrastructure, family policy, and the occupational sector [1]. To avoid overburdening social structures, one of the main goals is to promote healthy, independent aging and improve the quality of life in old age. As part of efforts to promote healthy aging, the World Health Organization (WHO) launched the *Decade of Healthy Aging (2021-2030)*, which aims to encourage global action to improve the lives of older people, their families, and the communities in which they live with the ultimate goal of adding years to life [1]. An essential part of promoting healthy aging and enabling participation in society includes the development and evaluation of targeted interventions, the design of assistive technologies, for older adults, or the early identification of pathological conditions. To accomplish this an understanding of the dynamics of aging in the context of individual trajectories and general patterns is required. Understanding and quantifying aging at the level of the brain is of particular interest, as changes in the brain are highly interrelated to declines in behavior and cognition in older age. Not only the phenomenon of aging is highly complex but also the brain can be understood as a complex system that is nonlinear, dynamic and multi-scale in space and time [2].

Modern data-driven methods from the field of machine learning offer a lot to cope with this complexity. Moreover, these methods form the basis for solving various practical problems, as demonstrated by applications in many socially relevant areas, such as public transport, e.g. autonomous or self-driving vehicles [3], the medical sector, e.g. diagnostic imaging [4], or social interaction, e.g. tools for communicative interaction [5], and are thus one of the basic building blocks for assistive technology. Yet, progress in science is more and more characterized by the application of methods from artificial intelligence (AI) including machine learning algorithms, which make it possible to systematically analyze large and complex amounts of data [6]. This has led to proclamations of an "AI revolution in science" [7] or promoting science has entered a new area characterized by *data-intensive computing* [8]. AI and machine learning as a key technology become a hope for solving societal challenges.

In comparison to the rapid development in the commercial sector, the implementation of machine learning approaches in the study of aging is still in its early stages and the most effective applications and integration into the traditional science system remain to be evaluated [9].

The aim of this thesis is to identify and apply machine learning techniques to address brain aging such as the study of neurophysiological underpinnings and influencing factors of sensory, motor and cognitive alterations. Using machine learning the intention is to test to what extent hypotheses about the aging brain can be confirmed, new hypotheses can be formed and derivations for the development of targeted interventions and assistive technologies can be made.

1.2 Outline

This thesis is separated in five main chapters. In this chapter 1 the theoretical framework of this thesis is described. A description of aging at the level of the brain forms the starting point for introducing the added value of applying machine learning in the context of this work. Building on this, machine learning as well as basic approaches are introduced to provide the methodological framework. The general terminology as well as a literature-based overview of the use of machine learning methods in neuroscience and especially in the neuroscientific research on aging will form the basis for the deduction of the research aim and scope of this thesis in the following chapter chapter 2. The following chapter chapter 3 includes a description of the methodological approach of this work. In the subsequent chapter chapter 4 the published sub-projects underlying this thesis will be presented. These include:

- Chapter 4.1:
  Goelz, C. *et al.* Classification of visuomotor tasks based on electroencephalographic data depends on age-related differences in brain activity patterns. *Neural Networks* **142,** 363–374 (2021)

- Chapter 4.2:
  Goelz, C. *et al.* Classification of age groups and task conditions provides additional evidence for differences in electrophysiological correlates of inhibitory control across the lifespan. *Brain Informatics* **10,** 11 (2023)

- Chapter 4.3:
  Goelz, C. *et al.* Electrophysiological signatures of dedifferentiation differ between fit and less fit older adults. *Cognitive Neurodynamics* **15,** 1–13 (2021)

- Chapter 4.4:
  Gaidai, R. *et al.* Classification characteristics of fine motor experts based on electroencephalographic and force tracking data. *Brain Research* **1792,** 148001 (2022)

The thesis concludes with an overreaching discussion highlighting consequences and future research topics (chapter 5).

1.3 Aging

Biologically aging can be broadly characterized as "the time-dependent functional decline that affects most living organisms" [14]. It can be observed in the reorganization of multiple interacting physiological systems operating at different spatial and temporal scales [15]. The underlying patterns of reorganization within and between these systems are highly individual, as they are subject to internal (e.g., genetic, cellular, molecular) as well as external (e.g., environmental, and lifestyle) influences [15–17]. At the same time, however, overarching, generalizable patterns can be identified [18]. The most recognizable consequences of aging are alterations in cognitive, sensory, and motor abilities that challenge the daily lives of older adults [19]. However, not all abilities are equally affected by declines and the alterations are highly individual. While sensory, motor abilities and cognitive abilities, such as memory and processing speed, are described as generally declining, abilities in the context of acquired knowledge, such as verbal abilities, tend to be stable or even improve with age [20]. Understanding brain reorganization is of particular interest because of its interrelation with behavioral alterations.

1.3.1 Age-related reorganization of the brain

Reorganization in the structure of the brain include, among others, atrophy of the gray and white matter as well as enlargement of cerebral ventricles [21]. The efficiency of neuromodulation declines mainly driven by the loss of dopaminergic receptors indicative of a reorganization of neurotransmitter systems [22]. Besides this, the study of the functional properties of the brain and their relationship to behavioural changes is of great interest. In neuroimaging studies, both under-activation and over-activation of brain areas have been reported in older adults compared to younger adults during performance in various tasks with sensory, cognitive as well as motor demands [23, 24]. In terms of activation dynamics, brain activity in response to a stimulus is often slower or delayed. Moreover, the frequency distribution of neural oscillatory activity changes with respect to a slowing of the main rhythms and altered temporal dynamics which is interpreted as changes in neural communication [25].

By emphasising neural communication and information flow, rather than viewing the brain as functionally separate, it can be conceptualised as a complex system whose functional units, i.e. neurons, areas and subsystems, are interconnected both structurally and functionally [26, 27]. In this concept, functional connectivity reflects coherent patterns of activation within and between these units. Several distinct but interconnected functional networks were identified. The dynamic interplay between and within these networks is characterized by segregation and integration at different levels, characterizing the flow of information in the brain [28]. Older adults information flow tend be less efficient and is characterized by lower within network connectivity and higher between network connectivity associated with a less segregated, less modular and more integrated brain network organization [24, 27, 29]. However, studies on sensorimotor and visual networks seem to be very heterogeneous, which could indicate very individual reorganization patterns [27].

Dedifferentiation

The functional reorganization patterns described in the previous section have been be attributed to dedifferentiation [30]. Dedifferentiation refers to the loss of neural specialization or reduced distinctiveness of neural responses resulting in a diffuse, non specific recruitment of brain resources [31]. Historically, the term originates from behavioral research in which an increased correlation of performance between sensory, cognitive and sensorimotor domains was reported in older adults [19, 32]. In order to explain this behavioral dedifferentiation Li and colleagues [19, 22] provided a computational model. According to this model, deficient neurotransmitter modulation observed in older adults may affect the responsiveness of cortical neurons, leading to higher levels of neuronal noise and ultimately to less differentiated, more diffuse neuronal activation patterns in response to different stimuli [19, 22] (see Figure 1.1 for an overview on the computational model). In several computational simulations, the authors demonstrated that the proposed model can explain not only behavioral co-variation, but also several other phenomena, such as the decrease in average behavioural performance or the increase in behavioral intra- and inter-person variability [19, 33]. In addition, the proposition of a less distinctive, less specific neuronal activation in response to stimuli could be confirmed in neuroimaging studies showing that the neural responses to various visual, cognitive and motor stimuli are less specific in older compared to young adults [31, 34, 35].

Recently the reorganization of functional networks as described above, i.e. less segmented and modular, and less specialized organization in older adults was framed in terms of dedifferentiation [24, 27, 31]. Fornito *et al.* [36] describe dedifferentiation as a fundamental maladaptive mechanism of brain networks that requires compensation. This is consistent with the argument that dedifferentiation and compensation are complementary mechanisms [23]. However, dedifferentiation could also itself represent a compensatory response, in that the brain attempts to maintain function in the face of deterioration [37]. By definition compensation refers to the ability to recruit additional brain resources to compensate for decline and functional loss in order to maintain cognitive or behavioural functioning [23, 30]. Here, the compensation-related utilization of neural circuits hypothesis (CRUNCH) hypothesizes that compensatory activity changes as a function of task demands. Moreover, compensation often occurs in a specific pattern of under-activation of posterior areas and prefrontal over-activation, known as posterior–anterior shift in aging (PASA) [38]. Another often reported pattern is the more bilateral recruitment and loss of hemispheric specialization, known as hemispheric asymmetry reduction in older adults (HAROLD) [39].

Reserve

It is important to note that age-related alterations of the brain and behavior are highly individual and dynamic [16, 31, 40]. In this context, the concept of reserve was defined as the accumulated capacity of neural resources over the lifespan that can withstand decline or pathology [37, 41]. Although the concept was originally based on observations that the degree of pathological changes in the brain do not necessarily mean clinical manifestation, it has also been applied to explain individuality of non-pathological

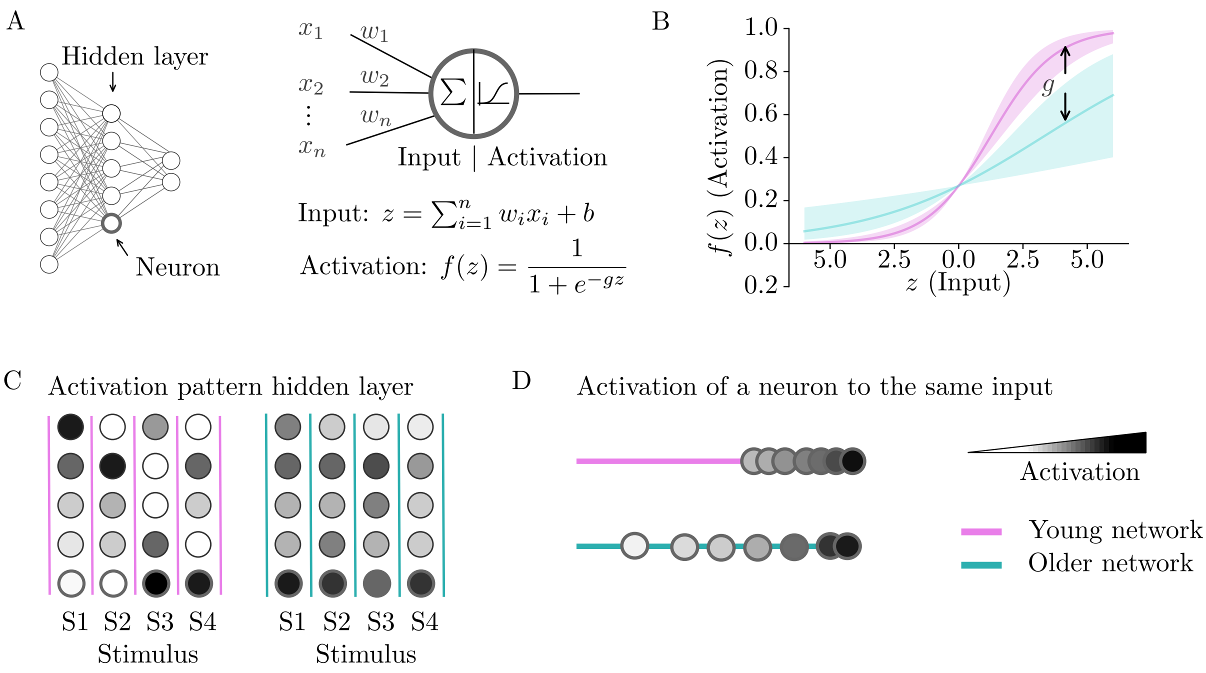

Figure 1.1: The computational model proposed by Li and colleagues [19, 33]. The authors used a feedforward backpropagation neural network model with logistic activation function $f(z)$ and simulated altered neuromodulation by varying the gain parameter g in $f(z)$ of each neuron (A). Deficient neuromodulation and responsiveness due to aging is simulated by lower g values resulting in a dampened activation of a neuron (B). Simulations showed that the activation pattern of simulated neurons differs less for different stimuli, i.e. the hidden layer of the network shows a less distinctive representation of the stimulus (C). The activation of a single neurons is more variable for multiple stimulations with the same stimulus (D).

aging [37, 41, 42].

Reserve can be both anatomically quantifiable, which is referred to as brain reserve, and more functional in nature, which is referred to as cognitive reserve [37]. At the functional level, compensatory activation as well as more efficient utilisation (less activation of neural resources), increased capacity (increased availability of neural resources) were described as key mechanisms of cognitive reserve [37, 43]. Brain and cognitive reserve influence each other and Cabeza *et al.* [41] argue against a strict separation of brain reserve and cognitive reserve.

One aspect that explicitly determines the definition of reserve is the lifelong ability of the brain to adapt its structure and function to internal and external requirements. It is known from the animal model that environments rich in cognitive, social, as well as sensory and motor stimuli, contribute to positive plastic changes [44]. As a result, reserve is influenced by an interplay between genetic and environmental factors including lifestyle factors [41]. Important factors for increasing reserve have been identified in education, occupation as well as physical activity, with cognitive training, physical fitness, and professional expertise having a considerable impact on the brain's functional organization [45–47].

This is further supported by other complementary concepts such as the maintenance or the scaffolding theory of cognitive aging (STAC) models. The concept of maintenance emphasizes the ability to repair. STAC postulates that lifelong positive and negative plasticity define a framework that enables compensation and shapes the individual trajectory of aging [48].

1.3.2 Studying brain aging by electroencephalography

The complex interplay of the aforementioned factors leading to the dynamics of age-related reorganization of the brain is highly complex. Understanding these dynamics in terms of individual trajectories and overarching patterns is a prerequisite to differentiate healthy from pathological changes and to develop and verify treatments as well as targeted interventions. This requires uncomplicated, easy-to-use, and cost-effective methods and novel analyses to quantify changes in brain organization. Several noninvasive methods are available to study the brains' structure and function. Magnet resonance imaging (MRI) is the most widely used method in science to image the structure or, using functional magnetic resonance imaging (fMRI), the function of the brain, which is the dominant method in the study of the functional reorganization described in the previous section [23]. However, this method is very costly and requires expertise that is not widely available. As a result, its use in the public health system is mostly limited to cases with a clear indication, so that early detection of unfavourable aging trajectories is rather difficult. In addition, limited availability substantially restricts the development of preventive and rehabilitative interventions and therapies and excludes areas and sites with low levels of equipment and expertise. Here, electroencephalography (EEG) could represent a real added value, since it is characterized by a simple use, mobility, and relative cost effectiveness. Although it has a lower spatial resolution than MRI based methods, EEG measures neuronal activity directly with high temporal resolution which allows for the detection of age-related changes in the temporal dynamics of brain activity and networks, which could be of special interest to understand age-related changes of the brain and their relation to behavior [25].

Excursus: A brief overview on electroencephalography

EEG measures time varying electrical fields on the surface of the head by using several sensors placed in a standardized position [49]. The measured signals reflect synchronously active populations of neurons. Electrical activity can only accumulate and be detected on the surface of the head if spatially similar neurons, aligned perpendicular to the surface, are synchronously activated. Based on the conductive properties of the brain the signal can travel through the different layers to the surface due to volume capacitive conduction. For this reason, and due to the orientation of neural cell assemblies, the signal in each sensor reflects a summed signal of different neuron patches. The signals expressions are in the range of a few micro-volts and is much lower than other biological and non-biological electrical generators, e.g. muscular activity or line noise, so that the EEG signal is often affected by a low signal-to-noise ratio [50].

One of the most striking signal characteristics of the EEG is the rhythmic fluctuations in voltage that define the signal and are summarized under the term oscillation. It is common that the EEG signal is analyzed based on the frequency composition of oscillatory activity in loosely defined frequency ranges, i.e., δ (<4 Hz), θ (4-8 Hz), α (8-12 Hz), β (12-30 Hz) and γ (>30 Hz), which have been demonstrated to be related to perceptual, cognitive, motor and emotional processes [50]. Furthermore, the analysis of frequency-dependent synchrony or functional connectivity in terms of a statistical dependence of the signals, e.g. by coherence or the phase synchrony of the signal, can provide information about the network characteristics of the brain [51]. Finally, the analysis of event-related activation, so called event related potentials (ERPs), can furthermore provide information on the direct processing of stimuli. This involves time-locking the EEG data to the onset of a specific stimulus and averaging the EEG signal across multiple trials to extract a reliable signal that is related to the processing of the stimulus.

Electroencephalographic signatures of age-related reorganization

Age-related changes in EEG characteristics have been extensively studied. Specifically it has been reported that aging is associated with changes in the frequency composition of the EEG signal, regardless of any specific task involvement. These changes include a decrease in amplitude within the α frequency band, a shift in the α peak frequency towards lower frequencies, an increase in amplitude within the β frequency band, and varying results regarding changes in the amplitude of the θ and δ bands [25, 52, 53]. Moreover, age-related changes have also been reported in terms of reduced EEG synchrony and a more random less segregated organization of EEG derived network topology [54, 55].

EEG changes in relation to tasks are highly dependent on the task context or domain studied. For example, unilateral motor tasks may display lower frequency specificity and more bilateral spatial expression of α and β frequency power modulations, while attention tasks may demonstrate enhanced frontal network involvement as well as power in the θ frequency band [56, 57]. In addition, the neural response to stimuli may exhibit a temporal slowing and altered spatial expression. This can be seen, for example, in a delay of early ERP components as well as a more frontal expression of later ERP components in visual attention tasks [58, 59].

Often these changes are discussed in relation to the mechanisms of dedifferentiation and compensation described above. These have been shown to be modulated by lifetime experience such as occupational expertise [45] or physical fitness [40]. However, the relationship between EEG parameters and these mechanisms often seems to be ambiguous. As such, other EEG findings may point in the opposite direction than described above. Hübner *et al.* [60] for instance found no age effects in central lateralization in the β frequency band in a complex fine motor control task, which again highlights the dependency to the task context considered. Age-related changes in decreased ERP latency as well as lower or increased functional connectivity of the examined networks depending on the task context are also reported [25]. Moreover, the interpretation of dedifferentiation is often based on fMRI findings that report over-activation and loss of segregation of brain networks. However, the relationship between frequency-specific EEG and fMRI findings acting on different spatial and temporal scales as well as measurement principles might be unclear. Koen & Rugg [31] further points out that over-activation should be interpreted cautiously and does not necessarily imply loss of neural specificity, as predicted in the original model of Li *et al.* [33]. He therefore proposes to operationalize dedifferentiation clearly in terms of the selectivity of the neural response between two or more task modulations. While in this operationalization the evidence regarding dedifferentiation in fMRI studies is quite clear, this has not been explored in EEG studies so far [31].

Altogether the EEG represents an easy-to-use, low-cost method that can provide valuable insights into age-related changes. However, the link to age-related changes reported consistently in the fMRI such as dedifferentiation is often difficult and not entirely clear. Furthermore, EEG signals are temporally and spatially highly dimensional and have a low signal-to-noise ratio, which makes the detection and visualization of age-related brain reorganization and their dynamics difficult and requires advanced signal analysis methods. Advanced methods such as methods from the field of machine learning could be of special interest in this context.

1.4 Machine learning

Machine learning emerged in the 1950s to enable computers to learn without being explicitly programmed [61]. It is defined by computational methods combining fundamental concepts from computer science, statistics, probability and optimization that automatically extract patterns and trends, i.e., *learn* from data [62]. The notion of *learning* therein describes the automated inference of general rules based on the observation of examples using algorithms with the goal to solve a certain task or problem [63]. Often, in its basic form these tasks involve making predictions based on learned relationships or the extraction of information based on automatically detected patterns and structures from data. Many problems can be formulated by these tasks and a rise in machine learning started in the 1990s to 2000s with the availability of computing resources, data, and the development of algorithms, which have found their way into everyday life not only since the current hype about generative AIsystems. Examples can be found in numerous areas, such as predicting stock prices, personalized advertising, or autonomous driving [64]. In science machine learning is increasingly used as a complementary method to classical statistical analyses because of the ability to make predictions as well as to deal with the multidimensional structure and non linearity in real world data sets for drawing inference [65]. Especially in areas where high-dimensional data is prevalent, such as in neuroscience, the use of methods from machine learning offers insight by extracting complex patterns purely data driven [6]. In terms of EEG this means that machine learning can help identify subtle patterns and nonlinear relationships from the multidimensional complex structure of EEG data, allowing for more accurate and efficient analysis of brain recordings. A wide variety of methods are available for this purpose, which can be roughly characterized on the basis of various properties.

1.4.1 Forms of machine learning

The three main forms of machine learning are supervised, unsupervised, and reinforcement learning which are defined by the type of feedback a machine learning algorithm has access to during learning [66].
In supervised machine learning the goal is to learn a generalizable relationship between data and associated information, so-called labels or target. This can then be used to predict the label of new data that not have been used during the process of learning. If the labels are categorical, the prediction task

is called classification; for continuous labels, the term is regression. The goal of unsupervised machine learning is to find hidden structure in data without taking into account associated labels. This could be grouping similar data points, i.e. clustering, or uncovering a meaningful low dimensional representation of high dimensional data, i.e. dimensionality reduction. This type of learning is also referred to as *knowledge discovery*[67]. Reinforcement learning describes the task to learn optimal actions to solve a certain problem by maximizing the reward linked to that action. See Figure 1.2 for an overview.

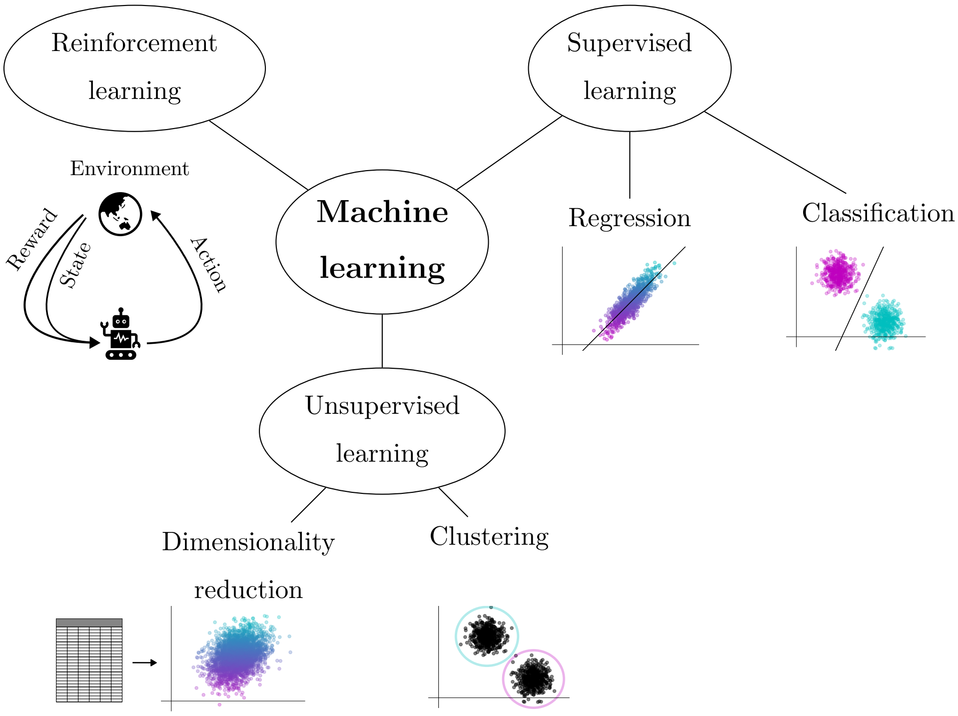

Figure 1.2: The three main forms of machine learning

In practice however a clear separation is often not possible. As such, dimensionality reduction can also be supervised, i.e. labels are provided to learn a new representation of the data [68]. Besides, in semi-supervised learning, for example, the goal is the same as for supervised learning. However the data set used to learn the relationship contains both, labeled and unlabeled examples and the hope is to build a stronger representation by providing more information in form of data [69].

In addition traditional machine learning is often contrasted to deep learning methods involving the use of artificial neural networks which are composed of many layers of interconnected nodes often used in an end to end fashion in which features are extracted within the network. Usually they require huge amount of data and computational power. In the context of this thesis the tasks considered involve the processing of a EEG from experiments with mid to small sample sizes with the goal to learn meaningful patterns and relationships in data. The most commonly used forms in this contexts are supervised and unsupervised learning focusing traditional machine learning. For this reason these forms will be the focus in the following chapters.

Excursus: How does a machine learn?

"A computer program is said to learn from experience E with respect to some task T and some performance measure P, if its performance on T, as measured by P, improves with experience E" [70]. In other words learning in the context of machine learning typically involves solving a specific task by using algorithms that improve their performance by using example data. There are numerous algorithms designed to solve the problems outlined above. Thereby some basic building blocks can be defined which can be used to describe computational learning in a formal way. In the following description the view of statistical learning theory is considered, notation is adapted from Shalev-Shwartz & Ben-David [66], von Luxburg & Schölkopf [63].

Learning always is based on data, i.e. measurable information of some phenomenon, which consists of attributes of the phenomenon, so called features, and in supervised learning an associated label. It can mathematically defined as open bounded set $\mathcal{Z} \subset \mathbb{R}^n$ of dimension n. Typically there is only a set of examples or training data $S = \{z_i, ..., z_m\} \subset \mathcal{Z}^m$ available, where $i = 1, \dots, m$, and each z_i is sampled independently from $\mathcal{Z}$ according to an underlying probability distribution $\mathcal{D}$. Thus the only assumption made is that the example data are independent and identically distributed. No assumption on D is made.

In supervised learning $\mathcal{Z}$ comprises the space of input data $\mathcal{X}$ and the space of labels or output $\mathcal{Y}$. The example data S consists of labeled input-output pairs $z_i = x_i, y_i \in (\mathcal{X} \times \mathcal{Y})^m$, where x_i is an input data vector and y_i is its corresponding output label. The pairs are sampled by some unknown joint probability distribution $\mathcal{D}$ on the space $\mathcal{X} \times \mathcal{Y}$.

The space $\mathcal{Z}$ in unsupervised learning comprises the input data space $\mathcal{X}$ only and the example set S consists of unlabelled examples $z_i = x_i \in \mathcal{X}^m$, sampled according to some unknown probability distribution $\mathcal{D}$ on the space $\mathcal{X}$.

Learning ultimately can be thought of as approximating an underlying ground truth function f, also called model, that represents the relationship between input and output in supervised learning, i.e.,

$$f : \mathcal{X} \to \mathcal{Y}, \tag{1.1}$$

or the mapping to a space of hidden patterns or structure $\mathcal{W} \subset \mathbb{R}^p$, where p can be equal or smaller than n, i.e,

$$f : \mathcal{X} \to \mathcal{W}. \tag{1.2}$$

A learning task can be conceptualized as searching through the space of all possible solution functions. As this is not feasible a finite class of functions, so called hypotheses, is typically selected a priory. Thus, learning can be thought of as selecting a hypothesis h from a space of potential solutions $\mathcal{H}$ with $\mathcal{H} = \{h : \mathcal{X} \to \mathcal{Y}\}$ in supervised learning and $\mathcal{H} = \{h : \mathcal{X} \to \mathcal{W}\}$ in unsupervised learning.

A learner or learning algorithm is the means of selecting the best element from $\mathcal{H}$. The cost of

a false prediction or an inaccurate representation of the data is quantified using a loss function, $\ell : \mathcal{H} \times \mathcal{Z} \to \mathbb{R}_{+}$. In other words it measures how well a specific hypothesis is doing.
The expected risk is measure of the average loss of a hypothesis, $h \in \mathcal{H}$ with respect to the probability distribution $\mathcal{D}$ over $\mathcal{Z}$ and can be defined as

$$L_D(h) := \mathbb{E}_{z \sim D}[\ell(h, z)] \tag{1.3}$$

A learner should select a hypothesis with lowest possible expected risk. However, the underlying probability distribution is unknown. By using S the expected risk can be estimated by using the empirical risk over the training data. This is defined by:

$$L_S(h) := \frac{1}{m} \sum_{i=1}^{m} \ell(h, z_i). \tag{1.4}$$

Following this, learning can be formalized solving an optimization problem of the form:

$$\hat{h} = \arg\min_{h \in \mathcal{H}} L_S(h), \tag{1.5}$$

which can be solved computationally. In parameterized models, this often involves the automated selection of those parameters $\theta \in \Theta$ of a chosen class of models that minimize $L_S(h_\theta)$. This optimization problem can then be solved by various methods such as gradient descent, or e.g., analytically using least squares estimation. The solution $\hat{h}$ is the learned model that can be used to solve the task at hand, e.g. predicting the label of new input data or uncovering patterns or structure in data. This is known as empirical risk minimization (ERM).
Upon ERM more complex learning paradigms can be used addressing common problems such as overfitting, in which the learned hypothesis to closely relies on the training data and therefore has low generalization performance, e.g. regularized risk minimization which introduces regularization to ERM or structural risk minimization that penalizes complex models and encourages simplicity.

Although most machine learning can conceptualized within the framework of ERM there are models that instead of minimizing risk assume that the underlying distribution over the data has a specific parametric form and the goal is to estimate these parameters by using maximum likelihood estimation (MLE) which seeks to find the model parameters that maximize the likelihood of the observed data under the assumed parametric distribution, i.e.

$$\hat{\theta}_{\mathrm{MLE}} = \arg\max_{\theta \in \Theta} \prod_{i=1}^{m} p_\theta(z_i), \tag{1.6}$$

where $p_\theta(z)$ is the joint probability function of the assumed parametric distribution and $\hat{\theta}_{\mathrm{MLE}}$ is the estimated value of the parameter vector θ.

1.4.2 Applications in the context of aging research

Traditionally, machine learning has been the core building block for the development of intelligent systems that can automate tasks or enhance and assist humans in performing their tasks. Such systems are not only important in terms of assistive technology, for example to support elderly people with disabilities to live their daily lives, but are also relevant in the medical fields. In the latter the hope is to develop intelligent medical systems to inform clinical theory and support clinical decision making, i.e. assist in diagnosis, and risk management by predicting health status or forecasting of treatment responses [71]. In this context, supervised learning is often used to identify markers from EEG by identifying signal features that are predictive of a particular disease or health condition, which is highly important in terms of promoting a healthy aging trajectory [72, 73]. An application is the estimation of biological age based on regression models trained on the basis on neural data, e.g. EEG data, recorded in large population studies [74]. Using data of an individual person, a regression model can predict the age of that person. If the brain appears older than it would chronologically, this can be an early indication of an unfavorable state of health [75].

Another in the context of aging highly relevant application is the development of devices with the goal to assist, augment or enhance humans capabilities such as brain computer interfaces (BCIs). In BCIs, neural activity is decoded, using classification to generate control commands for various external devices such as computers or prosthetic limbs [76, 77]. Decoding hereby refers to learning a classification or regression model that is capable of predicting behavioral outcomes or cognitive states based on neural data.

Beyond the application in BCIs, decoding techniques are widely used in neuroscientific research to gain insights into the neural mechanisms underlying perception, cognition, and behavior. This type of analysis is often referred to as multivariate pattern analysis (MVPA) because its goal is to detect multivariate patterns, e.g., a set of voxels in fMRI or an electrical pattern at a given time point in EEG, associated with an experimental condition [78]. While the use has a long history in the field of fMRI analysis, it has only become more widespread in the field of EEG in recent years. Therefore, decoding approaches to understand age-related reorganization are mostly limited to fMRI studies. A common approach is to measure dedifferentiation, i.e. the loss of neural specificity, at the individual level. Since dedifferentiation by definition results in more similar brain activation patterns for different tasks or stimuli, poorer performance of classifiers trained to discriminate between them based on neural recordings is indicative of a less distinctive neural representation [31, 79].

Furthermore, the classification of group membership or group level regression can provide information about interesting relationships and their generalizability. Particularly for EEG markers representing functional network characteristics can reveal insightful findings about the relationship to age-related changes [80].

In addition to the application of supervised learning algorithms, unsupervised learning algorithms have long been used in neuroscience. Unsupervised methods are often used as a preprocessing step to reduce the complexity of EEG data but can also provide interesting insights into the structure of data sets. Dimensionality reduction algorithms can provide insights into high-dimensional data by providing a possibility to visualize high dimensional patterns of EEG data [81, 82]. This can be used to study the temporal structure of EEG signals in terms of the dynamic of brain networks with aging [45, 83].

In summary, the use of machine learning is very diverse and ranges from engineering applications to scientific knowledge discovery. Especially in the latter case, it offers the advantage of automated extraction of patterns from highly complex data that can contribute to the study of age-related changes. While decoding approaches are particularly interesting for measuring age-related changes in the organization of neural systems, such as the level of differentiation, group analysis could provide new insights into datasets. Especially classification methods that allow to predict a certain experimental condition or a group membership are particularly suitable. The combination with unsupervised learning algorithms such as dimensionality reduction methods could be particularly beneficial and used for the visualization of high-dimensional data. Based on this, the next section will present common approaches with a focus on the classification and dimensionality reduction of EEG data.

State of the art approaches

Selecting a suitable learning algorithm for classification, i.e. classifier, involves an iterative approach that divides the available data into training and testing sets, trains and validates various classifiers within the training portion (cross-validation), and finally tests the best performing model on the testing portion to estimate its ability to generalize [62]. Different classifiers may have varying strengths and weaknesses, with popular examples including support vector machines (SVMs), linear discriminant analysis (LDA), and random forests (RFs) (see [84] for an overview).

While deep neural networks are capable of learning on the basis of raw data their advantage comes into play with large labeled data resources, which are often expensive to acquire in the case of EEG [82]. Traditional learning approaches can be more efficient with good performance and promise better interpretability, especially for comparatively smaller data sets and limited computational resources [85]. Due to the low signal-to-noise ratio and high complexity of EEG data, the inputs in these approaches are typically represented by well known EEG characteristics, or features, that are believed to be related to the problem being learned. Typical features include parameters of time, frequency, time-frequency, connectivity and information theoretical parameters extracted for each sensor (see [85] for common choices). However, this approach may lead to less flexible and generalizable models with low spatial resolution and vulnerability to low signal-to-noise ratios [86].

To address this, some approaches compute the sources of the EEG signals in the brain using biophysical models as a preprocessing step prior to feature extraction [87, 88]. Other approaches use supervised and unsupervised decomposition techniques belonging to the field of dimensionality reduction as a preprocessing step for further prediction tasks or provide information themselves in the sense of knowledge discovery. These methods aim at *unmixing* the highly correlated sensor time series by assumptions about the underlying signal components. For example, independent component analysis (ICA) assumes statistical independence, while principal component analysis (PCA) assumes that the extracted components are maximally uncorrelated to each other, capturing the largest amount of variance in the data [50]. Dynamic mode decomposition (DMD) is a method that explicitly considers the temporal structure of the signals, which requires the extracted signal patterns (modes) to be temporally coherent, thus accounting for the network character of the brain [83]. Additionally, supervised methods such as common spatial patterns (CSP) [89] or xDAWN [90] extract signal components that correlate with the labels to be predicted.

While supervised and unsupervised ways of examining the complex EEG signals in terms of components and patterns to generate knowledge, non-linear methods such as t-distributed stochastic neighbor embedding (t-SNE) and uniform manifold approximation and projection for dimension reduction (UMAP) take into account the non-linear relationships between the data points and provide a lower-dimensional representation of the data that is often easier to interpret and visualize [68]. These methods can be particularly useful for exploring the relationships between different EEG features or for identifying subgroups within a dataset.

It is important to note that these methods can be applied not only to the EEG signals itself, but also to previously extracted EEG parameters or in combination in terms of knowledge discovery. Thus, supervised and unsupervised dimension reduction provides data-driven insights into the complex underlying information, but also serves as preprocessing for further tasks such as prediction.

Chapter 2

Aims and scope

The overall goal of this dissertation is to apply established methods from the field of supervised and unsupervised machine learning to analyze EEG signals with the primary objective of capturing the age-related reorganization of the brain both in terms of overreaching patterns as well as individual trajectories. The focus is on studying age-related phenomena, such as dedifferentiation and investigate the replicability of hypotheses such as reserve. In four empirical studies diverse datasets are utilized with subjects spanning different life stages and lifestyle backgrounds, including occupational expertise and physical fitness. The following empirical studies will be presented.

> Goelz, C. *et al.* Classification of visuomotor tasks based on electroencephalographic data depends on age-related differences in brain activity patterns. *Neural Networks* **142,** 363–374 (2021)

In this empirical study, the focus was on determining whether classification techniques applied to EEG data could effectively reflect dedifferentiated brain network characteristics in older people with the the motor system serving as an example. We therefore compared the classification performance, i.e. the discriminability of different visuomotor task, between younger and older adults.

> Goelz, C. *et al.* Classification of age groups and task conditions provides additional evidence for differences in electrophysiological correlates of inhibitory control across the lifespan. *Brain Informatics* **10,** 11 (2023)

Continuing previous research, this study aimed to investigate whether the cortical representation of inhibitory control differs across age groups. For this purpose, the performance of the classification of different stimulus types of a flanker task was compared between different age groups. Furthermore, it was investigated whether the age group membership can be predicted based on the EEG data.

> Goelz, C. *et al.* Electrophysiological signatures of dedifferentiation differ between fit and less fit older adults. *Cognitive Neurodynamics* **15,** 1–13 (2021)

The objective of this study was to examine the potential influence of cardiorespiratory fitness, a lifestyle factor, on patterns of dedifferentiation extracted through dimensionality reduction. This investigation was motivated by the reserve hypothesis, which postulates that cardiorespiratory fitness could impact age related brain reorganization and therefore the observed patterns of dedifferentiation.

> Gaidai, R. *et al.* Classification characteristics of fine motor experts based on electroencephalographic and force tracking data. *Brain Research* **1792,** 148001 (2022)

In addition to cardiorespiratory fitness, another significant lifestyle factor is professional expertise. Therefore, our subsequent analyses aimed to characterize middle-aged experts using supervised and unsupervised machine learning techniques.

The application of machine learning methods both on individual and on group level, will allow to draw conclusions about predictors of reorganization of the brain and will help to identify the individual status as well overreaching trajectories. The information gained from these tools could be used to determine and evaluate intervention programs, on-the-job-trainings, support diagnosis, and may have applications in the development on assistive technological systems.

Chapter 3

General methodology

Chapter 4

Results

4.1 Paper 1

4.2 Paper 2

4.3 Paper 3

4.4 Paper 4

Chapter 5

General discussion

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